BACTERIAL DISEASE CONTROL, ANTIBIOTICS AND THE ENVIRONMENT

IN MARINE FINFISH CULTURE:

A Review

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A technical report to the
Marine Working Group
Scottish Wildlife and Countryside Link

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Summary

Antibiotics are used to control bacterial disease. They are of great importance in human medicine and are frequently used in intensive farming where animals are reared at high stocking densities.

In northern temperate aquaculture, antibiotics are mostly used as a treatment for the disease furunculosis in farmed salmonids. This disease has been a serious threat to salmon culture in the past causing high losses. It is currently controlled by a combination of avoidance, fallowing and antibiotic therapy. There are disadvantages associated with antibiotic therapy which include inefficient uptake, bacterial resistance and high cost. Changes in practice by the industry such as strategic health management agreements between farms and widespread vaccination of fish have reduced the need for antibiotic therapy in recent years.

Intensive use of antibiotics in aquaculture in many countries worldwide has raised concerns about the possible hazards of this practice. The rapid expansion of the industry together with greater public awareness of environmental issues has focused attention on many of the potential problems associated with the addition of quantities of potent chemical compounds to the aquatic environment.

Where antibiotics or their metabolites occur in the marine environment, they may have come from a variety of sources, either indirectly via domestic / hospital sewage and agricultural runoff, or directly via aquaculture. The fate of these drugs in the marine environment is reviewed. Not all antibiotics are biologically active once they reach the marine environment, but some drugs reach the sediment under fish cages in a largely unchanged and active form, where they are slow to degrade and may be ingested by wild fish and invertebrates. Bacteria in the sediment may develop resistance to the drug.

The effect this may have on the marine environment is to a large extent unknown. For this reason such drugs should be used with caution. Adoption of a rational and usable strategy to safeguard the environment is essential.

Future prospects for the control of furunculosis are outlined. Ways of further reducing current impacts are explored including site selection and development of drugs more appropriate for use in an aquatic environment, when therapy is necessary. Alternatives to chemotherapy for the control of furunculosis are discussed including efficacious vaccines and in the longer term, breeding for genetic resistance.

Conclusions and recommendations follow at the end of the report.

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Part I: Antibiotics in the marine environment: uses and effects

1 Introduction

1.1 This paper will explore why antibiotics may be found in the sea and what is known about the possible impacts of these drugs in the marine environment. They may come from a variety of sources, either indirectly, for example from agricultural runoff and domestic and hospital sewage, or directly. A direct source of antibiotics is from aquaculture. However other direct applications for these compounds in the marine environment continue to arise, such as their incorporation with antifoulants for use on boats (Peterson *et al.*, 1993). This paper will specifically focus on direct inputs from salmon farming to control the bacterial disease furunculosis, which is currently the major use of antibiotics in finfish culture.

1.2 An ever-increasing demand for seafood, coupled with a decline in wild stocks, has led to intensive aquaculture programmes in both northern and southern hemispheres. The long sheltered coast of Scotland with its relatively unpolluted waters provides excellent conditions for aquaculture. At present marine finfish culture consists almost entirely of the production of Atlantic salmon (*Salmo salar*) in net pens (cages). Marine shellfish culture includes mussels, oysters, and scallops. Nearly all farms are located on the West coast and in the Northern and Western Isles.

1.3 The rapid expansion of marine finfish culture seen in Scotland and Norway was followed by increasing bacterial disease problems (Roed, 1991). There are several bacterial diseases to which marine farmed fish are susceptible, for example, furunculosis, vibriosis and bacterial kidney disease. This in turn led to increased use of antibacterial drugs. In 1992 production of Atlantic salmon in Scotland exceeded 36,000 tonnes. Survival of salmon fell by 21% from the previous year, with the bacterial disease furunculosis a major cause of losses. Fears about the inability to control disease and loss of confidence in the market for salmon were major factors for a projected plateau in production (SOAFD, 1993).

1.4 Furunculosis has been one of the main scourges of the salmon farming industry, and probably the principal bacterial pathogen of salmonid culture (Branson, 1991). By far the most common use of antibiotics in the marine environment is in the treatment of this disease. Up to 25-35% of the total farmed Atlantic salmon production of Scotland may have been lost to furunculosis in past years, despite the availability of chemotherapeutants and vaccines (Newman, 1991). Recently however, losses due to furunculosis have decreased considerably, and it is not the serious threat it used to be.

1.5 Molluscs are also susceptible to bacterial diseases. Few of these are sensible to chemotherapy, either because of the impossibility of applying a chemotherapeutant to extensive shellfish beds covering many hectares in area, or because the pathogen is not sensitive to any available chemotherapeutant (Alderman, 1992). Effective chemotherapy in mollusc culture is, so far, only applicable under controlled hatchery conditions where the volume of water to be treated is very limited.

1.6 Crustaceans are very susceptible to a variety of bacterial diseases and intensification of farms in tropical aquaculture has led to increasing disease problems. Concern about the prophylactic use of antibiotics in relation to shrimp hatchery practice and pond growout has been expressed (Brown, 1989; Brown & Higuera-Ciapara, 1992). These issues are outside the scope of this paper but serve to emphasize that too little is known about the behaviour of antibiotics in the aquatic environment.

1.7 Antibiotics have been used in finfish culture for many years. Recently there has been a growing interest in the possible hazards associated with the intensive use of antibiotics aquaculture is Norway. Whilst there is strict veterinarian control of the prescription of these drugs in both Norway and the UK, Norway has a monopolised import and distribution system which ensures reliable figures as to their use. In 1989 the total amount of antibacterial agents used in Norwegian aquaculture was 19,350 kg, measured as active components (Lunestad, 1992). This figure rose to about 30,000 kg in 1990 (Leffertstra, 1991) but has decreased since then. In that year the quantity of antibiotics used in veterinary medicine including aquaculture was about double that employed in human medicine (50,000 kg compared with 25,000 kg in 1990) (Yndestad, 1992).

2.4.2 For many years in Norway and Scotland oxytetracycline and furazolidone were the agents of first choice in aquaculture, but since 1987 the quinolones, especially oxolinic acid, found a broader use (Lunestad, 1992). In recent years in Scotland amoxycillin has been very useful in cases of "triple-resistance" (see 3.2).

2.4.3 The total amount of antibiotics currently used by the aquaculture industry in Scotland is difficult to assess as no central record is kept. Records of discharges within their respective areas are held by the individual River Purification Authorities, and drug prescriptions are recorded by individual veterinarians. These records are not neccessarily available to the public.

3 Disadvantages with oral antibiotic therapy

3.1 Inefficient uptake

3.1.1 Chemotherapy relies on the fish being treated receiving therapeutic (i.e. effective) doses. There is however, a degree of uncertainty in dose rates. Farmers must be sure of the numbers of fish in the cage, accurate average weights and feeding regimes etc. so that all the fish are certain to receive the correct dose. Even then there is still no guarantee.

3.1.2 Food uptake by individual fish can be very uneven and the resulting efficacy of oral therapy may be less than expected. To overcome this, treatments may be prolonged so that every fish attains the proper dose and any non-feeders present will die off during the course of treatment, thereby not posing as a source of infection to treated fish once antibiotic therapy has ceased.

3.1.3 The effect of antimicrobial treatments does not always eliminate the disease from the population and repeat treatments may be necessary, especially in the case of furunculosis where fish are susceptible to re-infection (Rae, 1992). Since fish suffering from bacterial diseases usually show reduced appetite, much of the drug intended for therapy can pass through the cages and into the environment (Samuelson, 1992). To compensate for this, feed rates of medicated feedstuffs are normally set at levels below the "normal" feed rate for a particular site during treatment.

3.1.4 Even when eaten, not all of the drug may be taken up by the fish. Some antibiotics such as oxytetracycline are very poorly absorbed from the intestinal tract of fish (Samuelson, 1992). In contrast amoxycillin is rapidly absorbed due to its high solubility.

3.2 Resistance

3.2.1 Antibiotic resistance develops through continued use of the same drug on a site. There is some debate as to which strategy is most appropriate to minimise the occurrence of resistance. One drug may be used continuously until resistance develops, after which a different drug is used, or alternatively, a strategy of alternating between drugs may be deployed.

3.2.2 Many sites have had "triple-resistant" (i.e. resistant to oxytetracycline, oxolinic acid and potentiated sulphonamides but sensitive to amoxycillin) strains of *A. salmonicida*, although this has been less evident recently, probably as a result of changed management practices. There have on occasion been strains by leaching from feed and fish faeces. Loss rates from fish and feed are variable depending on uptake, tissue distribution, elimination, formulation, fish species, physico-chemical characteristics of the antibiotic, feed composition and environmental factors.

4.1.4 However, given current knowledge on the distribution of cage wastes on the benthos, it would seem likely that benthic areas which might be affected by the presence of antibiotics would be small, and in relation to the Scottish coastline largely insignificant.

4.2 Presence in sediments

4.2.1 Most published work on persistance of antimicrobials in sediments pertains to oxytetracycline, oxolinic acid and furazolidone. Furazolidone remains in the sediment for a very short time (the half-life is 18 hours in aquarium sediment), being actively metabolised by the micro-organisms in the sediment. Oxytetracycline and oxolinic acid persist in the sediment for a much longer period than furazolidone. The bulk of oxytetracycline and oxolinic acid disappears from the sediment during the first few weeks, but residual concentrations persist in the sediment for months after an enrichment or a medication (Samuelson, 1992). Approximately 10% of the initial concentration of antibiotic administered to fish is found in sediments seven months after the onset of medication.

4.2.2 However, persistence of oxytetracycline in fish farm sediments is highly dependent on the sedimentation after a medication. The drug first disappears from the upper layers of the sediment. If the drug-containing layer is covered with additional faeces and food residues, the persistence time is longer (Samuelson, 1992).

4.2.3 Under stagnant anoxic conditions, oxytetracycline may be very persistent in fish farm sediments. Bjorklund *et al.*, (1990a) reported that the half-life of oxytetracycline in the sediment under treated cages in a farm located in a bay with slow water exchange was 419 days. The temperature in the sediment was 9-9.5°C after the medication, and declined to 4°C during the winter. Conversely, in a farm located in a narrow strait with currents fluctuating in both directions, the half life of oxytetracycline in sediment was 9 days at a sediment temperature of 15°C.

4.2.4 It has also been suggested that oxytetracycline enhances development of anaerobic conditions in the sediments (Jacobsen & Berglind, 1988). This may affect the process of aerobic degradation of organic sediments under fish cages.

4.2.5 No reports concerning possible microbiological degradation processes of oxytetracycline or oxolinic acid in marine sediments have yet been published. It is therefore likely that since both drugs are soluble in seawater, a solvation and diffusion process is the most likely mechanism whereby they escape from the sediment. Decreased diffusion due to sedimentation may not be the only reason for these drugs to persist for such an extended period in the sediment. Crystallisation, complexation and binding to particles may prevent the drug molecules from dissolving in the interstitial water (Lunestad & Goksoyr, 1990; Samuelson, 1992), limiting their biological availability. As long as drug molecules are bound their effect is minimalised, and this may in turn lead to their inactivation.

4.3 Ingestion by wild fish

4.3.1 The water bodies surrounding fish farms are frequently populated by 'resident' shoals of wild fish. These fish feed on waste feed rejected or missed by the farmed fish as well as on their faeces. Thus, during chemotherapy of the farmed fish, the wild fish population may be exposed to varying amounts of antibiotics, sometimes on several occasions during one summer. Whether such small subtherapeutic doses of antibiotics may, for example, induce development of antibiotic-resistant strains of bacteria in the wild fish is largely unknown.

4.3.2 In Norway, residues of antibiotics have

Part II: Furunculosis in farmed salmonids

6.1 Introduction

6.1.1 Furunculosis may affect all species of salmonids, both wild and cultivated and has been described from most areas where salmonids are found, including Europe, North America, Japan, Korea, Australia and South Africa (Munro & Hastings, 1993). Since it was first described it has caused serious losses in salmonid hatcheries and farms. The commercial development of salmon farming in Scotland suffered significantly in the 1980's with increasing numbers of outbreaks and estimated losses in sea water running at 15-20% by number, at the end of the decade (SOAFD, 1990). A similar situation developed in Norway. Farming practices and other diseases contributed to the severity of furunculosis outbreaks and recent changes in management strategies have considerably lessened both incidence and severity of this disease.

6.1.2 The following is a short discussion of the nature of the disease (epizootiology), its exacerbation by stress, and current ways of minimising outbreaks including avoidance, eradication and fallowing.

6.2 Epizootiology

6.2.1 Furunculosis is a systemic infection (affecting the entire body) caused by a rod-shaped bacterium, *Aeromonas salmonicida*. It is a natural disease of salmonids which has been known to cause significant mortality in wild stocks. The bacterium can survive in fish tissue and mucus, including fish slime on cage nets, for up to 30 days, and any salmonid exposed to such material is susceptible to infection. Healthy unstressed fish can withstand a certain level of infection, but this level is reduced by concurrent disease and stress. Furunculosis is also an immunosuppressive disease.

6.2.2 The disease can take several forms depending on the rate at which it progresses. Often it is acute, and in this form usually affects young salmon as S1 and S2 parr in fresh water, as smolts, and in their first sea summer. Older populations in sea water suffering an epidemic usually show many individuals with chronic furunculosis, displaying the characteristic boil-like 'furuncle' from which the disease derives its name. With either condition, acute or chronic, the outcome is likely to be fatal if untreated (Munro, 1988).

6.2.3 In populations of apparently healthy fish many may carry infection by *A. salmonicida*. In Scotland all wild, feral and farmed salmonids are potential carriers. Furunculosis has also been isolated in freshwater and marine non-salmonid species, but at present no carrier status has been confirmed. Salmon farms using fresh water bodies populated with wild anadromous salmonids (i.e. those which migrate up rivers from the sea in order to breed) are at greatest risk of clinical furunculosis. At sea water sites, transfer of infected smolts can be a source of disease. Another route of infection is by lateral transmission between year classes. As the bacterium may survive in sea water for up to 8 days (or possibly longer if temperatures are low) and be carried by water movements, inter-site transfer of infection within a sea loch is common.

6.2.4 Depending on the severity of the mortality pattern, oral antibiotic therapy may be started immediately furunculosis is suspected. The antibiotic used is usually based on site history and clinical history of the fish, which is then confirmed by sampling and changed if necessary. Otherwise an antibiotic sensitivity test determines treatment. A change of antibiotic may be necessary after the results of tests for antibiotic sensitivity are available.

6.2.5 In general, furunculosis in parr and smolts is readily controlled by dosing with antibiotic in the feed for 5-10 days. In sea water antibiotic is fed as per the data sheet or sometimes until the mortality rate returns to normal, which can mean extended periods of antibiotic feeding. Control of outbreaks is

6.5 Eradication by fallowing

6.5.1 Where furunculosis has already been introduced, fallowing biological areas (not just of individual sites but of large areas covering all adjacent sites and probably adjacent sea lochs/areas of coastline), for a minimum of 6 weeks, followed by restocking with clean fish can lead to prolonged disease-free periods, even up to a complete cycle, depending on the individual system.

6.5.2 *A. salmonicida* may survive for many months in the sediments beneath cages. Where fallowing has been insufficient, release of bacteria may occur from disturbance of the sediments due to gas-bubbling, moving animals, storms, anchor-laying etc. Exposing the bacteria to aerobic conditions, e.g. by periodic harrowing of the sediment, may in some situations be appropriate to speed up eradication (Munro & Hastings, 1993).

6.5.3 "All in-all out" strategies, whereby different year classes are not grown together on the same site, are an excellent method of preventing the spread of disease between year classes. Fallowing of sites to allow year class separation is strongly recommended by the Scottish Office Agriculture and Fisheries Department (SOAFD) for disease control purposes. In 1992 60% of sea cage sites used fallow periods, but clearly many more operators have yet to follow this procedure (SOAFD, 1993). Problems exist for small companies which have only one site and therefore have to mix their year classes, although recently many such farms have acquired extra sites for fallowing purposes.

Part III: Future prospects

7 Strategies for minimising impacts

The furunculosis problem which has faced salmon farming in Scotland and Norway has been severe, with increasing losses, and spreading and persistent multiple resistance to antibiotics. However in the last two years this situation has been reversed, despite the fact that the distribution of farms is now so widespread that no area is likely to be free from the risk of disease (Munro & Hastings, 1993). This reversal has been achieved largely by sustained improvements in fish farm management.

7.1 Strategic health management agreements

7.1.1 In recent years strategic health management agreements have been introduced between different companies sharing the same loch system, incorporating a common policy for growing fish of similar year classes, stocking with smolts of tested status, synchronisation of treatments where possible, and site fallowing etc.

7.1.2 The importance of these agreements in disease control cannot be over-emphasised. Where these have been implemented they show beneficial results, both in reducing outbreaks of furunculosis and infestations of sea lice, as well as a decline in resistance patterns of *A. salmonicida* to antimicrobial medicines and of sea lice to dichlorvos (Spencer, 1992).

7.1.3 Many farms throughout Scotland are now involved in such loch management system agreements, in tandem with the more widespread use of vaccines (see 8.1). Reports suggest a considerable reduction in the use of antibiotics in the last 2-3 years, and some farms have reared fish without recourse to chemotherapy, where previously parasites and disease were a problem.

7.1.4 Current evidence shows that these management measures have considerably such an approach should not preclude amongst other things, experimental husbandry in the marine environment when necessary, despite the problem of containment of substances within a water body. It may also have to be accepted that even with the most rigorous small-scale trials in areas of low-priority environmental significance, potentially damaging impacts of substances may in some instances be unavoidable.

7.4.5 Another approach to environmental protection would be to employ risk analyses similar to those practised in the guidelines and rules for the use of genetically modified organisms.

7.5 Proposed standards for aquaculture antibiotics

7.5.1 It is accepted that on occasion chemotherapy is the only recourse for farmers in the treatment of disease. However, the aquatic environment represents a unique milieu for pollution and the spreading of resistance to other ecosystems. Austin & Austin (1987) proposed a set of standards in order to minimise the impacts of antibiotics which may be utilised in aquaculture. These standards included a drug which would have a rapid breakdown to non-toxic components, would not give rise to generation of cross-resistance to other groups of antimicrobial drugs and which was not medically important.

7.5.2 It is unlikely that any drug will ever be 'ideal' from an ecological, veterinary *and* medical viewpoint. However recent years have seen the development of more environmentally-sensitive but nevertheless efficacious chemotherapeutants for use in aquaculture. One such example is the use of hydrogen peroxide to control sea lice infestations

8 Non-chemotherapeutic methods of control

8.1 Vaccines

8.1.1 The use of efficacious vaccines would obviate the need for the repeated use of antibiotic and antiparasitic agents. Vaccines for fish have been developed and they are being used successfully to control a number of diseases e.g. vibriosis and enteric redmouth disease (Rae, 1992).

8.1.2 There has been much research into developing an effective vaccine against furunculosis. The vaccines developed so far afford some degree of protection, with vaccines administered by injection being more effective than bath vaccines, but they are less effective than the vaccines used against enteric red mouth disease and vibriosis.

8.1.3 Current furunculosis vaccines are not an alternative to antibiotic therapy. The vaccines reduce the numbers of mortalities, but not to a sufficient level to prevent the need for antibiotic treatment, and so are most likely to be used in conjunction with antibiotics.

8.1.4 The ideal vaccine preparation for the farmer to administer is an oral one, since it does not incur stress from removal and handling of the fish. No effective oral preparations are currently available, however it is generally agreed that oral vaccines will be the products of the future (Rae, 1992). Some products are being tested now and may be commercially available in Scotland within 1-2 years (P. Smith, Aquaculture Vaccines Ltd. *pers. comm.*).

8.2 Breeding and genetic manipulation for disease resistance

8.2.1 Heritable differences in resistance to furunculosis have been demonstrated in salmonid species (Olivier *et al.*, 1988). Selection and breeding of such strains may well offer in the long-term future a practical means of controlling this disease in farmed salmonids (Munro & Hastings, 1993).

References

Alderman D (1992) Chemotherapy in the control of molluscan diseases. In: Chemotherapy in aquaculture; from theory to reality, 39-45. Paris, France: Office International Des Epizooties. (ISBN 92-9044-301-4).

Alderman D J & Michel C (1992) Chemotherapy in aquaculture today. In: Chemotherapy in aquaculture; from theory to reality, 3-25. Paris, France: Office International Des Epizooties. (ISBN 92-9044-301-4).

Anon (1988) Norwegian aquaculture: controlling the "antibiotic explosion". Animal Pharm 166, 8-9.

Austin B (1985) Antibiotic pollution from fish farms: effects on aquatic microflora. Microbiol. Sci. 2(4), 113-117.

Austin B & Austin D A (1987) Bacterial fish pathogens. Disease in farmed and wild fish. Ellis Horwood Ltd., Chichester, England, 364pp.

Bjorklund H, Bondestam J & Bylund G (1990a) Residues of oxytetracycline in wild fish and sediments from fish farms. Aquaculture 86 (4), 359-367.

Bjorklund H & Bylund G (1990b) Temperature-related absorption and excretion of oxytetracycline in rainbow trout. Aquaculture 84 (3/4), 363-372.

Branson E (1991) Veterinary notes. Scottish Fish Farmer 33, 7.

Brown J H (1989) Antibiotics: their use and abuse in aquaculture. World Aquaculture 20 (2), 34-43.

Brown J H & Higuera-Ciapara I (1992) Antibiotic residues in farmed shrimp - a developing problem? In: Chemotherapy in aquaculture; from theory to reality, 394-404. Paris, France: Office International Des Epizooties. (ISBN 92-9044-301-4).

Ellis A E (1991) Tissue residues of chemotherapeutants in fish. Bull. Eur. Ass. Fish Pathol. 11 (1), 22-29.

Fish Farmer (1991) Residues found in wild fish. International file Jan/Feb p.3.

Giroud J P (1992) Incidents et accidents des antibiotiques. In: Chemotherapy in aquaculture; from theory to reality, 141-152. Paris, France: Office International Des Epizooties. (ISBN 92-9044-301-4).

van der Heijden M H T, van Muiswinkel W B, Grondel J L & Boon J H (1992) Immunomodulating effects of antibiotics. In: Chemotherapy in aquaculture; from theory to reality, 219-231. Paris, France: Office International Des Epizooties. (ISBN 92-9044-301-4).

Jacobsen M D (1989) Withdrawal times of freshwater rainbow trout, Salmo gairdneri Richardson, after treatment with oxolinic acid, oxytetracycline and trimethoprim. J. Fish Diseases 12, 29-36.

Jacobsen P & Berglind L (1988) Persistence of oxytetracycline in sediments from fish farms. Aquaculture 70, 365-370.

Leffertstra H (1991) Steps towards a sustainable fish farming industry, environmental goals and new regulations to achieve these for fish farming in Norway. In: Aquaculture and the Environment (ed. N De Pauw & J Joyce) European Aquaculture Society Special Publication 16, 461-466.

Levy S B (1988) Tetracycline resistance determinants are widespread. Am. Soc. Microbiol. News 54, 418-421.

Lunestad B T (1992) Fate and effects of antibacterial agents in aquatic environments. In: Chemotherapy in aquaculture; from theory to reality, 152-162. Paris, France: Office International Des Epizooties. (ISBN 92-9044-301-4).

Wichardt U-P, Johansson N & Ljundberg O (1989) Occurrence and distribution of Aeromonas salmonicida infections on Swedish fish farms, 1951-1987. J. Aquatic Animal Health 1, 187-196.

Yndestad M (1986) Problems associated with drug residues in fish farming. Proc. 15th Nordic Vet. Congr., Stockholm, 65-68.

Yndestad M (1992) Public health aspects of residues in animal products: fundamental considerations. In: Chemotherapy in aquaculture; from theory to reality, 494-511. Paris, France: Office International Des Epizooties. (ISBN 92-9044-301-4).

Table 2. Licensed aquaculture antibiotic products available in Scotland.

Company	Product name	Composition
Peter Hand Ltd	Aquacil Aquinox Tetraplex Sulfatrim	50% amoxycillin 50% oxolinic acid 50% oxytetracycline 50% trimethoprim/ sulphadiazine
Vetrepharm Ltd	Vetremox Aqualinic Tribrissen	100% amoxycillin 100% oxolinic acid 40% trimethoprim/ sulphadiazine

Table 3. Withdrawal periods for licensed antibiotics if used according to the licence data sheet. (Any use outside these recommendations requires a withdrawal period of 500 °C d)

Drug	Withdrawal period (°C days)
Oxytetracycline	400
Oxolinic acid	500
Sulphadiazine/trimethoprim	
Tribrissen	350
Sulphatrim	400
Amoxycillin	50 at 40 mg/kg/d (Aquacil) 40 at 80 mg/kg/d (Vetremox)