Previous and current trends in the usage of antimicrobial drugs in Norwegian aquaculture

Kari Grave
Professor, Norwegian School of Veterinary Science
Scientific adviser, National Veterinary Institute, Norway
(kari.grave@veths.no)

Magne Kierulf Hansen
DMV; PhD
Agder Fiskehelsetjeneste AS, Norway

The sales figures of antimicrobial (AM) drugs for farmed Atlantic salmon (S*almo salar*) and rainbow trout (*Oncorhynchus mykiss*) in Norwegian aquaculture was high, although varying, in the period 1981-1994. Since then the usage in these species has been negligible in spite of the huge increase in the biomass fish produced. This is mainly due to the introduction of efficient vaccines against the major bacterial diseases in these fish species. Also, the selection of fish-farm locations with good water exchange rates as well as a general improvement of the hygiene is believed to have contributed to the favourable health status of farmed salmonids in Norwegian aquaculture.

In the period 2000–2005 a minor increase in AM drug usage was observed - both when expressed in terms of amount of active substance prescribed, in numbers of prescriptions issued and as calculated biomass fish treated with AM drugs. The major part of this increase was due to increased usage in Atlantic cod (*Gadus morhua)*. This increase was, however, strongly positively correlated to the biomass farmed cod produced. The number of prescriptions relative to biomass cod produced declined from 2002-2005. Thus the increasing usage of AM drugs for farmed Atlantic cod does not indicate emerging bacterial disease problems in this species in the period 2000-2005. A considerable increase in the number of AM drug prescriptions issued for cod classified as fry (i.e., prior to vaccination by injection) was observed, especially in the period 2004-2005. For cod in the grow-out phase the number of AM drug prescriptions decreased substantially from 2004-2005; this is explained by the introduction of more efficient vaccines and vaccination procedures from 2003.

In Atlantic halibut the usage relative to the amounts produced declined in the study period, while for the other "new" fish species the usage was negligible reflecting the minor production of these species.

In 2005, approximately 95% of the prescriptions for farmed fish were for an AM drug belonging to the quinolone group (mainly oxolinic acid). The production of farmed Atlantic cod is expected to increase strongly in the future. If the AM drug usage in cod increases to the same extent as currently and the usage pattern is maintained this may pose a risk factor regarding development of AM drug resistance in Norwegian cod farming.

From 1981-2001, drug wholesalers and feed mills in Norway reported sales of AM drugs for use in aquaculture on a voluntarily basis whereas from 1 January 2002 it was made mandatory to report such figure to the National Institute of Public Health (Fig. 1). This enabled publication of sales statistics on antimicrobial (AM) drug usage in Norwegian aquaculture (Grave et al., 1996; Grave et al., 1999; Grave et al., 2002; Lillehaug et al., 2003; Lunestad and Grave, 2005) and since 1999, such data has been made public available through an annual report on usage of antimicrobial agents and occurrence of antimicrobial resistance in Norway, the so-called NORM/NORM-VET report (Kruse and Simonsen, 2006).

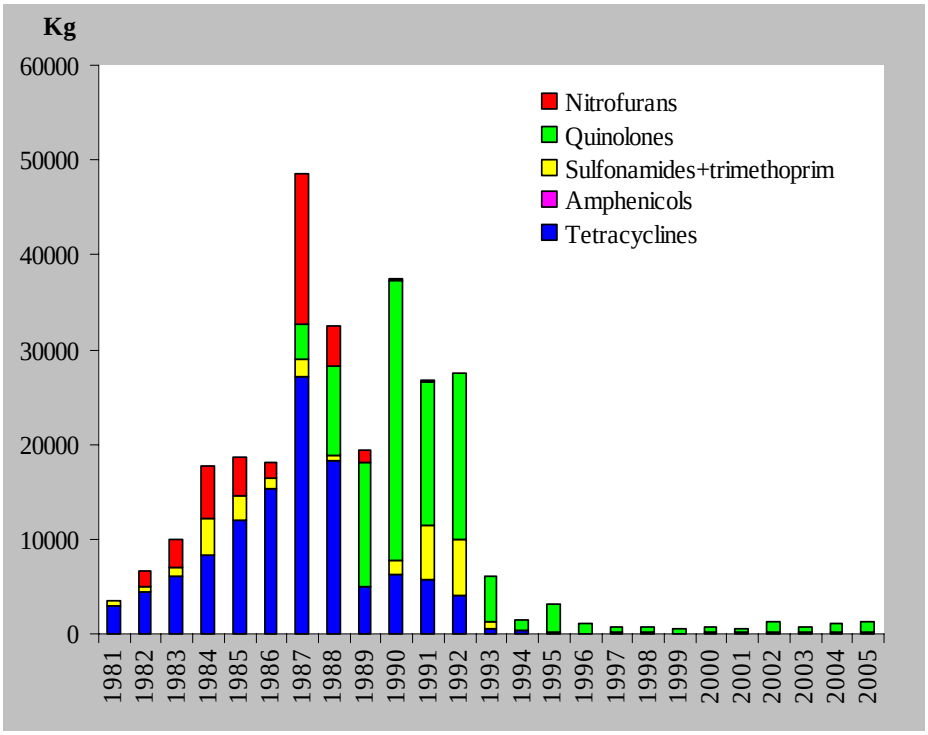

Fig. 1. Sales, in weight of active substance, of antimicrobial drugs in Norwegian fish farming in the period 1981-2005. Data represent sales from drug wholesalers and feed mills and was obtained from Norwegian Medicinal Depot (1981-1995), WHO Collaborating Centre for Drug Statistics Methodology, Oslo (1996-1999) and National Institute of Public Health (2000-2005), respectively

The dosage approved/used for the various AM drugs may vary considerably. In order to adjust for differences in dosages between the various AM drugs, annual AM drug sales may be presented as the biomass farmed fish that can be treated with the amounts (given as weight of active substance) of the various AM drug sold (Grave et al., 1996; Grave et al., 2005) (Fig. 2). Also, annual AM drug usage data have to be related to the amounts of fish at risk of being treated with an AM drug for the various years. A pragmatic approach to correct for changes in the amounts of fish at risk of being treated is to apply the biomass farmed fish produced annually as the “denominator”. This approach does not take into account the variations in the size of the fish treated; therefore the data should be interpreted with caution. Nevertheless, to present the biomass farmed fish, overall or by species, treated with an AM drug relative to the biomass produced (Fig. 2) offer an

improved description of the exposure of AM drugs in farmed fish as compared to when the usage is given in terms of kg active substance sold (Fig. 1).

Usage in Atlantic salmon and rainbow trout

Until the late 1990'ties sales of AM drugs for use in Norwegian aquaculture were for use in Atlantic salmon and rainbow trout only and sales data prior to 2000 can be analyzed in view of that. In the early seventies vibriosis (*Listonella anguillarum)* was the most important bacterial disease problem in Norwegian salmonid farming while in the late seventies and in the eighties cold-water vibriosis due to *Vibrio salmonicida* became the major bacterial disease problem (Egidius et al., 1981); as reflected in the AM drug usage figures (Fig. 1, 2) the magnitude of the cold-water vibriosis problem peaked in 1987. Due to the introduction of effective vaccines against this disease in the late 1987 the usage of AM drugs in aquaculture in Norway relative to the biomass farmed fish produced declined considerably (Fig. 2).

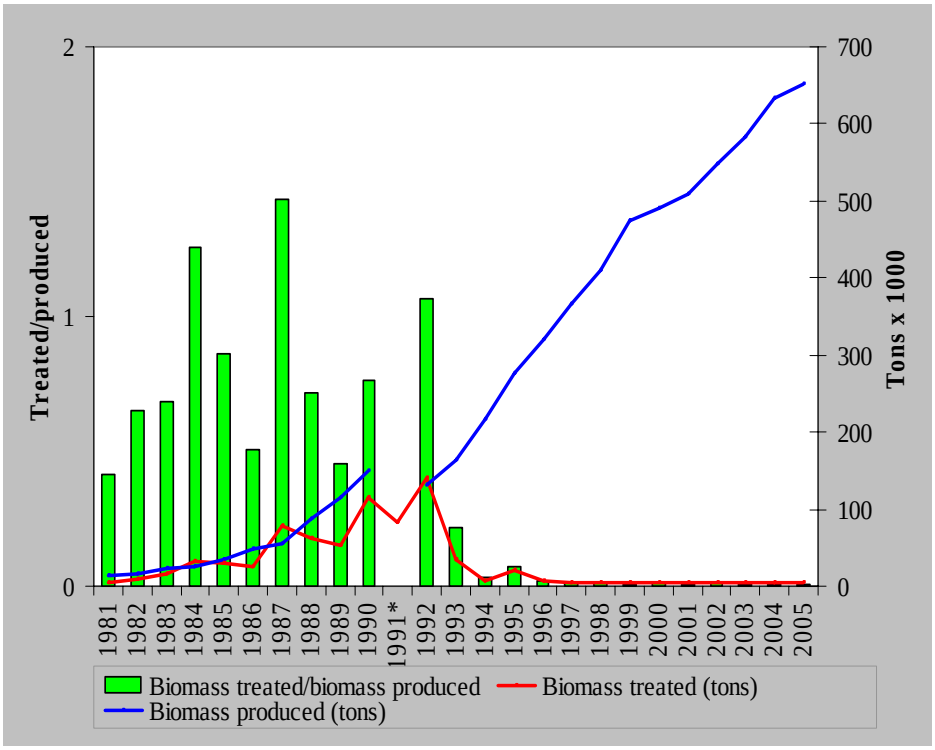

Fig. 2. Calculated biomass (in 1000 tons) farmed fish treated with an antimicrobial drug cure, biomass farmed (in 1000 tons) fish produced (round-weight) and calculated biomass treated/biomass produced in Norwegian aquaculture. ***Data on biomass produced not published for 1991 as they were considered to be unreliable*

In the period 1990–1992, AM drug usage in salmonid farming in Norway yet again increased (Fig. 1). This was caused by furunculosis (*Aeromonas salmonicida*) that became endemic in Norwegian salmonid farming for the first time in 1989. However, from 1993 to 1994 a remarkable 78% decline of AM drug usage in Norwegian aquaculture was observed (Fig. 1, 2). This was primarily due to the replacement of water adjuvanted vaccines by oil-adjuvanted vaccines (Markestad and Grave, 1997) substantially increasing

the efficacy of the vaccines against furunculosis. Also, management measures such a location of the fish farms at sites with adequate water-exchange rates as well as general improvement of the on-site hygiene may have contributed to the decline in the AM drug usage. From 1995 and onward the sales of AM drugs for use in Norwegian aquaculture, i.e. in Atlantic salmon and rainbow trout, continued to decrease even though slight year to year variations were seen (Fig. 1, 3).

Usage in "new" fish species

A notable increase in the number of "new" fish species cultivated in Norwegian aquaculture, such as Atlantic cod (*Gadus morhua*), Atlantic halibut (*Hippoglossus hippoglossus*), turbot (*Scopthalmus maximus*) and Arctic char (*Salvelinus alpinus*) occurred in the 1990'ties and onward (Statistics Norway, 2004; Directorate of Fisheries, 2006a; Directorate of Fisheries, 2006b). These new cultivated fish species accounted for 0.3% of the production (in metric tons round weight) in 2000 whereas in 2005 this figure was approximately 1.8%.

In 1989, it became mandatory to submit copies of prescriptions issued to farmed fish to the Norwegian Government Fish Inspection and Quality Control Service (NFCS) and from 2004 to the Norwegian Food Safety Authority (NFSA). These prescription data show that since 2003 the major proportion of the AM drugs prescribed for use in Norwegian aquaculture was for these new fish species. In 2005 approximately 46% of the amounts (in weight of active substance) prescribed was accounted for by prescribing for Atlantic cod (Norwegian Food Safety Authority, 2006).

Concern has been expressed whether the reported increase in the usage of AM drugs in new fish species in Norwegian aquaculture was due to emerging bacterial disease problems, especially in Atlantic cod. To analyze the AM drug usage in the new fish species cultivated in Norwegian aquaculture prescription data obtained (Excel® file) from NFCS and NFSA for the years 2000-2003 and 2004-2005, respectively, were employed. The prescription data were validated against national sales data and were found to be highly valid ($r = 0.95$).

In addition to be presented in terms of active substance prescribed and biomass treated, AM drug usage may also be presented as number of prescriptions issued. Usage data given as number of prescriptions offers a description of the number of initiated treatments against bacterial diseases in the various fish species and production stages in Norwegian aquaculture.

Atlantic cod

For Atlantic cod the usage, both in terms of amounts prescribed, the number of AM drug prescriptions issued and the calculated biomass treated annually, increased from 2000 to 2005 (Fig. 3). The usage was strongly positively correlated to the biomass farmed cod produced (the correlation factors were >0.85). The number of prescriptions relative to the biomass Atlantic cod declined from 2002 to 2005. Thus the increase in the annual usage of AM drugs in cod does not indicate emerging bacterial disease problems in this species.

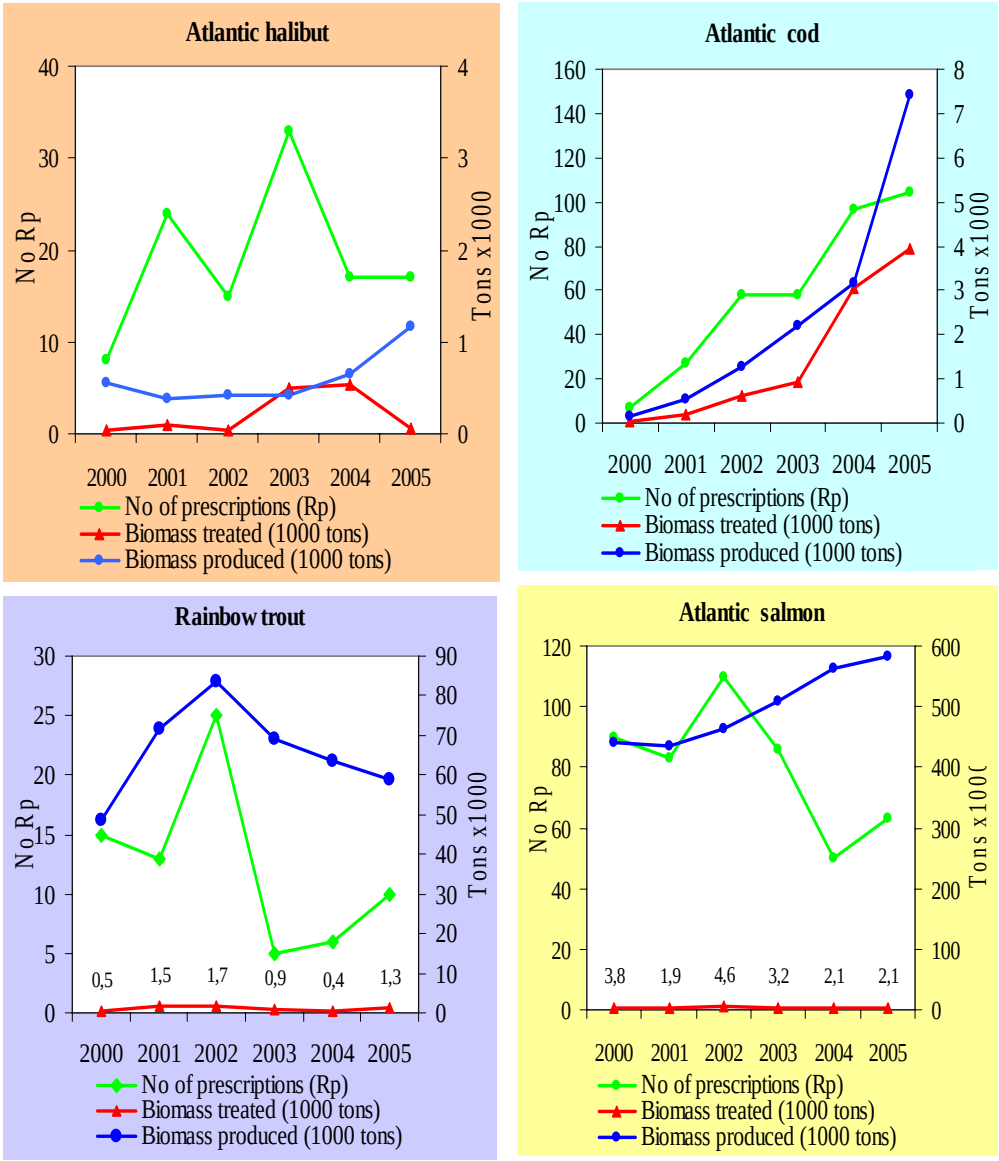

Fig. 3. Number of prescriptions (Rp) issued, biomass treated and biomass produced of Atlantic halibut (*Hippoglossus hippoglossus*), Atlantic cod (*Gadus morhua*), rainbow trout (*Oncorhynchus mykiss*) and Atlantic salmon (*Salmo salar*). Prescriptions data were obtained from the Norwegian Government Fish Inspection and Quality Control Service (2000-2003) and the Norwegian Food Safety Authority (2004-2005). *Prescriptions (n=16) on injectable drugs for use in brood fish (all species) are not included. The values of biomass treated are displayed for rainbow trout and Atlantic salmon*

Data on fish weight treated was entered into in the fish prescription database for the years 2000-2003 but only for a proportion of the data. For the years 2004-2005 such data were not available in the electronic database. Eventual increased usage or emerging bacterial disease problems in specific weight classes could therefore not be identified by use of the data obtained from the fish prescription database. However, the database contained data regarding production stages (hatchery, fry, smolt/young fish, and grow-out phase in sea cages/net pens) of the fish to be treated with the AM drug prescribed. These data showed

a considerable increase in the number of AM drug prescriptions for cod fry relative to young cod/grow out phase cod in 2005 when approximately 38% of the prescriptions was for use in fry. For young cod and for cod in the growth-out phase the corresponding figure decreased substantially. This may be explained by the introduction, from 2003 and onward, of more effective injectable vaccines against vibriosis (*Listonella anguillarum*) developed especially for cod. This decreased the vibriosis problems considerably, except for in cod fry that due to the size has to be vaccinated against vibriosis through immersion.

Atlantic halibut

The usage of AM drugs in Atlantic halibut varied in the study period (Fig. 3), but relative to the biomass halibut produced usage decreased (correlation factors <-0.28). The production cycle of halibut is relatively long. The increase seen in the halibut-production from 2004 and onward (Directorate of Fisheries, 2006a) implies an increase in fry/small fish production in 2003. This may in part explain that the number of AM prescriptions issued relative to the produced biomass was considerably higher in 2003 compared to the previous years.

In response to the *Aeromonas salmonicida* problems, halibut farmers started to vaccinate fry against atypical *Aeromonas salmonicida* using autogenous vaccines or vaccines available against "typical" *Aeromonas salmonicida* (i.e., furunculosis inAtlantic salmon) in the autumn of 2003. Water disinfection by use of UV radiation was introduced in halibut farms and showed positive health effects on halibut larvae, fry and small fish, apparently reducing the incidence of *Aeromonas salmonicida* infections (Karl Fjell, Bioserve AS, personal communication).Vaccination and improved water quality are the most probable reasons for the reduction in the numbers of AB drug prescriptions issued seen in Atlantic halibut in 2004 and 2005.

Other "new" species

For the other new farmed fish species such as turbot, coalfish and wolffish AM drug usage was negligible, i.e., 16 of 1,081 prescriptions for the period 2000-2005. This reflects the minor production of these species.

Prescribing patterns of AM drugs

In 2005, approximately 95% (Fig. 4) of the prescriptions for farmed fish were for a drug belonging to the quinolone group (mainly oxolinic acid). For Atlantic cod this figure was 98%. The production of Atlantic cod in Norwegian aquaculture is expected to increase strongly in the future; provided that the AM drug usage in cod increases to the same extent as currently and the usage pattern is maintained this may pose a risk factor regarding development of AM drug resistance in Norwegian cod farming.

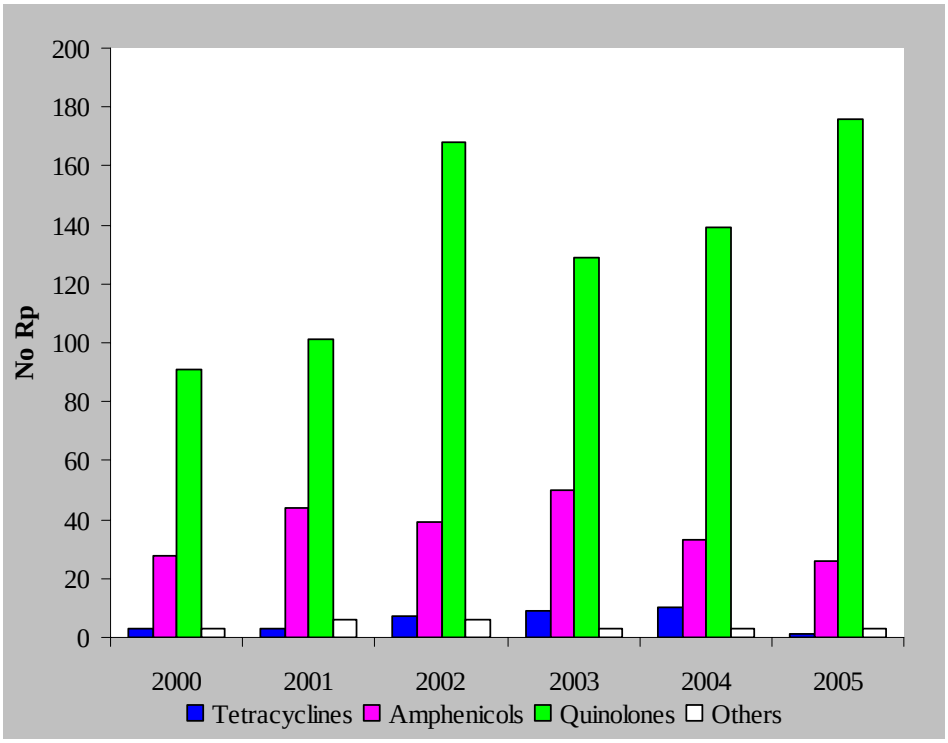

Fig. 4. Number of prescriptions for farmed fish in Norway during the period 2000-2005 split into the various AM drug groups. Others include enrofloxacine (n_1=21) and procaine penicillin+dihydrostreptomycin (n_2=2) prescribed as injection preparations for brood fish and one prescription for sulfadiazine+trimethoprim

Acknowledgement
The authors would like to thank Reidun Agathe Medhus, Norwegian Food Safety Authority, for providing the prescription data and for valuable information regarding the basis for the data.

References

Directorate of Fisheries, 2006a. Other species than salmon and trout. Sale specified on whether the production is based on produced juveniles or wild catched fish. Directorate of Fisheries, Bergen, Norway. http://www.fiskeridir.no/fiskeridir/content/download/7272/59835/file/stat_salg_5_andre.xls

Directorate of Fisheries, 2006b. Salmon and trout. Sale of slaughtered fish by county. Directorate of Fisheries, Bergen, Norway. http://www.fiskeridir.no/fiskeridir/content/download/7274/59841/file/stat_salg_5_laks.xls

Egidius, E., Andersen, K., Clausen, E., Raa, J., 1981. Cold-water vibriosis or Hitra disease in Norwegian salmonid farming. Journal of Fish Diseases 4, 353-354.

Grave, K., Jensen, V.F., McEwen, S., Kruse, H., 2005. Monitoring of antimicrobial drug usage in animals: Methods and applications. In: Aarestrup, F. (Ed.), Antimicrobial resistance in bacteria of animal origin, chapt. 22. AMS, Washington DC, pp. 375-395.

Grave, K., Lingaas, E., Bangen, M., Ronning, M., 1999. Surveillance of the overall consumption of antibacterial drugs in humans, domestic animals and farmed fish in Norway in 1992 and 1996. Journal of Antimicrobial Chemotherapy 43, 243-252.

Grave, K., Litleskare, I., Lunestad, B.T., 2002. Forbruksmønsteret for legemidler til oppdrettfisk i Norge i perioden 1996-2001: et gullkantet eksportsertifikat for norsk oppdrettsnæring. Norsk Veterinærtidsskrift 114, 564-567.

Grave, K., Markestad, A., Bangen, M., 1996. Comparison in prescribing patterns of antibacterial drugs in salmonid farming in Norway during the periods 1980-1988 and 1989-1994. J. Vet. Pharmacol. Ther. 19, 184-191.

Kruse, H., Simonsen, G., NORM/NORM-VET 2005. Usage of antimicrobial agents and occurrence of antimicrobial resistance in Norwy. 1-86. 2006. National Veterinary Institute, University Hospital of North Norway and Norwegian Institute of Public Health. Ref Type: Serial (Book,Monograph)

Lillehaug, A., Lunestad, B.T., Grave, K., 2003. Epidemiology of bacterial diseases in Norwegian aquaculture--a description based on antibiotic prescription data for the ten-year period 1991 to 2000. Dis. Aquat. Organ 53, 115-125.

Lunestad, B.T., Grave, K., 2005. Therapeutic agents in Norwegian aquaculture from 2000-2004: Usage and residue control. Bulletin of the European Association of Fish Pathologists 25, 284-290.

Markestad, A., Grave, K., 1997. Reduction of antibacterial drug use in Norwegian fish farming due to vaccination. Dev. Biol. Stand. 90, 365-369.

Norwegian Food Safety Authority, 2006. Mindre bruk av antibiotika i norsk lakseoppdrett samtidig som forbruket til nye arter øker. Norwegian Food Safety Authority. http://www.mattilsynet.no/fisk/havbruk/mindre_bruk_av_antibiotika_i_norsk_lakseoppdrett_samtidig_som_forbruket_til_nye_arter__ker_38235.

Statistics Norway, 2004. Sal av slakta matfisk. Mengd, etter fiskeart og fylke. 2003. Tonn. Statistics Norway, Oslo, Norway. http://www.ssb.no/emner/10/05/nos_fiskeoppdrett/arkiv/nos_d335/tab/3.2.html.