Minireview

Heavy use of prophylactic antibiotics in aquaculture: a growing problem for human and animal health and for the environment

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Summary
The accelerated growth of finfish aquaculture has resulted in a series of developments detrimental to the environment and human health. The latter is illustrated by the widespread and unrestricted use of prophylactic antibiotics in this industry, especially in developing countries, to forestall bacterial infections resulting from sanitary shortcomings in fish rearing. The use of a wide variety of antibiotics in large amounts, including non-biodegradable antibiotics useful in human medicine, ensures that they remain in the aquatic environment, exerting their selective pressure for long periods of time. This process has resulted in the emergence of antibiotic-resistant bacteria in aquaculture environments, in the increase of antibiotic resistance in fish pathogens, in the transfer of these resistance determinants to bacteria of land animals and to human pathogens, and in alterations of the bacterial flora both in sediments and in the water column. The use of large amounts of antibiotics that have to be mixed with fish food also creates problems for industrial health and increases the opportunities for the presence of residual antibiotics in fish meat and fish products. Thus, it appears that global efforts are needed to promote more judicious use of prophylactic antibiotics in aquaculture as accumulating evidence indicates that unrestricted use is detrimental to fish, terrestrial animals, and human health and the environment.

Introduction
Industrial aquaculture is a rapidly growing industry in many developed and developing countries. It is expected that this growth will increase at an even faster rate in the future, stimulated by the depletion of fisheries and the market forces that globalize the sources of food supply (Goldburg et al., 2001; Goldburg and Naylor, 2005). The last 20 years have seen a fourfold growth in industrial aquaculture worldwide (Naylor et al., 2000; 2003; Naylor and Burke, 2005). This impressive industrial development has been accompanied by some practices potentially damaging to human and animal health (Goldburg and Naylor, 2005; Naylor and Burke, 2005) that include passing large amounts of veterinary drugs into the environment (Haya et al., 2000; Boxall et al., 2004). For example, the aquaculture of shrimp and salmon has been accompanied by an important use of prophylactic antibiotics in the aquatic environment of rivers, lakes and oceans (Grave et al., 1999; Le and Munekage, 2004; Le et al., 2005). As expected, and as has occurred in other industrial settings of animal husbandry (Angulo and Griffin, 2000; Witte, 2000; Anderson et al., 2003; Angulo et al., 2004; Nandi et al., 2004), this use has resulted in an increased antibiotic resistance of bacteria in the environment (Rhodes et al., 2000a; Miranda and Zemelman, 2002a,b; Petersen et al., 2002; Alcaide et al., 2005). Moreover, this development has been accompanied by an increase of antibiotic resistance in fish pathogens (Davies et al., 1999; Rhodes et al., 2000a,b; Schmidt et al., 2000; 2001a,b; Sørum, 2000; 2006; L'Abee-Lund and Sørum, 2001). The emergence of antibiotic resistance among fish pathogens undermines the effectiveness of the prophylactic use of antibiotics in aquaculture (L'Abee-Lund and Sørum, 2001; Sørum, 2006) and increases the possibilities for passage not only of these antibiotic-resistant bacteria but also of their antibiotic resistance determinants to bacteria of terrestrial animals and human beings, including pathogens.

Antibiotic use in aquaculture
In the aquaculture of fish, especially that of salmon and trout, nearly all manipulations undergone by the fish as they are being raised are stressors (Barton and Iwama,
Because these manipulations decrease the effectiveness of the fishes’s immune system to clear up bacterial colonization and infection (Barton and Iwama, 1991; Cabello, 2003; Naylor and Burke, 2005), it has become common to increase the use of prophylactic antibiotics. Moreover, hygienic shortcomings in fish raising methods, including increased fish population densities, crowding of farming sites in coastal waters, lack of sanitary barriers and failure to isolate fish farming units with infected animals (Naylor et al., 2000; Naylor and Burke, 2005), have increased the possibility of rapid spread of infections. This scenario also results in an augmented use of prophylactic antibiotics, often with the misplaced goal of forestalling these sanitary shortcomings (Grave et al., 1996; Cabello, 2003; Sørum, 2006). Fish are given antibiotics as a component of their food, and occasionally in baths and injections (Markestad and Grave, 1997; Sørum, 2006). The unconsumed food, and fish faeces, containing antibiotics reach the sediment at the bottom of the raising pens; antibiotics are leached from the food and faeces and diffuse into the sediment and they can be washed by currents to distant sites (Hektoen et al., 1995; Kerry et al., 1996; Coyne et al., 1997; Holten et al., 1999; Guardabassi et al., 2000; Sørum, 2000; Sørum and L’Abée-Lund, 2002; Boxall et al., 2004; Sørum, 2006). These residual antibiotics will remain in the sediment, exerting selective pressure, thereby altering the composition of the microflora of the sediment and selecting for antibiotic-resistant bacteria (Kruse and Sørum, 1994; Hektoen et al., 1995; Davison, 1999; Miranda and Zemelman, 2002a,b; Burrus and Waldor, 2003; Balaban et al., 2004; Beaber et al., 2004; Hasting et al., 2004; Kim et al., 2004; Sørum, 2006). There are a number of important studies that indicate that the bacterial flora in the environment surrounding aquaculture sites contain an increased number of antibiotic-resistant bacteria (Huys et al., 2000; Schmidt et al., 2000; 2001a,b; Sørum, 2000; Miranda and Zemelman, 2002a,b; Furushita et al., 2005; Sørum, 2006), and that these bacteria harbour new and previously uncharacterized resistance determinants (Miranda et al., 2003; Furushita et al., 2005; Poirel et al., 2005a,b; Roberts, 2005; Saga et al., 2005). The determinants of antibiotic resistance that have emerged and selected in this aquatic environment have the potential of being transmitted by horizontal gene transfer to bacteria of the terrestrial environment, including human and animal pathogens (Kruse and Sørum, 1994; Sandaa and Enger, 1994; Rhodes et al., 2000a,b; L’Abée-Lund and Sørum, 2001; Sørum, 2006). The exchange of resistance determinants between the aquatic and terrestrial environment can also stem from the movement of antibiotic-resistant bacteria between these two environments, a result of transporting fish between bodies of freshwater and the ocean, a step that is needed to fulfil the developmental requirements of salmonids (Cabello, 2003; Goldburg and Naylor, 2005; Naylor and Burke, 2005). Horizontal gene transfer mechanisms involved in exchanging resistance determinants between aquatic and terrestrial bacteria include conjugation and conjugative transposition (Bushman, 2002a,b; Agero and Guardabassi, 2005; Casas et al., 2005). However, transduction also has the potential to play an important role in these processes because of the high concentrations of viruses in seawater and the marine sediment (Fuhrman, 1999; Bushman, 2002a). In many aquaculture settings in developing countries, the possibilities of these exchanges have been amplified by the high level of contamination of seawater and freshwater with untreated sewage and agricultural and industrial wastewater containing normal intestinal flora and pathogens of animals and humans usually resistant to antibiotics (Miranda and Zemelman, 2001; Cabello, 2003; Sørum, 2006). This is also the case in settings in which aquaculture is integrated with agriculture (Petersen et al., 2002), and such practices such as the use of manure and other agricultural residues as fish feed are widespread (Petersen et al., 2002).

Aquaculture as a source of antibiotic resistance in human pathogens

Not unexpectedly, exchange of genes for resistance to antibiotics between bacteria in the aquaculture environment and bacteria in the terrestrial environment, including bacteria of animals and human pathogens has recently been shown (Sørum, 1998; Rhodes et al., 2000a,b; Schmidt et al., 2001a,b; Sørum, 2006). For example, strong epidemiological and molecular evidence exists indicating that fish pathogens such as *Aeromonas* can transmit and share determinants for resistance to antibiotics with pathogens such as *Escherichia coli* isolated from humans (Rhodes et al., 2000a,b; Sørum, 2000; L’Abée-Lund and Sørum, 2001; Sørum and L’Abée-Lund, 2002; Sørum, 2006). Incompatibility IncU plasmids containing determinants for resistance to tetracycline encoded by Tn1721, have been disseminated between *Aeromonas salmonicida*, a fish pathogen, and the human pathogens *Aeromonas hydrophila*, *Aeromonas caviae* and *E. coli* obtained from different geographical locations in Europe (Rhodes et al., 2000a). Similar molecular epidemiology studies in *A. salmonicida* have shown that plasmids that contain class 1 integrons found in human pathogenic bacteria, and are able to transfer with high frequency to *E. coli* and *Salmonella*, are responsible for the resistance to trimethoprim, sulfonamide and strepto-
Sulfa-resistant determinant

Molecular and epidemiological evidence has demonstrated that antibiotic resistance determinants of resistant *Salmonella enterica* serotype Typhimurium DT104, an emergent pathogen and the cause of several outbreaks of salmonellosis in humans and animals in Europe and the USA, probably originated in aquaculture settings of the Far East (Angulo, 2000; Angulo and Griffin, 2000; Angulo et al., 2004). The antibiotic resistance determinants of *S. Typhimurium* DT104 are encoded by a transmissible genetic element in the chromosome that contains a resistance gene for florfenicol, an antibiotic extensively used in aquaculture in the Far East (Briggs and Fratamico, 1999; Angulo, 2000). This florfenicol determinant, *floR*, was detected for the first time in the fish pathogen *Vibrio damselae* (Bolton et al., 1999). The tetracycline resistance determinant carried by this *Salmonella* genetic element belongs to the class G that was also, for the first time, detected in the fish pathogen *Vibrio anguillarum* (Briggs and Fratamico, 1999; Angulo, 2000; Angulo and Griffin, 2000). Moreover, the DNA sequence of the transmissible element harbouring these antibiotic resistance determinants has an important DNA sequence similarity to a plasmid of *Pasteurella piscicida*, which is also a fish pathogen (Kim and Aoki, 1993; Angulo, 2000; Angulo and Griffin, 2000). This molecular evidence strongly suggests that there was horizontal transmission of antibiotic resistance determinants from bacteria in the aquatic environment to a human and terrestrial veterinary pathogen (Angulo, 2000; Angulo and Griffin, 2000). The epidemiology of the dissemination of *S. Typhimurium* DT104 also suggests this pathogen could have been spread by fish meal as has happened with the *Salmonella Agona* that originated in Peru several years ago (Clark et al., 1973; Angulo, 2000; Boyd et al., 2001). This process illustrates the potential role of transport of antibiotic-resistant bacteria as an alternative mechanism responsible for the spread of antibiotic resistance determinants from the aquatic environment to the terrestrial environment (Clark et al., 1973; Angulo and Griffin, 2000).

The presence of antibiotics in the aquatic environment can result in the appearance of resistance among human pathogens forming part of its microbiota (Angulo, 2000). For example, *V. cholerae* of the Latin American epidemic of cholera that started in 1992 appeared to have acquired antibiotic resistance as a result of coming into contact with antibiotic-resistant bacteria selected through the heavy use of antibiotics in the Ecuadorian shrimp industry (Weber et al., 1994; Angulo, 2000). The widespread transmission of antibiotic resistance determinants between bacteria of the aquatic and terrestrial environment has been recently demonstrated by the emergence of plasmid-mediated quinolone resistance among human Gram-negative pathogens (Jacoby, 2005; Li, 2005; Nordmann and Poirel, 2005; Robicsek et al., 2005; 2006), and the potential tracing of the origin of these resistant determinants to the aquatic bacteria *Shewanella algeae* and *Vibrio* (Poirel et al., 2005a,b). Interestingly, one of these quinolone-resistant determinants has been recently detected in Japan and in Chile in the emergent human pathogen *Vibrio parahaemolyticus* (Gonzalez-Escalona et al., 2005; Poirel et al., 2005a; Saga et al., 2005; F.C. Cabello and L. Dubytska, unpublished), a marine bacterium transmitted to humans by the ingestion of raw shellfish and that is most likely able to exchange genetic information with other bacteria of the marine environment (Sørum, 2006). Thus, the commonality of antibiotic resistance determinants and of genetic elements between aquatic bacteria, fish pathogens and bacteria from the terrestrial environment strongly supports the concept that antibiotic usage in aquaculture will influence the appearance of resistance in bacteria of other niches, including resistance in pathogens able to produce a variety of human and animal diseases (Wegener, 1999; Angulo, 2000; Rhodes et al., 2000a; L’Abee-Lund and Sørum, 2001; Cabello, 2003; Poirel et al., 2005a,b; Sørum, 2006).

**Additional effects of the excessive use of antibiotics in aquaculture**

Another problem created by the excessive use of antibiotics in industrial aquaculture is the presence of residual antibiotics in commercialized fish and shellfish products (Grave et al., 1996; 1999; Goldburg et al., 2001; Cabello, 2003; 2004; Angulo et al., 2004; Sørum, 2006). This problem has led to undetected consumption of antibiotics by consumers of fish with the added potential alteration of their normal flora that increases their susceptibility to bacterial infections and also selects for antibiotic-resistant bacteria (Grave et al., 1996; 1999; Alderman and Hastings, 1998; McDermot et al., 2002; Greenlees, 2003; Cabello, 2004; Salyers et al., 2004). Moreover, undetected consumption of antibiotics in food can generate problems of allergy and toxicity, which are difficult to diagnose because of a lack of previous information on antibiotic ingestion (Alderman and Hastings, 1998; Cabello, 2004). Allergy to antibiotics and problems of toxicity can also be created for the unprotected workers in the aquaculture industry through the use of large amounts of antibiotics that come in contact with the skin, and intestinal and
The use of antibiotics in the aquaculture industry of developed countries, therefore indicating that it is economically feasible to develop a productive aquaculture industry without excessive prophylactic use of antibiotics (Grave et al., 1996; 1999; Markestad and Grave, 1997; Lillegaard et al., 2003; Sørum, 2006). However, the use of quinolones and many other antibiotics remains totally unrestricted in aquaculture in countries with growing aquaculture industries such as China and Chile (Cabello, 2004; Jacoby, 2005). For example, in Chile, statistics indicate that annually 10–12 metric tons of quinolones are used in human medicine and approximately 100–110 metric tons of these antibiotics are used in veterinary medicine per year, most of them in aquaculture (Cabello, 2004; Bravo et al., 2005). In this country the use of flumequine, a fluoroquinolone used exclusively in aquaculture, has increased from approximately 30 metric tons in 1998 to close to 100 metric tons in 2002 (Bravo et al., 2005). This increase in the use of this broad-spectrum fluoroquinolone parallels the increase in the production of salmon from 258,000 metric tons in 1998 to 494,000 metric tons in 2002 (Bravo et al., 2005). This suggests that in Chile, aquaculture use of quinolones and not human use will probably be the most important selective pressure to generate the emergence of quinolone-resistant bacteria (Bakken, 2004; Cabello, 2004; Bravo et al., 2005; Hernandez et al., 2005). Similarly in China, quinolone resistance has emerged as an important public health problem as result of the unrestricted use of this group of antibiotics in aquaculture and in industrial animal husbandry (Wang et al., 2001; Jacoby, 2005). The potential of these events to precipitate the emergence of antibiotic-resistant bacteria across the globe is already illustrated in the appearance and global distribution of S. Typhimurium DT104 described above (Angulo, 2000; Angulo et al., 2004).

Policies of antibiotic use in aquaculture

Evidence indicating that antibiotic-resistant bacteria and antibiotic resistance determinants pass from the aquatic to the terrestrial environment has resulted in a drastic restriction of the use of antibiotics in aquaculture in many countries (Markestad and Grave, 1997; Lillegaard et al., 2003; Angulo et al., 2004; Cabello, 2004; Goldburg and Naylor, 2005; Sørum, 2006). Restrictions have included, increased control of the prescription of therapeutic antibiotics (Grave et al., 1996; 1999; Markestad and Grave, 1997; Lillegaard et al., 2003; Sørum, 2006), almost total elimination of the use of antibiotic prophylaxis in this setting (Grave et al., 1996, 1999; Sørum, 2006) and proscription of the use of antibiotics in therapeutics that are still very useful in the therapy of human infections (Grave et al., 1996; 1999; Markestad and Grave, 1997; Goldburg et al., 2001; Lillegaard et al., 2003). In this way, the use of quinolones has been totally restricted in aquaculture in industrialized countries, not only because they are a highly effective group of antibiotics for human infections but also because of their ability to generate cross-resistance among all the members of this group (Grave et al., 1996; 1999; Gorbach, 2001; Cabello, 2004; Moellering, 2005; Sørum, 2006). Quinolones also remain active in sediments for prolonged periods of time as they are not readily biodegradable (Hansen et al., 1992; Samuelsen et al., 1992, 1994; Jacoby, 2005). This increased control of antibiotic use, accompanied by sanitary measures that include the use of vaccines, have drastically reduced the use of antibiotics in the aquaculture industry of developed countries, therefore indicating that it is economically feasible to develop a productive aquaculture industry without excessive prophylactic use of antibiotics (Grave et al., 1996; 1999; Markestad and Grave, 1997; Lillegaard et al., 2003; Sørum, 2006). However, the use of quinolones and many other antibiotics remains totally unrestricted in aquaculture in countries with growing aquaculture industries such as China and Chile (Cabello, 2004; Jacoby, 2005). For example, in Chile, statistics indicate that annually 10–12 metric tons of quinolones are used in human medicine and approximately 100–110 metric tons of these antibiotics are used in veterinary medicine per year, most of them in aquaculture (Cabello, 2004; Bravo et al., 2005). In this country the use of flumequine, a fluoroquinolone used exclusively in aquaculture, has increased from approximately 30 metric tons in 1998 to close to 100 metric tons in 2002 (Bravo et al., 2005). This increase in the use of this broad-spectrum fluoroquinolone parallels the increase in the production of salmon from 258,000 metric tons in 1998 to 494,000 metric tons in 2002 (Bravo et al., 2005). This suggests that in Chile, aquaculture use of quinolones and not human use will probably be the most important selective pressure to generate the emergence of quinolone-resistant bacteria (Bakken, 2004; Cabello, 2004; Bravo et al., 2005; Hernandez et al., 2005). Similarly in China, quinolone resistance has emerged as an important public health problem as result of the unrestricted use of this group of antibiotics in aquaculture and in industrial animal husbandry (Wang et al., 2001; Jacoby, 2005). The potential of these events to precipitate the emergence of antibiotic-resistant bacteria across the globe is already illustrated in the appearance and global distribution of S. Typhimurium DT104 described above (Angulo, 2000; Angulo et al., 2004).

Conclusions

This brief review suggests that the unrestricted use of antibiotics in aquaculture in any country has the potential to affect human and animal health on a global scale, and further suggests that this problem should be dealt through unified local and global preventive approaches (Grave et al., 1996; 1999; Cabello, 2004; Bravo et al., 2005). The use of antibiotics in aquaculture shares characteristics with a heavy use of antibiotics in alternative industrial processes of animal husbandry. It, nonetheless, has specific characteristics (Cabello, 2004; Sørum, 2006). It would appear that the transfer of antibiotic resistance determinants among bacteria of the aquatic and terrestrial environment would be readily attained, simply as a result of the high concentrations of bacteria in seawater and aquatic sediments and the abundant presence of bacte riophages to facilitate such a transfer (Fuhrman, 1999; Bushman, 2002a). Contamination of the bodies of water...
where aquaculture is practised with bacteria of the normal flora and pathogens of the intestine of humans and animals will also accelerate this transfer (Miranda and Zemelman, 2001; Cabello, 2003; Sørum, 2006). Approximately 20 years after industrial aquaculture had begun, evidence emerged of the transfer of antibiotic resistance determinants between aquatic bacteria, including fish pathogens and human pathogens (Sørum, 2006). Historical evidence appears to indicate that in terrestrial animal husbandry this process took a longer time (Sørum, 2006). The acceleration of this process strongly suggests that heavy antibiotic use in aquaculture needs to be reduced drastically and replaced with improved sanitation in fish husbandry to avoid the emergence of antibiotic resistance in fish pathogens and environmental bacteria and the passing of this resistance to human pathogens, thus endangering effective therapy to treat human bacterial infections (Angulo, 2000; Sørum, 2006). Experience with alternative processes of animal husbandry and aquaculture itself (Sørum, 2006) indicates that these much-needed changes to protect human and animal health can be achieved without detrimental effects, in financial terms, to the industry (Grave et al., 1996; 1999; Wierup, 2001; Sørum, 2006).

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References


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