

Mechanisms of antimicrobial resistance in finfish aquaculture environments

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Introduction

Through a continuous process of expansion, intensification, and diversification, aquaculture has become the fastest-growing food industry in the world ([Bostock et al., 2010](#)). With production of new species and the expansion of the production of current species to new geographical locations, the risk of disease and need for treatment continues to increase. This risk is compounded by the uncertainties introduced by global climate change, which may affect the emergence and dynamics of new and existing pathogens ([Tirado et al., 2010](#)), and consequently the use of antimicrobials and the prevalence of antimicrobial resistance.

The major concern surrounding the use of antimicrobials in aquaculture is considered to be the potential to favor the development of a reservoir of antimicrobial resistance genes (ARGs) that may be eventually transferred to clinically relevant bacteria ([FAO/OIE/WHO, 2006](#)). So far, lack of data, methodological constraints, and the complexity of characterizing exposure pathways have prevented the derivation of quantitative estimates of the risk that this may pose to public health. Nevertheless, there is consensus in the scientific community and international organizations concerned with human health, animal health, and food security that steps should be taken to minimize it ([FAO/OIE/WHO, 2006](#) ; [Smith, 2008](#) ; [Heuer et al., 2009](#) ; [WHO, 2011](#)). On a global scale, several of the major classes of antimicrobials are being used or have been used in aquaculture. Among these are sulphonamides, penicillins, macrolides, quinolones, phenicols, and tetracyclines ([Sapkota et al., 2008](#)), all of which are listed as critically or

highly important antimicrobials in human medicine ([WHO, 2011](#)). However, the judicious use of antimicrobials in global aquaculture is important to effectively treat bacterial fish diseases and maintain fish health and welfare.

The molecular mechanism, genomic context, and prevalence of genes conferring resistance to antimicrobials determine their clinical relevance (i. e., whether they confer low- vs. high-level clinical resistance, their ability to be mobilized by lateral gene transfer, and their frequency of occurrence). Thus, knowledge of ARGs from aquaculture environments is important to design and prioritize monitoring programs that may generate data that eventually becomes relevant for performing quantitative risk assessments and develop sound treatment strategies to control fish disease. Within this general scope, we provide this article as an overview of the molecular mechanisms, genomic context, and prevalence of quinolone, tetracycline, and phenicol resistance genes that have been reported to occur in aquaculture environments.

Antimicrobial Resistance Genes in Aquaculture Environments

Quinolones (i. e., oxolinic acid, flumequine, and enrofloxacin), tetracyclines [i. e., oxytetracycline (OTC)], and phenicols (i. e., florfenicol) are among the most widely used antimicrobial compounds in aquaculture, and they have been used extensively to control bacterial fish disease in salmon farming [[SERNAPESCA \(Chile\), 2009](#) ; [BurrIDGE et al., 2010](#) ; [Rico et al., 2012](#)].

Although the use of quinolones in salmon farming currently accounts for less than 1% of the overall use of antimicrobials, they continue to be used in aquaculture production in several Asian countries [[SERNAPESCA \(Chile\)](#), <https://assignbuster.com/mechanisms-of-antimicrobial-resistance-in-finfish-aquaculture-environments/>

[2009](#) ; [Burridge et al., 2010](#) ; [Rico et al., 2012](#)]. Quinolones, tetracyclines, and phenicols have been reported to be selective for a variety of ARGs and tend to occur in mobile genetic elements that favor their dissemination (i. e., transposons, plasmids, and integrons; [CloECKaert et al., 2000](#) ; [Chopra and Roberts, 2001](#) ; [Kümmerer, 2004](#) ; [Schwarz et al., 2004](#) ; [Roberts, 2005](#)).

Quinolone Resistance

The protein targets of quinolones are the bacterial enzymes, DNA gyrase and topoisomerase IV. DNA gyrase is a tetrameric enzyme encoded by the *gyrA* and *gyrB* genes, and its main activity is to catalyze the negative supercoiling of bacterial DNA. Topoisomerase IV is also a tetrameric enzyme and it is encoded by the *parC* and *parE* genes; its function is to decatenate and relax the activity of daughter replicons following DNA replication ([Anderson et al., 1998](#) ; [Hawkey, 2003](#)).

The acquisition of quinolone resistance is primarily due to chromosomal mutations in topoisomerases genes (i. e., *gyrA* , *gyrB* , *parC* , and *parE*) and mutations that reduce drug accumulation by decreasing uptake or increasing efflux ([Drlica and Zhao, 1997](#) ; [Ruiz, 2003](#)). Additionally, at least three mechanisms of quinolone resistance are known to be plasmid encoded: (1) Qnr proteins; (2) AAC(6)-Ib-cr aminoglycoside acetyltransferases; and (3) QepA and OqxAB efflux pumps. Qnr proteins protect DNA gyrase and type IV topoisomerase from quinolone inhibition ([Tran and Jacoby, 2002](#) ; [Jacoby, 2005](#)) and the AAC(6)-Ib-cr determinant acetylates several fluoroquinolones. Plasmid-encoded QepA and OqxAB are active efflux pumps that may extrude hydrophilic fluoroquinolones such as enrofloxacin ([Li, 2005](#) ; [Poirel et al.,](#)

[2008](#) , [2012](#) ; [Cattoir and Nordmann, 2009](#) ; [Rodríguez-Martínez et al., 2011](#)).

Various point mutations in the quinolone resistance-determining regions of the *gyrA* and/or *parC* genes have been detected in quinolone-resistant strains of the fish pathogens *Aeromonas hydrophila* , *Vibrio anguillarum* , and *V. parahaemolyticus* ([Okuda et al., 1999](#) ; [Rodkhum et al., 2008](#) ; [Lukkana et al., 2012](#)). Levels of quinolone resistance in Gram-negative bacteria are suggested to be high when associated with point mutations in both the *gyrA* and *parC* genes, whereas only an intermediate level of resistance is associated with point mutations in the *gyrA* gene only. However, high-level resistance to oxolinic acid associated with a single mutation in the *gyrA* gene has been reported for strains of the fish pathogens *Aeromonas salmonicida* , *Edwardsiella tarda* , and *Photobacterium damsela* ([Oppegaard and Sørum, 1994](#) ; [Goñi-Urriza et al., 2002](#) ; [Kim et al., 2005](#) , [2011](#) ; [Ozanne et al., 2005](#)). The extensive administration of quinolones in fish farming has been linked to increased mutations in DNA gyrase and topoisomerase IV in quinolone-resistant fish pathogens such as *Yersinia ruckeri* , *Flavobacterium psychrophilum* , and *V. anguillarum* ([Gibello et al., 2004](#) ; [Izumi and Aranishi, 2004](#) ; [Colquhoun et al., 2007](#) ; [Izumi et al., 2007](#) ; [Shah et al., 2012](#)).

Plasmid-mediated quinolone resistance in bacteria associated with fish farms has been detected in several countries. [Ishida et al. \(2010\)](#) detected the *qnr* and *aac(6′)-Ib-cr* resistance determinants in bacterial strains isolated from fish farm water samples in Egypt. Recently, [Buschmann et al. \(2012\)](#) reported the occurrence of topoisomerase protection genes *qnrA* , *qnrB* , and

qnrS, the putative enzymatic inactivation gene *aac(69)-Ib-cr* and the efflux pump gene *oqxA* among strains isolated from un-polluted and fish farm-impacted marine sediments in Chile. [Jiang et al. \(2012\)](#) found a high prevalence of *qnrB* and *qnrS* genes in *Escherichia coli* strains recovered from Chinese farmed fish while *qnrD* and *aac(6')-Ib-cr* genes occurred less frequently. [Han et al. \(2012\)](#) found 17 strains encoding chromosomal mutations in *gyrA*, 11 strains encoding mutations in *parC*, and a few strains carrying the *qnrS1*-like and *qnrS2* genes among 33 *Aeromonas* spp. isolated from diseased fish and from water samples. The identification of QnrS determinants in *Aeromonas* spp. suggests that they may act as an environmental reservoir of *qnrS* genes, as already described for *tet* genes ([Rhodes et al., 2000](#); [Schmidt et al., 2001a](#)). Some *qnr* genes have also been described in the Vibrionaceae family and it is suggested that water-borne Vibrionaceae may constitute a natural reservoir for Qnr-like quinolone-resistance determinants ([Poirel et al., 2005](#); [Cattoir et al., 2007](#); [Cattoir and Nordmann, 2009](#)). Evidence suggests that *qnr*-plasmids are most commonly integron associated and carry multiple resistance determinants, providing resistance to several classes of antimicrobials, including beta-lactams and aminoglycosides ([Li, 2005](#)).

Tetracycline Resistance

Oxytetracycline is a broad-spectrum bacteriostatic antimicrobial, active against a wide variety of Gram-positive and Gram-negative bacteria, which is extensively used in fish farming. Tetracyclines bind reversibly to the 70S ribosome of prokaryotes and block protein synthesis ([Chopra, 1985](#); [Roberts, 1996](#)).

Mechanisms of tetracycline resistance include active efflux, ribosomal protection, ribosomal RNA mutations, and tetracycline inactivation ([Speer and Salyers, 1989](#) ; [Salyers et al., 1990](#) ; [Burdett, 1991](#) ; [Levy, 1992](#) ; [Speer et al., 1992](#) ; [Taylor and Chau, 1996](#)). Tetracycline resistance in fish farm-associated bacteria has been found to be mainly mediated by one or more of the Tet family of proton-dependent efflux pumps or via ribosomal protection by cytoplasmic proteins found widely in Gram-negative bacteria ([Roberts, 2005](#) ; [Roberts et al., 2012](#)).

Several *tet* determinants have been identified in fish farm bacteria from a number of geographical locations and fish species ([DePaola et al., 1988](#) ; [Adams et al., 1998](#) ; [Rhodes et al., 2000](#) ; [Schmidt et al., 2001a](#) ; [Furushita et al., 2003](#) ; [Miranda et al., 2003](#) ; [Akinbowale et al., 2007](#) ; [Seyfried et al., 2010](#) ; [Gao et al., 2012](#)). The genes *tet* (A), *tet* (B), *tet* (E), *tet* (H), *tet* (L), *tet* (34), and *tet* (35) were found in tetracycline-resistant bacteria isolated from Chilean salmon farms ([Miranda et al., 2003](#)). Recently, [Seyfried et al. \(2010\)](#) detected the presence of *tet* (A), *tet* (B), *tet* (D), *tet* (E), *tet* (G), *tet* (M), *tet* (O), *tet* (Q), *tet* (S), and *tet* (W) genes in medicated and non-medicated feed samples and water samples from non-commercial fish farms in the United States. Similarly, [Jun et al. \(2004\)](#) found a high prevalence of *tet* (A) and *tet* (D) genes associated with mobile plasmids and *tet* (B) and *tet* (G) genes associated with non-mobile elements in *Edwardsiella tarda* strains isolated from fish farms in Korea. [Nonaka et al. \(2007\)](#) found a high incidence of *tet* (M)-carrying *Vibrio* strains in fish farms and [Agersø et al \(2007\)](#) detected *tet* (E) in *Aeromonas* strains from Danish fish farms associated with large plasmids capable of horizontal transfer to *Escherichia coli* . [Nawaz et al.](#)

(2009) found a high prevalence of *tet* (B) and, to a lesser extent, *tet* (A), *tet* (C) and the co-occurrence of *tet* (A) and *tet* (B) in *Escherichia coli* isolated from farm-raised catfish. Kim et al. (2004) reported the occurrence of *tet* (M) and *tet* (S) in tetracycline-resistant bacteria from fish farms in Korea and Nonaka and Suzuki (2002) found the novel OTC-resistance determinant *tet* (34) in a *Vibrio* strain isolated from cultured yellowtail (*Seriola quinqueradiata*).

The spread of *tet* genes is often facilitated by their location on mobile genetic elements, such as plasmids and transposons (Roberts, 1994 ; DePaola and Roberts, 1995 ; Chopra and Roberts, 2001). Tn1721 and Tn1721-like elements, for example, are known to play a significant role in the global dissemination of the *tet* (A) gene (Rhodes et al., 2000 ; Sørum, 2003 ; Chenia and Vietze, 2012). Miranda et al. (2003) found the *tet* (H) gene as part of the transposon Tn5706 in *Moraxella* and *Acinetobacter* strains isolated from salmon farms. In addition, they were able to transfer *tet* (B) and *tet* (34) genes from strains of *Serratia liquefaciens* , *Pseudomonas pseudoalcaligenes* , and *Brevundimonas vesicularis* . Similarly, Furushita et al. (2003) transferred *tet* (B), *tet* (D), and *tet* (Y) genes from bacterial isolates from different Japanese fish farms by conjugation and Adams et al. (1998) reported that various OTC-resistant isolates of *Aeromonas salmonicida* transferred R-plasmids carrying the *tet* (A) gene to environmental and clinical isolates of *Aeromonas* spp. Class 1 integrons harboring different combinations of the resistance gene cassettes *ant(3'')Ia*, *aac(6'')Ia*, *dhfr1*, *oxa2a* , and/or *pse1* and *tet* genes were also detected in a large number of plasmid bearing *Aeromonas* spp. strains isolated from

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tilapia, trout, and koi cultures in South Africa ([Jacobs and Chenia, 2007](#)). In *Edwardsiella ictaluri* strains isolated from diseased freshwater catfish in Vietnam, [Dung et al. \(2009\)](#) found the *tet* (A) gene associated with a high-molecular weight plasmid belonging to the Inc K group. In addition, all strains were able to transfer their *tet* (A)-carrying plasmids to *Escherichia coli* recipients.

Several studies have also reported the co-occurrence of tetracycline and sulphonamide resistances genes. [Agersø \(2007\)](#) showed that *tet* (39) and *sul2* genes located on plasmids of different sizes to be common among clonally distinct *Acinetobacter* spp. from fish farms in Thailand. [Su et al. \(2011\)](#) detected the genes *tet* (A), *tet* (C), and the sulphonamide-resistance gene, *sul2* , in more than 50% of the strains of Enterobacteriaceae they isolated from fish farms in China. [Gao et al. \(2012\)](#) recently reported the co-occurrence of tetracycline- and sulphonamide-resistance genes in *Bacillus* species isolated from aquaculture farms in China.

Phenicol Resistance

Florfenicol is a synthetic fluorinated analog of chloramphenicol whose bacteriostatic activity is based on a reversible binding to the 50S subunit of 70S bacterial ribosomes that prevents peptide elongation ([Schwarz et al., 2004](#)). The replacement of a hydroxyl group with a fluorine atom protects florfenicol from inactivation by chloramphenicol acetyltransferases (CATs), a common mechanism of bacterial resistance to chloramphenicol ([Shaw and Leslie, 1991](#) ; [Schwarz et al., 2004](#)). The effectiveness of florfenicol against a number of relevant fish pathogens makes it a very valuable drug for the fish farming industry ([Fukui et al., 1987](#) ; [Nordmo et al., 1994](#) ; [Samuelsen et al.,](#) <https://assignbuster.com/mechanisms-of-antimicrobial-resistance-in-finfish-aquaculture-environments/>

[1998](#) , [2003](#) ; [Bruun et al., 2000](#) ; [Gaunt et al., 2003](#) ; [McGinnis et al., 2003](#) ; [Michel et al., 2003](#) ; [Samuelsen and Bergh, 2004](#)).

Mechanisms of resistance to florfenicol include specific and non-specific drug transporters, RNA methyltransferases, and specific hydrolases ([Paulsen et al., 1996](#) ; [Schwarz et al., 2004](#) ; [Poole, 2005](#) ; [Long et al., 2006](#) ; [Tao et al., 2012](#)). Genes *floR* and *fexA* belong to the major facilitator superfamily and code for efflux proteins that export florfenicol out of the cell ([Schwarz et al., 2004](#)). The gene *cfr* , which has been shown to be an RNA methyltransferase that belongs to the recently discovered radical *S*-adenosylmethionine (SAM) superfamily of proteins ([Sofia et al., 2001](#)), inhibits ribose methylation and thereby causes resistance to florfenicol, chloramphenicol, and clindamycin ([Long et al., 2006](#)).

Most studies of florfenicol resistance in fish farming have reported the occurrence of the *floR* gene. [Dang et al. \(2007\)](#) detected the *floR* gene in tetracycline-resistant bacteria isolated from aquaculture sites in China, and [Ishida et al. \(2010\)](#) detected the *floR* gene in four strains of Gram-negative bacteria isolated from fish farms in Africa. In North America, [McIntosh et al. \(2008\)](#) reported the occurrence of *Aeromonas salmonicida* strains carrying a conjugative IncA/C plasmid harboring *floR* , *sul2* , and *tetA* genes that were transferable to *Aeromonas hydrophila* and *Edwardsiella tarda* . [Welch et al. \(2009\)](#) detected IncA/C plasmid-mediated florfenicol resistance in the catfish pathogen *Edwardsiella ictaluri* , and [Gordon et al. \(2008\)](#) reported a multiresistant *Aeromonas bestiarum* strain carrying a plasmid harboring the *floR* , *tetY* , *sul2* , and *strA-strB* resistance genes. A relatively recent study

showed that many florfenicol-resistant bacterial strains isolated from Chilean salmon farms carried the *floR* gene, whereas others possessed non-specific efflux pumps that conferred florfenicol resistance ([Fernández-Alarcón et al., 2010](#)). In fish farm impacted marine sediments, [Buschmann et al. \(2012\)](#) recently reported the occurrence of several strains containing plasmid-borne *floR* , *tet* , and *qnr* genes.

Prioritizing Research and Policy Needs

The studies discussed in the previous sections support the hypothesis that fish farms represent a reservoir of diverse ARGs, many of which may be readily mobilized by lateral gene transfer. Given the extent of global aquaculture and its fast-paced growth, it is imperative that research needs with regards to the use of antimicrobials and the emergence and potential spread of antimicrobial resistance are prioritized. This research should form the basis of sound, science-based policies that contribute to the sustainability of the aquaculture industry and minimize risks to public health. Further studies are needed to explore the prevalence of antimicrobial resistance in zoonotic fish pathogens such as *Aeromonas hydrophila* , *Edwardsiella tarda* , *Mycobacterium fortuitum* , *Mycobacterium marinum* , *Photobacterium damsela* , *Pseudomonas fluorescens* , and *Streptococcus iniae* ([Austin and Austin, 2012](#)). Moreover, there are important knowledge gaps regarding the co-occurrence of antimicrobial-resistant bacteria from aquaculture environments with human pathogens throughout production cycles and across a range of aquaculture environments, the transfer rate of resistance genes between aquaculture and clinically relevant bacteria under

field or semi-field conditions, and the epidemiology of antimicrobial resistance in areas of intense aquaculture activity.

Good management strategies can make a significant contribution to minimize the use of antimicrobials in fish and the emergence and spread of antimicrobial resistance in aquaculture environments. Among these precautionary practices are the use of “ good quality” fish stocks, reducing stocking densities, maintaining overall good environmental conditions (e. g., dissolved O₂ levels), the implementation of proper biosecurity measures, the development of effective vaccines and vaccination programs, and the rotation of antimicrobial compounds in the treatment of fish disease. Although the use of antimicrobials in human medicine places constraints on the type of antimicrobials that may be used in veterinary medicine, the rotation of antimicrobials in aquaculture may play an important role in reducing the chances of selection, co-selection, and dissemination of antimicrobial resistance. In this context, it is also important that efforts are directed toward creating incentives for the development and registration of antimicrobials for aquaculture use in addition to implementation of antimicrobial stewardship practices.

Conflict of Interest Statement

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

References

- Adams, C. A., Austin, B., Meaden, P. G., and McIntosh, D. (1998). Molecular characterization of plasmid-mediated oxytetracycline resistance in *Aeromonas salmonicida*. *Appl. Environ. Microbiol.* 64, 4194-4201.
- Agersø, Y., Bruun, M. S., Dalsgaard, I., and Larsen, J. L. (2007). The tetracycline resistance gene tet(E) is frequently occurring and present on large horizontally transferable plasmids in *Aeromonas* spp. from fish farms. *Aquaculture* 266, 47-52. doi: 10. 1016/j. aquaculture. 2007. 01. 012
- Agersø, Y., and Petersen, A. (2007). The tetracycline resistance determinant Tet 39 and the sulphonamide resistance gene sulII are common among resistant *Acinetobacter* spp. isolated from integrated fish farms in Thailand. *J. Antimicrob. Chemother.* 59, 23-27. doi: 10. 1093/jac/dkl419
- Akinbowale, O. L., Peng, H., and Barton, M. D. (2007). Diversity of tetracycline resistance genes in bacteria from aquaculture sources in Australia. *J. Appl. Microbiol.* 103, 2016-2025. doi: 10. 1111/j. 1365-2672. 2007. 03445. x
- Anderson, V. E., Gootz, T. D., and Osheroff, N. (1998). Topoisomerase IV catalysis and the mechanism of quinolone action. *J. Biol. Chem.* 273, 17879-17885. doi: 10. 1074/jbc. 273. 28. 17879
- Austin, B., and Austin, D. (2012). *Bacterial Fish Pathogens: Disease of Farmed and Wild Fish*. Dordrecht: Springer Science + Business Media.

Bostock, J., McAndrew, B., Richards, R., Jauncey, K., Telfer, T., Lorenzen, K., et al. (2010). Aquaculture: global status and trends . *Philos. Trans. R. Soc. Lond. B Biol. Sci.* 365, 2897–2912. doi: 10. 1098/rstb. 2010. 0170

Bruun, M. S., Schmidt, A. S., Lone Madsen, L., and Dalsgaard, I. (2000). Antimicrobial resistance patterns in Danish isolates of *Flavobacterium psychrophilum* . *Aquaculture* 187, 201–212. doi: 10. 1016/S0044-8486(00)00310-0

Burdett, V. (1991). Purification and characterization of tet(M), a protein that renders ribosomes resistant to tetracycline. *J. Biol. Chem.* 266, 2872–2877.

Burridge, L., Weis, J. S., Cabello, F., Pizarro, J., and Bostick, K. (2010). Chemical use in salmon aquaculture: a review of current practices and possible environmental effects. *Aquaculture* 306, 7–23. doi: 10. 1016/j. aquaculture. 2010. 05. 020

Buschmann, A. H., Tomova, A., López, A., Maldonado, M. A., Henríquez, L. A., Ivanova, L., et al. (2012). Salmon aquaculture and antimicrobial resistance in the marine environment. *PLoS ONE* 7: e42724. doi: 10. 1371/journal. pone. 0042724

Cattoir, V., and Nordmann, P. (2009). Plasmid-mediated quinolone resistance in Gram-negative bacterial species: an update. *Curr. Med. Chem.* 16, 1028–1046. doi: 10. 2174/092986709787581879

Cattoir, V., Poirel, L., Mazel, D., Soussy, C. J., and Nordmann, P. (2007). *Vibrio splendidus* as the source of plasmid-mediated QnrS-like quinolone resistance

determinants. *Antimicrob. Agents Chemother.* 51, 2650–2651. doi: 10.1128/AAC.00070-07

Chenia, H. Y., and Vietze, C. (2012). Tetracycline resistance determinants of heterotrophic bacteria isolated from a South African tilapia aquaculture system. *Afr. J. Microbiol. Res.* 6, 6761–6768. doi: 10.5897/AJMR10.840

Chopra, I. (1985). “ Mode of action of the tetracyclines and the nature of bacterial resistance to them,” in *The Tetracyclines. Handbook of Experimental Pharmacology* , Vol. 78, eds J. J. Hlavka and J. H. Boothe (Berlin: Springer-Verlag KG), 317–392.

Chopra, I., and Roberts, M. C. (2001). Tetracycline antibiotics: mode of action, applications, molecular biology, and epidemiology of bacterial resistance. *Microbiol. Mol. Biol. Rev.* 65, 232–260. doi: 10.1128/MMBR.65.2.232-260. 2001

Cloeckaert, A., Baucheron, S., and Chaslus-Dancla, E. (2001). Nonenzymatic chloramphenicol resistance mediated by IncC plasmid R55 is encoded by a *flo R* gene variant. *Antimicrob. Agents Chemother.* 45, 2381–2382. doi: 10.1128/AAC.45.8.2381-2382. 2001

Cloeckaert, A., Baucheron, S., Flaujac, S., Schwarz, S., Kehrenberg, C., Martel, J., et al. (2000). Plasmid-mediated florfenicol resistance encoded by the *flo R* gene in *Escherichia coli* isolated from cattle. *Antimicrob. Agents Chemother.* 44, 2858–2860. doi: 10.1128/AAC.44.10.2858-2860. 2000

Colquhoun, D. J., Aarflot, L., and Melvold, C. F. (2007). *gyr A* and *par C* mutations and associated quinolone resistance in *Vibrio anguillarum* serotype O2b strains isolated from farmed Atlantic cod (*Gadus morhua*) in Norway. *Antimicrob. Agents Chemother.* 51, 2597–2599. doi: 10. 1128/AAC. 00315-07

Dang, H., Zhang, X., Song, L., Chang, Y., and Yang, G. (2007). Molecular determination of oxytetracycline-resistant bacteria and their resistance genes from mariculture environments of China. *J. Appl. Microbiol.* 103, 2580–2592. doi: 10. 1111/j. 1365-2672. 2007. 03494. x

DePaola, A., Flynn, P. A., McPhearson, R. M., and Levy, S. B. (1988). Phenotypic and genotypic characterization of tetracycline- and oxytetracycline resistant *Aeromonas hydrophila* from cultured channel catfish (*Ictalurus punctatus*) and their environments. *Appl. Environ. Microbiol.* 54, 1861–1863.

DePaola, A., and Roberts, M. C. (1995). Class D and E tetracycline resistance determinants in Gram-negative catfish pond bacteria. *Mol. Cell. Probes* 9, 311–313. doi: 10. 1016/S0890-8508(95)91572-9

Drlica, K., and Zhao, X. L. (1997). DNA gyrase, topoisomerase IV, and the 4-quinolones. *Microbiol. Rev.* 61, 377–392.

Dung, T. T., Haesebrouck, F., Sorgeloos, P., Tuan, N. A., Pasmans, F., Smet, A., et al. (2009). IncK plasmid-mediated tetracycline resistance in *Edwardsiella ictaluri* isolates from diseased freshwater catfish in Vietnam. *Aquaculture* 295, 157–159. doi: 10. 1016/j. aquaculture. 2009. 07. 010

<https://assignbuster.com/mechanisms-of-antimicrobial-resistance-in-finfish-aquaculture-environments/>

FAO/OIE/WHO. (2006). *Report of a Joint FAO/OIE/WHO Expert Consultation on Antimicrobial Use in Aquaculture and Antimicrobial Resistance: Seoul, Republic of Korea , June 13-16, 2006* . Seoul: WHO.

Fernández-Alarcón, C., Miranda, C. D., Singer, R. S., López, Y., Rojas, R., Bello, H., et al. (2010). Detection of the *flo R* gene in a diversity of florfenicol resistant Gram-negative bacilli from freshwater salmon farms in Chile. *Zoonoses Public Health* 57, 181-188. doi: 10. 1111/j. 1863-2378. 2009. 01243. x

Fukui, H., Fujihara, Y., and Kano, T. (1987). In vitro and in vivo antibacterial activities of florfenicol, a new fluorinated analog of thiamphenicol, against fish pathogens. *Fish Pathol.* 22, 201-207. doi: 10. 3147/jsfp. 22. 201

Furushita, M., Shiba, T., Maeda, T., Yhata, M., Kaneoka, A., Takahashi, Y., et al. (2003). Similarity of tetracycline resistance genes isolated from fish farm bacteria to those from clinical isolates. *Appl. Environ. Microbiol.* 69, 5336-5342. doi: 10. 1128/AEM. 69. 9. 5336-5342. 2003

Gao, P., Mao, D., Luo, Y., Wang, L., Xu, B., and Xu, L. (2012). Occurrence of sulphonamide and tetracycline-resistant bacteria and resistance genes in aquaculture environment. *Water Res.* 46, 2355-2364. doi: 10. 1016/j. watres. 2012. 02. 004

Gaunt, P., Endris, R., Khoo, L., Leard, T., Jack, S., Santucci, T., et al. (2003). Preliminary assessment of the tolerance and efficacy of florfenicol against *Edwardsiella ictaluri* administered in feed to channel catfish. *J. Aquat. Anim. Health* 15, 239-247. doi: 10. 1577/H03-022

<https://assignbuster.com/mechanisms-of-antimicrobial-resistance-in-finfish-aquaculture-environments/>

Gibello, A., Porrero, M. C., Blanco, M. M., Vela, A. I., Liébana, P., Moreno, M. A., et al. (2004). Analysis of the *gyrA* gene of clinical *Yersinia ruckeri* isolates with reduced susceptibility to quinolones. *Appl. Environ. Microbiol.* 70, 599–602. doi: 10.1128/AEM.70.1.599-602.2004

Goñi-Urriza, M., Arpin, C., Capdepuy, M., Dubois, V., Caumette, P., and Quentin, C. (2002). Type II topoisomerase quinolone resistance-determining regions of *Aeromonas caviae*, *A. hydrophila* and *A. sobria* complexes and mutations associated with quinolone resistance. *Antimicrob. Agents Chemother.* 46, 350–359. doi: 10.1128/AAC.46.2.350-359.2002 PMCID: PMC127024

Gordon L, Cloeckert A, Doublet, B., Schwarz, S., Agnès Bouju-Albert, A., Ganière, J. P., et al. (2008). Complete sequence of the *flo* R-carrying multiresistance plasmid pAB5S9 from freshwater *Aeromonas bestiarum*. *J. Antimicrob. Chemother.* 62, 65–71. doi: 10.1093/jac/dkn166

Han, J. E., Kim, J. H., Cheresca, C. H., Shin, S. P., Jun, J. W., Chai, J. Y., et al. (2012). First description of the *qnrS*-like (*qnrS5*) gene and analysis of quinolone resistance-determining regions in motile *Aeromonas* spp. from diseased fish and water. *Res. Microbiol.* 163, 73–79. doi: 10.1016/j.resmic.2011.09.001

Hawkey, P. M. (2003). Mechanisms of quinolone action and microbial response. *J. Antimicrob. Chemother.* 51, S1, 29–35. doi: 10.1093/jac/dkg207

Heuer, O. E., Kruse, H., Grave, K., Collignon, P., Karunasagar, I., and Angulo, F. J. (2009). Human health consequences of use of antimicrobial agents in aquaculture. *Clin. Infect. Dis.* 49, 1248–1253. doi: 10.1086/605667

Ishida, Y., Ahmed, A. M., Mahfouz, N. B., Kimura, T., El-Khodery, S. A., Moawad, A. A., et al. (2010). Molecular analysis of antimicrobial resistance in Gram-negative bacteria isolated from fish farms in Egypt. *J. Vet. Med. Sci.* 72, 727–734. doi: 10.1292/jvms.09-0538

Izumi, S., and Aranishi, F. (2004). Relationship between *gyrA* mutations and quinolone resistance in *Flavobacterium psychrophilum* isolates. *Appl. Environ. Microbiol.* 70, 3968–3972. doi: 10.1128/AEM.70.7.3968-3972.2004

Izumi, S., Ouchi, S., Kuge, T., Arai, H., Mito, T., Fujii, H., et al. (2007). PCR-RFLP genotypes associated with quinolone resistance in isolates of *Flavobacterium psychrophilum*. *J. Fish Dis.* 30, 141–147. doi: 10.1111/j.1365-2761.2007.00797.x

Jacobs, L., and Chenia, H. Y. (2007). Characterization of integrons and tetracycline resistance determinants in *Aeromonas* spp. isolated from South African aquaculture systems. *Int. J. Food Microbiol.* 114, 295–306. doi: 10.1016/j.ijfoodmicro.2006.09.030

Jacoby, G. A. (2005). Mechanisms of resistance to quinolones. *Clin. Infect. Dis.* 41, S120–S126. doi: 10.1086/428052

Jiang, H. X., Tang, D., Liu, Y. H., Zhang, X. H., Zeng, Z. L., Xu, L., et al. (2012). Prevalence and characteristics of β -lactamase and plasmid-mediated quinolone resistance genes in *Escherichia coli* isolated from farmed fish in China. *J. Antimicrob. Chemother.* 67, 2350–2353. doi: 10. 1093/jac/dks250

Jun, L. J., Jeong, J. B., Huh, M. D., Chung, J. K., Choi, D. L., Lee, C. H., et al. (2004). Detection of tetracycline-resistance determinants by multiplex polymerase chain reaction in *Edwardsiella tarda* isolated from fish farms in Korea. *Aquaculture* 240, 89–100. doi: 10. 1016/j. aquaculture. 2004. 07. 025

Kim, J. H., Hwang, S. Y., Son, J. S., Han, J. E., Jun, J. W., Shin, S. P., et al. (2011). Molecular characterization of tetracycline- and quinolone-resistant *Aeromonas salmonicida* isolated in Korea. *J. Vet. Sci.* 12, 41–48. doi: 10. 4142/jvs. 2011. 12. 1. 41

Kim, M. J., Hirono, I., and Aoki, T. (2005). Detection of quinolone-resistant genes in *Photobacterium damsela* subsp. piscicida strains by targeting-induced local lesions in genomes. *J. Fish Dis.* 28, 463–471. doi: 10. 1111/j. 1365-2761. 2005. 00652. x

Kim, S. R., Nonaka, L., and Suzuki, S. (2004). Occurrence of tetracycline resistance genes tet(M) and tet(S) in bacteria from marine aquaculture sites. *FEMS Microbiol. Lett.* 237, 147–156. doi: 10. 1111/j. 1574-6968. 2004. tb09690. x

Kümmerer, K. (2004). Resistance in the environment. *J. Antimicrob. Chemother.* 54, 311–320. doi: 10. 1093/jac/dkh325

- Levy, S. B. (1992). Active efflux mechanisms for antimicrobial resistance. *Antimicrob. Agents Chemother.* 36, 695–703. doi: 10.1128/AAC.36.4.695
- Li, X. Z. (2005). Quinolone resistance in bacteria: emphasis on plasmid-mediated mechanisms. *Int. J. Antimicrob. Agents* 25, 453–463. doi: 10.1016/j.ijantimicag.2005.04.002
- Long, K. S., Poehlsgaard, J., Kehrenberg, C., Schwarz, S., and Vester, B. (2006). The Cfr rRNA methyltransferase confers resistance to phenicols, lincosamides, oxazolidinones, pleuromutilins, and streptogramin A antibiotics. *Antimicrob. Agents Chemother.* 50, 2500–2505. doi: 10.1128/AAC.00131-06
- Lukkana, M., Wongtavatchai, J., and Chuanchuen, R. (2012). Class 1 integrons in *Aeromonas hydrophila* isolates from farmed Nile tilapia (*Oreochromis nilotica*). *J. Vet. Med. Sci.* 74, 435–440. doi: 10.1292/jvms.11-0441
- McGinnis, A., Gaunt, P., Santucci, T., Simmons, R., and Endris, R. (2003). In vitro evaluation of the susceptibility of *Edwardsiella ictaluri*, etiological agent of enteric septicemia in channel catfish, *Ictalurus punctatus* (Rafinesque), to florfenicol. *J. Vet. Diagn. Invest.* 15, 576–579. doi: 10.1177/104063870301500612
- McIntosh, D., Cunningham, D., Ji, B., Fekete, F. A., Parry, E. M., Clark, S. E., et al. (2008). Transferable, multiple antibiotic and mercury resistance in Atlantic Canadian isolates of *Aeromonas salmonicida* subsp. *Salmonicida* is associated with carriage of an IncA/C plasmid similar to the *Salmonella*
<https://assignbuster.com/mechanisms-of-antimicrobial-resistance-in-finfish-aquaculture-environments/>

enterica plasmid pSN254. *J. Antimicrob. Chemother.* 61, 1221–1228. doi: 10.1093/jac/dkn123

Michel, C., Kerouault, B., and Martin, C. (2003). Chloramphenicol and florfenicol susceptibility of fish-pathogenic bacteria isolated in France: comparison of minimum inhibitory concentration, using recommended provisory standards for fish bacteria. *J. Appl. Microbiol.* 95, 1008–1015. doi: 10.1046/j.1365-2672.2003.02093.x

Miranda, C. D., Kehrenberg, C., Ulep, C., Schwarz, S., and Roberts, M. C. (2003). Diversity of tetracycline resistance genes in bacteria from Chilean salmon farms. *Antimicrob. Agents Chemother.* 47, 883–888. doi: 10.1128/AAC.47.3.883-888.2003

Nawaz, M., Khan, A. A., Khan, S., Sung, K., Kerdahi, K., and Steele, R. (2009). Molecular characterization of tetracycline-resistant genes and integrons from avirulent strains of *Escherichia coli* isolated from catfish. *Foodborne Pathog. Dis.* 6, 553–559. doi: 10.1089/fpd.2008.0204

Nonaka, L., Ikeno, K., and Suzuki, S. (2007). Distribution of tetracycline resistance gene, *tet* (M), in Gram-positive and Gram-negative bacteria isolated from sediment and seawater at a coastal aquaculture site in Japan. *Microbes Environ.* 22, 355–364. doi: 10.1264/jsme2.22.355

Nonaka, L., and Suzuki, S. (2002). New Mg²⁺-dependent oxytetracycline resistance determinant Tet 34 in *Vibrio* isolates from marine fish intestinal contents. *Antimicrob. Agents Chemother.* 46, 1550–1552. doi: 10.1128/AAC.46.5.1550-1552.2002

<https://assignbuster.com/mechanisms-of-antimicrobial-resistance-in-finfish-aquaculture-environments/>

Nordmo, R., Varma, K. J., Sutherland, I. H., and Brokken, E. S. (1994).

Florfenicol in Atlantic salmon, *Salmo salar* L.: field evaluation of efficacy against furunculosis in Norway . *J. Fish Dis.* 17, 239–244. doi: 10.1111/j.1365-2761.1994.tb00219.x

Okuda, J., Hayakawa, E., Nishibuchi, M., and Nishino, T. (1999). Sequence analysis of the *gyr A* and *par C* homologues of a wild type strain of *Vibrio parahaemolyticus* and its fluoroquinolone-resistant mutants. *Antimicrob. Agents. Chemother.* 43, 1156–1162.

Oppegaard, H., and Sørum, H. (1994). *gyr A* mutations in quinolone-resistant isolates of the fish pathogen *Aeromonas salmonicida* . *Antimicrob. Agents Chemother.* 38, 2460–2464. doi: 10.1128/AAC.38.10.2460

Ozanne, B., Benveniste, R., Tipper, D., and Davies, J. (2005). Molecular cloning of the *gyr A* gene and characterization of its mutation in clinical isolates of quinolone-resistant *Edwardsiella tarda* . *Dis. Aquat. Org.* 67, 259–266. doi: 10.3354/dao067259

Paulsen, I. T., Brown, M., and Skurray, R. (1996). Proton-dependent multidrug efflux systems. *Microbiol. Rev.* 60, 575–608.

Poirel, L., Cattoir, V., and Nordmann, P. (2008). Is plasmid-mediated quinolone resistance a clinically significant problem? *Clin. Microbiol. Infect.* 14, 295–297. doi: 10.1111/j.1469-0691.2007.01930.x

Poirel, L., Cattoir, V., and Nordmann, P. (2012). Plasmid-mediated quinolone resistance: interactions between human, animal, and environmental ecologies. *Front. Microbiol.* 3: 24. doi: 10.3389/fmicb.2012.00024

Poirel, L., Liard, A., Rodriguez-Martinez, J. M., and Nordmann, P. J. (2005). *Vibrionaceae* as a possible source of Qnr-like quinolone resistance determinants. *J. Antimicrob. Chemother.* 56, 1118–1121. doi: 10.1093/jac/dki371

Poole, K. (2005). Efflux-mediated antimicrobial resistance. *J. Antimicrob. Chemother.* 56, 20–51. doi: 10.1093/jac/dki171

Rhodes, G., Huys, G., Swings, J., McGann, P., Hiney, M., Smith, P., et al. (2000). Distribution of oxytetracycline resistance plasmids between aeromonads in hospital and aquaculture environments: implication of Tn1721 in dissemination of the tetracycline resistance determinant Tet A. *Appl. Environ. Microbiol.* 66, 3883–3890. doi: 10.1128/AEM.66.9.3883-3890.2000

Rico, A., Satapornvanit, K., Haque, M. M., Min, J., Nguyen, P. T., Telfer, T. C., et al. (2012). Use of chemicals and biological products in Asian aquaculture and their potential environmental risks: a critical review. *Rev. Aquac.* 4, 75–93. doi: 10.1111/j.1753-5131.2012.01062.x

Roberts, M. C. (1994). Epidemiology of tetracycline-resistance determinants. *Trends Microbiol.* 2, 353–357. doi: 10.1016/0966-842X(94)90610-6

Roberts, M. C. (1996). Tetracycline resistance determinants: mechanisms of action, regulation of expression, genetic mobility, and distribution. *FEMS Microbiol. Rev.* 19, 1–24. doi: 10. 1111/j. 1574-6976. 1996. tb00251. x

Roberts, M. C. (2005). Update on acquired tetracycline resistance genes. *FEMS Microbiol. Lett.* 245, 195–203. doi: 10. 1016/j. femsle. 2005. 02. 034

Roberts, M. C., Schwarz, S., and Aarts, H. J. M. (2012). Erratum: acquired antibiotic resistance genes: an overview. *Front. Microbiol.* 3: 384. doi: 10. 3389/fmicb. 2012. 00384

Rodkhum, C., Maki, T., Hirono, I., and Aoki, T. (2008). *gyr A* and *par C* associated with quinolone resistance in *Vibrio anguillarum* . *J. Fish Dis.* 31, 395–399. doi: 10. 1111/j. 1365-2761. 2007. 00843. x

Rodríguez-Martínez, J. M., Cano, M. E., Velasco, C., Martínez-Martínez, L., and Pascual, A. (2011). Plasmid-mediated quinolone resistance: an update. *J. Infect. Chemother.* 17, 149–182. doi: 10. 1007/s10156-010-0120-2

Ruiz, J. (2003). Mechanisms of resistance to quinolones: target alterations, decreased accumulation and DNA gyrase protection. *J. Antimicrob. Chemother.* 51, 1109–1117. doi: 10. 1093/jac/dkg222

Salyers, A. A., Speer, B. S., and Shoemaker, N. B. (1990). New perspectives in tetracycline resistance. *Mol. Microbiol.* 4, 151–156. doi: 10. 1111/j. 1365-2958. 1990. tb02025. x

Samuelsen, O. B., and Bergh, Ø. (2004). Efficacy of orally administered florfenicol and oxolinic acid in the treatment of vibriosis in cod (*Gadus morhua* L.) . *Aquaculture* 235, 27–35. doi: 10.1016/S0044-8486(03)00446-0

Samuelsen, O. B., Bergh, Ø., and Ervik, A. (2003). A single-dose pharmacokinetic study of florfenicol in cod (*Gadus morhua* L.) held in seawater at 8°C and in vitro antibacterial activity against some *Vibrio anguillarum* strains isolated from diseased cod. *Dis. Aquat. Org.* 56, 127–133. doi: 10.3354/dao056127

Samuelsen, O. B., Hjeltnes, B., and Glette, J. (1998). Efficacy of orally administered florfenicol in the treatment of furunculosis in Atlantic salmon. *J. Aquat. Anim. Health.* 10, 56–61. doi: 10.1577/1548-8667(1998)010<0056:EOOAFI>2.0.CO;2

Sapkota, A., Sapkota, A. R., Kucharski, M., Burke, J., McKenzie, S., Walker, P., et al. (2008). Aquaculture practices and potential human health risks: current knowledge and future priorities. *Environ. Int.* 34, 1215–1226. doi: 10.1016/j.envint.2008.04.009

Schmidt, A. S., Bruun, M. S., Dalsgaard, I., and Larsen, J. L. (2001a). Incidence, distribution, and spread of tetracycline resistance determinants and integron-associated antibiotic resistance genes among motile aeromonads from a fish farming environment. *Appl. Environ. Microbiol.* 67, 5675–5682. doi: 10.1128/AEM.67.12.5675-5682.2001

Schmidt, A. S., Bruun, M. S., Larsen, J. L., and Dalsgaard, I. (2001b).

Characterization of class 1 integrons associated with R-plasmids in clinical

<https://assignbuster.com/mechanisms-of-antimicrobial-resistance-in-finfish-aquaculture-environments/>

Aeromonas salmonicida isolates from various geographical areas. *J. Antimicrob. Chemother.* 47, 735–743. doi: 10. 1093/jac/47. 6. 735

Schwarz, S., Kehrenberg, C., Doublet, B., and Cloeckaert, A. (2004). Molecular basis of bacterial resistance to chloramphenicol and florfenicol. *FEMS Microbiol. Rev.* 28, 519–542. doi: 10. 1016/j. femsre. 2004. 04. 001

SERNAPESCA (Chile). (2009). *Informe De Uso De Antimicrobianos 2005–2009*. Report available at: http://www. sernapesca. cl/index. php? option= com_repositorio&Itemid= 246&func= select&id= 35vderby= 2&page= 2 .

Seyfried, E. E., Newton, R. J., Rubert, K. F., Pedersen, J. A., and McMahon, K. D. (2010). Occurrence of tetracycline resistance genes in aquaculture facilities with varying use of oxytetracycline. *Microb. Ecol.* 59, 799–807. doi: 10. 1007/s00248-009-9624-7

Shah, S. Q., Nilsen, H., Bottolfsen, K., Colquhoun, D. J., and Sørum, H. (2012). DNA gyrase and topoisomerase IV mutations in quinolone-resistant *Flavobacterium psychrophilum* isolated from diseased salmonids in Norway. *Microb. Drug Resist.* 18, 207–214. doi: 10. 1089/mdr. 2011. 0142

Shaw, W. V., and Leslie, A. G. (1991). Chloramphenicol acetyltransferase. *Annu. Rev. Biophys. Biophys. Chem.* 20, 363–386. doi: 10. 1146/annurev. bb. 20. 060191. 002051

Smith, P. (2008). Aquaculture and florfenicol resistance in *Salmonella enterica* Typhimurium DT104 (letter). *Emerg. Infect. Dis.* 14, 1327–1328. doi: 10. 3201/eid1408. 080329

<https://assignbuster.com/mechanisms-of-antimicrobial-resistance-in-finfish-aquaculture-environments/>

Sofia, H. J., Chen, G., Hetzler, B. G., Reyes-Spindola, J. F., and Miller, N. E. (2001). Radical SAM, a novel protein superfamily linking unresolved steps in familiar biosynthetic pathways with radical mechanisms: functional characterization using new analysis and information visualization methods. *Nucleic Acids Res.* 29, 1097–1106. doi: 10.1093/nar/29.5.1097

Sørum, H., L’Abee-Lund, T. M., Solberg, A., and Wold, A. (2003). Integron-containing incU R plasmid pRAS1 and pAr-32 from the fish pathogen *Aeromonas salmonicida*. *Antimicrob. Agents Chemother.* 47, 1285–1290. doi: 10.1128/AAC.47.4.1285-1290.2003

Speer, B. S., and Salyers, A. A. (1989). Novel aerobic tetracycline resistance gene that chemically modifies tetracycline. *J. Bacteriol.* 171, 148–153.

Speer, B. S., Shoemaker, N. B., and Salyers, A. A. (1992). Bacterial resistance to tetracycline: mechanisms, transfer, and clinical significance. *Clin. Microbiol. Rev.* 5, 387–399.

Su, H. C., Ying, G. G., Tao, R., Zhang, R. Q., Fogarty, L. R., and Kolpin, D. W. (2011). Occurrence of antibiotic resistance and characterization of resistance genes and integrons in Enterobacteriaceae isolated from integrated fish farms in South China. *J. Environ. Monit.* 13, 3229–3236. doi: 10.1039/c1em10634a

Tao, W., Lee, M. H., Wu, J., Kim, N. H., Kim, J.-C., Chung, E., et al. (2012). Inactivation of chloramphenicol and florfenicol by a novel chloramphenicol hydrolase. *Appl. Environ. Microbiol.* 78, 6295–6301. doi: 10.1128/AEM.01154-12

<https://assignbuster.com/mechanisms-of-antimicrobial-resistance-in-finfish-aquaculture-environments/>

Taylor, D. E., and Chau, A. (1996). Tetracycline resistance mediated by ribosomal protection. *Antimicrob. Agents Chemother.* 40, 1-5.

Tirado, M. C., Clarke, R., Jaykus, L. A., McQuatters-Gollop, A., and Frank, J. M. (2010). Climate change and food safety: a review . *Food Res. Int.* 43, 1745-1765. doi: 10. 1016/j. foodres. 2010. 07. 003

Tran, J. H., and Jacoby, G. A. (2002). Mechanism of plasmid-mediated quinolone resistance. *Proc. Natl. Acad. Sci. U. S. A.* 99, 5638-5642. doi: 10. 1073/pnas. 082092899

Welch, T. J., Evenhuis, J., White, D. G., McDermott, P. F., Harbottle, H., Miller, R. A., et al. (2009). IncA/C plasmid-mediated florfenicol resistance in the catfish pathogen *Edwardsiella ictaluri* . *Antimicrob. Agents Chemother.* 53, 845-846. doi: 10. 1128/AAC. 01312-08

WHO. (2011). *Critically Important Antimicrobials for Human Medicine* , 3rd Revision. Available at: http://apps.who.int/iris/bitstream/10665/77376/1/9789241504485_eng.pdf.