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Emergence of antimicrobial resistance by drug abuse in aquaculture

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Abstract
The development and spread of antimicrobial resistance has become a global public health problem nowadays. This emergence of AMR in aquaculture industry increased due the overuse or misuse of antimicrobials as therapeutic and prophylactic agents. Even though India has banned about 22 antibiotics, there has been an uncontrolled usage prevails causing maximum shrimp entry line rejections in past years. Moreover in aquaculture for combating bacterial diseases, antimicrobials such as oxytetracycline, florfenicol, sarafloxacin, and enrofloxacin were commonly in usage. This high reports on the antimicrobials leads to the increased incidences of antibiotic resistance (ABR) in the aquatic environments thus paves the way for antibiotic residues to easily reach the environment through fish-farm wastes, thus exerting higher implications on the environment. This mini review clearly shows the spread of AMR and its effect on environment and human health.

Keywords: AMR, aquaculture, antibiotics

Introduction
The increased use of antimicrobials has begun due to the promotion of intensive fish farming which leads to the growth of several bacterial diseases. Although the common routes of administration in aquaculture are through the use of medicated feed and by the addition of antimicrobial agents directly to the water (immersion therapy), both of these methods imply flock treatment of the animals. The term "antimicrobials" is any substance of natural (Friedman, M. 2015) [13], semisynthetic or synthetic (Ramos *et al.*, 2002; Fernandes, 2003) [23, 12] origin that act against all types of microorganisms – bacteria (antibacterial), viruses (antiviral), fungi (antifungal) and protozoa (antiprotozoal). In India, a total of twenty-two antibiotics which includes chloramphenicol, nitrofurans, sulfonamides, glycopeptides etc., were banned for usage in aquaculture by Coastal Aquaculture Authority. Even though, there has been an uncontrolled usage of antibiotics as prophylactic and growth promoters. The most frequently used antimicrobials in shrimp farming to combat bacterial diseases include oxytetracycline, florfenicol, sarafloxacin, and enrofloxacin (Roque *et al.*, 2001; Soto Rodríguez *et al.*, 2006) [26, 29]. In addition to this various antimicrobials are also in use globally and to determine whether this antibiotic is effective for the control of these diseases, it is important to relate the accumulation levels reached with the Minimal Inhibitory Concentration of the drug that can treat bacterial infections among shrimp (Bermúdez-Almada, M.C. and Espinosa-Plascencia, A., 2012) [6].

Antibiotics usage in shrimp farming
India has set highest record in shrimp entry line rejections in 2016. This rising rejection indicates the widespread use of antimicrobials in aquaculture for therapeutic and non-therapeutic uses in India (press release by the MPEDA). Accounting the usage of the antibiotics in pond management, about 27% used them to prevent or treat viral diseases. According to MPEDA report, in 2012-2015, about 17 cases of exported shrimp products were reported for the presence of prohibited substances such as nitrofuran metabolite (furazolidone), nitrofurazone and chloramphenicol or for exceeding the amount of oxytetracycline by European countries as per the Rapid Alert System for Food and Feed of the European Commission. Research indicates that the 70-80% of the drugs used in aquaculture ends up in the environment. Moreover, antibiotics and antibacterial substances are indiscriminately being

used as prophylactic and/or growth promoting agent in shrimp farms of Andhra Pradesh, Tamil Nadu, Kerala and Karnataka and some manufacturers are even incorporating certain antibiotics in shrimp feed as a preservative (Surendran, 2002) [31]

Mechanism of action of Antimicrobials

The mechanism of antimicrobials incorporated in the fish farming generally falls into 5 categories which are cell wall synthesis (eg, beta-lactams and glycopeptide agents), inhibition of protein synthesis (macrolides and tetracyclines), interference with nucleic acid synthesis (fluoroquinolones and rifampin), inhibition of a metabolic pathway (trimethoprim-sulfamethoxazole), and disruption of bacterial membrane structure (polymyxins and daptomycin). Use of antibacterial agents creates selective pressure for the emergence of resistant strains. Normally bacteria may be intrinsically resistant to > or =1 class of antimicrobial agents, or may acquire resistance by de novo mutation or via the acquisition of resistance genes from other organisms.

Antimicrobial resistance

The antibiotics have been a cornerstone of innovation in the animal health management. The risk from use of antibiotics in aquaculture in developing countries in the tropics may be higher than in industrialized countries in temperate regions. Normally the development of antibiotic resistance due to the use of antibiotics (Bjorklund *et al.*, 1991; Herwig *et al.*, 1997; Alderman and Hastings, 1998; Schmidt *et al.*, 2000) [15, 1, 27] can cause human health problems locally among the farmers. The prophylactic use of antibiotics at sub therapeutic levels (Wegener *et al.*, 1999; Inglis, 2005) [36, 16] and the use of antibiotics causing multiple resistances (Threlfall *et al.*, 2000) [33] are the factors contributing antimicrobial resistance development. The widespread use of fluoroquinolones e.g. norfloxacin and ciprofloxacin, is a particular cause for concern (WHO, 2006) [37]. Another risk is that resistance may develop among shrimp pathogens and thereby increase the difficulty of treating bacterial infections in shrimp ponds. Many factors contributing growth of micro-organisms in tropical intensive shrimp ponds, such as *V. cholerae* and *Salmonella* are high water temperature, pH and salinity and high organic load (Reilly and Twiddy, 1992) [24].

Antimicrobial resistance and its effects

Effects on Environment

Nowadays antibiotic resistance genes are present everywhere in the natural aquatic environments due to the bioaccumulation and toxic actions of antibiotics used in farming. Today, development and spread of antimicrobial resistance has become a global public health problem that is impacted by both human and non-human antimicrobial usage (OIE/FAO/WHO 2004) [28]. It is generally acknowledged that any use of antimicrobial agents can lead to the emergence of antimicrobial resistant microorganisms and further promote the dissemination of resistant bacteria and resistance genes (OIE/FAO/WHO 2004) [28]. Furthermore, resistance genes neither respect phylogenetic, geographical nor ecological borders. Thus, the use of antimicrobials in one area, such as aquaculture, can have an impact on the resistance situation in another area, such as in human medicine, and resistance problems in one country can spread to another country. The studies have reported that antibiotics can leach from the feed pellets into the pond water before the pellets are consumed by the shrimps (Inglis, 2000), while some feed will be left uneaten on the pond bottom. Moreover, antibiotics that are added to the pond environment may remain in the sediment for months. Antimicrobial resistance deriving from usage of antimicrobials in aquaculture presents a risk to public health owing to development of acquired resistance in bacteria in aquatic environments that can infect humans. This can be regarded as a direct spread of resistance from aquatic environments to humans. Another release of AMR to the environment can occur due to development of acquired resistance in bacteria in aquatic environments whereby such resistant bacteria can act as a reservoir of resistance genes from which the genes can be further disseminated and ultimately end up in human pathogens. This can be viewed as an indirect spread of resistance from aquatic environments to humans caused by horizontal gene transfer. Some recent studies showed that several antibiotics such as ciprofloxacin, oxolinic acid, chlortetracycline, oxytetracycline, tetracycline and trimethoprim, are acutely toxic to algae and aquatic invertebrates. The antibiotic residues in cultured shrimps can be regularly monitored by National food authorities with the maximum residue limits (MRL). Guidelines for governmental control programmes of veterinary drug residues in food and recommended MRLs are continuously developed by the Codex Alimentarius Commission of the Food and Agriculture Organization of the United Nations (FAO) and the World Health Organization (WHO) (Codex Alimentarius Commission, 2001).

Effects on human health

We know that the aquaculture environment and human environment can interact closely. In Europe the release of tetracycline resistance-encoding plasmids can interact with human health (Rhodes *et al.*, 2000) [25]. Resistance to certain antibiotics e.g. chloramphenicol, ciprofloxacin and tetracycline is developing in human pathogens in Southeast Asia (WHO, 2001). Various research works have stated that resistance to tetracycline, oxytetracycline, furazolidone and sulphamethoxazole were most common. It should be noted that from tropical Asian shrimp farms, some human pathogens, such as pathogenic Salmonella and *V. cholerae* strains, have been isolated (Reilly & Twiddy, 1992; Bhaskar *et al.*, 1995; Dalsgaard *et al.*, 2000) [24, 7, 10, 27]. Other human pathogens that occur in marine waters or sediment are, for example, *Aeromonas hydrophila* and *Plesiomonas shigelloides* (WHO, 1999). Another study have reported that antibiotic-resistant *Salmonella*, *A. hydrophila* and *P. shigelloides* occurred in ponds where antibiotics had been used routinely (Twiddy & Reilly, 1995). This can be evidenced in 1988 in Taiwanese shrimp farm in which the unlimited use of antibiotics resulting in the development of resistant strains of shrimp pathogens (Lin, 1989). An Indian *P. monodon* hatchery was experienced mass mortality of postlarvae due to V. harveyi with multiple resistance to cotrimoxazole, chloramphenicol, erythromycin and streptomycin (Karunasagar *et al.*, 1994) [18].

Spread of AMR

Nowadays the spread of antimicrobial resistance has become an extremely complex area due to the emergence of antimicrobial resistant microorganisms and further promote the propagation of antimicrobial resistant bacteria and resistance genes (OIE/FAO/WHO 2004) [28]. Moreover human exposure to resistant bacteria and resistance genes in aquaculture and products of aquaculture has been increased with the increasing importance of the aquaculture industry and increasing consumption of products of aquaculture. This emergence of AMR has 2 pathways to infect humans which are direct and indirect ways. The direct spread happens through the development of acquired resistance in bacteria in aquatic environments that can infect humans. Whereas the indirect method of transfer occurs by horizontal gene transfer which can be viewed by initially development of acquired resistance in bacteria in aquatic environments happens whereby such resistant bacteria can act as a reservoir of resistance genes from which the genes can be further disseminated and ultimately end up in human pathogens (WHO, 2006) [37]. Rather than the circumstance in land-based animals, microbes causing disease in humans via the oral route are uncommon in aquaculture. The report submitted by WHO and FAO has stated that the transmission of disease by means of aquaculture were low with respect to *Vibrio cholerae, , Plesiomonas shigelloides, Listeria monocytogenes, Edwardsiella tarda, Salmonella spp,* other *Enterobacteriaceae* and *Campylobacter* spp and they also added that there occurs much difference between the bacterial species causing diseases in fishes and humans. But fishes are considered as zoonotic pathogen reservoirs as the handlers of aquaculture facilities has occur some common infections such as *Aeromonas hydrophilia, Mycobacterium marinum, Streptococcus iniae, Vibrio vulnificus, and Photobacterium damselae* (Haenen, 2013) [14]. In addition to mutation, via natural transformation, transduction a bacteria can get AMR through horizontal gene Transfer (HGT) in the environment (Iwasaki *et al.*, 2009, Taylor *et al.*, 2011 , Stalder *et al.*, 2012) [17, 32, 30] .This rising tide of AMR in shrimp farming has started to focus on examining how AMR pathways spread and evolve which confined to an apparent term “Resistome” (a collection of all AMR genes in a microbial community) (Aminov 2011, Allen *et al.*, 2010, Berendonk *et al.*, 2015., Watts *et al.*, 2017) [3, 2, 5, 35]. It is unexpected that the present antimicrobial utilization of shrimp farmers will prompt to adequate antimicrobial concentrations in the diseased aquatic animals needed for effective therapeutic treatment. Fish farmers are nowadays by mixing the antimicrobial powder or solution with the clean water without recognizing that some antimicrobials are hydrophobic eg- trimethoprim, sulfamethoxazole they began to prepare their own medicated feed for shrimp (Khalil *et al.*, 2008) [19]. Another major practice causing large variations in antimicrobial concentration in the feed is applying antimicrobial solutions to the feed pellets which were confirmed by Phu *et al.* 2015 in his recent study. In this way, there is an urgent need for fish farmers to choose quality medicated feeds and antimicrobials to reduce significantly farmer’s direct physical contact with antimicrobials while preparing medicated feed and the associated health risks (Chi *et.al*, 2017) [9].

Molecular characterization of Antimicrobial resistance

For several years, various studies have been done to characterize the effect of antibiotics on specific strains within the gut bacterial communities. But in recent years, these researches have turned out on the overall taxonomic composition of fecal microbiota and on the abundance and diversity of antibiotic resistant genes. Moreover the metagenomics works have been undertaken to study the antibiotic resistance development in the gut microbiota (Zhang *et al.*, 2011)) [38]. There occurs a clear fact that occurrence of antimicrobial resistance varies between countries and regions. The resistance genes can be transferred among bacteria of different taxonomic and ecological groups. So the molecular characterization of the antimicrobial resistant genes should be focused to know the clear cut data on the development of antimicrobial resistance in the environments. Using the non-specific culture methods and culture independent real time PCR, the abundance of the antimicrobial resistance was revealed and a broad spectrum of non-pathogenic beneficial bacteria were found carrying transmissible AMR genes (Duran and Marshall, 2005, Wang *et al.*, 2006, Manuzon *et al.*, 2007) [11, 34, 21]. This becomes evident in early mitigation measures for preventive AMR management (Andremont, 2015; Wang *et al*., 2006) [4, 34]

Conclusion

The use and misuse of antimicrobials in aquaculture has led to an increase in antibiotic resistance in fish pathogens, in the transfer of these resistance determinants to and from the sediment microbial community. Aquaculture has been shown to select for AMR in the fish microbiome and the surrounding environment. It is for the most part recognized that any utilization of antimicrobial agents can prompt the development of antimicrobial resistant microorganisms and further advance the production of resistant bacteria and resistant genes. Moreover, the newly formed resistance genes neither regard phylogenetic, geographical nor ecological borders. The pathway and the likelihood of the antimicrobial resistance factor transfer in aquatic environments are poorly understood. Knowledge, programmatic, and management gaps can be identified and, if filled, would foster prudent antimicrobial use, perhaps reduce general use of antimicrobials and provide a means to measure progress.

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