Int.J.Curr.Microbiol.App.Sci (2018) *7*(8): 26-41

International Journal of Current Microbiology and Applied Sciences
***ISSN: 2319-7706* Volume 7 Number 08 (2018)**
Journal homepage: http://www.ijcmas.com

Review Article https://doi.org/10.20546/ijcmas.2018.708.004

Issues of Antibiotic Resistance in Aquaculture Industry and Its Way Forward

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Keywords

Alternative approach, Antimicrobial resistance, Bacteriophage therapy, Immunostimulants, Prebiotics, Probiotics, Quorum sensing inhibition, RNA interference, Synbiotics, Vaccine

Article Info

Accepted:
04 July 2018
Available Online:
10 August 2018

A B S T R A C T

Use of antibiotics as a therapeutic measure is the most used method for the treatment of infectious diseases including in fisheries and aquaculture. The successful use of any antibiotic in aquaculture is compromised due to the emergence of antimicrobial resistance in bacteria. Bacteria may be intrinsically resistant to different antimicrobial agents or they may acquire resistance through horizontal gene transfer. A number of biochemical and physiological mechanisms are responsible for the development of this resistance. Antimicrobial resistance developed in one ecological niche can spread to another ecological niche and finally can reach the human resulting in a number of treatment failures and high life threatening diseases. The unregulated use of antimicrobial agents has led to the development of antimicrobial resistant fish pathogens as well as other aquatic bacteria. The resistance has been observed in a number of bacterial species including *Aeromonas hydrophila*, *A. salmonicida*, *Yersinia ruckeri*, *Edwardsiella tarda*, *E. ictaluri*, *Vibrio anguillarum*, *V. salmonicida*, *Photobacterium damselae.* Multidrug-resistant strains of *A. salmonicida* and *Vibrio harveyi* have been reported from different parts of the country. The residues of antimicrobial agents also possess a threat to human health causing allergy, toxicity, alterations of the intestinal flora etc. Antibiotic residues represents potential health hazard and also affects the trade prospects. In this critical scenario different alternative approach can play a crucial role, such as Probiotics, prebiotics and synbiotics, immunostimulants, bacteriophage therapy, vaccine, RNA interference, quorum sensing inhibition etc. All this alternative measures can be used as prophylactic or control measure for fish disease management without hampering the environment. Vaccination is one of the most promising alternatives for the disease management which is being already in use in so many countries. There is every day increasing research in this field of antimicrobial alternatives measures and there are many success stories in the lab as well as in the field also. So days are coming when we can proudly say no to antibiotic use in aquaculture.

Introduction

Exponential growth of the world population keeps on challenging the fish productivity to meet the protein requirement. There is huge sift of the fish culture practices from extensive to intensive. But to attain this intensification we have saddled lots of stress to the culture animal and environment which leads to devastating diseases. So to combat with these diseases we have used so many remedial measures and antibiotics are one of those. Different Antibiotics are the most widely used remedial measures against bacterial fish infections. Antibiotics are drugs of natural or synthetic origin that have the capacity to kill or to inhibit the growth of micro-organisms (Serrano, 2005). A therapeutic level of antibiotics is used for treatment, control, or prevention of animal diseases (Landers *et al.,* 2012). Sub-therapeutic levels of antibiotics, such as penicillin or tetracycline, are provided to food animals in their feed in order to enhance their feed / weight efficiency ratios (Marshall and Levy 2011). In aquaculture, the antimicrobials are mainly administered either through medicated feed or adding antimicrobial agents directly to the pond water. Both the methods may result in heavy use of antimicrobial agents and provide a strong selective pressure in the aquatic animals, as well as in the exposed environments (Le and Munekage, 2004). Intensive use of antimicrobial agents in aquaculture has resulted in the emergence of reservoirs of antimicrobial-resistant bacteria in fish and other aquatic animals. From these reservoirs the resistant genes may reach human pathogens indirectly through horizontal gene transfer or the drug resistant pathogens may reach human directly from the aquatic environment (Heuer*et al.,* 2009). Because of the antibiotic resistance problem the bacterial diseases are becoming hard to control. So antibiotic resistance is a big concern, which stands true for whole animal kingdom as a whole as resistance can be easily transferred from one bacteria to another.

Major classes of antibiotics

There are several major classes of antibiotics based on their mechanism of action.

Antibioticsthat inhibit cell wall synthesis

Inhibition of cell wall synthesis is the most common bactericidal activity. The major group of antibiotics under this category is β-lactams. These antibiotics are so named because they have a common β-lactam ring structure (Murray *et al.,* 2012). Examples are penicillins, cephalosphorins, cephamycins, carbapenems, monobactams, and β-lactamase inhibitors. β-lactam antibiotics act as bactericidal agents. Bacterial cell wall forms by chain of alternating N-acetylglucosamine and N-acetylmuramic residues. In the final step of cell wall synthesis transpeptidase catalysed cross-linking of polypeptidoglycan chain and cell wall form. Binding of β-lactams drugs to the bacterial transpeptidase cause hydrolysis of β-lactams bond thereby inhibiting the final transpepdation step of cell wall synthesis. Thus β-lactamsbind to specific penicillin binding proteins (PBPs) 1, 2 and 3 in the bacterial cell wall results in cell wall lysis, disruption of cell shape and inhibition of cell division respectively.Other antibiotics under this category are vancomycin, daptomycin and bacitracin.

Antibioticsthat inhibit protein synthesis

These antibacterial agents inhibit protein synthesis either by binding to 30s ribosomal subunit or 50s ribosomal subunit (Neu and gootz 1996, Murray *et al.,* 2012). Aminoglycosides such as streptomycin, neomycin and kanamycin irreversibly bind to 30s ribosomal proteins (bactericidal). Tetracyclines such as tetracycline,

doxycycline and minocycline also inhibit protein synthesis by reversibly binding to 30s ribosomal subunits (bacteriostatic).They block tRNA binding to 30s ribosome-mRNA complex. Chloramphenicols bind peptidyltransferase component of 50s ribosome, blocking peptide elongation (bacteriostatic). Macrolides such as erythromycin, azithromycin and clarithromycin reversibly bind to the 23s ribosomal RNA of the 50s ribosomal subunit, which blocks peptide elongation (bacteriostatic).Clindamycin binds to the 50s ribosome, blocks peptide elongation; Inhibits peptidyl transferase by interfering with binding of amino acid-acyl-tRNA complex.

Antibiotics that inhibit nucleic acid synthesis

Quinolonesinhibit DNA gyrases or topoisomerases required for supercoiling of DNA. Rifampicin binds to DNA-dependent RNA polymerase and inhibits the initiation of RNA synthesis (Neu and gootz, 1996).

Antibiotics that inhibit metabolic pathways

Sulfonamides and Dapsone compete with p-aminobenzoic acid (PABA) preventing synthesis of folic acid. Trimethoprim inhibits dihydrofolate reductase preventing synthesis of folic acid (Murray *et al.,* 2012).

Bacterial resistance mechanisms to antimicrobial agents

Bacteria have found ways to overcome the growth-inhibitory properties of the antimicrobial agents and gain resistance towards that. Bacterial pathogens that are resistant to a single drug quite frequently become resistant to multiple antimicrobial agents and are considered potentially untreatable "superbugs" (Morris *et al.,* 1998, Levy, 2005). The general mechanisms that are responsible for bacterial resistances to antimicrobial agents are (a) enzymatic inactivation of drugs (b) drug target modification(c) decreased membrane permeability and (d) active efflux of drugs (Kumar and Varela 2013). Bacteria which harbour these drug resistant mechanisms can survive, or even actively grow in the presence of a given antimicrobial agent.

Enzymatic inactivation of drugs

Bacteria have evolved several mechanisms of drug inactivation such as the enzymatic hydrolysis of antibiotics, group transfer and the redox process (Davies 1994). Certain bacteria produce the enzyme β-lactamases that hydrolyze the β-lactam ring of penicillins. β-lactamases such as TEM, SHV (sulphydril variable active site) can hydrolyze a broad range of extended spectrum cephalosporins, and these are collectively called extended spectrum β-lactamases, or ESBLs (Philippon *et al.,* 1989). ESBLs hydrolyze a wide range of cephalosporins such as ceftriaxone, ceftazidime, cefotaxime and aztreonam, but do not hydrolyze cephalomycins and carbapenems (Bradford, 2001). Other hydrolysing enzymes are esterases and epoxidases which can hydrolyse the antibiotics macrolides and fosfomycin respectively.

Another mechanism of antibiotic inactivation is enzyme mediated structural alteration of the drug via transfer of a functional group such as an acyl, ribosyl, phosphoryl or thiol group (Wright, 2005). This results in change in structure of the antibiotics which make it unable to bind to the target. Redox process is a less common mechanism which involves flavin-dependent monoxygenase enzyme TetX. This enzyme transfers a single hydroxyl group to tetracycline and makes it less able to sequester Mg+ ions which are critical for binding of tetracycline to its bacterial target (Yang *et al.,* 2004).

Drug target modification

Bacteria have developed various means to alter and modify the molecular targets of antimicrobial agents. Modification of the drug target makes the drug unable to bind to its specific site. For example; DNA gyrase is a target of the drug quinolone. Modification in DNA gyrase makes the drug unable to bind to its target (Fabrega *et al.,* 2009). Other examples of drug targets are prokaryotic ribosome, a target for protein synthesis inhibitors; RNA polymerase, a target of rifampin (Spratt, 1994; Drapeau *et al.,* 2010), penicillin binding protein (PCB), a target of β-lactam antibiotics (Neu and gootz 1996, Fisher *et al.,* 2005).

Decreased membrane permeability

The drug molecules can penetrate the bacterial outer membrane either by diffusion through porins or by diffusion through the bilayer. Drug resistance in a bacterium may arise due to the inability of the drug to gain entry into the cell where the drug targets are located (Kumar and Schweizer, 2005). Bacteria having lipopolysaccharide (LPS) moieties show resistance to erythromycin, roxithromycin, clarithromycin and azithromycin in Gram-negative bacteria such as strains of *Pseudomonas aeruginosa*, *V. cholerae* and *S. enterica*, especially in immune-compromised patients (Strateva and Yordanov, 2009; Kitakoa *et al.,* 2011; Monack, 2012). Another drug resistance mechanism is through reducing the number of porin channels which allow small molecular weight molecules, such as antimicrobial agents, to gain cellular entry (Pages *et al.,* 2008).

Active efflux of drugs

Drug efflux pumps are located on the cytoplasmic or plasma membranes of bacteria and prevent drug accumulation inside the bacterial cells, thereby conferring resistance (Levy, 2002). There are two main categories of active efflux pump; called the primary active transporters which use the energy from hydrolysis of ATP to actively efflux drugs from cells (Higgins, 2007). The second category is called secondary active transporters that use an ion gradient for transportation of drugs across the membrane (Poolman and Konings, 1993; Kramer, 1994)

Development and spread of antimicrobial resistance

Development and spread of antimicrobial resistance due to the use of antimicrobial agents in both humans and animals has become a global public health concern (Heuer *et al.,* 2009). Unregulated use and misuse of antimicrobials allows the less susceptible bacteria to survive and adapt to the low drug concentration and develop resistance (Levy, 1998). Antimicrobial resistance developed in one ecological niche can spread to another such as use of antimicrobials in aquaculture can lead to occurrence of antimicrobial resistance in human environment. This is because several antibiotics which are classified by World Health Organization (WHO) as critically important for the treatment of human disease are also used in aquaculture (Heuer *et al.,* 2009). Bacteria may be intrinsically resistant to different antimicrobial agents. Intrinsic resistance refers to the existence of genes in bacterial genomes that could generate a resistance phenotype (Davies and Davies 2010). Bacteria can acquire resistant genes by various means and transfer it to a new bacterium with the help of mobile genetic elements, such as plasmids and transposable elements (Romero *et al.,* 2012). Viruses can also transfer resistance genes occasionally by extracting genes from one bacteria and injecting it to a new one (Levy, 1998).

Antimicrobial resistance in aquaculture

In aquaculture, antibiotics are used for the treatment of various infectious diseases. Apart from treatment antibiotics are also used as prophylactic measures and as growth promoter. During administration of antibiotics several factors need to be considered such as safety of the target animal, safety of the fish product, integrity of the environment and safety of the person administering it (Serrano, 2005). But the unauthorised and unregulated use of antimicrobial agents has led to the development of antimicrobial resistant fish pathogens as well as other aquatic bacteria. The resistance has been observed in a number of bacterial species including *Aeromonas hydrophila, Asalmonicida Yersinia ruckeri, Edwardsiella tarda, E. icttaluri, Vibrio anguillarum, V. salmonicida, Photobacterium damselae* (De Paola, Peeler and Rodrick 1995). As the time passes the number of resistant bacteria is increasing day by day.

Aeromonas salmonicida, the causative agent of furunculosis disease in fish from cold and temperate areas easily develops resistance against antimicrobials. Recent evidence shows multi resistant strains of *A. salmonicida* from different parts of the country that carry transferable resistant plasmid (Romero *et al.,* 2012). Similar cases of other multi resistant bacterial pathogens have been reported from different countries. Multiresistant strains of *Vibrio harveyi* resistant to chloramphenicol, cotrimoxazole, erythromycin and streptomycin caused mass mortality in *Penaeusmonodon* larvae as reported by Karunasagar *et al.,* (1994). From these pathogens, the resistance genes can reach the human pathogens either directly or indirectly. The indirect means of dissemination is through horizontal gene transfer for example, transfer of resistance genes from *Aeromonas* species to *Escherichia coli*. Direct transfer of resistance genes is through certain bacteria which are common pathogens of aquatic animals as well as human e.g *Vibrio* species (Heuer *et al.,* 2009). Due to the emergence of resistant bacteria antibiotics have become less effective in controlling infectious diseases. Only a few antimicrobial drugs have been approved by the U.S. Food and Drug Administration (USFDA) for use in aquaculture (Table 1).

The consequences of antimicrobial resistance in bacteria that infect human are- increased number of infections, increased frequency of treatment failures and increased severity of infection (Kruse and Sørum1994). Apart from the human health risk from antimicrobial resistant bacteria the residues of antimicrobials also possess a threat to human health causing allergy, toxicity etc. Some of the antibiotics can accumulate in the flesh of shrimp and the concentration gradually increases with the subsequent use of antibiotics. The antibiotic residues represents potential health hazard and also affects the trade prospects. Therefore, the shrimp health management should focus mainly on disease prevention rather than disease control. Keeping these points in view coastal aquaculture authority (CAA) has banned 20 antibiotics from using in shrimp aquaculture. Avoiding or reducing the use of antimicrobial agents will also improve the environmental integrity and reduce cost of farm management (Table 2).

There are so many pros and cons of using antibiotics but major issues lies with the indiscriminate use. We need to find other safer ways of combating fish diseases. There are several alternative methods which can be used:

Probiotics, prebiotics and synbiotics
Immunostimulants
Bacteriophage therapy
Vaccine
RNA interference
Quorum sensing inhibition

Probiotics, prebiotics and synbiotics

Because of the problems lies with the antibiotic use and numerous beneficial effect of probiotics now there is huge increase in the research finding the best and useful probiotics for the use in the aquaculture. A variety of feed additives, including probiotics and prebiotics having beneficial effects to the host was used in aquaculture as prophylactic measure to combat diseases, they are also beneficial as supplements, to improve growth increasing the size and weight gain, and in some cases, act as an alternative antimicrobial compounds (Irianto and Austin, 2002) as well as to stimulate immunity response of the host. Probiotics are the live microbial feed additives that modulate gastrointestinal microbial communities of the host whereas Prebiotics are non-digestible forage additives stimulate the activity or abundance of beneficial gastrointestinal bacteria. Both of these have received widespread attention, showing the improved production, health and disease resistance of aquatic animals (Dimitroglou *et al.,* 2011).When probiotics and prebiotics are used together to an animal so that the probiotic bacteria can grow easily with the help of the probiotics, this system known as the synbiotic.

Probiotics interact with the immune cells such as mononuclear phagocytes (monocytes, macrophages) and polymorphonuclear leukocytes (neutrophils), natural killer (NK) cells, to enhance innate immune responses. Some probiotics can increase the number of erythrocytes, granulocytes, macrophages and lymphocytes in various fishes (Irianto and Austin, 2002; Irianto and Austin, 2003; Kim *et al.,* 2006; Kumar *et al.,* 2008; Nayak *et al.,* 2007). There is report of increase in different innate immune system upon administration/intake of probiotics i.e. In tilapia (*Oreochromis niloticus*) a two weeks feeding of *Lactobacillus rhamnosus* significantly stimulates phagocytosis (Pirarat *et al.,* 2006), Stimulation of lysozyme activity in rainbow trout was observed after two weeks feeding with Kocuria sp. SM1 (Sharifuzzaman and Austin, 2009) and *Carnobacterium divergens* B33 (Sakai *et al.,* 1995), Probiotics such as *L. rhamnosus*, *E. faecium* and *B. subtilis* are found to up regulate the pro-inflammatory cytokines such as IL-1b1 and TGF b in the spleen and head kidney of the *O. mykiss* (Panigrahi *et al.,* 2007), Sharifuzzaman and Austin(2009) also reported significantly higher anti-protease activity in *O. mykiss* within two weeks of the completion of probiotic species *Kocuria*. There are numerous numbers of prebiotics are available for the use and they are broadly classified into two categories i.e. oligosaccharides and polysaccharides. The immunomodulatory activity of prebiotics is mediated through direct interactions with their receptors (pattern recognition receptors; PRR), such as b-glucan receptors and dectin-1 receptors that are expressed on macrophages (Brown *et al.,* 2002). This ligand receptor interaction activates signal transduction molecules, such as NF-kB, that stimulate immune cells (Yadav *et al.,* 2002). Also the prebiotics helps by giving direct nutrition to the probiotic bacteria's. Some of the examples for the oligosaccharides are Fructooligosaccharides (FOS), Mannan oligosaccharide (MOS), Immunogen® (a commercial product containing two prebiotics, MOS and b-glucan), Galactooligosaccharide (GOS), Arabinoxylan-oligosaccharide (AXOS) etc. Examples of polysaccharides are Inulin, b-glucan, chitin/chitosan etc.

Immunostimulants

Immunostimulants comprise a group of biological and synthetic compounds that enhance the nonspecific cellular and humoraldefence mechanism (Maqsood *et al.,* 2011). Immunustimulants mainly activates the white blood cells which plays major role in the

fish defence mechanism. It may be chemical, drug or naturally occurring compound that elevates the nonspecific defence mechanisms or the specific immune response of the host and may be given alone to activate non-specific defence mechanisms as well as increasing a specific immune response. Such substances may also, but not necessarily, render animals more resistant to infectious diseases and reduce the risk of disease outbreaks if administrated prior to situations known to result in stress and impaired general performance (e.g. handling, change of temperature and bad environmental condition, weaning of larvae to artificial feeds) or prior to expected increase in exposure to pathogenic microorganisms and parasites (e.g. spring and autumn blooms in the marine environment, high stocking density). In addition, aquaculture may benefit from the use of such immune-stimulants when they are used prior to, and during, developmental phases when the organisms are particularly susceptible to infectious agents (such as fry and fingerling for fishes and larval stages for shrimps or prawns) (Raa, 1996).

The chemical nature nature of different immunostimulant available are mentioned (Raa, 1996). Structural elements of bacteria (lipopolysaccharides (LPS), lipopeptides, capsular glycoproteins and muramylpeptides). Various β-1,3-glucan products from bacteria (Curdlan) and mycelial fungi (Krestin, Lentinan, Schizophyllan, Scleroglucan, SSG, VitaStim)

β -1,3/1,6-glucans from the cell wall of baker's yeast (MacroGard, Betafectin)

Complex carbohydrate structures (glycans) from various biological sources including seaweed Peptides present in extracts of certain animals or made by enzymatic hydrolysis of fish protein Nucleotides, and Synthetic products (Bestatin, muramylpeptides, FK-156, FK-565, Levamisole).

Immunostimulants gives so many health benefits like it reduces the fish mortality due to the opportunistic pathogens, prevents different bacterial, viral or parasitic diseases, it enhances the diseases resistance of the young fishes by elevating the non-specific immune system and it can also excel the efficacy of other antimicrobial substances i.e. vaccines. Some examples of efficacy of immunostimulants with injection of b-1,3/1,6-glucan into fish produces very effective resistance to several bacterial diseases (Robertsen *et al.,* 1990), addition of levamisole HCl to the diet of *Oreochromis niloticus* significantly enhanced both cellular and humoral innate immune responses and increased resistance to *A. hydrophila* infection although they had a little growth promoting activity.

While addition of vitamins C and E to *Oreochromis niloticus* higher than the requirements needed for growth lead to maximum growth compared to levamisole but little enhancement of the immune response as well as resistance to *A. hydrophila* infection (Abdelkhalek *et al.,* 2008). β-1,3/1,6-Glucans have proved to enhance the biological activity of shrimp hemocytes and to improve growth, survival rate and feed conversion efficacy under experimental conditions (Sung *et al.,* 1994; Song and Hsieh, 1994; Sung *et al.,* 1996).

Bacteriophage therapy

Considering the negative impact of antibiotics and other chemotherapeutants, biological control of pathogens would be a very useful strategy to combat diseases (mainly bacterial diseases). Historically, they were discovered by Twort (1915) and Dâ€™ Herelle (1917) in the preantibiotic era. Now it has been proved that phage therapy decline the bacterial population below threshold number to a level where the host defence can take care of remaining bacteria. There are two types of

bacteriophage reproduction occurs in the bacteriophages: (1) Lytic and (2) Lysogenic, in lytic cycle the virus attaches to a host cell and injects its nucleic acid into the cell, directing the host to produce numerous offsprings. These are then released by bursting of the cell, again enters to other cells and the cycle continues.

In lysogenic cycle nucleic acid of the virus becomes part of the host genome and reproduces genetic material in the host cell using the host machinery. In general, the replication of phage in the bacterial cell occurs in five steps: adsorption, penetration of genetic material, replication, maturation and lysis.

Lysogenic bacteriophages incorporate into the genome of the bacterium rather than being lytic. These lysogenic phages are poor candidates for therapy as they do not provide the rapid growth in phage numbers unlike lytic phages. Therefore, lytic phages are good candidate for therapeutic as well as prophylactic use against pathogenic bacterial fish diseases. During the lytic life cycle the number of phages released (burst size) after lysis varies from 50-409 new phage particles (Yang *et al.,* 2010).

Phage control of the disease caused by *Pseudomonas plecoglossicida* in *Plecoglossus altivelis* was demonstrated by Park *et al.,* 2000**.** Park and Nakai (2003), demonstrated the efficacy of Bacteriophage control of *Pseudomonas plecoglossicida* infection in ayu (*Plecoglossus altivelis*)**.** Karunasagar *et al.,* 2005 showed the efficacy of bacteriophages to control luminous bacterial disease in shrimp hatcheries by reducing the number of *V. harveyi* counts in water and in larvae and tremendously improved larval survival. A double stranded DNA bacteriophage of *Vibrio harveyi* was isolated from shrimp farm water which shown efficacy of reducing the luminous bacterial disease to great extent (Vinod *et al.,* 2006). Protective effect (100% survival). After 6 h of phage treatment host bacterium concentration reduced (less than 10-3 cfu ml^{-1}) in the sera, gill, liver and kidney against *Flavobacterium columnare* in *Clarius batracus* (Prasad *et al.,* 2011).

Phage therapy against *vibriosis* shows good result with elimination of the disease but when the disease is in advanced stage efficacy of phage reduces (Diaz and Morales, 2013). Bacteriophages can be administered to the fishes by different routes i.e. through water bath, oral, injection etc. Various researchers found that no phage neutralizing antibodies were found in phage treated fish (Park and Nakai, 2003). This demonstrate the potential of specific phages to reduce bacterial diseases, with a resulting no negative effect on fish body. There is the need for further investigations of the possibilities in using phages as an alternative to antibiotic treatment of different fish diseases in aquaculture.

Vaccine

Prevention and control of fish diseases in Aquaculture is a high priority in aquaculture industry. Unlike treating human or other animal diseases, few drugs are available for controlling diseases in fish. Therefore, Control of different diseases in aquaculture and fish farms relies on a combination of good management practices and use of the few approved and commercially available drugs and vaccines for prevention of infections. The immune system is to protect the fish from bacteria, virus, or any foreign antigen (protein).

Table.1 Drugs approved by USFDA for use in aquaculture

Immersion	Injection	Medicated Articles/Feeds
Chloramine-T	Chorionic gonadotropin	Florfenicol
Formalin		Oxytetracycline dihydrate
Hydrogen peroxide		Sulfadimethoxine/ormetoprim
Oxytetracycline hydrochloride		
Tricainemethanesulfonate		

Table.2 List of antibiotics and other pharmacologically active substances banned for using in shrimp aquaculture by CAA

Sl. No.	Antibiotics and other Pharmacologically Active Substances
1.	Chloramphenicol
2.	Nitrofurans including: Furaltadone, Furazolidone, Furylfuramide, Nifuratel, Nifuroxime, Nifurprazine, Nitrofurantoin, Nitrofurazone
3.	Neomycin
4.	Nalidixic acid
5.	Sulphamethoxazole
6.	Aristolochiaspp and preparations thereof
7.	Chloroform
8.	Chlorpromazine
9.	Colchicine
10.	Dapsone
11.	Dimetridazole
12.	Metronidazole
13.	Ronidazole
14.	Ipronidazole
15.	Other nitroimidazoles
16.	Clenbuterol
17.	Diethylstilbestrol (DES)
18.	Sulfonamide drugs (except approved Sulfadimethoxine, Sulfabromomethazine and Sulfaethoxypyridazine)
19.	Fluroquinolones
20.	Glycopeptides

Therefore, before attempting any vaccination strategy, it is important to determine when the immune system and immune cells are both morphologically and functionally mature (Toranzo *et al.*, 2009). Fish immunology has a more recent history than human and veterinary immunology but the techniques used are similar. However, methods of administering vaccines to fish differ and are dependent upon species, pathogen, temperature and environment (Anderson, 1974). There are different types of vaccines available for treating fishes i.e. 1. Killed vaccine 2. Live attenuated vaccine 3. Recombinant vaccine. Under recombinant vaccine there are so many types of vaccine

i.e. a. recombinant subunit vaccine, b. recombinant attenuated vaccine, and c. recombinant vectored vaccine available. The ideal vaccine formulation for the fisheries sector is polyvalent vaccine, which protects simultaneously against the majority of the fish pathogens to which a particular fish species is susceptible (Busch, 1997). Depending upon fish species and temperature, vaccination must be performed within a certain minimum period before the risk of their exposure to pathogens. In addition to temperature, stress caused by environments, crowding, handling and transport, can induce immune suppression and be a limiting factors for vaccine efficacy (Sommerset *et al.,* 2005). Fish are commonly immunized by three procedures: intraperitoneal injection (ip), immersion in a diluted vaccine solution (short or long bath), or oral administration of the vaccine (Komar *et al.,* 2004). All this different mode of vaccine delivery methods have its own pros and cons most effective method is vaccine delivery by injection but most widely used and practical vaccine delivery method in fisheries sector is immersion, oral is also a good option for vaccine delivery but intestinal degradation of vaccine and feed acceptability is big concern.

First commercially available fish bacterial vaccine were against enteric red mouth disease causes by *Yersinia ruckeri* and *vibriosis* commercialised in the USA in the late 1970s (Evelyn *et al.,* 1997). The first viral vaccine for fish was produced by a Czechoslovakian company (Bioveta) in 1982. The vaccine was against a carp rhabdovirus, causing spring viremia of carp (SVC) in salmonids and was based on two inactivated strains of SVC virus emulsified in oil and administered by injection. Till date no commercial vaccine against parasitic diseases are available but so many experimental vaccines are there. Currently, there are only 14 licensed fish vaccines in U.S., including 11 killed bacterial, 1 killed viral, and 2 live attenuated bacterial prophylactics. Vaccination in the fishes stars with mainly killed vaccines and attenuated vaccine but both of this type of vaccines are having disadvantages like poor immunogenic and pathogenicity reversion in the case of attenuated vaccines. So new generation vaccines like recombinant vaccines are coming up which are showing good results in experimental conditions and believed to be the next generation vaccine. Most of these recombinant vaccines are based on only the virulent gene or the protein expressed. Some of the recombinant vaccines which are licensed in different countries are infectious hematopoietic necrosis virus (IHNV) form recombinant G protein, licensed in Canada; spring viremia of carp virus (SVCV) from recombinant G protein in baculovirus expression system, licensed in Belgium; infectious salmon anemia virus (ISAV) from recombinant hemagglutinin esterase protein, licensed in Chile; infectious pancreatic necrosis virus (IPNV) from VP2 and VP3 capsid proteins and VP2 protein (Trivalent SRS/ IPNV/Vibrio) licensed in Canada and Chile, respectively (Dhar *et al.,* 2014). Till date most of the vaccine that have been commercialized is for the cold water high value fishes very few vaccines are available commercially for tropical fishes i.e. vaccine against Grass carp reovirus in China and KHV in Israel (Tian *et al.,* 2013).

Aquaculture industry is rapidly growing and vaccination for prevention of fish diseases will play a major role in the coming future. Till date only some vaccines are available that to for some important bacterial and viral diseases, till date no commercial fungal or parasitic vaccines are available. There are so many hurdles in vaccine development for the aquatic environment such as high pathogenic variation, cost effectiveness of the vaccine, lack of knowledge about fish immune system,

problem related to vaccine administration etc. But laboratory experiments are showing hope for the effective vaccine development which may in the near future.

RNA interference

The phenomenon of RNA interference (RNAi) was first observed in the late 1980s and has since evolved into a powerful laboratory technique for potent and specific gene silencing (Caplen *et al.,* 2004, Leung and Whittaker 2005). The presence of a double-stranded RNA (dsRNA) in eukaryotic cells triggers this post-transcriptional gene-silencing mechanism, leading to a sequence-specific degradation of the target mRNA (Krishnan *et al.,* 2009). Turning off the expression of a gene is possible at two levels 1. Transcriptional gene silencing and 2. Post transcriptional gene silencing. Among the many applications of RNAi technology therapeutic silencing of virulent genes has received maximum attention. There are 3 broad stages in developing an RNAi based therapy: design, synthesis and delivery. In each of these broad stages, one has to consider a number of specific details in order to develop an efficient RNAi-based therapy (Krishnan *et al.,* 2009). The post-transcriptional activity of the RNAi machinery to degrade cytoplasmic RNA in a sequence-specific manner is the key to its antiviral function in invertebrates. For effective RNAi treatment identification of target gene is very much important. After identification of the gene of interest we can go for different strategies of RNAi treatment i.e. 1. siRNA -These are designed after the natural Dicer cleavage products. The in vitro synthesized siRNAs are 21 nucleotide long with 2neocleotide 3' overhangs (Elbashir *et al.,* 2001). The key advantage with these molecules is that they avoid overloading of cellular elements and result in fewer non-specific side effects, 2. shRNA -shRNA designed after pre-miRNAs having a small apical loop and 3' UU overhang and are designed as plasmids that express anti-viral short hairpin RNA from a pol III promoter (Paddison *et al.,* 2002). shRNAs are translocated from the nucleus to the cytoplasm with the help of Exportin-5 and further processed in the cytoplasm by cellular Dicer to form functional siRNAs. They can be used for long-term silencing, inducible expression and tissue specific delivery, 3. lhRNA - These are similar to shRNAs except that they are larger and induce RNAi by intracellular expression of long hairpin RNAs. 4. miRNA - They constitute the second generation of RNAi-mediating constructs based on the structure of existing miRNA (Stegmeier *et al.,* 2005). This RNAi technology is getting very much focus in the treatment of viral diseases and mainly the shrimp diseases as we know that shrimps don't contains adaptive immunity so vaccination to the shrimps is not possible. RNAi based vaccines experimentally show good results in controlling diseases like WSSV, YHV, IHHNV etc. So more research is needed before commercialization of the technology and RNAi technology is having a very promising future in the field of therapy.

Quorum sensing inhibition

Quorum sensing is a mechanism in which bacterial population as a whole coordinate's gene expressions in response to their population density by producing, releasing and recognizing small signal molecules called auto inducers (Suga and Smith 2003, Defoirdt *et al.,* 2004). Quorum sensing regulates various phenotypes such as biofilm formation (Merritt *et al.,* 2003, Parsek and Greenberg 2005), bioluminescence (Waters and Bassler 2005, Bodman *et al.,* 2008), virulence factors (Mellbyeand Schuster, 2011) and swarming (Shrout *et al.,* 2006) which have been shown its contribution towards bacterial virulence.

Since virulence traits of bacteria are controlled by quorum sensing, disruption of quorum sensing has been suggested as a new treatment strategy to control pathogenic bacteria (Finch *et al.,* 1998) in the field of aquaculture and animal husbandry. Quorum quenching (QQ), the disruption of Quorum sensing, can be performed by small antagonists molecules (Givskovm *et al.,* 1996) or signal degrading enzymes (Roy *et al.,* 2011). Many microorganisms can produce enzymes which can degrade N-Acyl homoserinelactones (AHLs) which plays major role in the quorum sensing (Christiaen *et al.,* 2011). The Quorum quenching enzymes produced by microorganisms were classified into three major types according to their enzymatic mechanisms: AHL lactonase (lactone hydrolysis), AHL acylase (amidohydrolysis) and AHL oxidase and reductase (oxidoreduction). These enzymes can degrade AHLs, and as a results of this they can prevent pathogenic bacteria from producing virulence factors, forming biofilms thus reducing virulence. So the Quorum quenching microorganisms can be used as potential quenchers of quorum-sensing-regulated functions in pathogenic bacteria (Kalia, 2013). This method of bacterial inhibition can be very effective for the aquaculture industry. Cam *et al.,* (2009a) reported isolation of two different mixtures of AHL degrading enrichment cultures (ECs) from European sea bass [*Dicentrarchus labrax*, EC5(D)] and from Asian sea bass [*Lates calcarifer*, EC5(L)]. These novel ECs can act as quorum quencher and as probiotics in aquaculture system (Cam 2009b). Nhan *et al.,* (2010) investigated the effect of EC5(D) and EC5(L) on *Macrobrachium rosenbergii* larval performance against *vibrio harveyi*, which shows encouraging results. In-vitro quenching of *Edward seillatarda* AHLs by *Tenacibaculum* sp. strain 20J (Romero *et al.,* 2014). Still this Quorum quenching of bacteria is in experimental phage but if we can use it in a holistic approach then it can be good candidate treatment method in the aquaculture industry.

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How to cite this article:

Nilav Aich, Naznin Ahmed and Anirban Paul. 2018. Issues of Antibiotic Resistance in Aquaculture Industry and Its Way Forward. *Int.J.Curr.Microbiol.App.Sci.* 7(08): 26-41.
doi: https://doi.org/10.20546/ijcmas.2018.708.004