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Antibacterial Resistance in African Catfish Aquaculture: a Review

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Abstract

Antibacterial resistance (AR) is currently one of the greatest threats to mankind as it constitutes health crisis. Extensive use of antibacterial agents in human and veterinary medicine, and farm crops have resulted in emergence of antibacterial-resistant organisms in different environmental settings including aquaculture. Antibacterial resistance in aquaculture is a serious global concern because antibacterial resistance genes (ARGs) can be transferred easily from aquaculture setting to other ecosystems and the food chain. African catfish (ACF) aquaculture has increased at a phenomenal rate through a continuous process of intensification, expansion and diversification. Risk of bacterial diseases has also increased and consequently there is increased use of antibacterial agents for treatment. Antibacterial resistance in ACF aquaculture has huge impact on the food chain and thus represents risk to public and animal health. In "one health" approach of curbing AR, knowledge of the sources, mechanisms and magnitude of AR in ACF aquaculture and its potential impact on the food chain is important in designing and prioritizing monitoring programs that may generate data that would be relevant for performing quantitative risk assessments, implementation of antibacterial stewardship plans, and developing effective treatment strategies for the control of ACF disease and reducing risk to public health. This review provides insight on the sources, mechanisms, prevalence and impact of antibacterial resistance in ACF aquaculture environment, a setting where the impact of AR is neglected or underestimated.

Keywords: African catfish, aquaculture, antibacterial resistance, piscine

Introduction

Aquaculture is the fastest growing food industry in the world, providing approximately 50% of animal protein required by individuals and employment opportunities for the growing population (FAO/OIE/WHO, 2006; Rodgers and Furones, 2009; Bostock *et al*., 2010; Khairnar *et al*., 2013). Intensification of fish results in explosion of bacterial organisms in aquaculture and the need for antibacterial agents to control and/or treat bacterial infections (Ishida *et al*., 2010; Defoirdt *et al*., 2011; Jiang *et al*., 2013). African catfish (ACF), *Clarias gariepinus*, also called African sharptoothed catfish, African magur, Barbel or Skerptand barber is freshwater finfish which originated in Africa and has been introduced into the Middle-east and Eastern Europe (DeMoor and Bruton, 1988; Ibrahem and Mesahly, 2010; Hamid *et al*., 2012; Anyanwu *et al*., 2015). The ACF is the most widely farmed freshwater finfish in Africa. African catfish aquaculture has helped in the provision of animal protein and employment in low and medium income food deficient countries (LMIFDCs) especially African countries, where many obtain <15gm daily animal protein intake (DAPI) far less than 35gm DAPI recommended by the WHO/FAO (FAO, 2000; FAO/OIE/WHO, 2006; Ekine *et al*., 2012). Attributes of ACF that encourage its increased farming include: adaptability to tropical environment, suitability for monoculture and polyculture with other freshwater fish species, tolerance to high stocking density, ability to withstand handling stress, disease resistance, high fecundity, high weight gain, palatability and nutritional quality, low production cost and less bias when compared with other animal protein sources (Haylor, 1991; Musefiu *et al*., 2011; Kumar *et al*., 2012; Anyanwu *et al*., 2015). ACF aquaculture has increased at a phenomenal rate in the last decennium (Olatoye and Basiru, 2013; Anyanwu *et al*., 2014; Ibrahem *et al*., 2015). The rapid increase in ACF farming is due to the decline in wild/feral fish population as a consequence of overfishing, drying up of natural water bodies due to climate change, increasing population, and pollution of water bodies by oil spills and other anthropogenic contaminants (FAO, 2008; Clausen and York, 2008; Cruz *et al*., 2012; Ibrahem, 2015).

Majority of the countries where ACF is farmed are developing/less industrialized nations (i.e. LMIFDCs) where the use of antibacterial agents is not regulated, a factor that may facilitate the development of antibacterial resistance (AR) (FAO/OIE/WHO, 2006; Cabello *et al*., 2013; Laxminarayan *et al*., 2013). This sort of practice contrasts that in finfish aquaculture in developed countries, where few regulated antibacterial agents are allowed for use (Armstrong *et al*., 2005; FAO/OIE/WHO, 2006; Rodgers and Furonone, 2009; Cabello *et al*., 2013). The warm humid tropical climate of these countries also facilitates the development and spread of AR (Okeke and Edelman, 2001). Many antibacterial drugs in the same class as those used in human medicine are used in finfish aquaculture (FAO/OIE/WHO, 2006; Laxminarayan *et al*.,

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2013; Canica *et al*., 2015). The major concern surrounding the use of antibacterial agents in aquaculture is considered to be the potential to favour the development of a reservoir of antibacterial resistance genes (ARGs) that may be eventually transferred to clinically relevant bacteria, especially via the food chain (FAO/OIE/WHO, 2006; Miranda *et al*., 2013). Mobile genetic elements (MGE) (mobilomes) of bacterial genomes (such as plasmids, transposons, insertion sequences, genomic islands and phages) facilitate the spread of ARGs by horizontal transfer in aquaculture environments and subsequently by lateral transfer to other environmental settings (Canica *et al*., 2015). Non-mobile genetic elements such as integrons (especially the class 1 integrons) also carry gene cassettes, transposons and plasmids containing ARGs (Jacobs and Chenia, 2007; Patridge *et al*., 2009; Ndi and Barton, 2011). The global climatic change may worsen the problem of AR as it may affect the emergence and dynamics of new and existing pathogens and consequently the use of antibacterial agents and prevalence of AR (Tirado *et al*., 2010; Miranda *et al*., 2013). Antibacterial-resistant organisms (AROs)/ARGs emanating from ACF aquaculture can spread to other parts of the world through international travel and importation/exportation of food, thereby changing the dynamics of AR globally (Okeke and Edelman, 2001; Canica *et al*., 2015). Indeed, different types/classes of antibacterial drugs critical to human medicine are used in aquaculture, a situation that may have facilitated AR in ACF aquaculture (Heuer *et al*., 2009; Defoirdt *et al*., 2011; Cabello *et al*., 2013).

The "one health" approach recently proposed by the WHO in monitoring and devising strategy for curbing AR in any ecological niche requires that the sources, route of spread and impact on the food chain be taken into consideration (WHO, 2014). Thus, knowledge of the molecular and genetic mechanisms of phenotypic AR in ACF aquaculture environment, and the impact on the food chain is important to design and prioritize monitoring programs that may generate data that would be relevant for performing quantitative risk assessments, implementation of antibacterial stewardship plans, and developing sound treatment strategies for the control of ACF disease and reducing the risk to public health. This review provides information on the sources, molecular and possible genomic mechanisms, and prevalence of phenotypic resistance to β-lactam, aminoglycoside, quinolone, tetracycline, glycopeptide, nitrofuran, potentiated sulphonamide and phenicol that has been reported to occur in ACF aquaculture environments, and the impact of the resistance on the food chain and public health.

Sources of antibacterial resistance in African catfish aquaculture environment

Although AR is a natural phenomenon for adaptation (i.e., innate resistance) (Moellering and Krogstad. 1979; Livermore, 2003; Tenover, 2006), bacterial organisms develop acquired resistance by mutation of genes and/or acquisition of ARGs through horizontal transfer (transformation, conjugation and transduction) following exposure to sub-therapeutic/low doses of antibacterial agents (Wegener *et al*., 1999; Okeke and Edelman, 2001; Livermore, 2003; Waters *et al*., 2011; Vaz-Moreira *et al*., 2014). Exposure of bacteria to sub-therapeutic doses of antibacterial agents causes use (exposure) selection pressure, acquisition of ARGs and exhibition of resistance mechanisms by the organisms so as to counter or thwart the effects of antibacterial agents in the environment (Tenover, 2006; Laxminarayan *et al*., 2013). The use of substandard/counterfeit drugs (i.e. low concentrations) in ACF aquaculture as often the case in developing countries facilitates the development of AR (Okeke and Edelman, 2001; Laxminarayan *et al*., 2013). Low concentrations of drugs results in selection for resistance to other drug classes while target strains remain susceptible to the drug; this occurs because of random mutagenesis and such resistance is irreversible (Cogliani *et al*., 2011).

Several factors contribute towards the emergence of AR in an ACF aquaculture environment. The major trigger of AR in ACF aquaculture is the routine use of antibacterial agents in prevention of bacterial infections (prophylaxis), treatment of infected fish both poorly and adequately diagnosed (therapeutics) and treatment of infected fish in a population of healthy fish (metaphylaxis) (Cabello, 2006; Smith, 2008; Heuer *et al*., 2009; Vaz-Moreira *et al*., 2014). From its inception the ACF aquaculture industry, like any other finfish aquaculture, has used antibacterial agents as means to mitigate bacterial infections (Armstrong *et al*., 2005; Cabello *et al*., 2013). Lowered host defenses associated with culture at high density with suboptimal hygiene in enclosures in close proximity led to heavy reliance on antibacterial agents (Cabello *et al*., 2013). The absences of biosecurity and vaccination programs, which are either not effectively applied or available, coupled with the ban of malachite green in aquaculture may also have exacerbated the use of antibacterial agents in ACF aquaculture (Armstrong *et al*., 2005; Jiang *et al*., 2013; Anyanwu *et al*., 2014). Antibacterial agents are administered to individual fish either orally with feed or water, injected directly intramuscularly, or immersed in drug solution by dipping for a short period of time or bathing for a long duration (Komar *et al*., 2004; Smith, 2008; Rodgers and Furonones, 2009). The immersion method is also used for treating several numbers of fish (Komar *et al*., 2004; FAO/OIE/WHO, 2006; Aly *et al*., 2014). However, these methods are rarely used because they are laborious, time-consuming (because fish are brought out of rearing water and returned thereafter) and costly than administering medicated feed in rearing water which is easier, more convenient, and time-saving (Harper, 2002; Jacobs and Chenia, 2007; Smith, 2008; Cabello *et al*., 2013). Bacterial organisms colonizing treated fish become exposed to the antibacterial drug, and may develop resistance especially if the therapeutic concentration/dose of the drug is not attained (Okeke and Edelman, 2001).

Although feed medication in fish-rearing water (i.e. metaphylactic) is the most convenient and widely practiced method of drug administration (Smith, 2008; Vaz-Moreira *et al*., 2014), it induces AR in ACF aquaculture more than the other methods (Armstrong *et al*., 2005; Cabello, 2006). Infected fish often have a reduced appetite, thus the administered drugs may not be taken by the fish (Armstrong *et al*., 2005; Smith, 2008; Cabello *et al*., 2013). Adjustment of feeding rates to minimize loss of uneaten food may not improve absorption of antibacterial drugs (Armstrong *et al*., 2005; Smith, 2008). Uningested drug associated with the feed and approximately 75-80% of ingested drug which pass into the environment in unabsorbed form in faeces or after absorption, in secreted forms in urine and other secretions, deposits in the pond sediment by gravity (Armstrong

et al., 2005; Burridge *et al*., 2010; Cabello *et al*., 2013). This results in increased concentrations of the antibacterial agent in the aquaculture (Alderman *et al*., 1994; Weston, 1996; Armstrong *et al*., 2005). Thus, bacterial population in the ACF aquaculture continually becomes exposed to the deposited drug, consequently resulting in development of AR mechanisms (Armstrong *et al*., 2005). However, the extent/length of exposure of organisms by sediment antibacterial (i.e. time antibacterial activity of drug remains) is dependent on the initial concentration of the agent (i.e. proportional to the amount of the drug administered), its chemical structure and half life, environmental chemical and physical variables such as sediment characteristics, temperature, light and pH (Boxall *et al*., 2004; Kummerer, 2009; Cabello *et al*., 2013). Introduction of large amounts of antibacterial agents into the aquatic environment results in emergence of significant numbers of multiple-resistant bacteria since ARGs enhances fitness for growth in sediments containing antibacterial agents (Cabello *et al*., 2013).

Antibacterial-resistant organisms colonizing aquaculture workers can enter the aquaculture when contact is made with the fish-rearing water (Jacobs and Chenia, 2007). The workers can also contaminate the fish feed. Movement of AROs/ARGs from the workers to ACF aquaculture can be easy due to poor sanitation (antibacterial agents often used in replacement of poor hygiene) and infection control practices often observed in developing countries (Okeke and Edelman, 2001).

Another source of AR in ACF aquaculture is the fish feed. ACF is fed with variety of materials including commercially manufactured feed, dead animals, insects, animal manures, slaughterhouse wastes (e.g., intestines, meat) and kitchen wastes (Kumar *et al*., 2012; Omojowo and Omojasola, 2013). Antibacterial agents are usually incorporated into the commercial fish feeds at sub-therapeutic doses for prophylaxis and/or growth-promotion (Castanon, 2007; Rodgers and Furonones, 2009). This also exposes the bacterial population in the aquaculture to non-lethal concentration of the drugs, consequently AR may develop. The feed itself may be contaminated with AROs by humans during the manufacturing, transportation or fish feeding process (FAO/OIE/WHO, 2006). The AROs then disseminates ARGs by horizontal transfer to others in the aquaculture.

Feeding of fish with invertebrates (such as insects, maggots, earthworms), dead animals, slaughterhouse wastes and animal manure which also promotes algal growth, are often considered economical by ACF farmers (Kumar *et al*., 2012; Omojowo and Omojasola, 2013). An often neglected source of AR in ACF aquaculture is invertebrate vectors (e.g. insect vectors such as houseflies, and soil dwellers e.g., earthworms) which are potential carriers of AROs (Devi and Murray, 1991; Blaak *et al*., 2014). Insects are often available in ACF aquaculture environment because the humid tropical climate in most of the countries rearing this species of finfish favours their development (Okeke and Edelman, 2001). These invertebrates are vectors of AROs/ARGs which colonize them in their ecological niches (Zurek and Ghosh, 2014). In some ACF aquaculture systems, light source placed over the rearing water attract these insects which are consumed by the fish. Maggots harvested from decomposing animal manure are also used in feeding ACF; these potentially carry AROs/ARGs into ACF aquaculture. Unfortunately, slaughterhouse wastes and animal manure used in feeding ACF are reservoirs of AROs/ARGs (Sayah *et al*., 2005; Omojowo and Omojasola, 2013). Dead animals used in feeding ACF are also potential sources of AROs, their death often resulting from poorly diagnosed, misdiagnosed or inappropriately-treated bacterial infections.

Livestock manure often loaded with myriads of AROs is used to feed ACF and for fertilization of rearing water to promote the growth of photosynthetic organisms (phytoplanktons, algae) consumed by the fish (Peteersen *et al*., 2002; Sayah *et al*., 2005; Omojowo and Omojasola, 2013). Integrated African catfish farming (IACF) combines livestock production with ACF farming (Peteersen *et al*., 2002; Omojowo and Omojasola, 2013). In this IACF, animal manure shed directly into the rearing water is consumed by fish (Little and Edwards, 1999; Petersen *et al*., 2002; Aly *et al*., 2014). Although the IACF system produces high yields with low input, since the fish receive limited, if any, supplementary feed, the livestock on the integrated farms (usually chickens and pigs), is reared intensively with antibacterial agents for growth-promotion, prophylaxis and therapeutics (Petersen *et al*., 2002). Thus, within IACF farming systems, antibacterial drugs, their residues, and AROs enter the aquaculture through livestock manure (Petersen

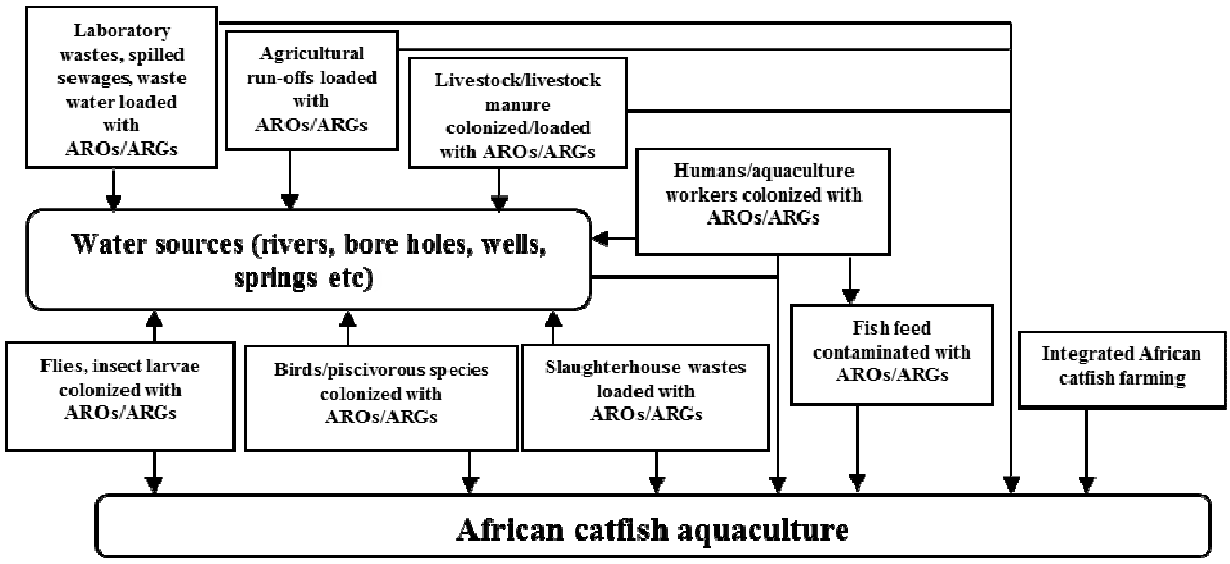

Fig. 1. Sources of antibacterial resistant organisms (AROs)/antibacterial resistance genes (ARGs) in African catfish aquaculture

et al., 2002; Aly *et al*., 2014). The AROs in the manure potentially transfer ARGs to bacterial population in the aquaculture (Petersen *et al*., 2002; Omojowo and Omojasola, 2013). Therefore, supposedly economical feeding strategies become crucial source of AR in ACF aquaculture environments.

Non-selective micro-feeders habouring AROs and ARGs-habouring bacteria in rearing water, particularly water contaminated with materials from anthropogenic activities (as often the case in developing countries), are very important sources of AR in ACF aquaculture (FAO/OIE/WHO, 2006). Over-flying and piscivorous birds also serve as sources of AR in ACF aquaculture; these birds are reservoirs of AROs/ARGs (Shobrak and Abor-Amey, 2014). The use of antibacterial agents as biocides and additives in crops facilitates AR in bacterial organisms colonizing plants (Canica *et al*., 2015). Run-offs may carry AROs from the crops and those from anthropogenic activities (e.g., laboratories, animal manure used for fertilizing crops, spilled sewages, waste water, etc) into natural water bodies (potential sources of water for ACF aquaculture) and aquaculture (Rhodes *et al*., 2000; Heuer *et al*., 2011; Nikiema *et al*., 2013; Canica *et al*., 2015). This is an important source of AR in earthen ACF ponds with low surface barriers. By horizontal transfer, bacterial population in aquaculture acquire ARGs from diverse sources (Fig. 1) and consequently develop resistance to different antibacterial agents.

Antibacterial resistance among isolates from African catfish aquaculture

Quinolone and fluoroquinolone resistance

Quinolones (e.g., nalidixic acid) and fluroquinolones (quinolone with fluorine atoms attached; e.g. ciprofloxacin, enrofloxacin, ofloxacin etc) are bactericidal agents which kill bacteria by inhibiting DNA synthesis, specifically DNA supercoiling and stability (Khodursky and Cozzarelli, 1998; Hooper, 2001; Miranda *et al*., 2013). Quinolones target bacterial enzymes, DNA gyrase and topoisomerase IV (Hooper, 2001; Miranda *et al*., 2013). Both DNA gyrase and topoisomerase IV are tetrameric enzymes encoded by the *gyrA* and *gyrB* genes, and *parC* and *parE* genes, respectively (Hooper, 2001; Rodhkum *et al*., 2002; Miranda *et al*., 2013). While the main activity of DNA gyrase is to catalyze the negative supercoiling of bacterial DNA, topoisomerase IV decatenate and relax the activity of daughter replicons following DNA replication (Hawkey, 2003; Miranda *et al*., 2013). Chromosomal mutation of the gyrase and topoisomerases genes (*gyrA*, *gyrB*, *parC*, *parE*), mutations that reduce drug accumulation by decreasing uptake or increasing efflux, and at least three plasmid-mediated/encoded quinolone resistance (PMQR) mechanisms such as rQnr proteins, AAC(6)-Ib-cr aminoglycoside acetyltransferases, and QepA and OqxAB efflux pumps, have been reported to be mechanisms of acquired quinolone resistance in bacteria, including isolates from finfish aquaculture (Drlica, and Zhao, 1997; Tran and Jacoby, 2002; Ruiz, 2003; Buschmann *et al*., 2012; Miranda *et al*., 2013). It has been suggested that hydrophilic fuoroquinolones (such as enrofloxacin) can be extruded by plasmid-encoded active efflux pumps QepA and OqxAB (Li, 2005; Poirel *et al*., 2008, 2012; Miranda *et al*., 2013). Topoisomearse protection genes *qnrA*, *qnrB*, *qnrD* and *qnrS* have been reported in isolates from several finfish farms (Ishida *et al*., 2010; Buschmann *et al*., 2012; Takjbash *et al*., 2015). Water-borne Vibrionaceae are known to habour several *qnr* genes, thus they are speculated to be natural reservoirs of Qnr-like quionolone resistance determinants (Cattoir and Nordmann, 2009; Miranda *et al*., 2013). The putative enzymatic inactivation genes *aac(69)-Ib-cr*, *aac(6)-Ib-cr* have also been detected in bacterial isolates from finfish aquaculture (Buschmann *et al*., 2012; Jiang *et al*., 2012). Some authors suggested that QnrS determinants may act as reservoirs of *qnr* gene similar to the *tet* genes (Rhodes *et al*., 2000; Schmidt *et al*., 2001; Miranda *et al*., 2013). Most importantly, *qnr*-plasmids are often associated with intergrons and they carry multiple resistance determinants, providing resistance to several classes of antimicrobials, including β-lactams and aminoglycosides (Li, 2005; Miranda *et al*., 2013).

In ACF aquaculture, resistance of bacterial isolates to quinolones and fluoroquinolones have been reported. Kumar *et al*. (2012) reported that *Flavobacterium columnare* isolates from ACF in India, exhibited resistance to nalidixic acid (100%) and ofloxacin (100%). Efuntoye *et al*. (2012) reported 9.1% resistance to ciprofloxacin among *Pseudomonas* isolates from ACF in Nigeria. The study also reported 5.9%, 63.6%, 14.3% and 6.7% resistance to nalidixic acid among *Escherichia coli*, *Pseudomonas*, *Salmonella* and *Staphylococcus* isolates, respectively. Another Nigerian study reported 100% resistance to nalidixic acid among *Staphylococcus* and *Streptococcus* isolates from ACF (Adedeji *et al*., 2011). The study also reported 37.5% resistance to ofloxacin among the *Streptococcus* and *Staphyloccocus* isolates, and 75% ciprofloxacin resistance and 100% norfloxacin resistance among the *Salmonella* isolates. Anyanwu *et al*. (2014) reported 11% resistance to enrofloxacin among *Aeromonas* isolates from ACF in Nigeria. In Bangladesh, Nahiduzzaman *et al*. (2000) reported 20% resistance to oxolinic acid among *Aeromonas* and *Pseudomonas* isolates from rearing water and ACF. In Malaysia, Wei *et al*. (2011) reported 42.9% resistance to nalidixic acid among 7 *Edwardsiella tarda* isolates from polycultured ACF. It is evident from these studies that quinolone/fluoroquinolone resistance has emerged in bacterial agents from ACF.

Aminoglycoside resistance

Aminoglycosides are bactericidal agents which kill bacteria by binding to the 30S ribosomal subunit for streptomycin (Mingeot-Leclercq *et al*., 1999; Carter *et al*., 2000) and to both 50S and a site on the 30S subunit different from that of streptomycin for kanamycin and neomycin (Greenwood, 2000). Mechanisms of bacterial resistance to aminoglycosides is by reduction in drug uptake/decreased permeability, alteration of ribosomal binding sites, enzymatic drug modifications (the most common mechanism), and efflux pump (Aires and

Nikaido, 2005; Abatcha *et al*., 2014). Bacterial aminoglycoside modifying enzymes include: acetyltransferases, adenyltransferases and phosphotransferases encoded by the genes *aac*, *aad* and *aph*, respectively (Szczepanowski *et al*., 2009; Abatcha *et al*., 2014). Gene cassettes containing both *aph* and *aac* genes, have been reported in bacterial isolates from finfish farm environment (Su *et al*., 2011). Aminoglycoside determinants such as *aac(3)-IIa* in *E. coli* (Tajbakhsh *et al*., 2015), *aad* associated with class 1 intergrons in *Aeromonas* (Ndi and Barton, 2011), *E. coli* (Ryu *et al*., 2012) and *Pseudomonas* (Ndi and Barton, 2012) have been reported in isolates from aquaculture. The genes *strA*(*aph(3)-Ib*) and *strB*(*aph(6)-Id*) encoding aminoglycoside 3'-phosphotransferase and aminoglycoside 6-phosphotransferase, respectively (Szczepano-wski *et al*., 2009), have also been detected in isolates from finfish aquaculture (Shah e*t al*., 2012; Pereira *et al*., 2013). The AAC(6)-Ib-cr aminoglycoside transferase determinant which mediates resistance to quinolones and aminoglycoside has been reported in finfish aquaculture (Ishida *et al*., 2010; Miranda *et al*., 2013). Co-occurrence of aminoglycoside genes with other determinants associated with class 1 integrons (e.g., *tetA/florA/sul1-sul2/int1-dfrA12-aadA*) (Ryu *et al*., 2012) and class 2 integrons (e.g., *dfrA1-sat-aadA1*) (Pereira *et al*., 2013) have been reported in finfish aquaculture.

Varying resistance rates to different aminoglycosides have been reported among bacterial isolates from ACF aquaculture. *Flavobacterium columnare* isolates from ACF in India exhibited 100% resistance to gentamicin, amikacin, oleandamycin and tobramycin (Kumar *et al*., 2012). In Malaysia, Laith and Najiah (2013) reported 9.09% resistance to novobiocin among *A. hydrophila* isolates from ACF. In Nigeria, 11.8%, 9.1% and 6.7% resistance to novobiocin among *E. coli*, *Pseudomonas* and *Staphylococcus* isolates from ACF, respectively, were reported by Efuntoye *et al*. (2012). The study also reported 7.6%, 18.2% and 40% resistance to gentamicin among the respective isolates, and 71.4% among *Salmonella* isolates. The rates of streptomycin resistance reported by the study were 29.4%, 36.4%, 42.9% and 46.7% among the respective isolates. Anyanwu *et al*. (2014) reported 66% resistance to streptomycin among *Aeromonas* isolates from ACF in some states in Southeastern Nigeria. A different Nigerian study reported 100% resistance to gentamicin among *Streptococcus* isolates from ACF (Adedeji *et al*., 2011). A Bangladeshi study reported 10% and 40% resistance to streptomycin among *Aeromonas* and *Pseudomonas* isolates from rearing water and ACF hybrid (Nahiduzzaman *et al*., 2000). In Malaysia, Wei *et al*. (2011) reported 14.3% resistance to kanamycin among 7 *E. tarda* isolates from ACF.

Tetracycline resistance

Tetracyclines are broad-spectrum bacteriostatic antibiotics that interfere with protein synthesis by reversibly binding to the 30S and 70S ribosomal subunit, thereby blocking the binding of the aminoacyl tRNA to the mRNA/ribosome complex (Roberts, 1996; Armstrong *et al*., 2005; Miranda *et al*., 2013). Mechanisms of bacterial resistance to tetracycline include active efflux, ribosomal protection, ribosomal RNA mutations, and tetracycline inactivation (Speer and Salyers, 1989; Burdett, 1991; Speer *et al*., 1992; Taylor and Chau, 1996; Miranda *et al*., 2013). The commonest tetracycline resistance mechanisms in fish farm-associated bacteria include one or more of the Tet family of proton-dependent efflux pumps and/or via ribosomal protection by cytoplasmic proteins found widely in Gram-negative bacteria (Roberts, 2005; Roberts *et al*., 2012; Miranda *et al*., 2013).

Several tetracycline determinants including *tetA*, *tetB*, *tetE*, *tetH*, *tetL*, *tet34*, *tetC*, *tetD*, *tet35 tetG*, *tetM*, *tetO*, *tetQ*, *tetS*, and *tetW* have been detected in bacterial isolates from many finfish farms (Furishita *et al*., 2003; Ishida *et al*., 2010; Miranda *et al*., 2013). The prevalence of these genes in aquaculture habitats vary (Nawaz *et al*., 2009; Miranda *et al*., 2013). The spread of *tet* genes is often facilitated by their location on mobile genetic elements, such as plasmids and transposons, factors that are known to play a significant role in global dissemination of *tet* genes (Chopra and Roberts, 2001; Sørum *et al*., 2003; Miranda *et al*., 2013). The *tet* genes have been associated with both mobile and non-mobile plasmids (Miranda *et al*., 2013). *Edwardsiella* isolates from a fish farm in Korea carried *tet*A and *tet*D on mobile plasmids while *tet*B and *tet*G were associated with non-mobile plasmids (Juan *et al*., 2004; Miranda *et al*., 2013). Co-occurrence of *tet* genes with other resistance genes (usually harboured by class 1 intergron) in finfish aquaculture have been reported (Jacobs and Chenia, 2007; Su *et al*., 2011; Miranda *et al*., 2013). The frequent occurrence of the *tet* gene in finfish aquaculture reflects the fact that it has being in use for long, being the first antibacterial agent to be approved for use in aquaculture (USFDA, 2009).

Resistance to tetracycline has severally been reported among different bacterial isolates from ACF aquaculture. Efuntoye *et al*. (2012) reported 82.4%, 72.7%, 28.6% and 40% resistance to tetracycline among *E. coli*, *Pseudomonas*, *Salmonella* and *Staphylococcus* isolates from ACF in Nigeria. A similar study in Nigeria reported 37.5% resistance to tetracycline among *Staphylococcus* isolates, and 100% among *Salmonella* and *Streptococcus* isolates, respectively, from ACF (Adedeji *et al*., 2011). Another Nigerian study reported 89% resistance to tetracycline among *Aeromonas* isolates from ACF (Anyanwu *et al*., 2014). Nahiduzzaman *et al*. (2000) reported 70% and 80% resistance to oxytetracycline among *Aeromonas* and *Pseudomonas* isolates from rearing water and ACF hybrid in Bangladesh. Tetracycline resistance of 42.9% was reported by Wei *et al*. (2011) among 7 *E. tarda* isolates from ACF in Malaysia. Apart from the fact that tetracycline (particularly oxytetracycline) is frequently used in ACF aquaculture because of its broad-spectrum effect (Olatoye and Basiru, 2013; Anyanwu *et al*., 2014), the source of tetracycline resistance in ACF aquaculture environment is most probably from livestock manure, dead animals and aquaculture workers because the drug has been tremendously abused in veterinary and human medicine especially in developing countries (Hart and Kariku, 1998; Roberts, 2003).

Macrolide and lincosamide resistance

Macrolides and lincosamides are bacteriostatic agents which inhibit bacterial protein synthesis by binding to the 50S ribosomal subunit (Canu and Lerclerq, 2009). Lincosamides can

also elicit bactericidal effect depending on the concentration and sensitivity of the targeted organism (Tenson *et al*., 2003). Although macrolides and lincosamides are chemically/structurally distinct, they share a similar mode of action (Isnard *et al*., 2013). Their activity is limited mainly to Gram-positives and bacilli, Gram-negative cocci, and intracellular bacteria such as *Chlamydia* and *Rickettsia* (Lerclerq, 2002). Mechanisms of bacterial resistance to macrolide and lincosamide include: target site modification by methylation or mutation that prevents the binding of the drug to its ribosomal target, efflux of the drug, and drug inactivation (Lerclerq, 2002; Hot *et al*., 2014). Mutations at several sites of the ribosome allosterically prevent macrolide binding and a common alteration is dimethylation of one nucleotide (a single adenine) in the 23S rRNA by the Erm methylases (Gaynor and Mankin, 2003). This dimethylation not only prevents macrolide binding, but also confers resistance to lincosamide and streptogramin antibiotics (Tait-Kamradt *et al*., 2000; Gaynor and Mankin, 2003). So far, up to 40 plasmid and transposon-borne determinants (*erm* genes) of the Erm methylases with four major classes (*ermA*, *ermB*, *ermC*, and *ermF/A*) have been reported in pathogenic bacteria (Weisblum, 1995; Tait-Kamradt *et al*., 1997; Roberts *et al*., 1999) including isolates from finfish aquaculture environments (Peteersen and Dalsgaard, 2003; Shah *et al*., 2012; Di Cesare *et al*., 2012; Munoz-Antienza *et al*., 2013). Lincosamides are inactivated by lincosamide nucleotidyl transferases encoded by *lnuA* (formerly *linA*) and *lnuB* (formerly *linB*) genes (Roberts *et al*., 1999; Lerclerq, 2002). Recently, Si *et al*. (2015) reported co-occurrence of *lnuB* gene with other resistance genes in bacterial plasmids. A rarely detected *mphC* gene encoding phosphotransferases which also modify macrolide has been reported (Matsuoka *et al*., 1998). The efflux proteins are encoded by the plasmid-borne genes *mrSA* and *mefA* (Ross *et al*., 1990; Kataja *et al*., 2000; McGee *et al*., 2001). Innate genes *eat* and *salA* encoding proteins have been reported to confer resistance to macrolides and lincosamides including pleuromutilins and streptogramins (Isnard *et al*., 2013; Hot *et al*., 2014)

There are reports on resistance to macrolides and lincosamide in ACF aquaculture isolates. Kumar *et al*. (2012) reported 100% resistance to erythromycin and lincomycin among *F. columnare* isolates from ACF in India. In Nigeria, 47.1%, 9.1%, 85.7%, 66.7% and 100% resistance to erythromycin among *E. coli*, *Pseudomonas*, *Salmonella*, *Staphylococcus* and *Edwardsiella* isolates, respectively, from ACF was reported by Efuntoye *et al*. (2012). In Bangladesh, Nahiduzzaman *et al*. (2000) reported 60% and 80% resistance to erythromycin among *Aeromonas* and *Pseudomonas* isolates, respectively, from ACF aquaculture. A study in Malaysia reported 100% resistance to lincomycin among *Flavobacterium*, *E. tarda*, *Hafnia alvei*, *P. aeruginosa* and *A. hydrophila* isolates from ACF (Musa *et al*., 2009).

Glycopeptide resistance

Glycopeptides are bactericidal agents which kill bacteria by binding to the *N*-acyl-d-Ala-d-Ala termini of peptidoglycan and its precursor lipid II (Mendez-Alvarez *et al*., 2000; Yim *et al*., 2014). This binding effectively sequesters the substrate for two key enzymes critical to cell wall synthesis: the transglycosylases that transfer the *N*-acetyl-muramic acid-*N*-acetyl-glucosamine pentapeptide subunits from lipid II to the anchored cell wall, and the D, D-transpeptidases that crosslink strands of peptidoglycan (Yim *et al*., 2014). The result is inability to grow, rigidified cell wall and cell death (Sujatha and Praharaj, 2012; Yim *et al*., 2014). The mechanism of bacterial resistance to glycopeptides is by formation of abnormal peptidoglycan receptors (by precussors D-ala-D-lactate which has 1000 fold decreased glycopeptides affinity or D-ala-D-serine which has 6 times decreased glycopeptide affinity) with reduced glycopeptide affinity; this results in decreased binding of glycopeptides and decreased inhibition of cell wall synthesis (Cooper *et al*., 2000; Sujatha and Praharaj, 2012). Glycopeptide determinants are chromosomal-borne gene clusters *vanA*, *vanB*, *vanC*, *vanD*, *vanE*, *vanG*, *vanL*, *vanM* and *vanN* encoding the corresponding resistance phenotypes which are either inducible (use/exposure selection) and characterized by high-level (i.e. MIC of 64-1000μg/ml) or low-level (i.e. MIC of 8-32μg/ml) vancomycin resistance; or constitutive, non-inducible intrinsic (VanC1-3) (Depardieu *et al*., 2004; Courvalin, 2006; Lebreton *et al*., 2011; Sujatha and Praharaj, 2012).

The *van* genes have been associated with transposon Tn1546 (Sujatha and Praharaj, 2012). The *vanA* (*vanHAX*) and *vanB* (*vanH$_B$BX$_B$*) genes encode for 3 enzymes: a dehydrogenase (VanH/VanH$_B$ phenotype) which reduces pyruvate to D-Lactate, a ligase (VanA/VanB phenotype) which synthesizes D-alanine-D-lactate, and a dipeptidase (VanX/VanX$_B$ phenotype) which hydrolyses D-alanine-D-alanine precussors (Arthur and Quintiliani, 2001; Sujatha and Praharaj, 2012). While there is no report in available literature with regards to the presence of *van* genes in finfish aquaculture, it is known that vancomycin resistance is critical in *Enterococcus* (i.e. vancomycin-resistant enterococci [VRE]), a commensal bacterium inhabiting the gut of humans and animals, and also highly adapted to varying environments (Werner *et al*., 2013). Enterococci have been reported in tropical freshwater finfish aquaculture (Petersen and Dalsgaard, 2003) and it has also been reported to be highly prevalent in ACF aquaculture (Amanda and Nwaka, 2013). Since human and animal wastes easily find their way into ACF aquaculture in developing countries, there is a high likelihood that enterococcal isolates from ACF aquaculture systems would habour *van* genes. Nevertheless, Kumar *et al*. (2012) reported 100% resistance to vancomycin among *F. columnare* isolates from ACF in India.

Phenicol resistance

Phenicols are broad-spectrum bacteriostatic agents which inhibit bacterial protein biosynthesis by reversible binding to the 50S subunit of 70S bacterial ribosomes thus preventing peptide elongation (Schlunzen *et al*., 2001; Schwarz *et al*., 2004; Miranda *et al*., 2013). Chloramphenicol and its synthetic fluorinated analog florfenicol are phenicols that are or have been used in aquaculture (Armstrong *et al*., 2008; Miranda *et al*., 2013). Acetylation of the drug via different types of chloramphenicol acetyltransferases (CATs) has been the most common mechanism of chloramphenicol resistance (Schwarz

et al., 2004; Miranda *et al*., 2013). Other mechanisms of bacterial resistance to chloramphenicol include: expression of efflux systems, inactivation by phosphotransferases, mutations of the target site and permeability barriers (Shaw, 1983; Murray and Shaw, 1997; Schwarz *et al*., 2004). The replacement of a hydroxyl group with a fluorine atom protects florfenicol from inactivation by CATs (Shaw and Leslie, 1991; Schwarz *et al*., 2004). Thus, chloramphenicol-resistant strains in which resistance is exclusively based on CATs activity, is susceptible to florfenicol (Cannon *et al*., 1990; Schwarz *et al*., 2004). The CATs are encoded by the *cat* gene while the genes *cml* and *cmr* codify chloramphenicol efflux proteins (exporters) (Schwarz *et al*., 2004). These chloramphenicol determinants have been associated with mobile genetic elements such as plasmids and transposons (Desomer *et al*., 1992; Nagy *et al*., 1997; Tauch *et al*., 1998; Schwarz *et al*., 2004). Chloramphenicol determinants *cat1*, *cat2*, *cat3* and *cat4* genes have been reported in isolates from finfish aquaculture (Shah *et al*., 2012; Ng *et al*., 2014).

Mechanisms of bacterial resistance to florfenicol include: specific and non-specific drug transporters, RNA methyltransferases, and specific hydrolases (Paulsen *et al*., 1996; Schwarz *et al*., 2004; Miranda *et al*., 2013). The efflux proteins that export florfenicol out of the cell are encoded by genes *floR* and *fexA* which belong to the major facilitator superfamily (Schwarz *et al*., 2004; Miranda *et al*., 2013). The radical S-adenosine methionine (SAM) superfamily of protein, encoded by an RNA methyltransferase gene *cfr*, has been reported to inhibit ribose methylation and thereby causes resistance to florfenicol, chloramphenicol, and clindamycin (Sophia *et al*., 2001; Long *et al*., 2006; Miranda *et al*., 2013). Reports abound on the occurrence of *floR* gene in aquaculture settings (Miranda *et al*., 2013). Bacterial isolates from aquaculture have also been reported to habour plasmids containing *floR* gene and other genes such as in *tetY*, *sul2*, *qnr* and *strA-strB* (Gordon *et al*., 2008; Buschmann *et al*., 2012; Miranda *et al*., 2013). The presence of *floR* gene in aquaculture is critical because it is among the five antibacterial resistance genes which constitute the main component of the multidrug resistance region of *Salmonella* genomic island 1 (SGI1) (Ahmed *et al*., 2007; Ishida *et al*., 2010). Thus, the presence of the *floR* gene in aquaculture could result in its spread in *Salmonella* colonizing humans and animals following consumption of fish habouring bacteria with *floR* gene (Smith, 2008).

The use of chloramphenicol in food animals, including aquaculture, was banned in European countries in 1994 because it causes dose-independent irreversible aplastic anaemia in humans (Schwarz *et al*., 2004). Because the effect (aplastic anaemia) is dose-independent, the "non-observed effect level" (NOEL) (the dose at and below which adverse effects do not occur) and the "maximum residue level" (MRL) the maximum level of antibacterial residues acceptable in carcasses at slaughter without any adverse effect on public health, deduced from NOEL, could not be determined (Schwarz *et al*., 2001; Schwarz *et al*., 2004). Therefore, florfenicol, considered to be more active and safer than chloramphenicol (since florfenicol has not shown dose-independent aplastic anaemia in animals) is allowed and commonly used in aquaculture in developed countries (Schwarz *et al*., 2004; Armstrong *et al*., 2005). Detection of chloramphenicol residues and/or chloramphenicol-resistant organisms in aquaculture products resulted in international ban of the products in Europe (Hatha *et al*., 2005; Ng *et al*., 2014).

In ACF aquaculture, resistance to chloramphenicol has been reported more than to florfenicol. Laith and Najiah (2013) reported 9.09% resistance to florfenicol among *A. hydrophila* isolates from ACF in Malaysia. In Nigeria, Efuntoye *et al*. (2012) reported 82.4%, 36.4%, 57.1% and 53.3% resistance to chloramphenicol among *E. coli*, *Pseudomonas*, *Salmonella* and *Staphylococcus* isolates respectively, from ACF. A similar study in Nigeria reported 78% resistance to chloramphenicol among *Aeromonas* isolates from ACF (Anyanwu *et al*., 2014). In Bangladesh, chloramphenicol resistance of 20% and 40% among *Aeromonas* and *Pseudomonas* isolates from rearing water and ACF, respectively, was reported (Nahiduzzaman *et al*., 2000). These reports on chloramphenicol resistance in ACF aquaculture setting may be a pointer that chloramphenicol is used in ACF aquaculture, so it calls for concern. The use of chloramphenicol in ACF aquaculture may be due to the high cost and/or unavailability of florfenicol in LMIFDCs where ACF is farmed, a situation that results in resorting to the use of chloramphenicol by the farmers. However, the florfenicol resistance reported in ACF aquaculture could be as a result of selection pressure due to inclusion of florfenicol in commercial fish feed at sub-therapeutic dose (Hayes *et al*., 2013). This is evidence for lax control of antibacterial use in ACF-rearing countries (Cabello *et al*., 2013).

Nitrofuran resistance

Nitrofurans (e.g. nitrofurantoin, furazolidone) are old broad-spectrum bactericidal agents (Sandegeren *et al*., 2008). Reduction of nitrofurans by bacterial flavoproteins to reactive intermediates which subsequently inactivate or alter bacterial ribosomal proteins and other macromolecules results in bacterial cell death (McCalla *et al*., 1970; Petersen *et al*. 1979; Sandegeren *et al*., 2008). The mechanisms of action of nitrofurans are yet to be fully understood. The mechanism of bacterial resistance to nitrofurans is by production of nitroreductases I and II which are encoded by *nfsA* and *nfsB* genes, respectively (McCalla *et al*., 1975; Whiteway *et al*., 1998; Sandegeren *et al*., 2008). In Europe, the use of nitrofurans together with nitroimidazoles in food-producing animals, including aquaculture, was banned in 1993 because their NOEL and MRL could not be determined (Schwarz *et al*., 2004). In 1995, the use of nitrofurans in livestock was completely prohibited due to concerns about the carcinogenicity and mutagenicity of the drug residues and their potential harmful effects on humans (Vass *et al*., 2008).

In India, 100% resistance to nitrofuranoin among *F. columnare* isolates from ACF have been reported (Kumar *et al*., 2012). In Nigeria, 37.5% of streptococci and 87.5% of *Salmonella* and staphylococcal isolates from ACF were reported to be resistant to nitrofurantoin (Adedeji *et al*., 2013). Another Nigerian study recorded 17.6%, 27.3%, 28.6% and 6.7% resistance to nitrofurantoin among *E. coli*, *Pseudomonas*, *Salmonella* and *Staphylococcus* isolates, respectively, from ACF

(Efuntoye *et al*., 2012). A Malaysian study observed 27.2% nitrofurantoin resistance among *A. hydrophila* isolates from ACF (Laith and Najiah, 2013) while another Malaysian study reported 14.3% resistance to furazolidone among 7 *E. tarda i*solates from polycultured ACF (Wei *et al*., 2011). These reports on resistance to nitrofurans in ACF aquaculture environments suggest that the determinants of nitrofurans may have entered into ACF aquaculture system from other anthropogenic sources, or that these drugs are used in livestock and/or ACF aquaculture systems. This calls for concern because of the health impacts of these drugs when their residues are found in aquaculture products (Schwarz *et al*., 2004).

Sulfonamide and diaminopyrimidine resistance

Sulfonamides and diaminopyrimidines are bacteriostatic agents which inhibit nucleic acid synthesis by competitive inhibition of dihydropteroate synthase (DHPS) and dihydrofolate reductase (DHFR), enzymes involved in the synthesis of tetrahydrofolic acid, a necessary factor for the synthesis of folate, a co-enzyme involved in the synthesis of purines and pyrimidines (Then, 1982; Richards *et al*., 1996; Abatcha *et al*., 2014). Sulfonamides are analogs of *p*-aminobenzoic acid hence they inhibit DHPS, an enzyme that catalyzes an early step in folate synthesis while diaminopyrimidines inhibits DHFR, an enzyme that catalyzes the final step in folate synthesis (Normark and Normark, 2002; Bukhart and Bukhart, 2009; Abatcha *et al*., 2014). Sulfonamides and diaminopyrimidines (e.g., trimethoprim) act synergistically, and when combined they are called potentiated sulfonamides (Richards *et al*., 1996). In aquaculture, sulphamethoxazole/trimethoprim combination is commonly used because of its broad-spectrum activity (Serrano, 2005; Muziasari *et al*., 2014).

Mechanism of bacterial resistance to sulfonamides is by mutations in the chromosomal DHPS gene *folP*, or through acquisition of an alternative DHPS gene *sul* whose product has a low affinity for sulfonamides (Petersen and Dalsgaard, 2003; Hoa *et al*., 2010) The sulfonamide determinants *sul1*, s*ul2* and *sul3* genes encoding DHPS have been reported in bacteria, including isolates from aquaculture environments (Lopez *et al*., 1987; Hoa *et al*., 2008; Su *et al*., 2011; Suzuki *et al*., 2013; Muziasari *et al*., 2014; Tajkbash *et al*., 2015). The *sul1* and *sul2* genes were reported to be more prevalent than *sul3* gene in aquaculture environment (Hoa *et al*., 2008; Hoa *et al*., 2010; Su *et al*., 2011; Suzuki *et al*., 2013; Takjbash *et al*., 2015). The *sul* genes are associated with the chromosome more than the plasmids (Hoa *et al*., 2008). The occurrence of *sul1* and *sul2* genes in class 1 integrons in bacterial isolates from aquaculture environment has been reported (Su *et al*., 2011; Muziasari *et al*., 2014). The *dfr* gene is the determinant for trimethoprim and it is also associated with class 1 integrons (Shah *et al*., 2012). The *dfr* gene encodes production of DHFR thereby countering the inhibitory effect of trimethoprim (Szczepanowski *et al*., 2009). Several variants of *dfr* gene such as *dfrA1*, *dfrA2 dfrA5*, *dfrA7*, *dfrA12*, *dfrA15* and *dfrA17* have been reported in bacteria, including isolates from finfish aquaculture environment (Ishida *et al*., 2010; Su *et al*., 2011; Shah *et al*., 2012; Muziasari *et al*., 2014). Co-occurrence of *dfr* gene with *aad*, *orfF* and *cat* genes in class 1 integrons have been reported in isolates from finfish aquaculture (Ishida *et al*., 2010; Su *et al*., 2011). Okoh *et al*. (2010) reported that *Vibrio* isolates from wastewater effluents harboured *dfr* genes; these are potential contaminants of aquaculture because they are often present in sewage and hence water bodies (Fawell and Nieuwenhuijsen, 2003).

Resistance to sulfonamide and potentiated sulfonamide in ACF aquaculture environments has been reported. In Nigeria, Efuntoye *et al*. (2012) recorded 9.1%, 57.1%, 20% and 100% resistance to sulfamethoxazole among *Pseudomonas*, *Salmonella* and *Staphylococcus* and *E. tarda* isolates from ACF, respectively. Another Nigerian study reported 100% resistance to sulfamethoxazole/trimethoprim among *Staphylococcus* and *Streptococcus* isolates from ACF (Adedeji *et al*., 2011). Nahiduzzaman *et al*. (2000) reported 30% resistance to sulfamethoxazole among *Aeromonas* and *Pseudomonas* isolates from rearing water and ACF hybrid in Malaysia while Wei *et al*. (2011) reported 85.7% resistance to sulfamethoxazole among *E. tarda* isolates from polycultured ACF.

β-lactam resistance

β-lactams are bactericidal agents which kill bacteria by interfering with the cross-linking of penicillin binding protein (PBPs) (i.e. tanspepidases and carboxypeptidases) resulting in the synthesis of a defective peptidoglycan layer, and hence fragile spheroplast for Gram-negatives or cells easily autolyzed by lipotechoic acid for Gram-positives (McManus, 1997; Greenwood, 2000; Armstong *et al*., 2005; Tenover, 2006). β-lactams which include the penicillins, cephalosporins (1st, 2nd, 3rd and 4th-generations), monobactams, aztreonam, cephems, cephamycins, and carbapenems are differentiated by the number of the cyclic amide β-lactam ring in their structure (Bradford *et al*., 1999; Greenwood, 2000; Urmunova, 2015). The β-lactams are the most commonly used therapeutic class of antimicrobials for treatment of bacterial infection because of their broad antibacterial spectrum and excellent safety profile (Piscitelli *et al*., 2011; Abdallah *et al*., 2015). This may have resulted in use (exposure) selection pressure and evolution of diverse resistance mechanisms by bacterial organisms to this class of antibacterial agents (Abdallah *et al*., 2015). Mechanisms of bacterial resistance to β-lactam include: production of β-lactamases which hydrolyze the amide cyclic bond (β-lactam ring) forming penicilloic or cephalosporic acid, change in the permeability of the cell wall, expression of active efflux pump, gene mutation and alteration of penicillin binding protein (PBP) receptors (Livermore and Brown 2001; Livermore and Woodford, 2006; Urmunova, 2015).

Production of β-lactamases is by far the major mechanism of β-lactam resistance in bacterial organisms (Livermore and Brown, 2001; Abdallah *et al*., 2015). β-lactamases are distinguished by their structure and function; they are grouped according to the Ambler and Bush-Jacoby-Medeiros classifications (Bush and Jacoby, 2010; Urmunova, 2015). Penicillinase and cephalosporinases mediate resistance to penicillins, 1st- and 2nd-generation cephalosporins (Livermore and Brown, 2001; Wilke *et al*., 2005; Bush and Jacoby, 2010). The extended-spectrum β-lactamases (ESBLs) (i.e., Cefotaximase Munich [CTX-M], *Pseudomonas aeruginosa* β-

lactamases [PER], *Klebsiella pnuemoniae* carbapenemase [KPC], New Delhi metallo- β-lactamase [NDM], Temoneira [TEM], sulfhydryl variable [SHV], Guiana extended-spectrum β-lactamases [GES] and Oxacillinase type β-lactamase [OXA]-types) are point-mutational variants of the classical β-lactamases (especially the SHV and TEM) belonging in the molecular class A of Ambler classification and group 2be of Bush-Jacoby-Medeiros classification (Paterson and Bonomo, 2005; Bush and Jacoby, 2010; Zurfluh *et al*., 2013). The carbapenemases (OXA-48, Imipinem β-lactamases [IMP], Verona integrons-encoded β-lactamase [VIM], Sao Paulo metallo-β-lactamases (SPM), NDM and KPC-types) mediate resistance to all classes of antibacterial agents including carbapenem which is the only remaining class of therapeutic agents that can kill ESBL-producing organisms (Abraham *et al*., 2013). Superbugs are carbapenemase-producing organisms which are resistant to all known therapeutic agents, infection by them are often untreatable and fatal (Johnson and Woodford, 2012; Bush, 2013). Resistance to β-lactam-β-lactamase inhibitors (e.g., amoxicillin/clavulanic acid) occur following hyper production of class A β-lactamases (TEM-1 or SHV-1), production of class D plasmid-mediated enzyme, chromosomal or plasmidic class C β-lactamase, ampicillinase C (AmpC) β-lactamases/cephalosporinases and/or modification of outer membrane permeability (Chaïbi *et al*., 1999; Dwarz and Bonomo, 2010).

The *bla* genes encode the β-lactamases. Several β-lactamase determinants such as $bla_{\text{TEM-104}}$, $bla_{\text{TEM-1}}$, $bla_{\text{SHV -}}$ non-ESBL ($bla_{\text{SHV-1}}$, $bla_{\text{SHV-11}}$, $bla_{\text{SHV-25}}$, $bla_{\text{SHV-26}}$) and ESBL ($bla_{\text{SHV-12}}$, $bla_{\text{SHV-27}}$, $bla_{\text{SHV-89}}$), ESBL $bla_{\text{CTX-M}}$ ($bla_{\text{CTX-M-14}}$, $bla_{\text{CTX-M-79}}$, $bla_{\text{CTX-M-15}}$), AmpC β-lactamase ($bla_{\text{CMY-2}}$), $bla_{\text{LEN-17}}$ and $bla_{\text{LEN-26}}$ genes have been reported in bacteria, including isolates from finfish aquaculture environment (Ishida *et al*., 2010; Chikwendu *et al*., 2011; Jiang *et al*., 2012; Shah *et al*., 2012; Ryu *et al*., 2012; Pereira *et al*., 2013; Abgottspon *et al*., 2014 Chikwendu *et al*., 2014). The bla_{TEM} is the most prevalent *bla* gene reported in finfish aquaculture (Jiang *et al*., 2011; Chikwendu *et al*., 2011). The presence of ESBL determinants in aquaculture is a matter of growing concern because they confer co-resistance to many other classes of therapeutic agents including aminoglycosides, potentiated sulfonamides, fluoroquinolones, tetracyclines, and phenicols (Gniadowlski, 2001; Coque *et al*., 2008; Abraham *et al*., 2014). Currently, the $bla_{\text{CTX-M-15}}$ gene is the most predominant ESBL determinants reported in humans (Urmunova, 2015), thus its presence in aquaculture can increase the prevalence in humans and *vice versa*. Carbapenem determinants include: $bla_{\text{OXA-48}}$, $bla_{\text{NDM-1,}}$ bla_{KPC} and bla_{VIM} genes (Ellington *et al*., 2007; Poirel *et al*., 2011; Zurfluh *et al*., 2013). Ishida *et al*. (2010) detected $bla_{\text{OXA-90}}$ in two enterobacterial isolates from freshwater finfish aquaculture in Egypt. Contamination of water sources with human sewage which is of high possibility in developing countries has been suggested to be a crucial source of ESBL and carbapenem determinants in aquatic systems and aquaculture (Mesa *et al*., 2006; Fontes *et al*., 2011; Jiang *et al*., 2012; Araujo *et al*., 2014). This is of tremendous consequence as dissemination of these genes would result in emergence of superbugs in aquaculture settings. The presence of ESBL and carbapenem determinants in aquaculture can result in fast global spread of the genes through international travel and importation since the genes are associated with integrons, transposons and other mobile genetic elements (Jiang *et al*., 2011; Abraham *et al*., 2014).

Methicillin-resistant staphylococci (MRS) are multidrug-resistant exhibiting resistance to other classes of antibacterial agents including aminoglycoside, fluoroquinolones, lincosamides, potentiated sulfonamide and tetracycline (Morris *et al*., 2006; Chambers, 1997; Febler *et al*., 2011). MRS has been reported in staphylococcal isolates from finfish aquaculture (Albuquerque *et al*., 2007; Soliman *et al*., 2011). Recent studies detected staphylococci habouring *mecA* gene in fish products; typing of the *S. aureus* protein a (*spa*) in the isolates revealed that they belonged to the zoonotic clones (Hammad *et al*., 2012; Sergelidis *et al*., 2014). Therefore, it is possible that human carriers contaminated the fish products and aquaculture with MRS also known to colonize external surfaces and mucous membranes of humans (Fitzgerald, 2012; Schamburg *et al*., 2013; Sergelidis *et al*., 2014). Human colonization in developing countries is high and having being reported to colonize livestock (Wulf and Voss, 2008), MRS can easily enter ACF aquaculture. Thus, the presence of MRS/*mecA* gene in aquaculture is another β-lactam resistance issue of serious global concern.

Many investigators have reported β-lactam resistance among different bacterial genera/species in the ACF aquaculture. Using microdilution method to determine minimum inhibitory concentration (MIC), Wei *et al*. (2011) recorded 42.9% resistance to ampicillin among 7 *E. tarda* isolates from ACF in a Malaysian polyculture. Another Malaysian study reported 100% ampicillin resistance among *A. hydrophila* isolates from ACF (Laith and Najiah, 2013). In Nigeria, Anyanwu *et al*. (2014) also reported 100% and 20% resistance to ampicillin and amoxicillin/clavulanic acid resistance among *Aeromonas* species isolated from ACF. Another Nigerian study also reported 100% resistance to ampicillin among A*eromonas*, *Alcaligenes*, *Citrobacter*, *Enterobacter*, *Escherichia*, *Klebsiella*, *Proteus*, *Pseudomonas*, *Salmonella*, *Serratia*, *Micrococcus*, *Staphylococcus*, *Streptococcus*, *and Bacillus* isolates from rearing water, sediments and ACF (Ekundayo *et al*., 2014). Efuntoye *et al*. (2012) reported 82.4%, 63.6%, 42.9% and 73.3% resistance to ampicillin, and 41.2% 54.5%, 57.1%, and 66.7% resistance to amoxicillin among *E. coli*, *Pseudomonas*, *Salmonella* and *Staphylococcus* isolates, respectively, from ACF in Nigeria. Also, Adedeji *et al*. (2011) reported 37.5% resistance to ampicillin among *Salmonella* isolates from ACF in Nigeria. *Staphylococcus* and *Streptococcus* isolates obtained in the study exhibited 100% and 75% resistance to amoxicillin. In India, Kumar *et al*. (2012) reported 100% resistance of *F. columnare* isolates from ACF to ampicillin, amoxicillin/clavulanic acid, amoxicillin, cloxacillin and penicillin G. However, the 100% resistance to ampicillin recorded in some of the reports in ACF aquaculture may be related to the inherent ampicillin-resistance in *Aeromonas* species except for *A. trota* which is susceptible to ampicillin (Janda and Abott, 2010). The CITM cluster gene encoding AmpC *β*-lactamase which hydrolyses *β*-lactams, including ampicillin, has also been reported in *E. coli* isolate from aquaculture (Van *et al*., 2008).

Reports in ACF aquaculture revealed that there is ongoing resistance to extended spectrum *β*-lactams and carbapenems.

Kumar *et al*. (2012) reported that *F. columnare* isolates from ACF in India showed 100% resistance to cefotaxime, cefoxitin and ceftazidime. Anyanwu *et al*. (2014) reported 71% resistance to ceftriaxone among *Aeromonas* isolates from ACF in Nigeria. Using imipineme-EDTA method, Khainar *et al*. (2013) detected metallo-β-lactamase (MBLs)-producing *P. aeruginosa* from ACF in India. Emergence of MBLs-producing *P. aeruginosa* in ACF aquaculture is alarming and reflects excessive use of antibacterial agents in the system (Khainar *et al*., 2013; Johnson and Woodford, 2012). This is a public health emergency because MBLs are carbapenemases which mediate resistance to all antibacterial agents. This calls for concern and for early detection and prompt infection control measures to prevent further spread of MBLs to other Gram-negative rods (Khainar *et al*., 2013; Abraham *et al*., 2014). The reported resistance to β-lactams in ACF aquaculture could be related to the fact that this class of antibacterial agents is frequently used in human and veterinary medicine in LMIFDCs due to their affordability and over-the-counter availability (Laximarayan *et al*., 2014). It is projected that in few years to come, the prevalence of ESBL and carbapenem resistance in ACF aquaculture environments may outnumber that in any other environmental setting. This prediction is feasible because of the current rise in the use of extended-spectrum β-lactams and carbapenems in human and veterinary medicine especially in developing countries.

Multiple antibacterial resistance in African catfish aquaculture

Multiple antibacterial resistance (MAR) has been defined as resistance to three or more classes of antibacterial agents by an isolate (Tenover, 2006). Some investigators regard isolates that exhibit resistance to two or more different classes of antibacterial agents to be multidrug-resistant. Multidrug resistant genotyopes are detected by the presence of two or more resistance genes in their genome (Ishida *et al*., 2010). Nevertheless, some investigators (Miranda and Zimmelman, 2002; Su *et al*., 2011) of AR in ACF aquaculture evaluated the health risk associated with AR phenotypes by calculating the multiple antibacterial resistance (MAR) index using the formular first described by Krupperman (1983). The MAR index, when applied to a single isolate, is defined as a/b, where a represents the number of antibacterial agents to which the isolate was resistant, and b represents the number of antibacterial agents to which the isolate was exposed. If indexing is applied to a sample from which several isolates were taken, the index of the sample would be a/(b*c), where a is the aggregate antibacterial resistance score of all isolates from the sample, b is the number of antibacterial agent, and c is the number of isolates from the sample. When the use of antibacterial agents in an aquaculture is seldom or low (i.e. low-risk exposure), the MAR index value is usually ≤ 0.2, whereas in a farm where antibacterial agents are frequently used (i.e. high risk of exposure), the MAR index value is usually > 0.2 (Jones *et al*., 1986; Wei *et al*., 2011; Laith and Najiah, 2013).

Varying MAR indexes have been reported for different bacterial isolates from ACF. In Malaysia, Musa *et al*. (2009) reported MAR index among different bacterial isolates from ACF such as *Pseudomonas aeruginosa* (0.24), *Hafnia alvei* (0.29), *Flavobacterium* (0.52), *Edwardsiella tarda* (0.42) and *Aeromonas hydrophila* (0.28). In another Malaysian study, Laith and Najiah, (2013) reported MAR index of 0.10-0.50 among *Aeromonas hydrophila* isolates from ACF. In Nigeria, 80% of pooled *Aeromonas*, *Pseudomonas*, *Micrococcus*, *Moraxella*, *Escherichia coli*, *Acinetobacter*, *Staphylococcus aureus*, *Proteus*, *Moraxella*, *Streptococcus faecalis* and *Shigella* isolates from rearing water obtained from an ACF farm exhibited MAR (Torimiro *et al*., 2014). Anyanwu *et al*. (2014) also reported 96% MAR among *Aeromonas* isolates from ACF in Nigeria.

Impact of antibacterial resistance in African catfish aquaculture on the food chain and public health

Antibacterial resistance in aquaculture has overwhelming impact on the food chain and public health (Heuer *et al*., 2009; Cabello *et al*., 2013; Vaz-Moreira *et al*., 2014). It has been observed that AR in aquaculture can easily enter the food chain undetected (WHO, 2014; Morrison and Rubin, 2015). This is because among a plethora of microorganisms in aquaculture environment, only few indicator organisms can easily be cultured unlike in livestock animals (Morrison and Rubin, 2015). Antibacterial-resistant organisms in ACF aquaculture can be transferred to humans (especially those with wounds) who come in direct contact with ACF aquaculture ecosystem. The bacterial population in fish rearing water is the same with those colonizing the fish (Cabello *et al*., 2013). Therefore, contact with fish rearing water or consumption of fish habouring ARO/ARGs can result in colonization with the organisms. Fish-farm workers or processing plant workers are more at risk of acquiring AROs since they are frequently exposed to contaminated water and/or fish in the aquaculture or in downstream handling of fish for food preparation (Harper, 2002; Petersen and Dalsgaard, 2003; Jacobs and Chenia, 2007). Due to poor infection control practices and sanitation often observed in developing countries, the AROs can be spread from person to person, magnifying the effect of their selection (Okeke and Edelman, 2001). The total mobile genetic elements (mobilomes) (i.e. water current-transported naked DNA, insertion sequences, transposons, integrative and conjugative elements [ICEs], insertion sequence with common regions [IS*CR*], integrons mobilized by plasmids, bacteriophages, conjugative transposons, and phage-like elements called gene transfer agents [GTA]) of aquatic bacteria transfer easily from aquaculture organisms to human and animal pathogens and *vice versa* (Kruse and Sørum, 1994; Jacobs and Chenia, 2007; Cabello *et al*., 2013). Movement of mobile genetic elements contributes to the emergence of novel genotypic and phenotypic variants (Canica *et al*., 2015).

Fish meal used as source of animal protein for livestock (especially poultry), may be produced using ACF which haboured AROs/ARGs or contaminated with the organisms by aquaculture workers. Following consumption, the AROs colonize livestock gut and subsequently transfer the resistomes to other organisms in the animal by horizontal transfer. The AROs are subsequently transferred to humans following ingestion of contaminated meat from the livestock or from other animals contaminated during slaughter. The colonized

livestock can also discharge the AROs/ARGs into the terrestrial and/or aquatic environment as in IACF. Natural water bodies, aquatic animals and farm crops get contaminated or colonized with AROs which continue to recycle the resistomes, genomes and mobilomes across and within different environmental settings (Vaz-Moreira *et al*., 2014; Berendonk *et al*., 2015). Discharge of fish-rearing water loaded with AROs/ARGs into the environment can also result in contamination of farm crops and vegetations (Vaz-Moreira *et al*., 2014). Consumption of contaminated vegetation/crops by animals and humans represents risk to human and animal health (Vaz-Moreira *et al*., 2014; Berendonk *et al*., 2015). Run-offs can potentially carry AROs into natural freshwater bodies and subsequently into the food chain (Vaz-Moreira *et al*., 2014; Musefiu *et al*., 2015). With the rise in international travel now worsened by surging migrant crisis, genomes and resistomes emanating from ACF aquaculture can easily spread to other parts of the world, thereby increasing the mobilome in those places (Okeke and Edelman, 2001; Canica *et al*., 2015). Colonized individuals transfer AROs directly or indirectly to livestock and aquaculture (Cabello *et al*., 2013).

It is established that mobile genetic elements associated with ARGs of bacteria recovered from aquatic environment can share very high sequence homology to clinically important plasmids and ARGs (Venner-Jeffreys *et al*., 2009; Cabello *et al*., 2013). Thus, acquisition of ARGs from aquaculture pathogens can result in compromise and jeopardy of subsequent antibacterial therapy in colonized humans and animals (Heuer *et al*., 2009; Geser *et al*., 2011; Cabello *et al*., 2013), since most antibacterial agents used in humans are similar to those used in veterinary medicine and aquaculture (Gacia-Alvarez *et al*., 2012; Canica *et al*., 2015). The cost of treatment, morbidity and mortality often resulting from acquired AR especially when associated with multidrug resistance (such as VRE, MRS, ESBL- and carbapenemase-producing organisms) is overwhelming. These multidrug-resistant organisms have been associated with most community-acquired, nosocomial and hospital-linked infections worldwide (Ewers *et al*., 2011; Kleinkuf *et al*., 2014). Plasmids harbouring multidrug-resistance genes are highly promiscuous (Abraham *et al*., 2014), a factor that may facilitate their spread from ACF aquaculture to other environmental settings and *vice versa*. Thus, the flow of antibacterial resistance in ACF aquaculture and its subsequent impact on the food chain and public health is a continuous cycle (Fig. 2). Although not within the scope of this review, the fate of antibacterial residues in aquaculture sediment and their subsequent dissemination to natural water bodies by run-offs, leaching, exposure of organisms and development of resistance in other environmental settings have been severally reported (Hektoen *et al*., 1995; Kumerre, 2004; Armstrong *et al*., 2005; Cabello *et al*., 2013; Canica *et al*., 2015).

Strategies for curbing antibacterial resistance in African catfish aquaculture

Practicable ways of minimizing the emergence and spread of AR in ACF aquaculture include: good management strategies such as the use of good quality fish stock, reducing stocking densities, maintaining overall good environmental conditions (pH, dissolved oxygen, etc), the implementation of proper biosecurity measures, development of effective vaccines and vaccination programs, proper diagnosis of diseases before treatment, and the rotation of antibacterial agents in treatment of fish bacterial diseases (Smith, 2008; Miranda *et al*., 2013). Alternative strategies to combating bacteria such as bacteriophage and probiotics therapy have been applied in other types of finfish aquaculture (Defoirdt *et al*., 2011; Cruz *et*

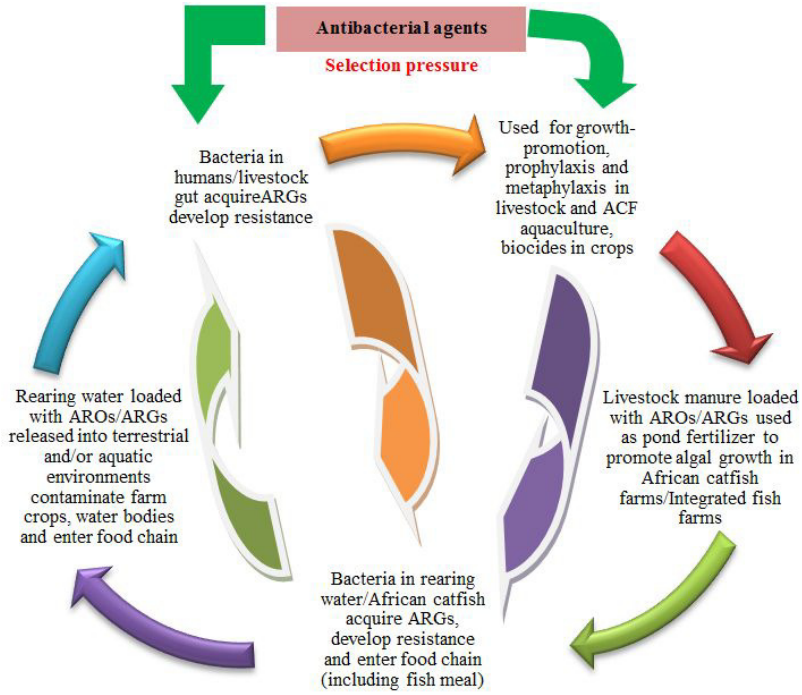

Fig. 2. Flow of antibacterial resistance [antibacterial-resistant organisms (AROs)/antibacterial resistance genes (ARGs)] in African catfish (ACF) aquaculture and impact on the food chain

al., 2012; Ibrahem, 2015). Although bacteriophages are usually host (bacterial)-specific and have a narrow-spectrum of activity, a bacteriophage with broad-spectrum activity has been used in a shrimp aquaculture (Vinod *et al*., 2006; Defoirdt *et al*., 2011). Encouragingly, a recent study in India reported a novel bacteriophage therapy for controlling metallo-β-lacatamse-producing *P. aeruginosa* isolated from ACF (Khainar *et al*., 2014). The use of probiotics in combating AR in ACF aquaculture seems very promising (Cruz *et al*., 2012; Sihag and Sharm, 2012; Ige, 2013; Ibrahem, 2015), but its limitation is that the organisms may habour ARGs which can complicate the problem of AR in aquaculture (Khainar *et al*., 2014). Some researchers (Ogunshe and Olabode, 2009; Hamid *et al*., 2012; Olayinka and Afolabi, 2013) reported the isolation of bacterial organisms that have probiotic potential from ACF, but the applicability of these organisms in ACF aquaculture is yet to be realized. Defoirdt *et al*. (2011) reported other sophisticated alternative strategies such as genome manipulation and antivirulence therapy that can be used in place of antibacterial agents in combating bacteria in aquaculture. Essential oils have also been reported to be potential alternative to antibacterial agents for combating bacteria in aquaculture (Romero *et al*., 2011; Chenia *et al*., 2015).

In the absence of vaccines, bacteriophage and probiotics therapy for ACF aquaculture for now, a rational use (i.e. adoption of treatment regimen that have improved clinical efficacy but that result in minimal selective pressure for emergence of resistant variants) of antibacterial agents can be helpful (Smith 2008). Although similar classes of antibacterial agents are used in human and veterinary medicine, rotation of antibacterial agents may be useful in reducing the chances of selection, co-selection and dissemination of AR (Miranda *et al*., 2013). The example of what happened in Europe on how AR (especially vancomycin-resistance) was controlled by minimizing their use in food-producing animals can be borrowed (Cogliani *et al*., 2011). However, because of the ease of transfer of AROs/ARGs from aquaculture environments to other ecosystems, the use of antibacterial agents in aquaculture is being discouraged (FAO/WHO/OIE, 2014). Therefore, efforts should be made by those responsible in countries where ACF is farmed to develop and register antibacterial agents for use in aquaculture and to develop strictly enforced policy guiding their use. Antibacterial resistance surveillance is the hallmark approach for controlling the crisis and for formulation of measures for mitigation. Those responsible should know that the long term effects of AR is that, even in the absence of selective pressures, when the use of an antibacterial agents is banned from an aquaculture system, genes conferring low susceptibility to that agent will persist (Tamminen *et al*., 2011; Cabello *et al*., 2013; Vaz-Moreira *et al*., 2014).

Concluding remarks

The reviewed reports have shown that ACF aquaculture represent a reservoir of diverse AROs which can habour variety of ARGs, many of which may be mobilized by lateral gene transfer. Numerous factors (particularly the use of antibacterial agents uncontrollably) are responsible for emergence of AR in ACF aquaculture, this relates to the fact that this fish species is mainly reared in less industrialized or developing countries (Okeke and Edelman, 2001; Cabello *et al*., 2013). Antibacterial resistance in ACF aquaculture impacts food chain and represents threat to animal and human health. The presence of wide variety of AROs especially the ESBLs-producing and carbapenemase-producing organisms in ACF aquaculture, is a cause for concerns as these organism can easily spread genes encoding multidrug resistance to other parts of the world and ecological niches. Change in dynamics of AR and emergence of novel phenotypic and genotypic strains can occur following transfer of ARGs from ACF aquaculture environments to other places (Miranda *et al*., 2013). The economic and health impact of AR in ACF aquaculture could be disastrous if timely efforts are not made to curb this menace.

Indeed, rapid increase in ACF aquaculture makes it imperative that research needs with regards to the use of antibacterial agents and emergence and potential spread of AR are prioritized (Miranda *et al*., 2013). Adequate, science-based policies that contribute to sustainability of ACF aquaculture industry, implementation of antibacterial stewardship and minimize risks to public health should be based on the research. Because the spread of AR in aquaculture is facilitated by genetic elements, molecular studies are needed to explore the prevalence of ARGs in isolates from ACF aquaculture environments including in zoonotic aquaculture pathogens. Knowledge gap exists on the co-occurrence of AROs from ACF aquaculture environment with human pathogens, transfer rate of resistance between ACF aquaculture and clinically relevant bacteria, and epidemiology of AR in ACF aquaculture. The emergence and prevalence of AR bacteria in ACF aquaculture setting may be greater than the reports reviewed in this study since most studies in ACF aquaculture have been limited to demonstrating AR in culturable bacteria, which constitute only a small proportion of the total bacteria present in the aquatic environment (Bissett *et al*., 2006; Cabello *et al*., 2013). Surveillance studies on AR in ACF aquaculture are needed to provide information on trends and magnitude of resistance. This review is a call for the establishment of ACF aquaculture AR surveillance monitoring programmes and for stringent policy to control the use of antibacterial agents in ACF aquaculture.

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