

The Antimicrobial Resistance (AMR):

The ICAR-CIFT contributions in addressing the problem

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The current population of India is 1,346,739,954 (at 0934hrs on 03 January 2018) constituting 17.86% of the total world population of 7,592,342,830 and, is projected to increase up to 1500 million by 2050 with a contribution of 18.95% of world population. This is exerting tremendous pressure on natural resources while meeting the demographic demands of food and nutritional security. In this context fish as food in meeting the animal protein requirements is playing a pivotal role in palatally of high end consumers to economically under privileged hinterland residents of the country. In India total fish trade is nearly one trillion. But the potential as per trade estimates is 5 trillion when the fish is processed and sold with proper hygiene, quality and shelf life. India exported 945,892 tons of seafood worth US \$ 4.7 billion in the previous financial year and it is estimated to reach US \$ 5.6 billion in the next financial year. As on today India exports marine products to more than 100 countries. The trend of exponential is plausible in the coming years as India is bestowed with abundant aquatic resources to promote culture as

well as capture fisheries. The challenges include the post-harvest losses of different foods amount to one trillion in India and out of which fish losses of (marine and freshwater) is nearly 10% or 10,000,000,000. The prevention of losses is not only helpful in meeting food security needs millions across the country but takes care of primary producer's fiscal needs in all walks of fisheries sector that includes sea food industry.

The important concern of seafoods is microbial safety. The continued occurrence of seafood and fish borne illness is not evidence of the failure of our seafood, fish and fishery products safety system. As a matter of fact, many of our prevention and control efforts have been and continue to be highly effective. In advanced countries like US where food supply is one of the safest in the world, however, significant food borne illness continues to occur. Despite great strides in microbiological food safety, much remains to be done. The new challenges in microbial safety are antibiotic residues and the concomitant development of antimicrobial resistance (AMR) in human health hazard pathogens (HHHP) and nonpathogenic bacteria.

Use of antibiotics in both animal production and human medicine has increased in recent decades and allowing the bacteria to become resistance. The subsequent transmission and spread of resistant pathogenic bacteria sets the scene for development of drug-resistant infections (DRIs). At present, DRIs are estimated to account for 50,000 deaths each year in Europe and the USA alone, but by 2050 it is estimated that DRIs will account for 10 million deaths per year worldwide, posing a possible economic burden tuning to 20 trillion \$USD and also biosecurity threat. In 2000, globally it was estimated 54 billion standard units of antibiotics have been consumed, and this figure increased by 36% in the following 10 years, creating the preconditions of a public health crisis. Use of antibiotics is fourfold increase in India. In this context the Microbiology, Fermentation and Biotechnology Division of Central Institute of Fisheries Technology is continuously working on antimicrobial resistance bacteria in seafood and aquaculture environment.

In the present day world, the antimicrobial resistant bacteria spread all over from farm to fork, hospitals, workplaces, animals, humans, soil, and oceans. They are near ubiquitous in nature. A consumer report published in 2013 indicated that more than half of ground turkey meat sold in the U.S. contained strains of drug-resistant bacteria. According to the CDC, some 2 million people in the U.S. are infected with drug-resistant bugs every year, and 23,000 of them die from these infections. Those numbers are likely to get worse in the coming decades, according to recent reports. The report on antibiotic resistance by Rustav Aminov in 2010 revealed the complexity of the imminent hazard "It is not a single grand challenge; it is rather a complex problem requiring concerted efforts of microbiologists, ecologists, health care specialists, educationalists, policy makers, legislative bodies, agricultural and pharmaceutical industry workers, and the public to deal with. In fact, this should be of everyone's concern, because, in the end, there is always a probability for any of us at some stage to get infected with a pathogen that is resistant to antibiotic treatment".

As long as antibiotics have existed, bacterial resistance has existed alongside them- but not the magnitude of present day. "The natural history of antibiotic resistance genes can be revealed through the phylogenetic reconstruction and the long-term presence of genes conferring resistance to several classes of antibiotics in nature well before the antibiotic era." The threat perception of US CDC report on AMR indicates 'simply using antibiotics creates resistance' (CDC, 2013: 14). Solutions have become problems, putting biopower out of joint. Sources of AMR included pets, supermarket meat, hospital drains, locker rooms, and lungs, guts and sores. Antibiotic resistance is a collective ecological condition of late industrialism. From the intended targets of therapeutic control, and increasingly off-target the AMR seeped into urban crows, plants, coastal waters, beached whales, lice, soil, aquarium fish etc.,

Drug-resistant infections have the potential to cause a level of economic damage similar to and likely worse than that caused by the 2008 financial crisis, according to a new report by the World Bank Group entitled "Drug Resistant Infections: A Threat to Our Economic Future." The research shows that a high-case scenario of antimicrobial resistance (AMR)-where antibiotics and other antimicrobial drugs no longer treat infections the way they are supposed to- could cause low-income countries to lose more than 5% of their GDP and push up to 28 million people, mostly in developing countries, into poverty by 2050. And unlike the financial crisis of 2008, there would be no prospects for a cyclical recovery in the medium term, as the costly impact of AMR would persist (World Bank, 2016; Adeyi Olusojiet al, 2017)



The historical developments in antibiotics & Antimicrobial Resistance are provided in Table 1

Table 1. Historical developments in Antibiotics & Antimicrobial Resistance	
Year	Type of development
350-550 CE	The discovery of Tetracycline in skeletons from Sudanese Nubia (part of ancient Egypt) disapproved the commonly held belief that antibiotics didn't exist before 1928. It is believed that ancient Nubians were actually brewing tetracycline into their beers or otherwise incorporating it into their diets over a long period of time as the same was found embedded deep in their bones and the population's documented infectious diseases seem to be quite low. It's difficult to detect other ancient antibiotics, as most didn't accumulate into bones and tooth enamel the way Tetracycline do. Records show antimalarial drug presently known as artemisinin, was used in ancient Chinese medicine. Similarly in Jordan, red soils rich in antibiotic-producing bacteria were used to treat skin infections like rashes.
1928	Alexander Fleming, a Scottish biologist, took the fight against infections to a new level when he identified penicillin, making this the year that the modern antibiotic era began. Penicillin from <i>Penicillium rubens</i> became the first compound to be used officially as an antibiotic.
1943	The mass production Penicillin saved thousands of lives army men in WW II and Alexander Fleming warned of development of resistance upon over and excessive use.
1948	The works of Robert Stokstad and Thomas Jukes, at Lederle to develop an "animal protein factor" for enhancing chicken growth and boost poultry profits through vitamin B12, believed to boost animal growth contained cellular remains of <i>Streptomyces aureofaciens</i> bacteria resulted in 24 % more growth than those receiving liver extract, with high levels of B12. This becomes basis for employment of antibiotics for animal growth. During this period, <i>Staphylococcus</i> too started developing resistance in hospitals. According to Harvard Magazine , staphylococcal resistant infections rose from 14 % in 1946 to 59 % in 1948
1952	Though scientists were aware of AMR, optimism prevailed on development of new drugs.
1955	The predictions of Alexander Fleming turned out to be true. The attempts to slow down the process of AMR by many countries in 1955 futile as it was too late: Many bacterial strains had already defeated the antibiotic, including staphylococci. At the same next 20 years are considered to be golden age of antibiotics in view of discovery of new antibiotics Such as streptomycin, to treat serious infections viz., endocarditis and plague; ampicillin, to treat respiratory tract infections and meningitis.
1960	In an attempt to overcome penicillin-resistant strains, 'methicillin was developed. But within a year, resistance to Methicillin was developed in the form of MRSA (Methicillin-Resistant <i>Staphylococcus aureus</i>). Now, MRSA leads multiple-drug resistant (MDR) bacteria.
1976	At Tufts University, Stuart Levy led from the front awareness on resistance development in bacteria due antibiotics use in animal products.
1990	A stronger resistant strain of MRSA began sickening normal, healthy people in the 1990s. This perhaps created a greater public awareness of the danger of antimicrobial resistance. In the midst of emerging superbugs and MDR bacteria, the CDC and other public health organizations began issuing public service announcements to curb the liberal use of antibiotics.
2002	60 percent of <i>S. aureus</i> cases in hospitals were resistant to Methicillin

2005	Over 100,000 Americans were stricken with MRSA infections and some 20,000 died, more than the amount of people who were dying from HIV and tuberculosis combined, according to Harvard Magazine
2012	In a 2012 study, proposal was made to add the terms extensively drug-resistant (XDR) and pan drug-resistant (PDR) to multidrug-resistant (MDR) bacteria to better help them classify and potentially defeat these superbugs. It was the first time that scientists had a unified set of definitions for MDR bacteria to better understand them.
2013	The USFDA finally implemented a plan to phase out certain antibiotic use in animals. But the extent to which this plan is effective at reducing the massive damage already done is difficult to identify.
2014	In response to major superbug outbreaks like <i>Klebsiella pneumoniae</i> the WHO released a statement noting that “this serious threat is no longer a prediction for the future, it is happening right now in every region of the world and has the potential to affect anyone, of any age, in any country.”
2015	McDonald's announced that it would phase out all meat sources that contained antibiotics, marking the first step of a major fast food company to heed the public health warnings and take action.

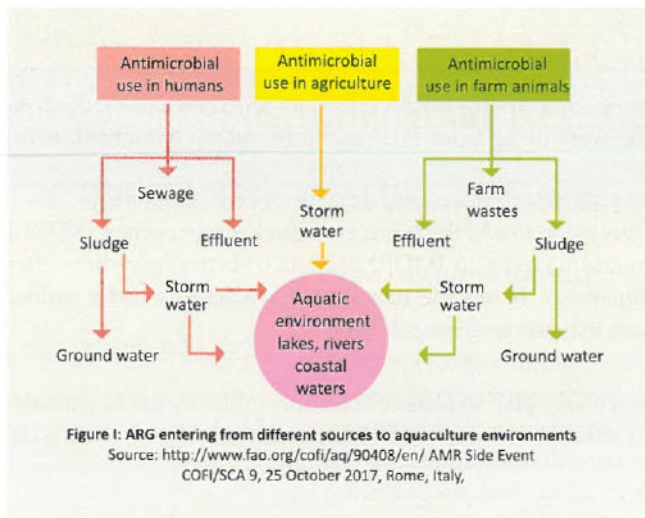
The AMR was not taken seriously in the beginning for the following reasons:

1. Altering the existing drug
2. Availability of another drug
3. Confined to non-compliant patients
4. The drug resistant mutants are rare and confined to next generation
5. Vertical genetic inheritance in nature
6. Treating it as reaction to new drugs by the same principle
7. Not treating it as fundamental challenge to the model

Antibiotics have been called a 'societal drug': when one person in a household takes an antibiotic for an extended period, for example to treat acne, density of antibiotic resistant bacteria on the skin of everyone else in the household increases. Similarly, oxytetracycline which is reported as the most widely used antibiotic for prophylactic treatment in aquaculture perhaps be called “aquaculture drug”.

Antimicrobial resistance genes (ARGs) may have evolved naturally, indiscriminate use of antibiotics in human and animal sectors has led to selection and spread of resistant bacteria. But ARGs found in aquatic systems may be derived from multiple sources. Hospital effluents carry significant pool of ARGs. There are also evidence using metagenomics approach that the abundance of ARGs in effluents entering a river catchment area is higher than that in the receiving environment (Figure 1).





FAO Action Plan on AMR: 2016-2020 Awareness

- National/regional/international fora
- Book: Responsible management of bacterial diseases in aquaculture
- CCRF Technical Guidelines on Prudent and Responsible Use of Drugs
- World Antibiotic Awareness Week (13-19 November 2017)
 Evidence: Surveillance (AMU and AMR)
 Practices: Best practice guidance (shrimp, tilapia and carp)
 Governance: Assistance to the development of the aquaculture component (within food and agriculture) of NAP on AMR

CIFT Contributions in addressing the AMR issue

CIFT is in forefront from 1980's in Antimicrobial Resistance (AMR) related research in fish and fishery products and in aquatic systems before this became a global concern. ICAR-CIFT specially Microbiology, Fermentation and Biotechnology (MFB) Division made tremendous progress in identifying the bacteria responsible for AMR in seafood and fish curing environments viz., *Listeria monocytogenes*, *Salmonella*, *Vibrio parahaemolyticus*, *Vibrio cholerae*, *Escherichia coli*, *Staphylococcus aureus*. Advanced studies were also carried on Extended Spectrum Beta Lactamase (ESBL) producing *E. coli* and Methicillin Resistant *Staphylococcus aureus* (MRSA), their molecular characterization, identification of a new clone of MRSA r15669 and latest feather in cap is the whole genome sequencing (WGS) of MRSA isolated from the contaminated seafood. Aquatic products or sea-foods exported to the other developed countries increasingly tend to get rejected due to the presence of antibiotics residues which cause not only serious financial loss to the seafood industry and dent to much needed foreign exchange. In a neglected case scenario by 2050 the mortalities at global level will be 10 million and

the health care expenditure is estimated to be ₹ 1300 trillion annually. In this regard CIFT has made significant contributions in source tracking of microbial contaminants and also guiding the seafood industry in production of safe foods.



Taking cue from the global concern, in the last year itself CIFT has organized FAO sponsored meeting wherein the scientists from various parts of country were brought together for chalking out the research projects and possible remedial measures associated with the AMR. World AMR awareness week was also observed from 13 to 19 November 2017 at CIFT. Expert speakers were invited to deliver lectures on AMR in Indian perspective, and also taking this serious issue to school and college students and public in the forms of delivering lectures by scientist of MFB Division of CIFT. Recently an ICAR sponsored winter school on "Antimicrobial resistances in fish and aquatic environment and its impact on human health" was organized from 01 to 21 December 2017. Participants from 9 states viz., Andhra Pradesh, Arunachal Pradesh, Kashmir, Kerala, Madhya Pradesh, Rajasthan, Uttar Pradesh, Uttarakhand and Tamil Nadu belonging to other ICAR institutions, State agricultural universities, Veterinary colleges, State Officers, in the profile of Scientist, Assistant professors, Associate professors, Field Officers etc.

Series of lecture cum demonstrations were delivered on very important issues of antimicrobial resistance viz., starting from history of antimicrobial resistances dating back to 350 CE to the recent additions, methods to determine antimicrobial resistance both qualitatively and quantitatively, molecular fingerprinting tools to source tracing the contamination, alternative to antibiotics and recent advances in gene editing called CRISPR (Clustered Regularly Interspaced Short Palindromic Repeats). It is indeed a great pleasure for CIFT to play a forerunner role in frontier research areas in AMR and seafood safety and at the same time it shares that knowledge in the form of imparting training, conducting workshops to various stakeholders associated with the fisheries sectors. Further CIFT is open for the inter-institutional collaborative research to find long lasting solutions to the problems of AMR before it leads to a catastrophic proportion not only in aquatic environment but also in public health sector.