ANTIMICROBIAL RESISTANCE: A GLOBAL MENACE: ONE HEALTH APPROACH[†]

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Human civilization is at risk of zoonotic infection via direct contact due to close proximity with livestock/poultry/fish, environmental contamination, and intake of contaminated food items which causes enormous economic losses due to loss of man-days and associated production level. The situation becomes more complicated due to transmission of antimicrobial resistant bacteria into human food chain from livestock or fishes. It creates mortality and extra financial burden associated with increased treatment cost and prolonged hospital stay. Recent estimate indicates about possibility of 10 million deaths every year due to infection with antimicrobial resistant organisms to be occurred by 2050 which is even more than projected death by cancer. This is a multifactorial and complex issue which is associated with several core sectors such as human and animal health, fishery, agriculture, environment etc. We have wasted a sufficient time in 'blame game' to each other. Time has come to work together under same umbrella with a true 'One medicine: One world: One health' approach. Considerable efforts and initiatives are taken by different Universities / Institutes / Private Companies to address the issue to sustain normal production and productivity of animals, poultry and fishes.

Key words: Antimicrobial resistance, Food animals, One health, Veterinary

Human civilization is at risk of zoonotic infection via direct contact due to close proximity with livestock/poultry/fish, environmental contamination, and intake of contaminated food items which causes enormous economic losses due to loss of man-days and associated production level. The situation becomes more complicated due to transmission of antimicrobial resistant bacteria into human food chain from livestock or fishes. It creates mortality and extra financial burden associated with increased treatment cost and prolonged hospital stay. Every year 700,000 people lose their life battling to antimicrobial resistance (AMR) and 10 million deaths throughout the world is projected from it by 2050 which is even more than projected death by

cancer (Taneja and Sharma, 2019). Bacterial resistance to antibiotics is an immediate threat to human, livestock, fish and environment all over the world. This problem has tormented clinicians and policy makers but it seems there is no straightforward way to outwit this problem. The issue of AMR has become so crucial that United Nations held a special meeting in 2016 to monologue only this issue (Holpunch, 2016). In that meeting, the issue was said to be of as much significance as climate change and it was considered to require a global response (Holpunch, 2016).

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human and animal health, fishery, agriculture, environment etc. We have wasted a sufficient time in 'blame game' to each other. Time has come to work together under same umbrella with a true 'One medicine: One world: One health' approach. Considerable efforts and initiatives are taken by different Universities / Institutes / Private Companies to address the issue to sustain normal production and productivity of animals, poultry and fishes.

AMR: Global peril

Increase in antibiotic resistant poses a remarkable threat to development, food security and health. Economic prognosis estimates that AMR would reduce gross domestic product (GDP) by 2-3.5% with a drop in livestock by 3-8%, costing USD 100 trillion to the world by 2050 (O'Neill, 2014). In 2019 AR Threats Report, it was reported that more than 2.8 million antibiotic-resistant infections occur in the U.S. each year, and more than 35,000 people die as a result i.e. is roughly one death from ABR every 15 minutes and one infection every 11 seconds (CDC, 2019). By trainings, technical support and workshops, WHO supported 57 low and middle income countries to monitor AMR. Since the AMR, was prioritized by World Health Organization (WHO), several world chief from Europe and other parts of the world has framed their action plans for the regulation of AMR (Smith *et al.*, 2016). It will be a big provocation to address the problem for the health care providers and policy makers. Consumption of antimicrobial in production of food animal, globally, is expected to increase as high as 67% by 2030 by BRICS countries (Brazil, Russia, India, China and South Africa) thus shifting to intensive farming system in large scale where sub-therapeutic doses of antibiotics are used routinely (Brower *et al.*, 2017). WHO established Global Antibiotic Resistance Partnership (GARP) to develop short and long term policy recommendations in low and middle income countries (India, Kenya, South Africa and Vietnam) where the MDR is severe. Considering AMR as a global threat, UN General Assembly in New York considered AMR as the fourth health related issue in September 2016 preceded by HIV, non-communicable diseases and Ebola (ICAR News, 2019).

AMR: Indian peril

India carries one of the largest loads of drug resistant pathogens worldwide as it is one of the world's largest consumers of antimicrobial drugs. By 2050, two million deaths are estimated to occur in India due to AMR (Gelband *et al.*, 2015). The current mortality rate of infectious disease in India is 416.75/100,000 persons (Laxminarayan *et al.*, 2013) which is double the rate present in United States where it is 200/100,000 persons (Armstrong *et al.*, 1999). Unbridled use of antimicrobial agents in livestock, hospitals, aquaculture farms and poultry, aimless disposal of waste and wastewater from animal farms, municipalities and pharmaceutical industries into lakes, rivers and other water bodies over the years, have contributed to the development of colossal issue of antibiotic resistance (Shivagami *et al.*, 2020). In the recent times, the quantity of diet obtained from wheat and rice gradually decreased and the intake of animal protein grew from seven to twenty-five grams per capita in five decades (CDDEP, 2017). Because of the increasing demand, there is an increasing trend to establish commercial livestock and poultry farms, and aquaculture establishments in developing countries.

Research on AMR in India

Out of 2152 studies, 48.3%, studies were done on humans while 4.2% studies done on environment, 3.3% studies on animals, 0.5% studies on 'One Health' and the rest were miscellaneous (Gandra *et al.*, 2017).

In commercial livestock, poultry farms and in aquaculture, the antibiotics are used mainly for three reasons, i.e. therapeutic, metaphylaxis and as antibiotic growth promoters. Because of the partial metabolism of antimicrobials, most of the antibiotic dose (30-80%) given to animals that are used for food are excreted into the environment. Also the antibiotics which are included in animal feeds will reach the soil sediments directly. Another origin of antimicrobial contamination in environment is through use of waste generated by animal farms which are used as manure to fertilize

the soil (Ramesh, 2016). Most of the antibiotics are deposited in aquatic systems such as rivers and lakes. If the soil is loaded with these antibiotics it becomes the best source for spreading antibiotic resistant bacteria through agricultural practices. For example, *Pseudomonas* and *Acinetobacter* which are opportunistic pathogens residing in soil, can acquire antibiotic resistance genes from the soil and become resistant bacteria (Argudin *et al.*, 2017). Antibiotics are also used in aquaculture sector for prophylactic and therapeutic purposes. There is a common practice where the organic waste from poultry and livestock which are sometimes rich in resistant bacteria are fed to farm fish under the integrated farming system. It is in fact 70-80% antibiotics end up in the environment which are used in the aquatic farming (Washer and Joffe, 2006).

Some studies on AMR in India are as follows:

AMR research in humans: Resistance rate among bacteria that cause infections in India is high. Rajivgandhi *et al.* (2018) identified TEM, SHV, OXA and CTX-M genes in ciprofloxacin resistant uropathogen strains. Out of 300 blood samples collected from clinically diagnosed neonatal septicemia from tertiary care center, South India, 97.43% of *K. pneumoniae* and 2.56% of *K. oxytoca* were ESBL producers (Anitha and Anuradha, 2019). Mehdi and Neema (2018) estimated the prevalence of beta-lactamase production among *Enterobacteriaceae* on routine basis using simple phenotypic methods. They found 38.11% of isolates were ESBL producers followed by 3.20% isolates were MBL producers and 0.56% were AmpC producers out of 530 *Enterobacteriaceae*. Out of 180 *P. aeruginosa* isolates, 23.88% isolates were isolated from pus and 18.88% isolates were isolated from urine. In these samples, 59.01% isolates were MBL producers, 27.71% isolates were ESBL producers and 21.66% isolates were Amp C producers. And 14.11% isolates showed co-production of ESBL/AmpC/MBL production, 18.89% isolates were MDR, 1.66% were XDR (Choudhary *et al.*, 2018).

AMR research in food animals: The same antibiotics which are used commonly in humans

are sometimes used in food animals, raising the concern of effectiveness of these antibiotics in human health. Meta-analysis report of animals on India suggested that the pooled prevalence of ESBL were 26, 11, 6 and 8% on north, east, south and central zones, respectively and 12, 5, 8, 8, 12, 13 and 33% for the years 2013, 2014, 2015, 2016, 2017, 2018, 2019, respectively and the species wise stratified results showed a predominance of 11% ESBL producing *K. pneumoniae* strains compared to *E.coli* (7%) and *Pseudomonas* spp. (5%) (Kuralayanapalya *et al.*, 2019). Mahanti *et al.* (2018) detected the presence of CTX-M producing *Klebsiella* spp. in healthy broiler, indigenous and kuroiler birds reared in West Bengal during November 2014-February 2015. Out of 321 cloacal swabs, 10.7% of *Klebsiella* spp. isolates were CTX-M producers whereas 51.5% possessed blaSHV and 48.5% possessed blaTEM with blaCTX-M genes, respectively which could be transmitted to the human food chain directly or indirectly. Out of 219 faecal samples collected from piglets with diarrhoea, pig farmers and water sources in North-East India, 66.98%, 70.91%, and 56.25% were ESBL producers and 9.68%, 1.21%, 2.02% were recorded as Shiga toxin *E.coli* (STEC). 59.38% of STEC isolates harboured ESBL/beta-lactamase genes with 32.81% STEC isolates being positive for multiple ESBL/beta-lactamase genes (Puii *et al.*, 2019). Out of 450 composite milk samples collected from all agro-climatic zones of West Bengal, 9.6% of *S. aureus* detected were methicillin resistant *S. aureus* (MRSA) whereas 12.8% and 4.3% isolates possessed staphylococcal enterotoxins *sei* and *seg*, respectively (Mahanti *et al.*, 2020).

AMR research in fishery: Situation of aquaculture is different from that of livestock. Out of total 131 bacteria isolated, resistance pattern of streptomycin, cephalixin, rifampicin and nitrofurantoin were found to be more than 60% both by marine and freshwater bacterial isolates (Sunder *et al.*, 2006). Saharan *et al.* (2019) obtained 160 faecal fish samples from Rajasthan, out of which 95% of *E.coli* and *Salmonella* spp. Isolates were resistant against streptomycin while

for *S. aureus* it was observed against trimethoprim. Singh *et al.* (2017) collected fresh seafood from retail market from Western Mumbai between August 2013 and April 2014. They observed that 90% of the isolates were resistant to 3rd generation cephalosporins and 65% of the isolate were resistant to aztreonam, 40.82% resistant to ertapenem and 31.36% were resistant to meropenem. Within these 38.46% isolates were MDR and 76.92%, 63.3% and 44.37% of the isolates were detected with blaCTX, blaSHV and blaTEM genes. Moreover, blaNDM was detected in two of the ESBL isolates.

AMR research in environment: Use of animal manure in agriculture is one of the common practices in India. Waste of animal is one of the main links in spreading AMR as they generally containing ARB. Water sources laden with ARB and ARGs are being reported from various parts of India. Pharmaceuticals waste water and hospital effluents are also released into water bodies without any treatment contaminating the environment. Out of 18 agricultural sampling points in Kalyani, West Bengal 158 multidrug resistant bacteria were isolated and 90% of them were resistant against cefotaxime and 68.75% of isolates harbored at least 2 ESBL genes and 31.25% either have blaSHV or blaTEM gene (Sen and Sarkar, 2018). The rate of ESBL producers was 17.4% among gram negative bacteria isolated from north Indian rivers with detection of resistance genes like *bla*_{NDM} and *bla*_{oxA} (Azam *et al.*, 2016).

Lacunae on AMR control: Due to the poor management of waste which contains antibiotics, ABR bacteria, ARGs from pharmaceutical factories, farms, healthcare settings, it has led to the emergence and spread of AMR. Limited awareness among public and government commitment, over the counter sale of antibiotics, endemic infections, malnutrition, poor sanitation, weak surveillance and regulatory system, availability of inexpensive antibiotics, and poor income are creating the perfect conditions for a large-scale selection and dissemination of ABGs in India. Evaluation of nationwide comparison of

AMR rise and fall in India is also prevented by lack of adequate research. While many research have been done to study the resistance profiles of bacteria isolated from poultry, livestock and aquaculture, mechanism of AMR, resistant bacteria biology, expanding the existing antimicrobials chemical diversity and using non-antibiotic agents as substitutes, the reason for antibiotic use during animal rearing and rate of antibiotic used are poorly represented in published literature. There is not much research into the rapid antimicrobial susceptibility diagnostics, qualitative studies on farmer's knowledge and the antibiotic they use in their operations.

Conclusion

The One health approach spotlights the inter-relatedness among animal health, human health, environment and food and fosters synergistic efforts on the part of health officials dealing with these spheres (Dahal *et al.*, 2017). This condition is worsen by the fact that the environmental contribution for AMR resistance differs geographically all over the world and hence conditions established by one developed nation may not be applicable in developing nations like India. India has recently launched National Action Plan (NAP) on AMR in April 2017 along with 'Delhi declaration on Antimicrobial Resistance' supported by 12 stakeholder ministries with the key strategy to promote investment for research to mitigate the issue (Government of India, 2017).

In March 2018, a set of draft standards for antibiotic discharge in pharmaceutical industry effluents was prepared by Central Pollution Control Board (CPCB). Government of India has also launched a 'National Programme on Containment of Antimicrobial Resistance' during the 12th Five Year Plan (2012-2017) under which 10 medical colleges and labs were included initially and afterwards extended to 20 state medical colleges from 18 states (as of October 2018) to tackle this issue. FAO in alliance with Indian Council of Agricultural Research (ICAR) organized a meeting at Kolkata, India on 7-8th March 2017 and facilitated establishment of Indian

Network for Fishery and Animals Antimicrobial Resistance (INFAAR) with sole objective to generate nationwide, structured, quality data through surveillance and research on AMR specific to livestock and fisheries sectors for strengthening knowledge and better understanding of AMR. In India, the Ministry of Agriculture's early implementation of programs such as Assistance to the States for Control of Animal Diseases (ASCAD), the National Animal Disease Reporting System (NADRS), and the National Livestock censuses, indicates that the

capacity for widespread data collection is in place, and more extensive data collection on antibiotic use in farming may be possible in the coming years (CDDEP, 2016). However, many of the planned activities on AMR surveillance have yet not been completed due to lack of cooperation between central and state governments. "What India needs is a clear roadmap for two things- one to phase out use in animals of antibiotics which are critically important for humans, and two, to stop antibiotic misuse for mass disease prevention", says Khurana (CSE assessment, 2018).

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