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Antimicrobial resistance in humans and livestock population in India

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ABSTRACT

Antimicrobial resistance (AMR) is considered as one of the biggest threats to modern civilization. The review is published with a view to provide awareness about this growing menace, which if not monitored and controlled could lead to major public health consequences with greater economic impact. Very little data and information is available regarding AMR in livestock and aquaculture. An attempt was made to collate the available information on AMR subsequent to constitution of INFAAR (Indian Network on Fishery and Animals Antimicrobial Resistance) by ICAR and FAO, in reference to National Action Plan on AMR by GoI in April, 2017.

Keywords: AMR, Antibiotics, Aquaculture, INFAAR, Livestock, Resistance

India, being a developing country, tackling the AMR problem is a huge challenge keeping in mind the existing preparedness and infrastructural capabilities. Among the key factors responsible for AMR in India are the irrational use of antibiotics in livestock production and hospitals. This allows the resistant strains to take over and the sensitive one gets killed or eliminated from the environment. Incidence of resistance to last resort antibiotics is reported frequently from time-to-time in India specifically in bacteria from hospital environments. Globally, *E. coli*, *K. pneumoniae*, and *S. aureus* are the three agents of greatest concern, associated with both hospital- and community-acquired infections. There is negligence in the public health care delivery system with regard to quantification of the AMR problems and various determining factors related to antimicrobial resistance. There is an urgent need to develop and strengthen antimicrobial policy, standard treatment guidelines, real time national plan for containment of AMR and research related to public health aspects of AMR at community and hospital level in India.

Antimicrobial resistance (AMR) is a stark reality across the globe, including India. Increased antimicrobial (commonly called as antibiotic) use is leading to increase in AMR in both humans and animals as resistant bacteria can be transmitted between human and animals through contact, food products and the environment. The challenges associated with controlling antibiotic resistance, particularly in India, are many and multifaceted, hence require multifaceted solution. Antibiotics are necessary in many life-threatening cases, however, injudicious use of antibiotics can be disastrous in the long run. Little efforts were done to tackle the proliferation of antibiotic resistant bacteria until the detection of New Delhi metallo-beta-lactamase-1 super bug in 2008 (Yong *et al.* 2009), which put policy makers, health specialists and researchers to put emphasis on AMR as a serious problem and developed policies and strategies to control/monitor this burgeoning problem.

The limited information and data available through research articles and government publications indicate that AMR is a major problem in India, and that the use of antibiotics in agriculture is widespread (Taneja and Sharma 2019). As per 2010 estimate, India accounts for 3% of global consumption of antibiotics and is among the top consumers worldwide, along with China, the United States, Brazil and Germany (Van Boeckel *et al.* 2015). Worldwide, there were significant increases in use of the two 'last-resort' antibiotic classes: carbapenem (approximately 40%) and polymyxins (13%). The growth in retail carbapenem sales was particularly steep in India, Pakistan and Egypt (Boeckel *et al.* 2014). In India, hotspots for consumption include the south coast, Mumbai and Delhi.

There is no national level data on AMR in humans in India, but limited data available from published studies indicate high resistance to frontline and 'last-resort' antibiotics in bacteria-causing common infections. These common bacteria encountered in hospitals and humans include *Escherichia coli* and *Klebsiella pneumoniae*, which are associated with urinary tract and bloodstream

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infections; *Staphylococcus aureus*, which is associated with skin and bloodstream infections and *Pseudomonas aeruginosa*.

In livestock and environment, the most common bacteria reported are *Pseudomonas, Aeromonas, P. aeruginosa*, *Enterobacter* spp., *Salmonella* typhi, *Salmonella* paratyphi, and *Enterococcus* spp.

World Health Organization (WHO) is working closely with the Food and Agriculture Organization of the United Nations (FAO) and the World Organization for Animal Health (OIE) in a 'One Health' approach to promote best practices to avoid the emergence and spread of AMR including optimal use of antibiotics in both humans and animals.

Antibiotic resistance in human hospitals and surrounding areas

Hospitals around the world are notorious places where bacteria thrive and are transmitted from patient to patient, often through unsuspecting healthcare workers. The crowded conditions in many public hospitals, including those in India, are prime territory for bacteria. Many of the bacteria found in hospitals are resistant to a large range of antibiotics (sometimes to some of the last resort antibiotics). Among the key factors responsible for resistant bacteria in India are the widespread use and availability of practically all the antimicrobials across the counter, increasing and unnecessary use of antibiotics in livestock production, inappropriate doses, and irrational use of antibiotics in hospitals. This allows the resistant strains to take over and the sensitive one gets killed or eliminated from the environment.

The estimation of World Health Organization (WHO) for healthcare associated infections (HAIs) among hospitalized patients globally is about 7% to 12%, conversely among Indian hospitals, it ranges from 11% to 83% (Rama *et al.* 2014). In Indian hospitals, *E. coli*, *S. aureus*, *K. pneumonia* and *P. aeruginosa* appear to be the common causes of hospital-acquired infections, along with a few other pathogens (GARP 2011). The worldwide estimates of global antibiotic resistance, published by WHO list *E. coli*, *K. pneumoniae*, and *S. aureus* as the three agents of greatest concern, associated with both hospital- and community-acquired infections (WHO 2016). India has a number of the highest antibiotic resistance rates among bacteria that frequently cause difficult-to-treat infections in the hospitals and community. Resistance to the fluoroquinolones and third generation cephalosporin was more than 70% in *A. baumannii*, *E. coli*, and *K. pneumoniae*, and more than 50% in *P. aeruginosa* (Gandra *et al.* 2017).

The carbapenem group of antibiotics is one of the last-hope antibiotics in humans to combat severe bacterial infections and resistance to carbapenem class amongst gram-negative bacteria was tremendously elevated (Gandra *et al.* 2016). The highest carbapenem resistance was observed in *A. baumannii*, followed by *K. pneumoniae, P. aeruginosa* and *E. coli* (Gandra *et al.* 2017). In India, colistin is generally used to treat carbapenem-resistant gram-negative bacterial infections, which consequently resulted in emergence of colistin resistance among these bacteria (Kaur *et al.* 2017, Manohar *et al.* 2017). It has been documented that blood stream infections owing to carbapenem cum colistin resistant *K. pneumoniae* are allied with 69.3% mortality among patients (Kaur *et al.* 2017). Nevertheless, known colistin resistance genes *mcr-1* and *mcr-2* which are plasmid-mediated were seldom encountered. Antibacterial resistances in humans by bacteria are discussed below.

Staphylococcus aureus

S. aureus is often found as a commensal on the bodies of healthy individuals and can survive for days and months on dry surfaces. It can also cause range of problems, from minor skin infections to pneumonia, sepsis and meningitis. *S. aureus* bacteremia bears significant mortality and is chiefly caused by methicillin resistant *S. aureus* (MRSA). MRSA is the most recognizable antibiotic resistant bacterium worldwide and it has become a common problem in hospitals and communities. Nasal carriage of *S. aureus* among health care providers make them reservoir and disseminator of MRSA not only to the hospitalized patients but also to the community at large (Thilakvathy *et al.* 2015). Although MRSA is declining in most of the western countries, it is still rising in sub-Saharan Africa, India (47%), Latin America (90%), and Australia (CDDEP 2015).

In most countries, about 20% of antibiotics are used in hospitals and other healthcare facilities, and 80% are used in the community, either prescribed by healthcare providers or purchased directly by consumers or caregivers, without prescription (Kotwani and Holloway 2011). Unknowingly, half of the community use of antibiotics, especially for coughs and colds, is inappropriate. In fact, it does not treat, but adds to the burden of antibiotic resistance. Hospitals generate some of the most dangerous and difficult-to-treat infections, as a result of heavy use of antibiotics (especially in LMICs, where antibiotics may substitute for infection control), especially in immune-compromised and elderly/chronic patients. MRSA is now endemic in India. Its incidence varies from 25% in Western India to 50% in South India (Patel *et al.* 2010, Gopalakrishnan *et al.* 2010). MRSA was recorded at 47% in India in 2014 (CDDEP 2015), increased from 41% recorded in hospital isolates during 2013 (Joshi *et al.* 2013). MRSA strains are often resistant to a range of antibiotics and recent reports hinting growing resistance to vancomycin is alarming and worrisome because vancomycin is the 'last-resort' drug for treating MRSA. Penicillin used to be the first-line drug of choice to treat *S.aureus* infections but is now useless in most regions due to resistance. In 1993-94, 24% of 1,382 strains of *S. aureus* isolated from pus and blood sample in Vellore were reported to be MRSA, and among the MRSA strains, resistance to gentamicin, norfloxacin, ciprofloxacin, co-trimoxazole and netilmicin was above

75% for each (Pulimood *et al.* 1996). The Indian Network Surveillance of Antimicrobial Resistance (INSAR) conducted a comprehensive analysis based on 26,310 isolates of *S. aureus* during 2008–09 from 15 tertiary care hospitals. Of these 41% were found to be MRSA. None were resistant to vancomycin and linezolid (INSAR 2013).

Various studies conducted in India have revealed that MRSA is distributed among all of the major staphylococcal cassette chromosome *mec* (SCC*mec*) types. Most of the hospital associated (HA) MRSA isolates fit in to SCC*mec* type III and sequence type (ST) 239. On the contrary, community associated (CA) MRSA mostly belong to ST22 (SCC*mec* IV), ST772 (SCC*mec* V) and ST672 (SCC*mec* V) genotypes. Analogous to the global picture, CA-MRSA is turning more invasive with higher transmissibility potential and also becoming tricky to be differentiated from HA-MRSA (Sunagar *et al.* 2016). Vancomycin has been the cornerstone in the treatment of MRSA infected patients. One study from the Sher-e-Kashmir Institute of Medical Sciences reported that 22 of 120 MRSA strains from clinical samples had intermediate sensitivity to vancomycin, although none was fully resistant (Assadullah *et al.* 2003).

Publications around the world including India, have reported prevalence of vancomycin resistant *S. aureus* in the range of 0% to 74%. In Northern India, two vancomycin resistant and six vancomycin intermediate *S. aureus* were isolated from different clinical specimens screened between 2002 and 2005 (Tiwari and Sen 2006). In 2008, 16 and 7 strains of the 358 methicillin resistant *S. aureus* isolates from clinical samples in Hyderabad, showed intermediate sensitivity and resistance to vancomycin, respectively (Thati *et al.* 2011). Another study reported that, among Gram-positive bacteria, the fraction of methicillin-resistant *S. aureus* (MRSA) was 46.5% and vancomycin resistant and linezolid-resistant *S. aureus* were also reported as 1.6% and 0.7%, respectively (Gandra *et al.* 2016). A study involving 47 *S. aureus* isolates collected over 2 years (2013 to 2015) from blood samples of patients admitted to one hospital in Odisha revealed 60% MRSA. AST showed that 2 isolates were highly resistant to vancomycin, linezolid and tigecycline. Both the isolates harbored *mecA* (methicillin resistant), *VanA* (vancomycin resistance) and CFR (linezolid resistance) genes. This study provides evidence for the emergence of multiresistant MRSA with co-resistance to vancomycin, linezolid and tigecycline (Kumar 2016). Increased exploitation of vanocomycin has resulted in the emergence of MRSA with decreased susceptibility to vancomycin (Niveditha *et al.* 2015). Many alternatives for treatment of MRSA infection including linezolid and daptomycin are currently approved by the USA Food and Drug Administration (FDA). Teicoplanin is currently not approved by the FDA for use in the USA but is widely used in Europe, Asia and South America. But, the emergence of resistance to linezolid and daptomycin in MRSA isolates has also been reported (Dortet *et al.* 2013, Basireddy *et al.* 2014,). Daptomycin can be used as alternative agent for the treating MRSA infections. However, it should be set aside as reserve drug since it has clear therapeutic advantage over other anti-MRSA drugs (Husain *et al.* 2018).

Pseudomonas aeruginosa

P. aeruginosa is commonly found in soil, water, and biofilms, and living as planktons. *P. aerugionosa* has become one of the most troublesome pathogens associated with range of infections including septicaemia, pneumonia, lower respiratory tract infections, chronic suppurative otitis media and cystic fibrosis. Aminoglycosides, cephalosporins, fluroquinolones and carbapenems have been used for treating *P. aerugionosa* implicated ailments (Chaudhary and Payasi 2013). However, resistance of *P. aeruginosa* to β-lactams, carbapenems, quinolones and aminoglycosides has been developed (Mehta *et al.* 2007, Rajat *et al.* 2012, Paulet *et al.* 2017). In a hospital study of burn patients, 96% of 42 *P. aeruginosa* isolates were multidrug resistant with a high resistance to tobramycin and amikacin (Shahid and Malik 2005). A large-scale study of 10,835 patients in 7 hospitals in Indian cities between 2004 and 2007, found 29% of *P. aeruginosa* resistant to ciprofloxacin, 65% to ceftazidime, 42% to imipenem and 43% to piperacillin-tazobactam (Mehta *et al.* 2007). During 2009-10, among the 100 clinical *P. aeruginosa* isolates from tertiary care hospital in Ahmadabad, 68%, 63%, 50%, 49%, and 43% were resistant to tobramycin, gentamicin, piperacillin, ciprofloxacin, and ceftazidime, respectively (Rajat *et al.* 2012). Another study in Trauma center hospital in New Delhi recorded 95.5%, 95.2%, and 76.7% of the 2,224 *P. aeruginosa* isolates resistant to tetracycline, chloramphenicol, and meropenem, respectively (Rajkumari *et al.* 2014).

Hospital samples in Kolkata reported 75% of *Pseudomonas* spp isolates were resistant to aminoglycosides (Paul *et al.* 2017). Number of mechanisms are involved in the development of resistance in *P. aeuroginosa* like, efflux pump, modification of target regions, weakened outer membrane permeability, structural alterations of topoisomerases II and IV determining quinolone resistance, de-repression of chromosomal AmpC cephalosporinase, synthesis of aminoglycoside-modifying enzymes (phosphoryltransferases, acetyltransferases and adenylyltransferases), metallo-β-lactamases (MBLs) and extended spectrum β-Lactamases (ESBLs) acquisition (Li *et al.* 1995, Manchanda and Singh 2003, Strateva and Yordanov 2009, Zavascki *et al.* 2010). The simultaneous presence of the above said mechanisms in *P. aeruginosa* is troublesome and thereby it confers multi-resistant phenotypes (Strateva and Yordanov 2009).

Studies conducted in India showed 20-45% ESBL production in *P. aeruginosa* (Aggarwal *et al.* 2008, Chaudhary and Payasi 2013). Several studies have also documented the prevalence of MBLs among *P. aeruginosa* varying from 7 to 20% (Gupta *et al.* 2006, Varaiya *et al.* 2008, Chaudhary and Payasi 2013). Interestingly an

investigation conducted in Himachal Pradesh revealed that 14.36% *P. aeuroginosa* isolates co-produced both ESBL and MBL (Chaudhary and Payasi 2013).The co-existence of MBLs in carbapenem-resistant *P. aeruginosa* has also been demonstrated in Puducherry (Ellappan *et al.* 2018). The emergence of multi-drug resistant *P. aeruginosa* has created many clinical challenges and treatment failures. In the cephalosporin class of antibiotics, ceftazidime is often prescribed in treating Pseudomonal infections because of its exceptional anti-pseudomonal activity. However, resistance to ceftazidime is rising alarmingly (Upadhyay *et al.* 2010, Tripathi *et al.* 2011).

The carbapenems and β-lactam and β-lactamase inhibitor combination such as piperacillin plus tazobactam are the antibiotics frequently opted to combat ESBL producing *P. aeruginosa*. However, resistance to these drugs has also been growing (Gupta *et al.* 2006). Infections associated with MBLs generating *P. aeruginosa*, ceftriaxone plus disodium edetate plus sulbactam (Elores) can be the drug of choice for the treatment (Chaudhary and Payasi 2013). Recently doripenem is found to be susceptible to *P. aeruginosa* which are not susceptible to meropenem, imipenem (Negi *et al.* 2017).

Escherichia coli

E. coli is a coliform bacterium commonly found in the lower intestine of warm-blooded organisms and in the environment. Most *E. coli* strains are harmless but some serotypes produce toxins and can cause serious food poisoning, urinary tract infections and neonatal meningitis. Urinary tract infections (UTIs) are the most common bacterial infection in women. *Presently* UTI caused by the multi-drug resistant *E. coli* are gaining momentum due to irrational usage of antibiotics. Studies from India have witnessed that *E. coli* as one of the most common organisms causing UTI (Hasan *et al.* 2007, Kothari *et al.* 2008). Formation of bacterial biofilms inside the urinary bladder leads to recurrent infections and amplifies the likelihood of MDR strain causing UTI (Elder 2007).

Diarrhoeagenic *E. coli* (DEC) is accounted as one of the principal causes of diarrhoea and other gastrointestinal disorders. Antibiotics are not usually needed as diarrheal disease is generally self-limiting. However, traveller's diarrhoea, acute invasive diarrhea and persistent diarrhoea, in which *E. coli* is usually, associated, exhibit severe infection and long recovery time which warrants the use of antibiotics such as ampicillin, cefixime, nalidixic acid, norfloxacin and cotrimoxazole. This leads to the development and spread of multi-drug resistance (Thakur *et al.* 2018). *E. coli* produces extended-spectrum-beta-lactamase (ESBL), an enzyme responsible for resistance to many antibiotics including penicillin and cephalosporins. Over 80% of *E. coli* isolates in India are ESBL producers (CDDEP 2015); and as per 2013 data, 13% were resistant to carbapenems, an increase of 3% since 2008. *E. coli* strains carrying the New Delhi metallo-β-lactamase (NDM-1) enzyme, first reported in 2008 in India, are now found worldwide both in clinical as well as environmental samples.

In India, *E. coli* isolated from the community showed high overall resistance to ampicillin, nalidixic acid, and co-trimoxazole (75%, 73%, and 59%, respectively) between 2004 and 2007 (Holloway *et al.* 2009). Antibiotic resistance in *E. coli* isolated from urine samples collected from Christian Medical College, Vellore, showed 42% of commensal *E. coli* resistant to at least one antibiotic, and 8% were resistant to ampicillin, co-trimoxazole and nalidixic acid (Mathai *et al.* 2008). Another study in rural school children in Tamil Nadu, found that 63% of 119 *E. coli* isolated from stool samples were resistant to at least one antibiotic and 32% were resistant to more than one antibiotic (Kaul *et al.* 2007). India, especially New Delhi, also has high levels of ciprofloxacin resistance among community-acquired *E. coli* isolates, meaning there is likely a large reservoir of resistance genes among healthy *E. coli* carriers in the community (CDDEP 2009). Study conducted by Eshwarappa *et al.* (2011) in South India revealed that *E. coli* was the most frequent microorganism causing UTIs with extended spectrum beta-lactamase which also evidenced slight resistance against carbapenems (3.9%) and an elevated resistance to most of the common antibiotics. Since 2008 to 2013, *E. coli* resistance to third generation cephalosporins increased from 70% to 83%, and fluoroquinolone resistance increased from 78% to 85% (CDDEP 2015). Of late, in *E. coli* due to the existence of ESBL and AmpC enzymes, carbapenems have turned into the drug of choice to treat such kind of infections. However, resistance to carbapenems owing to carbapenemase production poses further therapeutic challenges (Livermore and Woodford 2006).

A study conducted among healthy children of rural Central India concluded that commensal *E. coli* may turn as potential reservoirs of cephalosporins and fluoroquinolones resistance spread and virulence coding genes like tx_1, stx_2, *eae, bfp, etc.,* for urinary tract and diarrheal infections (Chandran *et al.* 2017). *E. coli* strain carrying a plasmid-borne new gene (mcr-1) was reported in 2016, and this strain was resistant to colistin-considered as the last mile antibiotic, the human race currently has access to (Kumar *et al.* 2016). Seventy percent of human *E. coli* isolates in Gardi Medical College, Ujjain, Central India, showed multi-drug resistance properties and co-resistance was frequent against penicillin, cephalosporin, and quinolone (Purohit *et al.* 2017). For the first time, the co-emergence of *blaNDM-16* and *mcr-1*–producing *E. coli* clinical isolates was encountered in India (Kumar *et al.* 2016).

In light of the findings of several studies, it is evident that commonly used antibiotics for various therapeutic reasons are rapidly becoming obsolete owing to the emergence of MDR bacteria or the so-called superbugs. The multidrug resistance acquired by the *E. coli* isolates may be involved in the dissemination of such resistance

among other nosocomial *E. coli* isolates. Such spread of MDR may profusely affect the empiric therapy of common *E. coli* infections and also pave way for the co-selection of the antimicrobial resistance which is mediated by MDR plasmids.

Klebsiella pneumoniae

Klebsiella is ubiquitously present in the mouth, skin and intestines of human, but it can also cause urinary tract infection, ventilator-acquired pneumonias and blood stream infections (sepsis) especially in immune-compromised individuals. *K. pneumoniae* readily colonizes mucosal surfaces like gastrointestinal tract and oropharynx (Rock *et al.* 2014). In immunocompromised persons, it marches into other sites ending in severe infections (Paczosa and Mecsas 2016). It is a common cause of difficult-to-treat community and hospital acquired infections. *K. pneumonia* isolates of nosocomial origin are most often capable of producing ESBLs, carbapenemases such as *K. pneumonia*e carbapenemase (KPC) and NDM, consequently ending up as a therapeutic challenge (Nordmann and Poirel 2014). Globally, NDM-1 was first reported in 2008 in a *K. pneumoniae* isolate from a patient from Sweden, earlier hospitalized in New Delhi, India (Yong *et al.* 2009). Apart from producing ESBL and carbapenamase enzymes they are often resistant to multiple antibiotics. *K. pneumonia* resistance rates to third-generation cephalosporinsare above 30% in most WHO member countries and exceed 60% in some regions (WHO 2014).

From 2008 to 2014, *K. pneumoniae* isolates resistant to third-generation cephalosporins decreased from 90% to 80%, and fluoroquinolone resistance increased from 57% to 73% in India (CDDEP 2015). Carbapenems are considered as the 'last-resort' antibiotics, often used to treat *K. pneumoniae* infections that are resistant to all other known agents, but incidence of carbapenem resistant strains are increasing at an alarming rate. India has the highest incidence of carbapenem-resistant *K. pneumoniae* anywhere in the world. Overall, 29% *K. pneumonia* were resistant to carbapenem in 2008, increasing to 57% in 2014 (CDDEP 2015). Carbapenem resistance among *K. pneumoniae* increased from 2% in 2002 to 52% in 2009 in one tertiary-care hospital in New Delhi (Datta *et al.* 2012). Recently, a carbapenem resistant *Enterobacteriaceae* (CRE) identified as *K. pneumoniae* was isolated from a 70 years old patient in USA who had extended trip to India. This isolate believed to be originated in India was resistant to 26 different antibiotics, including all aminoglycosides and polymyxins (CDC 2017). In India, carbapenems are frequently used to treat *K. pneumoniae* infections, as most of them are high ESBL producers (Ah *et al.* 2014). Rising carbapenem resistance and limited treatment options available for carbapenem resistant *K. pneumoniae* has forced the healthcare professionals to employ colistin (polymyxin E) and tigecycline as last resort drugs for treating infections caused by such *K. pneumoniae* (Carmeli *et al.* 2010). However, due to irrational sustained use of colistin, its resistance is increasing recent days (Pragasam *et al.* 2016, Kaur *et al.* 2017, Manohar *et al.* 2017). Colistin resistance is largely interceded by LPS moiety modification with the addition of positively charged (L-Ara4-N and PEtN) molecules (Falagas *et al.* 2010). This alteration reduces the negative charge of the outer membrane, limiting its interaction with colistin (Velkov *et al.* 2013). This modification arises due to mutations in the two component regulatory systems. The most common mutations are in *mgrB, phoP/phoQ, pmrA, pmrB, pmrC*, and *crrABC* (Cheng *et al.* 2010, Wright *et al.* 2015). Of late, plasmid mediated colistin resistance i.e. *mcr-1* encoding for phosphoethanolamine transferase has been reported in *E. coli* and *K. pneumoniae* from China (Liu *et al.* 2016). Subsequently, in Italy, *mcr-1.2* which is a variant of *mcr-1*, was recognized in KPC producing *K. pneumoniae* (Di Pilato *et al.* 2016) followed by the *mcr-2* gene from Belgium (Xavier *et al.* 2016). Alarming rise in newer resistance mechanisms in a very short period is worrying. A recent study from Christian Medical College, Vellore, India analyzed eight colistin resistant *K. pneumoniae* isolated from bloodstream infections.

The results identified various alterations including silent mutations, point mutations, insertions and/or deletions. Notably, mutations in *mgrB* gene were found responsible for resistance to colistin. No colistin resistant isolates harbored *mcr-1* and *mcr-2* genes (Pragasam *et al.* 2016). In a single center study, bloodstream infections due to carbapenem- and colistin co-resistant *K. pneumoniae* were associated with 69.3% mortality among Indian patients (Kaur *et al.* 2017). Worryingly, India is also one of the leading producers of colistin for veterinary use (Liu *et al.* 2016). To save the last resort drug and to prevent the further spread of resistance, irrational use of colistin in hospitals and agriculture sectors should be forbidden.

Salmonella

Salmonella enterica subspecies are found worldwide in all warm-blooded animals and in the environment, but *S. bongori* is restricted to cold-blooded animals, particularly reptiles. Strains of *Salmonella* cause typhoid fever, paratyphoid and food poisoning. In India, Indian Council of Medical Research (ICMR), through the Anti-Microbial Resistance Surveillance Network, set up in 2011, has focused on *Salmonella* enterica serovar Typhi (*S.* Typhi) and *Salmonella* enterica serovar Paratyphi A (*S.* Paratyphi A). Enteric fever caused by *S.* Typhi and *S.* Paratyphi continues to be one of the major public health problems in developing countries like India. Antimicrobial therapy is indispensable in enteric or typhoid fever treatment. Fever may become serious in 30% cases due to complications in the absence of suitable antibiotic therapy. From 1996-1999, 105 drug resistant *S.* Paratyphi were isolated from hospitals in and around New Delhi with 32% of strains resistant to ciprofloxacin, the drug of choice for treating

this disease in India (Chandel and Choudhary 2000). During 2007, 67% of the *S*. Typhi, isolated from children admitted to hospitals in New Delhi had multidrug resistant profiles. Sensitivity was below 35% for ampicillin, co-trimoxazole, chloramphenicol and amoxicillin, and less than 80% for norfloxacin, ciprofloxacin andcefotaxime (Kumar and Gupta 2007). Increased incidence of MDR *S*. Typhi, (resistant to chloramphenicol, ampicillin, and co-trimoxazole with or without tetracycline) has been reported from various parts of India which restricted the use of these antibiotics in typhoid therapy (Saha *et al.* 1992, Pillai and Prakash 1993). Following this, in adult patients, ciprofloxacin was used as the drug of choice for the treatment of typhoid. But recurrent ciprofloxacin usage guided to the global emergence of nalidixic acid resistant *S*. Typhi and *S*. Paratyphi A allied with diminished susceptibility to ciprofloxacin (Chandel and Chaudhry 2001, Mohanty *et al.* 2006, Menezes *et al.* 2011). Subsequently, emergence of ciprofloxacin resistance in *S*. Typhi and *S*. Paratyphi A supplemented the treatment failures (Manchanda *et al.* 2006, Menezes *et al.* 2011). Resistance to fluoroquinolones among invasive *S.* Typhi isolates in India increased from 8% in 2008 to 28% in 2014. As per the report based on large private laboratory network in India: 2008-2014, ciprofloxacin resistance in *Salmonella* spp. increased from 13% in 2008 to 22% in 2014 (Gandra *et al.* 2015). However, resistance in 2014 to two older antibiotics-ampiciliin (5%) and co-trimoxazole (4%) is decreasing and much lower than the rates of resistance to fluoroquinolones. During 2002-2010, 77 non-typhoid *Salmonella* strains were isolated from clinical samples from 7 states of Northern India and the resistance profile observed were 77%, 58%, 35%, 23.5%, and 33% to nalidixic acid, amoxicillin, norfloxacin, co-trimoxazole, and ciprofloxacin, respectively (Taneja *et al.* 2014). Another study by Kavita *et al.* (2010), in Gulbarga, Karnataka, found 10% of the 95 clinical and environmental *S*. Typhi isolates, to be multi-drug resistant (amipicillin, chloramphenicol and co-trimoxazole). A network of microbiology laboratories of leading hospitals in India (under the Indian Network for Surveillance of Antimicrobial Resistance) reported 83% of the 2,511 *S. enteric* serovar Typhi and 93% of the 764 *S. enteric* serovar Paratyphi resistant to nalidixic acid, and sensitive to third generation cephalosporins (Indian Network for Surveillance of Antimicrobial Resistance Group 2013).

Some sporadic reports of resistance of *S. enterica* to higher generation cephalosporins like ceftazidime, cefuroxime, cefotaxime wiped away even the last option for treating typhoid fever (Pokharel *et al.* 2006, Rotimi *et al.* 2008, Al Naiemi *et al.* 2008). Thereafter, azithromycin has been used as a successful alternative; however, resistance to azithromycin has also been reported from India and other countries (Molloy *et al.* 2010, Rai *et al.* 2012). The trend of multidrug resistance in *Salmonella* suggests that, azithromycin, may be used with caution for empirical treatment of enteric fever.

Acinetobacter

Acinetobacter is usually non-virulent in healthy people, although it commonly causes nosocomial infections of the skin and wounds, bacteraemia and meningitis. They are innately resistant to some antibiotics, but new patterns of resistance have emerged. *A. baumannii*, once considered as opportunistic, low virulence pathogens now become a troublesome pathogen in healthcare settings. *A. baumannii* is basically resistant to a range of antibiotics and capable of acquiring resistance genetic determinants from the environment (Dijkshoorn *et al.* 2007). Resistance to β-lactams in *A. baumannii* is due to production of beta lactamases or modification of membrane permeability or expression of efflux pump or loss/decrease in outermembrane porin expression (Dijkshoorn *et al.* 2007, Roca *et al.* 2012). Carbapenems are used for the treatment of infections caused by MDR *A. baumannii.* However, resistance to carbapenems is emerging and gaining attention worldwide. Carbapenem resistance in *A. baumannii* can be either carbapenemase mediated like production of serine proteases, metallo-beta-lactamases and oxacillinases or non-carbapenemase mediated like higher expression of efflux pumps or loss/decrease of outer membrane porins (Poirel and Nordmann 2006). However, development of resistance against carbapenem in *A. baumannii* is most often due to intrinsic or acquired oxacillinases. The intrinsic *bla*OXA-51 gene is believed to be specific for *A. baumannii*, as the gene is located in its chromosome (Kim *et al.* 2014). *Acinetobacter* isolates from clinical samples screened during 2005-06, in SKN Medical College and General Hospital, Pune, India, showed high resistance to ampicillin (100%), third- and fourth-generation cephalosporins, fluoroquinolones and aminoglycosides (Shete *et al.* 2010). One hundred fifty *Acinetobacter* isolates from clinical samples of St. John's Medical College and Hospital in Bengaluru were found resistant to multiple antibiotics, including third-generation cephalosporins, but sensitive to carbapenems and cefoperazone-sulbactam. Extended-spectrum β-lactamases (ESBL) were detected in 28% of isolates, and 36% of isolates were found resistant to ciprofloxacin (Sinha *et al.* 2007). In another study, more than 80% of the 265 *Acinetobacter* spp. were resistant to second- and third-generation cephalosporin, aminoglycosides, and quinolones. Resistance to cefoperazone/sulbactam and meropenem were also observed in 30% and 6% of the strains respectively (Gaur *et al.* 2008).

High levels of resistance was seen for ampicillin-sulbactam (96%), ampicillin (94%), aztreonam (94%), cefuroxime (92%), and ceftazidime (91%) in 53 *Acinetobacter* spp. isolated from clinical specimens in SMI Hospital, Dehradun, in 2013 (Dimple *et al.* 2016). A study from South India has reported 34–93.6% carbapenem susceptibility in *A. baumannii* isolates (Saranathan *et al.* 2015). So, presently *A. baumannii* isolates are resistant to most of the antibiotics and emergence of pan drug-

resistance and extremely drug-resistance are reported (Park *et al.* 2009). Colistin and tigecycline are the last hope antibiotics left to treat MDR *A. baumannii* infections (Cai *et al.* 2012). However, resistance against colistin have also been reported in India and other parts of the world (Oikonomou *et al.* 2015, Gupta *et al.* 2016).

Antibiotic resistance in Livestock/food animals

More antimicrobials are used in livestock production to maintain health and to increase productivity than are used by the entire human population. Chickens and pigs consume most of the antibiotics used in food animals around the world. The amount of antibiotics used in aquaculture worldwide is also increasing alarmingly. Significant amounts of the antibiotics used by people and animals eventually find their way into the environment, particularly in surface and ground water and in soil. Antibiotic-resistant bacteria arise and spread in animals and in the environment and may cause human disease. The projected increase in antibiotic use in food animals is a result of an increase in human population, from 7 billion today to an expected 9 billion to 10 billion by 2050, and increasing global prosperity. Demand for meat and other animal products is predicted to nearly double in the next 35 years. According to the FAO, meat consumption will increase by 73% and dairy consumption by 58% over 2011 levels (FAO 2011). In 2010, China was estimated to consume the most antibiotics in livestock, followed by the United States, Brazil, Germany, and India (Boeckel *et al.* 2015).

Presently, no global picture of antibiotic resistance in food animals exists. In the laboratories around the world, high levels of antibiotic-resistant bacteria were found in all types of animal products. The highest resistance levels were recorded for the most frequently used antibiotics: tetracyclines, sulfonamides, penicillins, and streptomycins (CDDEP 2015). In addition, livestock associated methicillin resistant *S. aureus* (LA MRSA) and extended-spectrum beta-lactamase *E. coli* (ESBL *E. coli*) is emerging problems throughout the world including India (Grace 2015). Resistant *Salmonella* and *Campylobacter* species are commonly found in animal products and pose significant risks to human health, especially in India. A joint report from the FAO, OIE, and WHO, identified these food-borne pathogens as priorities for research and risk assessment (Elliott 2015). The food animals receive antimicrobials from many sources and ways. It may be through direct or indirect routes. The direct source is through animal growth promoters, which is sub-therapeutic or low dose. It is included in feed to improve feed conversion efficiency and lean to fat ratio (Hao *et al.* 2014). Indirect routes are mainly through contaminated environment. The contamination may be in the form of antibiotic treated animal or human excreta, effluents from pharmaceutical industries (Kummerer 2009). Partially treated such wastes contaminate the surface water bodies. By drinking such water, food animals may get exposed to high/low doses of antibiotics. Alarmingly in India, effluent from water treatment plants was found to hold 31 mg/L of broad spectrum fluoroquinolone antibiotics, including ciprofloxacin (Larson *et al.* 2007).

In Hyderabad, high concentrations of antibiotics (ciprofloxacin 14 mg/L, enrofloxacin up to 0.16 mg/L, norfloxacin up to 0.52 mg/L) were detected in lake water and effluents of treatment plant (Fick *et al.* 2009). In addition, high amount of antibiotic resistant genes (ARGs) were demonstrated in soils manured with animal excreta and river water polluted by animal farm run offs (Martinez *et al.* 2008, Knapp *et al.* 2010). Further, in India, rising incomes and a growing population are driving an increased demand for animal products. This transition is causing a shift into intensive farming, and in order to stay competitive producers often rely on antibiotic as a stopgap in place of improving hygiene and sanitation in large-scale operations and the practice gained widespread use during the early 1950s. These have exerted selection pressure on gut microbes in animals and on other bacteria in the aquatic environment (FAO/OIE/WHO 2006). The antimicrobial resistance may get transmitted from food animals to humans through various modes such as through food, direct contact, antibiotic residues in manure, environmental contamination etc.

India is one of the top consumers of agricultural antibiotics worldwide, accounting for 3% of global consumption which is, estimated to double by 2030. This is leading to the detection of resistant bacteria and antibiotic

Table 1. Fluoroquinolone resistant enterobacteriaceae (*E. coli* and *K. pneumoniae*) in food animals

State	Species	Occurrence mean (%)	PMQR	Efflux pumps	QRDR
Tripura	Lactating cattle	9.56	qnrA, qnrB, qnrS, aac(6′)-Ib-cr	QepA AcrAB	Mutation in gyrA and ParC
Mizoram	Lactating cattle	14.1			
West Bengal	Lactating cattle	11.3			
	Poultry	19.56			
	Buffalo	2.3			
Jharkhand	Lactating cattle	12.8 (6.6-22.7)			
	Poultry	20.9 (12.9 – 32)			
Odisha	Lactating cattle	10.37 (5.9-17.6)			

Source: Samiran Bandopadhyay (2018). https://cdn.cseindia.org/userfiles/CSE-pdf)

Table 2. Occurrence of MRSA is substantially low in Indian livestock

State	Species	Occurrence mean (%)	SCC mec*	SPA*	MLST*
Tripura	Lactating cattle	2.17	SCC mec type IVa, V and NT	t005, t202, t267, t524, t527, t740, t800, t852, t3626, t4463, t4931, and t6297 Novel spa type t15798 (caprine) t16344 (buffalo)	ST-63, ST-71, ST-97, ST-2219, ST-1297,
Mizoram	Lactating cattle	1.26			
Haryana	Lactating cattle	5.64			
West Bengal	Lactating cattle and goats	1.66			
	Pigs	3.27			
	Buffalo	0.84			
Odisha	Lactating cattle	1.66 (0.28 – 5.3)			

Source: Samiran Bandopadhyay(2018). https://cdn.cseindia.org/userfiles/CSE-presentation.pdf

residues in bovines, chickens, fish and other related food products. In many cases, the same strains of resistant bacteria are found in animal, human, and environmental sources within the same community.

A number of researchers in India have isolated bacteria from animals or seafood and tested them for resistance to common antibiotics. The levels of resistance reported are consistently high in food animals including livestock, poultry, fish, and shellfish. Resistance has been detected in *Staphylococcus*, *P. multocida* and other bacteria in poultry, reaching 100% resistance to some drugs (Shivachandra *et al.* 2004, Dhanarani *et al.* 2009).

Bovine

Multi-drug resistant bacteria are frequently encountered in bovine samples throughout India. Fourteen *E. coli* O157 strains isolated from stool samples of adult cattle and diarrhoeic calves in West Bengal showed resistance to most commonly used antibiotics: nitrofurantoin (57%), co-trimoxazole (29%), tetracycline (2%), and ampicillin (21%). Seventy-one percent of the strains were resistant to at least one antibiotic, and over 50% were multi-drug resistant (Manna *et al.* 2006). Antibiotic resistance pattern observed in 55 STEC isolates recovered from diarrhoeic calvesin Kashmir valley were 51% resistant to oxytetracycline and nalidixic acid, and 42% to co-trimoxazole, 21% to oflaxacin, 18% to enrofloxacin and chloramphenicol (Kawoosa *et al.* 2007). About 20-30% of *S. aureus* isolates from milk samples of mastitis cow and buffalo were resistant to tetracycline, gentamicin, erythromycin, and lincomycin (Kumar *et al.* 2011). Similarly, *S. aureus* isolates from milk samples of mastitis cattle were resistant to streptomycin (36%), oxytetracycline (34%), and gentamicin (30%), and 13% were methicillin-resistant (Kumar *et al.* 2011). Another study on mastitis cattle found that resistance to ampicillin, carbenicillin, and oxacillin were near 100% for all bacteria tested (Dutta *et al.* 2007). Analysis of milk and milk products from shops in Mizoram showed similar resistance patterns, with complete resistance against ampicillin as well as high resistance to penicillin (87%) and cefotaxime (59%) (Tiwari *et al.* 2011). A similar study in Meghalaya found 12.5% of *E. coli* strains isolated from mastitis cow milk were found multi-drug resistant (Ghatak *et al.* 2013). In 2015, high concentrations of coagulase-negative *Staphylococci* (64.8%), *Streptococci* (18.1%), *E. coli* (9.8%) and *S. aureus* (7.3%) were isolated from mastitis dairy buffalo in South India and found that majority of pathogens were resistant to multiple antibiotics, especially betalactams (Preethirani *et al.* 2015). Multiple drug resistant *E. coli* and *S. aureus* strains were also reported from raw milk samples in Rajasthan. Ampicillin, ciprofloxacin, and norfloxacin resistant *Staphylococcus, Streptococcus, Escherichia coli, Klebsiella, Salmonella* were recovered from 25 raw milk samples in Aizawl Town between October 2013 and February 2014, and numerous resistance pattern and high ESBL producing pathogens (61.54%) were present (Karuppasamy *et al.* 2015). Presence of ESBL producing *K. pneumoniae* were reported from milk samples of healthy, sub-clinical, and clinical mastitis cow of West Bengal, Jharkhand and Mizoram (Koovapra *et al.* 2016).

MRSA isolates of bovine milk samples showed 86.36% and 95.45% strains resistant to penicillin and ampicillin, respectively (Mausam *et al.* 2017). In dairy farms of Dehradun, *E. coli, Salmonella* and *S. aureus* isolated from raw milk samples showed that strains of *S. aureus* were resistant to penicillin and erythromycin, *Salmonella* was resistant to streptomycin and tetracycline while *E. coli* to tetracycline and chloramphenicol (Pant *et al.* 2013). Reports are available on gram-negative bacteria from milk obtained from cows with mastitis carrying NDM-1 (Ghatak *et al.* 2013) and ESBL (Das*et al.* 2017). Another study reported isolation of vancomycin-resistant *S. aureus* (VRSA) strains from mastitis milk samples (Bhattacharyya *et al.* 2016).

Porcine

Consumption of antibiotics in piggery sector is one of the highest in India, used either for control of diseases or to increase production. This has led to development of antibiotic resistant microbes at an alarming rate and many multi-drug resistant bacteria are encountered regularly. In the North East region, 72 *P. multocida* isolates from swine showed 70% resistant to amikacin, streptomycin, penicillin-G, and vancoymcin (Dutta *et al.* 2009). In another instance in Mizoram, 80% resistance to ampicillin, cefixime, erythromycin, lincomycin, nalidixic acid, oxytetracycline, roxythromycin, sulfadiazine, and penicillin were seen in 774 *E. coli* strains isolated from piglets with or without diarrhea (Dutta *et al.* 2011). In

Assam, 14.4% of the 782 *E. coli* isolates from piglet faecal samples were Shiga toxin producing strains and their antibiotic resistance profiles were ampicillin (100%), tetracycline (99%), streptomycin (98%), lincomycin (97%), nalidixic acid (95%), sulfadiazine (94%), penicillin (92%), gentamicin (88%), kanamycin (85%) and ceftriazone (85%). Ninety-seven isolates showed resistance to more than 2 antimicrobials, and 8 resistance groups (Rajkhowa and Sharma 2014). Similarly, 49 MRSA strains isolated from pigs of North East India were resistant to penicillin. Seventeen resistance groups were observed where 87.75% isolates showed multidrug resistance. The most predominant resistant group observed was oxytetracycline + penicillin + sulfadiazine + tetracycline accounting 12.24% of the isolates (Rajkhowa *et al.* 2016). *E. coli* isolated from pork samples collected from local markets of Mathura, Uttar Pradesh were found to be resistant to one or more commonly used antibiotics screened (ciprofloxacin, ampicillin, nitrofurantoin, gentamicin, cotrimoxazole, trimethoprim, kanamycin, erythromycin and norfloxacin) (Sharma and Bist 2010).

In a cross sectional study conducted in ten government organized piggery from seven states of India, out of 112 *E. coli* isolated, 23 were found phenotypically resistant to carbapenem and 8 isolates carried *blaNDM* gene (Pruthvishree *et al.* 2017). In the same sampling population, 243 isolates were phenotypically confirmed as ESBL producers (Nirupama *et al.* 2018). Nirupama *et al.* (2018) also reported 27 carbapenem resistant *E. coli* from pigs, however, only three of them carried carbapenem-resistance gene OXA-48. Such instances of carbapenem resistance without the presence of carbapenemase gene was also noticed by other workers from eastern India and it possibly indicated towards other resistance mechanism like overproduction of beta-lactmase as reported by Koovapra *et al.* (2016). Multilocus sequence typing (MLST) of blaOXA-48-positive *E. coli* isolates - ST10- and ST5053-like sequence showed the evidence of possible public health linkage. Of late, Tewari *et al.* (2019) reported IMP, SIM type metallo β-lactamase producing *Escherichia coli* from livestock and poultry in Northeastern India. Presence of multiple beta-lactamases were recorded by several workers particularly in pig isolates. Lalruatdiki *et al.* (2018) reported co-occurrence of ESBL genes and CMY-2 in pigs from North Eastern India and Samanta *et al.* (2019) also reported abundance of such co-producers in pig. Various reports suggested that ESBL producers from other food animals also harboured multiple resistance genes including those conferring resistance to tetracycline, aminoglycosides and fluoroquinolones as recently reported by Bandyopadhyay *et al.* (2019) in buffaloes.

Poultry

The level of resistance in Indian poultry is reported to be high for many antibiotics. In 1995, isolates of *Enterococcus* from State Duck Farms in Assam showed total resistance to oxytetracycline, chlortetracycline, erythromycin, oleandomycin, lincomycin and clindamycin. Some strains were also resistant to streptomycin and nitrofurantoin, and high sensitivity remained only for chloramphenicol (Saikia *et al.* 1995). Across 11 states in India, 123 *P. multocida* strains isolated from chickens and other birds showed 100% resistance to sulfadiazine. Majority of isolates were also resistant to amikacin, carbenicillin, erythromycin, and penicillin (Shivachandra *et al.* 2004). Suresh and colleagues reported *Salmonella* in 7.7% of 492 eggs in South India in 2006 and found 100% resistance to ampicillin, neomycin, polymyxin-B, and tetracycline (Suresh *et al.* 2006). Multi-drug resistant *Staphylococcus* spp. (120) and other bacteria also observed in poultry litter in Salem, Tamil Nadu, showing resistance to streptomycin (75%), erythromycin (57%), tobramycin (54%), ampicillin (50%), rifampicin (46%), and kanamycin (40%) (Dhanarani *et al.* 2009). An investigation carried out to study antimicrobial resistance in *Salmonella* isolated from chicken eggs revealed multi-drug resistance and all the isolates were found resistant to bacitracin, polymyxin-B and colistin, whereas sensitivity was recorded for ciprofloxacin, streptomycin and enrofloxacin (Singh *et al.* 2010).

Twenty-one non-typhoidal *Salmonella* resistant to oxytetracycline were also isolated from poultry farms in Southern India (Saravanan *et al.* 2015). The first systematic study of multi-drug-resistant ESBL-producing *E. coli* in Indian poultry and cattle found 18 of 316 *E. coli* isolates sampled in Odisha were ESBL producers and were resistant to oxyiminocephalosporins and monobactam, as well as a host of other antibiotics (Kar *et al.* 2015). Ruban and coworkers, in 2017, reported 66.7% chicken meat of retail outlets harbored MRSA where the methicillin resistant observed was 67.5% (Ruban *et al.* 2017). Eleven *Helicobacter pullorum* isolates from retail poultry markets in Hyderabad city, India, showed 100% resistant to multiple antibiotic classes such as fluoroquinolones, cephalosporins, sulfonamides, and macrolides. The isolates were also found to be extended-spectrum-lactamase producers and were even resistant to clavulanic acid (Qumar *et al.* 2017). Another study also documented CTX-M-producing *Klebsiella* spp. in broiler, indigenous, and kuroiler birds reared in West Bengal. In this study, 10.7% *Klebsiella* spp. isolates were detected phenotypically as CTX-M producers and all the isolates possessed *blaCTX-M* gene (Achintya *et al.* 2018).

In Punjab, Brower *et al.* (2017), reported that broiler farms were more likely to harbor resistant *E. coli* than layer farms and increased prevalence of multidrug resistance (94% compared to 60% in layers), including prevalence of ESBL producing strains (87% compared to 42% in layers). Recently, Ghafur *et al.* (2019) reported both chromosomal and plasmid-mediated colistin resistance in *Escherichia coli* and *Klebsiella pneumonia* isolated from various food samples including poultry meat, mutton meat, fish, fruit and vegetables, collected from food outlets in Chennai. Of 110 samples, the author recovered three *E. coli* harbouring *mcr-1* and 10 *Klebsiella pneumonia* with alteration in mgrB leading to colistin resistance.

Fishery/Aquaculture

The aquaculture situation is slightly different from that in livestock, and in general, feed for aquaculture is not manufactured with antibiotics, but may be added to the feed by the farmers themselves. Aquaculturists in many parts of India use various antibiotics such as oxytetracycline, ampicillin, enrofloxacin, ciprofloxacin, sparfloxacin, and other drugs for prophylaxis, treatment and to improve larval survival. Responsible use of antibiotics in the hatcheries is lacking and these have contributed to the development of drug resistance. So, an extensive ban on antibiotics in aquaculture was put in place by the Food Safety and Standards Authority in India which include tetracycline, oxytetracycline, trimethoprim, and oxolinic acid, all below 0.1 mg/kg feed (Gazette 2011). In spite of multiple regulation steps and guidelines, more and more antibiotic resistance bacteria are reported regularly in both freshwater- and sea-fish. For instance, 90 *Vibrio* spp. isolated from shrimp hatcheries and ponds on the East coast were resistant to ampicillin (100%), chlortetracycline (66%), erythromycin (53%) and all seven *Aeromonas* spp. showed resistance to ampicillin, streptomycin, kanamycin and furazolidone. Isolates from hatcheries were more resistant than isolates from ponds (Vaseeharan *et al.* 2005). In a study conducted in south India, total 319 strains of *A. hydrophila* were isolated from 536 fish and 278 prawns for a 2-year period. The isolated strains were tested for its antibiotic susceptibility against 15 antibiotics and were found 100% resistant to methicillin and rifampicin followed by bacitracin and novobiocin (99%) (Vivekanandhan *et al.* 2002). Similarly, *Aeromonas caviae* and *Aeromonas schubertii* obtained from fish and water samples of North India were resistant to erythromycin, furazolidone and penicillin. Oxytetracycline was found to be effective against 60% of the isolates (Rathore *et al.* 2005).

In 2009, oxytetracycline resistant isolates comprising *Flavobacterium* (21%), *Alcaligenes* (14.5%), *Aeromonas* (11%), *Pseudomonas* (10%) and *Enterobacteriace* (19%) were isolated from freshwater carp aquaculture systems in Lucknow and nearby areas. Dominant genus were Flavobacterium (23%) and Enterobacteriace (41%) (Singh *et al.* 2009). *E. coli* O157:H7 isolates from fish and shrimp samples of retail markets in Cochin were bacitracin and polymyxin-B resistant (Surendraraj *et al.* 2015). Jayayignesh *et al.* 2011, reported *A. hydrophila* isolated from diseased catfish resistant to ampicillin, amoxicillin, erythromycin, clindamycin, cloxacillin, oxytetracycline and streptomycin; and also similar strains recovered from fish of retail markets in India showed resistant to ampicillin and colistin (Kaskhedikar and Chhabra 2010). Another study involving shrimp, shellfish and clams collected from fish markets of Kerala, *Vibrio* species associated with food poisoning were found 100% resistant to ampicillin but turned sensitive to chloramphenicol (Sudha *et al.* 2014). A study from Cochin and Mumbai coast reported that 252 *S. aureus* isolates obtained from 105 fishes carried only one MRSA isolate, while resistance to tetracycline, vancomycin and TMP-SMX, was 3.2%, 0%, and 4.8%, respectively (Visnuvinayagam 2015).

Eighty two multi-drug resistant *V. parahaemolyticus* were isolated from finfish samples from four retail fish outlets in and around Cochin, with high resistance to ampicillin (89%), streptomycin (89%), carbenicillin (83%), cefpodoxime (80%), cephalothin (80%), colistin (77%), and amoxicillin (63%) (Sudha *et al.* 2012). In another study conducted in Estuaries in Cochin and Kumarakom and a shrimp farm located along the southwest coast of India, the incidence of *V. coralliilyticus* was very high and they exhibited multiple antibiotic resistances towards amoxicillin, ampicillin, carbenicillin, oxytetracycline, trimethoprim, nitrofurantoin, furazolidone, sulphamethoxasole, and erythromycin (Reshma *et al.* 2016). In a study conducted in Tilapia fish collected from urban rivers and lakes, 42% entero-bacteriaceae recovered from the fish guts were found to be ESBL producers (Marathe *et al.* 2016).

FAO in collaboration with ICAR organized a meeting at Kolkata, India on 7-8 March 2017 and facilitated establishment of a national network of veterinary laboratories for antimicrobial resistance (AMR) in India. Provisionally the network has been named as Indian Network for Fishery and Animals Antimicrobial Resistance (INFAAR). The meeting, attended by 32 experts and senior officials from the Indian Council of Agricultural Research (ICAR) finalized the core structure of network, its broad functions, quality component and also identified the activities to be undertaken by INFAAR. A high-level advisory body comprising ICAR officials, senior scientists and external experts shall be established by ICAR to guide all aspects of network, review the data generated and have an oversight on its operations. INFAAR shall be gradually expanded to include laboratories from other sectors subject to their meeting the criteria on competence and willingness to agree to the mandate of the network. National Institute of Veterinary Epidemiology and Disease Informatics, Bengaluru (NIVEDI) shall coordinate the overall technical and data management operations of the network. National Bureau of Fish Genetic Research (NBFGR) shall collaborate with NIVEDI in coordinating technical activities of laboratories from fishery sector. INFAAR shall extend support to researchers in undertaking studies on AMR. FAO shall provide technical assistance to INFAAR in strengthening national efforts to mitigate AMR in India.

Initiatives in India

Importance of AMR as a major challenge has been accepted by India during past few years. In 2011, the Health Ministers of all 11 Member States of the WHO South-East Asia Region signed a declaration – popularly called as Jaipur Declaration to prevent and contain AMR articulating national commitment to combat this growing menace of AMR. Subsequent to WHA 68.7, enunciation of acceleration of efforts to contain AMR in the UN Sustainable Development Goals (SDGs) and the political

declaration by the United Nations General Assembly asking all Member States to develop respective National Action Plan against AMR (NAP), India finalized its NAP in May 2017. This NAP is an example of One Health approach in which equal parts are to be played by health, veterinary and environment sectors. The implementation of NAP has begun but requires greater energy.

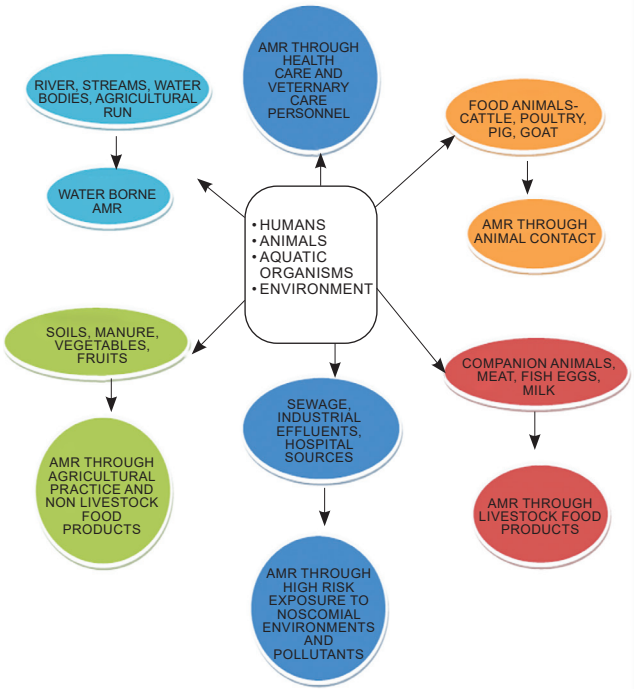
Conclusion

This review focuses on prevalence of antibiotic resistance in humans, food animals and fishes in India. The widespread exploitation of antibiotics along with easy transmission of resistance determinants among bacteria mediated by plasmids, integrons and transposons has aggravated the problem of antimicrobial resistance. Although antibiotic-resistant bacteria occur naturally in the environment, resistance patterns observed in bacteria to many of the newly introduced and 'last resort' antibiotics pose a great challenge from public health point of view. In addition, horizontal transfer of resistance properties to drug-sensitive bacteria is worrisome scenario worldwide, as this give rise to more and more antibiotic resistant and eliminating the sensitive strains. Another major challenge is the absence of a good monitoring or surveillance system for antibiotic prescriptions. An approach that integrates surveillance for drug resistant organisms in animals and humans is also a current need. A rigid surveillance system for community- and hospital-based prescribing is the first step towards determining the magnitude of the problem and instituting appropriate remedial measures. Once a good surveillance system is in place, it should focus on physicians who inappropriately use antibiotics. The data of the antibiotic resistance pattern in a particular geographical region and the devising suitable hospital/area based antibiotic policy will go a long way in the control of these infections. The stewardship in usage and good antibiotic policy in place are needed to limit the emergence and dissemination of antibiotic resistance in bacteria. While addressing the immediate concerns regarding antibiotic resistance should remain a priority, long-term goals should also be kept in mind. These include formulating strategies and incentives to start new antimicrobial research and development by the pharmaceutical industry. Instituting effective public-private-partnerships may be crucial to initiate and sustain a strong antimicrobial drug pipeline over the long term. All efforts should occur simultaneously, in order to check misuse, abuse, or overuse of antibiotics.

Way forward

AMR is a huge health and economic challenge. Cost of inaction shall be huge as has been projected by the O'Neill Report on AMR (2016). One Health approach is the ideal mechanism and multisectoral approach in a coordinated way with sustained national funding, consistent oversight, hard work to address challenges pertaining to community awareness, surveillance mechanism, stewardship to ensure rational use of antibiotics, phasing out of use of antibiotics as growth promoters, good infection control and biosecurity practices and development of alternatives to antibiotics are the solutions for which work needs to be done vigorously. Constants awareness and intervention programmes about the implications of irrational use of antibiotics need to be conducted at village and community level. Policy makers both at the center and states have to formulate an effective action plan in coordination with global agencies to successfully tackle the AMR problems in India.

EPIDEMIOLOGY OF AMR



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