REVIEW ARTICLE

Rational use of antimicrobials in animal production: a prerequisite to stem the tide of antimicrobial resistance

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Antimicrobial resistance (AMR) is a worldwide 'One Health' problem. The spread of AMR has limited the treatment options against infectious diseases. Inappropriate use of antimicrobials, is a major contributor for the development of AMR and its spread. In animal husbandry, antimicrobials are used for treating infectious diseases and in sub-therapeutic concentrations for growth promotion and disease prophylaxis. The use of antimicrobials in sub-therapeutic concentrations exerts selective pressure on bacteria and results in the emergence of bacterial strains resistant to one or more antimicrobials. The food animals raised on sub-optimal doses of antibiotics become reservoirs of resistant bacterial strains, transmitted subsequently to man and the environment. Various human, animal and environmental health agencies have decided to jointly address this problem. Establishment of integrated and harmonized AMR surveillance programmes, reduced use of antimicrobials in animal production, good governance of veterinary services, and development of new antimicrobials and their alternatives are some of the AMR management strategies in animals. Antibiotics are indispensable for human health; however, they should be totally banned in the food animals to preserve effectiveness of these drugs. In India, use of antimicrobials in food animals is limited for disease prophylaxis and growth promotion. However, absence of uniform regulations on the use of antimicrobials in animal production threatens the rationale use of these drugs in livestock.

Keywords: Antibiotics, food animals, growth promoters, surveillance, veterinary governance

ANTIMICROBIALS have saved millions of lives around the world. The widespread use of antimicrobials has led to the development of antimicrobial resistance (AMR) among bacteria. The problem of AMR has aggravated due to inappropriate use of antibiotics in the medical, veterinary and agricultural sectors. Globally, AMR causes about 700,000 deaths annually[1]. AMR is a public health threat both in the developing and developed world[2]. In developing countries, guidelines on the use of antimicrobials are generally absent and even if present, are not followed. In spite of several rules and regulations governing the use of antimicrobials and public awareness about the ill-effects of these drugs, the problem still exists in developed countries[3]. Continuous evolution and development of new AMR mechanisms render antimicrobials ineffective for therapeutic use. In May 2015, the World Health Assembly approved the Global Action Plan on Antimicrobial Resistance, which directs all countries to execute national AMR control plans within two years[4]. AMR is a 'One Health' problem; it affects human and animal health, and adversely impacts the environment. The Food and Agriculture Organisation (FAO)/World Organization for Animal Health (OIE)/World Health Organization (WHO) have jointly identified AMR alongside rabies and zoonotic influenza as one of the three priority public health issues under the One Health concept at animal–human–ecosystems interface[5].

Global antibiotic consumption has increased in the recent past. Increase in incomes has allowed greater access to antibiotics, and the increased appropriate and inappropriate use of these drugs. Increase in animal protein demand has shifted the animal production systems to more intensive practices with higher use of antibiotics. Both these factors have hugely added to the development and dissemination of AMR[6]. Drug-resistant bacteria can be transferred from animals to humans either directly by the food (e.g. meat, fish, eggs and dairy products) and direct contact, or, more indirectly, through the environment[6–10]. A number of foodborne outbreaks involving antibiotic resistant strains of *Escherichia coli*, *Enterococcus*, *Aeromonas* and various species of *Salmonella* have been linked to animal food products across the world[6]. Antimicrobial-resistant strains of *Salmonella* and *Campylobacter* are transmitted to man through foods of animal origin and result in higher mortalities than susceptible strains[11–13]. Patterns of antibiotic use in animals are reflected by trends of resistant bacteria recovered from animals, humans and the environment[6–8]. In Canada, occurrence of ceftiofur-resistant strains of *Salmonella* and *E. coli* in chickens and humans was shown to vary with the use of ceftiofur in broiler chicken farming[14]. The

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antibiotics used in agriculture and animal production end up in the environment, which adds to the total burden of antibiotic resistance in both animals and humans[6–15]. Increased movement of people, global trade of animals and food products, changing lifestyles and food habits, and increased contact between different living communities have also contributed to the worldwide spread of antimicrobial-resistant bacteria[3,16].

Evolution of antimicrobial resistance and mechanisms

Emergence and development of AMR is a natural, adaptive and ongoing process. It is believed that resistant bacteria were present in the environment long before the use of antibiotics started[17–19]. Antibiotic-resistant bacteria have been found in 30,000-yr-old permafrost, more than 4 million-yr-old caves, and in the guts of Amazonian tribes never exposed to drugs[20,21]. Antimicrobial resistance imparting genetic determinants also evolved in antibiotic-producing environmental microorganisms, as an auto-protective measure[19,22]. These resistance genotypes were later transferred to commensals and pathogenic bacteria through natural processes of genetic exchange[23]. However, presence of resistance genes is not restricted to antibiotic producers[24]. Quinolone resistance gene, *qnrA* was evolved in a waterborne, non-antibiotic-producing bacterium, *Shewanella algae*[25].

Bacteria acquire AMR either through spontaneous mutations (natural AMR) or by acquiring genetic material (acquired AMR) from other microorganisms. Acquired AMR involves horizontal gene transfer between bacteria and/or acquisition of new genetic material from the environment[26]. This occurs by bacteriophage-mediated transduction (transfer of plasmids or transposons), conjugation (involving cell-to-cell contact) and/or by transformation (the direct uptake of free DNA from the environment)[27]. AMR mechanisms can be categorized into four groups[28,29]: (1) limiting intracellular drug concentration inside the bacterium by influx and efflux; (2) chemical modifications or destruction of drugs; (3) modification of drug target sites in bacterium, and (4) development of bacterial-tolerant states, biofilm formation and swarming. Some mechanism impart cross-resistance to multiple unrelated drugs. More than one AMR mechanism can co-exist in a microorganism against a single antimicrobial. AMR can be chromosomal and plasmid-mediated. Chromosomal AMR occurs due to mutations in one or more genes which render the bacterium resistant against one or more antibiotics[30]. Plasmid-mediated AMR involves the transfer of plasmids or transposons carrying various resistance genes for one or more antibiotics from donor to recipient bacterium[31]. It is further important to note that exposure to only one antibiotic can act as the selective pressure for a set of the resistance genotypes.

The selective pressure due to exposure to antimicrobials also selects resistant bacterial strains with increased survival fitness. It causes a transient and non-hereditary bacterial mechanism called persistence and selects bacterial clones with elevated mutation rates (hypermutators or mutators). A series of selection of such mutants can increase the prevalence of such strains to 100% in a selected population[32]. Therefore, exposure to a given antibiotic or antibiotic residue not only selects a bacterium for resistance to itself, but also chooses strains resistant to non-related antibiotics. AMR genes are transferred between commensals and pathogens[33]. For example, cephalosporin resistance imparting extended spectrum β-lactamase (ESBL) can be transferred from *E. coli* to other commensals or pathogenic bacteria in the gastrointestinal tract[13,34].

Use of antimicrobials in animal husbandry

Antimicrobials in animal husbandry are primarily used for therapy, prophylaxis and growth promotion. They are used in bulk for prophylaxis and growth promotion in animal production[6]. Onset of disease outbreaks in animal farms is generally rapid and results in heavy mortalities. Crowded and dirty farm settings facilitate disease transmission, and antibiotics are used to check the spread of infection[35]. Antimicrobials in mass prophylaxis (metaprophylaxis) are used by mixing in feed or water to prevent infections in poultry, vertical transmission of pathogens from eggs to chicks, post-weaning infections in pigs, respiratory problems of young animals and shipping fever after transportation[2]. In dairy farms, antimicrobials are administered systematically and locally in different stages of the lactation cycle before calving as mastitis prophylaxis and its treatment during lactation[2]. Antimicrobials are used as growth promoters primarily in animal production and have no counterpart in human medicine. This dates back to the 1940s and 1950s, and accounts for the majority of antibiotic use in farm animals[6,36]. Antibiotics act as growth promoters in food animals when fed in ultra-low doses with feed. It is estimated that between 2006 and 2050, global consumption of animal food products will double. This will result in much higher use of antimicrobial growth promoters in future[35]. In animal production, poultry and pig farming are the major consumers of antibiotics worldwide[6].

Global consumption of antimicrobials in animals is twice that of humans[37]. In the United States, 80% of the total annual antimicrobial consumption is in animals[38]. In 2013, an estimated 14,788 tonnes of antimicrobials were used in animals in USA alone. It also included 4434 tonnes of ionophores, a class of antimicrobials used only in veterinary medicine[39]. Around 8046 tonnes of veterinary antimicrobials was consumed in 2012 in 26 European Union (EU) countries[39]. The global consumption of antimicrobials in food animal production is expected to rise by 67% between 2010 and 2030. In Asia alone, antimicrobial consumption will increase by as much as 46% by 2030 (ref. 38). It is projected that in Brazil, Russia, India, China and South Africa (BRICS), the antimicrobial use for food animal production will increase by 99% between 2010 and 2030 (ref. 38). In Asia, per capita per day animal protein intake increased from 7 g in 1960 to 25 g in 2013 (ref. 38). To meet this ever-rising animal protein demand, antimicrobials are used on a large-scale to keep animals healthy and maintain high productivity under intensive livestock production systems. It is projected that shifting of animal production practices to large-scale intensive farming operations in low and middle-income countries will increase antimicrobial consumption by 33% between 2010 and 2030 (ref. 38). In these regions, antimicrobials are used routinely in sub-therapeutic doses for disease prevention and growth promotion to counterbalance poor hygiene and unorganized animal management systems[40,41].

In aquaculture, antibiotics are used for therapy and prophylaxis but not for growth promotion[35]. A large proportion of aquatic food production systems are in regions with inadequate regulations and restricted enforcement of law on the use of antimicrobial agents in food animals[42]. Aquaculture industry represents a significant share of the antimicrobial consumption in animal production. Extremely high rates of antimicrobial consumption have been recorded in aquaculture farming in middle and low-income countries[43,44]. It is believed that growth in aquaculture production systems will increase the antimicrobial consumption and contamination of the aquatic environments with antimicrobial residues in future[45].

Antimicrobial resistance and animal husbandry sector

Antimicrobials used in animal husbandry and human medicine are mostly the same, or are from the same class. Exposure of bacteria to antibiotics or antibiotic residues in the farm environment exerts a strong selective pressure and facilitates the emergence of antibiotic-resistant bacterial strains. The farm animals may become potential reservoirs of resistant pathogens[11]. Antibiotic use in food animals influences the occurrence and distribution of resistant bacteria in humans[35,46]. The load of resistant bacteria is higher in the guts of farmers using antibiotics as animal growth promoters than those not using them and the general population[9]. Prevalence of multidrug-resistant *Staphylococcus aureus* in humans has been directly associated with the time spent on animal farms[47,48]. Similarly, occurrence of resistant bacterial strains in humans decreases with decrease in the use of antibiotics in animals[14,35]. There are several reports on transmission of AMR strains from food animals (e.g., *Salmonella* spp., *S. aureus*, *Campylobacter jejuni*, *Listeria monocytogenes*, *Yersinia enterocolitica*, *E. coli* and *Enterococcus*) to humans[6,35].

Emergence of methicillin-resistant *Staphylococcus aureus* (MRSA) and colistin-resistant *E. coli* in high-density swine production units and presence of ESBL (CT-X enzymes) producing *E. coli* in livestock are direct health threats to livestock handlers, farmers and veterinarians[2,3,35,49]. The transmission of livestock-associated MRSA from infected animals to humans is difficult to track as MRSA infections are often asymptomatic[35]. Emergence and development of AMR in zoonotic pathogens is a serious direct public health risk because transmission is natural between animals and humans. The transfer of MRSA (clonal complex 398) has been shown to occur from infected humans to pigs and later from infected pigs to humans[50].

The selective pressure exerted by prophylactic use of antimicrobial drugs in poultry production has also resulted in the emergence of resistant *E. coli* and *Enterococcus* strains[51]. The ubiquitous nature of these organisms and their ability to adapt to different hosts and environments, further increases the transmission threats to susceptible human and animal populations. A number of studies conducted in USA and Europe have reported isolation of resistant strains of *Salmonella* (including non-Typhi *Salmonella*), *S. aureus*, *Campylobacter*, *E. coli* and *Enterococcus* from poultry, swine and cattle[6]. In these studies, AMR was reported against penicillin, tetracyclines, sulphonamides, ampicillin, quinolones, cephalosporins, macrolides and aminoglycosides[6]. The Global Antibiotic Resistance Partnership (GARP) programme has reported isolation of a variety of multidrug-resistant bacterial strains from poultry, cattle and pigs in Nepal, Uganda Tanzania and India[6].

The weaker selective pressures present in the environments other than hospitals, medical facilities and animal farms also result in the emergence of AMR[18]. Resistant bacteria, as well as antibiotic residues, have been detected in rivers, sediments, soil and other environmental sites[52]. It is reported that up to 90% of an antibiotic dose used in animals can be excreted in their urine and up to 75% in their faeces[53]. Antimicrobials or their residues are not fully biodegradable and survive water-processing or sewage treatment. They enter natural environments in different active forms[54]. They also get diluted several folds in aquatic environments and soil giving rise to new resistant bacterial strains through gene transfer[15,52]. The effluents from animal husbandry units and slaughterhouses can discharge resistant bacteria and antibiotic residues in the receiving environments[3,55,56]. Application of sludge or farmyard manure carrying resistant bacteria on the fields, pastures and farmland can contaminate ground and surface waters[57,58]. High prevalence of resistant bacteria on animal farms and in surface water directly relates to higher agricultural use of antibiotics[59].

Biocides (e.g. alcohols, phenols, quaternary ammonium compounds and heavy metal compounds) exert selective pressure on the bacteria and also contribute to the development of AMR. Biocides in animal husbandry are used for cleaning and disinfection of farm building, preventing skin and foot infections, and to check contamination of animal products such as eggs. Biocide resistance and AMR-conferring genes are present on the same genetic elements, e.g. plasmids[14,60]. This indirect enrichment of AMR can trigger one or more mechanisms such as up-regulation of efflux pumps or modification of target enzymes. Exposure to biocides has resulted in the emergence of *E. coli* isolates resistant to cotrimoxazole and amoxicillin, and *Salmonella* Typhimurium strain with multidrug-resistance[61,62]. Cross-resistance to quaternary ammonium compounds and β-lactam antibiotics has been reported in staphylococci[13].

Indian scenario

Antimicrobial use in antimicrobial husbandry and antimicrobial resistance

India accounts for 3% of the global consumption of agricultural antibiotics, which is estimated to double by 2030 (ref. 41). Studies conducted in various regions of the country have shown the presence of resistant bacteria and antimicrobial residues in food animal products (Table 1)[35,63–83]. The recent report published by Center for Disease Dynamics, Economics and Policy provides a detailed account of antibiotic use in animal production and prevalence of resistant bacterial strains in different species of livestock in India[35]. However, systematic studies estimating actual national burden of AMR are lacking. It is important to note that the use of antibiotics as growth promoters and prophylactic agents in food animals is limited in India. However, indiscriminate use of antibiotics by farmers, quacks and untrained para-veterinary staff is not monitored strictly. It is projected that India will be the fourth largest consumer of antibiotics in food animal production after China, USA and Brazil by 2030 (ref. 38). In India, only 30% of antibiotics used in poultry is for therapy and the remaining 70% is for growth promotion[35]. The consumption of antibiotics for intensive poultry production is expected to grow by 312% between 2010 and 2030 in India[38]. Eleven of 15 antimicrobial agents considered critically important for human health by WHO and banned for agricultural use in the EU, are used in poultry feed in India[84]. Residues of antibiotics used to treat mastitis and other infectious diseases in bovines have been detected in milk samples from different parts of the country[35]. Antibiotics such as oxytetracycline, althrocin, ampicillin, sparfloxacin, enrofloxacin and ciprofloxacin are commonly used in India on fish farms, both for prophylaxis and treatment. Several studies conducted in the country have reported isolation of resistant strains of *Salmonella*, *Vibrio cholera*, *Vibrio parahaemolyticus*, *Aeromonas*, *Pseudomonas*, and *E. coli* O157:H7 from fish, crustaceans, shellfish, prawns, cuttlefish, shrimp and freshwater hatcheries[35].

Efforts to regulate antimicrobial use in animal production in India

In India, absence of uniform regulations on antimicrobial use in animal production poses a serious challenge to the enforcement of rational antibiotic use. The exact estimates of antibiotic usage in animals are not available[85]. The National Policy for Containment of Antimicrobial Resistance released in 2011, advocates the development of strict guidelines for antibiotic use in food animals, and complete ban on non-therapeutic use of antibiotics in animals. The development of inter-sectorial collaborations for containment of AMR is emphasized in this report[35]. ‘Chennai Declaration – a roadmap to tackle the challenge of antimicrobial resistance’, was the first ever joint meeting of medical societies in India to address issues related to AMR[86]. It recommended the need to evaluate and regulate antibiotic usage in the veterinary practice. This document stresses the need to strictly monitor the presence of antibiotic residues and to determine the prevalence of resistant bacteria, especially zoonotic, in animals and foods of animal origin. The declaration recognized observation of proper withholding or withdrawal periods between the use of antibiotics and animal slaughter or milking as the single most important measure to circumvent antibiotic residues in milk and meat[86].

An international effort on control of AMR was made in 2011 by GARP through the ‘New Delhi Call to Action on Preserving the Power of Antibiotics’. This action plan was approved by the Governments of India, Ghana, Kenya, Mozambique, South Africa and Vietnam. It emphasized the need for a multi-sectorial approach for AMR surveillance and to discourage the use of antibiotics for animal growth promotion[87].

The use antibiotics in food animals in India is broadly governed by two laws: General Statutory Rule (GSR) 28(E) and GSR588 (E). The former advocates strict observation of antibiotic withdrawal periods in food-producing animals between the time of antibiotic administration and the production of meat/milk. The latter stipulates that antibiotics are H1 category drugs and their dispensing requires proper prescription. It is specified that withdrawal periods in meat/poultry and marine products should be 28 days and 500 degree-days respectively, for antibiotics with no defined withdrawal periods[35,87].

Statutory Order (S.O.) 722(E) limits the use of some antibiotics in aquatic animals for export. It also provides provision to monitor antibiotic residues in eggs, honey, milk and poultry for export[41]. In 2002, S.O. 722(E)

Table 1. Various studies reporting isolation of antibiotic-resistant bacterial strains from food animals and animal products in India

Source	Place	Isolates recovered	Resistance*	Plasmid	Reference
Cattle, pig	Nagpur	*Salmonella* spp.	Amp, Tmp	Not reported	64
Buffalo	Southern India	*Staphylococcus* spp., *Escherichia coli*, *Streptococcus* spp.	MDR	Not reported	65
Poultry faeces and cow milk	Odisha	*E. coli*	cephalosporins, monobactam	ESBL† (blaCTX-M, blaTEM, blaSHV, blaamp C)	66
Raw egg-surface, raw chicken, milk and meat	Hyderabad	*E. coli*	MDR	ESBL	67
Diarrhoeic lambs	Kashmir	*E. coli*, *Salmonella typhimurium* or S. Enteritidis	MDR	Not reported	68
Mastitic milk	Kolkata	*E. coli*		New Delhi metallo-beta-lactamase, ESBL	69
Lambs	Mathura	*Streptococcus pneumoniae*	MDR	Not reported	70
Buffalo faecal samples	West Bengal	*E. coli*	MDR	Not reported	71
Mastitic milk	Anand	*Staphylococcus* spp., *Bacillus pumilus*, *Staphylococcus chromogenes*, *Bacillus* sp., *Pseudomonas* sp.	Pen G, Oxa, Tmp, Lin, Nal	Not reported	72
Cattle mastitic milk	Not provided	Methicillin-resistant *S. aureus*	Meth, Stm, Oxy, Gen, Amp, Pen-G , Cam, Pri, Cip, Rmp, Lin	Not reported	73
Intra-mammary infections in buffaloes	Not provided	*S. aureus*	Tet, Gen, Ery, Lin	Not reported	74
Buffalo meat and diseased buffaloes	Not provided	*Salmonella enterica* subspecies enteric serovars	MDR, Ami, Oxy, Amp, Cex	One plasmid	75
Cattle mastitic milk	Not provided	*S. aureus*	Tet, Gen, Stm, Kan, Pen G, MDR	Not reported	76
Ruminant species	Different parts	*Pasteurella multocida*	Van, Bac, Sud, MDR	Not reported	77
Poultry litter	Salem	*Streptococcus*, *Micrococcus*, *E. coli*, *Salmonella*, *Aeromonas*	MDR	4.2 kb, 5.1 kb	78
Fish	West Bengal	*Aeromonas*	MDR	23 kb, 56 kb, 64 kb	79
Seafood	Cochin	*Salmonella* spp.	MDR	Nine plasmid	80
Foods of animal origin	Aligarh	*Klebsiella*, *Citrobacter*, *E. coli*, *P. aeruginosa*, *Acinetobacter*, *Enterococcus*	Gen, Amk, 3GCs, Flour, Olx, Tzp, Ipm	ESBL (blaCTX-M, blaTEM, blaSHV, blaamp C)	81
Diarrhoeic calves	Gujarat	*E. coli*	MDR	Not reported	82
Dairy cattle	Assam and Meghalaya	*S. aureus*	MDR	Not reported	83

*3GCs, Third-generation cephalosporins; Ami, Aminoglycosides; Amk, Amikacin; Amp, Ampicillin; Bac, Bacitracin; Ery, Erythromycin; Cam, Chloramphenicol; Cex, Cephalexin; Cip, Ciprofloxacin; Efx, Enrofloxacin; Ery, Erythromycin; Flour, Fluoroquinolone; Gen, Gentamicin; Ipm, Imipenem; Kan, Kanamycin; Lin, Lincomycin; MDR, Multidrug resistance; Meth, Methicillin; Nal, Nalidixic acid; Oxa, Oxacillin; Olx, Ofloxacin; Oxy, Oxytetracycline; Pen G, Penicillin G; Tzp, Piperacillin-tazobactam; Pri, Pristinomycin; Stm, Streptomycin; Rmp, Rifampicin; Tmp, Trimethoprim; Sud, Sulfadiazine; Tet, Tetracycline; Van, Vancomycin.
†ESBL, Extended spectrum beta-lactamase.

amended an order from 1995, restricted the use of antibiotics in fresh, frozen, and processed fish and fishery products for export. This amendment also provides maximum residue limits for tetracycline oxytetracycline, trimethoprim and oxolinic acid. It forbids the use of certain antibiotics in units processing all types of seafood. In 2003, S.O. 1227(E) prohibited the use of antibacterial substances, including quinolones in seafood processing units without approval from qualified veterinary surgeons or fishery scientists[35,87].

What needs to be done?

Antimicrobial resistance surveillance programmes

It is important to establish global and national AMR surveillance programmes for livestock. Such programmes are functional only in some EU countries, USA and Canada. According to OIE in 2012, only 27% OIE member countries officially recorded quantitative data on antimicrobial use in livestock[88]. Antibiotic resistance and its surveillance are not a priority in most low and middle-income countries. Systematic data on the use of antimicrobials are lacking for countries such as China, India and Brazil, where intensive livestock-rearing systems are increasing rapidly. WHO has recommended that countries should develop national antimicrobial surveillance programmes and assimilate AMR data from humans, food-producing animals and retail foods of animal origin[2]. A watchful surveillance of the amount and type of antimicrobials used in humans, food products and food animals could help in the development of regulations for correct use of antibiotics[89]. In Denmark, annual antimicrobial consumption data can be traced to the individual herd level by drug classes and animal species. These kinds of data can establish a relationship between prevalence of AMR in animals and consumption of antimicrobials in farm animals[90].

It is important to keep an active supervision of environmental AMR reservoirs along with programmes directed to reduce antibiotic use in animals. Prevention of initial emergence of resistant pathogens is more important than their control after spread in human and animal populations. In India, execution of programmes such as Assistance to the States for Control of Animal Diseases (ASCAD), the National Animal Disease Reporting System (NADRS), and the National Livestock Censuses shows that the capacity for widespread data collection from the animal husbandry sector exists in the country. Successful execution of such nationwide programmes shows that it is possible to collect data on antibiotic use in animal husbandry in the country[35,85].

Harmonization of surveillance programmes

The major obstacles in the implementation of integrated global and national AMR surveillance programmes are lack of uniform methods (sampling, testing and reporting) and differences in protocols used in various laboratories within a country or between different countries. In order to establish effective AMR surveillance programmes, it is important to have uniformity in the bacterial species monitored, antimicrobials tested, reporting clinical breakpoints, epidemiological cut-off values, interpretation criteria (resistant, intermediately susceptible and susceptible) and control strains used. This harmonization of AMR surveillance programmes will allow better comparison of AMR data on regional, national and global levels[2]. Implementation of synchronized AMR surveillance programmes will facilitate reliable AMR data generation and formulation of region-specific intervention strategies[91]. A global or national AMR surveillance programme lacking a defined objective and universally accepted epidemiological and microbiological approaches cannot comprehensively analyse the problems of AMR. There is also a need for capacity-building and training in resource-limited countries, where the problem of AMR is often underestimated and under-reported[2].

Emphasis on regulated use of antimicrobials in animal production

As early as the 1960s, concerns were raised about the use of antimicrobials in animal production and AMR. It was suggested that only drugs with limited or no use in human and animal therapeutics should be allowed for use as animal growth promoters[1,6]. Inappropriate use may account for up to 50–90% of all antimicrobials consumed in human medicine; even greater proportions of antibiotics are misused in the livestock sector[1]. The antibiotic treatment is effective against bacterial infections only and should be targeted to treat such illnesses. This targeted use will prevent unnecessary antibiotic exposure to commensal bacteria and non-pathogenic bacteria which can pass resistance genes to pathogenic bacteria[85,87].

OIE recognizes AMR as a global concern. OIE promotes the responsible and prudent use of antimicrobials in veterinary medicine to preserve their efficacy in both in animals and human. OIE has published the Terrestrial Animal Health Code and the Aquatic Animal Health Code, standards and guidelines to prevent the emergence and spread of resistant bacteria from animals[91,92]. These documents provide detailed information on testing antimicrobial susceptibility, creating surveillance systems for antibiotic use and resistance, promoting rational antibiotic use and conducting risk analyses[91,92]. These guidelines can be the basis for implementation of national or international AMR surveillance programmes. In 2007, the OIE International Committee approved the List of Antimicrobial Agents of Veterinary Importance (Resolution No. XXVIII)[93]. The OIE list has guidelines on restricted use of those antimicrobials in food animals that are essentially important for both animal and human health. These currently include fluoroquinolones, and third and fourth generation cephalosporins[93]. In the First Global Conference on the Prudent Use of Antimicrobials in Veterinary Medicine held at Paris in 2007, the member countries agreed to cooperate on the supervision of production, importation, marketing, distribution and use of antimicrobials[94]. Codex Alimentarius, developed by FAO and WHO, delineates maximum residue limits (MRLs) for antibiotics in foods of animal origin to warrant safety and quality in international food trade[95].

WHO Advisory Group on Integrated Surveillance of Antimicrobial Resistance (WHO-AGISAR) was set up in 2008, with an objective to minimize the public health hazards of AMR associated with the veterinary use of antimicrobials[96]. AGISAR updated the WHO list of critically important antimicrobials, meant to formulate and prioritize risk assessment and management strategies for containing AMR due to human and non-human antimicrobial use. In this list, veterinary drugs falling in the same classes of antimicrobials as those in the human medicine are now also classified separately[96,97]. Regrettably, 9 of 14 'critically important' classes of antibiotics to human health are widely used in veterinary practice. In 2009, worldwide three most commonly used antibiotic classes in the animal sector were macrolides (US$ 600 million), penicillins (US$ 600 million), and tetracyclines (US$ 500 million). These three classes of antibiotics are categorized as critically important in human medicine[6,98]. FAO, OIE and WHO have recommended monitoring the use of quinolones, third and fourth generation cephalosporins, and macrolides in animals for overall AMR risk assessment[6,54]. In India, existing regulations are restricted to the detection of antibiotic residues in seafood and antibiotics used in poultry intended for export. It is important to review existing laws and develop new guidelines and standards for antibiotic use in livestock, to increase the efficacy of existing Prevention of Food Adulteration Rules Act (1955 Part XVIII)[99].

Governance of veterinary services

OIE has stressed the need for good governance of veterinary services for better control in registration, import, distribution and for on-farm use of antimicrobials[100]. In order to prevent unnecessary chemotherapy and misuse of antibiotics in animals, the prescription and delivery of antimicrobials in animals must be performed by well-trained veterinarians. The control of ethics of veterinarians should be under the authority of a veterinary statutory body (i.e. Veterinary Council of India). Scarcity of sufficient and well-trained veterinary and para-veterinary staff is a major concern in India. The number of available veterinarians, veterinary scientists, veterinary technicians and support staff is much less compared to the proposed requirements[35]. Veterinarians, para-veterinary staff, farmers and consumers in general have failed to recognize the ill-effects antibiotic use in animal production[85]. These stakeholders need to be educated on the judicious use of antibiotics and health benefits of antibiotic-free animal products[85].

Coordinated efforts by different stakeholders

WHO/FAO/OIE had agreed to jointly address the problem of AMR in future through expert consultations and development of guidelines[6]. The other goals of the tripartite collaboration on AMR are raising awareness, capacity-building, development of appropriate national policies and promotion of prudent and responsible use of antimicrobial drugs. Such inter-sectoral alliances will ensure better utilization of resources at the global level against AMR. The US National Antimicrobial Resistance Monitoring System (NARMS) is a collaboration of the Food and Drug Administration (FDA), the Centers for Disease Control and Prevention (CDC), and the US Department of Agriculture against AMR[5]. Successful programmes such as NARMS involving participation of different agencies and departments can be adopted by other countries for better management of AMR. WHO-AGISAR in collaboration with FAO has implemented integrated foodborne pathogen and AMR surveillance programme in food animals and aquaculture[96]. Coordination between countries is essential to develop a truly global action plan to manage AMR. These plans should be based on the 'One Health' concept covering human and animal health, agriculture and the environment[1]. International initiatives such as GARP can go a long way in developing policy alternatives to manage antibiotic effectiveness by the sharing of experiences among countries[85].

Reducing and controlling antibiotic use in animal production sector

Emergence of resistant bacterial strains and evolution of new resistance mechanisms are directly associated with the amount and frequency of antibiotic use. Hence, phasing out the non-therapeutic use of antibiotics in animal production will decrease the burden of antibiotic-resistant infections. It has been shown that abolishing the use of antibiotics in food animals as growth promoters does not affect the production levels[101,102]. In January 2006, addition of non-therapeutic antimicrobial drugs to animal feeds was banned in the EU[103]. Interestingly, the amount of antimicrobial use in animals fell overall by 15% between 2010 and 2012 in Europe[39]. In 2011 and 2013 in the United States, FDA issued voluntary guidelines for the producers of veterinary drugs that are added to water or feed, with the aim of eliminating the use of medically important antibiotics as growth promoters by the end of 2016 (ref. 1). In 2014, the Canadian Government implemented a voluntary strategy similar to USA. Mexico, South Korea and New Zealand have also banned the use of antibiotics as animal growth promoters[1].

Studies conducted before 1980s reported as high as 5–15% improvement in the growth rate and feed utilization efficiency of food animals on feeding sub-therapeutic antimicrobials. Interestingly, studies conducted after 2000s point towards more limited (1–5%) effects of antimicrobials as growth promoters[39,104,105]. The effects of removing antibiotic-based growth promoters from animal production systems are likely to differ depending on animal husbandry practices and farm conditions[1]. Prohibition on the use of antibiotics as growth promoters had a greater effect on producers with lower hygiene standards[106]. In India, a complete ban on the use antibiotics in animal production will result in 1–3% loss of annual meat production, or US$ 1110 to 2599 million. Commercial poultry farmers will have the greatest impact as poultry accounts for 50–75% of total meat production in India[35].

The effects of phasing out of antimicrobials as growth promoters can be limited by replacing less optimized animal production systems with more advanced ones[46,107,108]. The productivity of food animals can be increased by improving nutrition (adding probiotics and feed supplements) and by selecting food animals with superior genetic potential[33]. Intensive vaccination, improved diagnostic tools, and better hygiene and water sanitation will moderate the antibiotic demand in animal production. These measures will help in maintaining the effectiveness of current and future antibiotics for treating both humans and animals[6].

Development of new antimicrobial agents

AMR is one of the most serious public health problems. This is of particular concern when the bacterium becomes resistant to various antimicrobial agents simultaneously. The need for new antimicrobial agents and alternatives is becoming one of the most urgent requirements in modern medicine. A systematic understanding of AMR mechanisms is critical for the development of new antimicrobial agents. After 1970s, the frequency of discovery of new antibacterial compounds dropped significantly[109]. The detection of new antimicrobial compounds from soil bacteria has become difficult because of similarity between the compounds produced[110]. The new sources which hold promise for novel antimicrobial compounds include plants, marine bio-resources, insects and venoms of various origins[111–117]. Antimicrobial peptides (AMPs) are an integral part of the natural host defence system and play a critical role in reducing the microbial load early during infection[118]. AMPs have potent antimicrobial activity, low resistance rates and a unique mode of action[116]. Due to rapid increase in antimicrobial resistance, antimicrobial peptides from synthetic and natural sources are being explored as an alternative to antimicrobial agents[118]. Lectins, the multivalent proteins present in microorganisms, animals and plants are being explored to develop novel antimicrobial agents[110].

The increasing availability of bacterial genome sequences encoding natural products has made it easier to identify the natural (including AMPs and antibiotics) products biosynthesized by microorganisms[109]. The use of synthetic biological approaches such as genome mining in combination with high-throughput sequencing platforms and integrated bioinformatic analysis can lead to the detection of novel antimicrobial compounds[111]. Three new classes of antibiotics [synercid (streptogramin combination), linezolid (oxazolidinone), and daptomycin (lipopeptide)] identified in the past were put into clinical use after improving their bioavailability and reducing the toxicity concerns[109]. Alternative therapeutic strategies like the use of inhibitors of resistance enzymes (clavulanic acid for β-lactamases) and efflux pumps (reserpine, in Gram-positive bacteria), pumping antibiotics from periplasm or cytosol to the extracellular medium and use of a combination of antibiotics with different mechanisms of actions can extend the life of antibiotics[109].

Improved sewage and farm waste disposal

Sewage treatment systems should be able to degrade antibiotic residues and destroy resistant bacteria significantly in both treated effluent and sludge[119,120]. Ozone treatment of sewage destroys pharmaceuticals, including antibiotics and kills essentially all types of pathogenic infectious agents. Thus, ozone treatment will not only remove the selective agents (antibiotic and biocide residues), but also break transmission cycles of both susceptible and resistant microbes[18].

Conclusion

Antimicrobials are critical in limiting the morbidity and mortality in humans and animals. The unabated use of antimicrobials in intensive animal production is decreasing the efficacy of these drugs, an indispensable component of modern medicine. In animal production, the vast majority of antibiotics are used for growth promotion and disease prevention, as a substitute for hygiene and nutrition. Use of medically ‘potent’ antibiotics in livestock production has raised serious concerns due to emergence and spread of AMR[1]. Antimicrobials are not ordinary products and careful considerations should be given to their use in animals. It is important to outlaw veterinary use of antibiotics critical for the preservation of human health. The farmers especially in the developing countries, should be offered incentives or subsidies to decrease antibiotic use without causing economic harm. Over the counter sale of antibiotics should banned and their end use should be ensured at the time of sale[121]. Complementary measures such as surveillance, mass education and alternative therapeutic measures will help further reduce the use of antibiotics in animals[98]. In India, too little is known about antibiotic use in food animals, and a nationwide surveillance system is required to determine antibiotic consumption and resistance patterns.

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