Antimicrobial Usage in Animal Production Systems

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Abstract

Antimicrobial usage (AMU) in human and veterinary medicine is the single-most important factor for the development of antimicrobial resistance (AMR), a global public health threat. Although AMR development is a natural process, misuse or overuse of antimicrobials can speed up the process. Surveillance of AMU in animal and agricultural system is the basis for understanding and combating AMR, as nonhuman AMU leads to the development of resistant bacteria in the case of drugs used by humans. Among various indications, mastitis is one of the most common reasons for AMU in dairy animals. However, the pattern of AMU and their influencing factors varies among the countries, species, breeds, production systems, drugs, and other factors. Therefore, it is very important to understand the influencing factors for better implementation of policies to regulate AMU animal production systems. Several methods have been explored in animal production systems for the collection of AMU data. However, the lack of

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M. P. Mothadaka et al. (eds.), *Handbook on Antimicrobial Resistance*,
https://doi.org/10.1007/978-981-19-9279-7_14

harmonized quantification methods is the major limiting factor encountered at present. Under the changing livestock production conditions from small holder, less intensive to highly intensive farming systems, identification of critical factors, and suitable metrics are important to make an evidence-based policy decision for regulation of antimicrobial usage. Several countries have taken measures to reduce AMU in food animal production system. The European Union has done it through regulations on veterinary medicines and medicated feed. Reduction and replacement of antimicrobials, along with redefined animal husbandry practices through preventive approaches, are important measures to reduce AMU in animal production systems.

Keywords

Antimicrobial use · Antimicrobial resistance · Antibiotic residue · Dairy animals · Poultry · India

Abbreviations

AGPs	Antimicrobial growth promoters
AMR	Antimicrobial resistance
AMU	Antimicrobial use
ATI	Antimicrobial treatment incidence
BIS	Bureau of Indian Standards
CAC	Codex Alimentarius Commission
CCC	Cow calculated courses
CDC	Centers for Disease Control and Prevention
CDDEP	Center for Disease Dynamics, Economics and Policy
CIPARS	Canadian Integrated Programme for Antimicrobial Resistance Surveillance
DAHDF	Department of Animal Husbandry, Dairying and Fisheries
DANMAP	Danish Integrated Antimicrobial Resistance Monitoring and Research Programme
DCDvet	Defined course dose for animals
DCGI	Drug Controller General of India
DDDvet	Define daily dose for animals
EFSA	European Food Safety Authority
EMA	European Medicines Agency
ESVAC	European Surveillance of Veterinary Antimicrobial Consumption
EU	European Union
FDA	Food and Drug Administration
FINRESVET	The Finnish Veterinary Antimicrobial Resistance Monitoring and Consumption of Antimicrobial Agents
FSSAI	Food Safety and Standards Authority of India
GERMVET	German National Antibiotic Resistance Monitoring
ICAR	Indian Council of Agricultural Research

ICMR	Indian Council of Medical Research
IPC	Infection prevention control
ITAVARM	Italian Veterinary Antimicrobial Resistance Monitoring
JVARM	The Japanese Veterinary Antimicrobial Resistance Monitoring System
MoHFW	Ministry of Health and Family Welfare
MRL	Maximum residue limit
NARMS	National Antimicrobial Resistance Monitoring System
NethMapMARAN	Monitoring of Antimicrobial Resistance and Antibiotic Usage in Animals in the Netherlands
NMDRD	National Milk Drug Residue Data Base
NORMVET	Norwegian Surveillance System for Antimicrobial Drug Resistance
NSAIDs	Nonsteroidal anti-inflammatory drugs
OIE	Office International des Epizooties
ONERBA	National Observatory of the Epidemiology of Bacterial Resistance to Antibiotics
PCU	Population corrected unit
RESAPATH	French surveillance network for antimicrobial resistance in pathogenic bacteria of animal origin
SVARM	Swedish Veterinary Antimicrobial Resistance Monitoring
USDA	United States Department of Agriculture
VARSS	Veterinary Antimicrobial Resistance and Sales Surveillance
VAV	Spanish Veterinary Antimicrobial Resistance Surveillance Network
WHO	World Health Organization

1 Introduction

Antimicrobials are commonly used for therapeutic, prophylactic, and metaphylactic purposes in livestock and poultry production systems. The administered drugs or its metabolites are secreted into milk, meat, and eggs as residue, mostly due to: (i) failure to monitor the withdrawal periods, (ii) illegal or off-label use of drugs, and (iii) incorrect dosage (Paturkar et al., 2005). The most important concern of antibiotic residues in foods of animal origin is the development of antimicrobial resistance (AMR), which is a global problem. The World Health Organization (WHO) declared AMR as one of the most important public health threats of the twenty-first century. Globally, AMR is estimated to cause about 300 million premature deaths by 2050, with economic loss up to $100 trillion (3.5% reduction in global GDP). By 2050, AMR would cause death of about 2.4 million people in high-income countries alone and 25% increase in health expenditure in low-income countries if current incidence rate of AMR continues (Jonas et al., 2017). Besides, repeated sub-chronic exposure of antibiotic residues causes allergic reaction, toxicity, hypersensitivity, carcinogenicity or mutagenicity, and gastrointestinal disturbances. For instance, about 5–10% of the population suffers from penicillin-induced allergic reactions even at concentration as low as 1 ppb. Further, 4% of patients with a history of penicillin allergy also experienced an anaphylactic reaction to cephalosporin drugs (Kelkar & Li, 2001). Antibiotic residues in milk also disrupt the milk processing industry by the interference of starter cultures, though it depends on drug levels, species of culture strain, the presence of other natural potential inhibitors, etc. (Packham et al., 2001; Broome et al., 2002). Besides, the excretion of active metabolites of antibiotics through urine and feces causes disturbance on the soil and water microflora.

Irrational antimicrobial use (AMU) is the single most important factor for the development of AMR in human and veterinary medicines (Grave et al., 1999). Though the AMR development is a natural process, inappropriate use of antimicrobials in human and veterinary medicine can speed up the selection and spread of AMR. In the European Union (EU), and in the USA, AMU in food animal production accounted for more than 70% of total antimicrobial consumption (ECDC/EFSA/EMA, 2017). The projected higher demand for animal products and intensive animal farming production systems in low- and middle-income countries is expected to increase the AMU up to 67% by 2030 (Cuong et al., 2018). Understanding AMU is also significant since AMU in humans and animals often overlaps due to the involvement of the same pathogens as a cause of infection. For instance, about 75% of veterinary-approved drugs are essential for human use in the USA, and extensively used drugs in dairy animals like penicillin, cephalosporin, and tetracycline group of antibiotics are also important in treating the same pathogens in humans. Lesser investment by global pharmaceuticals in research and development of antimicrobials when compared to that for noncommunicable diseases like obesity and cardiovascular diseases and the lack of veterinary-specific drugs due to the huge human market are also other causes of concern which put emphasis on the judicious use of available drugs. The health and economic consequences of AMR would be heavier when many infections cannot be treated like in the pre-antibiotic era, if AMR control strategy is not set in place. Therefore, understanding of AMU pattern in dairy animals and consequent prevalence of the veterinary drug residues in milk and other livestock products is a very important prerequisite to control AMR problems. Without detailed information of current AMU in livestock, future strategies to restrict the antimicrobial usage are impossible (Doane & Sarenbo, 2014). The global action plan against AMR also emphasized a multisectoral approach including the understanding of AMU and AMR development in food-producing animals.

2 Indications for AMU and Residue Violation in Animal Production Systems

In dairy animals, among the various reasons for AMU, mastitis, respiratory diseases, infectious foot problems, uterine infections, and parasitism are important driving forces. Among the various groups of antibiotics, β-lactams (penicillins and cephalosporins), aminoglycosides, macrolides and lincosamides, sulfonamides and trimethoprims, and tetracyclines are mostly used in veterinary medicines (Grave et al., 1999). About 93% of antibiotic residue violations were associated with mastitis treatments, with 30% due to dry cow therapy (DCT) in Michigan dairy farms (Mellenburger, 1998). The majority of antibiotic residue violations was due to intramammary infusions, DCT, and intrauterine administration in UK farms, particularly in herds with more extra label use of antibiotics (McEwen et al., 1991). Herds with separate milking machine for treated animals and practices of following increased withdrawal period during a higher dosage administration were associated with a low residue violation, while accidental transfer of milk collected from treated cows to bulk tanks and prolonged excretion or persistence of drug even after withdrawal period are the most common reasons for residue violation (Tan et al., 2007, 2009). Among the management practices to avoid drug residues, withholding of milk from treated animals for a certain period is an important practice, and it often varies with the type of drugs, dosage, and route of administration. However, it is not strictly followed particularly in low-income countries including India.

The occurrence of antimicrobial residues in food of livestock origin is not only an indicative of AMU but also a predictor of potential threats. In general, residue violations in the USA, the EU, and certain other animal husbandry developed countries are very less due to regular monitoring through national-level programs. For example, the National Milk Drug Residue Data Base (NMDRD) being coordinated by the Food and Drug Administration (FDA) is regularly monitoring and reporting the extent of animal drug residue violation in milk in the USA. When the surveillance was initiated in 1996, it was observed at 6% positive, and it was reduced to 1% by the end of 2002, mostly due to the usage of penicillin and its combinations, followed by tetracyclines and aminoglycosides (Hall et al., 2003). Similarly, the EU reported very less incidence of violation (0.2%) in milk due to antibacterial, anthelmintic, and nonsteroidal anti-inflammatory drugs (NSAIDs), organochlorine compounds, and other chemicals (EFSA, 2015).

It is reported that 19–22% of the raw milk samples were positive with β-lactams and tetracycline residue in Palestine (Al Zuheir, 2012). Mangsi et al. (2014) found that 50% of the marketed milk samples were positive with β-lactam and tetracycline group of antibiotics in Pakistan. More violation of quinolone and penicillin residues was seen in Korea (Kim et al., 2013). The occurrence of tetracycline residues was lesser in milk of Brazilian dairy animals (Prado et al., 2015). The rate of violation due to antibacterial, anthelmintic, and nonsteroidal anti-inflammatory drugs was far less in Lithuania (Serniene et al., 2013). Zheng et al. (2013) found 0.5%, 47%, and 20% positive for βlactams, quinolones, and sulfonamides, respectively, in China. However, only one (0.5%) sample contaminated with βlactams was found to be above the maximum residue limits (MRLs), while sulfonamides and quinolones were found to be below MRLs. Collectively, the available studies indicated the difference in residue prevalence rate between the countries, farming systems, types of antibiotic class, sampling methods, sample size, and methods of screening.

Although, sporadic studies indicated veterinary drug residue violation in milk and milk products in India, the results are based on a lesser sampling size with a small number of targeted group of antibiotics. Sudershan and Bhat (1995) indicated more usage of oxytetracycline in Hyderabad (India) and found that 73% of the milk samples from private dairies and 9% from market milk vendors had oxytetracycline levels above permissible limits. Patil et al. (2003) found 6% of the pasteurized liquid milk samples had antibiotic residues in the northern part of India. Raghu (2007) using charm detection kits found more of β-lactam residues in raw and processed milk. Bhavadasan & Grover (2002) reported 11% antibiotic residue prevalence in milk samples due to β-lactams and tetracycline group of antibiotics in southern India and also found that milk from the organized farms had more violation than unorganized farms. Chowdhury et al. (2015) also reported that the level of antibiotic residue violation in milk was significantly higher in commercial than local farms. Gaurav et al. (2014) found that 3 out of 133 samples exceeded the MRLs of tetracycline as per the EU and Codex Alimentarius Commission (CAC) in 5 districts of Punjab (India). We also found that only 10% of the samples exceeded the MRL of β-lactams and tetracycline antibiotics as per CAC in southern India (Raosaheb, 2016).

3 Pattern of AMU and Its Influencing Factors in Livestock and Poultry

Monitoring AMU is a basic requirement for AMR surveillance, and several studies correlated the AMU data with AMR development and found a direct relationship between them. Surveillance of AMU along with AMR studies at global and local levels is an important insight to understand AMR pattern (Masterton, 2008). However, the OIE reported that many member countries do not have the perfect and relevant law for the import, manufacturing, distribution, and use of veterinary drugs, including antimicrobial agents. As a result, these products are available extensively with virtually no restriction at all (OIE, 2017). However, in recent times several countries have started programs to monitor AMU. The European Medicines Agency (EMA), a nodal body for the evaluation and supervision of sales of veterinary antimicrobial agents in EU countries through the European Surveillance of Veterinary Antimicrobial Consumption (ESVAC), reported the overall sales of antimicrobials for food animals (including horses) in 26 EU countries in 2013. The studies revealed that the largest proportions of sales (mg/population corrected unit: PCU) were accounted for tetracyclines (37%), penicillin (25%), and sulfonamides and trimethoprim (11%) followed by macrolide and lincosamide groups (11%), polymyxins (6%), aminoglycosides (4%), fluoroquinolones (2%), and other drugs (6%) (ESVAC, 2013). However, the sales of critically important third- and fourth-generation cephalosporins, fluoroquinolones, and macrolides in food-producing animals were proportionately lesser (0.2%, 1.9%, and 7.4%, respectively), in total sales. The data was collected from wholesalers, marketing authorization holders (MAH), pharmacies, and prescriptions which revealed variations in prescribing patterns due to differences in the prescription behavior of the veterinarians, variation in animal species, animal-production systems, the market availability of drugs, prices, and other situations related to infectious diseases between the countries. For instances, Hungary and Bulgaria sold more quantity of tetracyclines, while

Sweden, Norway, and Iceland sold more quantity of penicillins in 2013. The countries with more population of pigs used more quantity of antibiotics (e.g., Spain 317 mg/PCU, Germany 230 mg/PCU, and France 95 mg/PCU). In contrast, Cyprus with a low PCU of food-producing animals sold the highest quantity (426 mg/PCU) among EU countries (EMA, 2015). Cuong et al. (2018) reported more AMU in chickens, followed by swine and dairy cattle. Further, tetracycline and polypeptide classes of antibiotics were highly used in swine, penicillins and cephalosporins in cattle, and tetracyclines and macrolides in poultry. When individual antibiotic was considered, penicillin was the most commonly used antibiotic in pig and cattle, while doxycycline was highly used in poultry.

A survey on the usage of feed additives in poultry farms of Tamil Nadu (India) with special reference to antibiotics revealed that chlortetracycline or oxytetracycline alone or combined supplementation of tylosin with any one of the antibiotics among oxytetracycline, chlortetracycline, bacitracin, and lincomycin was most commonly used as feed additive in broilers. Combined administration of any one of the anti-mycoplasmal drugs (tiamulin, tylosin, tylvalosin, and tilmicosin) and antibacterial agents (oxytetracycline, chlortetracycline, and bacitracin) through feed is a common practice in layer farms. Any one of the fluoroquinolone antibiotics like enrofloxacin, ciprofloxacin, and levofloxacin or other antibiotics such as sulfonamides/trimethoprim combinations, neomycin, and oxytetracycline were frequently administered via drinking water in layer farms (Kavitha, 2021).

The observation of a small-holder dairy production system in Peru revealed that >83% of the affected animals were treated with antibiotics, mostly with oxytetracycline, penicillin, and trimethoprim-sulfamethoxazole antibiotics and antiparasitic drugs (Redding et al., 2014). The study suggested for improvement in farm management practices and prescribed practices for improving animal health and the judicious use of antibiotics. They also suggested incentivizing farmers to withhold antibiotic residue-contaminated milk. Zwald et al. (2004) studied the antibiotic usage based on a farmer's recall of the previous 60 days and found that 85% of farmers treated at least 10% milch cows. Ceftiofur was the most commonly used antibiotic, and 80% of conventional herds used antibiotics to treat mastitis. Similarly, several researchers reported the AMU in dairy animals in the USA and other countries (Sawant et al., 2005; Pol & Ruegg, 2007). Mastitis is the most common reason for antibiotic usage, and about 80% of all antimicrobial drugs were used for the treatment or prevention of mastitis in Wisconsin dairy farms (Pol & Ruegg, 2007). In 2007, about 16% of the approximately nine million cows in the USA were treated for mastitis, which is equal to nearly 1.5 million mastitis cases per annum (USDA, 2008). In general udder health management is carried by preventive (mostly by intramammary DCT) or therapeutic approach (either by local intramammary or systemic therapy). Report indicates that nearly 27% of all intramammary antibiotics were used for clinical mastitis therapy, whereas 73% were used on DCT (Kromker & Leimbach, 2017). A survey on AMU and treatment practices in 809 dairy farms in California, New York, Pennsylvania, Virginia, and Wisconsin revealed that 60% farms had written treatment records and 39% farms conducted on-farm screening tests in these states (Wilson et al., 1998). About 52% of the producers were familiar with milk quality assurance program and recognized the treated cows. Doane & Sarenbo (2014) reported about 493 kg of AMU in US cattle farm, of which ionophores (monensin and lasalocids) were used predominantly (76%) than penicillin (16%), lincosamides (3%), aminoglycosides (1.6%), and sulfonamides (1.6%). They use a minimum quantity (<1%) of cephalosporin, macrolides, amphenicols, and fluoroquinolones. Most of the antibiotics (excluding ionophores) were administered to milking cows (74 kg), followed by calves (25 kg) and heifers (19 kg). The most common indications were mastitis and bovine respiratory diseases, while general infections, hoof disorders, metritis, ketosis, and calf diarrhea were the other common disorders. Drugs were administered mostly through oral (78%) followed by injectable (11%), intramammary (10%), and topical (1%) routes. Ekakoro et al. (2018) explored the AMU among Tennessee (USA) dairy cattle producers using focus group discussion and survey questionnaires. They observed the presence of disease symptoms, and to ensure the animal welfare, on-farm pathogen surveillance through bacterial culture and sensitivity tests; economic value and lactation stage of animals; veterinarian recommendation; producer's personal experience and their knowledge-based decision-making ability; drug attributes, viz., drug efficacy, cost, and withdrawal period; and the Veterinary Feed Directive were the most common drivers for AMU. They perceived that good animal husbandry practices like udder health management, clean milking practices, vaccinations, usage of immunomodulatory products, and early disease diagnosis using appropriate technology were considered alternatives to AMU. Most of the farmers were moderately concerned about AMR, and they trusted the veterinarian as a source of information for prudent AMU.

In Canada, intramammary administration of antimicrobials accounted for 35% of total AMU in dairy farms (Saini et al., 2012). Further, the study indicated that cephalosporins (especially third-generation ceftiofur), penicillins and its combinations with other antibiotics, tetracyclines, trimethoprim with sulfonamides, and lincosamides were the most commonly used drugs. They observed that herd-level milk production, herd size, and geographic region were significantly associated with variation in AMU. Similarly, about 68% of antibiotics were used for udder health purposes (DCT and treatment of clinical mastitis) in the Netherlands in 2005–2012, where the use of third- and fourth-generation cephalosporins and fluoroquinolones (i.e., third-choice drugs) decreased from 18% of total usage in 2005 to 1% in 2012 (Kuipers et al., 2016). Restricted use of third- and fourth-generation cephalosporins and fluoroquinolones correspondingly increased the use of penicillin and some of the broad-spectrum antibiotics such as trimethoprim and sulfadoxine combinations. These third-choice drugs were banned in Australia and Denmark and restricted in New Zealand (McDougall, 2012; Katholm, 2014). In Denmark, the prescription of antibiotics by veterinarians reduced by about 14% during the period from 2013 to 2018, where pig farming consumes a significant amount of antimicrobials (DANMAP, 2018). Stevens et al. (2016a) reported that fourth-generation cephalosporins were most frequently administered than penicillins and third-generation cephalosporins in Belgian dairy cattle. On the contrary, cephalosporins were the most frequently administered first-choice antibiotic for clinical mastitis treatment in

Germany (Tenhagen et al., 2006). However, for all clinical conditions, tetracyclines were the most frequently used antibiotic followed by trimethoprim/sulfonamide and β-lactam groups in German cattle (Merle et al., 2012). Different dosage regimens of individual drugs are basic reasons for variation in percentages of the consumption of different antibiotic classes in kilogram basis. Based on the number of daily doses per animal year (DDay) metrics, they noted that pigs were more frequently treated than cattle, of which young animals (calves, piglets, and fattening pigs) were treated more frequently than adult animals. As per DDay, β-lactams (38%), aminoglycosides (15%), fluoroquinolones (8%), and cephalosporins (27%) were most commonly used than sulfonamides/trimethoprim (7%). Parenteral and intramammary routes of administration were common in dairy cattle, while oral route was common in piglets, fattening pigs, and calves. Gentamicin and streptomycin were the most frequently used antibiotics as revealed through a questionnaire-based survey in Lebanon; however, their residual levels were below the MRLs of 200 μg/L as set by the FAO/WHO (Zeina & Fawwak, 2013).

Despite the understanding of the relationship between AMU and AMR development, information available is scant regarding the level of antibiotic use in Indian dairy animals. Recently, Van Boeckel et al. (2015) reported that India is the fourth largest consumer of antimicrobials in food animal sector (3%) after China (23%), the USA (13%), and Brazil (9%) in 2010, which is expected to increase to about 4% in India by 2030. This is an indirect estimation based on population density of livestock and has many limitations. Manimaran et al. (2014) estimated the pattern of antibiotic usage for clinical mastitis in organized dairy farms in India and found that enrofloxacin, ampicillin with cloxacillin, gentamicin, and ceftriaxone drugs were most commonly used against clinical mastitis. Studies on the antibiotic use pattern in organized dairy farms and by field veterinarians in southern India by Raosaheb et al. (2020) revealed that mastitis and other udder health-related problems were the most common (34%) followed by gastrointestinal tract (GIT) infections (20%) and postpartum uterine infections (PUI: 20%). Overall, penicillins and its combinations (40%) and tetracycline (33%) group of antibiotics were mostly used for treatment of the above clinical conditions. About 13% of the milk samples were qualitatively positive for antibiotic residues in organized farms. Veterinarian-rated mastitis followed by PUI, respiratory disorders, and GIT problems were the most common reasons for administrating antibiotics in field conditions, based on Garrett's ranking method. Penicillins, cephalosporins, and tetracycline group of antibiotics were the most commonly prescribed for all clinical conditions. In the case of clinical mastitis, veterinarians preferred cephalosporin group followed by penicillins and its combinations. Besides, the available studies on antibiotic use in Indian dairy cattle (Grover & Bhavadasan, 2013; Unnikrishnan et al., 2005) were mostly based on indirect methods such as residue identification in milk rather than direct methods of data collection. Although periodic collection of drug use information from end user would be a more accurate way to understand the specific information (e.g., off-label use), such studies are rarely conducted in India. Similarly, most developing countries have a limited capacity for surveillance of antibiotic use in the animal husbandry system (Rushton et al., 2014).

The lack of data on the pattern of AMU and influencing factors are obstacles to design the measures to tackle the growing AMR problem. Jones et al. (2015) reported that the farmers' intention to reduce AMU was based on veterinarian's guidance, and hence the policymakers need to target veterinarians with information on the benefits and the ways to reduce AMU along with data on potential cost savings from reduced AMU, without affecting milk yield or compromising on the health of dairy animals. It is also noted that farmers had either recently reduced their AMU, or planned to do so, though they perceived that reduced AMU would be good and important to keep treatment records. Hommerich et al. (2019) estimated AMU in German dairy cows, calves, and beef cattle in 2011–2015 and found a decreased treatment frequency in dairy calves and beef cattle, while the treatment range in dairy cows was between 1.9 and 2.3 days. They identified a significant impact of time and farm size on production system, while region had no effect. Holstege et al. (2018) reported that dairy farmers who practiced immediate treatment of their sick calves using antimicrobials had a higher AMU than farmers who treated their sick calves with supportive, non-antimicrobial therapy (e.g., electrolytes, NSAIDs, etc.). Other risk factors associated with a high AMU in young calves were housing of calves on partially slatted floors, a high prevalence rate of respiratory diseases, *Salmonella* infections, and not agreeing with the statement "young calves need specific management" and different mindset of farmers in Dutch dairy farms. Gussmann et al. (2018) studied the determinants of antimicrobial treatment for managing udder health in Danish dairy cattle and found that somatic cell count was the most important health indicator for treatment on some farms, whereas other groups were treated based on production factors (milk yield) or culling status of the cows. However, these determinants varied between farms.

Zuliani et al. (2020) studied the influence of dairy farming systems on AMU in Italy and found that feeding management practices and rearing of local, dual-purpose breeds can reduce the treatment incidence and thus requirement for AMU. They suggested that reduced treatment incidence and AMU in dual-purpose breed could be due to lesser milk yield, smaller herd size, and limited concentrate ration and pasture access provision. Nyman et al. (2007) also reported the influence of breed in that Swedish Red and White breed cows in Sweden had a lower incidence rate of veterinary-treated clinical cases of mastitis than Holstein herds. Several other researchers also investigated the associations between AMU and management practices or farm performance (Stevens et al., 2016b; Hyde et al., 2017) in European countries. Stevens et al. (2016b) quantified the AMU using antimicrobial treatment incidence (ATI; number of defined daily doses animal (DDDA) used per 1,000 cow-days) metric in Flemish dairy herds. They observed a large variation of AMU between herds. Fourth-generation cephalosporins were the most commonly used drug, followed by penicillins and third-generation cephalosporins. The consumption of critically important antimicrobials (i.e., third- and fourth-generation cephalosporins and fluoroquinolones) was lower than other antimicrobials. For udder health management, they used more of systemically administered antimicrobials followed by dry-cow therapy and intramammary treatment of (sub)clinical mastitis. In herds with a low antimicrobial consumption, most of the antimicrobials were used for dry-cow therapy, while injectable or intramammary mastitis therapies were common in high-antimicrobial-consuming herds. The incidence rate of mastitis treatment was positively correlated with ATI. Herds that practiced blanket DCT had a higher ATI than herds that used selective DCT. The ATI was observed lesser with an increasing number of primiparous cows. Hyde et al. (2017) reported that AMU via oral and foot-bath routes increased the antimicrobial consumption. They also found that the top 25% of farms contribute >50% of AMU by mass, and thus identification and targeted AMU reduction strategies in these farms may facilitate the overall reduction of AMU in British dairy farms. McDougall et al. (2017) reported that dairy veterinarians prescribed antibiotics based on diagnosis and response to previous therapy. Nonclinical factors such as withdrawal period of antibiotics and farmers' preferences also influenced the prescribing pattern where culture and antimicrobial sensitivity testing were not commonly practiced by veterinarians. Alhaji et al. (2019) assessed the knowledge and practices in AMU in lactating cows by pastoralists' and potential AMR transmission pathways from cow milk to humans in Nigeria. They found that improper AMU, non-implementation of regulatory laws, weaker economics, and a low education level and knowledge significantly influenced the antimicrobial misuse in lactating cows. Tetracycline, penicillin, streptomycin, and sulfonamide were the frequently used antimicrobials, and raw milk and milk product consumption, direct contact with contaminated udder, and discarded milk were the recognized risk pathways for AMR transmission from cow milk. Chauhan et al. (2018) explored the drivers of irrational usage of veterinary antibiotics in peri-urban India (Ludhiana, Guwahati, and Bangalore) and identified the following as possible drivers: the low level of knowledge about antibiotics among dairy farmers, active informal service providers like para-vets, animal husbandry assistants, and inseminators; direct marketing of drugs to farmers, including to the abovementioned unauthorized prescribers or users; and easy availability of antibiotics even without proper prescriptions. Mutua et al. (2020) reported that animal disease surveillance and support delivery system are less, and over-the-counter availability of antibiotics to farmers is common in India. Antibiotics were mostly used for mastitis management, but farmers rarely observed withdrawal periods, and thus there is antibiotic residue violation in milk. They also reported less awareness on AMR and a lack of antimicrobial stewardship programs in the Indian livestock sector. Altogether it indicated that the pattern of AMU and their influencing factors vary between countries and production systems, and thus it is very important to understand those factors for better implementation of policies to regulate the AMU in dairy animals and other livestock species.

4 Methods and Metrics Used for AMU Data Collection and Quantification in Veterinary Medicine

Various methods have been explored in veterinary medicines to collect AMU data including usage of mailed questionnaires, surveillance of on-farm treatment records, sales records from pharmaceuticals and pharmacies, residue levels in food of animal origin, and collection of discarded drug packets in dairy farms (Redding, 2014), and many of these methods are not practiced in developing countries including India. The lack of consensus on the type of data collection and its recording system are the major limitations for AMU-related data collection, and thus harmonization of units and methods of AMU data collection from different sources has been a long goal in AMR research area (Ferreira, 2017). It is suggested that accurate data on AMU, ideally in a digital format, is of paramount importance. The lack of harmonized technical methods or metrics to collect AMU, the insufficient incentives (e.g., tax incentive) to motivate farm producers to report their AMU, and the lack of user-friendly technologies and electronic devices are the major limitations for collecting AMU data. Ferreira (2017) also suggested that the development and adoption of the globally standardized units such as ESVAC-recommended metrics, rewarding the animal producers for less AMU, and the development of suitable app, to which farmers, veterinarians, or pharmacists could orally report the AMU, are the solutions to overcome the current challenges. Implementation of electronic veterinary prescriptions and awareness campaigns through public private partnerships (PPP) mode are also suggested to control AMR problems. The advantages of having digitized data on AMU include:

(i) Species-level differentiation of AMU, which is not currently available for many countries as the same antibiotics in the same commercial name are licensed to be used in multiple species (Postma et al., 2015). Since species-level quantification of AMU based on pharmacy or pharmaceutical sales data is not possible (Bondt et al., 2013), having digital data is critical to understand AMR at species level and for consequent implementation of risk management protocol.
(ii) Based on digitized data, it is also possible to quantify good practices associated with reduced AMU either at the herd level, regional level, or national level, without compromising on the animal productivity (Collineau et al., 2017), and thus the same can be promoted through evidence-based policy interventions (Speksnijder et al., 2015).
(iii) Digital data is also useful for the identification of a temporal association between AMU and AMR development, when use of an antibiotic is terminated, either on a voluntary basis or on legal ban (Aarestrup, 2015). It is also useful for the evaluation of the impact of specific policies related to targeted reduction of AMU.

The animal daily dose (ADD), defined daily dose (DDD), total mg, mg/PCU, mg/kg, treatment frequency, and therapy index are some of the technical units currently used to measure AMU in EU countries (Ferreira & Staerk, 2017). Mills et al. (2018) reported that available metrics for quantification of AMU are somewhat different in interpretations. To facilitate the widespread use of metrics, the method should be explicable and relevant to the veterinarians and farmers who are prescribing and using antimicrobials. Clarity about the number, weight and physiological state of animals, and dose rates and duration of treatment should also be considered during estimation of AMU. The description of various metrics for estimation of

Table 1 Different metrics used for estimation of AMU and their advantages and disadvantages. (Source: Mills et al., 2018)

Metrics used	Data requirements for calculation	Advantages	Disadvantages
Total mgs	Total mg of each active drugs used	Simple method	• Do not consider the variations in animal weight (wt.) and numbers • Do not consider dose rates and duration of different antibiotics
Total mg/kg (or) mg/PCU of 425 kg	Total mg of each active ingredients used in a given population	Simple method and consider animal wt. and numbers	• Animal wt. varies with several factors (breed, age, etc.) • This method also ignores the differences in dose rates and duration of treatment of various antibiotics
Daily dose metrics (e.g., DDDvet)	It is calculated based on total mg of each active ingredients used as per daily dose rate in given (risk) population	• It considers animal wt., numbers, dose rate, and duration of different antibiotics • EU-recommended method • Country-specific dosage regimen and animal wt. may improve accuracy	• Complicated metric • Units such as dose rate and animal wt. vary with countries • Not possible for drugs that lack pharmacokinetics and defined dose rate data • It does not account for duration of treatment across antimicrobials
Course dose metrics (e.g., DCDvet)	It is similar to defined daily dose, but use defined course dose	• In addition to daily dose metrics, it also considers the duration of treatment for different antimicrobials • EU-recommended metric	• More complicated metric • Units vary with countries • Units may not be available for all drugs
Cow calculated courses (CCC)	CCC calculated based on course of each drugs used in 12 months period in the farm considering the young (<24 months) and adult (>24 months) stock, separately	Number of cattle, specific wt., and duration of treatment are considered for all drugs	• It requires information on the number of both young and adult stock • Units may vary with countries

AMU including data required, calculation methods, and advantages and disadvantages for each method used in UK dairy industry are given in Table 1. Cuong et al. (2018) reported that 67% of AMU-related studies in animal production systems reported quantitatively, with "daily doses per animal per administration" being the most common metric.

5 Global Strategies for Regulation of AMU

The OIE (2001) reported a comprehensive strategy to manage AMR arising from the agricultural and veterinary AMU (Fig. 1). They reported animals to be sampled (e.g., potential livestock species that is expected to cause AMR using AMU data), type of sampling (e.g., contaminated sample or sampling at different processing chain), sampling strategies (e.g., active or passive surveillance through simple random, random systematic, stratified random collection, or purposive sampling with optimum sample size), bacteria to be tested (e.g., species-wise animal, zoonotic, and indicator pathogens), and important antimicrobials that may be included in AMR surveillance program.

Several countries have taken measures to reduce AMU in food animal production, and recently approved regulations on veterinary medicines and medicated feed in EU member states are an evidence for such action plan. An outline of new regulations which is expected to come into force in the European Union from January 2022 is given below:

- Ban on the preventive use of antimicrobials in animals as well as in medicated feeds
- Restricted use of antimicrobials for metaphylaxis purpose
- Reinforced ban on the use of antimicrobial growth promoters (AGPs) to increase yield
- Reservation of certain antimicrobials for human use only
- Compulsory collection of data on the sales and AMU in food production system
- Ban on the use of AGPs and restricted use of antimicrobials of human importance on imported animals and products

The ban of all AGPs in Sweden in 1986 was an eye-opening policy to global agencies to reduce AMU in food-producing animals. The withdrawal of specific AGP (e.g., avoparcin) in 1997 followed by the complete ban of all AGPs used in animals by the WHO in 2006 forced a reduction of AMU in food-producing animals (Speksnijder et al., 2015). Upon perceiving potential threats of AMU in food

1. Risk assessment for the potential public health impact of AMR bacteria originated from animals

2. Prudent and responsible AMU in animal production system

3. Monitoring the quantities of antimicrobials used in animal husbandry

4. Standardization and harmonization of laboratory analytical techniques used for the detection and quantification of AMR

5. Harmonization of national AMR monitoring and surveillance programs in animals and food of animal origin

Fig. 1 OIE strategy to reduce AMU in food animals

Table 2 Global AMR surveillance programs. (Source: Walia et al., 2019)

Program and country	Actions	References
DANMAP in Denmark	It is an integrated program to understand the relationship between AMU and development of AMR bacteria in animals and humans	DANMAP, 2018
NARMS in USA	• It is a joint program between local public health departments, universities, FDA, CDC, and USDA • It tracks the changes in the antimicrobial susceptibility of enteric bacteria in humans, animals and its products • Providing information about emerging AMR and the impact of AMR interventions program • NARMS data are extensively used for making regulatory guidelines for AMU by FDA	NARMS, 1996
JVARM in Japan	• Monitor AMU and the development of AMR bacteria in food of animal origin • Identification of the efficacy of antimicrobials in food-producing animals and promote those antimicrobials to reduce public health problems	JVARM, 1999
APVMA in Australia	AMU for veterinary use in Australia in 2005–2010	APVMA, 2014
SWEDRES/SVARM in Sweden	Consumption (including sales) of antibiotics and occurrence of AMR (including zoonotic pathogens) in Sweden	SWEDRES/SVARM, 2018
NORM-VET in Norway	• Monitoring program for AMR in the veterinary and food animal system. • NORM-VET data provide basis for understanding the relationship between the AMU and AMR. • This program also essential for setting policies, risk assessment, and evaluating interventions.	NORM-VET, 2000
AURES in Austria	Comprehensive data collection and analyses from the human, veterinary, and phytosanitary sectors on AMU and AMR	Strauss et al., 2007
RESAPATH in France	• RESAPATH is a surveillance network for AMR in pathogenic bacteria of food-producing animals. • It is voluntary-based data from network of laboratories.	RESAPATH, 2001
GERM-VET in Germany	AMU and spread of AMR from food of animal origin	GERMVET, 2001
NethMap/MARAN in the Netherlands	Monitoring of Antimicrobial Resistance and Antibiotic Usage in Animals (MARAN) in the Netherlands	NethMap, 2019
FINRES-VET in Finland	• Monitors the antibiotic susceptibility of zoonotic bacteria, animal pathogens, and indicator (i.e., normal gut) bacteria • Monitors AMR, AMU, and feed additive use	FINRES-VET, 2002
ITAVARM in Italy	Report on AMR of zoonotic bacteria and commensal, particularly in poultry	Battisti et al., 2003
CIPARS in Canada	• Monitor the trends in AMU and its relationship with development of AMR in selected bacteria from	CIPARS, 2006

(continued)

Table 2 (continued)

Program and country	Actions	References
	humans and animals • Setting evidence-based antimicrobial stewardship policies and programs in humans and agriculture • Control the spread of AMR bacteria between animals and humans via food chain in Canada	
UK-VARSS in the UK	AMR of veterinary and zoonotic pathogens	Borriello et al., 2014, 2015
ARCH-VET in Switzerland	Monitoring sales of veterinary antimicrobials and resistance rates	ARCH-VET, 2016
VAV in Spain	Spanish Veterinary Antimicrobial Resistance Surveillance Network	Porrero et al., 2006

animals, several countries established monitoring systems for AMU in food animals and occurrence of AMR in bacteria in food-producing animals and its products (Table 2). Most of the programs were implemented by EU member countries through EU funding, industry funding, and direct national support. Though some harmonization was observed on AMR-related information among EU-funded monitoring programs, other national programs applied in livestock had heterogeneous sampling, testing, and reporting methods, and most reports are not publicly available or are written in the local language (Schrijver et al., 2018). New regulations on veterinary drugs and medicated feeds resulted in substantial alteration in antimicrobial prescription or AMU in Europe and in other countries. For example, Speksnijder et al. (2015) reported that the total AMU in farm animals was reduced about 56% in the Netherlands in 2007–2012. A 35% reduction of dispensed antibiotics was reported in the animal health sector in Germany between 2014 and 2015 (Kromker & Leimbach, 2017).

Although sporadic AMR surveillance programs were initiated in India during the past period, most of the schemes focused on the human medicine sector. Even though the recently initiated Indian National Action Plan on AMR emphasized on "one health" approach, there exists no such coordination in the collection of data from the human and animal health sectors on the ground level. Several isolated studies indicated the presence of AMR in animal production systems, but there is a limited national-level integrated AMR surveillance program implemented in animals and food of animal origin. The lack of consideration about AMU is another weakness of the existing AMR surveillance systems in India. Recommendations of various organizations to address the AMU and AMR in the food animal sector in India are presented in Table 3. However, no stringent regulatory framework has been implemented in India to limit the AMU in livestock and food animals. Walia et al. (2019) reported that the lack of a uniform policy; lack of standardized epidemiological studies to collect reliable, quality data in livestock sector; lack of veterinary surveillance of AMR and AMU; and lack of awareness among farmers and veterinary professionals were the major gaps of AMR studies.

Table 3 Recommendations by Indian organizations to address the AMU and AMR in livestock and poultry sector. (Source: Walia et al., 2019)

Organizations	Recommendations	References
Second amendment of the Drugs and Cosmetics Rules (2006)	About 536 drugs classified under Schedule H (i.e., sold only based on the prescription)	REACT Group, 2018
Poultry feed specifications-BIS 2007	Antibiotics with systemic action (e.g., chloramphenicol, doxycycline, tetracycline, nitrofurazone, and furazolidone) should not be used as AGP and phasing out of gut-acting antimicrobials in 5 years	Walia et al., 2019
National Policy for Containment of AMR – MoHFW	• Strengthening of regulatory provision for AMU in human, veterinary, and industry • Promote prudent use of antibiotics via awareness, education, and regulatory policies • Strengthening of diagnostics for AMR monitoring	National Policy for containment of AMR India, 2011
National Programme on Containment of AMR under the 12th 5-year plan (2012–2017)	• AMR surveillance in different geographical regions • Strengthening national IPC guidelines • Training and capacity building in the area of AMR • Promote prudent use of antibiotics • Establishment of national repository of bacterial strains	NPCAR, 2012
Directorate General of Health Services	Introduced a sub-rule for labeling the withdrawal period of antibiotics intended for use in food-producing animals. If this period is not validated, then recommended period of 7 days for egg or milk, 28 days for poultry meat, and 500 days for fish meat were advised	Directorate General of Health Services, 2013
Advisory on use of antibiotics in food-producing animals issued by DAHDF to States	• Requested states to review the use of AGP in food-producing animals • AMU based on veterinarian's prescription or supervision • Promotion of alternatives to antibiotics like probiotics, phytobiotics, etc. • Use of licensed drugs by registered users through registered distributor of veterinary medicine • Establishment of tracking system for antibiotics from manufacturers to users, by state drug controller	Department of Animal Husbandry, Dairying and Fisheries (DAHDF), 2014

(continued)

Table 3 (continued)

Organizations	Recommendations	References
FSSAI, 2015	• Judicious AMU and ban of AGP • Avoid the inclusion of meat meal and blood meal in commercial feed formulations of meat-producing animals and poultry • Separate slaughterhouse for poultry and livestock species • Strict ban on AGP in poultry and regulate the use of only permitted antibiotics	FSSAI, 2015
CDDEP (Center for Disease Dynamics, Economics and Policy) 2016	• Tracking the AMU, AMR, and residue prevalence through a national-level surveillance and monitoring programs in animal production system • Incentives to encourage prudent use of antibiotic in animals • Educate farmers, veterinarians, and consumers about AMR • Discontinue the sub-therapeutic use of antibiotics in animals in phased manner	CDDEP, 2016
2017: National Action Plan on AMR (NAP-AMR) 2017–2022	• Improving awareness about AMR • Strengthening knowledge through evidence-based surveillance program • Reducing the infection rate through efficient IPC measures • Optimizing the AMU in humans and animals • More investments for AMR programs, research, and innovations • Increasing India's commitment on AMR through international collaborations and national-level network projects	NAP-AMR, 2017
2017: ICMR Action plan for AMU in food-producing animals	• Guidelines on prophylactic, therapeutic, and metaphylactic use of antimicrobials by DAHDF • Ban on use of premix and loose antibiotic powder formulation by DAHAD and Drug Controller General of India (DCGI) • Improve awareness and education of farmers and veterinarians, by DAHDF and ICAR • Proper labeling of medicines by pharmaceuticals by DAHDF and DCGI • Regulation of WHO-listed human importance AMU in food animals by DCGI • Fixing MRL for antibiotic residues by DAHDF and ICAR	Walia et al., 2019

6 Conclusions

Understanding the AMU in various livestock sectors and their influencing factors is an important prerequisite to suggest a targeted action plan and regulate the antimicrobial usage. Global studies indicated that mastitis and other udder health management issues are the most important reasons for AMU in dairy production systems, and thus mastitis control programs are inevitable to reduce the AMU. Besides, prudent AMU in animals through improved biosecurity and antibiotic sensitivity testing were shown as important tools to reduce the AMR problems. Harmonized, uniform, and simple methodology to estimate the AMU in food animals is also the need of the hour. Under the changing dairy production conditions from small-holder, less intensive to highly intensive farming system, identification of influencing factors for AMU and suitable metrics for the above systems are important to make evidence-based policy decision. Since the AMR bacteria is expected to cause more damage in economically underdeveloped and developing countries, it is high time to start specific measures to control AMR. Reduction of critically important antibacterial use should be the immediate goal with a long-term aim for the overall reduction of AMU. Replacements of antimicrobials with alternative treatment like prebiotics, probiotics bacteriophages, phytochemicals, etc. are some of the long-term strategies to reduce AMU without compromising the health and welfare of the animals. Rethinking of animal husbandry practices through continuous education and awareness of AMR and by giving more emphasis on the prevention and control of diseases using vaccination or genetic selection rather treating diseased animals is also an important measure to reduce AMU in animal production system.

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