Review Article

Revealing the Scenario of Antimicrobial Resistance in Dairy Animals from Stakeholders' Perspective: Where Should we Focus?

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Abstract

Indiscriminate and over use of antimicrobials in animal production is a key contributor to antimicrobial resistance worldwide. Behavioural dimensions of the stakeholders needs to be unearthed to establish the valid veterinary- client relationship and design suitable policies and intervention to control the spread of antimicrobial resistance by acting locally in the lines of international approach for formulation of feasible policies, regulation and its adoption by end- users. Accurate monitoring of antimicrobial prescription and use by stakeholders has become imperative to formulate the policies in line with one health approach, antimicrobial conservation and antimicrobial stewardship. Our review highlights that unavailability of data regarding antimicrobial production, consumption, and dispensation from prescriptions is biggest lacunae. Planning for policies suffers due to over- the- counter sales, lack of development of new antibiotics, scarce alternatives to antimicrobials and perceives the strong need for surveillance and research initiatives to reduce antimicrobial use in animal production.

Key words: Antimicrobials, Monitoring, Prescription, Stakeholders, Veterinary-Client Relationship

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Introduction

Zoonoses are category of emerging infectious diseases, which could severely hamper targets of Sustainable Development Goals, Goal 3 is strongly associated with emerging infectious diseases. Recent emergence and dissemination of drug-resistant pathogens has prevented us reaching the targets of SDG, which led to shrinking of therapeutic arsenal, generally due to antimicrobial resistance. World Health Organization has identified antimicrobial resistance as one of three greatest threats to global health (Asokan and Kasimanickam, 2103). Antimicrobial resistance is the ability of a microorganism (like bacteria, viruses, and some parasites) to stop antimicrobials (such as antibiotics, antivirals and antimalarials) from working against it. As result, standard treatments become ineffective, infections persist and may spread to other healthy animals (Anonymous, 2014). When microbes become resistant to medicines, the choices for treating the diseases become limited. This resistance to antimicrobial medicines is occurring in all parts of the world for a broad range of microorganisms with increasing threat to animal and human health. Indirectly, antimicrobial resistance is a drain on the global economy leading to reduced productivity of animals caused by sickness and higher costs of treatment. Thus, the initiatives need to be directed towards increasing awareness and understanding of antimicrobial resistance among stakeholders, strengthening knowledge through surveillance and research, optimizing the use of antimicrobials and ensure the sustainable investment and involvement in countering antimicrobial resistance by ensuring active participation of stakeholders (Anonymous, 2015).

Antimicrobial resistance is spreading rapidly across geographical boundaries and can traverse among humans, animals across countries; mediated through resistant strains without any specific control on its mechanism intrinsically (Littmann and Veins, 2015). As a result, prescribed treatment fails to put a check over resistant strains, infectious diseases are becoming uncontrollable and major surgeries are jeopardized (Hawkey and Jones, 2009). The problem of antimicrobial resistance is equally imperative and widespread in humans and animals, but emphasized to a lower extent in livestock. Antimicrobial agents are used as therapeutic, metaphylactic, prophylactic, or as growth promoter in dairying and other livestock (Woolhouse *et al.*, 2015). The attributing factor to problem in dairying and livestock production is use of antimicrobials as growth promoter and prophylactic purpose (Brown *et al.*, 2017).

Use of Antimicrobials and Its Resistance in Dairy Animals

Worldwide, even more than 50 per cent of antibiotics are used for veterinary purpose (Teuber, 2001). On the account of antibiotic production at global level, it has been revealed that India manufactured about one third of the total antibiotics produced in the year 2012 (Kakkar *et al.*, 2017). Dairy animals maintained by large farmers and conventional dairy farms are more frequently exposed to antimicrobials in comparison to dairying practiced by small farmers (Krehbiel, 2013). With this increasing demand of animal source food, the value of veterinary drugs augmented from 20 billion dollar in 2010 to 42.9-billion-dollar mark by 2018 in international market (Hao *et al.*, 2014). Globally, animal farming relies heavily on the surplus use of antimicrobials for improving animal health and obtaining greater productivity. The consequences of widespread resistance are more severe for developing countries, including India, where the infectious disease burden is very high and, which attracts higher antimicrobial application for limiting morbidity and mortality in dairy production and other animal farming (Ganguly *et al.*, 2011). Predicting actual values of antimicrobial usage in dairy farms is challenged by several factors, like lack of antibiotic treatment records and written plans for treating sick animals, low dependence on veterinarian's advice, obtaining of antimicrobials from over- the- counter sales by the owner itself (Diaz, 2013). Due to variations in

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antimicrobials use over the farms, the details on antimicrobials use in dairy animals are more presumptive. According to a survey conducted by the World Organization for Animal Health (OIE) in 2012, only 27 percent of its member countries have adopted an official system for recording antimicrobial usage in livestock (Brower *et al.*, 2017).

Antimicrobial Resistance Reported in Dairy Products in India

A survey revealed the prevalence of *S. aureus* in meat and dairy products indicated around 68.8 percent strains were found resistant to at least one antibiotic tested. Usually, *S. aureus* is present on the skin and mucosae of animals, it is associated with subclinical mastitis, which leads to its entry of this bacteria into milk chain (Normanno *et al.*, 2007). It was revealed that methicillin- and vancomycin -resistant *S. aureus* were prevalent in dairy products (Sasidharan *et al.*, 2011). *L. monocytogenes* is another resistant bacteria frequently found in dairy products. Furthermore, resistance were found in *E. coli*, which have also been isolated from faeces of healthy lactating dairy cattle (Sawant *et al.*, 2007). Shiga toxin-producing multidrug resistance *E. coli* strains have also been isolated from cow stool samples in Calcutta, India (Khan *et al.*, 2002). Similarly, a number of studies have delineated the extended-spectrum β-lactamase producing *E. coli* in food-producing animals (Ewers *et al.*, 2012). Antimicrobial resistant *Salmonella* spp. has also been found in cattle, milk, and milk products (Addis *et al.*, 2011).

Worldwide Losses Due to Antimicrobial Resistance

Around 50,000 lives per year are estimated to be lost due to rise in antimicrobial resistance infections within the United States and Europe (Simlai *et al.*, 2016). These antimicrobial resistance infections are projected to cause 10 million deaths per annum by 2050, with 4.1 million and 4.7 million deaths due to resulting infections in Africa and Asia, respectively, at a cost of $100 trillion (Oneill, 2014).

Efforts in India to Combat Antimicrobial Resistance

The inter woven interest of stakeholders to earn profit, ignorance and low awareness towards the transfer of antimicrobial resistance among species has drawn the attention of the international health bodies towards the catastrophic condition of non- healing of surgery in humans due to antibiotic resistance. World Antibiotic Awareness week, 13-19 November, strategies formulated in G7 meetings in year 2017 (Anonymous, 2017). Efforts such as ICMR collaboration with ICAR to standardize antimicrobial susceptibility testing in the veterinary labs and integrating AMR surveillance in humans and animals and USAID collaboration with WHO, NCDC, ICMR and ICAR to provide technical assistance to scale up infection control assessments and assess AMR burden at both the national and state level are recognizable. In year 2016, United Nations resolution at the high level meeting on antimicrobial resistance at the United Nations General Assembly paved way for technical leadership in India to leverage the current conducive

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policies to control antimicrobial resistance The Red Line Campaign in 2016 was outlined the proposal for colour-coding antibiotic strips and newer molecules (carbapenems, tigecycline, daptomycin etc.) to abolish their use outside of tertiary care settings (Anonymous, 2016).

Multidrug Resistance

Multidrug resistant bacteria are found in both meat and fresh produce and high in farm- workers who are in direct contact with livestock (Mezali and Hamdi, 2012; Addis *et al.*, 2011). The close proximity with animals increases the chances of transmission of resistant microorganisms from animals to humans through animal handling to animal health care providers. In the absence of effective animal healthcare system, farmers depend on informal healthcare providers for treatment of their animals which increases the suboptimal use of antimicrobials with unhygienic animal husbandry practices in their conditions (Roess *et al.*, 2015).

Vaccination

Vaccines are a primary mode to prevent infectious diseases. Erstwhile vaccination may reduce severity of disease, provide defence against multiplication of pathogens and even raise the threshold load of pathogens required for causing infection (Hinman and Orenstein, 2007). Also, indirect population herd protection as result of vaccination to unvaccinated animals represents additional advantage of vaccination (Panhuis *et al.*, 2013). Although, need of antimicrobials or alternative treatment options cannot be eliminated due to vaccination, but can be reduced. Thus, there is a need to make the farmers aware about the advantages of vaccination over increased use of antimicrobials. The benefits of vaccination should be provided to farmers through campaign and extensive livestock extension activities to educate them about its ability to reduce economic losses due to less chances of disease occurrence (Rathod *et al.*, 2013).

One Health Approach

One health can be defined as "the co-operative effort of multiple disciplines by working locally, nationally, and globally to attain optimum health for people, animals, and the environment (Mackenzie *et al.*, 2014). The multifaceted one health concept links health systems of animals, humans, and the environment, respectively by considering both pathogenic and non-pathogenic microbial transfer between humans, animals, and the environment (Trinh *et al.*, 2018). This includes actions to preserve the continued effectiveness of existing antimicrobials by reducing their inappropriate use. Mass medication of animals in the animal health and agriculture sectors with antimicrobials is the major concern are critically important for humans, as third-generation cephalosporins and fluoroquinolones, use of antimicrobials for growth promotion could be dangerous for both species (Kahn, 2017).

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Awareness among Veterinarians about Antibiotic Resistance

The prescriptions of antibiotics are mostly in initial encounter of diagnosis, which need to focus on antibiotic conservation practices. The ethical awareness is one dimension which needs to be emphasized among veterinarians in developing countries to reduce counterfeit medicines and build a valid veterinary-client relationship with farmers by providing them counselling and continuing education (Kumar *et al.*, 2018). Heavy prescription of broad-spectrum antibiotics in initial encounter of diagnosis aggravates the antibiotic resistance because antibiotics of last resort should not be used initially. Sub-therapeutic prescription of antimicrobials by veterinarians is mostly due to the reliance of veterinarians on the experience in diagnosis and previous clinical encounters to cure the disease. Thus, there is need to check the sub-therapeutic and non-therapeutic prescription of antimicrobials with stringent implementation protocols (Kakkar *et al.*, 2017).

Antimicrobial Prescribing Behavior of Veterinarians

The prescribing behaviour of veterinarians are affected by the biasness in favour to prescribe antibiotics to avoid risk and farmer's demand to get antimicrobials for quick recovery of health of animals pressure from peers (Hulscher *et al.*, 2010). Veterinary consultation could be useful for obtaining information about restocking of herd during outbreak of disease and its rehabilitation to reduce overuse of antibiotics (Gwyther *et al.*, 2011). Veterinarians revealed that failure of initial antibiotic therapy was responsible for costly therapy, and it also biased them to opt for broad spectrum of antibiotics in future diagnosis (Boucher *et al.*, 2009). Shorter consultation time of veterinarians with farmers led the veterinarians to adopt the empirical treatment practice due to their busy schedule and work load (Gjelstad *et al.*, 2011). There is need to increase the awareness and consideration to MIC values and epidemiological cut-off values while prescribing antimicrobials, thus suitable training should be designed in these considerations (De Bryne *et al.*, 2013). Inadequate surveillance, limited availability of laboratories for antimicrobial sensitivity testing and its less preference by veterinarians in routine clinical practice are main reasons for irrational and over- prescription of antibiotics. Sensitivity testing may provide information on resistance trends, including emerging resistance which could be very essential for and for the development of effective policies against antimicrobial resistance (Ayukekbong *et al.*, 2017).

Drug Dispensers and Drug Quality

The driving factor in the misuse of antimicrobials is lack of appropriate regulations in the sales of antimicrobials leading to over- the- counter sale of drugs without obtaining medical prescription. The dispensation of drugs by paravets considers wide use of antimicrobials and depends on farmer's ability to pay. Even pharmacies operating without a license, are more accessible to farmers as they have shorter

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waiting time with no consultation fees and negotiable treatment options to adjust to the financial ability of the farmers (Okeke *et al.,* 2007). Retail pharmacies in developing countries render unauthorized services from consultation, diagnosis, prescription and dispensing of medication. It also leads to poor storage condition of drugs and prevalence of counterfeit medicines in market (Ayukekbong *et al.,* 2017). These counterfeit and sub- standard antimicrobials aggravate its use for sub- therapeutic use of antimicrobials due to its reduced potency to cure diseases (Kelesidis *et al.*, 2007).

Antibiotic Use by Dairy Farmers

Over-prescription or under-prescription of antimicrobials, inappropriate drug dosing, stop giving antimicrobials before the prescribed duration, incorrect choice of antibiotics due to over the counter sales and obtaining from paravets and the unnecessary use of an expensive antibiotic when cheaper drugs are available and clinically adequate (Schwarz *et al.,* 2001). The farmers demand the veterinarian to get antimicrobials which act as a barrier for judicious prescription of antimicrobials because it denies call for sensitivity testing as part of diagnosis (Gelband *et al.,* 2015). Large farmers opt to use antibiotic for prophylactic purpose on the basis (Kumar and Gupta, 2018) of argument that if disease with high probability of occurrence will not be controlled, it could result morbidity and mortality rates with accompanying financial losses and making the subsequent treatment more expensive (Speksnijder *et al.*, 2015). Large farmers were comparatively judicious than smallholder dairy farmers to use antimicrobials due to higher levels of awareness and knowledge about antibiotic resistance (Kitazono *et al.,* 2012).

Importance of the Stakeholders' Perspective

The control of antimicrobial resistance cannot be the sole responsibility of veterinary professionals and scientists. Although continuing education could be helpful in rational prescription practices and realise the importance of evidence-based prescription, the farmers and other stakeholders have a central role to play (Blakely *et al.,* 2006). Antimicrobials, mostly antibiotics are used in both human and animals. Since, generation and types of antibiotics are almost same in both species and spread of antibiotic resistance is very fast. So, it's time to educate and increase awareness among livestock owners, milk consumers, drug sellers, healthcare workers at farm, veterinarians/doctors and paravets, who are associated with livestock and are humans who use same generation of antibiotics for their own treatment too. Apart antimicrobial agents are commonly used in plant agriculture, poultry, dairy animals, piggery, commercial fish and seafood farming. There is lack of synchronised effort in policy formulation from the baseline data of the use of antimicrobials, antimicrobials to treat several diseases, generation of antibiotics in use and its availability in market, ease to obtain the antimicrobials over-the-counter, reporting of antimicrobial resistant genes to higher level or animal and plant protection authority, research and development needs of the drug

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manufacturing company to be balanced between production units, demands of veterinarians and their feedback. From farm to fork, the end users of antimicrobials are the livestock owners in animal agriculture, whose decisions regarding disease treatment are influenced by peers, veterinarians and paravets having the informal relations and previous experiences. The strategy for prudent use of antimicrobials among stakeholders needs should focus on integrated roles. Tracing the antibiotic residues in milk at the milk procurement site can be a check- site to policymakers, organizations and animal health-care professionals to ensure availability of quality milk to consumers (Gibbons *et al.,* 2013).

Spread of Antimicrobial Resistance in to Food- Chain

It has been observed that up to 90 per cent of antimicrobials given to animals are excreted in urine and stool. As result, it affects the environmental micro- biome profoundly because it is widely dispersed through manures, surface runoff and groundwater (Zaman *et al.,* 2017). The selective pressure due to overuse of antimicrobials in food-producing animals (including dairy animals) led to rise in horizontal transfer of antimicrobial-resistant elements in bacteria (Kuipers *et al.*, 2016). Apart from the overuse of antimicrobials, unique environmental conditions such as crowding and poor sanitation also contribute in the circulation and spread of resistant microorganisms. Transmission of resistant pathogens is facilitated by person-person contact, through contaminated water, food or by vectors. Improving basic hygiene and sanitation will reduce the spread of resistant organisms (Smith *et al.*, 2004).

Monitoring and Surveillance

The World Organization of Animal Health *Terrestrial Animal Health Code* chapter 6.7 describes the harmonization of surveillance and monitoring programs at national level in a country, chapter 6.8 highlights the monitoring aspect of antimicrobial usage pattern patterns in food-producing animals, chapter 6.9 embodies the judicious use of antimicrobials in veterinary practice; and chapter 6.10 incorporates the risk assessment for antimicrobial resistance arising from the antimicrobial use in animals (Anonymous, 2012). Thus, surveillance programmes aims at improved recording of emerging antimicrobial resistance, enhancing the active life of antimicrobial drugs, and providing guidance to the stakeholders for the development and usage of newer drugs. In order to monitor the status of antimicrobial resistance, the first model was named as *Danish Integrated Antimicrobial Resistance Monitoring and Research Programme* (DANMAP), initiated by the Danish Government in 1995. In Indian situation, there are no regulations for the use of antibiotics in food animals. An effort named as Global Antibiotic Resistance Partnership (GARP) was initiated in the year 2009 to develop actionable policy recommendations to antimicrobial resistance. In 2011, this working group recommended establishment of national antibiotic resistance and surveillance system. The antibiotic use in India has shown increasing trend, in which units of antibiotics sold increased

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by about 40 percent between 2005 and 2009 (Ganguly *et al.,* 2011). There is no national database on antimicrobial use surveillance in India.

Antimicrobial Stewardship

It is defined as optimal selection, dosage, and duration of antimicrobial treatment that promotes best clinical outcome for the treatment or prevention of infection, minimizes toxicity to the livestock and minimal impact on subsequent rise of resistance. The 3- fold goals constituting antimicrobial stewardship includes availability of most appropriate antimicrobial with the correct dose and duration, prevent the overuse, misuse, and abuse of antimicrobial and minimize the development of resistance (Doron and Davidson, 2011). The "4 D's of optimal antimicrobial therapy" includes right drug, right dose, de-escalation to pathogen-directed therapy and right duration of therapy (Joseph and Rodvold, 2008). The awareness campaigns should aim to increase knowledge and catalyse behaviour change in line of appropriate monitoring programmes (Kakkar *et al.*, 2017).

Complexity of Issue to Tackle in Livestock

The diversity of environmental conditions for rearing animals and large number of reared animal species had made the manifestation of antimicrobial resistance as intricate in veterinary medicine because of differences in the microbes involved, pathogenicity mechanisms, and the complex epidemiology (Acar *et al.,* 2012). Animal husbandry account for more than 50 percent use of all antimicrobial production for growth promotion and prophylaxis in dairy animals, poultry, swine, fish, and honeybee. It has been estimated that antibiotic use in animals and fish is as much as 1,000 fold higher than usage in human (Anonymous, 2011).

Role of Extension and Outreach Activities

The human behaviour, largely affects the emergence and spread of antimicrobial resistance as it is shaped by cultural, social, political, and economic factors (Wood 2016). There are variation in patterns of use and resistance to antimicrobials across the globe, which cannot always be explained by knowing difference between prevalent diseases, health care infrastructure and farming system (Carmo *et al.*, 2017; Grave *et al.*, 2010). Therefore, social sciences can identify multi-faceted reasons that lead to variations in application of antimicrobials and the development of antimicrobial resistance. Social sciences also play valuable role in identifying the most impactful and feasible interventions to counteract the phenomenon of antimicrobial resistance (Magouras *et al.,* 2017). The roles of veterinarians, farmers and paravets can be largely shaped by extension efforts when it comes to the catastrophic situation of drug failure due to antimicrobial resistance. Surveys and expert opinions could be well-accepted approaches for exploring and modifying the behaviours of stakeholders regarding antimicrobial use and antimicrobial resistance. These methods

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could provide relevant data on the attitudes, motivation, and knowledge of veterinarians, paravets and farmers toward antimicrobial use. Controlled experimental studies should lay the foundation for the design and implementation of intervention strategies to assess the success of specific interventions. This research area should be toward the reduction of antimicrobial use and resistance (Visschers *et al.*, 2015).

Strategies and Alternatives to Control Antimicrobial Resistance

There is need to implement global co-operative efforts at individual, community, local, regional, national, and international level to address antimicrobial resistance. The strategies should designed to optimize the antibiotic usage, minimize un-intended interaction between pathogenic microorganism and antimicrobials due to overuse and use of broad spectrum and higher generation antibiotics, control the spread of resistant strains through surveillance and reporting to higher authority about new incidence of resistance, and judiciously use the antimicrobials (Doyle *et al.*, 2006). Periodic updating of standard treatment guidelines into locally relevant and evidence-based guidelines with easy availability of the concerned documents and reports could be beneficial. Unbiased audit feedback mechanism on drug prescribing rates of individual practitioners and healthcare facilities could be useful to establish surveillance. There is need to manage the antimicrobial resistance in both human and veterinary pathogens which seeks concerted action of researchers, policy makers, veterinarians, industrialists, and also the end users such as farmers (Sharma *et al.*, 2018). The efforts to check the overuse of antibiotics have led attention toward the use of probiotics, prebiotics, and synbiotics for production along with improved gut health of the dairy animals (Baffoni *et al.*, 2014). Several study reveal that the irrational use of antibiotics as growth promoters can be checked by substitution of antibiotics with probiotic strains as growth promoters in livestock animals (Guillermo *et al.*, 2015; Muñoz *et al.*, 2013). Bacteriocins are bacterial antimicrobial peptides (AMPs) that can be beneficial to reduce the overuse of antibiotics by killing or inhibiting closely related bacterial strains. Antimicrobial Peptides are one among the leading alternatives to on-going antibiotic therapy which could be helpful in reducing the loads of antimicrobial resistance (Narayana and Chen, 2015).

Limitations and Solutions for Extension Approaches in Gathering Surveillance Data about Antimicrobial Resistance

Surveys research to farmers gathers data suffers from recall biases, because often farmers do not keep records, especially in small-holder farms and farmers (Beegle *et al.*, 2011). Since longitudinal on-farm surveys are time-consuming and require considerable farmer commitment, it may suffer due to low response rate, limiting their representativeness in sample (Callens *et al.*, 2012). When there is vast diversity of antimicrobial products, but the use of each individual product is low, then a small sample size may result in a 0 median (Filippitzi *et al.*, 2014; Saini *et al.*, 2012), which makes the results difficult to interpret. It would be better to work on mean and its associated standard deviation. In the most complex situations (i.e.

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countries with high heterogeneity of farming systems), a two-step cluster sampling procedure would be best. It involves random selecting regions within the country (clusters) at first stage, followed by stratification by farm type within each region, and systematic random sampling of farms with a selection probability proportional to their farm size (Cuong *et al.*, 2018).

Research and Innovation for Development of New Antimicrobials

Research and development of new antimicrobials is an issue because until 1980s, various new classes of antibiotics were discovered and modified and tailored to combat emerging diseases. But in 1990s, financial challenges for antibiotic development showed a poor investment return, as compared to, drugs that treat non communicable diseases. The comparatively lower NPV of these antibiotics and large time required from clinical testing to regulatory approval of antibiotics, low clinical approval success rate receded the development of new antibiotics (Asokan and Kasimanickam, 2011). Cadila approach of developing the antibiotic resistance breakers (ARBs) to restore effectiveness of older classes of antibiotics could be a good innovation. The reluctant approach of pharmaceutical companies to invest in research and development of antibiotics should be sorted out. The policies on conservation of newer classes of antimicrobials and use of antibiotic chemotherapy for treatment of infectious diseases should be emphasized. A separate Schedule H1 under the Drugs and Cosmetics Rules to regulate the sales of antibiotics should be established (Anonymous, 2016).

Conclusion

Antimicrobial resistance is a complex phenomenon which is biological in nature but, profoundly social, driven by socio-economic factors and affected by practices of various stakeholders. Bridging the gap from research and development to production of antimicrobials by pharmaceutical companies, prescription of antimicrobials to its usage by farmers, diagnosis to post- treatment follow-up, and policy formulation to surveillance requires huge and integrated effort to change knowledge, attitude, awareness and behavioural change towards ethical and sustainable efficacy for the antimicrobial drugs. The innovative approaches to fit in socio- economic conditions of farmers need to be designed on region basis in line with one health approach, antimicrobial conservation and antimicrobial stewardship. A valid veterinary-client relationship should be based on roles and responsibilities of veterinarians and farmers by realising their responsibilities to control the catastrophic effects of antimicrobials on human and animal health. Finally, the ecology of antimicrobial resistance should be addressed with a holistic and integrated approach by combining expertise from different disciplines and various stakeholder such as veterinarians, paravets, farmers, drug retailers, animal- health workers, pharmaceutical companies, extension functionaries, microbiologists, epidemiologists, policy makers and world organization on animal health.

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