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Combating Antimicrobial Resistance (AMR) in Animal Health: Strategies and Solutions

AUTHORS DETAIL

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Abstract

Antimicrobial resistance is emerging as a serious health concern due to reckless use of antibiotics in animal husbandry. Since their inception, antibiotics have revolutionized the medical field but now this increasingly emerging resistance is causing a significant distress worldwide. With rising demand of animal protein, AMU (antimicrobial usage) in animal farming has substantially increased ultimately affecting animals' microbiota and providing selective pressure for emergence of resistant microbes. Resistant pathogens by utilizing horizontal gene transfer mechanism pass their resistant genes to other microbes. There is an urgent need to discuss this issue under one health and adopt better surveillance systems to monitor AMU and AMR in animals to lower this escalating graph. Finding solution to address AMR adequately is complicated, success will involve communities, nations and individuals all working together to make sure that world should continue to have an armamentarium of effective antimicrobials that will sustain in animals and human both now and in future.

Keywords: AMR, AMU, Economic implications, Clinical consequences, Food producing animals

Introduction

AMR which stands for "Antimicrobial Resistance" is interpreted as the capability of bacteria or microorganisms to combat the germicidal activity of antibiotics/microbes over the usual sensitivity of a particular bacterial species (Tang et al., 2023a). Antibiotics have been vital in treating a number of infectious diseases, significantly enhancing health outcomes in animals as well as promoting faster growth by controlling foodborne infections. However, this progress is increasingly at risk due to the spread of antibiotic-resistant pathogens. The use of antibiotics in animal husbandry can disrupt the delicate balance of the intestinal microbiome—a microbial community essential to the health of both humans and animals (Mutua et al., 2020) .With the rising global demand for animal protein, it is projected that antimicrobial use (AMU) in food animal production will increase substantially, potentially rising by 67% between 2010 and 2030. In 2012, the average consumption of antimicrobials across 26 European Union countries was measured at 116.4 milligrams per kilogram of estimated biomass for humans and 144.0 milligrams per kilogram for animals (Tuševljak et al., 2013).
Antimicrobial resistance (AMR) stands out among global health issues as a chief example of the One Health approach. This approach involves communal efforts across multiple disciplines to address the health of humans, animals, and the environment (Bhat & Altinok, 2023). AMR is fundamentally connected to these three sectors due to the reckless and uncontrolled use of antibiotics across agriculture, livestock production, and human healthcare. Under selective antimicrobial pressure, bacteria develop resistance genes and mobile genetic elements that can transfer to other bacteria, even across different genera. Once

bacteria become resistant to antimicrobials/antibiotics, they gain an enhanced ability to proliferate in animals, humans, and the environment (Tang et al., 2023b). For example, Colistin (polymyxin B) is a powerful bactericidal antibiotic that has been applied in human and veterinary medicine for several decades. Fluoroquinolones are a key antimicrobial class, with resistance emerging in Campylobacter jejuni isolates in poultry. In Australia, where their use in animal feed is unapproved, such resistance is rare (Milijasevic et al., 2024).

Antimicrobial resistance to a specific antibiotic can either be an intrinsic trait of the microorganisms or a mechanism acquired over time. The capacity of a microbial cell to survive antimicrobial exposure is a naturally versatile response (Ahmed et al., 2023a). AMR is globally affecting all populations, with rising resistance in key pathogens like S. aureus, E. coli, and Klebsiella pneumoniae straining healthcare, veterinary, and agricultural systems. In the 'One Health' context, AMR in food animals impacts both animal and human health. As even last-resort antibiotics lose effectiveness, new strategies are being developed to address multidrug-resistant (MDR), extensively drug-resistant (XDR), and pan drug-resistant (PDR) infections (Brosh-Nissimov et al., 2023).

AMR Mechanisms

Microbes can develop antimicrobial resistance through various mechanisms, including enzymatic breakdown of anti-microbes, modification of antimicrobial targets, alteration of cell wall permeability, and activation of alternative pathways to evade antimicrobial effects (Ahmed et al., 2023a). A frequent resistance mechanism in bacteria involves the enzymatic breakdown of antimicrobial agents. For aminoglycosides, resistance is largely mediated by degradation enzymes, such as acetyltransferases, nucleotide transferases, and phosphotransferases. A notable example of naturally occurring resistance is seen with β-lactam antibiotics, as β-lactamase enzymes, which confer resistance, have been present in bacterial populations for thousands of years (Ahmed et al., 2023a). Target modification as a resistance mechanism involves altering the antibiotics target molecule, often an enzyme, so the antibiotic can no longer bind effectively, rendering it inactive. This mechanism is seen in mutations within the gyrase and topoisomerase genes, which serve as targets for quinolone and fluoroquinolone antibiotics. Methicillin-resistant Staphylococcus aureus (MRSA) exemplifies horizontally transmissible target modification, where resistance traits are shared across bacterial populations (Ali Alghamdi et al., 2023). Modifying cell wall or cell envelope permeability is another resistance strategy, where bacteria either limit antibiotic entry or increase its efflux, thereby controlling the antibiotic concentration within the cell. Alterations in pore structures can reduce or block antibiotic entry. Additionally, increased efflux may occur through the acquisition of specific genes, as seen in the case of tetracycline resistance (Lynch & Zhanel, 2023). Mechanisms of AMR adopt by bacteria are depicted in Fig 1.

Cells may develop resistance by passing their usual physiological pathways and incorporating an alternative step, often facilitated by an additional enzyme. An example of this mechanism is the production of an alternative dihydrofolate reductase enzyme, conferred by an R-plasmid, which provides trimethoprim resistance. This enzyme differs from the chromosomal version in its binding affinity to various antifolate compounds, as observed in Escherichia coli and Citrobacter species (Romanescu et al., 2023). Antibiotic resistance genes likely originated from environmental bacteria that produce antibiotics to compete for resources. Evidence, such as the 30,000-year-old vancomycin resistance element VanA, shows that resistance predates clinical antibiotic use. Both natural and acquired resistance can spread across pathogens in humans, agriculture, and animals, suggesting that antibiotic resistance is widespread and not context-dependent (Curtis et al., 2024).

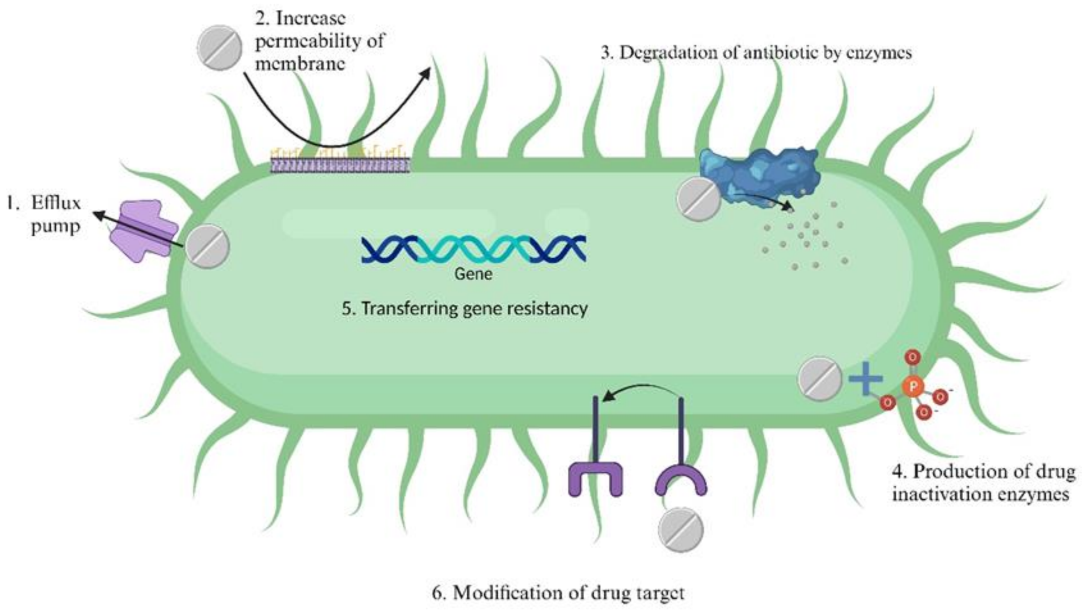

Fig. 1: Mechanisms of adopting AMR

Impact of AMR on Health and Welfare of Animals

AMR poses a significant threat to animal welfare and health globally. The injudicious usage of antimicrobials in veterinary sector, aquaculture and agriculture has resulted in the emergence of resistant pathogens, significantly reducing the effectiveness of available treatments for infectious diseases in animals (Zhang et al., 2024). Infections caused by resistant pathogens in animals result in severe pain, suffering and stress because they render the conventional antimicrobial treatment ineffective leading to prolonged illness. In some cases where animals may not receive proper relief from resistant infections, veterinarians are forced to use higher doses of antibiotics or broader spectrum of antibiotics. These broader spectrum antibiotics lead to more devastating effects on the health of animals and further contribute in development of AMR (Paramasivam et al., 2023).

Furthermore, AMR significantly increases the mortality and morbidity rates of animals, as once easily treatable infections have started to become hard to treat causing major distress. Companion animals are at higher risks because a failed treatment significantly impact the quality of life of such animals resulting in chronic pain and early euthanasia (Lynch & Zhanel, 2023). Moreover, in animal farming due to poor hygiene, intensive farming and close confinement, health of animals is compromised and AMR leads to longer recovery periods ultimately increasing duration of suffering. This is particularly concerning as it can also affect the emotional well-being of their owners (Stein et al., 2022).

Clinical Impacts of AMR on Animals

Clinical implications of AMR are far reaching which significantly affects the treatment, diagnosis and infectious disease management. Infections with resistant microbes are usually associated with increased fatality risks, increased treatment costs and increased morbidity rates as compared to their antimicrobial susceptible counterparts. AMR is the factor behind this making the situation worse (Brosh-Nissimov et al., 2023). Clinical implications of AMR are shown in Fig. 2. The significant increase in MDR infections in animals caused by Extended Spectrum beta Lactamases (ESBL) producing E. coli and Methicillin resistant Staphylococcus aureus (MRSA) pose a serious clinical challenge as they have become hard to treat due to limited therapeutic options. These hard to cure infections require use of last resort critical broad-spectrum antibiotics which have more devastating side effects instead of benefits. Moreover, use of such broad-spectrum antibiotics significantly increases the risk of secondary infections such as Clostridium defficile associated diarrhea, by disrupting normal microbiota of animal's gut (Ahmed et al., 2023b) .

Fig. 2: Clinical Implications of AMR

Economic Impacts of AMR

The economic impact of AMR is also devastating which ultimately affects the livelihood of farmers, cost of veterinary care and global economy. The failure of first line drugs treatment makes veterinarians to use less common and more expensive antibiotics which leads to need of more complex diagnostics, prolonged treatments and supportive care resulting in high veterinary expenses (Roope et al., 2019). Furthermore, AMR leads to reduced productivity in animals by significantly decreasing milk production, reduced growth rates and low eggs yields resulting in higher mortality rates. This major reduction in productivity rates impact the food security by lowering overall supply of animal products. Economic implications of AMR are listed in Fig. 3.

Moreover, the detection of antimicrobial residues in animal products leads to ban on export and trade of animal products. Countries can majorly reject import of dairy products, fish, and meat contaminated with resistant pathogens resulting in significant economic loss for exporters. For majority of countries especially the low middle income countries, the livestock and aquaculture are major source of income and food (Curtis et al., 2024). The economic burden caused by AMR can jeopardize the livelihoods of farmers, reduce household incomes, and exacerbate poverty. In the long term, this can affect food security, as the loss of productive animals and reduced agricultural output may lead to limited access to animal-based protein sources and higher food prices (Paramasivam et al., 2023).

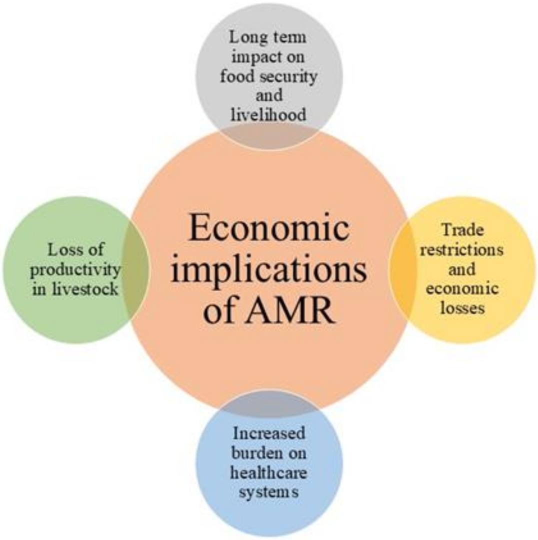

Fig. 3: Economic Implications of AMR

Current Strategies to Combat AMR in Animals

Following are some recommended strategies to tackle AMR in animals:

Antibiotic Stewardship Programs

Enhancing the ways to use antibiotics is a major public health concern. It was recognized by Centers of Disease Control and Prevention as a main approach to address antibiotic resistance. Antibiotic Stewardship Programs (ASP) are usually pointed to hospital-based programs, adopted to make proper use of antibiotics (Rahman et al., 2022). Implementation on these referred programs could enhance the frequency of appropriate prescription, augment the treatment of infections and reduce the calamitous events related to antibiotic use. Antimicrobials are widely used agents to prevent and treat numerous microbial infections in animals. Due to enhancement in the development of considerable antimicrobials, they are available for use without ultimate guidance. Consequently, improper use of antimicrobials notably causes antimicrobial resistance (Mascarenhas et al., 2024).

According to European Commission the excessive use of anti-infectives is remarkable. Subsequently from both sections humans and animal resistance has been seen in almost all antibiotic formats, databases and surveillance systems. Population Correction Unit (PCU) is vital antimicrobial usage (AMU) index in veterinary medicine (Zay et al., 2023). Regardless of the fact that AMU in animals is forecasted to enhance by 70% from 2010 to 2030, only 25% nations worldwide, have adapted a national policy to combat AMR. Till 2009 when Antibiotic Resistance Database (ARDB) was established, there was no such system to track resistant genes, mechanism of action, and attitude. But now antibiotic resistance data is available for almost 13,393 chromosomes, 377 groups of antibiotics, 632 genetic codes, 933 species followed by 124 genera in ARDB. The Comprehensive Antibiotic Resistance Database (CARD) has received data from ARDB. It is basically a type of biological database that gathers and organizes details about drugs classes and resistant procedures on genes, proteins and antimicrobial resistance phenotypes using specific modes (Chukwu et al., 2024).

Consequently, World Health Organization (WHO) set major target to start Antimicrobial Stewardship Programs (ASPs). Extensive antibiotic usage monitoring is one of the ASPs' strategies. However, the curative use of penicillin and starting in-depth broad cast of actinomycetes are significant acquirements in the exceptional period of antibiotic research and development. Antibiotics are produced from ancient times in long term microbial stationary growth phase, which means these are not needed for organism life (Restrepo-Arbeláez et al., 2023). Moreover, 'antimicrobial stewardship' is always accomplished in expanded number of settings. It includes veterinary and one health ASP, and WHO stewardship program structure. Antimicrobial stewardship can be expanded to worldwide activities in the major disciplines including one health approaches.

The most recent antimicrobial stewardship programs implemented by WHO are discussed here:

Southeast Asia Region Antimicrobial Stewardship 2022 Webinar Series

Extensive availability and accessibility of exceptional and inexpensive antimicrobial agents to limit contagious and life-threatening infections is an important concern of Universal Health Coverage (UHC). A webinar series was constructed for several member countries to assist and refine the objectives of AMS enterprises and their value to fight against AMR. Many countries are making use of WHO AMS tool case in training staff to provide scientific help in establishing significant AMS programs, so that to enhance public understanding and potentiality in initiating medical facility AMS programs in the WHO Southeast Asia Region (Sihombing et al., 2023). These programs are also concerned and linked with many other policies and practices to reduce the risk of bacterial resistance worldwide and promote wise use of antibiotics and antimicrobials.

The webinar series is easily accessible to public departments including state legislators at Ministries of Health and federal AMR-combating organizations, in addition to health assistants, medical personnel, contagious disease professionals and pharmacists.

European Society of Clinical Microbiology and Infectious Diseases (ESCMID)

ESCMID is working to promote constructive, multidisciplinary and science based antimicrobial stewardship programs in Europe. A pan-European competency in ASM is needed to manage the misuse of antimicrobials. Characteristic concern in antimicrobial stewardship is documented in ESCMID ASM program. The whole procedure involves almost 2 years covering in person practice, e-learning and research projects (Barksby, 2023). The deliberated operators of this program include contagious disease monitors, health care professionals, microbiology experts, pharmacists, interns, intensive care unit health providers, and other medical assistants (Venkatesan, 2024).

Vaccination and Biosecurity Measures

Preventing the spread of infections over one health approach is necessary for upgrading antibiotic use and labeling the disclosure of AMR. Antimicrobial use in animal production is contributing the existence of antimicrobial residues in animal products including milk and meat, antibiotic resistant bacteria and resistant genes in dung (Jimenez et al., 2023).

Bounded and sensible use of antimicrobials is weighted as major success in controlling and treating infections in humans and veterinary science. Farm biosecurity is an encouraging step in limiting the imprudent use of antimicrobials in maintaining animal husbandry.

Biosecurity

It covers procedures, including animal isolation and removal, encircle, inhibited movements, cleaning and sanitization practices, and symptomatic protocols, to inhibit the encounter and ultimate spread of contagious agents to animal locality. The application of farm biosecurity and herd control and management measures can mitigate the probability of contagious disease outbreaks, following the reduction in antimicrobial usage and possibility of AMR occurrence (Dhaka et al., 2023). Furthermore, all these mentioned practices and measures are money saving for infectious disease control in livestock.

Vaccination

WHO has drawn up many strategies to combat with AMR being a global issue, promoted by many administrations, organizations, medical agencies and health ministries. These approaches include antimicrobial stewardship programs, backing in production of modified and new classes of antibiotics, and launching of awareness programs to get rid of antibiotic misuse. On the other hand, vaccines as weapons to combat AMR have anciently been unrecognized, though they have played effective role in limiting AMR. Vaccines train immune system to recognize foreign particles and pathogens and to generate rapid immune response against that pathogen, limiting the establishment and severity of disease. Disease prohibition by the use of vaccination reduces antibiotic use and ultimately plays significant role in lowering AMR. Taking in to account the new bacterial modified mechanisms, production of antibiotics alone is insufficient. A combined policy involving many effective terms together includes vaccines with unique antibiotics, diagnostic practices, monoclonal antibodies (moAbs), precise and accurate diagnostic practices, micro biota and the use of bacteriophages is needed to combat AMR efficiently (Hegde, 2023).

Innovative Solutions and Future Directions

Global coordination and surveillance are essential constituents in international conflict against AMR. AMR is a global challenge that exceeds borders and affects communities adversely. Continuous increase in AMR has made it necessary to develop and implement collaborative efforts to combat this threat worldwide. Some collaborative solutions are addressed here because if this problem remains unaddressed then mortality rate due to AMR will meet 10 million per year (Cinti, 2022). Few policy recommendations regarding AMR are depicted in Fig. 4.

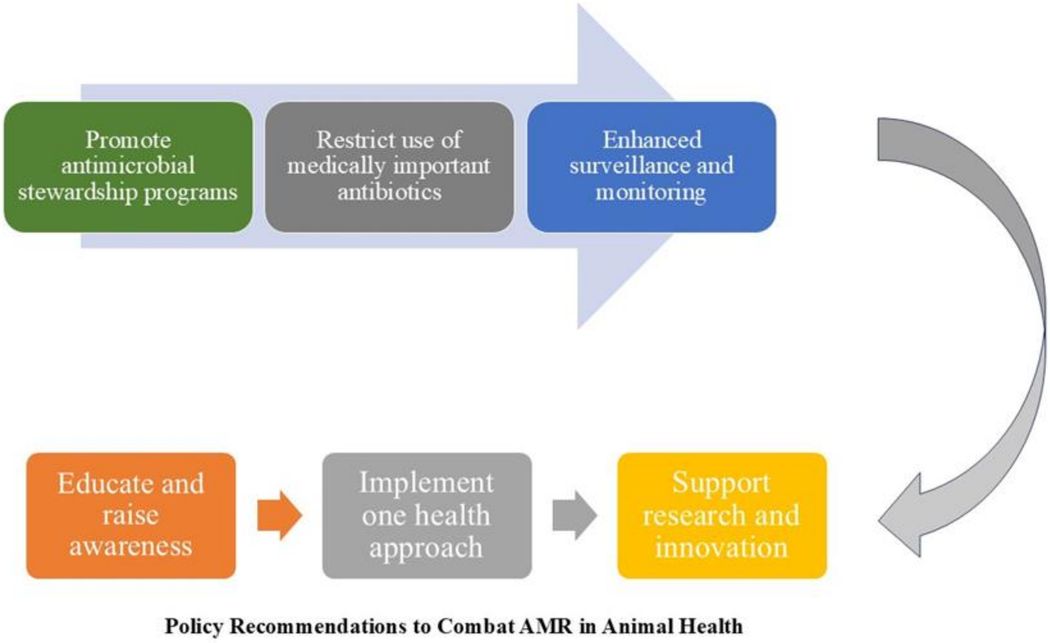

Fig. 4: Policy recommendations to combat AMR in animal health

Some strategies are recommended to address AMR:

Global Action Plan (GAP)

This plan was accepted and implemented in 2015 by WHO with mutual efforts of other organizations including Food and Agriculture Organization of United Nations (FAO) followed by World Organization for Animal Health (OIE), to combat and launch action plans against AMR. In conducted meeting of GAP, leaders from all countries pledged to implement multifaceted action plans on AMR (Kosiyaporn et al., 2020). The central target of GAP on AMR is to tackle basic five objectives:

1. Making better attention and understanding of AMR through productive reporting and communication.
2. Effective training and development, to reinforce strong knowledge based on monitoring and research
3. Implementing effective personal hygiene, sanitation and other infection control measures to limit the threat of infection
4. Set right ways to intake antimicrobials in animals as well as humans
5. Evolve economic case of feasible investments in developing new medications, vaccines and other interferences (Khouja et al., 2022).

Consequently, there is a strong need for collaborative approaches among representatives to tackle with irregular spread of AMR.

National Action Plans (NAP)

Countries have established NAPs on AMR on the basis of objectives of GAP and negotiated AMR in one health perspective. Deliberately, countries that have evolved NAPs should conduct effective surveillance and monitoring in restraining AMR. Until now, the countries that have successfully implemented NAPs have achieved significant advancement in controlling and preventing AMR. The shortage in expense and other facilities may cause provocation in establishing NAPs to combat AMR. Furthermore, in spite of accessibility of NAPs, the retaliation to AMR is not enough (Neale & Cullen, 2024). Most probably this is due to substandard calibration of NAP with GAP objectives, in addition to the poor policy of individual countries to establish NAP targets.

AMU and AMR Surveillance System

Monitoring and surveillance prove to be most important considerations of GAP in restraining AMR that assist countries and regions to gather information on prevailing AMU and AMR. This is significant in boosting effects on patients, acquainting policy, detecting people at risk and exposure and suggesting mediations. AMR monitoring needs strong multidisciplinary

attitudes and well-organized collaboration. Surveillance designs and approaches help to monitor AMR in a group of food yielding animals including swine, cattle, poultry and many other such animal products (Mudenda et al., 2023).
Moreover, WHO Global AMR Surveillance System suggested to use index organism in surveillance systems such as E. coli being an organism of prime concern and Enterococcus spp. whose existence in samples designate resistant orders of Gram-positive bacteria. However, other most suggested indicator microorganisms used in monitoring AMR in chickens comprise Salmonella spp. and Campylobacter spp. On the other hand, including this, the laboratory in which AMR surveillance is under consideration must keep appropriate resources for pathogen culturing and isolation. (Do et al., 2023).

Innovative Approaches and Research

Innovative approaches and advanced research have brought up essential support to public protection, in ongoing combat against AMR. Scientists and experimenters are investigating innovative policies to fight against AMR. These groundbreaking solutions include production of novel antimicrobial drugs, for instance phage therapy, host defence peptides (HDPs), and genomic medicine models that modify medications to individual convalescents. Advanced and progressive diagnostic is also being developed to efficiently recognize resistant strains of infectious agents, promoting more centred and effective use of antibiotics. Moreover, investigation on integrative medicine, such as using probiotics and micro biota (micro biome) in prevention of infections is promising (Cinti, 2022).

Future Directions

Future directions in combating AMR are decided by challenges and potentiality. Innovational research plays a major role in developing new antibiotics, diagnostics, and medication practices, paying positive hope to fight against resistant infections. However, considerable provocations also exist such as need for advancement in investment for antibiotic development, elaborated surveillance and proper monitoring, worldwide date sharing, execution of upgraded strategies to manage antibiotic consumption in human health, animals and environment.

Conclusion

AMR pose a significant challenge to public health, global food security and animal health. The resistant mechanisms i.e enzymatic degradation, efflux pumps, alteration of drug target, utilized by pathogenic microbes are playing major role in making AMR a persistent threat. The economic impact of AMR on livestock industry together with its clinical implications underscore the urgency to address this crisis. Current strategies like improved biosecurity measures, vaccination programs and antibiotic stewardship programs do provide the foundation to tackle AMR but these efforts should be complemented by a significant unified approach, given by Global and National Action Plans which emphasize on collaboration across sectors. To effectively combat the emerging threat of AMR, a holistic One Health approach is required integrating human, environment and animal health. Research along with stake holders' engagement coupled with strict policy implementation can become pivotal in restraining the spread of resistance.

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