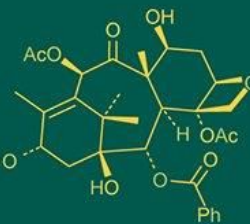
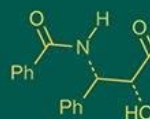
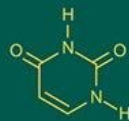
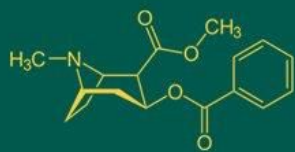


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Combating AMR: A futuristic battle and a race against time in the field of medicine: Narrative review

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Abstract

Antimicrobial resistance (AMR) is now a leading issue, particularly in the field of treatment of diseases, both in human and animals. Excessive and rampant use of antibiotics, lastly in the previous two decades has led to the evolution of stronger strains of bacteria, viruses and protozoa, causing a significant and sharp rise in the number of cases of hospitalization and mortality. Moreover, noted research and publications have now successfully explained the spontaneous evolution, mutation of certain species of bacteria and the passing of resistance genes through horizontal gene transfer, which are definitely contributing to the incidences of AMR. Increase in the cases and episodes of AMR across the whole globe is surely going to jeopardize the complex balance between treatment and recovery from diseases. In this review a narrative highlighting and focus is on the generation of resistance in different microorganisms against a wide spectrum of antibiotics, the global scenario and rising trends of failure of antibiotic therapy, socio-economic aspects of treatment failure, current commitments to lessen the rise of antimicrobial failure and ways to prevent the happenings of AMR.

Keywords: Veterinary medicine, antibiotics, antibiotic resistance, one health

Introduction

Antimicrobial Resistance (AMR) technically means resistance against antimicrobial agent. In this review, the terms “antibiotic” is more commonly used rather than antimicrobial since the main focus here would be on the bacteria more often.

The most significant discovery in the field of medicine in the last hundred years would be the accidental discovery of antibiotics or more specifically “Penicillin”, when in the year 1928, Sir Alexander Fleming discovered it while doing some culture plate study in his laboratory in London. This not so previously known drug soon became known to people as “Wonder Drug” or the “Magic Bullet” as it had the capability to cure any serious infection which was lethal at that time. However soon it’s rampant and aggressive use by physicians across the world caused ripples. In his Nobel Prize address, Sir Alexander Fleming said that “the use of antimicrobials can, and will, lead to resistance.” With no reasonable doubt it could be said that antibiotics are the foundation of modern medicine. Its use is highly important and crucial, be it for a case of simple infection or complex cases like elective surgeries, autoimmune diseases or cancer chemotherapies. True to words the use of antibiotics is an indispensable aspect of modern-day medical practices. In veterinary aspect antimicrobial use plays a crucial role in improving animal health and production performance. Antibiotics are used in food animal production for the curative treatment of diseased animals and for metaphylactic treatment or more precisely a herd treatment for both healthy and affected animals to control and arrest the spread of diseases. In some developing countries like more commonly in Southeast Asian countries, antimicrobial agents are used as growth promoters in animal feed to increase body performance.

Nowadays, the resistance towards the action of antibiotics is rising greatly. It starts when microorganisms like bacteria, fungi, parasite and viruses evolve to the extent that they cannot be either controlled or killed by the action of those therapeutic agents. Such resistance towards the antimicrobials is now one of the greatest global concerns in the 21st century due to the rapid growth of infections by the resistant organisms and the lack of new antimicrobial medications to combat this situation. One of the major causes of this scene is due to the reckless and irresponsible use of antimicrobials, primarily in clinical treatment along with growth

promoters and enhancers in animal feed. Thus this issue could be truly called as a 'Silent Epidemic' and is a problem where urgent action is needed with utmost priority intervention.

A no see look to the incidences of AMR would definitely lead to world's primary cause of death by 2050. According to figures provided globally, the number of fatalities linked to AMR is approximately 1.2 million in 2019 and this forecast would rise to around 10 million deaths per year by 2050, if no action is taken to control AMR.

Origin of AMR

AMR gets sincerely developed in a lot number of tactical ways, but it could be definitely classified mostly in two ways i.e. Intrinsic and Extrinsic. Intrinsic method is a specialty of both pathogenic and non- pathogenic microbe mostly in a dynamic environment. The typical mechanisms include impermeability of the bacterial cell to the antibiotic (e.g. Physiochemical properties of the molecules, presence of efflux pumps), inactivation of the antibiotic compound by the inactivating enzymes or the lack of target molecules or target site modification. Extrinsic ways of developing AMR includes the bacterial evolutionary machinery to make use of their genomic flexibility to better adjust with the surrounding environment. Theses development of genomic determinants i.e. the ensemble of genes involved in the AMR is sufficiently and efficiently transmitted to its next generation and to other bacterial specimens through mobile genetic elements like transposons, plasmids, integrons and ICE.

Transposons are the element that is a DNA sequence that changes its position within a genome. It is normally called a jumping gene as it jumps within the same DNA or between diverse DNA molecules including plasmids, thus changing position and creating a new genetic composition. Although it could cause harmful/delirious mutation, but when insertion sequence may include AMR genes, it establishes the resistance in the cell and enables survival traits under harsh condition, which is then subsequently propagated to next generation.

Plasmid is a small extrachromosomal DNA molecule that is physically separate from chromosomal DNA and can replicate independently. This plasmid thus plays the greatest role in resistance spread. Acquiring resistance encoding genes and subsequent spread of the genes indicates that plasmid help in propagation of AMR over the time and across species borders effortlessly and, in a time, conservative manner.

Integrons are the versatile genetic elements that capture, rearrange and express mobile DNA units called 'gene cassette'. They are associated with enormous advantages for bacterial robustness, empowering the much-needed apparatus for enabling survival under severe duress, distressing surroundings. Most notably when compared with other mobile genetic elements, integrons can be simultaneously mobilized both by the bacterial chromosome and plasmids, and can be propagated and integrated distant from their origin position, showing antimicrobial protection to a wide range of microorganisms.

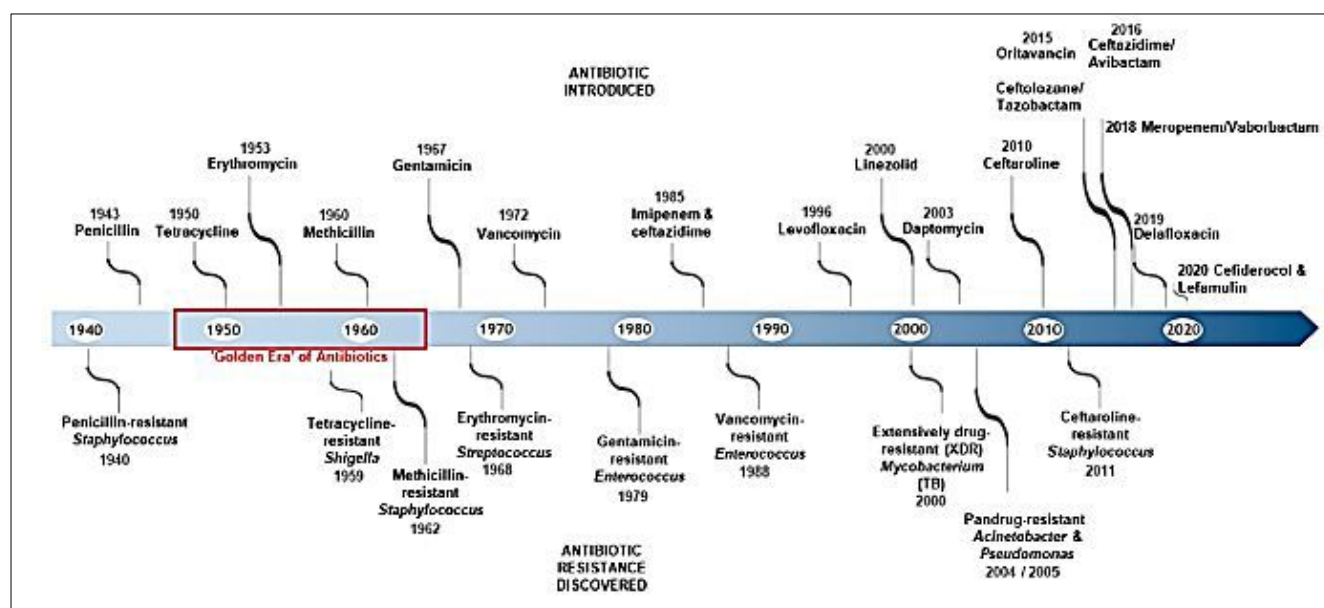


Fig 1: Timeline showing some of the key antibiotic discoveries and reports of the emergence of antibiotic resistance strains

Also, for horizontal gene transfer, a less known mobile element system is utilized by bacteria, known as Integrative and Conjugative Elements (ICE). It has now been proven that these elements, have one or more self-transmissible integrative units, each capable of self-mobilization to carry several bacterial traits such as virulence factors, biofilm formation capability, resistance to heavy metals and most notoriously AMR genes.

For antibiotic resistance, another picture comes into mind that is described as Bacterial Toxin- Antitoxin System/ TAS. TAS is positively identified in that bacterial specimen subjected to antibiotic treatment. When it is carried in a plasmid, TAS

system provides a vertical transmission of survival traits, of which it could be seen in chromosomal DNA. Though the mechanism is not closely understood and elucidated, studies prove that activation of TAS results in production of persister cells i.e. the dormant cells capable of surviving the harsh conditions.

A category of non-mobilizable non- inheritable elements play a significant role in AMR, contributing to the antimicrobial resistant phenotype, known as biofilm growth, swarming adoption and persister cells. Before categorically describing all these elements, it could be defined that phenotypic persistence means it is the condition where bacterial cells are

not killed by the dose/type of antibiotic administered but instead the cells are in a dormant/quiescent stage that could be reversed when the compound of stress is removed.

Biofilm growth proves that bacterial cells can be preserved from an antibiotic therapy. And it is very relevant in clinical point of view, specially in chronic infections and the potential colonization of surfaces (intubated patients, prothesis, catheters). The fundamental goes on a simple notion that bacteria growing colonies rely in the property of biofilm matrix and metabolic behavior of the colony, implying resistance to the antibiotic. Biofilm matrix reduce the action of antibiotics by reducing its diffusion within bacterial biomass or by entrapping the antibiotic molecules through its complex structure. The metabolic behavior of the microbial community has got a worthy role in causing antibiotic susceptibility, by simply changing the physiochemical condition (eg. Gradient of nutrient availability and gradient of oxygen) in the same biofilm mass, by different subpopulation of same bacteria.

Another interesting maneuver deployed by bacteria to save themselves from antibiotic therapy is the swarming movement. This encourages a complex physiological adaptation enabling several genes to include increased codification for porins and efflux pumps. These in return lead to reduced antibiotic activity on the target bacterial cell, moreover several proteases affecting swarming, motility are relevant for the formation of biofilms and therefore involved phenotypic antibiotic resistance.

Nevertheless, the complete molecular mechanisms leading to AMR is yet to be fully understood, since other elements might be involved. Many recent studies reveal complex elements like quorum sensing swarm cells, moonlighting proteins acting as independent role as a function of their localization are opening new avenue in the role of AMR. Hence new shade are being conducted to fully assess the different mechanisms of bacterial virulence that combine resistance along with evolution of more tougher strains of microbes.

Resistant Bacteria	Isolation Source	Antimicrobial Compound(s)	Major Resistance Mechanism
<i>Campylobacter spp.</i>	Cattle Chickens Turkey Pig Sheep Dog Cat Horse	Quinolones Macrolides Lincosamides Chloramphenicol Aminoglycosides Tetracycline β -lactams Cotrimoxazole Tylosin	Point mutation on <i>GyrA</i> gene <i>CmeABC</i> multidrug efflux pump Methylation of ribosomal target Point mutation in the ribosomal target
<i>Salmonella spp.</i>	Human Chicken Turkey Pig Cat Dog Horse	Tetracyclines Sulfonamides Streptomycin Kanamycin Chloramphenicol β -lactams Amoxicillin/clavulanic acid Nalidixic acid Ceftriaxone	Multiple point mutations on <i>GyrA</i> and <i>GyrB</i> , <i>parC</i> , and <i>parE</i> genes <i>AcrAB-TolC</i> multidrug efflux pumps Changing outer membrane proteins <i>qnr</i> genes-containing plasmid Salmonella Pathogenicity Island-1 and -2
<i>Staphylococcus spp.</i>	Human Farm animals Dog Cat Horse	Penicillin Methicillin Vancomycin	Staphylococcal Cassette Chromosome-mec genes (<i>SCC-mec</i>)
<i>Enterococcus spp.</i>	Human Farm animals	Vancomycin, Aminoglycosides Penicillin Chloramphenicol Erythromycin Tetracyclines	<i>lsa</i> gene
Other Gram-negative	Human Farm animals Pet	β -lactams	Extended-spectrum β -lactamases

Fig 2: Major microorganisms responsible of relevant infective disease and AMR onset and diffusion

Consequences of AMR

The primary consequence of AMR is the reduced efficacy of antibiotics. The growing space between the increased AMR and development of new age antibiotics means that the pace of emergence of new variants and spreading of resistance among cross species is quite fast rather than anticipated. In retrospective aspect, the spread of AMR in veterinary sector

be could broadly parted into three kinds, namely companion animals, aquaculture and domestic animal husbandry.

Contribution of companion/ pet animal

The pet animal population in industrialized countries has dramatically increased during the last decade and the growth curve is showing an increase. This means the flow on animal health status and hygiene condition has become a

trending role in improvement of animal welfare. The level of contact between the companion animals and humans also creates a condition for transmission of infection and cross transmission of AMR traits, and possibly reverse zoonosis condition. Antimicrobial resistance of pet origin is mainly involved for direct/ indirect danger on human health, most notably being Methicillin Resistant Staph aureus (MRSA), Methicillin Resistant Staphylococci, Vancomycin Resistant Enterococci, Carbapenemase producing Enterobacter and ESBL Gram negative bacteria.

Contribution of Aquaculture

Aquaculture accounts for almost half of the fish and its derived products produced for both human and animal consumption worldwide. So as a result, the use of antibiotics, used for both therapeutic and non-therapeutic use is increasing at an alarming rate. The use of sulphonamide penicillin, quinolone, tetracycline and phenicol are of most common, as its application in all animals and humans is well set so the transmission of AMR traits go on unnoticed. The lack of space for aquaculture is motivating farmers to go for more intensive production system, meaning massing of large population in small spaces, which definitely increase the stress and occurrence of infective diseases, thus sometimes causing catastrophic economic loss. To minimize it, farmers often go for antibiotic therapy for curative and prophylactic treatment. Since no specific antibiotic is still not available for aquaculture context, six of the antibiotic classes listed by WHO as critically important for human medicine are commonly employed in both terrestrial and aquaculture husbandry, causing strong selective pressure on the population that favors for emergence and selection of AMR strains, and the subsequent dissemination of AMR traits, hence implying reduced efficacy of such compounds in human treatment. Hence the use of antibiotic therapy thus creates a subtle atmosphere for microbial population to modify themselves in the harder strains, as the antibiotic residue persist in the fish species for a prolonged time due to inadequate bodily usage, thus accumulating in the ecosystem, to an estimate level of 70-80% active compound into the wastewater.

Contribution of domestic animal husbandry

In traditional animal husbandry, the use of antibiotics was limited to treatment of infectious diseases. But with the advancement of modern agricultural practices, a desired feeling to use for prophylactic and growth promotion rather than simple therapeutic use has now triggered to massive and enormous usage of antibiotics in feed, which has clearly established the pillars of AMR in animal husbandry. Administration of subtherapeutic dose of antibiotics though contributes to increased weight gain, but it causes reduced biodiversity of intestinal microbiota, reduced immune stimulation and altered metabolism, thus acting as selective pressure stimulating the bacterial evolutionary machinery to adapt to environmental stressors and allowing the harder, more resistant strains of pathogen to propagate the AMR strains. Further use of antibiotics in specific animals like pig industry where a chance of infection may cause loss during umbilical cord cutting, tail cutting, teeth trimming, vaccination, castration has lowered the mortality but the use

of penicillin, quinolone, tetracyclines, the same which is used for human treatment has led to emergence of multi drug resistant infections, making it harder for physicians to treat. Similarly, in cattle husbandry for meat production, recurrent infections arising from shipping fever, bovine pneumonia, and diarrhea, leads to heavy usage of antibiotics like penicillin, quinolones, gentamycin and tylosin. In dairy industry, use of wide spectrum antibiotics is highly common in non-lactating period, via intramammary route to prevent/reduce the chances of mastitis in lactating animals. Similarly in poultry industry, the therapeutic use of antibiotics is mostly given through drinking water which includes sulfonamide/trimethoprim, a common drug to reduce coccidiosis, along with tetracycline, penicillin and aminoglycosides to increase food conversion ratio and give a better weight gain, at the same time eliminating infections caused by stress and overpopulation. Similar classes of antibiotics are used in sheep and goat industry.

Economics of AMR: The correlation of AMR and its impact on economical aspect of healthcare is directly proportional. The havoc of AMR on healthcare systems is quite high, leading to systemic destabilization of health system. Those who suffer from infection caused by resistant infection are more likely to experience longer recovery and a higher incidence of septicemic infections and mortality. The extended hospital stay along with greater use of more expensive drugs means the healthcare cost increases. A finding estimated that the annual cost of medicinal health sector in Europe caused about 1.5 billion euros per year with an additional 600 million euros in lost productivity. In USA, the annual health care cost for AMR is estimated roughly around 55 billion dollars. Several economist have warned that the likely global cost of AMR by the year 2050 would mean an increase in both morbidity and mortality, thus causing a decrease in global population by 444 millions and thus reducing the world GDP by around 0.66-3.1%.

Control and strategies to prevent AMR

Although the concept of rearing animals “without antibiotics” is tough and challenging for veterinarians, farmers and animal health stakeholders, the time has come for all of the participants to come together to tackle antibiotic resistance and promote the idea of safe, responsible use of antibiotics. There must be a clear judgement about the need of judicious and tactical use of antibiotics, so as to preserve the efficacy and effectiveness. Veterinary medicine now has felt the urge and need to adopt a “Unified One Health” approach to mitigate worldwide escalating antibiotic resistance, since both human and animal health are at combined risk, so mitigation needs to be done equally while simultaneously protecting and treating animals for maintaining food security and safety effectively. Giant pharmaceutical companies, scientific establishments and governmental organizations have committed globally the five principles and determinant, namely protecting animal health & welfare by using one health approach, judicious use of antibiotics, limiting disease spread and prevention, increase access to biotech and technical expertise for treatment, and elevating the knowledge and communication by using science and evidence-based dialogues.

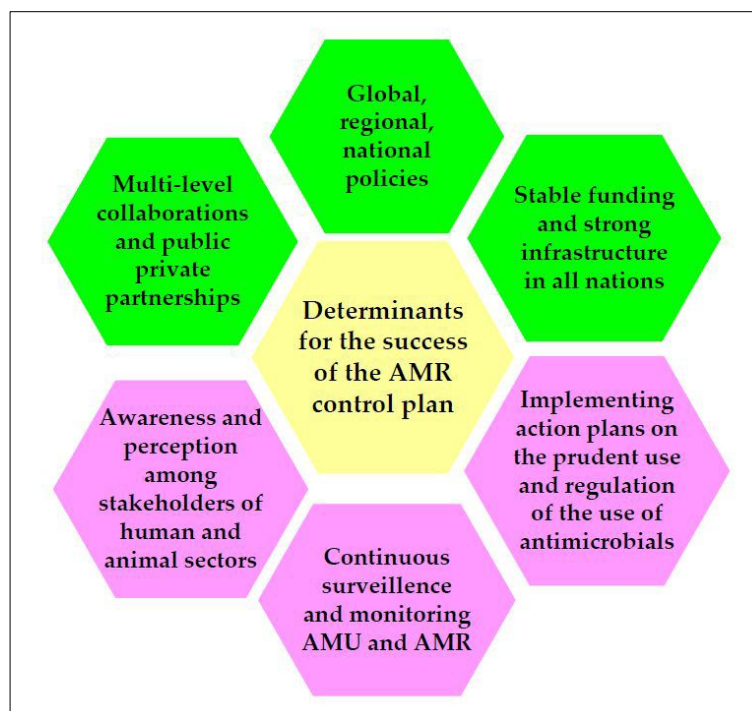


Fig 3: Key determinants deciding the success of the national, regional, and global level coordinated actions to combat AMR by reducing the use of antimicrobials and discovering alternatives.

AMR Global Action Plan

AMR Global Action Plan was adopted at the WHO World Health Assembly in 2015 and it contains five objectives, namely: *i*) raising awareness; *ii*) surveillance; *iii*) reduce the incidence of infections; *iv*) optimal use of and access to medicine; and *v*) research & development of new antimicrobials and diagnostics.

The major actions include

1. National Action Plans have been planned and finalized in the following 2 years after the adoption of the Global Action Plan in May 2015 for around 130 countries, which covers more than 95% of the global population.
2. AMR Awareness Week was launched in November 2015, the first time in AMR history as a major public communication program and continues since then.
3. AMR Global Surveillance System (GLASS) was launched in December 2015 to monitor the prevalence of AMR among major pathogens in clinical settings, where more than 40 countries across all continents have joined so far.
4. Roadmap on Global Framework for Development & Stewardship to Combat AMR was drafted in May 2017 for further elaboration.
5. AMR Research and Development Collaboration Hub was established in July 2017.

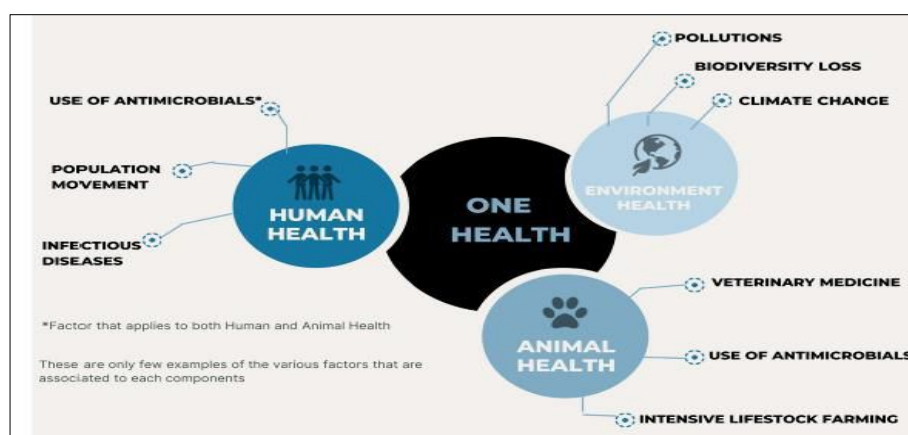


Fig 4: Illustration representing the concept of One Health Approach

Global strategies and undertakings

The WHO and the European Investment Bank (EIB) have been expanding investment to support the development of antibacterial treatment for public health priorities since 2018. Future investment and policies have been discussed in several international conferences, which includes the Biocom AMR Conference, World Health Summit in Berlin, and the World

AMR Congress in Washington. In 2019, WHO brought the International Federation of Pharmaceutical Manufacturers and Associations, the EIB, and Wellcome Trust together to launch an initiative, AMR Action Fund. AMR Action Fund intends to develop 2-4 new antibiotics for patients by 2030 through collaboration and partnership with companies and organizations to create market conditions that enable

sustainable investment in the antibiotic research and development(R&D).The AMR Action Fund initiated by leading pharmaceutical companies and supported bythe International Federation of Pharmaceutical Manufacturers and Associations expects toinvest more than US\$1 billion in smaller biotech companies and provide industry expertiseto support the clinical development of novel antibiotics.

The Government of Canada announced a federal guideline in response to the threat of AMR in 2014. The coordinated measures were undertaken jointly bythe Public Health Agency of Canada (PHAC), Health Canada (HC), the Canadian Food Inspection Agency (CFIA), the Canadian Institutes of Health Research (CIHR), Agriculture and Agri-Food Canada (AAFC), the National Research Council (NRC), and Industry Canada (IC) to prevent, limit, and control the emergence and spread of AMR. Additionally, the Government of Canada has been collaborating with international partners and agencies to develop and implement a Global Action Plan on AMR. While focusing on surveillance, stewardship, prevention and control of infection, and research and innovation nationally, it is also participating in “transnational network plus 2020” of Joint Programming Initiative on Antimicrobial Resistance (JPIAMR) along with other member countries, France, Italy, Latvia, the Netherlands, Norway, Spain, and Sweden to outline and implement AMR research in the areas of therapeutics, diagnostics, surveillance, transmission, environment, and interventions.

The Government of Australia has announced its own action plan: National Antimicrobial Resistance Strategy: 2020 and beyond, which was built on their first national AMR Strategy 2015-2019. The 2020 Strategy has an action plan for 20 years, and it continues to coordinate with the WHO’s global action plan on AMR to tackle the challenges of AMR at national and international levels.

The Government of United Kingdom built the current national action plan (2019-2024 based on the previous2013-2018 strategy, after making consultations with a broad range of stakeholders across various sectors and is affiliated with global plans and frameworks for action to confront antimicrobial resistance within and beyond its own borders. The blueprint has been designed accordingly to ensure progress towards its 20-year vision on antimicrobial resistance by which the escalation of resistance can be effectively contained and controlled. The scheme primarily focuses on reducing the need of, and unintentional exposure to, antimicrobials; optimizing the use of antimicrobials; and investing in research, innovation, supply, and availability.

The European Union (EU) makes it’s position very clear to address the regional and global challenges on AMR. The EU’s new action plan was built in 2016, based on the 2011 action strategy, and it commits to a high level of human health protection. The entire picture of the new EU action plan regarding AMR received contributions from 22 stakeholders and the public. Its primary goal is to preserve and sustain the effective treatment of infections in humans and animals. The new plan has a framework for more extensive action to reduce the emergence and spread of AMR, and to boost the development and availability of novel efficient antimicrobials inside and outside the EU. The main goals of this new plan are based on three main pillars, to assist member states in establishing, implementing, and monitoring their own national One Health action plans on AMR, and to make the EU a best practice region. The framework intends to enhance research, development, and innovation by closing current knowledge gaps, delivering novel solutions and tools to prevent and treat infectious diseases, and improving diagnosis to control the spread of AMR; and to strengthen the EU efforts worldwide to shape the global agenda on AMR and the related risks in an increasingly unified world.

Countries	Objectives of AMR Control Strategies	Year of Launching of Action Plan to Combat AMR and Website
Australia	Minimizing development and spread of AMR; Assurance of availability of effective antimicrobials.	2015-2019 – first national plan, 2020 and beyond—subsequent national plan. www.amr.gov.au/australia-response/national-amr-strategy (accessed on 21 February 2021)
Canada	Reacting to the threat of AMR to protect people, animals, and the environment in Canada.	2014. https://www.canada.ca/en/public-health/services/antibiotic-antimicrobial-resistance/antimicrobial-resistance-use-canada-federal-framework-action.html (accessed on 21 February 2021)
Ethiopia	Effective prevention and containment of AMR in humans, animals, agriculture, and the environment in Ethiopia.	2006-2014—initial plan; 2015-2020—second refreshment. http://www.ethiopia.gov.et/wp-content/uploads/2019/03/Strategy-for-the-Prevention-and-Containment-of-AMR-in-Ethiopia-Oct-2015.pdf (accessed on 21 February 2021)
France	Tackling AMR in human medicine and veterinary medicine promoting good practices and awareness among all stakeholders.	2009—three refreshments in human medicine and one plan in veterinary medicine since 2000. http://resistancecontrol.info/2016/government-engagement/the-french-approach-to-fighting-antibiotic-resistance-a-constant-and-coordinated-effort-since-2000/ (accessed on 21 February 2021)
Germany	Prevention of occurrence and spread of AMR adopting measures in human and veterinary medicine.	2008 initiative; DART2020 continuation strategy. https://www.bmi.de/EN/topics/animals/animal-health/DART2020.html (accessed on 21 February 2021)
India	Construction of implementable recommendations to tackle AMR involving human, animal, and environmental sectors in India	2012 initiative with a five-year plan. http://chemsolutionsforum.org/ (accessed on 21 February 2021)
Ireland	Implementing policies and actions to prevent, monitor and tackle AMR across the health, animal, and environmental sectors	2009 initiative; 2017-2020 subsequent national plan. https://www.hse.ie/eng/services/list/2/gp/antibiotic-prescribing/ (accessed on 21 February 2021)
Norway	Adapting appropriate use of antibiotics across the sectors, human, animal, aquatic and environmental sectors.	2008-2012 initial plan; 2015-2020 subsequent strategy. https://www.ngjering.no/en/scand/d5608/7ccm+antimicrobial-resistance (accessed on 21 February 2021)
Sweden	Raising general awareness on AMR, enhancing hygiene in the community and health care facilities, and using antibiotics rationally rational use of antibiotics.	2000 plan was based on Strama 1995. Overall use in Sweden has been significantly reduced. https://www.government.se/contentassets/168639e166d4375c4761880ce924229/second-strategy-to-combat-antibiotic-resistance.pdf (accessed on 21 February 2021)
Switzerland	Safeguarding long-term efficacy of antibiotics for human and animal diseases consulting all interested stakeholders.	2015. http://swissmediccontrol.info/2018-2/the-swiss-recipe-for-containing-antimicrobial-resistance/ (accessed on 21 February 2021)
United Kingdom	Advancing towards the 20-year vision on AMR focusing on reducing need of antimicrobials, optimizing use of antimicrobials, and investing in innovation, supply and access.	2013-2018 initial strategy; 2019-2024 subsequent plan. https://www.gov.uk/government/publications/uk-5-year-action-plan-for-antimicrobial-resistance-2019-to-2024 (accessed on 21 February 2021)
United States	Highlighting prevention and control of infections to slow the spread of AMR through multi sectors coordinated approach.	2013—release of AMR threat report by CDC; 2014—establishment of federal task force; 2015—first national action plan; 2020—second national strategy. https://aspe.hhs.gov/ppl/report/carf-plan-2020-2023 (accessed on 21 February 2021)

Fig 5: National action plans of various countries to combat AMR through coordinated measures from different sectors.

The Government of India's National Action Plan to combat the longstanding concerns of antibiotic misuse in the human and animal health sectors was released in 2017 by the Union Ministry of Health and Family Welfare. The goals of the action plan were to improve awareness, enhance surveillance measures, focus on prevention and control of infection, design research, develop alternatives to antimicrobials, promote investments, and collaborate activities between

various sectors. Based on the national plan, various states have begun implementing their State Action Plans in India. However, since the escalation of AMR is made more complex by several factors including lack of awareness and education about AMR, and limited financial allocation for implementation, periodical assessment for effectiveness is necessary, and significant efforts from all stakeholders are needed to achieve these goals.

Strategies	Countries Involved	Year of Establishment of Action Plan and Website
Global Antibiotic Resistance Partnership (GARP)	India, Kenya, South Africa, Vietnam, Mozambique, Nepal, Tanzania, and Uganda	2009 https://cddep.org/projects/global-antibiotic-resistance-partnership/ (accessed on 21 February 2021)
Global Health Security Agenda (GHSA)	Canada, the European Union (EU), Norway, and the United States (US)	2014 https://www.hhs.gov/about/agencies/oga/global-health-security/antimicrobial-resistance/index.html (accessed on 21 February 2021)
Jaipur Declaration on AMR	India and other countries in Southeast Asia	2011 https://www.who.int/southeastasia/health-topics/antimicrobial-resistance (accessed on 21 February 2021)
Strategic action plan to control AMR in the Asia-Pacific region	Countries in the Asia Pacific region	2010 https://www.apec.org/Publications/2011/10/International-initiatives-to-control-antimicrobial-resistance-in-the-Asia-Pacific-region (accessed on 21 February 2021)
European Commission Action Plan against the rising threats from AMR	Countries in the EC	2011 https://ec.europa.eu/health/antimicrobial-resistance/eu-action-on-antimicrobial-resistance_en (accessed on 21 February 2021)
Transatlantic Task Force on Antimicrobial resistance (TATFAR)	Canada, the European Union (EU), Norway, and the United States (US)	2009 https://www.cdc.gov/drugresistance/tatfar/index.html (accessed on 21 February 2021)

Fig 6: Predominant global and regional action strategies to combat AMR at global and regional levels in addition to the WHO universal action plan

The United Nations, as part of the 2030 Agenda for Sustainable Development, has published 17 Sustainable Development Goals (SDGs) including many aspects of societal and human interactions. One SDG is SDG3-“Good Health and Wellbeing.” Within this, AMR has anamed specific inclusion, with indicator 3.d.2, namely, “Percentage of bloodstream infections due to selected antimicrobial-resistant organisms.” The WHO have indicated that AMR impacts seven of the 17 SDGs.

Conclusions

Although the development and propagation of AMR is a natural phenomenon, but owing to the huge and reckless use of antimicrobials has now become a headache as it is now the major contributor to the rapid spread of AMR. The rampant and reckless use of antimicrobials in low and underdeveloped countries, along with a booming population in middle income countries plus the contamination of substandard drugs in the supply chain has caused the evolution of harder strains of the pathogens, which were previously easily curable, but at present times creating a burden on healthcare systems. The participation of animal husbandry has now become a focal point since the maximal use of antibiotics in the feeds as supplement ultimately reaches the human body, thus completing the chain of linkage in the food web. Thus, in the context it could be correctly assumed that if this trend goes

on like this unnoticed, soon a time will come where the modern medical practice will be overwhelmed to an extent that it will fail to address the common health aspects of both human and animal. The consequences of such failure will lead us to the era prior to antibiotics, where even a small injury of any kind would be sufficient to cause death. Hence the need of the hour is to fully understand the dynamics and address the results of incessant circulation of resistant genes in the microbial population and its transmission in the environment. Modern and technical expertise combined with political agenda and governmental action would challenge the shortfalls and difficulties, and provide a clear picture and plan to make strategy to combat and reduce the antimicrobial resistance, both in human and veterinary aspect.

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