IOSR Journal of Multidisciplinary Research (IOSR -JMR)
ISSN: 3048-7439 Volume 2, Issue 4, Series 1, July. - August. (2025), PP 34-49
www.iosrjournals.org

Antimicrobial Resistance, Challenges, Mechanism Of Development, And Strategies To Combat The AMR

Abid Nadeem Nomani. Birjis Fatma, Jamal Akhtar, Najeebul Hasan. Nirmala Devi MK, N Zaheer Ahmad.

Research Officer, Clinical Research Unit (U), Ribandar, Goa-403006.
M.S D/O Niswan WA Qabalat, Ajmal Khan Tibbiya College, AMU, Aligarh-202002.
Research Office-SIV, Central Council For Research In Unani Medicine, New Delhi-110058.
Deputy Director In Charge, Regional Research Institute Of Unani Medicine, Mumbai-410210.
Assistant Director, Regional Research Institute Of Unani Medicine, Mumbai-410210
Director General, Central Council For Research In Unani Medicine, New Delhi-110058

Abstract:
The discovery of antibiotics has helped to save the lives of an uncountable number of people. Antibiotics have been grouped in different classes based on their origin, structure, and mechanism of action. An intrinsic and acquired mechanism of antimicrobial resistance has been identified in many bacterial strains that are of high clinical importance. This has seriously jeopardized the use of antibiotics and has also caused the spread of microbes that are resistant to effective first-choice, or "first-line" drugs.
Thus, sensible use of antibiotics and the search for effective alternative measures are of high importance in order to minimize the effect due to existing and emerging antimicrobial resistant microbes. Antimicrobial resistance (AMR) has now emerged as a chronic public health problem globally. AMR occurs when viruses, bacteria, fungi and parasites do not respond to antimicrobial treatments in humans and animals, thus allowing the survival of the microorganism within the host. The prominent cause contributing to the current crisis remains to be the overuse and misuse of antimicrobials,
Particularly the inappropriate usage of antibiotics, increasing the global burden of antimicrobial resistance. The global consumption and usage of antibiotics are therefore closely monitored at all times. This review provides a current overview of the implications of strategies to address the problem of antibiotic resistance, as well as to achieve the best possible health outcome by acknowledging the clear connections between humans, animals and their shared environment. The importance of public awareness and health literacy of lay audiences still needs to be further emphasised as part of global and local action plans. Antimicrobial resistance continues to be a major global public health dilemma of the 21st century.

Keywords: *Antimicrobial resistance, Antibiotics, Chemotherapy, microbial toxicity, microbes,*

Date of Submission: 25-07-2025 Date of Acceptance: 05-08-2025

I. Introduction:

The most significant advancement in medicine throughout the 20th century was the development of antimicrobial medications. Their introduction altered doctors' perceptions of the potential of medications to treat illnesses. They are among the rare medications that can both treat and palliate illnesses. Since infectious diseases are more common in developing nations, their significance is increased. They are among the most often used and abused medications as a class. Unlike all other drugs, this class is made to inhibit or kill the infectious organism while having little to no effect on the receiver. This sort of therapy is commonly known as chemotherapy, which refers to the 'treatment of systemic infections with particular medications that selectively reduce the infecting microbe without severely damaging the host. The drug's action on a microbe component (e.g., bacterial cell wall) or metabolic processes (e.g., folate synthesis) that is not found in the host, or its high affinity for certain microbial biomolecules (e.g., trimethoprim for bacterial dihydrofolate reductase), is the foundation of selective microbial toxicity. Because of the parallel between the malignant cell and the dangerous microorganisms, the treatment of neoplastic illnesses with medications is also called 'chemotherapy'.

Antibiotics: Microbes create chemicals that selectively inhibit or kill other microbes at extremely low doses. This definition does not include those natural compounds that inhibit microorganisms but are created by higher forms (e.g., antibodies) or those produced by microbes but require large quantities (ethanol, lactic acid, H2O2). Chemotherapeutic agent was formerly restricted to synthetic compounds, but now that numerous antibiotics and their analogues have been made, this criterion is no longer applicable; both synthetic and microbiologically produced medications must be included.

It would be more accurate to refer to both synthetic and naturally occurring medications that inhibit germs as antimicrobial agents (AMAs). Three stages can be distinguished in the history of chemotherapy. (a) *The time of empirical use:* the Chinese used "mouldy curd" on boils, the Hindus used chaulmoogra oil to treat leprosy, the Aztecs used chenopodium to treat intestinal worms, (b) *Paracelsus* (16th century) used mercury to treat syphilis, and in the 17th century used cinchona bark to treat fevers. (c) *Ehrlich's (1890–1935) phase* of dyes and organometallic compounds. In the latter section, microorganisms were discovered.[1]

Antimicrobial Resistance: A Worldwide Public Health Emergency

The social burden of antimicrobial resistance: In a recent estimate, about 3.57 million of 4.95 million deaths worldwide were associated with antimicrobial resistance in 2019, [2] greater than a number of other well-known causes of death, such as HIV/AIDS and malaria. In contrast to the 700,000 annual deaths estimated by the United Nations and the World Health Organization (WHO), the study found that the global impact of AMR is far greater. It was previously predicted that by 2050, antibiotic resistance will claim the lives of 10 million people annually.[3]

However, it has now come to light that we are much closer to that number than we once believed. Globally, AMR developments fluctuate greatly between nations and frequently confront distinct main obstacles. Contrary to other health-care issues, AMR is a problem that affects all countries, regardless of their financial situation. The ongoing development of novel antibiotic classes used to lessen the prevalence of infectious diseases, but after a few years, harmful bacteria were able to become resistant to these novel substances.[4]

For instance, resistance was noted in certain individuals within a year of the US FDA approving the aminoglycoside streptomycin for the treatment of tuberculosis. As a last resort, antibiotics such as carbapenems and colistin are used to treat infections brought on by bacteria that are multidrug resistant or manufacture a variety of β-lactamases.[5]

Enterobacteriaceae, one of the WHO priority pathogens, have become more resistant to carbapenems and colistin everywhere in the world.[6, 7, 8]

A study by Hasunna et al. reported alarmingly high resistance rates of almost 83.35% among extensively drug-resistant (XDR) Klebsiella pneumoniae in neonatal sepsis [9]

In addition, about 500,000 new cases of rifampicin-resistant tuberculosis (RR-TB) were reported globally in 2018, the majority of which had multidrug resistance (MDR).[10] and the persistence of antibiotic tolerance can worsen medical conditions related to diseases such as HIV, malignancies, and malaria.

As the standard antibiotic treatment regimen becomes outdated, the dangers of AMR are expected to rise sharply, perhaps resulting in situations where patients near death require palliative care yet the drugs they are given are no longer clinically effective.[11]

And nosocomial MDR pathogens become hot spots in hospital intensive care units. Lastly, several studies have estimated that AMR-related epidemics could cost between $60 and $100 trillion by 2050, resulting in a 2% to 3.5% drop in the world's overall GDP.[12, 13, 14]

The population distribution of AMR: As a result of historical, ecological, and biological events coming together, AMR bacteria grow and spread unevenly throughout environment–animal–human interactions.[15] Geographic disparities in resistance and the impact of AMR mortality are seen in both human and animal monitoring data at both the regional and national levels.[16,17,18] ,and this is generally larger in the global South and in cultures with fewer resources and greater socioeconomic inequality.[16,18]

In many nations, there is little trustworthy epidemiological evidence at the subnational level. Urban regions with larger human densities have been reported to have higher AMR environmental burdens,[19,20] where water sources or environments may be contaminated, including by wet season flooding and animal contact [20,21]

At both area- and individual-levels, lower socioeconomic status and poverty including overcrowding, homelessness, lower income and lower education [21, 22] are linked to increased rates of AMR as well. According to ecological research, variations in antibiotic use may not entirely explain country disparities, and they identify specific types of political, economic, and governance structures as causes of increased AMR.[23]

The burden of AMR infections in humans is also differentially distributed according to key societal stratifies, such as age, gender, race and socioeconomic status.[17,24,25]

For example, AMR-related mortality peaks in the neonatal period and in the very old, and advanced age is a common risk factor, intersecting with gender in complex ways. Global population ageing and the projected expansion of (multi) morbidity presents additional risks through clinical vulnerability and increased contact with healthcare settings. [26]

The complicated process of layered vulnerabilities, exposures, treatments, and care opportunities leads to these observed disparities, necessitating meticulous investigation including a variety of data sources. Additionally, it is necessary to address the emergence of intersectional disparities in antibiotic usage and AMR risk, which stem from a mix of social disadvantage, [27]

One such intersecting lens that has drawn the most attention lately is gender. In addition to having differing access to care, men and women are likely to be exposed to infections, antibiotics, and drug resistance in different ways. For instance, women and girls living in low-resource environments may be more vulnerable to (drug-resistant) infections because of their menstrual hygiene requirements, but they also have less access to sanitary facilities and less authority to seek medical attention.[28]

One obvious obstacle to research on this topic is the absence of linked data on AMR cases that include demographic and socioeconomic variables. Obstacles in prescribing antibiotics correctly about 38% of participants said that they found it difficult to provide antibiotics to children (33.5%) to extremely difficult (4.6%), while the majority of general practitioners (52.4%) said that they found it difficult to prescribe antibiotics to adults.

Neither simple nor tough, according to the elderly (57.2%). The most difficult demographics to choose the appropriate antibiotic were found to be pregnant women (94.5%) and patients with comorbidities (89.7%). Acute bacterial rhino sinusitis, community-acquired pneumonia, and acute aggravation of chronic obstructive pulmonary disease were found to be the most difficult CA-RTIs to administer the appropriate antibiotic.

In a study, of the participants, almost 57% felt that it was difficult for them to prescribe the right antibiotics since they did not have access to the most recent susceptibility data. Other significant obstacles that made choosing the right antibiotic challenging were the inability to correlate the susceptibility data (53% agreed), the unavailability of suitable medications (51% agreed), and the restricted availability of information on antibiotics (52% agreed).[29]

In a study the causes of AMR As the primary motivations for using broad-spectrum antibiotics in their practices, the responses "to give patients an effective treatment as compared to narrow spectrum antibiotics," "concerns about AMR," and "to increase practitioner acceptability" were chosen "Data and/or guidelines are not simple to understand or to use," "reliance on clinical expertise/past-experience," and "patient/caregiver pressure to prescribe antibiotic" were found to be the top limiting factors that may impede the appropriate prescription of antibiotics, Concerns over inadequate or nonexistent healing or consequences in the absence of antibiotic treatment, "because additional diagnostic investigations are too costly or unavailable, and "if the patient wants to get back to work quickly" were listed as the main justifications for antibiotic prescriptions, even in the lack of solid diagnostic proof . The top-ranked causes contributing to AMR were found to be patient self-medication, inappropriate antibiotic prescriptions, and patients not finishing the antibiotic course .The main obstacles to having conversations with patients about AMR were found to be their lack of basic educational resources, their inadequate understanding, and their worries that the information would make them uncomfortable.[30]

II. Burden Of Over-The-Counter – Antibiotics In India:

The Cost of Over-the-Counter Antibiotics in India According to a study that used the database to estimate global antibiotic usage, the amount of antibiotics consumed worldwide rose by 65% between 2000 and 2015. Additionally, they claimed that the three nations that consume the most antibiotics among LMICs are China, India, and Pakistan, and that the daily antibiotic consumption rate in India rose from 8.2 to 13.6 DDDs (defined daily doses) per 1000 people.[31]

Another study by Kotwani et al, [32] in 2021, the reasons that led to the increase in the usage of over-the-counter antibiotics in two Indian states were assessed using data collected from retail pharmacies. According to this interview-based study, OTC antibiotics were administered for common ailments such as viral infections, colds, and coughs. Antibiotics that were given were cefixime, ciprofloxacin, azithromycin, and amoxicillin/clavulanic acid. According to the WHO's WATCH criteria, cefixime, ciprofloxacin, and azithromycin are at a higher risk of developing resistance.

The factors associated with the use of over-the-counter antibiotics include a lack of time, trouble assessing medical facilities, and an unwillingness to pay for a doctor's appointment. Due to their own financial interests and the absence of strict rules governing this issue, pharmacists routinely dispense medications without a legitimate prescription.[33]

III. Operation Anti-Microbial Resistance Intervention For Total Health:

The Kerala government started OPERATION AMRITH, or AMR Intervention for Total Health, on January 6, 2024, with the goal of reducing the usage of over-the-counter antibiotic prescriptions. Under this program, pharmacists and medical supply businesses are prohibited from dispensing antibiotics without a prescription from a physician. If any pharmacies are breaking this rule, the public can also report them.[34]

Additionally, the pharmacies must to keep precise records of the antibiotics they sell. Similar to this, the Kerala government has implemented the Antibiotic Literate Kerala campaign, the Kerala AMR surveillance network, and the Programme on Removal of Unused Drugs (PROUD) as measures to reduce the irrational use of antibiotics.

IV. Guidelines To Combat Antimicrobial Resistance By Indian Government:

With the primary goals of establishing an AMR surveillance system, bolstering infection control procedures, and encouraging the prudent use of antibiotics through antimicrobial stewardship initiatives, the National Programme on AMR Containment was initiated during the 12th five-year plan.

India's "National Programme on AMR Containment," which is run by the National Centre for Disease Control (NCDC), was created to address the problem of AMR spreading to more powerful agents like carbapenems, which are thought of as life-saving and last-resort medications. The goal is to establish a surveillance system to monitor and comprehend the use of antibiotics. E.coli and Staphylococcus aureus are two of the seven priority bacterial pathogens of public health relevance for which the Indian government has set up 35 labs under the National Antimicrobial Surveillance Network. These labs are mandated to produce AMR surveillance data. Additional initiatives include raising awareness of AMR and strengthening infection control protocols among healthcare professionals.[35]

V. National Action Plan On Antimicrobial Resistance:

In 2017, as part of a worldwide effort, the WHO encouraged its member nations to develop customized national action plans. India has created its own National Action Plan based on WHO recommendations, which include reducing the use of over-the-counter antibiotics, educating and training people about AMR, reducing the rate of infection through preventive measures, and encouraging the prudent use of antibiotics in food, animals, and humans.

VI. National Treatment Guidelines For Antimicrobial Use In Infectious Disease:

The purpose of the "Treatment guidelines for antimicrobial use in common syndromes" is to guarantee consistent treatment of infectious diseases included in the National List of necessary Medicines and to help rationalize the use of necessary antibiotics. The AMR surveillance network was created in 2012 by the Indian Council of Medical Research (ICMR) to collect nationally representative data on AMR to routinely used antibiotics in pathogens of public health significance.

These data are used to guide the treatment of various syndrome such as treatment of sepsis, urinary tract infection, respiratory infection, skin, and soft-tissue infection The key steps in rational use of antimicrobials include identifying the infection, starting empirical therapy in serious infected therapy of several syndromes, including sepsis, respiratory infections, urinary tract infections, and skin and soft tissue infections, is guided by these data. Identifying the infection, initiating empirical therapy for serious infections, choosing and optimizing the right medication, and de-escalating and ending treatment are the essential phases in the prudent use of antibiotics.[36]

VII. National Guidelines On Infection Prevention And Control In Healthcare Facilities (NGIPC):

NCDC and WHO collaborated to build NGIPC as part of the National Action Plan. These principles have been used to design training modules that health departments and healthcare facilities can use to control antimicrobial resistance. According to the modules, 10% of patients will get one hospital-acquired infection (HAI) for every 100 patients. This may lengthen hospital stays, increase costs, raise the risk of adverse drug reactions, and lower quality of life.

It is essential to follow strict hand hygiene guidelines, which guarantee thorough washing and sanitization, in order to successfully prevent diseases.

Furthermore, it is crucial to use personal protection equipment (PPE) such gowns, face masks, and gloves appropriately. A healthy and safe environment can also be maintained by taking precautions against injuries during medical procedures, implementing safe and hygienic waste disposal practices, and performing thorough and frequent environmental cleaning.,[37]

VIII. Strategies And Action Plan To Combat Antimicrobial Resistance:

AMR was acknowledged by the World Health Organization as a "significant universal challenge" in April 2014. The World Health Organization 2015 Global Action Plan on Antimicrobial Resistance was then announced by the World Health Assembly, which is the body that oversees all WHO member countries, [38] urging all participating nations to implement similar national action plans by May 2017. By requiring the proper use of antimicrobial drugs, several national and international representatives have put policies into place to limit the occurrence and spread of antimicrobial resistance. Measures to assess AMR outbreaks were formally announced by the US Food and Drug Administration.[39]

In countries with coordinated national strategies, AMR has been significantly reduced. AMR threats seem to be mitigated by a number of factors, including appropriate drug use, antimicrobial surveillance using the

One Health approach, medical practice improvements, medical coverage schemes, restricted drug commercialization, a coordinated epidemic management program, and communal management programs.

Rapid diagnostic testing is another urgent problem in the fight against AMR, particularly in developing countries where traditional microbiological technologies have been utilized to identify bacteria on a regular basis. By developing personalized therapies for suitable antimicrobial treatment based on cutting-edge genomic screening technologies, these shortcomings could be addressed.

Perhaps a One-Health method would be a noteworthy way to investigate the interactions between humans and animals and introduce cutting-edge evaluation techniques. Considering the known pathways of antimicrobial resistance transmission that are common throughout the three components—people, animals, and the environment. [40]

These are particularly important research issues that need to be properly addressed. However, particularly in low- and middle-income nations, the careless and irrational use of medications is a significant cause to AMR. Antimicrobial agents are misused for many reasons, such as inpatient treatment with doctor-prescribed drugs, ignorance of antibiotics, erroneous prognoses, particularly in developing nations, and upsetting pressures placed on clinicians by the pharmaceutical industry. The examination of the entire AMR problem is hampered mostly by the lack of novel treatments.[41] Therefore, breakthroughs in antibiotic discovery, combination therapy, and technological innovation [42] need to be met.

Subsequent research will concentrate on determining the negative impacts of human activity, the involvement of important AMR determinants, the effects of resistant strains on the health of humans and animals, and important technical, cultural, and financial strategies to lower environmental resistance to antibiotics.

Current national and international strategies to stop the spread of AMR include the Declaration of the 2016 high-level meeting on antimicrobial resistance at the United Nations General Assembly (OPGA/WHO/FAO/OIE 2016), the United States National Action Plan to Combat Antimicrobial Resistant Bacteria (White House 2015), and the FAO/OIE/WHO Tripartite Collaboration.[43]

IX. Antimicrobial Resistance: Potential Threats:

Since the early use of prontosil and Alexander Fleming's 1928 discovery of penicillin, significant progress has been made in the research and production of anti-infective medications, which has significantly advanced contemporary medicine in the last century.[44]

Only seven analyses (5% of the total screened papers) of scientific research on antibiotic use in agricultural production argued that there was no association between animal antibiotic intake and human resistance, whereas 100 (72%) were able to identify a significant association [45].The extent to which this animal-to-human transition also takes place is quite significant, with significant implications for both the welfare of the community and the welfare of animals.[46,47,48,49]

Following the injection of streptomycin to turkeys in 1951, the first instances of antibiotic tolerance in animals used for food production were noted.[50]

More recently and crucially, isolates of Escherichia coli from uncooked meat, cattle, and infected individuals were revealed to carry the transmissible mcr-1 gene, which confers resistance to the nephrotoxic last-line antibiotic medication colistin.[51]

More than twenty countries recognized the mcr-1 gene within three months of its discovery.[52, 53]

Furthermore, pan-drug Gram-negative bacilli (GNB) isolates are being increasingly reported around the world, [54]

Staphylococcus aureus associated with livestock methicillin (LA-MRSA) was first described in 2005, [55]

As a consequence of the acquisition of enterotoxin genes and other virulence factors, such as the Panton–Valentine leukocidin (pvl) gene, LA-MRSA poses a risk to people. [56, 57]

There have been worries that people may contract LA-MRSA from colonized animals like pigs, cattle, and poultry by direct animal contact, environmental contamination, or handling and eating meat . The emergence of vancomycin-resistant enterococci (VRE) poses a significant risk, more significantly.[58, 59] Through both inherent and acquired mechanisms, enterococci develop resistance to various antibiotics. [60]

Vancomycin-resistant Staphylococcus species (VRSA) have been demonstrated to have acquired vanA, the gene that confers resistance to vancomycin, from animal-associated VRE. Enterococci share genetic material with one another or with other genera. AMR against clinically relevant medications may increase as a result of enterococcal infections resistant to vancomycin developing resistance to other clinically significant antibiotics, such as daptomycin and linezolid.[61,62]

A Salmonella typhimurium strain harboring blaNDM-5 has been discovered in commercial pork for the first time in Jiangsu province in China, [63]

Diaz et al. reported an epidemic of Salmonella enteritidis resistant to nalidixic acid and showed that the source of contamination was chicken sandwiches, [64]

A 2010 study conducted in eight Chinese provinces discovered veterinary antibiotic metabolites in cattle manure, including oxytetracycline, chlortetracycline, enrofloxacin, and ciprofloxacin. The occurrence of

ceftiofur-resistant Salmonella enterica serovar Heidelberg in Québec and Ontario was found to be substantially correlated with chicken consumption and improper use of antibiotics in poultry animals, according to Otto et al. Additionally, it has been demonstrated that clinical human samples from the US share a significant relationship with Campylobacter jejuni cultivated from commercial chicken products.[65]

There is strong evidence from these and other cases that widespread animal husbandry is one of the main ways that AMR spreads.

However, ongoing exposure to and increased tolerance to antimicrobials have been caused by pressure from the current decline in antibiotic R&D from major pharmaceutical companies, the misuse of antibiotics, and the excessive use and exploitation of antimicrobials as animal growth promoters and in agricultural settings for animal feed. AMR is a serious public health concern.[66]

The bacteria associated with animals can potentially behave as a repository of antibiotic-resistant determinants that could be carried over to humans. [67, 68]

X. Mechanisms And Drivers Contributing To The Spread Of AMR:

Mechanism of AMR

The misuse of antibiotics in clinical and agricultural contexts is the main source of antimicrobial resistance (AMR), which is mostly brought on by exposing bacteria to sub inhibitory concentrations of antibiotic medicines.[69, 70]

Numerous mechanisms are employed by antibiotic-resistant bacteria, including changes to the antibiotic's intended target, alterations to the permeability of the cell membrane, efflux pump expression that keeps intracellular antibiotic concentrations below inhibitory levels, and antibiotic inactivation due to enzyme breakdown or a change in the enzymatic scaffold.[71]

One resistance mechanism that causes the medicine to lose its effectiveness is enzymatic degradation or alteration of the antibiotic scaffold. Two well-known examples of these enzymes are TetX antibiotic-modifying enzymes and β-lactamases.[72, 73, 74, 75]

Protecting, altering, or overexpressing the desired target might potentially result in the development of antibiotic resistance. The most well-known example is changing the cell-wall PBP to counteract the action of β-lactam antibiotics, by enzymatically altering the peptidoglycan, VRE employs this tactic to lower the target's affinity for vancomycin.[76]

The utilization of efflux pumps or modifications in membrane permeability to stop the antibiotics from penetrating the bacterial cells are two additional resistance strategies. One type of multidrug efflux pump produced by bacteria,[77] or an antibiotic-specific exporter, such as tetracycline efflux pumps,[78] to maintain sub inhibitory levels of antibiotics in the cell. In contrast, a small number of bacteria reduce the production of porin or create a more specific porin variation to reduce membrane or wall permeability, which stops antibiotics from entering the cell.[79]

Some bacteria can develop extensive resistance by using many complementary mechanisms. Clinical isolates of Enterobacter cloacae develop high-level resistance to carbapenems as a result of a porin mutation that reduces carbapenem absorption and increases the synthesis of a chromosomal β-lactamases. [80]

Both vertical and horizontal gene transfer are common ways for bacteria to gain antibiotic resistance. Genetic information, including mutations, is passed down from one generation to the next within a family through a process called "vertical gene transfer." Among various bacterial species, horizontal gene transfer (HGT) is the main mechanism by which antibiotic-resistant genes spread quickly.[81]

Because of a variety of special characteristics, resistant bacteria are able to flourish and spread across their surroundings. Through horizontal gene transfer (HGT), ARGs can be passed from native bacteria to pathogens after being stored by them in the environment.[82, 83]

HGT can occur through transformation, transduction, and conjugation, as well as other mechanisms, [84]

Under ideal circumstances, the processes of HGT are well recognized, but in environments where chemical stressors, like antibiotics and biocides are present, they are not as well understood. By inducing natural selection in microorganisms with somewhat greater antibiotic tolerance through mutation or horizontal gene transfer, sub inhibitory and sub therapeutic antibiotic dosages would encourage the development of drug resistance in microbes. In addition to the rapid emergence of antibiotic resistance at the molecular level, the state of AMR is getting worse because of a lack of funding, challenges with clinical research, and limitations in scientific innovation. There are few new antibiotics being used in clinical settings, and the discovery of novel antibiotics has reached a snag, [85]

The Excessive Use of Antibiotics:

The alarming rate at which AMR is emerging has been hastened by the abuse and misuse of currently available antimicrobials. Globally, the use of antibiotics rose by 65% from 2000 to 2015.[86]Antimicrobial usage and misuse are more prevalent among professionals treating babies and children, as well as in certain diseases or

syndromes, and in general and acute care wards. Up to 55% of South Africans 88% of Pakistanis 61% of Chinese and 15.4% of Canadians use antibiotics incorrectly in primary care.[87,88,89,90]

According to earlier studies up to 60% of antibiotic prescriptions in Louisiana, USA, primary care settings for patients with acute respiratory tract infections were clinically inappropriate.[91]

Because of this, the original treatment was rendered ineffective, which allowed the AMR bacteria to grow and multiply. The inappropriate kind or dosage of antibiotics are frequently used to treat other illnesses, such as middle ear infections, sinusitis, and acute bronchitis.[92]

Lastly, during the COVID-19 pandemic, more patients were prescribed antibiotic prophylaxis as part of their treatment plan, and numerous studies have documented an increase in AMR bacteria.[93] In particular, bacteria in the WHO priority pathogen category will be more likely to develop AMR over time if antibiotics are overused and misused.[94]

Since the 1950s, there has been a steady increase in the demand for meat and dairy products around the world, leading to an increase in the use of antimicrobial drugs in agriculture, [95] because they serve as growth accelerators, prophylactics, and metaphylactics in addition to being pharmaceuticals. Antibiotic-resistant bacteria and the AMR genes they carry have the potential to proliferate and be transferred to humans via the food chain as a result of this overuse. In 2017, around 85,330 tons of veterinary antibiotics were used globally.[96]

By 2030, it is anticipated that the usage of antibiotics in animals raised for food would have increased by 11.5%., [97]

Since 2003, the European Union (EU) has outlawed the use of antibiotics to promote development.[98] Then in 2012, the FDA finally made it illegal to give cattle antibiotics without a doctor's prescription.[99] In 2019, Out of 160 countries, 26 still employed antibiotics as growth promoters in agricultural settings .As stated by Ejo and colleagues,[100] Salmonellosis was detected in 5.5% of Ethiopian samples of raw meat, eggs, milk, minced meat, and burgers. There was 47.6% resistance among the isolates to tetracycline, ampicillin, and sulfamethoxazole–trimethoprim.

In addition, Rasheed et al.[101] discovered 14.7% of fresh milk, raw meat and chicken, vegetable salads, and the surface of raw eggs to be multidrug-resistant E. coli. These samples exhibited extended-spectrum β-lactamase activity in 4% of them.

Biocides

Biocides are frequently used antimicrobial agents in medical facilities, cosmetics companies, household disinfectants, wipes, and home furnishings, as well as in farmyards for applications like wheel and foot rinses and a variety of industrial processes like oil wells (e.g., hydraulic fracturing) and piping systems.[102]

Ethanol, formaldehyde, chlorhexidine, triclosan, quaterium ammonium compounds (QACs), alkyl dimethyl-benzyl ammonium chloride (ADBAC), stearalkonium chloride, isothiazolium-benzalkonium chloride, cetrimonium chloride/bromide, and cetylpyridinium chloride are a few commonly used biocides.[103] In contrast to antibiotics, biocides generally have several target sites. [104] The efficiency of a biocide is proportional to its concentration, at low levels, it may have only a limited impact,[105]

Antibiotic resistance may arise if the cell's adaptive mechanism prevents the antibiotic from reaching its single target area. We still don't fully understand how biocides work, especially at low or sub inhibitory doses. The biocide's overall mode of action can be explained by the structure of the bacteria it works best against. Three levels of interaction exist, (1) with the cytoplasmic membrane, (2) with cytoplasmic components, and (3) with cellular components outside the cell. A biocide can engage in one or all three levels of interaction with bacterial cells to produce its antimicrobial effect.[106]

The characteristics of the chemical agent and the type of organism treated have the biggest impact on how bacteria react to biocides. Additionally, factors including contact temperature, ambient pH, and the presence of organic matter can have a big impact on antibacterial activity.[107]

The bacterial structural characteristics, which can be acquired or innate, determine the biocide resistance mechanisms. Bacterial cells can avoid a biocide by virtue of an innate, chromosome-regulated trait known as intrinsic resistance. Endospore-producing bacteria exhibit a markedly higher resistance to biocides such bacillus and Clostridium. Additionally, it's thought that physiological adaptation plays a big role in bacterial resistance to biocides, like in the instance of Pseudomonas's resistance to specific alcohol concentrations.[108, 109,110,111,112]

E. coli, Proteus mirabilis, Pseudomonas aeruginosa, and S. marcescens are examples of bacteria resistant to chlorhexidine, a common hospital disinfectant.[113, 114]

Plasmids in Enterobacteriaceae can include genes for antibiotic resistance and, in certain cases, protection against mercury, organomercury, and other cations and some anions.[115]

Many bacterial species have been shown to possess biocidal resistance genes (BRGs), such as the qacE and qacA/B genes found in the Enterobacteriaceae family and Pseudomonas and the qacA/B genes found in S. aureus, which confer resistance to QACs.[116]

Hospitals are particularly affected by plasmid-mediated resistance to silver salts, since silver nitrate and silver sulfadiazine can be applied topically to heal serious burns and stop infections. A limited percentage of biocides have been demonstrated to be inactivated, and this only pertains to a portion of the entire biocide population. Protection is more likely to come from changes in the permeability of the cell membrane or increased biocide outflow since biocides can attack a wide variety of cellular targets.[117]

The Biocidal Products Regulation (EU) 528/2012 supervises commercialization, consumption, and management and specifically governs its use in veterinarian medicine in Europe [118] throughout 1992–2007, the world's economy for biocides expanded by 40%.[119]

Vaccines and Their Role in AMR:

Vaccines are regarded as one of the most promising prophylactic measures to address the issues brought on by AMR for several reasons. First, immunizations can directly prevent infections caused by lethal AMR pathogens. Additionally, they reduce the symptoms that usually result in the need for antibiotics, which indirectly reduces the need of antibiotics. Finally, immunizations prevent germs from growing to the huge numbers needed to produce resistance mutations.[120, 121]

In addition, vaccinations against the major AMR bacterial pathogens, including Salmonella typhi, Mycobacterium TB, P. aeruginosa, S. aureus, pathogenic Escherichia coli, and Clostridium difficile, may be possible with other vaccines that are presently in the clinical development stage. Over the past ten years, advances in immunology, genetics, structural biology, and microbiology have enabled the development of vaccination technologies that may greatly improve the chances that novel vaccines will effectively prevent diseases caused by AMR pathogens.[122]

Nonconventional Technologies and Approaches:

As with other treatment domains, a variety of techniques and modalities must be considered in order to treat bacterial infections. Some promising approaches are highlighted here, although more are being contemplated.[123]

Phage Therapy:

Bacteria, the most common life form on Earth, are infected by viruses known as phages. Even before penicillin was discovered, they were being used as antibiotics. Although there are many other types of phage viruses, the most common type for bacterial therapy is lytic phages, which cause cell lysis and bacterial cell death. After adhering to the bacteria and injecting their DNA or RNA, phages use the host's enzymes and cofactors to multiply.

Since there is currently no quick diagnostics that determines the need for empirical treatment, an impractical number of different phages would be needed to cover all the potential species of bacteria that could be involved in common infections like intra-abdominal infections, urinary tract infections, and community-acquired bacterial pneumonia, for example. Phage usage is therefore limited to latter stages of treatment or as a last resort once the pathogen has been identified.

Researchers are examining ways to improve the selectivity of phages.[124] As a result, fewer phages may be needed per species, altering this approach. Getting the phages to the site of action is the next major challenge because they lack beneficial PK properties. To alleviate these challenges, one group is developing a phage that targets P. aeruginosa in order to cure cystic fibrosis. The phages are directly inhaled into the lungs, while another team is developing an oral phage mixture to treat gastrointestinal tract infections caused by C. difficile.[125, 126]

These are intriguing ideas, but effectiveness in robust randomized controlled trials is necessary to conclusively assess the approach's utility. A recent review looked at a number of studies that treated a variety of bacterial infections with phages given orally, parenterally, transdermally, topically, intranasally, and transdermally.[127]

Utilizing phages as a delivery vehicle is an additional intriguing tactic. A research team is currently investigating the use of bacteriophages to directly introduce CRISPR CAS3 genes into bacteria as an alternative to antibiotics (www.locus-bio.com/). Even though phages have shown promise as antibiotics for decades, the fact that no medicine has been licensed may suggest that their prospects of success are low. The nature and timing of this revolutionary technology are unknown, but we think it has the ability to quickly turn this battle around and open up this sector to exploitation.

Microbiome:

It has been widely acknowledged in the last ten years that the host's stability and general health are significantly influenced by the human gut microbiota. Large percentages of commensal bacteria can be eradicated by broad-spectrum conventional antibiotics, which in certain situations may permit the establishment of

opportunistic harmful germs. The most well-known example of this is when broad-spectrum antibiotic therapy is followed by a C. difficile infection, which causes diarrhea, dehydration, and potentially death.

Antibiotics like vancomycin or metronidazole can be used to treat C. difficile, however the spores can persist in the gastrointestinal tract and potentially germinate and re infect after antibiotic treatment is stopped. It can be difficult to treat recurrent C. difficile, although methods to rebuild the microbiota are being developed. Patients suffering from C. difficile have had their microbiome restored by the use of unpleasant but effective fecal matter transplants.

By using a donor fecal sample (from a spouse, for example), the idea is to populate a patient's GI flora in such a way that the fecal bacteria return to the patient more quickly than the C. difficile spores can re-establish an infection. Because of its great success, this approach has inspired research teams to find better, more regulated ways to restore a patient's microbiome.

One method involves taking a combination of spores from various important bacteria that were separated from healthy donor fecal samples orally. While the early results were outstanding, they were not confirmed by later clinical trials.[128]

Another method uses a single strain of a nontoxinogenic C. difficile (NTCD) that is capable of outcompeting the toxic C. difficile that is causing the infection. The microbiome will gradually reestablish itself because the NTCD is not harmful to the host.[129]

Furthermore, teams are developing therapies that include a specific mix of bacterial strains from various species that are thought to be essential for a robust microbiome that is resistant to C. difficile infection or reinfection after receiving broad-spectrum antibiotics.[130]

Though definitive phase 3 success is still needed, these methods are making encouraging progress and might also be effective in de-colonizing patients of MDR infections. For a variety of illnesses, the microbiome is probably a rich source of potential treatments. We believe that a microbiome treatment for gastrointestinal tract C. difficile infection is very likely to become accessible soon due to AMR. Additionally, the lung microbiome may present a chance to avoid respiratory infections such as ventilator-associated pneumonia, HAP, and Pseudomonas in cystic fibrosis.

Host Modulation:

In addition to substances that affect bacteria or their products, research is being done to enhance the host's defences against bacteria. Opportunities for intervention to either increase the host response to bacterial infection in cases where the immune response is inadequate or to reduce the host response in cases where it has overreacted are becoming more and more apparent as more is learned about the host immune and inflammatory systems.[131]

Researchers are using computational techniques to examine and sort genome data in order to find possible host targets that could influence bacterial infections. This gives them additional targets to evaluate and possibly even opportunities for repurposing.[132]

A new generation of more potent and possibly resistant antibacterial medications could be developed by Immunotherapeutics, which are thriving in other therapeutic areas but have not yet been thoroughly studied for bacterial infections. However, they might need to be used in conjunction with conventional antibiotics. Since there are currently no proven targets for bacterial infection, host modulation has a lot of promise but will probably take a while to reach its full potential.

Unexpected results from host modulation drugs being developed for different reasons that are discovered to improve the patient's resistance to infections when compared to control patients could lead to breakthroughs. If a protective effect is identified, a more thorough method will be needed to show a clear link between host modulation and bacterial infection treatment in order to validate the target; specialized trials will then be required to repurpose such medications, and new research initiatives must be started to find more appropriate compounds.

Monoclonal Antibodies:

Because antibodies may target bacteria, it is not unexpected that a lot of work has gone into creating antibody therapy as an antibiotic substitute. In addition to successfully treating inflammatory illnesses, antibody treatment has lately influenced HIV research through the use of broadly neutralizing monoclonal antibodies (mAbs),[133.]

The restricted spectrum of antibodies, which only target a few strains of a certain species, is a significant obstacle to their use in treating bacterial illnesses. In contrast, an antibody designed as an antibiotic must be able to target a variety of bacteria. Thanks to new technology, scientists can now alter antibodies to make a bi specific monoclonal antibody (mAb) more capable of binding two targets and to lower the total number of mAbs required to treat an infection. By creating a bi specific monoclonal antibody (mAb) to target P. aeruginosa targets Psl and PcrV, Medimmune proved this strategy.[134]

Another strategy is to make the bacteria less harmful to the host by focusing on their virulence components, such as proteins or toxins.[135,136] Numerous candidate antibodies for different bacterial illnesses have been developed as a result of extensive study, and these have been examined.[137,138]

The conduct of clinical studies, which primarily concentrate on treating a particular pathogen, and the expense of mAbs are some of the difficulties that this technique now faces. Since most people only get infections once in their lifetimes, using monoclonal antibodies (mAbs) to protect high-risk patients against hospital-acquired infections like Acinetobacter, P. aeruginosa, or K. pneumoniae may be a more practical option than vaccination against these pathogens.[139]

Future growth in this field could be substantial if diagnostics and antibody engineering technologies improve and manufacturing techniques lower product costs. mAbs likely have the highest chance of effectively treating AMR out of all the strategies discussed, albeit each mAb treatment will most likely only be effective against a particular species of bacteria.

This means that after the infectious organism has been discovered, these therapies will be saved for second- or third-line therapy. The drawback is that every mAb will require a unique clinical development approach, significantly raising the development costs. The development of mAbs will undoubtedly be accelerated by technological or regulatory advancements that lower costs or quicken the development process.[140]

XI. Scientifically Proven Herbal Formulations Having Antibiotic Properties:

QURS-E-AFSANTEEN: The antibacterial activity of the test medications was assessed by Mudasir Khazir et al. at the University of Kashmir's Department of Pharmaceutical Sciences, compound formulation. To test for antibacterial activity, Qurs-Afsanteen (tablet) was used. Among the various ingredients in Qurs-Afsanteen (tablet), Artemisia absinthium is the main component. Numerous fevers, liver conditions, dysuria, and malarial fever are among the conditions for which this medication is prescribed.

10µg of tetracycline was used as a positive control in the Gentamicin antibiotic discs (SD016), which were purchased from HIMEDIA. According to the results, HAEQA exhibits the strongest effectiveness against strains of Salmonella typhi and Staphylococcus aureus.[141,142] Artemisia herb also contains antimalarial agents and its antimicrobial activities have been studies in detail (Panseeta et al., 2011).[143]

SHARBAT-UNNAB: An investigation conducted by Mudasir Khazir et al. The University of Kashmir's Pharmaceutical Sciences Department conducted the test drug's antibacterial activity. The test medications' antibacterial activity was evaluated using the agar well diffusion method. The antibacterial activity of the extract and (SU) against the chosen pathogens, Staphylococcus aureus, Salmonella typhi, Bacillus subtilis, and Escherichia coli was assessed using an antibiotic scale and contrasted with the standard. The test medications exhibited a notable zone of inhibition against the chosen microorganisms. Ziziphus jujuba HA extract demonstrated the largest zone of inhibition (30 mm) against S. aureus and a zone of inhibition (23 mm) against E. coli.[142]

MAZU (QUERCUS INFECTORIA): The active ingredients in crude ethanol extract have antimicrobial activity that demonstrates dose-dependent antibacterial activity. They may have an antibacterial action mechanism that involves inactivating microbial adhesions, enzymes, transport proteins in the cell membrane, complexing with polysaccharides, etc. Using various solvents with different polarities, the antibacterial activity of Quercus infectoria was investigated, and the effectiveness was contrasted. The study's findings demonstrate the antibacterial effectiveness of Quercus infectoria galls against Gram-negative microorganisms Escherichia coli, Staphylococcus aureus, and Gram-positive Bacillus subtilis. Gram-positive bacteria were suppressed more effectively than Gram-negative bacteria by all gall extracts.[144]

PHYLANTHUS NIRURI: The bactericidal qualities of several P. niruri extracts and fractions were investigated in a study by M. S. Hossain et al. utilizing the widely recognized disc diffusion method.[145]

The Biomedical Research Centre at the University of Dhaka provided pure cultures of the bacterial strains used in the experiment. In accordance with usual practice, nutrient agar medium was created.[146]

Following the relocation of the subcultures to the sterile Petridishes, all experimental organisms were moved to the agar slants. The discs that contained the reference antibiotic (ciprofloxacin), the test samples, and the blank (negative control) were put on agar plates that had solidified. In order to ensure adequate diffusion, the plates were subsequently chilled. To measure the zone of inhibition (mm) value, a clear, clean scale was used.

Strong antibacterial qualities of the entire plant, P. niruri, were discovered using pharmacological activity screening. Both antibacterial and antioxidant properties were present in the chloroform-soluble fractionate. It was found that the ethyl acetate fraction has strong antibacterial activity. In P. niruri, the investigation found phytocompounds with strong biological activity, primarily in the n-hexane and ethyl acetate fractions.[147]

Acorus calamus L. (Bachh): Research conducted on Acorus calamus IC50 values of 0.2, 0.2, and 0.4 mg/ml, respectively, demonstrated noteworthy efficacy against Microsporum gypseum, Penicillium marneffei, and filamentous fungus Trichophyton rubrum. Nonetheless, it showed strong activity against Saccharomyces cerevisiae, Cryptococcus neoformans, and yeasts (MIC 0.1 to 1 mg/ml) but limited action against bacteria (MIC 5 - >10 mg/ml). SEM showed that hyphae and conidia treated with this fraction contracted and collapsed, most likely due to cell fluid leakage.[148,149]

AQUILARIA AGALLOCHA ROXB. (AGARU): P. aeruginosa and S. flexneri responded to an aqueous extract of the leaf and bark with different inhibitory zones. The bark's methanol extract showed no inhibitory effect on B. subtilis, whereas the leaf's methanol extract did.[150]

AZADIRACHTA INDICA A.JUSS (NEEM): Most effective against S. aureus and S. typhi, but less successful against K. pneumoniae, E. coli, and Proteus vulgaris, with modest efficacy against Pseudomonas aeruginosa. A. indica had the biggest zone of inhibition against Gram-positive S. aureus and the smallest zone of inhibition against Gram-negative E. coli, according to zone of inhibition measurements (ZOI). Using 700 µg of extract resulted in a maximal inhibitory zone of 22±3 mm against S. aureus, which increased with increasing dose.[151]

Another study done by Ayesha Mateen et.al: At Central Research Institute of Unani Medicine, Hyderabad over Azadirachta indica A. juss (Fabaceae) Hemidesmus indicus roots, Smilax china, Piper cubeba fruit, and Trigonella foenum graceum seeds. Three species of Ocimum—O.basilicum, O.sanctum, and O.cannum, Among all the medications, extracts of Azadirachta indica (Bark) and Hemidesmus indicus (Root) shows the most effectiveness against all bacterial strains. Staphylococcus aureus and Salmonella paratyphi were shown to be the most sensitive organisms to the ethanol extracts of Azadirachta indica (Bark).

Additionally, Hemidesmus indicus ethanol extracts have no effect on Salmonella typhi or Salmonella paratyphi. Bacillus subtilis strains were shown to be more vulnerable to Smilax china (root) ethanol extracts. Staphylococcus aureus, Salmonella typhi, Salmonella paratyphi, and E. coli were all impacted by the ethanol and methanol extracts of Tigonella foenum graceum (seeds).[152]

BISEHRI BOOTI: Bisehri booti has strong antibacterial action against a variety of harmful bacterial strains, according to a study by S. Rehman et al., and as such, it may be used to make antibacterial medicines that combat a variety of infectious disorders. All investigated bacterial strains, including S. aureus, S. mutans, S. epidermidis, S. pyogenes, B. cereus, E. coli, K. pneuomoniae, P. aeruginosa, and P. vulgaris, were shown to be susceptible to it, however C. xerosis was completely resistant to it. The most notable sensitivity was shown to B. cereus, S. epidermidis, S. aureus, and E. coli.[153]

Antimicrobial Assay of Alcoholic and Hydroalcoholic Extract of a Unani Formulation by Agar Well Method: a study was conducted to investigate antibacterial activity of a Unani formulation containing (i) Sonth (Zanjbeel) (Zingiber officinale) (ii) Suranjan (Colchicum luteum) and (iii) Elwa (Aloe vera). The alcoholic and hydro-alcoholic extracts dissolved in DMSO (Dimethyl Sulphoxaside) were used to determine antibacterial activity by Agar Well Method, The efficacy of Unani formulation against Bacillus cereus and Pseudomonas aeruginosa, was found even better than Ciprofloxacin and Amikacin, respectively. The study demonstrated that Unani formulation possesses significant antibacterial activity and can be used in infectious diseases caused by a number of Gram +ve and Gram -ve microorganisms.

There are several Unani pharmacopoeial preparations having anti-microbial property include these herbs such as Ushban, Sadri, Sharbat-e-Adrak, Qurs-e- Sual, [15,](Anonymous, 2011) Jauhar-e-Kibreet Qawi, (Anonymous, 2007), [155] Kushta Marjan Sada (Anonymous, 2008) etc.[156, 157].

XII. Conclusion:

Antimicrobial resistance (AMR) poses a significant global health challenge by diminishing the effectiveness of conventional antibiotics, leading to increased morbidity, mortality, and healthcare costs. Modern medicine emphasizes the rational use of antibiotics, development of novel antimicrobials, and integrated stewardship programs to combat AMR. At the same time, Unani medicine presents promising complementary treatments that could lessen dependency on synthetic antibiotics and slow the emergence of resistance due to its holistic approach and use of herbal formulations. In order to successfully include some Unani herbs into modern therapy regimens, additional scientific research is necessary to confirm their antibacterial and immune-modulatory qualities. Combining evidence-based strategies from both systems could improve infection control and lessen the threat posed by AMR.

Acknowledgement:

We would like to express our deepest gratitude to the individuals and Institution whose support and contribution have been instrumental in the completion of paper, We are also indebted to the staff of Clinical Research Unit, Goa, for their technical support, Special thanks are also due to Central Council for Research In Unani Medicine (CCRUM), for providing this opportunity and access to the Classical literature and resources that played a crucial role in the preparation of this paper.

Funding: No funding sources
Conflict of interest: None declared
Ethical approval: Not required

References:

[1] (Tripathi KD "Essential Of Medical Pharmacology"7th Edition, JAYPEE BROTHERS MEDICAL PUBLISHERS (P) LTD.2013, ISBN: 978-93-5025-937-5.Page.788).
[2] Murray, C.J.; Ikuta, K.S.; Sharara, F.; Swetschinski, L.; Aguilar, G.R.; Gray, A.; Han, C.; Bisignano, C.; Rao, P.; Wool, E.; Et Al. Global Burden Of Bacterial Antimicrobial Resistance In 2019: A Systematic Analysis. Lancet 2022, 399, 629–655. [Crossref]
[3] Trotter, A.J.; Aydin, A.; Strinden, M.J.; O'Grady, J. Recent And Emerging Technologies For The Rapid Diagnosis Of Infection And Antimicrobial Resistance. Curr. Opin. Microbiol. 2019, 51, 39–45. [Crossref] [Pubmed]
[4] Davies, J.; Davies, D. Origins And Evolution Of Antibiotic Resistance. Microbiol. Mol. Biol. Rev. MMBR 2010, 74, 417–433. [Crossref] [Pubmed]
[5] Meletis, G. Carbapenem Resistance: Overview Of The Problem And Future Perspectives. Ther. Adv. Infect. Dis. 2016, 3, 15–21. [Crossref]
[6] Du, H.; Chen, L.; Tang, Y.-W.; Kreiswirth, B.N. Emergence Of The Mcr-1 Colistin Resistance Gene In Carbapenem-Resistant Enterobacteriaceae. Lancet Infect. Dis. 2016, 16, 287–288. [Crossref]
[7] Yao, X.; Doi, Y.; Zeng, L.; Lv, L.; Liu, J.-H. Carbapenem-Resistant And Colistin-Resistant Escherichia Coli Co-Producing NDM-9 And MCR-1. Lancet Infect. Dis. 2016, 16, 288–289. [Crossref]
[8] Savin, M.; Bierbaum, G.; Blau, K.; Parcina, M.; Sib, E.; Smalla, K.; Schmithausen, R.; Heinemann, C.; Hammerl, J.A.; Kreyenschmidt, J. Colistin-Resistant Enterobacteriaceae Isolated From Process Waters And Wastewater From German Poultry And Pig Slaughterhouses. Front. Microbiol. 2020, 11, 575391. [Crossref] [Pubmed].
[9] Hassuna, N.A.; Abdelaziz, R.A.; Zakaria, A.; Abdelhakeem, M. Extensively-Drug Resistant Klebsiella Pneumoniae Recovered From Neonatal Sepsis Cases From A Major NICU In Egypt. Front. Microbiol. 2020, 11, 1375. [Crossref] [Pubmed]
[10] Antimicrobial Resistance. Available Online: Https://Www.Who.Int/News-Room/Fact-Sheets/Detail/Antimicrobial-Resistance (Accessed On 12 March 2022)
[11] Ashiru-Oredope, D.; Kessel, A.; Hopkins, S.; Ashiru-Oredope, D.; Brown, B.; Brown, N.; Carter, S.; Cichowka, A.; Susan Hopkins On Behalf Of The English Surveillance Programme For Antimicrobial Utilization And Resistance Oversight Group. Antimicrobial Stewardship: English Surveillance Programme For Antimicrobial Utilization And Resistance (ESPAUR). J. Antimicrob. Chemother. 2013, 68, 2421–2423. [Crossref] [Pubmed]
[12] Antimicrobial Resistance: Tackling A Crisis For The Health And Wealth Of Nations/The Review On Antimicrobial Resistance Chaired By Jim O'Neill. Available Online: Https://Wellcomecollection.Org/Works/Rdpck35v (Accessed On 11 March 2022).
[13] .Sipahi, O.R. Economics Of Antibiotic Resistance. Expert Rev. Anti Infect. Ther. 2008, 6, 523–539. [Crossref] [Pubmed]
[14] Taylor, J.; Hafner, M.; Yerushalmi, E.; Smith, R.; Bellasio, J.; Vardavas, R.; Bienkowska-Gibbs, T.; Rubin, J. Estimating The Economic Costs Of Antimicrobial Resistance: Model And Results. Available Online: Https://Www.Rand.Org/Pubs/Research_Reports/RR911.Html (Accessed On 11 March 2022)
[15] Hinchliffe S. Postcolonial Global Health, Post-Colony Microbes And Antimicrobial Resistance. Theory Cult Soc 2022; 39: 145–68. Https://Doi. Org/10.1177/0263276420981606.
[16] Antimicrobial Resistance Collaborators. Global Burden Of Bacterial Antimicrobial Resistance In 2019: A Systematic Analysis. Lancet 2022; 399: 629–55. Https://Doi.Org/10.1016/S0140-6736(21)02724-0.
[17] World Health Organisation. 2022. Global Antimicrobial Resistance And Use Surveillance System (GLASS) Report: 2022. Https://Www.Who.Int/ Publications-Detail-Redirect/9.
[18] Allel K, Day L, Hamilton A Et Al. Global Antimicrobial-Resistance Drivers: An Ecological Country-Level Study At The Human–Animal Interface. Lancet Planet Health 2023; 7: E291–303. Https://Doi.Org/10.1016/S2542- 5196(23)00026-8
[19] Elder FCT, Proctor K, Barden R Et Al. Spatiotemporal Profiling Of Antibiotics And Resistance Genes In A River Catchment: Human Population As The Main Driver Of Antibiotic And Antibiotic Resistance Gene Presence In The Environment. Water Res 2021; 203: 117533. Https://Doi.Org/10.1016/J.Watres. 2021.117533.
[20] Cocker D, Chidziwisano K, Mphasa M Et Al. Investigating One Health Risks For Human Colonisation With Extended Spectrum B-Lactamase-Producing Escherichia Coli And Klebsiella Pneumoniae In Malawian Households: A Longitudinal Cohort Study. Lancet Microbe 2023; 4: E534–43. Https://Doi.Org/10.1016/S2666-5247(23)00062-9
[21] Cocker D, Chidziwisano K, Mphasa M Et Al. Investigating One Health Risks For Human Colonisation With Extended Spectrum B-Lactamase-Producing Escherichia Coli And Klebsiella Pneumoniae In Malawian Households: A Longitudinal Cohort Study. Lancet Microbe 2023; 4: E534–43. Https://Doi.Org/10.1016/S2666-5247(23)00062-9
[22] Keenan K, Papathomas M, Mshana SE Et Al. Evidencing The Intersection Of Environmental, Socioeconomic, Behavioural And Demographic Drivers Of Antibacterial Resistance In East Africa. 2024. Https://Doi.Org/10. 2139/Ssrn.4724376
[23] Collignon P, Beggs JJ, Walsh TR Et Al. Anthropological And Socioeconomic Factors Contributing To Global Antimicrobial Resistance: A Univariate And Multivariable Analysis. Lancet Planet Health 2018; 2: E398–405. Https://Doi.Org/10.1016/S2542-5196(18)30186-4
[24] Blackmon S, Avendano E, Nirmala N Et Al. Socioeconomic Status And The Risk For Colonization Or Infection With Priority Bacterial Pathogens: A Global Evidence Map. Medrxiv 24306293. Https://Doi.Org/10.1101/2024. 04.24.24306293. 24 April 2024
[25] Waterlow NR, Cooper BS, Robotham JV Et Al. Antimicrobial Resistance Prevalence In Bloodstream Infection In 29 European Countries By Age And Sex: An Observational Study. Plos Med 2024; 21: E1004301. Https://Doi. Org/10.1371/Journal.Pmed.1004301

[26] Abebe F, Schneider M, Asrat B Et Al. Multimorbidity Of Chronic Noncommunicable Diseases In Low- And Middle-Income Countries: A Scoping Review. J Comorb 2020: 10. Https://Doi.Org/10.1177/2235042X20961919

[27] Gautron JMC, Tu Thanh G, Barasa V Et Al. Using Intersectionality To Study Gender And Antimicrobial Resistance In Low- And Middle-Income Countries. Health Policy Plan 2023; 38: 1017–32. Https://Doi.Org/10.1093/ Heapol/Czad054

[28] World Health Organisation. 2024. Addressing Gender Inequalities In National Action Plans On Antimicrobial Resistance: Guidance To Complement The People-Centred Approach. Https://Iris.Who.Int/Bitstream/ Handle/10665/378639/9789240097278-Eng.Pdf?Sequence=1

[29] World Health Organisation. 2024. Addressing Gender Inequalities In National Action Plans On Antimicrobial Resistance: Guidance To Complement The People-Centred Approach. Https://Iris.Who.Int/Bitstream/ Handle/10665/378639/9789240097278-Eng.Pdf?Sequence=1

[30] (PLOS Global Public Health | Https://Doi.Org/10.1371/Journal.Pgph.0004558 May 7, 2025 9 / 19)

[31] Klein EY, Van Boeckel TP, Martinez EM, Pant S, Gandra S, Levin SA, Et Al. Global Increase And Geographic Convergence In Antibiotic Consumption Between 2000 And 2015. Proc Natl Acad Sci U S A 2018;115:E3463-70.

[32] Kotwani A, Joshi J, Lamkang AS. Over-The-Counter Sale Of Antibiotics In India: A Qualitative Study Of Providers' Perspectives Across Two States. Antibiotics (Basel). 2021;10:1123.

[33] Koya SF, Ganesh S, Selvaraj S, Wirtz VJ, Galea S, Rockers PC. Consumption Of Systemic Antibiotics In India In 2019. Lancet Reg Health Southeast Asia 2022;4:100025.

[34] Teamlease Regtech – Goverment Of Kerala Issued A Notification Regarding Operation Amrit – Action For Selling Medicine Without A Prescription. Available From: Https://Www. Teamleaseregtech.Com/Updates/Article/28994/Govt-Of-Keralaissued-A-Notification-Regarding-Operation-Amrit-Action-/ [Last Accessed On 2024 Jul 06].

[35] Antimicrobial Resistance (AMR) Containment. National Centre For Disease Control (NCDC). Available From: Https://Ncdc. Mohfw.Gov.In/Antimicrobial-Resistance-Amr-Containment/.[Last Accessed On 2024 Jul 06]

[36] Pinto-De-Sá R, Sousa-Pinto B, Costa-De-Oliveira S. Brave New World Of Artificial Intelligence: Its Use In Antimicrobial Stewardship-A Systematic Review. Antibiotics (Basel) 2024;13:307.

[37] Shravan Venkatraman.Et.Al,2025 National Journal Of Pharmacology And Therapeutics | Published By Wolters Kluwer – Medknow.

[38] Global Action Plan On Antimicrobial Resistance. Available Online: Https://Www.Who.Int/Publications-Detail-Redirect/9789241509763 (Accessed On 11 March 2022).

[39] Huang, Q.M.; Horn, M.A.; Ruan, S.G. Modeling The Effect Of Antibiotic Exposure On The Transmission Of Methicillin-Resistant Staphylococcus Aureus In Hospitals With Environmental Contamination. Math. Biosci. Eng. MBE 2019, 16, 3641–3673. [Crossref] [Pubmed]

[40] Cantón, R.; Akóva, M.; Carmeli, Y.; Giske, C.G.; Glupczynski, Y.; Gniadkowski, M.; Livermore, D.M.; Miriagou, V.; Naas, T.; Rossolini, G.M.; Et Al. Rapid Evolution And Spread Of Carbapenemases Among Enterobacteriaceae In Europe. Clin. Microbiol. Infect. Off. Publ. Eur. Soc. Clin. Microbiol. Infect. Dis. 2012, 18, 413–431. [Crossref]

[41] Bigdeli, M.; Jacobs, B.; Tomson, G.; Laing, R.; Ghaffar, A.; Dujardin, B.; Van Damme, W. Access To Medicines From A Health System Perspective. Health Policy Plan. 2013, 28, 692–704. [Crossref]

[42] Fischbach, M.A. Combination Therapies For Combating Antimicrobial Resistance. Curr. Opin. Microbiol. 2011, 14, 519–523. [Crossref]

[43] Mohammad Irfan Et.At, "Antimicrobial Resistance And Its Drivers—A ,Review"Antibiotics 2022, 11, 1362. Https://Doi.Org/10.3390/Antibiotics11101362 Https://Www.Mdpi.Com/Journal/Antibiotics

[44] Devasahayam, G.; Scheld, W.M.; Hoffman, P.S. Newer Antibacterial Drugs For A New Century. Expert Opin. Investig. Drugs 2010, 19, 215–234. [Crossref] [Pubmed]

[45] Tackling Drug-Resistant Infections Globally: An Overview Of Our Work/The Review On Antimicrobial Resistance Chaired By Jim O'Neill. Available Online: Https://Wellcomecollection.Org/Works/E8njjeed (Accessed On 11 March 2022).

[46] Woolhouse, M.; Ward, M.; Van Bunnik, B.; Farrar, J. Antimicrobial Resistance In Humans, Livestock And The Wider Environment. Philos. Trans. R. Soc. B Biol. Sci. 2015, 370, 20140083. [Crossref] [Pubmed].

[47] Weir, M.; Raji´C, A.; Dutil, L.; Uhland, C.; Bruneau, N. Zoonotic Bacteria And Antimicrobial Resistance In Aquaculture: Opportunities For Surveillance In Canada. Available Online: Https://Www.Ncbi.Nlm.Nih.Gov/Pmc/Articles/PMC3354819/ (Accessed On 31 January 2022).

[48] Klous, G.; Huss, A.; Heederik, D.J.J.; Coutinho, R.A. Human–Livestock Contacts And Their Relationship To Transmission Of Zoonotic Pathogens, A Systematic Review Of Literature. One Health 2016, 2, 65–76. [Crossref.

[49] Baki

[50] Starr, M.P.; Reynolds, D.M. Streptomycin Resistance Of Coliform Bacteria From Turkeys Fed Streptomycin. Am. J. Public Health Nations Health 1951, 41, 1375–1380. [Crossref] [Pubmed]

[51] Liu, Y.-Y.; Wang, Y.; Walsh, T.R.; Yi, L.-X.; Zhang, R.; Spencer, J.; Doi, Y.; Tian, G.; Dong, B.; Huang, X.; Et Al. Emergence Of Plasmid-Mediated Colistin Resistance Mechanism Mcr-1 In Animals And Human Beings In China: A Microbiological And Molecular Biological Study. Lancet Infect. Dis. 2016, 16, 161–168. [Crossref]

[52] Rhouma, M.; Beaudry, F.; Thériault, W.; Letellier, A. Colistin In Pig Production: Chemistry, Mechanism Of Antibacterial Action, Microbial Resistance Emergence, And One Health Perspectives. Front. Microbiol. 2016, 7, 1789. [Crossref]

[53] Baron, S.; Hadjadj, L.; Rolain, J.-M.; Olaitan, A.O. Molecular Mechanisms Of Polymyxin Resistance: Knowns And Unknowns. Int. J. Antimicrob. Agents 2016, 48, 583–591. [Crossref] [Pubmed]

[54] Karakonstantis, S.; Kritsotakis, E.I.; Gikas, A. Pandrug-Resistant Gram-Negative Bacteria: A Systematic Review Of Current Epidemiology, Prognosis And Treatment Options. J. Antimicrob. Chemother. 2020, 75, 271–282. [Crossref] [Pubmed]

[55] Voss, A.; Loeffen, F.; Bakker, J.; Klaassen, C.; Wulf, M. Methicillin-Resistant Staphylococcus Aureus In Pig Farming. Emerg. Infect. Dis. 2005, 11, 1965–1966. [Crossref] [Pubmed]

[56] Wendlandt, S.; Kadlec, K.; Feßler, A.T.; Monecke, S.; Ehricht, R.; Van De Giessen, A.W.; Hengeveld, P.D.; Huijsdens, X.; Schwarz, S.; Van Duijkeren, E. Resistance Phenotypes And Genotypes Of Methicillin-Resistant Staphylococcus Aureus Isolates From Broiler Chickens At Slaughter And Abattoir Workers. J. Antimicrob. Chemother. 2013, 68, 2458–2463. [Crossref] [Pubmed]

[57] Kadlec, K.; Ehricht, R.; Monecke, S.; Steinacker, U.; Kaspar, H.; Mankertz, J.; Schwarz, S. Diversity Of Antimicrobial Resistance Pheno- And Genotypes Of Methicillin-Resistant Staphylococcus Aureus ST398 From Diseased Swine. J. Antimicrob. Chemother. 2009, 64, 1156–1164. [Crossref]

[58] Prestinaci, F.; Pezzotti, P.; Pantosti, A. Antimicrobial Resistance: A Global Multifaceted Phenomenon. Pathog. Glob. Health 2015, 109, 309–318. [Crossref] [Pubmed]

[59] Melese, A.; Genet, C.; Andualem, T. Prevalence Of Vancomycin Resistant Enterococci (VRE) In Ethiopia: A Systematic Review And Meta-Analysis. BMC Infect. Dis. 2020, 20, 124. [Crossref] [Pubmed]

[60] Werner, G.; Coque, T.M.; Hammerum, A.M.; Hope, R.; Hryniewicz, W.; Johnson, A.; Klare, I.; Kristinsson, K.G.; Leclercq, R.; Lester, C.H.; Et Al. Emergence And Spread Of Vancomycin Resistance Among Enterococci In Europe. Euro Surveill. Bull. Eur. Sur Mal. Transm. Eur. Commun. Dis. Bull. 2008, 13, 19046. [Crossref]

[61] Arias, C.A.; Murray, B.E. The Rise Of The Enterococcus: Beyond Vancomycin Resistance. Nat. Rev. Microbiol. 2012, 10, 266–278. [Crossref] [Pubmed]

[62] Dadashi, M.; Sharifian, P.; Bostanshirin, N.; Hajikhani, B.; Bostanghadiri, N.; Khosravi-Dehaghi, N.; Van Belkum, A.; Darban-Sarokhalil, D. The Global Prevalence Of Daptomycin, Tigecycline, And Linezolid-Resistant Enterococcus Faecalis And Enterococcus Faecium Strains From Human Clinical Samples: A Systematic Review And Meta-Analysis. Front. Med. 2021, 8, 720647. [Crossref] [Pubmed]

[63] Wang, Z.; He, J.; Li, Q.; Tang, Y.; Wang, J.; Pan, Z.; Chen, X.; Jiao, X. First Detection Of NDM-5-Positive Salmonella Enterica Serovar Typhimurium Isolated From Retail Pork In China. Microb. Drug Resist. Larchmt. N 2020, 26, 434–437. [Crossref] [Pubmed]

[64] Díaz, M.Á.; Díaz, P.L.; Rodríguez, E.C.; Montaño, L.A.; Gartner, D.M.; Vernaza, M.E.; Eljach, V.; Realpe, M.E. A Nalidixic Acid-Resistant Salmonella Enteritidis Outbreak In Popayán, Cauca, 2011. Biomed. Rev. Inst. Nac. Salud 2013, 33, 62–69. [Crossref]

[65] Smith, K.E.; Besser, J.M.; Hedberg, C.W.; Leano, F.T.; Bender, J.B.; Wicklund, J.H.; Johnson, B.P.; Moore, K.A.; Osterholm, M.T. Quinolone-Resistant Campylobacter Jejuni Infections In Minnesota, 1992-1998. Investigation Team. N. Engl. J. Med. 1999, 340, 1525–1532. [Crossref] [Pubmed]

[66] Garcia-Migura, L.; Hendriksen, R.S.; Fraile, L.; Aarestrup, F.M. Antimicrobial Resistance Of Zoonotic And Commensal Bacteria In Europe: The Missing Link Between Consumption And Resistance In Veterinary Medicine. Vet. Microbiol. 2014, 170, 1–9. [Crossref]

[67] Marshall, B.M.; Levy, S.B. Food Animals And Antimicrobials: Impacts On Human Health. Clin. Microbiol. Rev. 2011, 24, 718–733. [Crossref] [Pubmed]

[68] Mohammad Irfan Et.Al,Antimicrobial Resistance And Its Drivers—A Review,Antibiotics 2022, 11, 1362. Https://Doi.Org/10.3390/Antibiotics11101362,P.1-18.

[69] Capozzi, C.; Volpi, A.; Maurici, M.; Lisena, F.P.; Visconti, G.; Panà, A. Healthcare-Associated Infections And Antibiotic Resistance: A Global Challenge For The 21st Century. Ig. Sanita Pubblica 2013, 69, 657–691.

[70] Levy, S.B. The Challenge Of Antibiotic Resistance. Sci. Am. 1998, 278, 46–53. [Crossref] [Pubmed]

[71] Crofts, T.S.; Gasparrini, A.J.; Dantas, G. Next-Generation Approaches To Understand And Combat The Antibiotic Resistome. Nat. Rev. Microbiol. 2017, 15, 422–434. [Crossref]

[72] Forsberg, K.J.; Patel, S.; Wencewicz, T.A.; Dantas, G. The Tetracycline Destructases: A Novel Family Of Tetracycline-Inactivating Enzymes. Chem. Biol. 2015, 22, 888–897. [Crossref]

[73] Shaw, W.V.; Packman, L.C.; Burleigh, B.D.; Dell, A.; Morris, H.R.; Hartley, B.S. Primary Structure Of A Chloramphenicol Acetyltransferase Specified By R Plasmids. Nature 1979, 282, 870–872. [Crossref]

[74] Yang, W.; Moore, I.F.; Koteva, K.P.; Bareich, D.C.; Hughes, D.W.; Wright, G.D. Tetx Is A Flavin-Dependent Monooxygenase Conferring Resistance To Tetracycline Antibiotics. J. Biol. Chem. 2004, 279, 52346–52352. [Crossref] 54.

[75] Bush, K. Bench-To-Bedside Review: The Role Of Beta-Lactamases In Antibiotic-Resistant Gram-Negative Infections. Crit. Care Lond. Engl. 2010, 14, 224. [Crossref]

[76] Arias, C.A.; Murray, B.E. The Rise Of The Enterococcus: Beyond Vancomycin Resistance. Nat. Rev. Microbiol. 2012, 10, 266–278. [Crossref] [Pubmed]

[77] Piddock, L.J.V. Clinically Relevant Chromosomally Encoded Multidrug Resistance Efflux Pumps In Bacteria. Clin. Microbiol. Rev. 2006, 19, 382–402. [Crossref]

[78] Roberts, M.C. Tetracycline Resistance Determinants: Mechanisms Of Action, Regulation Of Expression, Genetic Mobility, And Distribution. FEMS Microbiol. Rev. 1996, 19, 1–24. [Crossref]

[79] On The Mechanism Of Solute Uptake In Pseudomonas—Pubmed. Available Online: Https://Pubmed.Ncbi.Nlm.Nih.Gov/12700103/ (Accessed On 22 September 2022).

[80] Babouee Flury, B.; Ellington, M.J.; Hopkins, K.L.; Turton, J.F.; Doumith, M.; Loy, R.; Staves, P.; Hinic, V.; Frei, R.; Woodford, N. Association Of Novel Nonsynonymous Single Nucleotide Polymorphisms In Ampd With Cephalosporin Resistance And Phylogenetic Variations In Ampc, Ampr, Ompf, And Ompc In Enterobacter Cloacae Isolates That Are Highly Resistant To Carbapenems. Antimicrob. Agents Chemother. 2016, 60, 2383–2390. [Crossref] [Pubmed]

[81] Understanding Antibiotic Resistance. Available Online: Https://Www.Open.Edu/Openlearn/Mod/Oucontent/Science-Mathstechnology/Understanding-Antibiotic-Resistance (Accessed On 27 July 2022).

[82] D'Costa, V.M.; Mcgrann, K.M.; Hughes, D.W.; Wright, G.D. Sampling The Antibiotic Resistome. Science 2006, 311, 374–377. [Crossref] [Pubmed] 61.

[83] Vikesland, P.J.; Pruden, A.; Alvarez, P.J.J.; Aga, D.; Bürgmann, H.; Li, X.-D.; Manaia, C.M.; Nambi, I.; Wigginton, K.; Zhang, T.; Et Al. Toward A Comprehensive Strategy To Mitigate Dissemination Of Environmental Sources Of Antibiotic Resistance. Environ. Sci. Technol. 2017, 51, 13061–13069. [Crossref] [Pubmed]

[84] Vikesland, P.; Garner, E.; Gupta, S.; Kang, S.; Maile-Moskowitz, A.; Zhu, N. Differential Drivers Of Antimicrobial Resistance Across The World. Acc. Chem. Res. 2019, 52, 916–924. [Crossref]

[85] Payne, D.J.; Miller, L.F.; Findlay, D.; Anderson, J.; Marks, L. Time For A Change: Addressing R&D And Commercialization Challenges For Antibacterials. Philos. Trans. R. Soc. B Biol. Sci. 2015, 370, 20140086. [Crossref]

[86] Klein, E.Y.; Van Boeckel, T.P.; Martinez, E.M.; Pant, S.; Gandra, S.; Levin, S.A.; Goossens, H.; Laxminarayan, R. Global Increase And Geographic Convergence In Antibiotic Consumption Between 2000 And 2015. Proc. Natl. Acad. Sci. USA 2018, 115, E3463–E3470. [Crossref]

[87] Gasson, J.; Blockman, M.; Willems, B. Antibiotic Prescribing Practice And Adherence To Guidelines In Primary Care In The Cape Town Metro District, South Africa. S. Afr. Med. J. 2018, 108, 304–310. [Crossref] 67.

[88] Sarwar, M.R.; Saqib, A.; Iftikhar, S.; Sadiq, T. Antimicrobial Use By WHO Methodology At Primary Health Care Centers: A Cross Sectional Study In Punjab, Pakistan. BMC Infect. Dis. 2018, 18, 492. [Crossref] 68.

[89] Wang, J.; Wang, P.; Xinghe, W.; Zheng, Y.; Xiao, Y. Use And Prescription Of Antibiotics In Primary Health Care Settings In China. JAMA Intern. Med. 2014, 174, 1914–1920. [Crossref] 69.

[90] Schwartz, K.L.; Langford, B.J.; Daneman, N.; Chen, B.; Brown, K.A.; Mcisaac, W.; Tu, K.; Candido, E.; Johnstone, J.; Leung, V.; Et Al. Unnecessary Antibiotic Prescribing In A Canadian Primary Care Setting: A Descriptive Analysis Using Routinely Collected Electronic Medical Record Data. CMAJ Open 2020, 8, E360. [Crossref] .

[91] Richard, V.M.; Jonathan, K.W.; Jonathan, E.; Jonathan, H.; Pedro, C.; Jefferson, B. Reducing Inappropriate Outpatient Antibiotic Prescribing: Normative Comparison Using Unblinded Provider Reports. BMJ Open Qual. 2019, 8, E000351. [Crossref]

[92] Wang, J.; Wang, P.; Xinghe, W.; Zheng, Y.; Xiao, Y. Use And Prescription Of Antibiotics In Primary Health Care Settings In China. JAMA Intern. Med. 2014, 174, 1914–1920. [Crossref].

[93] Kariyawasam, R.M.; Julien, D.A.; Jelinski, D.C.; Larose, S.L.; Rennert-May, E.; Conly, J.M.; Dingle, T.C.; Chen, J.Z.; Tyrrell, G.J.; Ronksley, P.E.; Et Al. Antimicrobial Resistance (AMR) In COVID-19 Patients: A Systematic Review And Meta-Analysis (November 2019–June 2021). Antimicrob. Resist. Infect. Control 2022, 11, 45. [Crossref] [Pubmed

[94] WHO Publishes List Of Bacteria For Which New Antibiotics Are Urgently Needed. Available Online: Https://Www.Who.Int/News/Item/27-02-2017-Who-Publishes-List-Of-Bacteria-For-Which-New-Antibiotics-Are-Urgently-Needed (Accessed On 22 July 2022).

[95] National Research Council (US); Committee To Study The Human Health Effects Of Subtherapeutic Antibiotic Use In Animal Feeds. The Effects On Human Health Of Subtherapeutic Use Of Antimicrobials In Animal Feeds; National Academies Press: Washington, DC, USA, 1980

[96] Fifth OIE Annual Report On Antimicrobial Agents Intended For Use In Animals. Available Online: Https://Www.Woah.Org/En/Document/Fifth-Oie-Annual-Report-On-Antimicrobial-Agents-Intended-For-Use-In-Animals/ (Accessed On 10 June 2022).

[97] Tiseo, K.; Huber, L.; Gilbert, M.; Robinson, T.P.; Van Boeckel, T.P. Global Trends In Antimicrobial Use In Food Animals From 2017 To 2030. Antibiotics 2020, 9, 918. [Crossref]

[98] Regulation (EC) No 1831/2003 Of The European Parliament And Of The Council. Available Online: Https://Eur-Lex.Europa.Eu/Eli/Reg/2003/1831/Oj/Eng (Accessed On 23 September 2022).

[99] U.S. Food And Drug Administration. Food Code 2013. Available Online: Https://Www.Fda.Gov/Food/Fda-Food-Code/Food-Code-2013 (Accessed On 12 March 2022).

[100] Ejo, M.; Garedew, L.; Alebachew, Z.; Worku, W. Prevalence And Antimicrobial Resistance Of Salmonella Isolated From Animal Origin Food Items In Gondar, Ethiopia. Biomed Res. Int. 2016, 2016, 4290506. [Crossref]

[101] Rasheed, M.U.; Thajuddin, N.; Ahamed, P.; Teklemariam, Z.; Jamil, K. Antimicrobial Drug Resistance In Strains Of Escherichia Coli Isolated From Food Sources. Rev. Inst. Med. Trop. São Paulo 2014, 56, 341–346. [Crossref]

[102] Kahrilas, G.A.; Blotevogel, J.; Stewart, P.S.; Borch, T. Biocides In Hydraulic Fracturing Fluids: A Critical Review Of Their Usage, Mobility, Degradation, And Toxicity. Environ. Sci. Technol. 2015, 49, 16–32. [Crossref]

[103] Buffet-Bataillon, S.; Tattevin, P.; Bonnaure-Mallet, M.; Jolivet-Gougeon, A. Emergence Of Resistance To Antibacterial Agents: The Role Of Quaternary Ammonium Compounds—A Critical Review. Int. J. Antimicrob. Agents 2012, 39, 381–389. [Crossref]

[104] Poole, K. Mechanisms Of Bacterial Biocide And Antibiotic Resistance. J. Appl. Microbiol. 2002, 92 (Suppl. S1), 55S–64S. [Crossref]

[105] Hugo, W.B.; Longworth, A.R. Effect Of Chlorhexidine Diacetate On "Protoplasts" And Spheroplasts Of Escherichia Coli, Protoplasts Of Bacillus Megaterium And The Gram Staining Reaction Of Staphylococcus Aureus. J. Pharm. Pharmacol. 1964, 16, 751–758. [Crossref]

[106] Mcdonnell, G.; Russell, A.D. Antiseptics And Disinfectants: Activity, Action, And Resistance. Clin. Microbiol. Rev. 1999, 12, 147–179. [Crossref]

[107] Russell, A.D. Mechanisms Of Bacterial Resistance To Biocides. Int. Biodeterior. Biodegrad. 1995, 36, 247–265. [Crossref]

[108] Brown, M.R.; Gilbert, P. Sensitivity Of Biofilms To Antimicrobial Agents. J. Appl. Bacteriol. 1993, 74 (Suppl. S22), 87S–97S. [Crossref] [Pubmed]

[109] Similar To Antibiotic Resistance, The Development Of Biocide Resistance Is Mutational Or Acquired [87–89].

[110] Mcmurry, L.M.; Mcdermott, P.F.; Levy, S.B. Genetic Evidence That Inha Of Mycobacterium Smegmatis Is A Target For Triclosan. Antimicrob. Agents Chemother. 1999, 43, 711–713. [Crossref] [Pubmed] 88.

[111] Sasatsu, M.; Shirai, Y.; Hase, M.; Noguchi, N.; Kono, M.; Behr, H.; Freney, J.; Arai, T. The Origin Of The Antiseptic-Resistance Gene Ebr In Staphylococcus Aureus. Microbios 1995, 84, 161–169.

[112] Russell, A.D. Plasmids And Bacterial Resistance To Biocides. J. Appl. Microbiol. 1997, 83, 155–165. [Crossref]

[113] Prince, H.N.; Nonemaker, W.S.; Norgard, R.C.; Prince, D.L. Drug Resistance Studies With Topical Antiseptics. J. Pharm. Sci. 1978, 67, 1629–1631. [Crossref] 91.

[114] Fitzgerald, K.A.; Davies, A.; Russell, A.D. Sensitivity And Resistance Of Escherichia Coli And Staphylococcus Aureus To Chlorhexidine. Lett. Appl. Microbiol. 1992, 14, 33–36. [Crossref]

[115] Silver, S.; Misra, T.K. Plasmid-Mediated Heavy Metal Resistances. Annu. Rev. Microbiol. 1988, 42, 717–743. [Crossref]

[116] Vijayakumar, R.; Sandle, T. A Review On Biocide Reduced Susceptibility Due To Plasmid-Borne Antiseptic-Resistant Genes—Special Notes On Pharmaceutical Environmental Isolates. J. Appl. Microbiol. 2019, 126, 1011–1022. [Crossref]

[117] Mcdonnell, G.; Russell, A.D. Antiseptics And Disinfectants: Activity, Action, And Resistance. Clin. Microbiol. Rev. 1999, 12, 147–179. [Crossref]

[118] Regulation (EU) No 528/2012 Of The European Parliament And Of The Council Of 22 May 2012 Concerning The Making. Market And Use Of Biocidal Products Text With EEA Relevance. 2012. L 167/1, Pp. 1–123. Available Online: Https://Www.Legislation.Gov. Uk/Eur/2012/528/Contents (Accessed On 28 July 2022).

[119] Sattar, S.A.; Tetro, J.A.; Springthorpe, V.S. Effects Of Environmental Chemicals And The Host-Pathogen Relationship: Are There Any Negative Consequences For Human Health? In New Biocides Development; ACS Symposium Series; American Chemical Society: New York, NY, USA, 2007; Volume 967, Pp. 2–30. ISBN 978-0-8412-7405-1

[120] Rappuoli R, Bloom DE, Black S (2017) Deploy Vaccines To Fight Superbugs. Nature 552:165–167

[121] Stephen J. Baker,Et.Al, "Technologies To Address Antimicrobial Resistance".Www.Pnas.Org/Cgi/Doi/10.1073/Pnas.1717160115 PNAS | December 18, 2018 | Vol. 115 | No. 51 | 12887–12895

[122] Delany I, Rappuoli R, De Gregorio E (2014) Vaccines For The 21st Century. EMBO Mol Med 6:708–720

[123] Czaplewski L, Et Al. (2016) Alternatives To Antibiotics–A Pipeline Portfolio Review. Lancet Infect Dis 16:239–251.

[124] Fairhead H, Wilkinson A, Severi E (2017) US Patent WO 2017/174809, A1

[125] Sahota JS, Et Al. (2015) Bacteriophage Delivery By Nebulization And Efficacy Against Phenotypically Diverse Pseudomonas Aeruginosa From Cystic Fibrosis Patients. J Aerosol Med Pulm Drug Deliv 28:353–360.

[126] Nale JY, Et Al. (2015) Bacteriophage Combinations Significantly Reduce Clostridium Difficile Growth In Vitro And Proliferation In Vivo. Antimicrob Agents Chemother 60:968–981.

[127] Rastogi V, Et Al. (2018) An Overview On Bacteriophages: A Natural Nanostructured Antibacterial Agent. Curr Drug Deliv 15:3–20

[128] Khanna S, Et Al. (2016) A Novel Microbiome Therapeutic Increases Gut Microbial Diversity And Prevents Recurrent Clostridium Difficile Infection. J Infect Dis 214:173–181.

[129] Gerding DN, Et Al. (2015) Administration Of Spores Of Nontoxigenic Clostridium Difficile Strain M3 For Prevention Of Recurrent C. Difficile Infection: A Randomized Clinical Trial. JAMA 313:1719–1727

[130] Vedanta Biosciences (2017) Vedanta Biosciences Announces Initiation Of Phase 1a/1b Trial For New Drug Class Of Rationally-Defined Bacterial Consortia Derived From The Human Microbiome. Available At Https://Www.Vedantabio.Com/News-Media/Press-Releases/Detail/2298/Vedanta-Biosciences-Announces-Initiation-Ofphase-1a1b. Accessed August 1, 2018

[131] Pirofski LA, Casadevall A (2006) Immunomodulators As An Antimicrobial Tool. Curr Opin Microbiol 9:489–495

[132] Smith SB, Magid-Slav M, Brown JR (2013) Host Response To Respiratory Bacterial Pathogens As Identified By Integrated Analysis Of Human Gene Expression Data. Plos One 8:E75607
[133] Pegu A, Hessell AJ, Mascola JR, Haigwood NL (2017) Use Of Broadly Neutralizing Antibodies For HIV-1 Prevention. Immunol Rev 275:296–312.
[134] Digiandomenico A, Et Al. (2014) A Multifunctional Bispecific Antibody Protects Against Pseudomonas Aeruginosa. Sci Transl Med 6:262ra155
[135] Kummerfeldt CE (2014) Raxibacumab: Potential Role In The Treatment Of Inhalational Anthrax. Infect Drug Resist 7:101–109.
[136] Lowy I, Et Al. (2010) Treatment With Monoclonal Antibodies Against Clostridium Difficile Toxins. N Engl J Med 362:197–205
[137] Czaplewski L, Et Al. (2016) Alternatives To Antibiotics–A Pipeline Portfolio Review. Lancet Infect Dis 16:239–251
[138] Hey A (2015) History And Practice: Antibodies In Infectious Diseases. Microbiol Spectr 3:AID-0026-2014.
[139] Hey A (2015) History And Practice: Antibodies In Infectious Diseases. Microbiol Spectr 3:AID-0026-2014.
[140] Baker Et Al. | Www.Pnas.Org/Cgi/Doi/10.1073/Pnas.1717160115 ,12894
[141] Majusi AIA. Kamil Al-Sana'a. Idara Kitabus Shifa. New Delhi 2011.
[142] Mudasir Khazir Et.Al, "Antimicrobial Activity Of 'Qurs-Afsanteen': A Classical Unani Tablet Formulation Prepared From Artemisia Absinthium "International Journal Of Applied Research 2021; 7(10): 240-246
[143] Panseeta P, Lomchoey K, Prabpai S, Kongsaeree P, Suksamrarn A, Ruchirawat S, Et Al. Antiplasmodial And Antimicobacterial Cyclopeptide Alkaloids From The Root Of Ziziphus Mauritiana. Phytochem 2011;72:909- 915.
[144] Dr. Khem Chand Et.At,The Therapeutic Potential Of Mazu (Quercus Infectoria) In The Unani System Of Medicine: A Comprehensive Review,Journal Of Medicinal Plants Studies 2024; 12(1): 231-234.
[145] Bauer AW, Kirby WM, Sherris JC And Turck M (1966), Antibiotic Susceptibility Testing By A Standardized Single Disk Method, Am J Clin Pathol. 45: 493-496.
[146] Haque SS, Rashid MM, Prodhan MA, Noor S And Das A (2014), In Vitro Evaluation Of Antimicrobial, Cytotoxic And Antioxidant Activities Of Crude Methanolic Extract And Other Fractions Of Sterculia Villosa Barks, J Appl Pharm Sci. DOI: Org/10.7324/JAPS.2014.40308
[147] M. S. Hossain Et.Al, "Antibacterial, Antioxidant, Anti-Inflammatory And Anti-Diarrheal Potentiality Evaluation Of Whole Plant Extract Of Phyllanthus Niruri L"Bangladesh J. Sci. Ind. Res. 59(4), 195-204, 2024.Available Online At Www.Banglajol.Info/Index.Php/BJSIR .
[148] Balakumbahan, R., Rajamani, K., & Kumanan, K. (2010). Acorus Calamus: An Overview. Journal Of Medicinal Plants Research, 4(25), 2740-2745.
[149] Nidhi Bisen Et.Al, "ANTIMICROBIAL PROPERTIES OF SOME IMPORTANT MEDICINAL PLANTS"AYUSHDHARA,An International Journal Of Research In AYUSH And Allied Systems,ISSN: 2393-9583 (P)/ 2393-9591 (O).
[150] Dash, M., Patra, J. K., & Panda, P. P. (2008). Phytochemical And Antimicrobial Screening Of Extracts Of Aquilaria Agallocha Roxb. African Journal Of Biotechnology, 7(20).
[151] Pokhrel, B., Rijal, S., Raut, S., & Pandeya, A. (2015). Investigations Of Antioxidant And Antibacterial Activity Of Leaf Extracts Of Azadirachta Indica. African Journal Of Biotechnology, 14(46), 3159- 3163.
[152] Ayesha Mateen Et.Al, "A Study Of Antimicrobial Activity Of Few Medicinally Important Herbal Single Drugs Extracted In Ethanol, Methanol And Aqueous Solvents" June 2010 I Vol 2 I Issue 1, Free Access : Available Online
[153] Sumbul Rehman Et.Al, "ANTIBACTERIAL POTENTIAL OF BISEHRI BOOTI (AREVA LANATA LINN. JUSS.)"Pharmacophore (An International Research Journal) Pharmacophore 2016, Vol. 7 (2), 74-81 Available Online At Http://Www.Pharmacophorejournal.Com/
[154] Anonymous, 2011. National Formulary Of Unani Medicine, Part-VI. Ministry Of Health And Family Welfare, Deptt. Of AYUSH, Govt. Of India, New Delhi, Pp. 34, 67, 70-71, 123.
[155] Anonymous, 2007. National Formulary Of Unani Medicine, Part-II. Ministry Of Health And Family Welfare, Deptt. Of AYUSH, Govt. Of India, New Delhi, P. 42.
[156] Anonymous, 2008. National Formulary Of Unani Medicine, Part-V. Ministry Of Health And Family Welfare, Deptt. Of AYUSH, Govt. Of India, New Delhi, P. 56.
[157] Aziz Ur Rahman. "Antimicrobial Assay Of Alcoholic And Hydroalcoholic Extract Of A Unani Formulation By Agar Well Method "Hippocratic Journal Of Unani Medicine 59 January - March 2013, Vol. 8 No. 1, Pages.