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A COMPREHENSIVE REVIEW OF ANTIMICROBIAL RESISTANCE BEGINNING FROM THE DISCOVERY OF THE FIRST ANTIBIOTIC UNTIL THE PRESENT-DAY SITUATION WITH ONE HEALTH APPROACH WITH SPECIAL EMPHASIS ON BANGLADESH

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ABSTRACT

Background: Antimicrobial resistance (AMR) has become an emerging multifactorial and complex issue globally in both livestock and public health, especially more health risk in low-income countries including Bangladesh. The antibiotic-resistant bacteria (ARB) and antibiotic resistance gene (ARG) that confer resistance are transmitted and circulated within humans, animals, and the environment. Both the complex AMR and 'One Health' connect humans, animals, and the environment, which needs to be effectively addressed in all three interconnected domains of health. This article gives a comprehensive review of the antibiotic era, beginning from the discovery of the first antibiotics until the present-day situation including multidrug resistance (MDR) status with special reference to Bangladesh within the 'One Health' concept.

Objectives: This comprehensive review was carried out to describe an updated overview of AMR and associated risk factors in livestock and human health within one health approach in Bangladesh.

Methods: Review and research articles (n = 315) related to AMR published from Bangladesh (n = 156) and elsewhere (n = 159) in English language have been reviewed through Google search including, Cross-Ref, PubMade, and Bangladesh Journals online by using possible relevant keywords to identify the articles. Findings of antibiotic discovery and mode of action, development of resistance and its mechanism, drivers and risk factors, and measures against AMR including the 'One Health' approach have been reviewed and analyzed

Results: This review of AMR beginning from the discovery of the first antibiotic penicillin until the present-day situation with the 'One Health' approach has been reviewed based on 315 published research reports and their data are analyzed and presented in 51 tables with a high prevalence of AMR in both human and veterinary medicine and their results are discussed. Antimicrobials have diverse applications in different fields including aquaculture, livestock and crop production, and the prevention and treatment of human and livestock diseases, and overuse and misuse of antibiotics lead to the development of antibiotic-resistant bacteria that persist in the affected hosts and their environment. These resistant bacteria are shared between livestock and humans through food and environmental exposure. These resistant bacteria usually persist and circulate through contaminated environments associated with a significant threat to human and animal health. The antibiotic-resistant bacteria contain resistant genes that act as primary drivers (risk factors) which can transfer naturally or through human activities. Surveillance and rapid detection of antimicrobial-resistant bacteria are essential for judicious use of appropriate antibiotics only when necessary and preventing transmission of resistant bacteria will certainly help to prevent the AMR.

Conclusions: A high prevalence of AMR, especially in most antibiotics, has been reported from Bangladesh with limited routine antibiogram surveillance reports. Although 178 countries have developed national action plans, fewer than a fifth are funded or implemented. However, several international organizations including WHO, FAO, and World Organization for Animal Health (WOAH/OIE) have now included a 'One Health' approach within their action plans to address AMR, which action program would be required in medium and low-income countries including Bangladesh where the highest percentage of AMR occurs in both human and veterinary patients. The 'One Health' approach is important for AMR because resistant pathogens can spread quickly through livestock and human healthcare facilities, food, and environment (soil and water), making the treatment and prevention of certain infections shared between livestock and humans more challenging, and increasing the risk of disease spread, severe illness, and death. The judicial use of antimicrobials based on better regulation and policy, improved surveillance, stewardship, infection control, livestock husbandry practices, and finding new antibiotics and alternatives to antimicrobials including vaccines should be included in the action plan to prevent and spread the AMR in the environment. It may be concluded that the collaboration among human, livestock, and environmental health sectors by adopting a 'One Health' approach is important to achieve sustainable and long-lasting results.

Keywords: Review, Antimicrobial resistance, Veterinary medicine, Human medicine, 'One Health', Bangladesh

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INTRODUCTION

There are 2 to 3 billion microbe species, of which 1,415 species are pathogenic and induce infectious diseases in humans, animals, and plant hosts. Microorganisms have provided abundant sources of natural products which have developed as commercial products for human and veterinary medicine, and plant crop production. Alexander Fleming discovered that a specific mold species inhibited the development of Staphylococcus bacteria in 1928, and followed by Howard Florey and Ernst Chain worked out the industrial production of penicillin in 1940. All three researchers were awarded the Nobel Prize in 1945, and since then the era of antibiotics has been initiated. In 1935, Gerhard Domagk discovered the first sulfonamide- prontosil rubrum, and four years later he received the Nobel Prize. However, the first antibacterial, salvarsan, was developed in 1910 and for approximately 100 years antibiotics have drastically changed modern medicine and extended the average human lifespan by 23 years.[1] Since then, a gradual decline in antibiotic discovery and development and the evolution of drug resistance in many medical and veterinary pathogens has led to the current antimicrobial resistance crisis.[1] Humans developed antimicrobials to destroy disease-causing microbes (pathogens) and antimicrobial resistance (AMR) occurs when microbes resist the effects of antimicrobials. The first antibiotic was penicillin, discovered accidentally from a mold culture. Today, over 100 different antibiotics are available to cure minor, and life-threatening infections. Although there are well over 100 antibiotics, these antibiotics belong to the seven classes, which include ① Penicillins such as penicillin and amoxicillin, ② Cephalosporins such as cephalexin, ③ Macrolides such as erythromycin, clarithromycin, and azithromycin, ④ Fluoroquinolones such as ciprofloxacin, levofloxacin, and ofloxacin, ⑤ Sulfonamides such as co-trimoxazole and trimethoprim, ⑥ Tetracyclines such as tetracycline, oxytetracycline, and doxycycline and ⑦ Aminoglycosides such as gentamicin and tobramycin. Antimicrobials including antibiotics, antivirals, antifungals, and antiparasites, are medicines used to treat and prevent infectious diseases in humans, animals, and plants. Antibacterial is a drug, chemical, or other substance that kills bacteria (bactericidal) or stops their growth (bacteriostatic). Antibiotics are an important class of antibacterials used more specifically for the treatment and prevention of bacterial diseases. The discovery of penicillin in 1928 started the golden age of natural product antibiotic discovery that peaked in the mid-1950s. Since then, over 100 antibiotics have been developed and used but a gradually developed antibiotic resistance in most of the bacterial pathogens of livestock and humans has led to the current antibacterial resistance crisis globally.[1] AMR represents a global challenge of 4.95 million people who died in 2019 suffering from drug-resistant infections, AMR directly caused 1.27 million of those deaths, and 1 in 5 of those deaths occurred among children under five years old, whereas in Bangladesh in 2019, there were 26,200 deaths attributable to AMR and 98,800 deaths associated with AMR. Bangladesh has the 130th highest age-standardized mortality rate per 100,000 population associated with AMR across 204 countries.[2] In addition to over 50 years of research articles on ARB published in Bangladesh, some review articles on ABR with a limited period of study including 2004 to 2018,[3] 2010 to 2019,[4] 2015 to 2019,[5] 2004 to 2020[6] have been utilized. Therefore this paper describes a comprehensive overview of AMR beginning from the discovery of the first antibiotic until the present-day situation with the 'One Health' approach in Bangladesh.

Uses of antimicrobials

Antimicrobials are utilized in a variety of sectors, including agricultural activities (prevention of crop loss from bacterial diseases), aquaculture (treatment of fish diseases), veterinary and animal husbandry practices (treatment of bacterial infections and growth promoting agents), and human health (treatment of bacterial infections). The use of antibacterials in livestock is classified into three categories therapeutic agents (high doses), prophylactic agents (sub-therapeutic doses), and growth promoters (low amount of antibiotic is regularly used through its feed).

Table 1 shows the origin and classification of antimicrobial agents. Table 2 shows the classification of antibiotics based on the mode of action. Each antibiotic is effective only for certain types of infections. Cell wall synthesis is inhibited by β-lactams, such as penicillins and cephalosporins, which inhibit peptidoglycan polymerization, and by vancomycin, which combines with cell wall substances. Polymyxins disrupt the plasma

membrane, causing leakage. The plasma membrane sterols of fungi are attacked by polyenes (amphotericin) and imidazoles. Quinolones bind to a bacterial complex of DNA and DNA gyrase, blocking DNA replication. Nitroimidazoles damage DNA and Rifampin blocks RNA synthesis by binding DNA-directed RNA polymerase. Aminoglycosides, tetracycline, chloramphenicol, erythromycin, and clindamycin all interfere with ribosome function. Sulfonamides and trimethoprim block the synthesis of the folate needed for DNA replication.

Table 1. Origins and classification of antimicrobial agents[7]

S/N	Antimicrobial class	Antimicrobial agents	Producing organisms	Year(s) of isolation/report
01.	β-lactam antibiotics	Natural penicillins	*Penicillium notatum, Penicillium chrysogenum*	1929, 1940
		Cephalosporin C	*Cephalosporium acremonium*	1945, 1953
		Imipenem	*Streptomyces cattleya*	1976
		Azetreonam	*Gluconobacter* spp., *Chromobacterium violaceum*	1981
02.	Glycopeptides	Vancomycin	*Amycolatopsis orientalis*	Mid-1950s
		Teicoplanin, Avoparcin	*Amycolatopsis coloradensis subsp. labeda*	1975
03.	Macrolides	Erythromycin	*Streptomyces erythreus*	1952
		Spiramycin	*Streptomyces ambofaciens*	1955
04.	Lincosamides	Lincomycin	*Streptomyces lincolnensis*	1963
05.	Streptogramins	Streptogramin A + B	*Streptomyces diastaticus*	1953
		Virginiamycin A + B	*Streptomyces virginiae*	1955
06.	Tetracyclines	Chlortetracycline	*Streptomyces aureofaciens*	1948
		Oxytetracycline	*Streptomyces rimosus*	1950
07.	Phenicols	Chloramphenicol	*Streptomyces venezuelae*	1947
08.	Aminoglycosides	Streptomycin	*Streptomyces griseus*	1943
		Neomycin	*Streptomyces fradiae*	1943
		Kenamycin	*Streptomyces kanamyceticus*	1957
		Gentamicin	*Micromonospora purpura*	1963
		Tobramycin	*Streptomyces tenebrarius*	1961
09.	Aminocyclitols	Spectinomycin	*Streptomyces spectabilis*	1961
10.	Pleuromutilins	Pleuromutilin, Tiamulin	*Pleurotus* spp., Synthetic	1951, 1976
11.	Polypeptide antibiotics	Polymyxin B	*Bacillus polymyxa (aerosporus)*	1947
		Polymyxin E (colistin)	*Bacillus polymyxa (aerosporus)*	1947
		Bacitracin	*Bacillus licheniformis*	1943
12.	Epoxide antibiotics	Fosfomycin	*Streptomyces fradiae, S, wedmorensis, Pseudomonas syringae*	1969
13.	Pseudomonic acid	Mupirocin	*Pseudomonas fluorescens*	1971
13.	Steroid antibiotics	Fusidic acid	*Fusidium coccineum*	1960
14.	Streptothricins	Nourseothricin	*Streptomyces noursei*	1963
15.	Sulfonamides	Prontosil, Sulfamethoxazole etc,	Synthetic	1935
16.	Trimethoprim	Trimethoprim	Synthetic	1956
17.	Quinolones	Nalidixic acid	Synthetic	1962
18.	Fluoroquinolones	Flumequine, enrofloxacin	Synthetic	1973
19.	Oxazolidinones	Linezolid	Synthetic	1987, 1996

Table 2. Classification of antibiotics based on the mode of action [8]

SN	Mechanism of action	Antibiotic class		
1.	Inhibition of bacterial cell wall synthesis	•Penicillins	•Cephalosporins	•Monobactams
		•Carbapenems	• Glycopeptides	•Polypeptides
2.	Depolarization of the bacterial cell membrane	•Lipopeptides		
3.	Inhibition of protein synthesis- binding to 30S ribosomal subunits	•Aminoglycosides	•Tetracyclines	
4.	Inhibition of protein synthesis- binding to 50S ribosomal subunits	•Macrolides	•Amphenicols	•Lincosamides
		•Streptogramin	•Oxazolidinedione	
5.	Inhibition of DNA synthesis	•Quinolones	•Fluoroquinolones	•Nitroimidazoles
6.	Inhibition of RNA synthesis	•Rifamycins		

Table 3 shows the main mechanism of bacterial resistance of different classes of antibiotics. Table 4 shows the clinically important drug-resistant bacteria.

Table 3. The main mechanism of bacterial resistance of different classes of antibiotics [8]

S/N	Mechanism of resistance Primary	Secondary	Classes / Examples			
1.	Altered target	PBP	β-lactams:	•Penicillins	•Cephalosporins	•Carbapenems
				•Monobactams		
		Peptidoglycan biosynthesis (D-Ala-D-Ala ligase)	Glycopeptides:	•Vancomycin	•Teicoplanin	
		Overproduction of capsular polysaccharide	Cationic peptides:	•Colistin	•Polymyxin E	
		Lipopolysaccharides from bacterial outer membrane	Cationic peptides:	•Colistin	•Polymyxin E	
			Aminoglycosides:	•Amikacin	• Gentamicin	• Kanamycin
				• Spectinomycin	•Streptomycin	•Tobramycin
			Macrolides:	•Erythromycin	• Clarithromycin	•Azithromycin
		Ribosomal subunit	Tetracyclines:	•Tetracycline	•Doxycycline	•Minocycline
				•Tigecycline		
			Streptogramins:	• Quinupristin	•Dalfopristin	
			Oxazolidinones:	•Linezolid		
			Lincosamides:	•Clindamycin		
		DNA gyrase	Fluoroquinolones:	•Ciprofloxacin	• Ofloxacin	•Levofloxacin
				•Sparfloxacin		
		RNA polymerase	Rifamycins:	• Rifampin		
		Folate inhibitors	Folate inhibitors:	•Trimethoprim	•Sulfonamides	
2.	Ffflux pumps	Reduction of antibiotic absorption	Aminoglycosides:	•Amikacin	•Gentamicin	•Kanamycin
				•Spectinomycin	•Streptomycin	•Tobramycin
			β-lactams:	•Penicillins	•Cephalosporins	•Carbapenems
				•Monobactams		
			Tetracyclines	•Tetracycline	•Doxycycline	•Minocycline
				•Tigecycline		
			Streptogramins:	• Quinupristin	•Dalfopristin	
			Oxazolidinones:	•Linezolid		
			Lincosamides:	•Clindamycin		
			Fluoroquinolones:	•Ciprofloxacin	•Ofloxacin	•Levofloxacin
				•Sparfloxacin		
			Folate inhibitors:	•Trimethoprim	•Sulfonamides	
			Macrolides:	•Erythromycin	•Clarithromycin	•Azithromycin
			Cationic peptides:	• Colistin	•Polymyxin E	
			Rifamycins:	•Rifampicin		
		Hydrolysis	β-lactams:	•Penicillins	•Cephalosporins	•Carbapenems
				•Monobactams		
			Macrolides:	•Erythromycin	•Clarithromycin	•Azithromycin
		Acetylation	Aminoglycosides:	• Amikacin	•Gentamicin	•Kanamycin
				•Spectinomycin	•Streptomycin	•Tobramycin
			Fluoroquinolones:	•Ciprofloxacin	•Ofloxacin	•Levofloxacin
				•Sparfloxacin		
			Streptogramins:	•Quinupristin	•Dalfopristin	
		Carbon-Oxygen lyase	Streptogramines:	•Quinupristin	•Dalfopristin	
3.	Enzymes	Phosphorylation	Lincosamides:	•Clindamycin		
			Macrolides:	•Erythromycin	•Clarithromycin	•Azithromycin
			Aminoglycosides:	•Amikacin	•Gentamicin	•Kanamycin
				•Spectinomycin	•Streptomycin	•Tobramycin
		Glycosylation	Macrolides:	•Erythromycin	•Clarithromycin	•Azithromycin
		Nucleotidylation	Lincosamides:	•Clindamycin		
			Aminoglycosides:	• Amikacin	•Gentamicin	•Kanamycin

Hydroxylation (under FAD-requiring Monooxygenases Tetx and TetX2)	Tetracyclines	•Spectinomycin •Tetracycline •Tigecycline	•Streptomycin •Doxycycline	•Tobramycin •Minocycline

WHO Global Priority Pathogens List of antibiotic-resistant bacteria

Table 4 shows the WHO global priority pathogen list of antibiotic-resistant bacteria. More recently WHO has covered 24 pathogens, spanning 15 families of antibiotic-resistant bacteria especially drug-resistant *Mycobacterium tuberculosis* with other Gram-negative bacteria like *Salmonella* spp., *Shigella* spp., *Neisseria gonorrhoeae*, *Pseudomonas aeruginosa*, and *Staphylococcus aureus*.

Table 4. Who's global priority pathogens list of antibiotic-resistant bacteria[9]

Priority Bacterial pathogens	Antimicrobials	Resistance bacteria	Mechanism of resistance
Priority 1: Critical			
•*Acinetobacter baumannii*	Carbapenem	Carbapenem-resistant (CR)	-
• *Pseudomonas aeruginosa*	Multiple drugs	CR, Multiple drug resistance proteins (MDRPs)	Multiple factors including loss of porin, drug efflux pump and drug-modifying enzyme
		Metallo-β-lactamase-producing bacteria	Drug-degrading enzyme
• Enterobacteriaceae (e.g. *E. coli*)	β-lactam (carbapenem)	ESBL-producing bacteria	Drug-degrading enzyme
	Quinolone	Quinolone-resistant *E. coli*	Mutation in target (gyrA, parC)
Priority 2: High			
•*Enterococcus faecium*	Vancomycin	VRE	Consequent changes in target (vanA, vanB)
•*Staphylococcus aureus*	β-lactam (methicillin)	MRSA	Production of an additional enzyme that avoids drug binding (PBP2′)
	Vancomycin	VISA (VRSA)	Thickening of cell wall, Consequent changes in target
• *Helicobacter pylori*	Clarithromycin	-	(vanA, vanB, etc.)
•*Campylobacter* spp.	Fluoroquinolone	-	-
•Salmonellae	Fluoroquinolone	-	-
•*Neisseria gonorrhoeae*	Cephalosporin	Quinolone-resistant	Mutation in target (gyrA, parC)
Priority 3: Medium			
• *Streptococcus pneumoniae*	Penicillin	PISP / PRSP	Mutation in target (PBP)
	Macrolide	Macrolid-resistant *S. pneumoniae*	Modification of target (erm) Drug efflux pump (mef)
•*Haemophilus influenzae*	Ampicillin	BLNAR	Mutation in target (Penicillin-binding proteins)

VRE = Vancomycin-resistant Enterococci MRSA = Methicillin-resistant Staphylococcus aureus
VISA (VRSA) = Vancomycin-intermediate Staphylococcus aureus (Vancomycin-resistant Staphylococcus aureus)
PISP = Penicillin intermediate S. pneumoniae PRSP = Penicillin-resistant S. pneumoniae
BLNAR = β-lactamase-negative, ampicillin resistant

Microbes including bacteria can get resistance by mutating or by 'horizontal' transfer of resistance genes from already resistant microbes, even from very different species. Whenever microbes are exposed to antimicrobials (even for a short period), the selection pressure (evolution) inexorably results in the emergence of microbes that are resistant to the antimicrobials. These microbes and their AMR will then spread. The emergence and spread of AMR may take years, but resistance can also appear within days.[10] Pathogens can be resistant to several antimicrobials; a multidrug-resistant infection is harder to treat because fewer effective drugs are available and even treatment may be impossible. Drug resistance has been rising rapidly for certain highly prevalent infectious diseases, including gonorrhea, malaria, and tuberculosis.[10]

Antibiotics are antimicrobial agents defined as chemical substances produced by a microorganism that kills or inhibits the growth of another microorganism. Antimicrobials are drugs including antibiotics, antivirals, antifungals, and anti-parasitics, widely used to prevent and treat diseases, caused by microbes and parasites in humans, animals, aquaculture, and crop production. Their effectiveness is now in jeopardy because several

antimicrobial treatments that once worked no longer do so because microorganisms have become resistant to them. The AMR occurs when a micro-organism survives despite being exposed to antimicrobials designed to inhibit or kill it. The AMR occurs when microorganisms including bacteria, viruses, fungi, or parasites become resistant to antimicrobial treatment to which they were previously susceptible.[11]

Increased use and misuse of antimicrobials and other microbial stressors like pollution, create favorable conditions for microorganisms to develop resistance in humans, animals, and the environment. Bacteria in water, soil, and air can acquire resistance following contact with resistant bacteria human exposure to ARB in the environment can occur through contact with polluted waters, contaminated food, inhalation of fungal spores, and other pathways that contain antibiotic-resistant pathogens.

The ARB occurs when bacteria undergo adaptive evolutionary changes that enable them to withstand antibiotics, and no longer respond to antibiotics such drugs become ineffective, and infections become difficult or impossible to treat, increasing the risk of disease spread, severe illness, disability, and death.[12] ARB is a global public health concern associated with both health and economic implications. The global increase in ABR is considered one of the greatest public health and development threats, with a higher burden in low- and middle-income countries including Bangladesh. The WHO considers antibiotic resistance as one of the top 10 global public health threats facing humanity. It is estimated that ARB was directly responsible for 1.27 million global deaths in 2019 and contributed to 4.95 million deaths.[13-15] The UK Government-commissioned O'Neill report predicted that without urgent action 10 million people a year will die from drug-resistant infections by 2050.[16] If unchecked, AMR could shave US $ 3.4 trillion off GDP annually and push 24 million more people into extreme poverty in the next decade.[11] The World Bank estimates that AMR could result in US$ 1.0 trillion in additional healthcare costs by 2050, and US$ 1 to 3.4 trillion gross domestic product (GDP) losses per year by 2030.[17] The AMR is a natural process that happens over time through genetic changes in pathogens. Its emergence and spread are accelerated by human activity, mainly the misuse and overuse of antimicrobials to treat, prevent, or control infections in humans, animals, and plants.[15]

The emergence and spread of drug-resistant pathogens threaten our ability to treat common infections and to perform life-saving procedures including cancer chemotherapy and cesarean section, hip replacements, organ transplantation, and other surgeries. In addition, drug-resistant infections impact the health of livestock including poultry birds and crop production, reduce productivity in farm animals and poultry birds, and threaten food security. AMR has significant costs for both health systems and national economics overall. It creates the need for more expensive and intensive care, affects the productivity of patients or their caregivers through prolonged hospital stays, and harms agricultural productivity.[15]

Antimicrobials are essential for treating infectious diseases in mammals including humans and animals and birds including poultry and pets. However, despite their success, their continued use in the 21st century faces two challenges. The first is that the microbes targeted by these drugs develop resistance over time. The second is that antibiotic discovery and development are no longer cost-effective using traditional reimbursement models.

Antimicrobials have contributed considerably to clinical and preventive medicine in humans and veterinary medicine and some of them have played a very important role in the promotion of livestock growth and feed efficiency. The non-ethical uses of antimicrobials in multiple sectors including human medicine, veterinary medicine, animal husbandry, aquaculture, and agriculture might have evolved as a natural consequence of antimicrobial resistance (AMR).[18] The AMR has been recognized as a crucial multifactorial and complex global problem due to the rapid emergence and spread of resistant bacteria and associated antibiotic-resistant genes (ARGs) among humans, animals, and the environment.[19] Once a single bacterium mutates to become resistant to antibiotics, it can transfer that resistance to other bacteria around it through a process known as horizontal gene transfer from cell to cell by conjugation, transformation, or transduction. This gene exchange allows the resistance to rapidly spread throughout a population of bacteria and among different species of bacteria. Bacteria exhibit resistance to different drug classes by acquiring resistance determinants through multiple mechanisms including horizontal gene transfer. The presence of drug-resistance genotypes is mostly associated with corresponding phenotypic resistance against the particular antibiotic.[20]

The AMR is mainly associated with increased morbidity, mortality, disease burden, healthcare expenditure, and reduced livelihoods. Globally, it is estimated that 4.95 (3.62-6.57) million human deaths annually associated with bacterial AMR in 2019, including 1.27 million deaths attributable to bacterial AMR[21,] and importantly this trend continues to rise globally. If no remedial action is taken, it is estimated the mortality attributable to AMR could rise by 10 million globally and this would mean a cumulative financial loss of US $ 100 trillion to the global economy and an 11% fall in livestock production by 2050.[22] WHO risk assessment surveys have projected 389,000 deaths attributed to AMR in South Asia.[23]

The direct negative impact of AMR in the livestock industry is the production losses which ultimately result in reduced food security. Developing nations including Bangladesh are more vulnerable to AMR due to inappropriate and overuse of antibiotics, poor-quality antimicrobials, mostly used antibiotics as non-prescription drugs, prescription of antibiotics without sensitivity tests, lack of drug monitoring and surveillance systems, lack of awareness of AMR and low health care system and a majority of the populations are low-income class.[3]

Livestock (including food animals and poultry birds) farming systems in Bangladesh are diversified from rural household small farms to medium and limited large-scale commercial farms.[24,25] The government veterinary medical services are extended up to the Upazila level with inadequate facilities and most of the rural livestock farming systems are not covered under these facilities, as a result, most of the rural farm owners depend on non-vet personnel for the treatment of their livestock. Accordingly, irrationally prescribed and easy access to antibiotics leads to misuse, abuse, suboptimal, or overuse of these antibiotics in farm livestock.[24] In addition, antimicrobials are also used as prophylactic and sometimes as growth promoters, especially in large-scale commercial livestock farms in Bangladesh.[26] The irrational, suboptimal, or overuse of antimicrobials has probably resulted in the evolution of different species of pathogenic and zoonotic antibacterial-resistant (ABR) bacteria in livestock farming systems in Bangladesh.[27-29] The unhygienic animal and poultry husbandry farming practices in Bangladesh have been recognized as risk factors for the dissemination of these ABR pathogenic bacteria into humans and the environment.[30,31]

Globally, WHO estimates that only 50.0% of antibiotics are used correctly. Of the 150 million prescriptions for antibiotics prescribed by US doctors every year, fully 50 million were not necessary. In many countries, antibiotics can be brought over the counter from pharmacies, grocery stores, and street vendors. Up to 60.0% of the antimicrobials used in Africa and Asia may be substandard and counterfeit drugs have infested markets in these regions. Estimates of global annual use of antimicrobials range considerably from 63,000 tons to over 240,000 tons.[10]

Individual patients, farmers, fishermen, and others appear to have had more incentives to overuse and misuse antibiotics and other antimicrobials than to conserve them. The same is true for manufacturers, distributors, doctors, veterinarians, hospitals, and clinics. Easy access to diagnostic services can promote appropriate use, especially where many patients self-medicate because the private-market supply of antimicrobials without a prescription is available. The prevalence of antibiotic administration without prescription has been reported to be 37.02% in Bangladesh.[32,33] The use of counterfeit and substandard (poor quality) antimicrobials aggravates AMR and also harms patients directly. Substandard and counterfeit antimicrobials seem to be widely available in many developing countries including Bangladesh. WHO has estimated that some 10% of all the drugs worldwide may be counterfeits, with half of these factitious drugs mimicking antimicrobials. Public health in a country suffers when counterfeits penetrate its markets, and this damage is even greater when the counterfeits promote AMR. Overall, up to 60.0% of antimicrobials used in Africa and Asia including India, Bangladesh, China, and Thailand may have low quality, often containing none, or too little, of the active ingredients. The use of counterfeit and poor-quality drugs are not only aggravates AMR but also a major factor in harming animal health and livestock owners' incomes.[33]

Drivers (Risk factors) of Antibiotic-resistant bacteria (ARB)

Three major domains of antibiotic resistance have been identified which include the emergence of antibiotic-resistant bacteria from humans, animals, and the environment, and subsequently release of such resistant bacteria from animals and humans into the environment. The drivers of ARB are complex and multisectoral,

often involving the interplay between lack of medical infrastructure, agriculture, the environment, inadequate surveillance and prevention measures, lack of attention to the local context, and excessive antimicrobial use. The most significant drivers of the ARB with their resistant genes to different antibiotics, which could be developed due to misuse and overuse of antimicrobials in humans, animals, and plants. Antibacterial resistance is affected by several potential drivers such as the consumption of antibiotics in the human population, consumption in livestock, healthcare-related transmission, travel, and environmental contamination.[34] Lack of access to clean water, open rather than closed sewage systems, variation in healthcare infection control practice, inadequate provision of antimicrobials and diagnostics, and farming systems with sub-optimal regulation of antimicrobials and high population densities. Lack of clean water and sanitation and inadequate infection prevention and control promote the spread of microbes, some of which can be resistant to antimicrobial treatment.

Several pathways, including hospital effluent, agricultural waste, and wastewater treatment facilities, have been identified as potential routes for the spread of resistant bacteria and their resistance genes in soil and surrounding ecosystems. The overuse of uncontrolled antibiotics improper treatment and recycled wastewater are among the contributors to develop ARB.[35]

The global spread of antibiotic-resistant bacteria (ARB) and antibiotic-resistance genes (ARGs) between air, water, soil, and food are now well documented, while the factors that affect ARB and ARG dissemination e.g. water and air quality, antibiotic fluxes, urbanization, sanitation practices ARB is driven by various factors including inappropriate prescription practices, the dearth of novel antibiotics, and the overuse of uncontrolled antibiotics. Other contributors to ARB include the indiscriminate use of antibiotics in humans, animal husbandry, agriculture, fisheries, and the environment. Risk factors such as high infectious disease burden, inadequate public health infrastructure, lack of suitable diagnostic assistance, and inadequate infectious control methods also amplify the crisis of ARB. Additionally, the sale of antibiotics without prescription, the use of antibiotics for metaprophylaxis and as growth promoters in farming, fisheries, and aquaculture, and effluents with antibiotic residues from hospitals and the pharmaceutical industry contribute to the spread of ARB. Socioeconomic factors, including governance and poverty, also play a significant role in ARB rates in humans and animals. Overall, addressing ARB requires an integrated 'one health' effort from various sectors and stakeholders, including healthcare providers, researchers, policymakers, and governments.[36]

National antimicrobial resistance (AMR) surveillance report, Bangladesh

A national AMR surveillance in human patients was conducted in Bangladesh during the period from 2017 to June 2023 which includes 70,002 patients with 44,316 isolates. Of the 34,340 (24.26%) case-based samples, of which 8654 (25.0%) isolates were obtained (Table 5). In case-based surveillance, 49% of samples were collected from OPD, 39% from patients' wards, and 12.0% from ICU patients.

Table 5. Isolation and identification of bacteria in the culture of different specimens in humans[36] ETA = Endotracheal aspirate

S/N	Bacterial species	Urine (n = 3080)	Blood (n = 819)	Wound Swab (n = 3153)	ETA (n = 711)	Sputum (n = 501)	Stool (n = 371)	Total (n = 6854)
01.	*Escherichia coli*	61.0	17.0	17.0	08.0	11.0	0	31.0
02.	*P. aeruginosa*	06.0	06.0	38.0	19.0	10.0	0	19.0
03.	*K. pneumoniae*	15.0	09.0	11.0	32.0	48.0	0	15.0
04.	*Staph. aureus*	06.0	14.0	14.0	05.0	19.0	0	10.0
05.	*Proteus* spp.	04.0	01.0	10.0	03.0	<1.0	0	05.0
06.	(Acb) complex	02.0	07.0	04.0	30.0	02.0	0	05.0
07.	*Salmonella* spp.	0	43.0	0	0	0	0	04.0
08.	*Vibrio cholerae*	0	0	0	0	0	65.0	03.0
09.	*Enterococcus* spp.	04.0	01.0	01.0	<1.0	0	0	02.0
10.	CN Staphylococci	01.0	<1.0	01.0	<1.0	01.0	0	01.0
11.	*Shigella* spp.	0	0	0	0	0	17.0	01.0
12.	NT Salmonella	0	0	0	0	0	16.0	01.0
13.	*Strep. pneumoniae*	0	01.0	0	< 1.0	01.0	0	<1.0
14.	Others	02.0	02.0	04.0	03.0	07.0	02.0	03.0

The current clinical antibacterial pipeline contains 43 antibiotics and combinations with a new therapeutic entity. Only two of these are active against the critical MDR Gram-negative bacteria. Overall, the clinical pipeline and recently approved antibiotics are insufficient to tackle the challenge of increasing the emergence and spread of AMR. The AMR is a growing concern in Bangladesh, where it is aggravated by irrational use of antimicrobials, widespread availability without prescription, and consequent contamination of the environment. In a systemic review of 46 articles a high prevalence of resistance was detected in most tested pathogens, and many of the common first-line drugs were found mostly ineffective.[3] Misuse and overuse of antimicrobials are the main drivers in the development of drug-resistant pathogens. Antimicrobials used for treating infection lose effect because the microbes change- mutate and acquire genetic information from other microbes to develop resistance. The drivers of AMR lie in humans, animals, agriculture, aquaculture, and in environment, and thus AMR is a 'One Health' issue.

The presence of extended-spectrum beta-lactamase (ESBL)-producing organisms was indicated by the high resistance to beta-lactams. Methicillin-resistant *Staphylococcus aureus* (MRSA) was identified in four studies.[3] National AMR surveillance in Bangladesh conducted by IEDCR throughout the countries between 2017 to June 2023 found 8.0% of possible Pan Drug Resistant (PDR) among 6868 isolates which is truly alarming. Moreover, it showed that the resistance of most of the organisms over the period increased.[36] However, the review of the literature shows that China (41.0%) has the highest level of antibiotic resistance, followed by Kuwait (17.0%) and the United States (6.0),[37] whereas only in the US, at least 2.8 million people acquire antibiotic-resistant infection each year, and more than 35,000 people die as a result.[38] It indicates that AMR is a global problem of both developed and developing nations but with the highest in low-income countries of the world.

History of antibiotic discovery and development of antibiotic resistance

Penicillin was the first antibiotic discovered by Alexander Fleming in 1928 and it came into clinical use in the 1940s. Penicillin, which is an outstanding agent in terms of safety and efficacy, led the era of antimicrobial chemotherapy by saving the lives of many wounded soldiers during World War II. In 1935, sulfonamides were developed by Domagk and other researchers. These drugs were synthetic compounds and had limitations in terms of safety and efficacy.[39] During the subsequent two decades (the mid-20th century, especially the period from the 1940s to 1960s), new classes of antimicrobial agents were developed one after another, leading to a 'Golden Age' of antibiotic discovery. In 1944, Streptomycin, an aminoglycoside antibiotic, was obtained from the soil bacterium *Streptomyces griseus*, which was the first antibiotic developed effectively against tuberculosis. Thereafter, chloramphenicol, tetracycline, macrolide, and glycopeptide (e.g. vancomycin) were discovered from soil bacteria.[39] The synthesized antimicrobial agent nalidixic acid, a quinolone antimicrobial drug, was obtained in 1962. Post-1970s marked a decline in novel antibiotic development but witnessed significant progress in understanding bacterial resistance mechanisms, leading to the development of drugs like β-lactamase inhibitors (Table 6). The use of antibiotics has evolved from treating selected infections to preventable uses today, such as before surgeries to prevent potential bacterial infections, and also sees use in fields like oncology and livestock farming. Antibiotic resistance has emerged as a global health concern, driven by factors like overuse and misuse of antibiotics in healthcare and agriculture, prescribing antibiotics without need, non-completion of treatment courses, and the use of antibiotics in livestock feed for growth promotion. Table 6 shows some of the common classes of antibiotics, their year of discovery, the year in which AMR was first observed in them, the mechanism of resistance employed along an example from each class.

Table 6. Some common antibiotic classes with their discovery, and resistance status[40]

S/N	Antibiotic class	Year of discovery	Year of resistance	Mechanism of resistance	Target	Example	Ref. No.
01.	β-lactams	1928	1945	Hydrolysis, efflux, altered target	Peptidoglycan biosynthesis	Penicillins (ampicillin), CSP, MPN, AZN	41,42
02.	Aminoglyco-sides	1943	1946	Phosphorylation, acetylation, nucleotidylation, efflux pump, altered target	Translation	Streptomycin, Gentamicin Spectinomycin	26,43
03.	Tetracyclines	1944	1950	Monoxygenation, efflux pumps, and alter target	Translation	Minocycline, Tigecycline	44,45

Contd. Table 6

04. Quinolones	1961	1968	Efflux pumps, target modifications, acetylation, efflux, altered target	DNA replication	Ciprofloxacin	46,47
05. Lipopeptides	1986	1987	Modification of the cell wall and cell membrane permeability		Daptomycin	48,49
06. Glycopeptides	1953	1960	Reprogramming peptidoglycan biosynthesis, Efflux pumps, altered cell wall permeability	Peptidoglycan biosynthesis	Vancomycin, Teicoplanin	50,51
07. Phenicols	1946	1950	Reduced membrane permeability, mutation in the ribosomal subunit, acetylation, efflux, altered target	Translation	Chloramphenicol	52,53
08. Macrolides	1950a	1967b	Hydrolysis, glycosylation, Phosphorylation, efflux, altered target	Translation	Erythromycin, Azithromycin	42, 54,55
09. Lincosamides	1966	-	Nucleotidylation, efflux,altered target	Translation	Clindamycin	42,56
10. Oxazolidinones	1990s	2001c	Efflux, altered target	Translation	Linezolid	42,57
11. Pyrimidines	1962d	-	Efflux, altered target	C1 metabolism	Trimethoprim	42
12. Sulfonamides	1932e	-	Efflux, altered target	C1 metabolism	Sulfamethoxazole	42, 58
13. Rifamycins	1965	-	ADP-ribosylation, efflux, altered target	Transcription	Rifampin	42,59
14. Lipopeptides	1980	-	Altered target	Cell membrane	Daptomycin	42,60
15. Cationic peptides	1947	-	Altered target, efflux	Cell membrane	Colistin	61

CSP = Cephalosporins CIP = Ciprofloxacin MPN = Meropenem AZN = Aztreonam a = First clinical used as erythromycin in 1952
b = Resistance to erythromycin in *Strep. pneumoniae* was first discovered in 1967
1990 s = Linezolid was discovered in the mid-1990s and was approved for commercial use in 2000.
2001c = The first clinical Staphylococcus isolate with resistance to linezolid was reported in July 2001[57]
1962d = Trimethoprim was introduced in 1962 but only commercialized in 1969 together with sulfamethoxazole due to synergies.[62]
1932e = Sulfonamides were discovered in 1932 and put into clinical use in 1935

Timeline of antibiotic discovery[63,64]

1910: Salvarsan
1928: Penicillin
1930s: Sulfomide
1935: Prontosil rebrum (sulfonamides)
1940: Amphenicols
1942: Benzyl-penicillin
1944: Streptomycin (First aminoglycoside)
1948: Chlortetracycline (First tetracycline)
1949: Chloramphenicol
1950: Penicillin G
1952: Erythromycin (First macrolide)
1955: Vancomycin (1st glycopeptide)
1958: Colistin (First polymyxin)
1960: Methicillin
1960: Metronidazole
1961: Trimethoprim
1964: Gentamicin
1964: Cephalotin (1st cephalosporin)
1967: Nalidixic acid (First quinolone)
1968: Clindamycin
1970s: 9 Cephalosporins
1972: Amoxicillin, Minocycline
1975: Tobramycin
1976: Amikacin
1980s: 17 Cephalosporins, 5 Penicillins
1985: Imepenem (First Carbapenem)
1986: Aztreonam (1st monobactam)
1987: Ciprofloxacin
1988: Azithromycin
1989: Moxifloxacin
1990s: 8 Cephalosporins
1990: Clarithromycin
1992: Piperacillin-tazobactam
1993: Levofloxacin
1994: Cefapine
1999: Quinopristin dalfopristin
2000: Linezolid (First oxazolidinone)
2003: Daptomycin
2005: Tigecycline
2005: Doripenem
2009: Telavancin (First lipoglycopeptide)
2010: Ceftaroline
2011: Fidaxomicin
2014: Dalbavancin, Oritavancin, Tendizolid, Ceftolorance-tazobactam
2015: Ceftazidime-avibactam
2017: Delafloxacin, Meropenem-vaborbactam
2018: Plazomycin, Omadacycline, Eravacycline
2019: Imipenem-relabactam, Lefamulin, Celftderocol

Table 7. Antibiotics and antimicrobial resistance- a timeline[65]

Timeline	Discovery and use of antimicrobials	Scientific discoveries	Antimicrobial resistance develops
2500 BC	2500 BC Ancient civilizations use antimicrobials in medicine	-	-
1877	-	1877: Antibiosis described	-
1900	1900: Search begins for chemicals with antibiotics	-	-
1910	-	1910: First synthetic antimicrobial used in humans	-
1928	-	1928: Penicillin discovered	1928: Resistance identified
1930	-	1930: Sulfonamides discovered	-
1933	1933: Introduction of antibiotic use in animals.	-	1933: More resistance appears
1940	1940: Soil bacteria testing for antibiotic properties	-	-

1943	1943: Penicillin approved for clinical uses	1943: Streptomycin discovered	- Uses in humans
1944	-	1944: Golden age of antibiotics	1944: Penicillin resistance identified
1948	1948: First antibiotic licensed for use in animal feed.	-	-
1950	1950: Antibiotics used to promote animal growth and prevent plant disease.	-	-
1960	1960: Antibiotic use increasing in global food production.	-	-
1961	-	-	1961: Methicillin resistance identified in the bacteria *Staphylococcus aureus*.
1986	-	-	1986: Vancomycin resistance identified in the bacteria Enterococcus.
1987	-	1987: Lipopeptides discovered	-
1990	-	-	1990: Resistance to different antibiotics continues to emerge.
1997	1997: Some countries restrict use of growth-promoting antibiotics.	-	-
2002	2002: New Zealand bands use of antibiotics as growth promoters.	-	-

- 2500 BC: Ancient civilizations use antimicrobials in medicine. Humans have been using medicines since prehistoric times to treat various ailments- primary herbs and other natural substances with healing properties. Ancient civilizations such as the Egyptians, Greeks, and Chinese developed sophisticated medical systems that relied heavily on plant-based remedies.
- 1877: Antibiosis described- antibiosis, a biological process where one organism inhibits the growth of another, is observed by Louis Pasteur and Robert Koch. They observe that microbes can secrete material to kill certain bacteria.
- 1900: During the late 1800s, German physician and scientist Paul Ehrlich began to systematically search for a chemical agent that would selectively kill bacteria, leaving humans unharmed. His search came to fruition in 1907 with the synthesis of the arsenic-containing organic molecule arsphenamine, which has activity against the causative agent of syphilis (*Treponema pallidum*).
- 1910: Poul Ehrlich developed the first antimicrobial treatment used to treat humans- Salvarsan. It has severe side effects, partly because it contains arsenic, a poison.
- 1928: Penicillin discovered- Alexander Fleming discovered the first modern antibiotic, penicillin. He observes that the growth of the *Staphylococcus aureus* bacteria living in Petri dishes is inhibited by substances produced by the fungus *Penicillium chrysogenum*. This leads to the creation of the first antibiotic, penicillin.
- 1928: Resistance identified- Some bacteria become resistant to the antimicrobial Salvarsen.
- 1930: Sulfonamides are a group of synthetic antibacterial medicines. They are the first truly effective, broad-spectrum antimicrobials used for treating infection in humans and animals. They are still in use today but were largely superseded by the discovery of penicillin.
- 1933: Introduction of antibiotic use in animals- Antibiotics are initially used to only treat sick animals. Later, it is discovered they can be used to promote growth.
- 1933: More resistance appears- Certain bacteria become resistant to sulfonamides.
- 1943: Penicillin approved for clinical uses in humans- US scientists optimize penicillin production via fermentation and can produce enough for the Allied Armed Forces.
- 1943: Streptomycin discovered- Streptomycin is the first antibiotic to be successful against tuberculosis.
- 1944: Golden age of antibiotics- The discovery of natural product antibiotics peaks in the mid-1950s- including streptomycin, cephalosporins, tetracyclines, vancomycin, and methicillin. Most of the antibiotics discovered in this 'golden age'- 1944 to 1966-are still in use, but their effectiveness has been eroded by antimicrobial resistance
- 1944: Penicillin resistance identified- shortly after the introduction of penicillin, resistance is identified in the bacteria *Staphylococcus aureus*, a common cause of serious infection in people and animals.
- 1948: Sulfaquinoxaline becomes the first antibacterial to be routinely administered in poultry feed to prevent disease in the USA.
- 1950: During the 1950s, antibiotics are first used as growth promoters in animal feed. Horticultural sprays of antibiotics are used to combat disease in fruit trees.
- 1960: In the 1960s, antibiotics are widely used to promote growth in farm animals. Some countries restrict veterinary prescription of medically important antibiotics and warn of the risk of antibiotic resistance.
- 1961: The resistant bacteria are described as MRSA (methicillin-resistant Staphylococcus aureus). These bacteria are resistant to all antibiotics in the penicillin class of antibiotics so infection is difficult to treat.
- 1986: Vancomycin-resistant Gram-positive bacteria can become resistant to all antibiotics.
- 1987: Lipopeptides discovered- the last class of clinically used antibiotics is discovered.
- 1990: Resistance to common antimicrobial drugs increases, and readily treatable infections are becoming increasingly challenging to manage.
- 1997: The European Union bans the use of certain antibiotics used as growth promoters in animals.
- 2002: Concerns about the development of antibiotic-resistant bacteria and the potential impact on human health led to a ban on the use of antibiotics as growth promoters in animal feed in NZealand. The ban applies to all antibiotics that pose an antimicrobial resistance risk to animals or humans.
- 2015: Antimicrobial resistance is declared a global emergency by the World Health Organization. The World Health Assembly adopts a global action plan on AMR.
- 2023: In just over 100 years, antibiotics have drastically changed modern medicine and extended the average human lifespan by 23 years. The dangers of a post-antibiotic era have prompted policymakers to acknowledge this threat to human health. Appropriate use of antibiotics and preventing infection by vaccination and good hygiene are critical.

Table 8. All classes of clinically used antibiotics and their source [1]

S/N	Class	Discovery reported	Introduced clinically	Example	Producing organism	Molecular target
A.	**Antibiotics from Actinomyces**					
01.	Aminoglycosides	1944	1946	Kanamycin A	*Streptomyces kanamyceticus*	Protein synthesis: 30S ribosomal subunit
02.	Tetracyclines	1948	1948	Tetracycline	*Streptomyces aureofaciens*	Protein synthesis: 30S ribosomal subunit
03.	Amphenicols	1947	1949	Chloramphenicol	*Streptomyces venezuelae*	Protein synthesis: 50S ribosomal subunit
04.	Macrolides	1952	1952	Erythromycin	*Saccharopolyspora* erythraea	Protein synthesis: 50S ribosomal subunit
05.	Tuberactinomycins	1951	1953	Viomycin	*Streptomyces puniceus*	Protein synthesis: 30 & 50S ribosomal subunit
06.	Glycopeptides	1954	1958	Vancomycin	*Amycolatopsis orientalis*	Cell wall synthesis: D-Ala-D-Ala terminal of lipid II-
07.	Lincosamides	1962	1963	Clindamycin	*Streptomyces lincolnensis*[1]	Protein synthesis: 50S ribosomal subunit
08.	Ansamycins	1959	1963	Rifamycin SV	*Amycolatopsis rifamycinica*	Nucleic acid synthesis: RNA polymerase
09.	Cycloserines	1955	1964	Seromycin	*Streptomyces orchidaceus*	Cell wall synthesis: inhibition of alanine+
10.	Streptogramins	1953	1965	Pristinamycin	*Streptomyces pristinaespiralis*	Protein synthesis: 50S ribosomal subunit
11.	Phosphonates	1969	1971	Fosfomycin	*Streptomyces fradiae*	Cell wall synthesis: MurA (UDP-GlcNAc-3-ei
12.	Carbapenems	1976	1985	Meropenem[2]	*Streptomyces cattleya*	Cell wall synthesis: penicillin-binding proteins
13.	Lipopeptides	1987	2003	Daptomycin	*Streptomyces roseosporus*	Cell wall: cell membrane disruption
14.	Lipiarmycins	1975	2011	Fidaxomicin	*Dactylosporangium aurantiacum subsp. hamdenesis*	Nucleic acid synthesis: RNA polymerase
B.	**Antibiotics from other bacteria**					
15.	Polypeptides	1939	1941	Gramicidin A	Bacillus brevis	Cell wall: forms ion channels!
16.	Bacitracin	1945	1948	Bacitracin A	*Bacillus subtilis*	Cell wall synthesis:inhibition[3]
17.	Polymyxins	1950	1959	Colistin	*Paenibacillus polymyxa*	Cell wall: cell membrane disruption
18.	Mupirocin	1971	1985	Mupirocin	*Pseudomonas fluorescens*	Protein synthesis: isoleucyl t-RNA synthetase
19.	Monobactams	1981	1986	Aztreonam[4]	*Chromobacterium* violaceum	Cell wall synthesis: penicillin -binding proteins
C.	Antibiotics from fungi					
20.	Penecillins	1929	1943	Amoxicillin	*Penicillium chrysogenum*[5]	Cell wall synthesis: penicillin -binding proteins
21.	Fusidic acid	1958	1962	Fusidic acid	*Fusidium coccineum*	Protein synthesis: elongation Factor G
22.	Enniatins	1953	1963	Fusafungine	Fusarium lateritium	Cell wall: cell membrane disruption
23.	Cephalosporins	1948	1964	Cefacetrile	*Acremonium chrysogenum*[6]	Cell wall synthesis: penicillin -binding proteins
24.	Pleuromutilins	1951	2007	Retapamulin	*Pleurotus mutilus*[7]	Protein synthesis: 50S ribosomal subunit
D.	**Synthetic antibiotics**					
25.	Arsphenamines	1907	1910	Salvarsan	Synthetic	Not known
26.	Sulfonamides	1932	1936	Mafenide	Synthetic	Folate synthesis: IDS
27.	Salicylates	1902	1943	4-aminosalicylic acid	Synthetic	Folate synthesis:PIDR

Contd. Table 8.

28. Sulfones	1908	1945	Dapsone	Synthetic	Folate synthesis: IDS
29. Pyridinamides	1952	1952	Isoniazid	Synthetic	Cell wall: PISMA
30. Nitrofurans	1945	1953	Nitrofurantoin	Synthetic	DNA synthesis: DNA damage
31. Azoles	1959	1960	Metronidazole	Synthetic	DNA synthesis: DNA damage
32. Fluoroquinolones	1962	1962	Ciprofloxacin	Synthetic	DNA synthesis: IDG
33. Diaminopyrimidines	1950	1962	Trimethoprim	Synthetic	Folate synthesis: IDR
34. Ethambutol	1962	1962	Ethambutol	Synthetic	Cell wall: ATI
35. Thioamides	1956	1965	Ethionamide	Synthetic	Cell wall: PISMA
36. Phenazines	1954	1969	Clofazimine	Synthetic	DNA synthesis: BGB
37. Oxazolidinones	1987	2000	Linezolid	Synthetic	Protein synthesis: 50S RS
38. Diarylquinolines	2004	2012	Bedaquiline	Synthetic	ATP synthesis: PPSI

1= Semi-synthetic derivative of lincomycin
ei = enolpyruvyltransferase inhibition
! = that increases the permeability of the bacterial cell membrane
4= synthetic molecule based on SQ 26,180
6= Semi-synthetic derivative of cephalosporin C
PIDR = Prodrug that inhibits dihydrofolate reductase
IDG = Inhibition of DNA gyrase and topoisomerase IV
BGB = Binds to guanine bases
Salvarsan is no longer in clinical use
+ = racemase and D-alanine-D-alanine ligase
Synthetic molecule based on thienamycin
3 = of dephosphorylation of C_{55}-isopropyl pyrophosphate
5 = Semi-synthetic derivative of penicillin
IDS = Inhibition of dihydropteroate synthetase
PISMA = Prodrug that inhibits the synthesis of mycolic acids
ATI = Arabinosyl transferase inhibition
RS = Ribosomal subunit
PPI = Proton pump inhibition

Mechanisms of antibiotic action and resistance

Antibiotics- compounds that are literally 'against life' - are typically antibacterial drugs, that interfere with some structure or process that is essential to bacterial growth or survival without harm to the eukaryotic host harboring the infecting bacteria.[66] Antibiotic resistance is the loss of susceptibility of bacteria to the killing (bacteriocidal) or growth-inhibiting (bacteriostatic) properties of an antibiotic agent. When a resistant strain of bacteria is the dominant strain in an infection, the infection may be untreatable and life-threatening. A bactericidal antibiotic kills the bacteria while bacteriostatic antibiotics stop bacterial growth without being resistant to antibiotics killing them. Examples of bacteria that are resistant to antibiotics include methicillin-resistant *Staphylococcus aureus* (MRSA), penicillin-resistant Enterococcus, and multidrug-resistant *Mycobacterium tuberculosis* (MDR-TB).[67] There are several classes of antibiotics with different mechanisms of action and bacterial targets have been described.

- There are **three** main antibiotic targets in bacteria: (1) The cell wall or membranes that surround the bacterial cell, (2) The machinery that makes the nucleic acids DNA and RNA, and (3) The machinery that produces proteins (the ribosome and associated proteins).[68]
- There are **three** proven targets for the main antibacterial drugs: ① Bacterial cell-wall biosynthesis, ② Bacterial protein synthesis, and ③ Bacterial DNA replication and repair.[66]
- The mode of action of antibiotics is classified into **four** mechanisms based on their mechanism of action and chemical structures which include: ① Antibiotics inhibit DNA replication, ② Antibiotics inhibit protein synthesis, ③ Antibiotics inhibit cell wall synthesis, and ④ Antibiotics inhibit folic acid metabolism.[69]
- Various antimicrobial agents act by interfering with ① Cell wall synthesis, ② Plasma membrane integrity, ③ Nucleic acid synthesis, ④ Risomal function, and ⑤ Folate synthesis[70]
- There are **five** mechanisms of antibiotic action against bacterial cells which include ① Inhibition of cell wall synthesis, ② Inhibition of protein synthesis, ③ Alteration of the cell membrane, ④ Inhibition of nucleic acid synthesis and ⑤ Antimetabolite activity.[71]
- Five bacterial targets have been exploited in the development of antimicrobial drugs: ① Cell wall synthesis, ② Protein synthesis, ③ Ribonucleic acid (RNA) synthesis, ④ Deoxyribonucleic acid (DNA) synthesis, and ⑤ Intermediary metabolism.[72]
- The main groups of antibiotic action reported as five which include ① Agents that inhibit cell wall synthesis, ② Depolarize the cell membrane, ③ Inhibit protein synthesis, ④ Inhibit nucleic acid synthesis, and ⑤ Inhibit metabolic pathways bacteria.[73]

•Antimicrobial agents used for the treatment of bacterial infections are often categorized according to their principal mechanism of action. There are **six** major modes of action: (1) Interference with cell wall synthesis, (2) Inhibition of protein synthesis, (3) Interference with nucleic acid synthesis, (4) Inhibition of a metabolic pathway, and (5) Inhibition of membrane function and (6) Inhibition of ATP synthase (Table 9).[74]

These targets are absent or structurally different in human and mammalian cells, which means that antibiotics usually do not harm host cells. However, antibiotics can in some cases have unpleasant side effects.

Table 9. Mechanisms of action and resistance of commonly used antimicrobial agents[71]

S/N	Mechanism of antibiotic action	Antibacterials	Mechanism of action	Mechanisms of resistance
1.	Inhibition of cell wall synthesis	Beta-lactam antibiotics	Inhibition of peptidoglycan synthesis. Binds enzymes (PBPs) that help form peptidoglycans.	•Fails to cross the membrane & bind to alter PBPs •Beta-lactamase production primarily- bla genes. •Hydrolysis by beta-lactamases
		Beta-lactamase inhibitors	Inhibits/binds to beta-lactamase enzymes	•Extended-spectrum beta-lactamases (ESBLs). Class A-D
		Vancomycin	Disrupt peptidoglycan cross-linkage	•Fails to cross the Gram-negative outer membrane •Some intrinsically resistant (pentapeptide terminus)
		Bacitracin	Disrupt movement peptidoglycan precursors	•Fails to penetrate the cell
		Antimycobacterial agents	Disrupts mycolic acid or arabinogalactan synthesis	•Reduces uptake •Alteration of large sites
2.	Inhibition of protein synthesis (translation)/	Aminoglycosides	Irreversibly bind 30S ribosomal proteins (bactericidal)	•Mutation of ribosomal binding site •Decreased uptake •Enzymatic modification of antibiotic
		Tetracyclines	Block tRNA binding to 30S ribosome m-RNA complex(b-static)	•Decrease penetration •Active efflux of antibiotics out of the cell •Protection of 30S ribosome
		Chloramphenicol	Binds peptidyl transferase component of 50S ribosome, blocking peptide elongation	•Plasmid-encoded chloramphenicol transferase •Altered outer membrane (chromosomal mutations)
		Macrolides	Reversely bind 50S ribosomes, blocks peptide elongation (b-static)	•Methylation of 23S ribosomal RNA subunit •Enzymatic cleavage (erythromycin esterase) •Active efflux
		Clindamycin	Binds 50S ribosome and blocks peptide elongation; inhibits peptidyl transferase by interfering with the binding of amino-acyl-tRNA complex	•Methylation of 23S ribosomal RNA subunit.
3.	Alteration of cell membranes	Polymyxins (topical use)	Cationic detergent-like activity	•Inability to penetrate the outer membrane
		Bacitracin (topical)	Disrupt cytoplasmic membranes	•Inability to penetrate the outer membrane
4.	Inhibition of nucleic acid synthesis/	Quinolones	Inhibit DNA gyrases or Topoisomerases	•Alteration of α-subunit of DNA gyrase (chromosomal)
		(Fluoroquinolones)*	Required for supercoiling of DNA; binds to α-subunit	•Decreased uptake by alteration of porins (chromosomal)
	Inhibit DNA replication	Metronidazole	Metabolic cytotoxic byproducts disrupt DNA	•Decreased uptake •Elimination of toxic compounds before they interact
		Rifampin	Bind to DNA-dependent RNA polymerase inhibiting initiation & rifabutin of RNA synthesis.	•Altered beta subunit of RNA polymerase (Chrom) •Intrinsic resistance in Gram-negative (decreased uptake).
		Bacitracin (topical)	Inhibits RNA transcription	•Inability to penetrate the outer membrane
5.	Antimetabolite activity (inhibit folic acid metabolism)	Sulfonamides and Dapsone	Compete with p-aminobenzoic acid (PABA) preventing synthesis of folic acid	•Permeability barriers (e.g. *Pseudomonas*)
		Trimethoprim	Inhibit dihydrofolate reductase preventing the synthesis of folic acid.	•Decreased affinity of dihydrofolate reductase •Intrinsic resistance if using exogenous thymidine

- Beta-lactam antibiotics- all penicillins and cephalosporins with beta-lactam ring chemical structure are included in this group. This distinctive structure allows them to attach to peptidoglycan cross-linking enzymes, such as transpeptidase and carboxypeptidase, ultimately inhibiting bacterial cell wall synthesis and preventing cross-linking. This inhibition of cell wall manufacturing leads to the destruction of the bacterial cell [75]
- Fluoroquinolone antibiotics prevent the synthesis of bacterial DNA by inhibiting the activity of DNA gyrase and topoisomerase IV. These antibiotics have a particular affinity for binding to the complex formed by DNA gyrase and DNA. Such binding destabilizes the enzyme-DNA complex, causing DNA cleavage and ultimately leading to bacterial cell death.[76,77]
- Aminoglycosides are positively charged, which attracts the negatively charged outer membrane of bacteria, causing the membrane to develop large pores. These antibiotics are then able to enter the bacterial cell through these pores. The target of these antibiotics is the 16s rRNA of the 30s, which they bind to via hydrogen bonds and this binding inhibits protein biosynthesis before it can be completed.[78]
- Tetracyclines target the highly conserved sequence of the 16s rRNA present in the ribosomal 30S subunit, and function by hindering the binding of tRNA to the A-site of the ribosome, which ultimately impedes the process of protein synthesis.[79]
- Macrolides bind to the 50S subunit of the ribosome, thereby preventing the synthesis of polypeptide chains and inhibiting protein production.[80]
- Chloramphenicol inhibits peptidyl transferase, an enzyme located on the 50S ribosomal subunit that is necessary for protein synthesis. This inhibition prevents t-RNA from connecting to the ribosomal A site, leading to the inhibition of proteins.[81]
- Oxazolidinone antibiotics prevent the synthesis of the initiation complex by binding to the 50S subunit of the ribosome, thereby preventing the production of proteins.[82]
- Sulfonamide antibiotics target dihydropteroate synthase, an enzyme in the metabolic pathway, whereas trimethoprim targets dihydrofolate reductase, another enzyme in the same pathway.[83]

Mechanisms of antibiotic resistance

Some bacteria are naturally resistant (intrinsic resistance) to certain antibiotics, for example, Gram-negative bacteria (e.g. *Pseudomonas aeruginosa*) are resistant to most β-lactam antibiotics due to the presence of β-lactamase. Intrinsic resistance is when a bacterial species is naturally resistant to a certain antibiotic or family of antibiotics, without the need for mutation or gain of further genes. This means that these antibiotics can never be used to treat infections caused by that species of bacteria. Acquired resistance is gained by previously susceptible bacteria either through genetic mutation or horizontal gene transfer from other bacteria possessing. Only the resistant bacteria will continue to proliferate in the presence of the antibiotic and increase in number over time. The result is a population of mainly resistant bacteria. A complete understanding of the mechanisms by which bacteria become resistant to antibiotics is of paramount importance to designing novel strategies to counter the resistance threat. Classically, bacteria acquire external genetic material through three main strategies, (a) transformation (incorporation of naked DNA), (b) transduction (phase mediated), and (c) conjugation (bacterial sex).[84] Different authors have classified the mechanism of acquired antimicrobial resistance in different ways some of them are as follows:

- Three fundamental mechanisms of antimicrobial resistance are (a) Enzymatic degradation of antibacterial drugs, (b) Alteration of bacterial proteins that are antimicrobial targets, and (c) Changes in membrane permeability to antibiotics.[85]
- The main four types of resistance to antibiotics develop which include; ① Natural (intrinsic) resistance, ② Acquired resistance, ③ Cross-resistance, and ④ Multi-drug resistance and pan-resistance.[86]
- The biochemical resistance mechanisms used by bacteria include antibiotic inactivation, target modification, altered permeability, and 'bypass' of metabolic pathways.[69]
- The main mechanisms of resistance are: ① limiting uptake of a drug, ② modification of a drug target, ③ inactivation of a drug, and ④ active efflux of a drug. These mechanisms may be native to the microorganisms or acquired from other microorganisms.[73]
- Nine resistance mechanisms of bacteria to antibiotics have been described: (1) Target modification or mutation, (2) Permeability reduction, (3) Efflux pumps, (4) Hydrolyse or inactivating enzyme, (5) Metabolic enhancement or auxotrophy, (6) Target protective protein, (7) Initiation of self-repair systems, (8) Changes in cell morphology, and (9) Community cooperative resistance.[87]
- There are five mechanisms of bacterial resistance to antimicrobials which include (a) Enzyme inactivation and modification, (b) Modification of the antibiotic target site, (c) Overproduction of the target, (d) Replacement of the target site, and (e) Efflux and reduced permeability.[88]

- The main mechanisms of resistance to antibiotics can be caused by: (① Alteration of the target site of the antibiotic, ② Enzyme inactivation of the antibiotic, ③ Active transport of the antibiotic out of the bacterial cell, and ④ Decreased permeability of the bacterial cell wall to the antibiotic.[89]
- The mechanisms of antibiotic resistance against bacteria may be grouped into five which include:(a) Enzymatic modification of degradation of antimicrobial agents, (b) Decreased uptake of antimicrobial agent, (c) Changed antimicrobial target, (d) Efflux of antimicrobial agents, and (e) A combination of all above.[90]

Natural (Intrinsic, Structural) bacterial resistance

Intrinsic resistance may be defined as a trait that is shared universally within a bacterial species, is independent of previous antibiotic exposure, and is not related to horizontal gene transfer. The most common bacterial mechanisms involved in intrinsic resistance are reduced permeability of the outer membrane (most specifically the lipopolysaccharide, LPS, in Gram-negative bacteria) and the natural activity of efflux pumps. Multidrug-efflux pumps are also a common mechanism of induced resistance.[73] For example, Vancomycin does not pass through the outer membrane of Gram-negative bacteria which causes natural resistance to vancomycin. The cell wall-less organisms including *Mycoplasma* and *Ureaplasma* are naturally resistant to β-lactam antibiotics that inhibit the cell wall synthesis. Table 10 shows some examples of bacteria with intrinsic antimicrobial resistance.

Table 10. Examples of bacteria with intrinsic resistance[73]

S/N	Bacteria	Intrinsic resistance	S/N	Bacteria	Intrinsic resistance
1.	Bacteroides (anaerobes)	Aminoglycosides, many β-lactams, quinolones	07.	*Klebsiella* spp.	Ampicillin
			08.	*Serratia marcescens*	Macrolides
2.	All Gram-positives	Aztreonam	09.	*Pseudomonas aeruginosa*	Sulfonamides, ampicillin, 1st & 2nd generation CSP, CP & TET
3.	Enterococci	Aminoglycosides, Cephalosporins, lincosamides			
4.	*Listeria monocytogenes*	Cephalosporins	10.	*Stenotrophomonas maltophila*	Aminoglycosides, β-lactams, carbapenems, quinolones
5.	All Gram-negatives	Glycopeptides, Lipopeptides			
6.	*Escherichia coli*	Macrolides	11.	*Acinetobacter* spp.	Ampicillin, glycopeptides

CSP = Cephalosporins CP = Chloramphenicol TET = Tetracycline

Acquired antibacterial resistance

Acquired antibacterial resistance is the result of an evolutionary process by which bacteria adapt to antibiotics through several mechanisms including alteration of drug target by mutations and horizontal transfer of novel/foreign genes, referred to as resistance genes.[91] Bacteria can acquire resistance in two ways: either through a new genetic change that helps the bacterium survive, or by getting DNA from a bacterium that is already resistant. Resistant bacteria continue to multiply and antibiotic-resistant genetic materials are transferred between different bacteria cells in three different ways including transformation, transduction, or conjugation by horizontal gene transfer process. Some mechanisms of acquired antibiotic resistance are described below:

① Bacteria preventing antibiotic accumulation in their cells

a. Through limiting the entrance of drugs into bacterial cells

Gram-negative bacteria have porin channels in their outer membrane.[92] These channels act as gatekeepers, allowing only certain antibiotics like β-lactams and quinolones to enter the bacterial cell. Therefore, the reduced number of bacterial porins can hinder the entry of these antibiotics into the cell, leading to increased resistance to these drugs.[93]

b. Increasing the rate at which antibiotics leave bacterial cells

Efflux pumps, located in the cytoplasmic membrane of bacteria, play a crucial role in maintaining the balance of solutes within bacterial cells. However, these pumps also contribute to antibiotic resistance by removing drugs from bacterial cells before they can reach their intended targets.[77,94]

② Bacteria modifying the target molecule of antibiotics

Antibiotics are designed to target specific molecules, but even the slightest alteration can prevent their binding, leading to the emergence of antibiotic resistance.[77,92]

a. Modifications to the ribosomal 30s and 50s subunits

Bacteria can develop resistance to drugs that affect protein production by modifying their ribosomal 30s or 50s subunits.[94] This type of resistance is observed with antibiotics such as aminoglycosides, tetracycline, macrolides, chloramphenicol, lincosamides, and streptogramin.[95]

b. Changes in penicillin-binding protein (PBP)

The PBP are enzymes known as transpeptidases, which play a vital role in cross-linking peptidoglycan precursors during the biosynthesis of bacterial cell walls. As these enzymes are the primary targets of β-lactam antibiotics, any changes in their structure or function can lead to bacterial resistance to these drugs.[94]

c. Changes in DNA gyrase and topoisomerase enzymes

DNA replication involves the enzymes DNA gyrase and topoisomerase.[96] Quinolone antibiotics especially target these two enzymes, which is why modifications in their structure can lead to bacterial resistance against quinolones.[97]

d. Changes in D-alanyl-D-alanine

The peptidoglycan precursors contain a dipeptide residue known as D-alanyl-D-alanine, which plays a crucial role in cell wall formation.[98] Alternations to this D-alanyl-Dalanine residue can lead to bacterial resistance to antibiotics that target it.[99]

e. Protection of ribosome

Tetracycline antibiotics are known to target the ribosomal 30s subunit, but the ribosome has defense mechanisms that can resist their action[92]

f. Alteration in RNA polymerase enzyme importing resistance to rifampicin antibiotics

Rifampicin works by inhibiting the RNA synthesis process in bacteria, specifically by binding to the beta-subunit of the DNA-dependent RNA polymerase enzyme.[100] This binding prevents the enzyme from effectively transcribing DNA into RNA, leading to the inhibition of bacterial growth and ultimately causing cell death. Mutations in the rpoB gene, which encodes the beta-subunit of RNA polymerase can confer resistance to rifampicin.[101] These mutations can affect the binding affinity between rifampicin and the RNA polymerase enzyme, reducing the ability of the antibiotic to inhibit RNA synthesis.

③ Bacteria inactivate the antibiotic by enzymes

Three key enzymes are responsible for antibiotic inactivation, which include the following:[88,102]

a.Beta-lactamases enzymes (BLE)

These BLEs are produced by bacteria that can break down all β-lactam antibiotics that are bonded with ester and amide. This leads to the development of resistance in bacteria that can produce β-lactamase enzymes toward β-lactam antibiotics.[95] Penicillin-resistant strains of *S. aureus* were found to have acquired an enzyme known as a β-lactamase (originally known as penicillinase). β-lactamase enzymes target a part of β-lactam antibiotics known as the β-lactam ring which is found in all β-lactam antibiotics. The β-lactamase enzyme breaks this ring open, preventing the antibiotic from binding to its target. Certain members of the β-lactamase family, known as Carbapenemases, are the most problematic because they break down all members of the β-lactam family of antibiotics, including carbapenems, severely limiting treatment options.[88]

b. Enzyme modification

- First type, bacteria can acquire enzymes that chemically modify the target of the antibiotic in the bacteria by adding additional chemical groups. An example of this is the erm (erythromycin ribosomal methylation) gene that provides resistance against macrolide antibiotics like erythromycin. This enzyme methylates (adds a methyl group: CH_3) to part of the ribosome, which is the target of erythromycin. This means that erythromycin can no longer bind to the target, meaning the bacteria can continue to thrive in the presence of the antibiotic.[88]

- In the second type, the enzyme acts chemically modifying the antibiotic itself, which prevents the antibiotic from binding to its target site. An example is aminoglycoside modifying enzymes (AGEs) such as N-acetyltransferases, which add acetyl group (CH_3CO) to aminoglycoside antibiotics such as kanamycin. Many different types of these enzymes have different activities against antibiotics from different classes of antibiotics including aminoglycosides, tetracyclines, phenicols, and lincosamides (FL 2023). However, the AGEs have been found to prevent the attachment of aminoglycoside antibiotics to their ribosomal target.[103] These enzymes are present in various bacterial strains, including *E. faecalis*, *S. aureus*, and *S. pneumoniae*. In addition, these enzymes also aid in conferring resistance to aminoglycosides and fluoroquinolones.[92]
- Chloramphenicol-acetyltransferases modify the antibiotic chloramphenicol by acetylating its hydroxyl group, resulting in an altered form of the antibiotic that is unable to bind to its ribosomal target. Bacteria possessing the chloramphenicol-acetyltransferase enzyme are resistant to chloramphenicol antibiotics, rendering them ineffective.

④ Modification of the antibiotic target site

Multiple components in the bacterial cell may be targets of antimicrobial agents, and there are just as many targets that may be modified by the bacteria to enable resistance to those drugs. One mechanism of resistance to the β-lactam drugs used almost exclusively by Gram-positive bacteria is via alterations in the structure and/or number of penicillin-binding proteins (PBPs). PBPs are transpeptidases involved in the construction of peptidoglycan in the cell wall. A change in the number (increase in PBPs that have a decrease in drug binding ability, or decrease in PBPs with normal drug binding) of PBPs impacts the amount of drug that can bind to that target. A change in structure (e.g. PBP2a in *S. aureus* by acquisition of the mecA gene) may decrease the ability of the drug to bind or inhibit drug binding.[73,104]

The glycopeptides (e.g. vancomycin) also work by inhibiting cell wall synthesis, and lipopeptides (e.g. daptomycin) work by depolarizing the cell membrane. Gram-negative bacteria (thick LPS layer) have intrinsic resistance to these drugs.[105]

Resistance is mediated through the acquisition of van genes which results in changes in the structure of peptidoglycan precursors that cause a decrease in the binding ability of vancomycin.[73,104]
Resistance to drugs that target the ribosomal subunits may occur via ribosomal mutation (aminoglycosides, oxazolidinones), ribosomal subunit methylation (aminoglycosides, macrolides- Gram-positive bacteria, oxazolidinones, streptogramins) most commonly involving erm genes, or ribosomal protection (tetracyclines). These mechanisms interfere with the ability of the drug to bind to the ribosome.[73]

For drugs that target nucleic acid synthesis (fluoroquinolone antibiotics such as ciprofloxacin), resistance is via modifications (mutations) in the DNA gyrase (Gram-negative bacteria- e.g. gyrA) or DNA topoisomerase IV (Gram-positive bacteria-e.g. grlA) genes. These mutations cause changes in the structure of gyrase and topoisomerase which decrease or eliminate the ability of the drug to bind to these components.[106,107]

a. Replacement of the target site

Bacteria like *Streptococcus pneumoniae* mutate the targets of the antibiotics, another similar mechanism of resistance is to gain an additional copy of the gene that encodes a protein that remains active (e.g. the antibiotic can't bind to it) in the presence of the antibiotic. This is how the pathogen *S. aureus* becomes resistant to most *S. aureus* that is resistant to β-lactam antibiotics such as penicillin. Methicillin-resistant *S. aureus* (MRSA), which is the name given to *S. aureus* is resistant to β-lactam antibiotics and becomes resistant by gaining an extra copy of penicillin-binding protein 2, which is the target of β-lactam antibiotics. This additional version known as penicillin-binding protein 2a (PBP2a) can still function in the presence of β-lactam antibiotics.[88]

b. Overproduction of the target site

Bacteria can also overproduce the target of the antibiotics, meaning there is an excess of the protein target of the antibiotics compared to the antibiotic itself. This means that there is enough of the target protein for it to continue its role in the cell in the presence of antibiotics; this is a mechanism of resistance to trimethoprim in *E. coli* and *Haemophilus influenzae.*

Resistance is via mutations in enzymes- dihydropteroate synthase (DHPS) and dihydrofolate reductase (DHFR), involved in the folate biosynthesis pathway and/or overproduction of resistant DHPS and DHFR enzymes (sulfonamides- DHPS, trimethoprim- DHFR). The sulfonamides and trimethoprim bind to their respective enzymes due to their structural analogs of the natural substrates (sulfonamides- p-amino-benzoic acid, trimethoprim- dihydrofolate). The action of these drugs is through competitive inhibition by binding in the active site of the enzymes. Mutations of these enzymes are most often located in or near the active site, and resulting structural changes in the enzyme interfere with drug binding while still allowing the natural substrate to bind.[108,109] The overexpression is sometimes found in combination with mutations that lower the ability of the antibiotic to bind to its target. Trimethoprim is typically used with sulfamethoxazole, a combination known as co-trimoxazole or SXT.[88]

⑤ Inactivation of drugs

There are two main ways in which bacteria inactivate drugs; by either transferring a chemical group to the drug or by actual degradation of the drug.

a. β-lactamases

The most widely used group of antimicrobial agents are the β-lactam antibiotics. The members of this antibiotic group all share a specific core structure which consists of a four-sided β-lactam ring. Drug inactivation results in the production of β-lactamase hydrolyzing enzymes by many bacteria. These enzymes target and inactivate β-lactam antibiotics, which include widely used drugs like penicillin and cephalosporins. β-lactam antibiotics work by interfering with the synthesis of the bacterial cell wall, ultimately causing the cell to burst. However, β-lactamase enzymes can break the β-lactam ring, a key structural component of these antibiotics, rendering them inactive. As a result, the antibiotic no longer disrupts the cell wall synthesis and the bacterium remains unharmed. Resistance to the β-lactam drugs occurs through three general mechanisms: (a) Preventing the interaction between the target PBP and the drug, usually by modifying the ability of the drug to bind to the PBP, (b) The presence of efflux pumps that can extrude β-lactam drugs, and (c) Hydrolysis of the drug by β-lactamase enzymes.[110,111]

b. Inactivation of tetracycline by hydrolyzation

Tetracycline is another drug that can be easily hydrolyzed and inactivated by the tetX gene. Enzymatic inactivation modifies the tetracycline molecule by adding a functional group to specific sites on the tetracycline structure. This change of structure interferes with the tetracycline's ability to bind to the ribosome effectively. As tetracycline antibiotics depend on their specific interaction with the ribosome to inhibit protein synthesis, the altered tetracycline molecule can no longer bind to the ribosome with the same affinity or effectiveness. As a result, it cannot disrupt the translation process, and bacterial protein synthesis proceeds unimpeded. However, resistance to tetracyclines is usually attributed to one or more mechanisms which include (i) the acquisition of mobile genetic elements carrying tetracycline-specific resistance genes that code for energy-dependent efflux pumps of tetracyclines, mutation within the ribosomal binding site, and/or chromosomal mutations leading to increased expression of intrinsic resistance and (ii) a protein that protects bacterial ribosomes from the action of tetracyclines.[112, 113]

⑥ Efflux and reduced permeability

Many bacteria simply efflux the antibacterial agents outside the cells through certain pumps in their cell surface known as efflux pumps.[114] However, some bacterial species are intrinsically resistant to some antibiotics via reduced permeability and efflux pump. In addition, bacteria can acquire additional efflux pumps that specifically pump a single type of antibiotic, for example, TetA efflux pumps that specifically pump tetracycline from the cell. Via these molecular pumps, they can actively transport a wide variety of antimicrobial compounds and toxins out of the cells.[115] Efflux pumps can exhibit specificity towards a single substrate or have the ability to transport a variety of structurally dissimilar compounds. This includes antibiotics from various classes, and these pumps may be linked to the phenomenon of multiple drug resistance (MDR).[116]

Genes associated with efflux pumps can be obtained via intrinsic or acquired means. Certain bacteria possess these genes on their chromosomes, providing an inherent survival mechanism in challenging environments.

Other bacteria can procure these genes through diverse mechanisms such as mutations within local repressor genes, activation of a regulon controlled by a global transcriptional regulator, or the presence of efflux pump genes on plasmids. Chromosomal encoding is responsible for MDR efflux pumps, exemplified by NorA, NorB, MepA, and MdeA in *S. aureus*. Certain efflux pumps in Gram-positive bacteria are also carried around on plasmids or transposons, like QacA/B in *S. aureus* or MefA and MefB in *Streptococcus* spp., respectively.

Equally, the permeability of the cell can be altered by the acquisition of mutation in porns (protein channels through the cell membrane). These mutations can include porin loss, a modification of the size or conductance of the porin channel, or a lower expression level of a porin. Ultimately both mechanisms, efflux pumps reduced permeability, and lowered the intracellular antibiotic concentration in the bacterial cell by either exporting the antibiotic or by not allowing its importation, respectively.[88]

When a resistant strain of bacteria is the dominant strain in an infection, the infection may be untreatable and life-threatening. Examples of bacteria that are resistant to antibiotics include methicillin-resistant and life-threatening. Examples of bacteria that are resistant to antibiotics include methicillin-resistant *S. aureus* (MRSA), penicillin-resistant Enterococcus, and multidrug-resistant *Mycobacterium tuberculosis* (MDR-TB)

Many ways have been explored to inhibit efflux pumps, including, (a) disrupting channel protein assembly, (b) interfering with efflux pump gene expression, (c) preventing recognition by adding functional chains, and (d) developing small molecules as substrates to block activity of efflux pumps. Therefore, inhibition of efflux may result in several positive outcomes, including, (a) maintaining drug concentrations at therapeutic doses, (b) reducing multi-drug resistance, (c) reducing treatment periods, and (d) enhancing the activity of antibiotics susceptible to efflux.[117]

⑦ Genetic mechanisms of antibiotic resistance

A resistance gene contains the information for the production of a protein that makes an antibiotic ineffective and hence confers resistance against an antibiotic to a pathogen. Resistance genes are usually found on a ring-shaped piece of DNA, the plasmid. Like this, they can easily be passed on from one bacterium to another. Plants can possess resistance genes as well and they are usually directed against herbicides and pests. [118]

Antibiotic resistance genes are carried on mobile genetic elements such as transposons, integrons, and plasmids (the extrachromosomal genetic material that may be large and can contain a variety of resistance genes), which serve as vectors for transfer within the same species or between different species via processes of conjugation, transformation, and transduction.Two important types of genetic mechanisms can give rise to antibiotic resistance: (a) Genetic mutation and (b) Acquisition of new genetic material.

a. Genetic mutation

Through mutation and selection, bacteria can develop defense mechanisms against antibiotics. A mutation is a permanent change in an organism's genetic material. Mutation occurs naturally when cells divide. Bacteria are especially prone to mutation because their genome consists of a single chromosome and because they have a high rate of replication. The more replications a cell undergoes, the higher the chance it has to mutate. Bacterial pathogens can acquire genes and mutations that mediate resistance to antibiotics is called genetic resistance. Bacteria may acquire multiple mechanisms of resistance to the same antibiotic, and in MDR bacteria, they acquire resistance to multiple classes of antibiotics.

Mutation as a cause of antibiotic resistance has the greatest clinical impact on particular antibiotic classes or in particular bacterial pathogens. For example, some bacteria have developed biochemical 'pumps' that can remove an antibiotic before it reaches its target, while others have evolved to produce enzymes to inactivate the antibiotic. In specific species of bacteria, mutation is the primary, or sole, reason for AMR. Example-*Mycobacterium tuberculosis*, where the mutation is the primary cause of resistance to all clinical drugs in this bacterium.

Mutations are one way for bacteria to become resistant to antibiotics. Some spontaneous mutations (or genes that have been acquired from other bacteria through horizontal gene transfer) may make the bacterium resistant to an antibiotic. If the bacterial population is treated with a specific antibiotic, only the resistant bacteria will be able to multiply. These bacteria can now increase in numbers and the result is a population of mainly resistant bacteria.[68]

Resistance genes can be divided into the following categories based on the class of antibiotics they grant resistance to which include tetracyclines (tet), sulfonamides (sul), β-lactams (bla), macrolides (erm), aminoglycosides (aac), fluoroquinolone (fca), colistin (mcr), vancomycin (van), and multidrug (mdr).[119]

(b) Acquisition of new genetic material.

Acquisition of new genetic material that confers resistance is possible through all of the main routes by which bacteria acquire any genetic material: transformation, transposition, and conjugation (all termed horizontal gene transfer- HGT); plus, the bacteria may experience mutations to its chromosomal DNA

The acquisition of new genetic material also is a naturally occurring process in bacteria. This process appears to be the most common mechanism by which resistance develops; it is facilitated by the fact that bacteria are prokaryotic organisms (which means that they do not have a nucleus protecting the genome) and by the presence of small pieces of DNA called plasmids that exist in a bacterial cell separate from the chromosome

Genotypic and phenotypic profiles of antibiotic-resistant bacteria

When the AMR can be achieved without any genetic alteration is called phenotypic resistance. Non-inherited resistance is associated with specific processes such as growth in biofilms, a stationary growth phase, or persistence. Chromosomal-based genetic alteration drug resistance is called genotypic drug resistance. Mutation in drug targets is the most common mechanism of microbial resistance emergence. For example, the fluoroquinolone resistance mechanism can be attributed to genetic alterations as well as efflux pump machinery.

Out of 430 bacterial isolates obtained from patients with respiratory, intestinal, and wound infections and typhoid fever, 53% of isolates were multidrug-resistant (MDR) including 97% of *E. coli* (Table 11). *E. coli*, *P. aeruginosa* and *K. pneumoniae* strains harbored almost all of the resistance genes analyzed. *S. aureus* and *P. aeruginosa* isolates also had a high percentage of resistance genes, in particular ermB, aac(6′)-lb, and aac(3)-II. The most frequently identified ESBL gene was CTX-M-1 Amber class-A type) with the highest frequencies found in *E. coli* (30.0%), followed by *P. aeruginosa* (29.0%) and *K. pneumoniae* (28.0%). NDM-1, which is a metallo-lactamase of Amber class-B, was also commonly detected, which was predominant in *E. coli* (22.0%). The commonly detected macrolide resistance gene, ermB (55.0%) was detected in 24.0% *E. coli*, 19.0% *K. pneumoniae* and 16.0% in *P. aeruginosa*, whereas 30.0% of *P. aeruginosa* and 12.0% *S. aureus* were found to possess the aac(6′)-lb gene, which is a frequently detected aminoglycoside resistance gene. MDR pathogenic bacteria are highly prevalent in hospital settings in Bangladesh.[120]

Table 11. Phenotypic profiles of antibiotic-resistant bacteria in %[120]

S/N	Antibacterials	Gram-positive bacteria, %				Gram-negative bacteria, %				
		S. aureus (n = 84)	CNS (n=28)	*E. faecalis* (n=27)	*S. pneumoniae* (n = 36)	*E. coli* (n = 85)	*S. Typhi* (n = 82)	*P. aeru.* (n = 26)	*K. pneu-* (n = 42)	*A. baumannii* (n = 20)
01.	Vancomycin	08.0	06.0	19.0	09.0	-	-	-	-	-
02.	Cefoxitin	84.0	41.0	0	-	-	-	-	-	-
03.	Televancin	19.0	25.0	16.0	12.0	-	-	-	-	-
04.	Gentamicin	54.0	18.0	12.5	25.0	51.0	32.0	47.0	72.0	42.0
05.	Azithromycin	46.0	55.0	0	46.0	58.0	11.0	80.0	77.0	0
06.	Tetracycline	32.0	31.0	12.5	11.0	20.0	-	34.0	07.0	0
07.	Ciprofloxacin	53.5	68.0	38.0	03.0	36.0	10.0	59.0	67.0	09.0
08.	Clindamycin	50.0	38.0	12.0	25.0	-	-	-	-	27.0
09.	Chloramphenicol	0	10.0	08.0	0	07.0	09.0	23.0	21.0	-
10.	Rifampicin	61.0	38.0	19.0	10.0	-	-	-	-	-
11.	Linezolid	24.0	35.0	19.0	03.0	-	-	-	-	-
12.	SXT	06.0	12.0	12.0	0	-	-	-	-	-
13.	Penicillin	66.0	66.00	56.0	36.0	-	-	-	-	-
14.	Ampicillin	-	-	-	-	89.0	18.0	70.0	97.0	19.0
15.	Piperacillin-Tazobactam	-	-	-	-	21.0	-	41.0	17.0	0
16.	Cotrimoxazole	-	-	-	-	-	09.0	-	-	-
17.	Cetriaxone	-	-	-	-	40.0	0	45.0	50.0	34.0
18.	Cefixime	-	-	-	-	43.0	0	37.0	66.0	17.0
19.	Imipenem	-	-	-	-	56.0	0	45.0	14.0	-
20.	Nalidxic acid	-	-	-	-	-	89,0	-	-	-
21.	Colistin	-	-	-	-	0	-	11.0	10.0	0

CNS = Coagulase-negative Staphylococci SXT = Trimethoprim-sulfamethoxazole - = Not done

Antibiogram of Gram-positive and Gram-negative bacteria

The antibiogram study on combined data with case-based and lab-based surveillance has been analyzed to make it more representative of the country (Table 12). Linezolid has the highest sensitivity for Gram-positive bacteria including *S. aureus*, *Enterococcus* spp., and Coagulase-negative Staphylococci (CNS), whereas in the case of urine sample nitrofurantoin is the second highest sensitive antibacterial for all.

Fosfomycin (urine sample), and imipenem, meropenem, and amikacin are the topmost sensitive antibacterials against Gram-negative bacteria, especially *Escherichia coli*, *Klebsiella pneumoniae*, *Pseudomonas* spp. and *Proteus* spp. The imipenem, meropenem, and ceftriaxone showed the highest sensitivity against *Salmonella* spp., *Salmonella Typhi,* and non-typhoidal salmonella (NTS), whereas ceftriaxone showed the highest susceptibility to *Shigella* spp. In the case of the *Acinetobacter calcoaceticus-Acinetobacter baumannii* (ACB) complex, the susceptibility is less for most of the antibacterial drugs. The highest sensitive antibiotic is imipenem, followed by amikacin and meropenem against Gram-negative bacteria (Table 13).

Table 12. Antibacterial sensitivity pattern of Gram-positive and Gram-negative bacteria in Bangladesh (%)[36]

S/N	Antibacterials	Gram-positive bacteria			Gram-negative bacteria							
		S. aureus (n=4030)	ETC (n=3381)	CNS (n=212)	*S. pneu-* (n = 81)	*E. coli* (n=18067)	*K. pneu-* (n=7525)	*P. aeru.* (n= 3491)	Salmo- (n= 2916)	*S. Typhi* (n=2262)	*Proteus* (n=697)	*Shig.* (n=71)	NTS (n=39)
01.	Linezolid	79.0	90.0	85.0	93.0	-	-	-	-	-	-	-	-
02.	Nitrofurantoin*	72.0	85.0	82.0	-	79.0	41.0	-	-	-	-	-	-
03.	Doxycycline	66.0	-	70.0	65.0	-	-	-	-	-	-	-	-
04.	Tetracycline	-	22.0	-	-	-	42.0	-	-	-	-	-	-
05.	Gentamicin	64.0	-	36.0	-	69.0	55.0	-	-	-	46.0	-	-
06.	Clindamycin	44.0	-	35.0	72.0	-	-	-	-	-	-	-	-
07.	Oxacillin	36.0	-	66.0	-	-	-	-	-	-	-	-	-
08.	Ciprofloxacin	30.0	37.0	44.0	-	41.0	54.0	44.0	48.0	71.0	34.0	23.0	54.0
09.	Azithromycin	14.0	-	17.0	-	-	-	-	69.0	76.0	-	44.0	66.0
10.	Penicillin G	08.0	61.0	14.0	43.0	-	-	-	-	-	-	-	-
11.	Vancomycin	-	83.0	-	84.0	-	-	-	-	-	-	-	-
12.	Ampicillin	-	74.0	-	-	14.0	-	-	81.0	83.0	-	28.0	82.0
13.	Ceftriaxone	-	-	-	76.0	28.0	52.0	-	97.0	98.0	36.0	77.0	97.0
14.	Levofloxacin	-	-	-	52.0	-	-	-	86.0	94.0	-	-	86.0
15.	Erythromycin	-	-	-	26.0	-	-	-	-	-	-	-	-
16.	Fosfomycin	-	-	-	-	97.0	82.0	-	-	-	-	-	-
17.	Imipenem	-	-	-	-	92.0	84.0	68.0	99.0	99.0	67.0	-	-
18.	Amikacin	-	-	-	-	91.0	81.0	88.0	-	-	61.0	-	-
19.	Meropenem	-	-	-	-	91.0	82.0	68.0	98.0	99.0	82.0	-	-
20.	PT	-	-	-	-	74.0	68.0	60.0	-	-	55.0	-	-
21.	Cefepime	-	-	-	-	60.0	64.0	42.0	-	-	42.0	-	-
22.	Ceftazidime	-	-	-	-	57.0	59.0	38.0	-	-	29.0	-	-
23.	Aztreonam	-	-	-	-	50.0	58.0	35.0	-	-	41.0	-	-
24.	Amoxicillin-C	-	-	-	-	42.0	39.0	-	-	-	25.0	-	-
25.	Cefixime	-	-	-	-	27.0	37.0	-	-	-	29.0	-	-
26.	Cefuroxime	-	-	-	-	-	35.0	-	-	-	-	-	-
27.	Netilmycin	-	-	-	-	-	-	68.0	-	-	-	-	-

ETC = Enterococcus
CNS = Coagulase-negative staphylococci
S. pneu. = *Streptococcus pneumoniae*
K. pneu- = *Klebsiella pneumoniae*
P. aeru. = *Pseudomonas aeruginosa*
NTS = Non-typhoidal salmonella
Shig. = Shigella
SMT = Sulfamethoxazole-trimethoprim
PT = Piperacillin-tazobactam
Amoxicillin-C = Clavulanate

The highest resistance in the ACB complex was recorded with the carbapenem (42.0%), followed by *P. aruginosa* (32.0%) and *Enterobacteriaceae* (11.0%). *Proteus* spp. showed the highest resistance to ceftriaxone (64.0%), followed by *E. coli* (59.0%) and *K. pneumoniae* (48.0%).

Most of the tested antibacterials have developed more resistance with the increase of year time. *E. coli* was the most isolated bacteria in the laboratory. *Acinetobacter* spp., *P. aeruginosa*, *K. pneumoniae*, and *S. aureus* were reported more resistant among isolated bacteria. The sensitivity of most of the antibacterials tested against Gram-positive and Gram-negative bacteria was not satisfactory. However, linezolid and nitrofurantoin (in the

Table 13. Yearly trend of some antibacterial sensitivity against tested bacteria from 2017 to 2023[36]

S/N	Antibacterials	Sensitivity status of antibacterials in different years in %						
		2017	2018	2019	2020	2021	2022	2023
01.	Ampicillin	27.0	17.0	13.0	17.0	13.0	10.0	07.0
02.	Ceftazidime	38.0	33.0	33.0	39.0	25.0	18.0	15.0
03.	Clindamycin	39.0	40.0	39.0	40.0	55.0	47.0	52.0
04.	Ceftriaxone	48.0	40.0	36.0	43.0	38.0	29.0	20.0
05.	Cefuroxime	39.0	35.0	34.0	32.0	15.0	12.0	10.0
06.	Carbapenem	80.0	71.0	76.0	78.0	55.0	47.0	51.0
07.	Linezolid	70.0	73.0	74.0	82.0	83.0	81.0	88.0
08.	Norfloxacin	47.0	45.0	49.0	62.0	55.0	68.0	58.0
09.	Ofloxacin	43.0	51.0	45.0	34.0	32.0	17.0	-
10.	Piperacillin	38.0	22.0	27.0	33.0	25.0	18.0	12.0
A.	Overall MDR	71.0	76.0	71.0	74.0	78.0	80.0	82.0

case of urine samples) have been reported as more sensitive, whereas amikacin, imipenem, meropenem, and fosfomycin (in the case of urine) have been shown more sensitive against Gram-negative bacteria. Ceftriaxone and cefixime being the top listed used antibiotics have been reported poor sensitivity and the sensitivity has been decreased further. Ceftriaxone resistance has increased steadily and the carbapenem group of drugs has also shown an increased resistance trend. MDR bacteria (≥ 3 antibiotics) in case-based surveillance have increased over time from 71 to 82% from 2017 to 2023 (Table 13). More MDR bacteria have been recorded in *Acinetobacter* spp. followed by *Pseudomonas aeruginosa*. Increased sensitivity has been reported in clindamycin and surprisingly linezolid.

This study has recorded 69% non-ESBL and 31.0% ESBL-producing *E. coli* in the blood (n = 48), 30.0% MSSA, and 70.0% MRSA = Methicillin-resistant *S. aureus* in the blood (n = 150). Overall 51.0% of drugs have been reported as non-MDR and 49.0% as MDR bacterial pathogens. The overall percentage of MDR in some tested bacteria has been reported including 64.0% in *Acinetobacter* sp., 54.0% in *Pseudomonas aeruginosa*, 48.0% in *E. coli*, 47.0% in *Klebsiella pneumoniae* and 46.0% in *Staphylococcus aureus*.[36]

Spread of antibiotic resistance among bacteria

When a bacterium can survive or grow in an antibiotic concentration that would normally inhibit or kill other bacteria of the same species, it is considered resistant.[121] The development of resistance can occur through gene mutations or direct transfer of resistance genes, which can be carried on plasmids and transmitted through conjugation or the direct transfer of naked DNA through transformation or the transfer of similar DNA through bacteriophages.[77] Different resistant bacteria can be spread through various means including, person-to-person transmission, contaminated surfaces, healthcare settings, animal-to-human transmission, travel, and international spread. The spread of resistant bacteria can be influenced by factors such as poor hygiene, inadequate sanitation, and sub-optimal infection control practices.[122]

Drug resistance in bacterial pathogens

Most pathogenic microorganisms have the capability of developing resistance to at least some antimicrobial agents. The main mechanisms of resistance are: limiting uptake of a drug, modification of a drug target, inactivation of a drug, and active efflux of a drug. These mechanisms may be native to the microorganisms or acquired from other microorganisms.[73] Antimicrobial agents can be divided into groups based on the mechanism of antimicrobial activity. The main group includes: agents that inhibit cell wall synthesis (β-lactams-carbapenems, cephalosporins, monobactams, penicillins, glycopeptides), depolarize the cell membrane (lipopeptides), inhibit protein synthesis (bind to 30S ribosomal subunit- aminoglycosides, tetracyclines; bind to 50S ribosomal subunit- chloramphenicol, lincosamides, macrolides, oxazolidinones, streptogramins), inhibit nucleic acid synthesis (quinolones- fluoroquinolones), and inhibit metabolic pathway (sulfonamides, trimethoprim) in bacteria. Factors that have contributed to the growing resistance problem include: increased consumption of antimicrobial drugs, both by humans and animals; and improper prescribing of antimicrobial therapy.[73]

Antimicrobial resistance in diarrheal bacterial pathogens

The majority of both community and hospital participants have been reported to be colonized with Enterobacterales with resistance to extended-spectrum different antibiotics. The high burden of antimicrobial resistance (AMR) colonization observed among hospital and community participants may increase the risk of developing AMR infections and facilitate the spread of AMR in both the community and hospital.[123]

Bacteriological examination of 56132 stool samples and rectal swabs, of which 14428 bacterial pathogens were isolated. Among the isolated bacteria, *Vibrio* spp. (42.9%) was the most predominant, followed by *Shigella* spp. (20.3%), *Aeromonas* spp. (12.8%) and *Salmonella* spp. (6.4%). While *Vibrio cholerae* isolates remained sensitive to ciprofloxacin, an increase in resistance was observed in *Campylobacter* spp. and *Shigella flexneri.* Variations in susceptibility to other tested antibiotics were recorded among the isolated pathogens.[124]

Drug resistance in diarrheal bacterial pathogens

Diarrheal diseases are the second major cause of mortality in children under five years of age. Every year an estimated two billion clinical cases of diarrhea occur among children globally, of which nearly 0.5 million children aged under five years including about 50,000 neonates die annually due to diarrheal diseases.[125] Every year about 35,000 deaths have been reported among children with diarrheal diseases in Bangladesh[125,126]

Infectious diarrhea caused by bacterial pathogens contributes to the high level of morbidity and mortality in humans especially in children in developing countries including Bangladesh. A retrospectively analyzed of bacteriologically examined 56,132 stool samples and rectal swabs of diarrheic patients, of which 14,428 samples contained bacterial pathogens during the period from 2005 to 2008 in Dhaka. Among the recorded bacteria, *Vibrio* spp. (42.9%) has been reported to be predominant, followed by *Shigella* spp. (20.3%), *Aeromonas* spp. (12.8%), and *Salmonella* spp. (6.4%). While *Vibrio cholerae* isolates remained susceptible to ciprofloxacin, an increase in resistance was observed in *Campylobacter* spp. and *Shigella flexneri.* Variations of susceptibility to other tested antibiotics have been reported among the isolated pathogens (Table 14).[124]

Antibiotic-resistant bacteria have been found all over the world in common bacterial illnesses including diarrhea. Majority of the bacterial pathogens associated with diarrhea have been found developing antimicrobial resistance worldwide. Recent studies in Bangladesh have reported increased incidence of multi-drug resistance *E. coli*, *Salmonella* spp. and *Shigella* spp. in different human and environment samples (Table 14).[125]

Table 14. Antimicrobial resistance status of isolated bacteria from diarrheic patients in Dhaka[124]

Year	Isolated bacteria	No. of isolates tested	Resistance status to different antimicrobials, %							
			CIP	EM	CTM	TEC	AM	NA	CP	CRO
2005	*Vibrio cholerae* 01	2025	0	62.0	99.0	73.0	-	-	-	-
	V. cholerae non-01non-0139	0071	1	06.0	34.0	11.0	-	-	-	-
	Shigella flexneri	0587	1	-	67.0	-	34.0	73.0	-	-
	Shigella boydii	0193	0	-	54.0	-	34.0	55.0	-	-
	Shigella sonnei	0092	0	-	98.0	-	12.0	80.0	-	-
	Shigella dysenteriae	0053	0	-	72.0	-	26.0	49.0	-	-
	Salmonella spp.	0318	1	-	25.0	-	28.0	60.0	19.0	06.0
2006	Vibrio cholerae 01	1554	0	34.0	100	50.0	-	-	-	-
	V. cholerae non-01non-0139	0053	0	0	30.0	0	-	-	-	-
	Shigella flexneri	0475	5	-	75.0	-	54.0	82.0	-	-
	Shigella boydii	0159	0	-	43.0	-	28.0	62.0	-	-
	Shigella sonnei	0109	0	-	97.0	-	06.0	86.0	-	-
	Shigella dysenteriae	0060	0	-	68.0	-	32.0	55.0	-	-
	Salmonella spp.	0276	4	-	27.0	-	30.0	50.0	23.0	12.0
2007	*Vibrio cholerae* 01	1397	0	02.0	98.0	52.0	-	-	-	-
	V. cholerae non-01non-0139	0042	0	03.0	41.0	17.0	-	-	-	-
	Shigella flexneri	0064	14.0	-	69.0	-	54.0	88.0	-	-

Contd. Table 14.										
	Shigella boydii	0097	0	-	61.0	-	46.0	51.0	-	-
	Shigella sonnei	0057	0	-	97.0	-	02.0	79.0	-	-
	Shigella dysenteriae	0055	0	-	76.0	-	24.0	56.0	-	-
	Salmonella spp.	0189	4	-	20.0	-	35.0	40.0	16.0	08.0
2008	*Vibrio cholerae* 01	0956	0	0	99.0	70.0	-	-	-	-
	V. cholerae non-01non-0139	0067	0	0	31.0	05.0	-	-	-	-
	Shigella flexneri	0400	34.0	-	70.0	-	61.0	90.0	-	-
	Shigella boydii	0132	05.0	-	55.0	-	44.0	52.0	-	-
	Shigella sonnei	0069	15.0	-	97.0	-	06.0	90.0	-	-
	Shigella dysenteriae	0045	0	-	76.0	-	44.0	49.0	-	-
	Salmonella spp.	0175	4	-	23.0	-	25.0	56.0	16.0	16.0

CIP = Ciprofloxacin EM = Erythromycin CTM = Cotrimoxazole TEC = Tetracycline AM = Ampicillin NA = Nalidixic acid
CP = Chloramphenicol CRO = Ceftriaxone - = Not tested

These findings on the local burden of bacterial pathogens and their susceptibility pattern to different antimicrobial drugs will help physicians in the empirical treatment of diarrheal patients in endemic Bangladesh.

Antimicrobial resistance of *Vibrio cholerae*

Human cholera is caused by *Vibrio cholerae* and Bangladesh is one of the countries with the highest number of people at risk for cholera. Only two serogroups of *V. cholerae*, 01 and 0139 are considered causative agents of epidemic cholera. Developed high-income countries have controlled cholera but it is still a severe public health issue in low- and medium-income countries with an estimated 1,00,000 deaths per year.[127] Antibiogram study showed that the susceptibility to azithromycin increased slowly from 8.0% in 2006-2010 to 47.8% in 2016-2021 and the erythromycin sensitivity dropped substantially over 20 years period from 98.4% to 0.9%. Tetracycline susceptibility decreased in the urban site from 45.9% to 4.2%, and ciprofloxacin susceptibility decreased from 31.6% to 16.6% until 2015, then increased from 22.6% and 18.2% in 2016-2021, respectively. Since 2016, doxycycline showed 100% susceptibility (Table 15).

Table 15. Antimicrobial sensitivity (%) patterns of *Vibrio cholerae* in rural and urban Bangladesh[127]

S/N	Year	Samples sites	No. of isolates	Azithromycin	Doxycycline	Tetracycline	Ciprofloxacin	Erythromycin
1.	2000 -'05	Urban	2,582	-	-	45.91	31.56	98.45
		Rural	1,015	-	-	63.39	47.94	85.17
2.	2006 -'10	Urban	2.752	08.53	-	27.33	33.59	00.27
		Rural	0562	-	-	19.26	26.34	13.72
3.	2011-'15	Urban	1,370	43.69	-	04.16	16.63	00.32
		Rural	0293	42.14	-	02.69	13.60	00.50
4.	2016 -'21	Urban	1,518	47.78	100	22.59	18.22	00.96
		Rural	0259	57.86	-	14.66	12.13	00.61
	P-value	Urban	-	0.160	-	< 0.001	< 0.001	< 0.001
		Rural	-	-	-	< 0.001	< 0.001	< 0.001

n= No. of isolates - = not detected

Clinicians need access to up-to-date information on antimicrobial sensitivity for treating hospitalized patients. To achieve the WHO-backed objective of eliminating cholera by 2030, the health systems need to be put under a proper surveillance system that may help to improve water and sanitation practices and deploy oral cholera vaccines strategically.[127]

Enteric pathogens of human and animal sources

Diarrhea, defined as three or more loose stools per day, remains one of the leading causes of premature deaths in children under five with a 12.69% mortality in Bangladesh.[128] Transmission of diarrheal fecal pathogens to a new human host through different environmental pathways, including fingers, flies, fluids, and food.

Zoonotic enteric pathogens are transmitted where animal husbandry is a primary source of income, where livestock including poultry birds roam freely within the home environment and their enteric pathogens are transmitted through feces.

Bacterial pathogens with acute gastroenteritis in children (2014-2019)

Out of 387 diarrheic stool samples examined, of which 152 (39.27%) had bacterial infections. *E. coli* was the most prevalent (17.3%), followed by *Vibrio cholerae* (13.5%), *Salmonella* spp. (4.9%), and *Shigella* spp. (3.6%). A higher rate of concurrent infection with *E. coli* and rotavirus was recorded in 48.0% of cases. *E. coli* and *V. cholerae* were found most resistant against ciprofloxacin (62.7%) and tetracycline (88.5%), from which qnrA and sul4 resistance genes were isolated from these pathogens.[126]

Multidrug resistance pattern bacteria isolated from diarrheic children (2019-2021)

Of the 404 stool samples of diarrheic children examined, of which 251 (63.0%) had bacterial infections. *E. coli* (29.0%) was the most prevalent, followed by *Shigella* spp. (17.0%), *V. cholerae* (13.0%), and *Salmonella* spp. (5.5%) along with some concurrent infections. The isolated bacterial pathogens (*E. coli, Shigella* spp., *V. cholerae*, *Salmonella* spp.) showed the highest frequency of resistance against ceftriaxone (75-85%), and erythromycin (70-75%). About 10-20% of isolates of *E. coli*, *V. cholerae* and *Shigella* spp. showed MDR against cephem (ceftriaxone), macrolides (erythromycin), and quinolones including ciprofloxacin, and norfloxacin (Table 15).

Multidrug-resistant enteric pathogens

Diarrheal diseases are a leading cause of morbidity and mortality worldwide, causing over 6.3 billion episodes and 1.3 million deaths annually globally, with the majority of cases occurring in developing nations including Bangladesh.[129] Out of 2172 patients ≥ 5 years of age (including children, adults & elderly patients) with acute diarrhea, stool cultures were completed for 2135 patients, with 1198 (56.1%) samples having enteric pathogens, with antimicrobial susceptibility results. The overall prevalence of MDR was 54.3% with the highest in Aeromonas spp. (81.5%), followed by *Campylobacter* spp. (72.1%), *Vibrio cholerae* (28.1%), *Shigella* spp. (26.2%) and *Salmonella* spp. (5.2%). It appears that over half of all culture-positive samples of patients over 5 years of age with diarrhea in urban Bangladesh demonstrated MDR (Table 16). A lack of consistency in the risk factors assessed evaluating MDR in enteric pathogens, however, factors associated with having MDR organism in multiple logistic regression included longer transport time to the hospital (> 90 minutes), greater stool frequency, antibiotic use before hospital presentation, and non-flush toilet use have been reported.[129]

Table 16. Antibacterial resistance profiles of bacterial pathogens isolated from diarrheic children[125]

S/N	Bacterial species	No. of isolates	Resistant status of tested antibacterials, No. (%)										
			CRO	IPM	MEM	E	TET	DOX	CIP	NOR	CP	CL	COT
1.	*E. coli*	117	92 (79)	19 (16)	12 (10)	92 (79)	61 (52)	46 (39)	68 (58)	72 (62)	60 (52)	33 (28)	53 (45)
2.	*V. cholerae*	53	41 (77)	08 (15)	09 (17)	43 (81)	20 (38)	23 (43)	27 (51)	33 (62)	30 (56)	14 (26)	23 (44)
3.	*Salmonella* spp.	22	17 (77)	04 (18)	07 (32)	19 (86)	09 (41)	10 (45)	12 (55)	15 (68)	13 (59)	05 (23)	10 (45)
4.	*Shigella* spp.	68	60 (88)	11 (17)	17 (25)	52 (76)	17 (25)	32 (47)	38 (56)	49 (72)	42 (62)	19 (28)	36 (53)

CRO = Ceftriaxone IPM = Imipenem MEM = Meropenem E = Erythromycin TET = Tetracycline DOX = Doxycycline
CIP = Ciprofloxacin NOR = Norfloxacin CP = Chloramphenicol CL = Colistin COT = Cotrimoxazole

Antimicrobial resistance of *Campylobacter* species in diarrheal patients

Campylobacter spp. are considered to be zoonotic pathogens that cause foodborne gastroenteritis in humans globally including Bangladesh. A study recorded an overall 31.5% (104/330) *Campylobacter* spp. that comprised the prevalence of 21.8% *C. jejuni* and 9.6% *C. coli*. Among the isolates, 27.3% (n = 20) of *C. jejuni* and 31.2% (n = 10) of *C. coli* showed multiple drug resistance (MDR) to ≥ 3 antimicrobial agents.[130]

Drug resistance in bacteremia and septicemia-associated bacterial pathogens

Human patients affected with bloodstream infections (bacteremia) are treated empirically based on their

clinical findings in developing countries including Bangladesh. Therefore, a study was conducted to identify the bacterial pathogens causing major bloodstream infections and to determine their antibiotic susceptibility pattern in Dhaka. A total of 103,679 single-bottle blood samples cultured showed that 72.1% had Gram-negative and 13.6% had Gram-positive bacterial infections. *Salmonella typhi* was the most frequently isolated bacteria (36.9%) with a high rate of these strains being MDR (Table 17). Overall, Gram-positive bacteria were more resistant to most of the commonly used antibiotics than Gram-negative bacteria but the MDR level was high in both groups (Table 17).[131]

Table 17. Antimicrobial resistance status of major bacteria isolated from blood culture of human patients in Dhaka from 2005 to 2014[131]

S/N	Bacterial species/ Strains / Isolates	No. of isolates tested	Antimicrobials test results %															
			AMP	SXT	CIP^R	CIP^I	CRO	CFM	CN	NET	AK	IMP	CAZ	P-G	E	AZI	C	V
1.	*Salmonella typhi*	5190	43.0	39.0	02.0	92.0	0	01.0	-	-	-	-	-	-	-	-	-	-
2.	*S. paratyphi* A,B	1253	01.0	01.0	01.0	97.0	0	01.0	-	-	-	-	-	-	-	-	-	-
3.	*Escherichia coli*	0427	90.0	69.0	59.0	02.0	06.0	53.0	32.0	09.0	07.0	06.0	39.0	-	-	-	-	-
4.	*Strep. pneumoniae*	0276	01.0	80.0	02.0	13.0	0	06.0	-	-	-	-	-	04.0	14.0	06.0	-	-
5.	*Staph. aureus*	219	90.0	30.0	50.0	04.0	42.0	-	23.0	-	-	-	-	-	60.0	-	06.0	-

AMP = Ampicillin SXT = Cotrimoxazole CIP^R = Ciprofloxacin resistance CIP^I = Ciprofloxacin intermediate CRO = Ceftriaxone
CFM = Cefixime CN = Gentamicin NET = Netilmicin AK = Amikacin IMP = Imipenem
CAZ = Ceftazidime

Salmonellosis is an acute invasive enteric disease of a wide host range distributed worldwide, and non-typhoidal Salmonella (NTS) infection is of global public health importance, especially in low-income countries including Bangladesh. Treatment is critical for patients with severe disease, particularly children and immune-compromised people. The emergence of resistance to first-line therapy like ampicillin, chloramphenicol, and cotrimoxazole including ciprofloxacin among *Salmonella* spp. during the last decade has complicated the situation. Extended-spectrum cephalosporins (ESCs) are considered an alternative therapeutic choice but with the increased use of β-lactam antibiotics to treat enteric infection, *Salmonella* spp. has acquired resistance to third-generation cephalosporin and associated with clinical treatment failure.[132] Out of 128,312 stool samples of diarrheal patients examined, 2120 (1.7%) had *Salmonella* spp. infection. Among the typhoidal Salmonella (TS) serogroups, *S. typhi* was predominant (n = 404; 65.1%), followed by *S. paratyphi* B (n = 139; 22.4%), and *S. paratyphi* A (n= 78; 12.6%). Of the NTS isolates, the serogroup C1 (n = 560; 37.0%) was predominant followed by B (n = 379; 25.0%), C2 (n = 203; 14.0%), E (n = 127; 9.0%) and D (n = 94; 6.0%). Most of the resistance was found towards nalidixic acid (40.0%), ampicillin (36.0%), cotrimoxazole (20.0%), chloramphenicol (13.0%), ciprofloxacin (4.0%) and ceftriaxone (4.0%). Multiantibiotic resistance (MAR ≥ 3 drugs) was more common among TS than NTS strains.[132] It has concluded that the higher prevalence of MAR *Salmonella* spp. among children aged <5 years and bla_{TEM} gene-mediated ESBL production among *Salmonella* spp. isolated from stool samples of diarrheal patients in urban Bangladesh. The emergence of MAR *Salmonella* spp. in particular extended-spectrum beta-lactamases (ESBL) strains should be considered a public health concern.

Drug resistance in neonatal septicemia causative bacteria

The sensitivity pattern of the causative bacteria is very important for effective control of septicemia in neonate patients. Blood samples were collected from 1000 neonatal septicemic patients, of which bacteria were isolated in 194 (19.4%) neonatal patients. The bacteria that were isolated were *Pseudomonas* spp. (31.4%), *Klebsiella pneumoniae* (23.2%), *Staphylococcus aureus* (12.4%), *Escherichia coli* (7.2%), *Acinatobactor* (5.7%), Gram-negative Bacilli (4.1%), *Flavobacterium* spp. (3.6%), *Serratia* spp. (5.7%), *Citrobacter fruendi* (3.1%), *Streptococcus* spp. (2.6%), and *Enterococcus* spp. (1.0%). A majority of the bacterial isolates in neonatal sepsis were found sensitive to imipenem (91.9%), ciprofloxacin (57.2%) and resistant to commonly used antibiotics like ampicillin (96.4%) and cephalexin (89.2%).

Drug resistance in bacterial pathogens in intensive care unit patients

Healthcare-associated infections (HAIs) are especially important in intensive care units (ICUs) where they have a five-fold higher incidence rate compared to the general inpatient population.[133] This is due to the increased use of invasive medical instruments such as mechanical ventilators, monitoring devices, and blood, and urine catheters, which in turn is a result of the overt use of broad-spectrum antibiotics. The HAIs are important in clinical practices for which surveillance studies obtain the required data on the regional microorganisms and their susceptibility to antibiotics would be required. A cross-sectional study was conducted to collect 100 specimens (blood, urine, tracheal aspirate, sputum, wound swab, pus, and endotracheal tubes) from patients admitted to the ICU who had signs of nosocomial infection, subjected to culture and analyzed with antibiogram (Table 18).

Klebsiella spp., *Acinetobacter* spp., and *Pseudomonas* spp. have been reported to be the most common resistant bacterial pathogens among all bacteria (Table 17). Meropenem was the most sensitive antibiotic against *Klebsiella* spp. (84.6%) and cotrimoxazole in *Acinetobacter* spp. (60.0%). *E. coli* was a frequent bacterial pathogen in patients with UTI which were mostly sensitive to Amikacin (73.3%) and meropenem (86.6%) and resistant to ceftriaxone (80.0%), and ceftazidime (64.2%). The MAR *Klebsiella*, *Pseudomonas*, and *Acinetobacter* species have given new dimensions to the problem of hospital-associated infections. Regular monitoring of the pattern of resistance of common pathogens in the ICUs is essential to up-to-date the use of rational antibiotics regiments.

Table 18. Frequency of different bacterial pathogens isolated from ICU patients and their resistance (%) pattern of antibacterials[133]

S/ Antibacterials N	*Acinetobacter* (n = 29)	*Klebsiella* (n = 26)	*Pseudomonas* (n = 18)	*E. coli* (n = 15)	*Staph. aureus* (n = 6)	*Streptococcus* (n = 4)	*Salmonella* (n = 1)	*M. morganii* (n = 1)
01. Amoxicillin	100	100	100	-	-	50.0	-	100
02. P + R	33.3	66.6	50.0	33.3	0	-	-	-
03. Ceftriaxone	85.1	84.6	70.5	80.0	100	75.0	0	100
04. Ceftazidime	88.8	82.6	66.6	64.2	100	75.0	0	100
05 Cefotaxime	85.7	71.4	54.5	50.0	-	-	-	100
06. Amikacin	86.2	46.1	68.7	26.6	80.0	100	0	100
07. Gentamicin	84.4	66.6	38.8	50.0	84.4	75.0	0	100
08. Netilmicin	80.7	60.0	50.0	42.8	100	100	-	100
09. Azithromycin	100	100	75.0	-	-	100	-	100
10. Clindamycin	50.0	100	84.4	-	-	100	-	100
11. Ciprofloxacin	89.2	66.6	86.6	85.7	100	100	100	100
12. Levofloxacin	86.2	65.2	81.2	85.7	75.0	100	100	100
13. Meropenem	79.3	15.3	52.9	13.3	50.0	75.0	0	100
14. Colistin	60.0	33.3	80.0	0	100	50.0	-	100
15. Cotrimoxazole	40.0	81.8	100	66.6	75.0	100	-	100

P + R = Piperacillin + Tazobactum n = No. of isolates - = Not done

Antimicrobial resistance of bacterial pathogens in the neonatal care unit

A study was conducted to identify the antimicrobial susceptibility pattern and relevant treatment options in a Neonatal intensive care unit in Dhaka, for which 78 blood culture-positive isolates, of which 26.0% Gram-positive and 74.0% Gram-negative bacterial isolates. Most of the Gram-positive isolates exhibited higher resistance to penicillin, cephalosporin, macrolides, gentamicin, and quinolones. Susceptibility to commonly used antimicrobials was found to vancomycin (100%), chloramphenicol (100%), rifampicin (84.0%), and linezolid (100%). *Acinetobacter* spp. (32.1%), are the commonest bacteria responsible for sepsis infection in neonates followed by *Klebsiella* species (n =14, 18.0%). Most of the Gram-negative bacteria showed resistance to cephalosporin and aminoglycosides; about two-thirds showed resistance to meropenem, quinolones, and combination preparation of piperacillin and tazobactam. The best overall sensitivity among Gram-negative isolates was 100% with polymyxin B and 97.0% with minocycline (Table 19).[134]

Table 19. Antimicrobial sensitivity (%) patterns of Gram-positive and Gram-negative bacteria isolated from a neonatal intensive care unit in Dhaka[134]

S/N	Bacterial pathogens	Gram-positive bacteria (n = 20)			Gram-negative bacteria (n = 58)					
		CNS	SP	EF	ABTS	KS	SM	ES	BC	PS
01.	Ampicillin	2/13 (15.4)	1/4 (25.0)	1/3 (33.3)	-	-	-	-	-	-
02.	Cefuroxime	3/13 (23.1)	1/4 (25.0)	1/3 (33.3)	4/25 (16.0)	2/14 (14.3)	1/7 (14.3)	1/6 (16.7)	1/5 (20.0)	-
03.	Gentamycin	3/13 (23.1)	1/4 (25.0)	1/3 (33.3)	2/25 (08.0)	1/14 (07.1)	1/7 (14.3)	1/6 (16.7)	-	-
04.	Cotrimoxazole	6/13 (46.2)	2/4 (50.0)	1/3 (33.3)	6/25 (24.0)	3/14 (21.4)	2/7 (28.6)	2/6 (33.3)	1/5 (20.0)	-
05.	Ciprofloxacin	5/13 (38.5)	2/4 (50.0)	2/3 (66.7)	-	-	-	-	-	-
06.	Erythromycin	2/13 (15.4)	1/4 (25.0)	1/3 (33.3)	-	-	-	-	-	-
07.	Clindamycin	5/13 (38.5)	2/4 (50.0)	1/3 (33.3)	-	-	-	-	-	-
08.	Rifampicin	11/13 (84.6)	1/4 (25.0)	2/3 (66.7)	-	-	-	-	-	-
09.	Linezolid	13/13 (100)	4/4 (100)	3/3 (100)	-	-	-	-	-	-
10.	Vancomycin	13/13 (100)	4/4 (100)	3/3 (100)	-	-	-	-	-	-
11.	Chloramphenicol	13/13 (100)	4/4 (100)	3/3 (100)	10/25 (40.0)	5/14 (35.7)	3/7 (42.9)	3/6 (50.0)	2/5 (40.0)	-
12.	Ceftazidime	-	-	-	2/25 (08.0)	1/14 (07.1)	1/7 (14.3)	1/6 (16.7)	-	-
13.	Cefipime	-	-	-	2/25 (08.0)	1/14 (07.1)	1/7 (14.3)	1/6 (16.7)	-	-
14.	Cefixime	-	-	-	5/25 (20.0)	3/14 (21.4)	2/7 (28.6)	2/6 (33.3)	1/5 (20.0)	-
15.	Ceftriaxone	-	-	-	5/25 (20.0)	4/14 (28.6)	2/7 (28.6)	2/6 (33.3)	1/5 (20.0	-
16.	Amikacin	-	-	-	4/25 (16.0)	3/14 (21.4)	2/7 (28.6)	2/6 (33.3)	1/5 (20.0)	-
17.	Tobramycin	-	-	-	-	-	-	-	-	-
18.	Levofloxacin	-	-	-	7/25 (28.0)	4/14 (28.6)	2/7 (28.6)	2/6 (33.3)	1/5 (20.0)	-
19.	Piperacillin + TC	-	-	-	10/25 (40.0)	6/14 (42.9)	3/7 (42.9)	3/6 (50.0)	2/5 (20.0)	-
20.	Meropenum	-	-	-	6/25 (24.0)	4/14 (28.6)	2/7 (28.6)	2/6 (33.3)	1/5 (20.0)	-
21.	Colistin	-	-	-	21/25 (84.0)	11/14 (78.6)	6/7 (85.7)	5/6 (83.3)	4/5 (80.0)	1/1 (100)
22.	Polymixin B	-	-	-	25/25 (100)	14/14 (100)	7/7 (100)	6/6 (100)	5/5 (100)	1/1 (100)
23.	Minocycline	-	-	-	25/25 (100)	14/14 (100)	7/7 (100)	6/6 (100)	5/5 (100)	1/1 (100)

TC = Tazobactam combination; CNS = Coagulase negative Staphylococci; SP = *Streptococcus pneumoniae*; EF = *Enterococcus faecium*
ABTS = *Acinetobacter* spp.; KS = *Klebsiella* spp.; SM = *Stenotrophomonas maltophilia*; ES = *Enterobacter* spp.
BC = *Burkholderia cepacia*; PS = *Pseudomonas* spp.; No. of isolates, Sensitive / Tested

Drug resistance in blood bacterial isolates in septicemic patients

Septicemia in critically ill patients is a life-threatening condition that requires rapid antimicrobial therapy but infections caused by antibiotic-resistant bacterial pathogens are more likely to increase the risk of death in these patients. A study was conducted to identify the bacterial pathogens causing septicemia and their antibiotic resistance pattern in an intensive care unit (ICU) in Dhaka. Out of 696 blood samples examined from 363 septicemic patients, of which 92 blood samples yielded the growth of 94 microbes, which included 89 bacteria and five fungal isolates (Table 20).

Table 20. Frequency of isolated microbes from blood culture and their antibiogram status[135]

S/N	Microbes	Positive	Resistance status against different antimicrobials, %																
		No. (%)	AMP	AK	GN	NT	CFT	CTX	CP	P+T	CL	TC	ATN	CZ	CT	C	IPM	FA	VM
1.	*Acinetobacter*	28 (29.7)	-	85.7	100	78.6	100	100	92.6	92.0	0	43.5	-	100	-	-	85.2	-	-
2.	*Pseudomonas*	25 (26.5)	-	92.0	95.8	95.7	75.0	61.5	32.0	04.3	52.4	-	54.5	56.0	20.0	52.2	69.6	-	-
3.	*Klebsiella*	17 (18.1)	-	62.5	70.6	70.6	81.2	82.4	82.4	76.5	18.8	-	-	82.4	75.0	43.8	70.6	-	-
4.	*E. coli*	11 (11.7)	-	20.0	18.2	18.2	100	100	81.8	36.4	-	-	-	100	77.80	0	09.1	-	-
5.	Enterococci	04 (04.2)	25.0	100	100	100	-	-	100	-	-	-	-	-	100	100	-	100	0
6.	*Staph. aureus*	02 (02.1)*	-	0	100	0	-	-	100	-	-	-	-	100	100	100	-	-	0
7.	Flavobacteria	02 (02.1)	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
8.	Candida	05 (05.3)	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
	Total isolates	94																	

*Others resistance- Oxacillin, Amoxicillin, Erythromycin, and Rifampicin 100% - = Not done

AMP = Ampicillin; AK = Amikacin; GN = Gentamicin; NT = Netilmicin; CFT = Cefotaxime; CTX = Ceftriaxone
CP = Ciprofloxacin; P + T = Piperacillin + Tazobactam; CL = Colistin; TC = Tigecycline; ATN = Aztreonam; CZ = Ceftazidime
CT = Co-trim; C = Chloramphenicol; IPM = Imipenem; FA = Fusidic acid; VM = Vancomycin

All the isolates tested for antibiogram showed resistance (> 50.0%) to third-generation cephalosporins. Acinetobacter was highly resistant (>75.0%) to most of the tested antimicrobials except colistin. Isolated

Pseudomonas was also resistant to aminoglycosides (> 90%) and imipenem (> 65.0%). Klebsiella was resistant to aminoglycosides and imipenem, but *E. coli* was sensitive to these antibacterials (Table 19).[135] These findings on antibacterial resistance of blood isolates reported in ICU patients with septicemia will guide the intensivists to formulate the initial empiric antibiotic therapy for the critically ill patients of ICU.

Drug resistance of bacterial pathogens of diarrheic children

Bacteriological and antibiogram studies were conducted on 31 clinical cases of Pseudomonas bacteremia under five children showed a prevalence rate very low at 1.0% (31/5) but is associated with a high case-fatality rate (26.0%). The isolated Pseudomonas was found multi-drug resistant (gentamicin 48.0%, netilmicin 26.0%, amikacin 23.0%) but was sensitive to ceftazidime (84.0%) and imipenem (100%). These findings on Pseudomonas bacteremia under five children may help prompt as well as aggressive clinical management with rapid fluid infusion and sensitive antibiotics could result in reduced morbidity and mortality affected children.[136]

Antibiogram of isolated bacteria of diarrheic children

A bacteriological examination of 186 stool samples showed 55 (29.57%) cases affected with bacterial diarrhea, of which the predominant isolate was *E. coli* 39 (70.91%), followed by *Salmonella* 9 (16.36%), and *Shigella* spp. 7 (12.73%). Approximately 84.62% of *E. coli* were resistant to co-trimoxazole and cefuroxime while 92.31% of *E. coli* were sensitive to amikacin and 71.79% were sensitive to cefepime and gentamicin. Salmonella was 100% sensitive to cefepime, ceftriaxone, cefixime, ceftazidime, and ciprofloxacin, while *Shigella* spp. was 85.71% sensitive to amikacin and cefepime.[137] The results show that *E. coli* was the most frequently isolated bacterial pathogen in diarrheic children in Bangladesh. The majority of the bacterial isolates were resistant to multiple antibiotics and hence, antibiotic sensitivity before prescribing any antibiotics would be required.

Drug resistance of pneumonia-causing bacteria

Bacteriological culture and PCR methods have been used to detect bacterial infection in 105 sputum and blood samples collected from patients affected with clinical pneumonia. Out of 105 samples, 23 (37.12%) were positive by Gram stain, 29 (27.62%) yielded growth in culture media and 37 (35.24%) were positive by PCR. Overall bacteria were isolated from 55 (52.38%) sputum and only 2 (1.9%) blood samples. Only *Streptococcus pneumoniae* and *Pseudomonas aeruginosa* were isolated from blood samples. Three groups of bacteria viz. (a) Gram-positive cocci (*S. pneumoniae* 19.05%, *S. aureus* 2.86%), (b) Gram-negative bacilli (*Klebsiella pneumoniae* 13.33%, *P. aeruginosa* 5.71% & *E. coli* 1.9%) and (c) Gram-negative coccobacilli (*Haemophilus influenzae* 8.57% & *Acinetobacter baumani* 0.96%) were isolated and identified. It appears that *Streptococcus pneumoniae* was the most common causal agent (19.05%), followed by *Klebsiella pneumoniae* (13.33%), *Haemophilus influenzae* (8.57%), and *Pseudomonas aeruginosa* (5.71%). More than 80% of *Streptococcus pneumoniae* isolates were found to be sensitive to ampicillin, amoxicillin-clavulanate, and ceftriaxone, whereas other antimicrobials ranged from 65% for azithromycin to 70% for levofloxacin. The isolated Gram-negative bacteria were more sensitive to meropenem, ceftriaxone, amoxicillin-clavulanate, and amikacin.[138]

Drug resistance in invasive pneumococcal bacteria in rural children

Streptococcus pneumoniae infection is recognized as a global priority public health problem, and conjugate vaccines have been shown to prevent vaccine-type invasive pneumococcal disease (IPD) in children. Pneumonia was the single most common form of illness reported among 2596 hospitalizations (n = 977; 38%) of cases. A total of 26 *S. pneumoniae* isolates (25 isolates from 6925 blood cultures & 1 isolate from 41 CSF cultures), gave an overall IPD incidence of 86 cases per 100,000 children/year. The most prevalent pneumococcal serotypes are recorded as 1, 5, 14, 18C, 19A, and 38. Ten of the 26 isolates were completely resistant to trimethoprim-sulfamethoxazole, and another 10 isolates had intermediate resistance. Data on serotype distribution would help to guide appropriate pneumococcal conjugate vaccine formation.[139]

Drug resistance in *Escherichia coli* infection in humans

Enterotoxigenic *E. coli* (ETEC) is a common cause of bacterial infection leading to acute watery diarrhea in

children and travelers to ETEC-endemic countries. Out of 8580 stool samples examined, 1067 (12.0%) samples had ETEC infection. The majority of the ETEC strains isolated showed high resistance to the 12 different antibiotics tested, including members of the quinolone (nalidixic acid) and fluoroquinolone groups (ciprofloxacin or norfloxacin). The antibiotic resistance pattern was as follows: ampicillin 66%, azithromycin 27%, ciprofloxacin 27%, ceftriazone 13%, Sulfomethoxazole-trimethoprim 46%, doxycycline 44%, erythromycin 96%, nalidixic acid 83, norfloxacin 27%, streptomycin 48%, and tetracycline 42% respectively. Resistance to ciprofloxacin increased from 13% in 2005 to 34% in 2009. However, none of the strains was resistant to mecillinam.[140] The emergence of ciprofloxacin-resistant ETEC strains results in a major challenge in current treatment strategies for ETEC diarrhea.

A study was conducted on the antimicrobial sensitivity of *E. coli* isolated from clinical sources of Diagnostic Center Dhaka to facilitate the preference of drugs in the management of *E. coli*-induced symptoms and their findings are presented in Table 21.

Table 21. Antibacterial sensitivity pattern of clinical isolates of *E. coli* (n = 80 isolates) (Shahriar et al. 2010)[141]

S/N	Antibacterials	Sensitivity No. (%)	S/N	Antibacterials	Sensitivity No. (%)	S/N	Antibacterials	Sensitivity No. (%)	S/N	Antibacterials	Sensitivity No. (%)
01.	Ampicillin	03 (04.0)	05.	Chloramphenicol	18 (22.5)	09.	Doxycycline	10 (12.5)	13.	Netilmicin	28 (35.0)
02.	Aztreonam	03 (04.0)	06.	Ciprofloxacin	06 (07.5)	10.	Gentamicin	45 (56.0)	14.	Tetracycline	20 (25.0)
03.	Ceftazidime	13 (16.3)	07.	Cloxacillin	04 (05.0)	11.	Imipenem	76 (95.0)			
04.	Ceftriaxone	10 (12.5)	08.	Co-trimoxazole	16 (20.0)	12.	Nalidixic acid	04 (05.0			

Very low sensitivity of *E. coli* isolates was recorded in most of the tested antibacterials but a higher sensitivity pattern was observed for gentamicin (56.0%) and imipenem (95.0%) which could be considered for the therapeutic management of *E. coli*-induced patients.

Drug resistance in Shigella serotypes

A total of 227 *Shigella* spp. and their serotypes have been identified along with their antibacterial resistance pattern. The *S. flexneri* (54%) was most frequently isolated, followed by *S. dysenteriae* (20%), *S. boydii* (16%), and *S. sonnei* (10%). Among *S. flexneri* (n = 122), 29 (24%) were 2a and 23 (19%) were 2b. None of the Shigella strains were resistant to mecillinam or ciprofloxacin. Resistance to nalidixic acid was most frequent among *S. dysenteriae* type 1 (100%), followed by *S. flexneri* 2a (69%), and *S. flexneri* 2b (52%). Systemic monitoring is needed to identify the most prevalent serotypes and to detect changes in the prevalence and antimicrobial resistance pattern.[142]

Antimicrobial resistance of Shigella isolates

Shigellosis is one of the significant causes of diarrheal diseases in humans. Globally, an estimated 165 million cases and 1.1 million deaths mostly in low-income countries including Bangladesh occur annually.[143] Antibacterial therapy has been recommended in shigellosis patients because it can limit the clinical course of illness and reduce the risk of complications and the duration of fecal excretion of the causative agent reducing the spread of infection. However, the major problem is the increasing resistance of *Shigella* spp. to common antibacterial agents. Antibacterial resistance status of Shigella isolates in Bangladesh between 2001-2002[143] and 1991-1992[144] have been compared to identify the changes in resistance patterns and trends (Table 22).

Table 22. Comparison of antimicrobial resistance pattern of Shigella isolates between 1991-1992 and 2001-2002 in Bangladesh[143]

S/N	Study year	No. of isolates isolates	Resistant pattern of Shigella isolates with different antimicrobials, %											
			SXT	NA	ML	AMP	AZM	TET	CTX	CX	AMC	CP	GN	CIP
1.	1991-'92	369	52	19	0.5	53	-	74	0	-	-	49	0.2	0
2.	2001-'02	266	72	51	03	56	16	79	2	2	0	42	4	
	p-value		<0.01	<0.01	<0.01	ns	-	ns	ns	-	-	ns	<0.01	0

SXT = Trimethoprim-sulfamethoxazole NA = Nalidixic acid ML = Mecillinam AMP = Ampicillin AZM = Azithromycin
TET = Tetracycline CTX = Ceftriaxone CX = Cefxime AM-C = Amoxicillin-Clavulanate CP = Chloramphenicol
GN = Gentamicin CIP = Ciprofloxacin

The Shigella strains developed resistance to many antibacterial agents, including mecillinam, azithromycin, ceftriaxone, and cefixime in Bangladesh.

Multidrug resistance (MDR) to Shigella

MDR strains are defined as simultaneously resistant to ≥ 3 of eight common antimicrobial agents (ampicillin, trimethoprim-sulfamethoxazole, nalidixic acid, ciprofloxacin, mecillinam, tetracycline, azithromycin, and ceftriaxone/cefixime) were detected in 63% of the isolates. Resistance to ampicillin, trimethoprim-sulfamethoxazole, nalidixic acid, and tetracycline was most frequent (48%), followed by resistance to ampicillin, trimethoprim-sulfamethoxazole, and tetracycline (R-type ApSXTTe; 18%), nalidixic acid, trimethoprim-sulfamethoxazole, and tetracycline (R-type NaISXTTe; 14%). Resistance to one and two drug(s) was 8% and 19%, respectively. Only 26 (10%) isolates were susceptible to all eight drugs tested (Table 23).

Table 23. Patterns of resistance of Shigella isolates (n = 266) to antibacterial agents in 2001-2002[143]

S/ No. of drugs N resistance	No. of strains	Resistance phenotype	No. of MDR	S/No. of drugs N resistance	No. of strains	Resistance phenotype Types	No. of MDR
1. 6 drugs	3	AMP, AZT, CTX, NA, SXT, TET	02	5. 2 drugs	51 (19)	AMP, TET	11
		AMP, CTX, M, NA, SXT, TET	01			AZT, NA	05
2. 5 drugs	6	AMP, AZT, Ceftriaxone (CTX), NA, SXT	01			AZT, TET	02
		AMP, Mecillinam (M) NA, SXT, TET	03			Ampicillin (AMP), SXT	02
		AMP, AZT, NA, SXT, TET	02			NA, TET	02
3. 4 drugs	86	AMP, NA, SXT, TET	80			SXT, TET	29
		AZT, NA, SXT, TET	06	6. 1 drug	22 (8)	Azithromycin (AZT)	02
4. 3 drugs	72	AMP, NA, TET	05			Nalidixic acid (NA)	06
		AZT, NA, TET	02			Trimethoprim-sulfamethoxazole (SXT)	07
		AMP, SXT, TET	33				
		AZT, SXT, TET	05			Tetracycline (TET)	07
		NA, SXT, TET	24	7. Sensitive	26 (10)	-	26

Resistance to ≥ 3 drugs (MDR strains) 167 (63%) strains

Table 22 shows that the resistance to trimethoprim-sulfamethoxazole increased from 52 to 72% ($p < 0.01$), resistance to nalidixic acid from 16 to 51% ($p < 0.01$), and mecillinam from 0.5 to 3.0% ($p < 0.01$). Strains with MDR phenotype increased to 63% in 2001-2002 from 52% ($p < 0.01$) in 1991-1992.[143] Physicians should be aware of the high rates of antibacterial resistance and increasing spectrum of resistance of *Shigella* spp. in Bangladesh. Continuous monitoring of the resistance patterns is required, and antibacterial sensitivity testing should be carried out on clinical isolates, and empirical antibacterial therapy needs to change accordingly.

Changing trends in the prevalence of Shigella species and multidrug resistance

Bacillary dysentery such as shigellosis is endemic throughout the world and is one of the major causes of morbidity and mortality, especially among children < 5 years of age in many developing countries including Bangladesh. Shigellosis is caused by any one of the four species of Shigella which include *S. dysenteriae, S. flexneri*, *S. boydii*, and *S. sonnei* and outbreaks caused by Shigella infection are difficult to control due to their low infectious dose.[145] Of the 10,827 Shigella isolates from patients between 2001 and 2011, *S. flexneri* was found predominant species isolated throughout the period. However, the prevalence of *S. flexneri* decreased from 65.7 in 2001 to 47% in 2011, whereas the prevalence of *S. sonnei* increased from 7.2% in 2001 to 25% in 2011. *S. boydii* and *S. dysenteriae* accounted for 17.3% and 7.7% of the isolates, respectively throughout the period. Of 200 randomly selected *S. sonnei* isolates for extensive characterization, biotype g strains were predominant (95%) followed by biotype a (5.0%). Resistance to commonly used antibiotics including trimethoprim-sulfamethoxazole (89.5%), nalidixic acid (86.5%), ciprofloxacin (17.0%), mecillinam (10.5%), and ampicillin (9.5%). All isolates were susceptible to ceftriaxone, cefotaxime, ceftazidime, and imipenem. However, the declining susceptibility to

commonly used antibiotics and the emergence of MDR bacteria have been linked to the indiscriminate or inappropriate use of antibiotics. In addition, bacterial evolution, climate changes, cheap and ready availability of antibiotics, physician error, poor quality of available antibacterial drugs, and unhygienic sanitary conditions.[145]

Antimicrobial resistance in shigellosis

AMR patterns against shigellosis among under-5 children in the urban and rural sites in Bangladesh have been evaluated for the last 20 years from 2001 to 2020. Since 2001, a declining percentage of shigellosis in children recorded in urban and rural sites, but higher isolation rates of Shigella were found in the rural site [1263/15684 (8.1%)] compared to the urban site [883/26804 (3.3%)] in the last 20 years. The *S. flexneri* was reported as the predominant species and the upward trend of *S. sonnei* was statistically significant in both the study sites. Ciprofloxacin, azithromycin, mecillinam, ceftriaxone, and multidrug resistance (≥ 2 drugs) among under-5 children were found to be increasing significantly ($p < 0.01$) in the last 20 years in both the sites (Table 24).[146]

Table 24. Year-wise comparison of ABR against shigellosis in children under five years aged between urban and rural sites [146]

A. Urban site (Dhaka Hospital)																				
Drugs	2001	2002	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015	2016	2017	2018	2019	2020
CIP	0	0	0	0	0	2.2	6.2	27.7	14.0	47.50	56.67	45.45	54.17	64.52	76.67	80.0	74.19	65.71	71.43	68.4
AZM	-	-	-	-	-	-	-	-	-	22.86	11.76	25.00	18.52	27.59	37.50	57.14	43.33	56.00	56.00	66.67
MCN	1.49	0	1.35	0	0	0	6.25	37.21	48.78	37.50	26.47	09.76	19.23	13.33	16.13	14.71	0	32.26	33.33	11.11
CTO	-	-	-	-	-	0	-	0	0	02.63	0	0	0	03.33	03.03	03.13	0	13.51	16.00	10.53
MDR	0	0	0	0	0	0	0	0	0	25.81	21.43	21.88	27.27	48.48	36.00	61.29	36.00	52.00	65.00	58.82
B. Rural site (Matlab hospital)																				
CIP	0	0	0.85	0	0	0	4.76	14.14	23.19	40.91	41.46	53.19	67.44	68.42	78.95	76.47	71.43	92.86	93.55	91.67
AZM	-	-	-	-	-	-	-	-	-	-	0	-	26.29	23.33	37.50	55.88	55.88	50.00	00.63	56.25
MCN	10.11	1.06	0.85	0.88	1.39	6.35	6.98	9.80	16.42	06.52	04.76	08.89	22.00	11.54	13.04	36.36	53.85	44.44	06.90	25.00
CTO	-	0/1	-	-	-	-	-	-	-	-	0	-	04.17	03.39	0	02.94	14.29	16.10	12.50	18.75
DMR	0	0	0	0	0	0	0	0	0	0	0	0	40.00	20.93	31.25	60.61	59.09	73.91	39.29	55.56

CIP = Ciprofloxacin AZM = Azithromycin MCN = Mecillinam CTO = Ceftriaxone MDR = Multidrug resistance

Multidrug-resistant shigellosis is also gradually increasing both in urban and rural settings in Bangladesh. Pysicians should be aware of the high rates of antimicrobial resistance to *Shigella* spp. in Bangladesh. The treatment of shigellosis among under-5 children demands careful and judicial use of antimicrobials to avoid rapid emergence and spread of resistance. Therefore, the importance of therapeutic interventions for shigellosis by appropriate drugs based on their current antibiogram for under-5 children has been recommended.

Prescription antibiotics for outpatients

A study was conducted to analyze 900 physician prescriptions with antibiotics for patients who were suffering mainly from cold and fever, infections, diarrhea, and gonorrhea in three cities in Bangladesh. The highest prescribed antibiotic groups were cephalosporins (31.78%), macrolides (27.33%), quinolones (16.33%), penicillins (7.11%), and metronidazoles (6.78). Two or more antibiotics were prescribed in 25.44% of prescriptions. A total of 66.89% of prescriptions had complete information on dosage form, 57.0% had complete direction for antibiotics use, and 64.22% of patients completed a full course of antibiotics. Although 83.0% of prescriptions have no clinical test for using antibiotics, even though the percentages of patients' disease recovery were 61.78% and in compliance were 38.22%.[147] The irrational use of antibiotics leads to the spread of bacterial resistance to antibiotics and related health problems and accordingly, it urges the physician to be more professional and careful when prescribing antibiotics for the outpatients.

Self-medicated antibiotics

Self-medication of antibiotics is commonly used in developing countries including Bangladesh due to easy availability and lack of regulatory system of prescription drugs controls for selling by the drug pharmacy. A study shows that out of 1300 patients, of which 347 (26.69%) participants experienced self-medication with antibiotics. The highest percentage of self-medicated antibiotics was metronidazole (50.43%), followed by azithromycin (20.75%), ciprofloxacin (11.53%), amoxicillin (10.37) and tetracycline (7.49%). The main reasons for the self-medication of antibiotics have been reported to be pre-experience (45.82%), suggestions from others

(28.24%), and knowledge of the antibiotics (16.14%). Only 4.32% of patients used self-medicated antibiotics for longer than 10 years, and only 6.92% of patients reported side effects for self-medicated antibiotics.[148] The health sector has made complex with both commercial and government health services even same physicians work in both systems day and night, in addition, inadequate free clinical services for the general low-income population encouraged these populations to obtain drugs including antibiotics either directly from drug pharmacies or by prescription made by the village non-registered doctors. To reduce the frequency of antibiotic misuse and antibiotic drug resistance, the currently complex health sector needs to be updated as per the requirements of the general public in Bangladesh.

Antibiotic resistance pattern of *Salmonella* spp.

Salmonellosis is a zoonotic disease recognized globally and non-typhoidal Salmonella serovars cause as much as an estimated one billion cases of gastroenteritis in humans every year.[149] Among the 350 stool samples from the hospitalized diarrheic patients, of which 15 (4.0%) were positive for the *Salmonella* spp. Eight common antibacterials have been used to determine the drug resistance pattern of the identified *Salmonella* spp. The majority of the isolates were multidrug-resistant and showed resistance against more than three drugs (Table 25).

Table 25. Antibacterial sensitivity pattern of *Salmonella* spp. isolated from stool samples [149]

S/N	Pattern	Antibacterials used for sensitivity test (n = 15 isolates)							
		AZT	CP	SMT	MNZ	TET	DOX	EM	CIP
1.	Resistant	06 (40.00)	01 (06.67)	06 (40.00)	14 (93.33)	04 (26.67)	01 (06.67)	13 (86.67)	03 (20.00)
2.	Intermediate	04 (26.67)	0	01 (06.67)	01 (06.67)	03 (20.00)	06 (40.00)	01 (06.67)	05 (33.33)
3.	Sensitive	05 (33.33)	14 (93.33)	08 (53.33)	0	08 (53.33)	08 (53.33)	01 (06.67)	07 (46.67)

AZT = Azithromycin CP = Chloramphenicol SMT = Sulfamethoxazole-trimethoprim MNZ = Metronidazole
DOX = Doxycycline EM = Erythromycin CIP = Ciprofloxacin

Overuse and misuse of antimicrobial agents in food animals should be minimized and continued surveillance for resistance patterns for salmonellae would be required to reduce the public health risk in Bangladesh.

Bacteremic typhoid fever in children

Typhoid fever is caused by *Salmonella enterica subspecies enterica* serotype Typhi (*S. Typhi*) transmitted by both waterborne and foodborne with an annual incidence approaching 1.0% in disease-endemic areas. The global incidence in 2000 was an estimated 21,650,974 cases with 216,510 deaths.[150] *S. Typhi* was isolated from 26 preschool children and 23 older participants and resulted from a bacteremic typhoid fever incidence of 3.9 episodes /1,000 person-years in a Dhaka urban slum area. The relative risk for preschool children compared with older persons was 8.9 and the regression model showed that these children were clinically ill, which suggests a role for preschool immunization.[150]

Typhoid fever in children

Human host-restricted *Salmonella enterica* serotype Typhi (*S. Typhi*) causes typhoid fever in endemic areas especially low-income countries including Bangladesh. A study was conducted to determine the clinical and immunological characteristics of young children with *S. Typhi* bacteremia, and antimicrobial susceptibility patterns of isolated strains. Among 33 *S. Typhi* bacteremic young children, 8 (24%) patients reported prior antibiotic use, whereas out of 72 *S. Typhi* bacteremic patients, a significantly higher number of adults had a history of antibiotic taken before enrolment than older children but no significant differences reported.[151]

The emergence of MDR *S. Typhi* strains is seen in young children which does not impact the clinical symptoms or the immune responses (Table 26). The results of this study show that natural infections do induce immune responses in young children as well as in adults.[151]

Table 26. Antibacterial resistance pattern of strains of *S. Typhi* isolated from clinical patients[151]

S/N	Patient age	No. of patients	Resistance patterns of different antimicrobial drugs AMP	CP	COT	MDR *	NA	CIP	CTX	CXM	AZM
1.	Young children	33	13 (39.0)	10 (30.0)	10 (30.0)	05 (15.0)	33 (100)	33 (1000)	0	0	0
2.	Older children	23	06 (26.0)	03 (13.0)	03 (13.0)	03 (13.0)	23 (100)	23 (100)	0	0	0
3.	Adults	16	02 (13.0)	02 (13.0)	02 (13.0)	02 (13.0)	14 (88.0)	14 (88.0)	0	0	0

AMP= Ampicillin C = Chloramphenicol COT = Co-trimoxazole NA = Nalidixic acid CIP = Ciprofloxacin CTX = Ceftriaxone
CXM = Cefixime AZM = Azithromycin *MDR = Resistant to ampicillin, chloramphenicol & co-trimoxazole

Comparison of drug resistance of Salmonella between Bangladesh and elsewhere

Salmonella enterica serovar Typhi isolates from Bangladesh, Indonesia, Taiwan, and Vietnam have been characterized to investigate their genetic relatedness and antimicrobial resistance. The isolates from Bangladesh and Vietnam were genetically closely related but were distinct from those from Indonesia and Taiwan. The majority of isolates from Bangladesh and Vietnam were MDR and belonged to the widespread haplotype H58 clone. IncH11 plasmids were detected in all MDR *S. Typhi* isolates from Vietnam but in only 15% of MDR isolates from Bangladesh. Resistance genes in the majority of MDR *S. Typhi* isolates from Bangladesh should reside in the chromosome. Among the isolates from Bangladesh, 82% and 40% were resistant to various concentrations of nalidixic acid and ciprofloxacin, respectively. Intensive surveillance is necessary to monitor the spread of chromosome-mediated MDR and fluoroquinolone-resistant *S.Typhi* emerging in Bangladesh. [152]

Drug resistance in Klebsiella bacteria

Klebsiella pneumoniae and *K. oxytoca* are the two most common bacterial pathogens causing nosocomial infections in humans and are of great concern for developing multidrug resistance (MDR). Out of 500 clinical isolates, 120 were found positive for Klebsiella among which 108 were *K. pneumoniae* and 12 were *K. oxytoca*. Overall resistance pattern of Klebsiella isolates to ampicillin, amoxicillin, ceftriaxone, ciprofloxacin, co-trimoxazole, gentamicin, nalidixic acid, and tetracycline was 100%, 90%, 45%, 40%, 45%, 25%, 50%, 35% respectively. The MDR was found more common in *K. pneumoniae* (56%) than in *K. oxytoca* (50%). The prevalence rate of ESBL-producing Klebsiella was found 45% which was found to be higher in *K. pneumoniae* (50%) than in *K. oxytoca* (25.0%). All the ESBL-producing Klebsiella isolates were found to be MDR, showing 100% resistance to ampicillin, amoxicillin, ceftriaxone, and ciprofloxacin.[153] Continuous monitoring of ESBL, a strict antibiotic policy along with a conventional antibiogram will have a great impact in reducing bacterial resistance toward antibiotics and the development of proper treatment options against Klebsiella infections.

Antibacterial resistance in clinically significant bacterial pathogens

The antimicrobial resistant pattern of clinically significant bacterial pathogens has been studied on 2700 clinical samples (urine, pus, wound swab, sputum, blood, conjunctival swabs, throat swabs, HVS, & stool) for the detection of Gram-negative and Gram-positive bacteria and their antibiogram evaluation. The bacterial isolation and identification results and their antimicrobial resistance status are presented in Table 27. Most of the Gram-negative bacilli were reported to be resistant to ciprofloxacin, tetracycline, and cotrimoxazole (Table 27). The majority of Pseudomonas spp. have been reported to be resistant to most of the commonly used antibiotics. Approximately, half of the *S. aureus* isolates have been reported to be methicillin-resistant whereas vancomycin has been found highly sensitive antibiotic (Table 27).[154]

Antibiotic resistance of *Staphylococcus aureus*

The development of MDR strains of *S. aureus* is increasingly alarming in Bangladesh. Twenty-three clinical isolates of *S. aureus* (β-lactamase-producing and non-producing MRSA) have been evaluated for AMR pattern, of which 43.48% isolates have ensured methicillin resistance while the remaining 56.52% isolates were found to be methicillin-sensitive.[155] The β-lactamase test which was performed by acid formation method showed

Table 27. Distribution of clinically significant bacterial pathogens and their antimicrobial resistance pattern, %[154]

S/N	Bacterial species	Total isolates	AMC	CAZ	CXM	CL	CIP	TET	COT	NIT	IMI	AK	GEN	CAR	ESBL
A.	**Gram-negative**														
1.	*E. coli*	475	62.0	59.0	58.0	59.0	89.0	69.0	64.0	15.0	00.0	11.0	26.0	-	35.0
2.	*Klebsiella* spp.	120	58.0	51.0	52.0	51.0	78.0	53.0	49.0	17.0	00.0	09.0	11.0	-	22.0
3.	*Pseudomonas* spp.	045	97.0	95.0	96.0	96.0	89.0	95.0	97.0	100	11.0	70.0	73.0	94.0	-
4.	*Enterobacter* spp.	041	90.0	87.0	80.0	87.0	73.0	70.0	68.0	12.0	00.0	17.0	24.0	-	21.0
5.	*Citrobacter* spp.	032	68.0	56.0	59.0	59.0	81.0	71.0	78.0	14.0	00.0	15.0	25.0	-	19.0
6.	*Proteus* spp.	020	80.0	85.0	90.0	90.0	75.0	90.0	80.0	-	02.0	05.0	10.0	-	20.0
7.	*Acinetobacter* spp.	016	62.0	62.0	62.0	62.0	75.0	68.0	75.0	80.0	00.0	00.0	43.0	-	-
B.	**Gram-positive**		AMC	AMP	PEN	CL	CIP	TET	COT	OXA	VAN	AK*	GEN	MET	R
1.	*Staph. aureus*	103	66.0	80.0	93.0	51.0	69.0	44.0	49.0	46.0	00.0	29.0	31.0	46.0	MRSA
2.	*Staph. epidermidis*	026	76.0	84.0	92.0	61.0	73.0	57.0	69.0	30.0	00.0	23.0	34.0	30.0	MRSE
3.	*Strep. agalactiae*	039	94.0	97.0	97.0	56.0	74.0	69.0	100	-	00.0	33.0	20.0	-	-
4.	β-hemolytic Strep.	031	93.0	96.0	96.0	61.0	74.0	64.0	100	-	00.0	58.0	32.0	-	-
5.	*Strep. pyogenes*	019	00.0	00.0	00.0	00.0	73.0	31.0	100	00.0	00.0	52.0	05.0	-	-
6.	*Enterococcus* spp.	045	08.0	13.0	13.0	22.0	66.0	60.0	100	-	00.0	62.0	08.0	-	-
C.	**Others**														
1.	*Candida* spp.	015	-	-	-	-	-	-	-	-	-	-	-	-	
2.	Gr-D Non-enterococcus	4	-	-	-	-	-	-	-	-	-	-	-	-	
3.	Streptococcus (others)	4	-	-	-	-	-	-	-	-	-	-	-	-	
4.	*Moraxella* spp.	3	-	-	-	-	-	-	-	-	-	-	-	-	
5.	*Shigella* spp.	3	-	-	-	-	-	-	-	-	-	-	-	-	
6.	*Strep. pneumoniae*	1	-	-	-	-	-	-	-	-	-	-	-	-	
7.	*Salmonella typhi*	1	-	-	-	-	-	-	-	-	-	-	-	-	
8.	*Salmonella* spp.	1	-	-	-	-	-	-	-	-	-	-	-	-	

AMC = Amoxyclav (30µg) CAZ = Ceftazidime (10 µg) CXM = Cefuroxime (30 µg) CL = Cephalexin (30 µg)
CIP = Ciprofloxacin (5 µg) TET = Tetracycline (30 µg) COT = Cotrimoxazole (25 µg) NIT = Nitrofurantoin (300 µg)
IMI = Imipenem (10 µg) AK = Amikacin ((10 µg) GEN = Gentamicin ((10 µg) CAR = Carbenecillin (30 µg)
ESBL = Extended spectrum β-Lactamase AMP = Ampicillin (10 µg) PEN = Penicillin (10 µg)
OXA = Oxacillin (01 µg) AK = Amikacin (30 µg)* VAN = Vancomycin (30 µg) MET = Methicillin
MRSA = Methicillin Resistant Staphylococcus aureus MRSE = Methicillin Resistant Staphylococcus epidermidis
- = Not done R = Resistant

50.0% of the MRSA isolates produced β-lactamase. The MRSA-resistant isolates have been reported to be highly sensitive to vancomycin (100%), fusidic acid (90.0%), chloramphenicol (80.0%), neomycin (80.0%), rifampin (80.0%), gentamicin (70.0%), ceftriaxone (60.0%), cephalexin (60.0%), ciprofloxacin (60.0%), and cloxacillin (60.0%). Plasma profiling of the selected resistant *S. aureus* isolates showed severe resistance to amoxicillin (70.0%), co-trimoxazole (90.0%), and erythromycin (80.0%). Thus, these findings might provide guidelines for physicians to select and prescribe rational antibiotics in the treatment of MRSA at hospital and community levels.[155]

Antibacterial resistance of uropathogenic bacteria

Urinary tract infection (UTI) is a serious health problem affecting millions of humans globally. It is estimated that about 150 million cases of UTI in the world every year, which is one of the most common bacterial infections in low-income countries including Bangladesh.[156]

The antibiotic susceptibility patterns of 102 uro-pathogenic bacteria from non-catheterized associated urinary tract infection (NCAUTI) patients and 100 uro-pathogenic bacteria from catheterized associated urinary tract infection (CAUTI) patients were compared using the disc diffusion method. *Escherichia coli* has been reported to be the predominant isolate obtained from CAUTI (81%) and NCAUTI (67.0%) patients, followed by *Pseudomonas aeruginosa* with NCAUTI (28.0%) and CAUTI (15.0%) patients, respectively.[156] The two predominant isolates, *E. coli* and *P. aeruginosa*, were tested for their susceptibility pattern to 11 commonly used antibiotics. Overall, both the *E. coli* and *P. aeruginosa* isolates from CAUTI patients showed significantly higher resistance ($p < 0.05$) than those from NCAUTI patients against antibiotics tested, except for trimethoprim/sulfamethoxazole and gentamicin with *E. coli* (Table 28).

Table 28. Antibiotic resistance patterns of predominant bacteria isolated uropathogens in humans[156]

S/N	Antibacterials	*Escherichia coli*					*Pseudomonas aeruginosa*				
		CAUTI		NCAUTI		p value	CAUTI		NCAUTI		p value
		Total isolates	Positive No. (%)	Total isolates	Positives No. (%)		Total isolates	Positives No. (%)	Total isolates	Positives No. (%)	
01.	Amikacin	81	14 (17.28)	68	35 (51.47)	< 0.05	15	06 (40.0)	28	06 (21.43)	<0.05
02.	Amoxicillin/CVN	79	68 (86.07)	68	38 (55.88)	< 0.05	14	12 (85.71)	28	24 (85.71)	<0.05
03.	Azithromycin	32	20 (62.50)	48	22 (45.83)	< 0.05	03	02 (66.67)	19	08 (42.11)	<0.05
04.	Cefixime	80	60 (75.00)	70	44 (62.86)	< 0.05)	15	15 (100)	28	20 (71.42)	<0.05
05.	Ceftazidime	81	61 (75.31)	67	37 (55.22)	< 0.05	15	11 (73.33)	28	17 (60.71)	<0.05
06.	Ceftriaxone	81	57 (70.37)	68	35 (51.47)	< 0.05	15	11 (73.33)	28	17 (60.71)	<0.05
07.	Ciprofloxacin	74	46 (62.62)	68	32 (47.05)	< 0.05	13	10 (76.92)	28	14 (50.00)	<0.05
08.	TMP/SMZ	81	52 (64.19)	69	35 (50.72)	< 0.05	15	13 (86.66)	27	19 (70.37)	<0.05
09.	Doxycycline	80	53 (66.25)	69	38 (55.07)	< 0.05	15	12 (80.00)	26	17 (65.38)	<0.05
10.	Gentamicin	64	35 (54.68)	68	34 (50.00)	< 0.05	15	08 (53.33)	29	13 (44.83)	<0.05
11.	Meropenem	23	14 (60.87)	06	01 (14.29)	< 0.05	06	06 (100)	21	07 (33.33)	<0.05

CAUTI = Catheter-associated urinary tract infection
NCUTI = Non-catheter urinary tract infection
TMP/SMZ = Trimethoprim / Sulfamethoxazole
P value (Z test)

A study was conducted to detect the prevalence and antimicrobial sensitivity of uro-pathogenic bacteria isolated from 443 suspected urinary tract infection patients. Culture yielded growth of uro-pathogenic bacteria in 189 (42.66%) samples, of which 179 (94.71%) were monomicrobial (single bacterial species) and 10 (5.29%) polymicrobial (pair of two different bacterial species) growths. Table 29 shows the antimicrobial resistance status of the isolated uro-pathogens.

Table 29. Prevalence and antimicrobial resistance pattern of bacteria isolated from urine culture[157]

S/N	Bacteria species (n = 199)	Positive* No. (%)	Resistance status of different antibacterials									
			AMX	NIT	CL	CXM	CFL	CFA	CIP	GEN	NA	COT
1.	*Escherichia coli*	118 (59.30)	89.83	16.10	80.51	78.81	60.17	55.08	72.88	40.48	91.53	72.03
2.	*Staph. saprophyticus*	038 (19.09)	71.05	18.42	65.79	39.47	73.68	44.74	63.16	47.37	92.11	73.68
3.	*Enterococcus* spp.	023 (11.56)	60.87	21.74	78.26	60.87	78.26	47.83	82.61	56.52	95.65	73.91
4.	*Klebsiella* spp.	011 (05.53)	90.91	63.64	100	63.64	72.73	54.55	81.82	27.27	100	72.73
5.	*Pseudomonas* spp.	004 (02.01)	100	25.00	100	100	100	75.00	100	75.00	100	100
6.	*Proteus* spp.	003 (01.51)	100	66.67	100	100	100	66.67	100	33.33	100	100
7.	*Enterobacter* spp.	002 (01.00)	100	50.00	100	50.00	50.00	50.00	100	50.00	100	100
	Total	199 (100)										

*Single (n = 179) and poly-bacterial (n = 10) growths
AMX = Amoxicillin
NIT = Nitrofurantoin
CL = Cephalexin
CXM = Cefuroxime
CFL= Cefaclor
CFA = Ceftriaxone
CIP = Ciprofloxacin
GEN = Gentamicin
NA = Nalidixic acid
COT = Co-trimoxazole

It appears from Table 29 that a very high frequency of resistance of uropathogens has been reported against different tested antibacterials but the highest rate of susceptibility showed with nitrofurantoin and gentamicin which can be adapted for empirical treatment of urinary tract infections.[157] However, the selection of antibacterials for UTI should be guided by culture and sensitivity tests and empirical therapy must be considered in the recent antibiogram investigation.

Antibiotic sensitivity pattern of uro-pathogens

Urinary tract infections (UTIs) are one of the most important bacterial infections that cause morbidity and mortality in humans in developing countries including Bangladesh. It occurs in all populations and ages from neonate to the geriatric age group but is most common in sexually active women. Women are more susceptible than men due to several factors including anatomical differences, hormonal effects, and behavioral patterns.[158] A retrospective study was conducted to determine the prevalence of causative agents of UTI and their antibiotic

sensitivity pattern among suspected UTI patients. Out of 878 urine samples collected from suspected UTI patients, of which 182 (20.73%) were positive for pathogenic bacteria. Of the isolated bacteria, *E. coli* constituted 85.16%, followed by *Pseudomonas* spp. (4.39%), *Acinetobacter* sp. (2.19%), Group D *Streptococcus* (2.2%), *Staphylococcus aureus* (1.65%), *Klebsiella* spp. (1.65%), *Enterobacter* sp. (1.65), and *Salmonella Typhi* (1.09%).[158] Mainly Gram-negative bacilli were found responsible for UTI and the most frequently isolated bacteria was *E. coli,* which was found to be most sensitive to parenteral antibiotics including imipenem (87.86%), amikacin (84.25%), and meropenem (77.31%), whereas the majority of *E. coli* were resistant to most commonly used oral antibacterials including azithromycin (66.08%), cefixime (68.0%), cotrimoxazole (45.45%), ciprofloxacin (40.31%), and levofloxacin (40.97%). Therefore, the choice of antibiotic therapy for UTI should be depends on the local sensitivity pattern of the infecting bacteria.

Antibiotic resistance of uro-pathogenic bacteria in children

The spectrum of etiologic agents causing urinary tract infections (UTIs) and their antimicrobial resistance pattern has been continuously changing over the years. A study was conducted to isolate the causative agents of UTIs and their antimicrobial resistance pattern in pediatric patients. Out of 120 cases with pyuria, 58 (48.3%) were having culture positive. *E. coli* was the commonest isolate (62.1%), followed by *Enterococcus* (19.2%) and *Klebsiella* (10.2%). Table 30 shows the antibiotic sensitivity pattern of these isolates.[159]

Table 30. Antibacterial sensitivity pattern of uro-pathogens isolated from UTI of children.[159]

S/N	Antibacterials	Antibiogram tested bacteria (No. %)					
		E. coli (n = 36)	*Enterococcus* (n = 11)	*Klebsiella* (n = 6)	*Acinetobacter* (n = 2)	*Pseudomonas* (n = 2)	*Proteus* (n = 1)
01.	Amikacin	11 (31.0)	02 (18.0)	01 (17.0)	01 (50.0)	01 (50.0)	0
02.	Amoxycillin	01 (03.0)	06 (55.0)	0	0	0	0
03.	Azithromycin	08 (22.0)	03 (27.0)	02 (34.0)	02 (100)	01 (50.0)	01 (100)
04.	Aztreonem	02 (06.0)	02 (18.0)	0	0	0	0
05.	Ciprofloxacin	18 (50.0)	04 (36.0)	05 (83.0)	01 (50.0)	01 (50.0)	01 (100)
06.	Ceftriaxone	06 (17.0)	04 (36.0)	03 (50.0)	01 (50.0)	0	01 (100)
07.	Cotrimoxazole	01 (03.0)	0	0	0	0	0
08.	Cefixime	04 (11.0)	02 (18.0)	03 (50.0)	01 (50.0)	0	0
09.	Cefuroxime	01 (03.0)	0	03 (50.0)	01 (50.0)	0	0
10.	Cefepime	02 (06.0)	02 (18.0)	0	0	0	0
11.	Ceftazidime	06 (17.0)	0	03 (50.0)	01 (50.0)	01 (50.0)	0
12.	Colistin	03 (08.0)	02 (18.0)	01 (17.0)	0	0	0
13.	Gentamicin	08 (22.0)	02 (18.0)	01 (17.0)	0	01 (50.0)	0
14.	Levofloxacin	15 (41.0)	03 (27)	04 (67.0)	02 (100)	0	0
15.	Meropenem	05 (14.0)	02 (18.0)	01 (17.0)	0	01 (50.0)	0
16.	Netilmicin	06 (17.0)	02 (18.0)	01 (17.0)	01 (50.0)	01 (50.0)	0
17.	Nalidixic acid	07 (19.0)	0	05 (83.0)	0	0	0
18.	Nitrofurantoin	17 (47.0)	01 (09.0)	02 (34.0)	01 (50.0)	0	0
19.	Piperecillin	03 (08.0)	02 (18.0)	0	01 (50.0)	0	0
20.	Vancomycin	0	08 (73.0)	0	0	0	0

E. coli was found to be most sensitive to ciprofloxacin, nitrofurantoin, amikacin, and levofloxacin (Table 30). There was a generally high level of resistance of isolates to cotrimoxazole, Amoxycillin, aminoglycosides, azithromycin, and cephalosporins like cefuroxime, ceftazidime, cefixime, and ceftriaxone compared to ciprofloxacin, nitrofurantoin and levofloxacin (Table 30). It appears that ciprofloxacin, levofloxacin, and nitrofurantoin are appropriate for initial empirical therapy for UTI children in Bangladesh. However, the empirical antibiotic selection is based on the knowledge of the local prevalence of bacterial organisms and antibiotic sensitivities rather than on universal guidelines.

Antibacterial resistance in bacteria of UTI in women in Dhaka city

Urinary tract infection (UTI) is commonly experienced by women of various age groups especially elderly ones. The urinary sample was collected from 462 UTI-suspected females, of which 9.0% had bacteriuria. *Escherichia coli* (69.0%), *Streptococcus* spp. (15.0%), and *Pseudomonas aeruginosa* (7.0%) were more frequently isolated from the urine samples compared to *Enterococcus faecalis* (3.0%), *Staphylococcus aureus* (2.0%), *Klebsiella pneumoniae* (2.0%) and *Hafnia alvei* (2.0%). The *E. coli* isolates showed complete resistance to commonly used drugs, and 58.0% of these isolates were multidrug-resistant (MDR). This study suggests regular monitoring of drug resistance phenotype of the UTI pathogens to reduce the morbidity of female UTI patients and offer better treatment strategy in the healthcare system in Bangladesh.[160]

Antibacterial resistance in bacterial uro-pathogens

Urine samples from 100 clinically suspected 100 urinary tract infected patients were collected for isolation of bacteria and their antibacterial sensitivity test, of which 74 samples showed positive for five different types of bacterial infection. The *E. coli* was found predominant (69.0%), followed by *Staphylococcus* spp. (18.0%), *Pseudomonas aeruginosa* (8.0%), and *Klebsiella pneuminae* (6.0%).

Comparative antibacterial resistance profile showed that most of the strains were highly resistant to amoxicillin (85.14%) and co-trimoxazole (81.08%), whereas the strains showed significant sensitivity to amikacin (94.59%), azithromycin (93.24%), doxycycline (90.54%), and ceftriaxone (89.18%).[161] The bacteria isolated from UTI showed resistance to amoxicillin, cotrimoxazole, and nalidixic acid at an alarming state because these antibacterials have lost their capacity to inhibit uro-pathogens. In addition, levofloxacin, cephalexin, and ceftriaxone show trends of resistance. However, azithromycin, amikacin, and cefixime are relatively satisfactory and effective in treating UTIs.[161] The main risk factors associated with UTI in humans mostly in women include poor hygiene, long-time catheterization, uncontrolled sexual intercourse, pregnancy, and spermicidal contraception.[161]

Antibiogram of bacterial uropathogens

Urinary tract infections (UTIs) are one of the most frequently occurring infections majority of which are caused by multi-drug resistant (MDR) uropathogens. Among the bacterial uropathogens, *E. coli* (57.38%) was the predominant etiological agent, followed by *Enterococcus* spp. (36.06%), *Pseudomonas aeruginosa* (3.28%) and *Staphylococcus aureus* (3.28%). Gentamicin, ciprofloxacin, and amikacin have been found as reliable therapeutic antibiotics against tested uropathogens[162]

Antibiotic resistance of community-acquired UTI

Bacteriological culture and antibiotic sensitivity tests were performed in a study of 4,500 urine samples collected from clinical patients, of which 3,200 (71.0%) samples had bacterial growth with a bacterial count of $\geq 1.0 \times 10^5$ CFU/ ml indicating UTI. *E. coli* (51.6%) was the predominant causative bacteria followed by *Streptococcus* spp. (15.7%), *Klebsiella* spp. (12.1%), *Enterococcus* spp. (6.4%), *Pseudomonas* spp. (4.4%), Coagulase-negative *Staphylococcus* spp. (2.0%), and other pathogens (.7.8%). Both *E. coli* (85.0%) and *Klebsiella* spp. (95.0%) were predominantly resistant to penicillin, followed by macrolides (70-76%), third-generation cephalosporins (58-69%), fluoroquinolones (53-69%), and carbapenem (5-9%). Approximately 65.0% of patients tested positive for MDR organisms uropathogens with 71.0% Gram-negative and 46.0% Gram-positive bacteria MDR. These findings will guide clinicians to be more selective about their antibiotic choice for empirical treatment of UTI and alleviate misuse/overuse of antibiotics in the community.[163]

UTI is referred to as one of the most common infections in humans worldwide and AMR is also a global threat to humans that is related to many diseases. As antibiotics are used for the treatment of infectious diseases, the rate of resistance is increasing day by day. Mostly *Enterococcus* spp. (33.05%), *S. aureus* (27.27%), *Streptococcus* pp. (20.66%), and beta-hemolytic Streptococci (19.0%) were found as causative agents of UTI compared to others. The majority of the isolates have been detected as MDR. A higher percentage of ABR was found against azithromycin (75.0%), and cefixime (64.46%). These findings focused on a regular basis

of surveillance for the Gram-positive bacteria antibiotic susceptibility to increase awareness about the use of proper antibiotics thus minimizing the drug resistance.[164]

Antibiotic resistance in bacteria of lower respiratory tract infections (LTRIs)

The LTRIs are responsible for the vital causes of morbidity and mortality in all ages in humans globally. Proper identification of the causative agents and their antibiotic sensitivity pattern is required for the selection of antibacterial therapy and to improve the outcome. Recently, antibiotic resistance among respiratory pathogens has been increasing emergently. A study was conducted to identify the bacterial agents of LRTIs and to update clinicians about the current scenario of antibiotic resistance in LRTIs. Out of 100 processed sputum samples, 64% of cases had established bacterial etiology. *Staphylococcus aureus* (n = 37; 57.81%) was found to be the prominent bacteria in LRTIs, followed by *Streptococcus pneumoniae* (n=16; 25.0%), *Klebsiella* (n=3; 4.68%) and *Pseudomonas* (n = 2; 3.12%) species (Table 31). Gram-positive bacteria showed maximum sensitivity to imipenem (94.6%), meropenem (97.3%), and cefotaxime (75.0%). *S. aureus* isolates were mostly resistant to amoxicillin and ceftazidime (89.2%), whereas *Strep. pneumoniae* was to ceftazidime, amoxicillin, and cotrimoxazole (81.2%). Gram-negative isolates, *Klebsiella* spp. was mostly resistant to ceftriaxone, ceftazidime, and amoxicillin (100%), whereas *E. coli* were resistant to amoxicillin, cotrimoxazole, and vancomycin (100%).[165] Therefore, appropriate identification of the causative bacteria and their antibacterial resistance is crucial for the right choice of antibiotic therapy in LRTIs in humans.

Table 31. Prevalence of antibacterial resistance to bacteria isolated from the sputum of humans affected by LTRIs[165]

S/N	Antibacterials	Antibacterial resistance status, No. (%)					
		S. aureus (n = 37)	*S. pneumoniae* (n = 16)	*S. pyogenes* (n = 4)	*Klebsiella* spp. (n = 3)	*Pseudomonas* spp. (n = 2)	*E. coli* (n = 2)
01.	Azithromycin	10 (27.0)	07 (43.7)	1 (25.0)	0	0	1 (50.0)
02.	Ciprofloxacin	12 (32.4)	06 (37.5)	2 (50.0)	0	1 (50.0)	0
03.	Ceftriaxone	20 (54.0)	06 (37.5)	3 (75.0)	3 (100)	2 (100)	1 (50.0)
04.	Ceftazidime	33 (89.2)	13 (81.2)	4 (100)	3 (100)	2 (100)	1 (50.0)
05.	Cefixime	22 (59.4)	07 (43.7)	2 (50.0)	0	2 (100)	0
06.	Imipenem	02 (05.4)	0	0	0	0	0
07.	Cefuroxime	10 (27.0)	08 (50.0)	2 (50.0)	1 (33.3)	1 (50.0)	1 (50.0)
08.	Amoxicillin	33 (89.2)	13 (81.2)	3 (75.0)	3 (100)	2 (100)	2 (100)
09.	Gentamicin	07 (18.9)	02 (12.5)	1 (25.0)	0	0	0
10.	Cotrimoxazole	16 (43.2)	13 (81.8)	2 (50.0)	1 (33.3)	0	2 (100)
11.	Meropenem	0	02 (12.5)	1 (25.0)	1 (33.3)	0	0
12.	Cefotaxime	12 (32.4)	03 (18.7)	1 (25.0)	2 (66.7)	1 (50.0)	0
13.	Cloxacillin	18 (48.6)	07 (43.7)	1 (25.0)	3 (33.3)	1 (50.0)	0
14.	Vancomycin	11 (29.7)	04 (25.0)	0	0	1 (50.0)	2 (100)

n = No. of isolates tested

Antibiogram of bacteria isolated from wound infection

Infections due to antibiotic-resistant bacteria have increased alarmingly in both developed and developing countries. Wound infection is becoming a major concern among patients and healthcare practitioners because of its increased toll on morbidity and financial loss. The prevalence of different bacterial pathogens and their antibiotic sensitivity in various types of wound infections have been studied on 105 collected wound swab samples, of which 92.3% had bacterial infections. *Staphylococcus aureus* was found to be the most frequent isolate (55.7%), followed by *Escherichia coli* (23.7%), *Pseudomonas* spp. (8.2%), and *Streptococcus pyogenes* (7.2%).[166]

The sensitivity pattern of the antibacterial study indicates that most of the isolated strains were multidrug resistant which causes difficulty in controlling wound infection due to widespread bacterial resistance to antibiotics (Table 32). However, in countries with inadequate facilities for laboratory drug sensitivity including Bangladesh, physicians generally do not wait for the culture and sensitivity reports, and physicians could start

an empirical therapy with a combination of antibiotics based on the drug sensitivity results of this report. Therefore, the judicious use of antibiotic prophylaxis and reporting can be the most effective means to reduce the wound infection rate.

Table 32. Sensitivity pattern of isolated Gram-positive and Gram-negative bacteria isolated from wound infections[166]

S/N	Antibacterial agents	Gram-positive bacteria (n = 61)		Gram-negative bacteria (n = 36)			
		Staph. aureus (n = 54) No. (%)	*Strep. pyogenes* (n = 07) No. (%)	*E. coli* (n = 23) No. (%)	*Klebsiella* (n = 3) No. (%)	*Pseudomonas* (n = 8) No. (%)	*Proteus* spp (n = 2) No. (%)
01.	Amoxicillin (10 µg)	32 (59.3)	4 (57.1)	-	-	-	-
02.	Penicillin (10 µg)	30 (55.6)	4 (57.1)	08 (34.8)	0	0	0
03.	Vancomycin (30 µg)	41 (75.9)	6 (85.7)	-	-	-	-
04.	Azithromycin (15 µg)	44 (81.5)	5 (71.5)	-	-	-	-
05.	Cephradine (30 µg)	32 (59.3)	4 (57.1)	10 (43.5)	0	0	0
06.	Tetracycline (30 µg)	32 (59.3)	4 (57.1)	14 (60.9)	0	3 (37.5)	1 (50.0)
07.	Cloxacillin (05 µg)	31 (57.4)	4 (57.1)	11 (47.8)	0	0	0
08.	Co-trimoxazole (23.7 µg)	31 (57.4)	3 (42.9)	12 (52.2)	1 (33.3)	1 (12.5)	1 (50.0)
09.	Cefixime (05 µg)	-	-	19 (82.6)	1 (33.3)	1 (12.5)	1 (50.0)
10.	Aztreonam (30 µg)	-	-	17 (73.9)	1 (33.3)	1 (12.5)	2 (100)
11.	Cefuroxime (30 µg)	-	-	18 (78.3)	0	0	2 (100)

MDR bacteria isolated from clinical pus samples

Bacterial isolated from 891 pus samples, of which *E. coli* showed the highest resistance (98.92%), followed by *Pseudomonas* (92.66%), *Proteus* sp. (91.58%), *Klebsiella* spp. (87.5%), whereas *Acinetobacter* spp. showed 100% resistance to different tested antibiotics. *Streptococcus* spp. showed resistance in 66.66%, *Enterococcus faecalis* in 92.23%, and *Staphylococcus aureus* in 95.06%. Overall Gram-negative bacteria showed 92.98% and Gram-positive 87.5% resistance to the tested antibiotics.[167]

Antibiotic sensitivity of bacteria isolated from wound and pus

Culture and sensitivity tests were conducted in 1709 samples collected from wounds and pus from clinical patients, of which 72.0% of samples yielded growth of bacteria including 86.4% Gram-negative and 13.6% Gram-positive bacteria. *Pseudomonas* spp. was the most common (43.8%) isolated bacteria from both wound swabs and pus samples, followed by *E. coli* (16.6%), *S. aureus* (11.8%), *Klebsiella* spp. (9.8%). Among Gram-negative bacteria, 14.9% were ESBL-producing bacteria and *Klebsiella* spp. were the most commonly isolated ESBL producers. Gram-negative bacteria were mostly resistant to amoxicillin followed by fluoroquinolones, cotrimoxazole, and cephalosporins whereas colistin, carbapenem, and piperacillin/tazobactam were the most effective drugs against them (Table 33). The majority of the Gram-positive bacteria were resistant to fluoroquinolones and co-trimoxazole but 100% *S. aureus* were sensitive to vancomycin, followed by linezolid (98.0%) and teicoplanin (86.0%) and 32% of them were methicillin-resistant (MRSA) (Table 33).[168]

Table 33. Sensitivity pattern of Gram-positive and Gram-negative bacteria isolated from wound and pus samples[168]

S/N	Antibacterial agents	Gram-positive bacteria (sensitivity %)				Gram-negative bacteria (sensitivity %)							
		S. aureus (n = 145)	CNS (n =13)	Strep. (n = 08)	Enteroc- (n = 02)	Pseudo- (n = 539)	*E. coli* (n = 204)	*Klebsiella* (n = 121)	*Proteus* (n = 93)	Enterob. (n = 65)	Citrob- (n= 14)	ACB (n = 20)	Serratia (n = 07)
01.	Amikacin	41.0	62.0	50.0	0	27.0	43.0	48.0	33.0	45.0	57.0	15.0	57.0
02.	Amoxicillin	-	-	88.0	50.0	-	07.0	-	03.0	08.0	14.0	-	29.0
03.	Clindamycin	76.0	69.0	50.0	-	-	-	-	-	-	-	-	
04.	Ciprofloxacin	20.0	31.0	-	100	20.0	21.0	18.0	23.0	18.0	21.0	-	0
05.	Co-trimoxazole	29.0	38.0	50.0	-	22.0	19.0	29.0	42.0	45.0	50.0	25.0	71.0
06.	Doxycycline	35.0	62.0	50.0	50.0	-	-	-	-	-	-	-	
07.	Cefoxitin	68.0	62.0	-	-	-	-	-	-	-	-	-	
08.	Gentamicin	39.0	69.0	75.0	0	27.0	41.0	30.0	23.0	37.0	64.0	10.0	71.0
09.	Levofloxacin	24.0	38.0	63.0	50.0	11.0	39.0	48.0	33.0	37.0	42.0	15.0	57.0

Contd. Table 33.

10. Linezolid	98.0	100	-	100	-	-	-	-	-	-	-	
11. Teicoplanin	86.0	69.0	-	-	-	-	-	-	-	-	-	
12. Vancomycin	100	100	-	100	-	-	-	-	-	-	-	
13. Amoxyclav	-	-	-	-	08.0	10.0	09.0	13.0	11.0	28.0	10.0	29.0
14. Ceftazidime	-	-	-	-	56.0	20.0	11.0	19.0	23.0	28.0	0	0
15. Ceftriaxone	34.0	-	100	-	09.0	23.0	13.0	21.0	22.0	28.0	10.0	57.0
16. Colistin	-	-	-	-	97.0	95.0	93.0	04.0	97.0	100	100	100
17. Imipenem	-	-	-	-	66.0	91.0	87.0	89.0	97.0	86.0	40.0	100
18. Meropenem	-	-	-	-	68.0	82.0	85.0	81.0	95.0	86.0	35.0	100
19. Piperacillin / Tazobactum	-	-	-	-	62.0	71.0	65.0	78.0	82.0	79.0	35.0	100

The susceptibility pattern shows that some common antibiotics, especially antibiotics of oral form have very limited usefulness in the treatment of infections and also highlight the need for regular reporting and antibiogram-guided antibiotic prescription.

Multidrug-resistant bacteria isolated from the trachea of ICU-admitted patients

Recent reports have shown that antibiotic-resistant bacteria are becoming more prevalent in intensive care units (ICUs) at an exceptional rate. Patients in the ICU can get infected by pathogens due to invasive operation procedures and clinical health conditions. A study was conducted on 200 tracheal specimens, of which 273 bacterial isolates were identified, of which 81.0% Gram-negative 10.0% Gram-positive bacteria, and 9.0% fungi. The most prevalent Gram-negative bacteria were *Acinetobacter* spp. (34.0%), *Klebsiella* spp. (22.0%), *Pseudomonas* spp. (14.0%), and *E. coli* (9.2%), whereas Gram-positive bacteria were *Staphylococcus aureus* (5.9%), and fungi were *Candida* spp. (7.3%). Among the most prevalent bacteria, except *Staphylococcus aureus* isolates, approximately 90.0% were resistant to multiple drugs, whereas 60.0% of *Acinetobacter* spp. and *Pseudomonas* spp. were extensively drug-resistant. However, colistin was found most effective against all Gram-negative, and linezolid, vancomycin, and fusidic acid were most effective against all isolated Gram-positive bacteria.[169]

Single drug-resistant (SDR) and multiple drug resistant (MDR) were reported in 1.08% and 98.92% in *Acinetobacter* spp., 7.89% and 92.09% in *Pseudomonas* spp., 9.99% and 90.01% in *Klebsiella* spp., 68.75% and 31.25% in *S. aureus* and 4.00% and 96.00% in *E. coli*, respecyively.[169]

Appropriate information on drug sensitivity and resistance status is an essential concern for the formulation of antibiotic prescribing for clinical patients. Multi-drug resistant Gram-positive bacteria including MRSA, MRSE, VRSA, methicillin-resistant coagulase-negative Staphylococci (MRCNS), and penicillin-resistant *Streptococcus pneumoniae* (PRSP) are known to be a serious problem in clinical practices.[154] Most of the isolated bacterial pathogens showed resistance against ≥ 2 of commonly used antibacterials in Bangladesh. As there is a limited possibility of getting new antimicrobial drugs in the market to treat patients with multi-drug resistance situations, the suggestion could be random documentation of antibiogram of the isolated pathogens from the clinically sick patient for the rational and effective use of antimicrobial agents in low-income countries including Bangladesh. However, the proposed antibiotic resistance index could serve as a guideline for physicians for prescribing effective antibacterial drugs for appropriate therapy of the patients.

ESBL-producing nosocomial bacteria and their drug resistance

Extended-spectrum-lactamases (ESBLs) represent a major group of lactamases currently being identified in large numbers globally mostly produced by Gram-negative bacteria. A study was conducted on 125 wound swabs collected from surgical swabs and burn cases to detect the frequency of ESBLs in Gram-negative bacterial isolates causing nosocomial wound infections. Culture yielded 71 (56.8%) bacterial growth with 60 (84.51%) Gram-negative and 11 (15.49%) Gram-positive bacteria (*Staph. aureus*). Gram-negative isolates included 23 (32.39%) *E. coli*, 19 (26.76%) *Klebsiella* spp., 16 (22.54%) *Pseudomonas* spp., and 02 (02.82%) *Proteus* spp. The number of ESBL-producing bacteria in modified double disc and phenotypic confirmatory methods was 28 (46.67%), and 25 (41.66%) respectively. The highest rate of ESBLs was recorded in *Klebsiella* spp. (57.89%), followed by *Proteus* (50.0%), *E. coli* (47.83%), and *Pseudomonas* spp. (31.25%), which showed significantly

Increasing antimicrobial drug resistance (AMDR) to 3rd generation cephalosporins, aminoglycosides, quinolone, and trimethoprim-sulfamethoxazole (Table 34).[170]

Table 34. Patterns of antimicrobial drug resistance among ESBL producers[170]

S/N	Bacteria	No. of isolates	Antimicrobial drugs AMP	COT	CIP	GEN	IPM	CFA	CZN	ATN	NT
1.	*Escherichia coli*	11	11 (100)	11 (100)	10 (90.91)	05 (45.45)	0	09 (81.82)	08 (72.73)	07 (63.64)	06 (54.55)
2.	*Klebsiella* spp.	11	11 (100)	08 (72.73)	09 (81.82)	07 (63.64)	0	11 (100)	11 (100)	11 (100)	10 (90.91)
3.	*Pseudomonas* spp.	05	-	-	04 (80.00)	04 (80.0)	0	04 (80.00)	04 (80.00)	05 (100)	04 (80.00)
4.	*Proteus* spp.	01	01 (100)	01 (100)	01 (100)	0	0	01 (100)	01 (100)	01 (100)	0

AMP = Ampicillin COT = Cotrimoxazole CIP = Ciprofloxacin GEN = Gentamicin IPM = Imipenem CFA = Ceftriaxone
CZN = Ceftazidime ATN = Aztreonam NT = Netilmicin

The routine antibiogram sensitivity testing fails to detect ESBL resulting in treatment failure. Table 34 shows that the rate of isolation of ESBL Gram-negative bacteria is alarming in the investigated care hospital in Bangladesh, because treatment of these clinical cases is made with empirical antibiotic therapy including one of the 3rd generations of cephalosporins and virtually all ESBL-producing bacteria are resistant to them. Therefore, it an urgent need to address the therapeutic failure problem of hospital-acquired infection caused by ESBL-producing bacteria, where antibiotic abuse and irrational use a common practices.

Drug resistance of ESBL-producing bacteria of urinary tract infection (UTI)

Out of 200 samples collected from UTI, of which *E. coli* was the predominant pathogenic Isolate (57%), followed by *Enterococcus* spp. (10.5%), *Klebsiella* spp. (11.0%), *Staphylococcus* spp. (4.0%), *Pseudomonas* spp. (10.0%), *Acinetobacter* spp. (5.0%), and *Enterobacter* spp. (9.0%). ESBL production occurred more frequently in *Klebsiella* spp. (72.7%) than *E. coli* (53.5%), and *Enterobacter* spp. (66.7%) but a lower rate in *Pseudomonas* spp. (20.0%), *Acinetobacter* spp. (20.0%), and *Enterococcus* spp. (4.8%).[171] The higher frequency of antimicrobial resistance as well as ESBL production by the most common pathogens of UTI demonstrate a public health threat and therefore, concern government authority and physicians aware to control the problem.

Extended-spectrum beta-lactamases (ESBLs) are enzymes that mediate resistance to extended-spectrum, e.g. third-generation cephalosporins as well as monobactams. Infections caused by ESBL-producing bacteria represent a major problem, antibiotic resistance, and are of great importance because of their clinical implication with higher mortality rates and healthcare costs.[172] Out of 1113 samples tested, of which 179 (16.08%) Gram-negative bacilli were phenotypically detected and were reported as ESBL-producing isolates were included in the antibiogram study (Table 35).

Table 35. Isolation of ESBLs producing Gram-negative bacteria and their antibiogram patterns (Jobayer et al. 2017)[172]

S/N	Bacterial species	Total isolates	ESBL No. (%)	Sensitivity pattern of ESBL-producing bacteria IMP	MP	AK	GEN	CIP	COT	AMC	CL	P/T	LF
1.	*Escherichia coli*	565	89 (15.75)	97.7	94.7	77.9	35.8	25.3	22.6	10.1	85.0	87.9	34.4
2.	*Pseudomonas*	421	59 (14.01)	82.1	80.4	28.8	05.7	09.3	01.9	13.6	47.5	07.9	07.3
3.	*Proteus*	038	14 (36.84)	85.7	92.9	42.9	07.7	40.0	0	0	35.7	100	0
4.	*Klebsiella*	070	13 (18.57)	100	100	46.2	23.1	30.8	44.4	15.4	100	100	0
5.	*Acinetobacter*	019	04 (21.05)	75.0	50.0	25.0	0	0	0	0	100	0	0
	Total	1113	179 (16.08)										

IMP = Imipenem MP = Meropenem AK = Amikacin GEN = Gentamicin CIP = Ciprofloxacin
COT = Co-trimoxazole, AMC = Amoxyclav CL = Colistin P/T = Piperacillin / Tazobactam LF = Levofloxacin

Most ESBL producers have been reported to be resistant to commonly used antibiotics. Carbapenems especially imipenem the most effective drug showed excellent sensitivity; colistin and piperacillin/

tazobactam also had better sensitivity results. Most of the ESBL producers showed a good sensitivity to amikacin but all of them were highly resistant to ciprofloxacin. Sensitivity and resistance both categories of antibacterial are available for ESBL-producing bacteria. Therefore, early detection and appropriate antibiotic application remain a significant priority in controlling the development and spread of ESBL-producing bacteria.

Drug resistance in ESBL-producing *Pseudomonas* spp.

Extended spectrum-lactamases (ESBLs) represent a major group of lactamases responsible for resistance, mostly produced by Gram-negative bacteria, to newer generations of β-lactam drugs currently being identified in large numbers worldwide. Anaerobic bacterial culture of 600 swab samples yielded 120 *Pseudomonas* spp. and 82 of them were biochemically characterized for species. Of 82 isolates tested for ESBL, 31 (37.8%) were ESBL positive with 29 (93.5%) as *Pseudomonas aeruginosa*, the remaining 2 (6.5%) were *Stenotrophomonas maltophilia* and *Ralstonia pickettii*. Antibiogram revealed imipenem as the most effective drug (93.3%) among all antimicrobials used against *Pseudomonas* spp., followed by aminoglycosides (63.7%).[173] ESBL-producing *Pseudomonas* spp. was found to be a frequent isolate from two tertiary care hospitals in Bangladesh, showing limited susceptibility to antimicrobials and decreased susceptibility to Imipenem is a matter of great concern as it is the drug of choice in the treatment of Pseudomonas infection.[173]

The incidence of diseases caused by β-lactam-resistant bacteria due to the production of various enzymes has increased in recent years. Detection of ESBL production is of paramount importance in both hospital and community isolates. Infection-control practitioners and clinicians need the clinical laboratory to rapidly identify and characterize different types of resistant bacteria. This in turn is required to minimize the spread of these bacteria and help select appropriate antibiotics.

Antibiotic susceptibility and R-plasmid mediated drug resistance in *Staph. aureus*

A total of 28 *Staphylococcus aureus* strains were isolated from skin lesion samples and were subjected to antibiotic sensitivity test and results showed resistance to ampicillin (72.0%), amoxicillin (72.0%), penicillin (72.0%), cotrimoxazole (15.0%), cloxacillin (50.0%), tetracycline (11.0%), cephradine (22.0%), cephalexine (7.0%), and nalidixic acid (18%). Plasmid analysis of the transferred *E. coli* LE 392 revealed that it contains a 23 KB plasmid corresponding to that of the donor *S. aureus* strain which may harbor the gene(s) encoding multiple drug resistance in the donor *S. aureus*.[174]

Vancomycin-resistant *Staph. aureus* in methicillin resistant *S. aureus* strains

The increase in resistance of methicillin-resistant *Staphylococcus aureus* (MRSA) strains to vancomycin has been perceived as a formidable threat in the therapeutic field. The vancomycin resistance traits of MRSA isolates (vancomycin-resistant *S. aureus* (VRSA) collected from burn patients, and 29 of 40 isolates of *Staphylococcus* spp. were identified as *S. aureus* which were further tested against 20 commercially available antibiotics to determine antibiotic susceptibility pattern. Imipenem was the most potential antibiotic resulting in 90% sensitivity, followed by netilmicin, clindamycin, and nitrofurantoin (80% sensitivity). All isolates were found to be resistant to penicillin. Approximately 75% of them were found to be resistant to methicillin, oxacillin, azithromycin, ciprofloxacin, and tetracycline. Approximately, 45% of isolates exhibited resistance to amikacin, chloramphenicol, gentamicin, and tobramycin. Twenty-one of the 29 strains of *S. aureus* were MRSA, of which 11 were resistant to vancomycin when employing the disc diffusion method. However, when the broth micro-dilution procedure was used to measure the minimum inhibitory concentration (MIC) of vancomycin, eight isolates were resistant to vancomycin, six with a MIC of 32 µg/ml, and two with a MIC of 64 µg/ml.[175] A significant fraction of VRSA was found among MRSA strains, revealing the necessity for new and effective drugs against MRSA.

MRSA, VRSA and PVL-positive *S. aureus*

A study was conducted to detect the prevalence and antibiogram pattern of methicillin-resistant *Staphylococcus aureus* (MRSA), vancomycin-resistant *S. aureus* (VRSA), and Panton-Valentine leucocidin (PVL)-positive *S. aureus* in a tertiary care hospital, Dhaka. Out of 44 isolated strains of *S. aureus*, 15 (34.09%)

were MRSA (2 of them were VRSA) and 29 were methicillin-sensitive *S. aureus*. All MTSA isolates were highly resistant to oxacillin (MIC ≥ 256 µg / ml). Four (26.67%) of the 15 mecA-positive strains were also positive for PVL genes. The MRSA strains were highly resistant to ciprofloxacin (93.33%), ceftriaxone (86.63%), azithromycin (73.33%), gentamycin (73.33%), and amoxiclav (66.6%). All (100%) MRSA strains were sensitive to linezolid and 86.67% were sensitive to vancomycin (Table 36). The VRSA strains had a MIC ≥ 256 µg / ml for vancomycin and were positive for the vanB gene but negative for the vanA gene.[176]

Table 36. Antibiogram pattern of *Staphylococcus aureus* and MRSA strains[176]

S/N	Types of bacteria	No. of isolates	Antibacterial sensitivity and resistant pattern, %								
			Ceftriaxone	Ciprofloxacin	Azithromycin	Amoxiclav	Gentamycin	Oxacillin	Cefoxitin	Vancomycin	Linezolid
1.	*S. aureus*	44 R	15 (34.10)	25 (56.82)	18 (40.91)	13 (29.55)	14 (31.82)	14 (31.82)	15 (34.10)	02 (04.55)	00 (00.00)
		S	29 (65.90)	19 (43.18)	26 (49.09)	31 (70.45)	30 (68.18)	30 (68.18)	29 (65.90)	42 (95.45)	44 (100)
2.	MRSA	15 R	13 (86.67)	14 (93.33)	11 (73.33)	10 (66.67)	11 (73.33)	14 (93.33)	15 (100)	02 (13.33)	00 (00.00)
		S	02 (13.33)	01 (06.67)	04 (26.67)	05 (33.33)	04 (26.67)	01(06.67)	00 (00.00)	13 (86.67)	15 (100)

MRSA = Methicillin-resistant *Staphylococcus aureus*

Table 36 shows multidrug-resistant *S. aureus*, including MRSA, which tends to increase in many hospital patients, and some of the MRSA are recorded PVL positive. In addition, VRSA has been identified by phenotype, the MIC of vancomycin, and vanB gene detection in Bangladesh.

Epidemiology and antibiogram of clinical *Staphylococcus aureus* infection

All of the 185 (100%) clinical *S. aureus* isolates were positive for the femAgene, of which 76 (41.1%) were methicillin-resistant *S. aureus* (MRSA), and 109 (58.9%) were methicillin-susceptible *S. aureus* (MSSA). These isolates were found resistant against penicillin G (94.6%), followed by amoxicillin/clavulanic acid (82.7%), azithromycin (72.4%), amoxicillin (66.5%), and ciprofloxacin (63.2%).[177] All the 185 isolates of *S. aureus* were 100% sensitive to both vancomycin and linezolid and also sensitive to rifampicin (94.0%), mdedropenem (87.0%), gentamicin (85.4%), and cotrimoxazole 82.2%). However, most of the *S. aureus* (81.1%) were overall resistant with MRSA (97.4%) and MSSA (69.7%) multidrug-resistant (MDR).[177]

Antibiotic resistance and associated genes in bacterial pathogens

An investigation was conducted to detect the spectrum of antibiotic resistance and the associated genes for aminoglycoside, macrolide, and ESBL class antibiotics using 430 preserved bacterial species including *Acinetobacter baumannii* (n = 20), *Pseudomonas aeruginosa* (n = 26), *Klebsiella pneumoniae* (n = 42), *Escherichia coli* (n = 85), *Staphylococcus aureus* (n = 84), *Salmonella Typhi* (n = 82), *Enterococcus* spp. (n = 27), *Streptococcus pneumoniae* (n = 36), and Coagulase negative Staphylococci (n = 28). Of the total isolates, 53.0% came out as MDR with 96.6% of *E. coli*, and 90.0% of *Staphylococcus aureus*. There was a year-wise gradual increase of MDR isolates from 2015 to 2018 and by 2019 the increase in MDR isolates became almost 2-fold compared to 2015. Among the five ESBL genes investigated, CTXM-1 came out as the most prevalent (63.0%) followed by NDM-1 (22.0%) and *E. coli* isolates were the predominant reservoir of these genes. Ermb (55.0%) was the most frequently detected macrolide resistance gene, whereas aac(6)-lb(35.44%) was the most prevalent aminoglycoside resistance gene and these genes were most prevalent in *E. coli* and *P. aeruginosa* isolates, respectively.[178]

Antibiotic resistance (ABR) is a global problem in both human and veterinary medicine with a highly significant risk to health in the developing world including Bangladesh. The prevalence of ABR is significantly high in developing nations because of the widespread misuse of antibiotics, non-human antibiotic use, poor quality of antibiotics, inadequate surveillance, and factors associated with low income at family and national levels associated with poor healthcare standards, malnutrition, chronic and repeated infections, unaffordability of more effective and costly drugs.[3] A systemic review was conducted to summarize the present scenario of ABR in humans for which 46 articles on ABR have been reviewed to analyze the trend of resistance and to

identify gaps in surveillance in Bangladesh. A high prevalence of ABR was reported in most tested bacterial pathogens, and many of the common first-line drugs were mostly ineffective. A significant gap in the surveillance of ABR studies has been recorded because published data on ABR are available only from six out of 64 districts in Bangladesh (Table 37). Furthermore, among the six districts reported with ABR data, all five other than Dhaka have poorly been represented.[3]

Table 37. Antibiotic resistance status (in %) of bacterial pathogens isolated from humans in Bangladesh[3]

S/N	Antibiotics	*Acinetobacter* spp.		*Enterococcus* spp.		*Escherichia coli*		*Klebsiella* spp.	
		No. of samples	Range (Mean)	No. of samples	Range (Mean)	No. of samples	Range (Mean)	No. of samples	Range (Mean)
01.	Amikacin	418	25-85.8 (67.5)	161	63.2-78.4 (67.3)	1953	07.0-26.7 (12.0)	289	10.3-60.3 (37.4)
02.	Amoxicillin	-	-	055	31.6-60.9 (45.5)	0857	28.2-95.3 (91.1)	216	90.2-99.7 (94.4)
03.	Amoxiclav	-	-	-	-	0750	52.0-85.5 (67.1)	147	14.3-84.6 (58.0)
04.	Ampicillin	-	-	-	-	1464	85.9-100 (94.6)	176	100-100 (100)
05.	Azithromycin	-	-	-	-	1318	28.6-83.4 (58.9)	-	-
06.	Aztreonam	-	-	-	-	0150	35.5-95.8 (79.0)	-	-
07.	Cefalexin	-	-	-	-	0673	50.1-76.6 (62.0)	-	-
08.	Cefepime	-	-	-	-	0142	28.2-94.4 (46.3)	-	-
09.	Cefixime	-	-	-	-	804	28.7-76.3(69.3)	248	50.0-89.0 (78.6)
10.	Cefotaxime	063	60.9-96.4 (82.9)	-	-	0129	16.1-96.4 (55.4)	073	81.2-100 (97.8)
11.	Ceftazidime	427	55.0-92.0 (80.0)	-	-	1650	34.5-83.4 (65.3)	315	58.8-98.2 (82.5)
12.	Ceftriaxone	823	42.5-92.5 (82.6)	139	51.8-90.0 (74.3)	2731	41.7-81.8 (59.0)	718	54.1-84.6 (78.0)
13.	Cefuroxime	051	62.0-87.5 (84.0)	055	60.9-100 (100)	0691	39.9-90.9 (78.8)	156	54.9-96.4 (74.7)
14.	Cephradine	-	-	-	-	0623	55.8-74.0 (62.6)	-	-
15.	Chloramphenicol	-	-	-	-	0510	00.0-77.5 (33.7)	105	33.8-64.3 (43.8)
16.	Ciprofloxacin	815	43.6-90.7 (82.2)	184	64.3-87.7 (66.0)	3272	52.4-80.5 (65.2)	835	43.6-80.9 (67.4)
17.	Cloxacillin	-	-	-	-	-	-	-	-
18.	Colistin	-	-	-	-	-	-	044	00.0-21.4 (18.8)
19.	Co-trimoxazole	071	48.8-94.0 (75.5)	100	74.2-100 (100)	3170	56.6-82.2 (72.0)	402	48.0-78.9 (72.7)
20.	Doxycycline	-	-	-	-	1212	44.6-93.8 (61.1)	-	-
21.	Erythromycin	-	-	-	-	-	-	-	-
22.	Gentamicin	836	53.5-92.0 (83.3)	184	32.3-85.0 (57.1)	2230	25.8-50.0 (34.5)	849	26.2-73.8 (63.6)
23.	Imipenem	375	05.0-65.1 (27.3)	-	-	1718	00.0-08.9 (02.3)	666	00.0-23.9 (00.0)
24.	Levofloxacin	-	-	-	-	0863	48.7-69.2 (62.0)	124	40.0-69.9 (54.9)
25.	Mecillinam	-	-	-	-	-	-	-	-
26.	Meropenem	-	-	-	-	0884	00.3-37.2 (13.3)	361	00.0-41.9 (07.7)
27.	Nalidixic acid	-	-	055	95.7-100 (100)	1831	80.3-90.8 (85.9)	216	52.5-90.9) (61.8)

Multiple studies have reported therapeutic failures including multiple drug-resistant (MDR) in clinical cases of human bacterial diseases which have been attributed to irrational antibiotic prescribing by physicians, a habit of self-medication among patients, and the indiscriminate use of antibiotics in the field of livestock and farming system in Bangladesh.[147,148,179]

Antibiogram of *Helicobacter pylori* strains

The prevalence of *H. pylori* infection among infants, children, and adults are 61, 84, and 92%, respectively in Bangladesh. However, information on antimicrobial sensitivity to commonly used drugs in *H. pylori* treatment is limited in Bangladesh. Out of 278 selected patients, 162 had a peptic ulcer (PU) and 116 had non-ulcer dyspepsia (NUD). Of the 174 isolates, 120 were available for antimicrobial sensitivity testing. Among the tested isolates, 77.5% (93 of 120) metronidazole, 15% (18 of 120) tetracycline, 10% (12 of 120) clarithromycin, and 6.6% (8 of 120) amoxicillin were resistant. It appears that antibiotic resistance is an emerging problem in the treatment of *H. pylori*-infected patients. Therefore, there is a need for continuous monitoring of the antimicrobial susceptibility in *H. pylori* for the determination of optimal treatment regimens.[180]

An antimicrobial study conducted on 56 isolated *Helicobacter pylori* showed a higher rate of resistance to clarithromycin (39.3%) and metronidazole (94.6%) in comparison to those previously reported in Bangladesh.[180] The high rate of resistance to levofloxacin (66.1%) indicates emerging antimicrobial resistance.[181] MDR strains of *H. pylori* have been reported with double drugs (8.9% & 28.6%) and triple drugs (3.6% & 30.4%) in Bangladesh.[181]

Table 38. Antibiotic resistance status (in %) of bacterial pathogens isolated from humans in Bangladesh

S/N	Antibiotics	*Streptococcus pneumoniae* No. of samples	Range (Mean)[3]	Helicobacter pylori No. of samples	No. (%)[181]	S/N	Antibiotics	*Streptococcus pneumoniae* No. of samples	Range (Mean)[3]	*Helicobacter pylori* No. of samples	No. (%)[181]
01.	Amikacin	-	-			16.	Ciprofloxacin	457	04.0-31.3 (08.3)	-	-
02.	Amoxicillin	-	-	56	02 (03.57)	17.	Clarithromycin	-	-	56	22 (39.3)
03.	Amoxiclav	-	-	-	-	18.	Cloxacillin	-	-	-	-
04.	Ampicillin	322	00.0-15.0 (00.0)	-	-	19.	Colistin	-	-	-	-
05.	Azithromycin	160	31.0-65.0 (43.7)	-	-	20.	Co-trimoxazole	457	73.2-80.2 (77.0)	-	-
06.	Aztreonam	-	-	-	-	21.	Doxycycline	-	-	-	-
07.	Cefalexin	-	-	-	-	22.	Erythromycin	-	-	-	-
08.	Cefepime	-	-	-	-	23.	Gentamicin	-	-	-	-
09.	Cefixime	160	07.0-50.0 (43.7)	-	-	24.	Imipenem	-	-	-	-
10.	Cefotaxime	-	-	-	-	25.	Levofloxacin	-	-	56	37 (66.1)
11.	Ceftazidime	-	-	-	-	26.	Mecillinam	-	-	-	-
12.	Ceftriaxone	338	00.0-33.1 (10.0)	-	-	27.	Meropenem	-	-	-	-
13.	Cefuroxime	-	-	-	-	28.	Metronidazole	-	-	56	53 (94.6)
14.	Cephradine	-	-	-	-	29.	Nalidixic acid	-	-	-	-
15.	Chloramphenicol	-	-	-	-	30.	Tetracycline	-	-	0	0

The complete genome of *Citrobacter portucalensis* harbored eight antimicrobial-resistant genes which include, dfrA12 (trimethoprim), sul1 and sul2 (sulfonamides), mph(A) (macrolide), tet(A) (tetracycline), qnrS1 and qnrB13 (fluoroquinolones), blaCMY-39 ESBL, blaTEM-176 (non-ESBL) and aadA2, aph (30)-Id, strA, strB (aminoglycosides).[182]

Approximately 57.7% of rural households are rearing livestock in Bangladesh, which include large ruminant animals (cattle and buffaloes), small ruminant animals (sheep and goats), and poultry (backyard and commercial chickens & ducks) birds.[18] Government veterinary medical hospitals are extended up to the Upazila level with limited manpower and facilities that rarely (9.7%) are able to provide veterinary services at livestock farmers' household levels. Accordingly, mainly the pharmacies and village doctors (82.5%) provide veterinary medical services to the livestock farms in rural Bangladesh.[24] The prescribing and dispensing of antimicrobials in the livestock sector are neither lawfully regulated nor their use lawfully audited in Bangladesh.[183]

The global rise in antibiotic resistance poses a significant threat, diminishing the efficacy of common antibiotics against widespread bacterial infections. The 2022 Global Antimicrobial Resistance and Use Surveillance System (GLASS) report highlights alarming resistance rates among prevalent bacterial pathogens. The median reported rate in 76 countries of 42% for third-generation cephalosporin-resistant *E. coli* and 35.0% for methicillin-resistant *Staphylococcus aureus* are a major concern.

For urinary tract infections (UTI) caused by *E. coli*, 1 in 5 cases exhibited reduced susceptibility to standard antibiotics like ampicillin, co-trimoxazole, and fluoroquinolones in 2020. This is making it harder to effectively treat common infections.

Klebsiella pneumoniae, a common intestinal bacterium, also showed elevated resistance levels against critical antibiotics. Increased levels of resistance potentially lead to heightened utilization of last-resort drugs like carbapenems, for which resistance is in turn being observed across multiple regions. As the effectiveness of these last-resort drugs is compromised, the risks increase of infections that cannot be treated. Projections by the OECD (Organization for Economic Cooperation and Development) indicate an anticipated twofold surge in resistance to last-resort antibiotics by 2035, compared to 2005 levels, underscoring the urgent need for robust antimicrobial stewardship practices and enhanced surveillance coverage worldwide.[12,15]

Antimicrobial-resistant bacteria

The global rise of antibiotic resistance poses a significant threat, diminishing the efficacy of common antibiotics against widespread bacterial infections. Infections with antibiotic-resistant pathogens have a negative influence on the health of humans and animals because they increase the risk of treatment failure and illness severity.[184] The GLASS (Global Antimicrobial Resistance Surveillance System) report highlights alarming resistance rates among prevalent bacterial pathogens. Median reported rates in 76 countries of 42.0% for third-generation cephalosporin-resistant *E. coli* and 35.0% for methicillin-resistant *S. aureus* are a major concern.

Important examples of antimicrobial resistance strains of bacteria include: (a) Methicillin-resistant *Staphylococcus aureus* (MRSA), (b)Vancomycin-resistant *Enterococcus* (VRE), (c) Multidrug-resistant *Mycobacterium tuberculosis* (MDR-TB) and (d) Carbapenemase-producing Enterobacterials (CPE).[185]

a. Methicillin-resistant *Staphylococcus aureus* (MRSA)

The genus *Staphylococcus* is currently composed of more than 84 recognized species and 30 sub-species. The Staphylococci are divided into two distinct groups: the coagulase-positive staphylococci (CPS), such as *S. aureus* and six other species, and coagulase-negative staphylococci (CNS) such as *S. epidermidis*, *S. haemolyticus*, *S. lugdunensis* and *S. saprophyticus* are well known facultative pathogens.

The MRSA poses a specific problem, as it may cause serious human and animal infections, eventually resulting in death globally. The WHO has compiled data on bloodstream MRSA infection from about 80 countries from 2016 to 2020 with progressively increased rates which include 21.0% in 2016, 20.0% in 2017, 24.0% in 2018, 25.0% in 2019, and 35.0% in 2020.[186] Some high-income countries exhibited almost the highest prevalence rates of MRSA in humans which include United States (23.74%), Singapore (22.72%), Poland (22.18%), United Kingdom (18.66%), China (18.07%), Italy (16.34%), Spain (15.45%), Israel (14.82%), France (13.89%), and Switzerland (13.15%).[187] MRSA emerged within two years after the introduction of staphylococcal beta-lactamases-resistant beta-lactams, with methicillin being the first introduced. The emergence of methicillin-resistant *Staphylococcus aureus* of animal origin in humans has been recognized.[188] Acquisition of methicillin resistance is due to the integration of the staphylococcal cassette chromosome mec (SCCmec), which contains the mecA gene conferring resistance to β-lactams.

The selected major genomic elements in methicillin-resistant *S. aureus* and an overview of techniques used for molecular characterization of *S. aureus* have been reported elsewhere.[189,190] The occurrence of 13.3%Vancomycin-resistance *Staphylococcus aureus* (VRSA) strains in samples collected from hospitalized patients and the presence of vanB in the isolated strains have been reported.[191] The emergence of VRSA and MRSA clinical isolates has been reported and detected the presence of vancomycin resistance in 7.89% of the MRSA isolates. A similar study reported a prevalence of 28% VRSA.[175] Another study reported a prevalence of 93.44% VISA among clinical isolates, indicating the growing number of antimicrobial-resistant strains in Bangladesh.[192] The newly discovered CC80 clade was among the primary PVL-negative MRSA lineages distributed in an endemic manner throughout Bangladesh.[193] A study was conducted to ascertain the prevalence of MRSA and VRSA nasal colonization among healthcare providers, which revealed that there was a complete absence of resistance to vancomycin, whereas the prevalence of MRSA was 7.2%.[194] A cross-sectional observational was conducted to identify the presence of MRSA and its susceptibility to various antibiotics, which showed a 26.4% prevalence of MRSA among clinical isolates and the isolates exhibited a sensitivity rate of 100% towards vancomycin and gentamicin.[195] A related study recorded a 58.4% frequency of MRSA among clinical samples collected from Dhaka City in Bangladesh.[196] *S. aureus* isolates are resistant to methicillin, termed methicillin-resistant *S.aureus* (MRSA). MRSA is defined by the presence of the mecA gene, which encodes an altered penicillin-binding protein (PBP-2′). The mecA gene is located in staphylococcal cassette chromosome mec (SCCmec), which is a genetic element inserted at a specific site in the *S. aureus* chromosome.[197] Out of 94 clinical strains of *S. aureus* isolated from both humans and animals, the mecA gene was detected by PCR in 25.0% of human clinical isolates of *S. aureus*, whereas not a single mecA gene was detected in animal isolates of *S. aureus* (Table 39). Out of 100 animal samples, 29 (%) have been reported positive for *S. aureus*, only 4 (13.8%) samples of dogs were MRSA-positive, but none of the samples tested from cattle and cats were MRSA-negative. Of the 150 human samples tested, 64 (%) were *S. aureus* positive, of which 34 (53.1%) were MRSA-positive (Table 39).[198] The antibiotic susceptibility of *S. aureus* isolates with the mecA gene showed resistance to penicillin (100%), oxacillin (100%), erythromycin (73.5%), ciprofloxacin (70.6%), and gentamicin (67.7%). MRSA carriage in humans and animals appears to be a great threat to effective antimicrobial therapy.[198] A study was conducted on 65 clinical samples (urine, pus, wound swab), of which 53 (81.54%) isolates were confirmed phenotypically as *S. aureus.* These were positive for amplification of the nuc (270bp) gene of *S. aureus*. However, among 53 isolates were 33 phenotypically considered as MRSA, and 38

(72.0%) showed positive amplification for the mecA (162 bp) gene. Among 38 MRSA isolates 22 (57.89%) were confirmed as CA-MRSA and 16 (42.10%) as HA-MRSA.[196] The overall pooled prevalence of MRSA carriage among healthcare workers (HCWs) has been reported to be 9.23% with a range from 0.67 to 36.06%, and country-wise prevalence of 5.65% in India, 8.83% in Nepal, 17.20% in Pakistan, 22.56% Sri Lanka and 4.93% in Bangladesh. The pooled prevalence of MRSA carriage among nurses and doctors was 8.90% and 6.53% respectively.[199] A review of 19 articles on the isolation of MRSA strain ranged from 4.8 to 78.7%. of these 19 studies, 17 reported hospital cases, and only two studies from community settings (Table 40). The most effective antibiotics against MRSA were gentamicin (72.7%), rifampin (71.4%), vancomycin (69.2%), cefradine (62.5%), ceftriaxone (58.3%), neomycin (55.6%), fusidic acid (57.15), and chloramphenicol 50.0%).[20]

Table 39. Prevalence of methicillin-resistant *Staphylococcus aureus* (MRSA) in samples of humans and animals in Bangladesh

S/N	Location/ District	Institution	Host species	Clinical status	Sample source	No. of samples	No. of isolates	MRSA No. (%)	MSSA No. (%)	Ref. No.
1.	Chittagong	Hospitals	Human	Patients	SI	100	09 (09.0)	07 (77.8)	02	201
					HW	100	07 (07.0)	03 (42.9)	04	
					U & E	100	27 (27.0)	15 (55.6)	12	
					HDW	100	23 (23.0)	18 (78.3)	05	
					Total	100	66 (66.0)	43 (65.2)	23	
2.	Mymensingh	Hospital	Human	Patients	SWS	50	17 (34.0)	02 (5.0)	-	202
					BUE	14	04 (28.6)	02 (5.0)	-	
					AS	11	08 (72.7)	02 (5.0)	-	
					PSI	19	09 (47.4)	03 (7.5)	-	
					DUE	05	01(20.0)	0	-	
					VS	01	01(100)	01 (2.5)	-	
					Total	100	40 (40.0)	10 (25.0)	-	
3.	Mymensingh	Hospitals, Farms	Cattle	H & Sick	MPW	55	18 (32.7)	0	-	198
			Dogs	-	NS	36	09 (25.0)	04 (44.4)	-	198
			Cats	-	NS	09	02 (22.2)	0	-	198
					Total	100	29 (29.0)	04 (13.8)	-	
		Hospitals	Humans	Patients	SWS	95	34 (35.8)	18 (52.9)	-	
					PSI	19	11 (57.9)	07 (63.6)	-	
					DUE	14	07 (53.8)	03 (42.9)	-	
					BUE	13	07 (53.8)	03 (42.9)	-	
					AS	09	05 (55.6)	02 (40.0)	-	
					Total	150	64 (42.7)	34 (53.1)	-	
4.	Dhaka	BIRDEM Hospital	Human	Patients	Multiple	-	198	81 (40.9)a 07 (03.5)b	110 (55.6) -	203

SI = Skin infection; HW = Hospital workers; U & E = Utensils & equipment; HDW = Hospital drain water
MRSA = Methicillin-resistant *S.aureus*; MSSA = Methicillin-sensitive *S. aureus*
SWS = Surgical wound swabs; BUE = Burn ulcer exudate; AS = Aural swab; PSI = Pus from skin infection
DUE = Diabetic ulcer exudate; VS = Vaginal swab; Multiple = Pus, wound, blood and urine; [a]PVL -ve, [b]PVL +ve

Table 40. Isolation and identification of MRSA in hospital-registered patients of different districts in Bangladesh[204]

S/N	District	No. of samples	S. aureus +ve No. (%)	MRSA +ve No. (%)	S/N	District	No. of samples	*S. aureus* +ve No. (%)	MRSA +ve No. (%)
1.	Dhaka	2472	349 (14.1)	220 (63.0)	2.	Chittagong	0188	039 (20.7)	014 (35.9)
3.	Rajshahi	0190	028 (14.7)	009 (32.1)	4.	Mymensingh	0071	013 (18.3)	008 (61.5)
5.	Community	0690	081 (11.7)	033 (40.7)		Total	3611	510 (14.1)	284 (55.7)

A study evaluated 23 isolates of *S. aureus*, of which 43.48% isolates were ensured methicillin-resistant while the remaining 56.52% isolates were found to be methicillin-sensitive, and β-lactamase test showed that 50.0% of the MRSA isolates produced β-lactamase. Antimicrobial sensitivity showed that MRSA isolates were highly sensitive to vancomycin (100%), fusidic acid (90%), chloramphenicol (90%), neomycin (80%), rifampin (80%), gentamicin (70%) and others.[155] However, these findings could be useful for physicians to select and prescribe

rational antibiotics in the treatment of MRSA in hospital and community infections. Drug sensitivity test of the MRSA strains showed 100% resistance against penicillin, oxacillin, cloxacillin, and amoxicillin, whereas 100% sensitivity against vancomycin, ciprofloxacin, erythromycin, fusidic acid, and rifampicin.[205]

Phenotypic detection of MRSA has been conducted by cefoxitin disc diffusion method and genotype (mecA gene) by PCR. The bacteriological culture of 212 wound swab samples showed 89.62% of samples yielded growth in culture. Out of 21 *S. aureus* isolates, 7 (33.33%) were detected as MRSA by cefoxitin resistance and the presence of mecA gene (Table 41). The high prevalence and increased resistance rate of MESA to commonly used antibiotics have suggested to establishment of an antimicrobial surveillance system in hospital settings to prevent the spread of MRSA.[206]

Table 41. Prevalence of MRSA in human patients in Bangladesh[207]

Year	District/ Location	Sample source source	No. of samples	Types of samples	Growth +ve No. (%)	*S. aureus* +ve No. (%)	MRSA +ve No. (%)	Ref. No.
1998	-	Hospital	-	-	-	-	- (78.7)	208
1999	-	Community	-	-	-	-	- (25.0)	209
2002	-	Hospital	-	-	-	141	60 (42.5)	200
2002	-	Hospital	-	Multiple	-	142	67 (47.2)	210
2005	-	Multicenter	-	-	-	-	- (32.63)	204
2007	-	Hospital	-	Multiple	572	-	- (57.0)	211
2007	-	Hospital	-	-	-	79	40 (50.6)	212
2008	Mymensingh	MMCH	-	-	-	40	10 (25.0)	205
2008	Mymensingh	MMCH	50	ES	42 (84.0)	26 (61.90)	12 (46.2)	213
2008	Dhaka	AFI	50	Multiple	-	42 (84.0)	02 (04.8)	214
2008	M & D	DMCH, MMCH	-	P&W	-	59	26 (44.1)	197
2010	Dhaka	BIRDEM	1660	Multiple	564 (34.0)	09 (01.4)	07 (77.0)	215
2011	Dhaka	Diagnostic C	23	Multiple	-	23	10 (43.5)	155
2011	Mymensingh	Hospital (A)	100	Multiple	-	54 (54.0)	14 (25.0)	216
		(H)	100	Multiple	-	40	10 (25.0)	216
2011	Dhaka	Hospital	50	PUSTS	-	08	- (0)	217
2011	Dhaka	Hospital	-	-	-	-	- (43.2)	218
2012	Dhaka	NICVD	274	Multiple	102	06 (02.20)	- (-)	219
2013	Dhaka	NHNML	2,700	Multiple	-	103 (09.86)	47 (46.0)	154
2013	Dhaka	DMCH	180	Burn unit	-	80 (44.44)	20 (25.0)	220
2016	Mymensingh	Hospital	65	Multiple	-	13 (20.00)	02 (13.0)	221
2020	Rajshahi	BPSU, RMCH	212	Wound swab	190 (89.62)	21 (09.90)	07 (33.3)	206
2020	Dhaka	SIMCH	964	Blood	-	-	42 (04.4)	222*
2021	Dhaka	SIMCH	964	Blood	-	-	42 (04.4)	223*
2023	Mymensingh	MMCH	169	Multiple	-	-	61 (36.0)	224

M = Mymensingh D = Dhaka DMCH = Dhaka Medical College Hospital MMCH = Mymesnignh Medical College Hospital
BIRDEM = Bangladesh Institute of Research and Rehabilitation in Diabetes, Endocrine, and Metabolic Disorder AFI = Armed Forces Institute
NHN = National Healthcare Network Diagnostic C = Centre (Medinova Medical Services & Popular Diagnostic Centre
NICVD = National Institute of Cardiovascular Disease NHNML = National Healthcare Network Microbiology Laboratory
BPSU, RMCH = Burn and Plastic Surgery Unit, Rajshahi Medical College Hospital SIMCH = Sirajul Islam Medical College and Hospital
P + W = Pus + Wound ES = Endocervical swabs Multiple = Blood, urine, sputum/tracheal aspirate, pus/wound swabs
PUSTS = Pus, urine, sputum & throat swabs
*The same article is published in two different journals 204! *Acinetobacter baumannii*- the anti-bacterial effect of the phase cocktail (vB_AbaS_DO & vB_AbaP_D2) showed more effective than use of individual phages.

It appears from these observations that if the propagation (multiplication) of MRSA continues, then it can lead to a situation of an outbreak caused by MRSA infection. Therefore, appropriate effective control measures would be required to prevent outbreaks due to MRSA infections.

Genetic characterization of current MRSA / MSSA in Bangladesh revealed with first identification of *S. argenteus* at low prevalence (n = 2/172), which is genotyped as ST2250/coa-XId.[224]

b. Vancomycin-resistant Enterococcus (VRE)

Enterococcus species is a ubiquitously distributed member of the intestinal microbiota of both humans and animals. *E. faecium* along with *E. faecalis* can cause about 90% of clinical infections in humans. The zoonotic pathogens *E. faecium* can be transmitted from animals to humans and can develop bacteremia, urinary tract infections, infective endocarditis, wound infections, sepsis, and meningitis.[225] Vancomycin is a glycopeptide antibiotic that inhibits cell wall synthesis and is used to treat severe Gram-positive bacterial infections. Vancomycin-resistant enterococci (VRE) were first reported in England and France in 1986 and are now spread through hospitals worldwide. Currently, vanA and vanB genes are responsible for high or moderate-level vancomycin resistance.

The VRE are both of medical and public health importance associated with serious MDR infections and persistent colonization. By PCR, among 100 samples, 45.0% were positive for *E. faecium* in apparently healthy broiler chickens in Mymensingh. All the *E. faecium* isolates were found resistant to ampicillin, and frequently resistant to ceftriaxone, cefotaxime, streptomycin, erythromycin, and imipenem, and moderate to lower resistance to tetracycline, ciprofloxacin, norfloxacin, chloramphenicol, gentamicin, and vancomycin. However, 80.0% *E. faecium* isolates were MDR in nature and it ranged from 0.08 to 0.83 in this study. The detection of MDR and MAR *E. faecium* and their corresponding resistance genes from apparently healthy broiler chickens concern because of their potential to enter into the human food chain.[225]

If vancomycin-resistant Enterococcus is highly resistant to other antimicrobial therapies, the two major treatments linezolid and daptomycin were suggested. Linezolid, daptomycin, and tigecycline have been increasingly utilized over the past decade as last-line therapeutics, to combat MDR enterococci and staphylococci, but clinical isolates with reduced susceptibility have emerged.[226] However, new-generation oxazolidinones i.e. Tedizolid phosphate have been recently approved and demonstrated better efficacy against clinical MDR Gram-positive pathogens such as MRSA, VRE, and LRE.[226]

c. Multidrug-resistant *Mycobacterium tuberculosis* (MDR-TB)

MDR-TB is defined as tuberculosis caused by *Mycobacterium tuberculosis* which is resistant against the two first-line drugs isoniazid and rifampin, the two most potent TB drugs. Extensive drug-resistant TB (XDR-TB) is defined as an infection with an MDR-TB strain, which is additionally resistant to an injectable second-line drug (amikacin, kanamycin, capreomycin) and fluoroquinolone.

Zoonotic TB (zTB) is a form of TB in humans predominately caused by *M. bovis*, but to a lesser extent by *M. tuberculosis*, *M. caprae*, and *M. orygis* (*M. tuberculosis complex*, MTC). Sputum specimens from 1906 (84%) of 2270 enrolled patients were analyzed, of which 61 (3.2%) isolates were identified as having MDR-TB. The proportion of MDR-TB was 2.3% among new and 13.8% among previously treated TB patients in Bangladesh.[227]

The pooled prevalence of any (45.3%), mono (14.3%), multi (22.2%), poly (7.7%), and extensive (0.3%) anti-TB antibiotic resistance has been reported by reviewing 24 reports covering 13,336 patients with TB in Bangladesh.[228] Among many first and second-line anti-TB drugs, isoniazid (35.0%) and cycloserine (44.6%) resistances were the highest, followed by ethambutol (16.2%) and gatifloxacin (0.2%). The implementation nationwide surveillance system to detect suspected and drug-resistant TB cases, as well as to ensure a more encompassing treatment management by a national TB control program is highly recommended.[228]

d. Carbapenemase-producing Enterobacterials (CPE)

There are several species of bacteria within the Enterobacterales order, which include Escherichia, Klebsiella, Enterobacter, Salmonella, Shigella, Citrobacter, and Yersinia. Species of the Enterobacterales order may develop resistance to a group of antibiotics called carbapenems and these are called (CRE).

The carbapenemes are among the most active drugs against a wide variety of bacteria. Their spectrum includes a wide variety of aerobic and anaerobic bacteria, including most strains of Pseudomonas, Klebsiella, *E. coli*, Streptococci, Staphylococci, and Listeria.

The spread of carbapenem-resistant Enterobacteriaceae (CRE) in healthcare settings challenges clinicians worldwide. The CRE occurs globally in livestock, pets, wildlife, pets, and seafood, and directly exposed humans pose a risk to public health.[229] The emergence and spread of carbapenem-resistant bacteria are mainly due to the rapid dissemination of genes that encode carbapenemases through horizontal gene transfer. Carbapenem-resistant *E. coli* prevalence was high in market wastewater (30.0%) but low in humans (1.0%) and poultry (1.0%) samples in Bangladesh.[230]

Prevalence of ABR bacteria in poultry and other birds

The commercial broiler and layer chicken industry has rapidly improved in Bangladesh to address the increasing the high demand for poultry meat and eggs. The high prevalence of chicken diseases, which are usually treated and controlled by using antimicrobials caused the development of antimicrobial resistance in Bangladesh. An investigation showed that out of 140 commercial chicken farms, 137 (97.9%) used 24 different types of antimicrobials.[231] Overall 75.2% of farmers reported clinical signs for which they administered antimicrobials, while 24.8% of farmers reported no clinical signs but still administered antimicrobials.[231]

The poultry hatchery and feed dealers usually provide financial support and farming-related technical information to the farmers to initiate and operate their farms and farmers become obliged to buy poultry chicks, feed, and medicine from the dealers. Sales representatives of pharmaceutical companies are another influencing group in poultry farming systems that provides product information and also provide treatment advice directly to the farmers. Recently, registered veterinary medical doctors have been appointed by the hatcheries, feed companies, and pharmaceutical companies that are providing poultry management and treatment services to the farmers.[232] Poultry farmers use antimicrobials indiscriminately in both the broiler and layer chickens in Bangladesh. Broiler chicken farmers use antimicrobials for treatment, prevention, and growth promotion, whereas layer farmers use antimicrobials to prevent egg production fall and, for therapeutic and prophylaxis purposes in suboptimal doses. Most of the commercial poultry farmers (>60%) and small-scale layer farmers (94.16%) use antimicrobials without a prescription by the registered Vets and do not maintain the withdrawal period of drugs.[233,234] In addition, poultry bird sellers in live bird markets also use antibacterials to prevent unwanted deaths.[235] A total of 27 types of antimicrobials have been used against *E. coli*, *Salmonella* spp., *Enterobacter* spp. and *Citrobacter portucalensis* in poultry birds reared under farming systems and approximately eight anti-bacterial resistant (ABR) bacterial species have been reported in different species of poultry birds (Table 42).

Table 42. Antibiotic resistance status (in %) of bacterial pathogens reported in poultry and other birds in Bangladesh[18] *

S/N	Antibiotics	*Escherichia coli* No. of samples	Mean (%) SS-1, D-1 27, 29, 235-245	*Salmonella* spp. No. of samples	Mean (%) SS-2, D-2 236, 238,246-250	*Enterobacter* spp. No. of isolates	Range (Mean) SS-3. D-3 Ref.No. 251	*Citrobacter portucalensis* No. of samples	Range (Mean) SS-4, D-4 Ref. No. 182
01.	Ampicillin	432	276 (63.9)	18	17 (94.4)	18	17 (94.4)	-	-
02.	Amoxicillin	106	095 (89.6)	18	16 (88.9)	-	-	-	-
03.	Aminoglycosides	-	000 (71.0)	-	-	-	-	62	R
04.	Carbapenems	-	000 (09.0)	-	-	-	-	-	-
05.	Cephalexin	010	008 (80.0)	18	11 (61.1)	-	-	-	-
06.	Chloramphenicol	022	002 (09.1)	10	-	-	-	-	-
07.	Ciprofloxacin	309	047 (15.2)	10	02 (10.0)	-	20.0-40.0	-	-
08.	Clindamycin	-	-	-	-	18	17 (94.4)	-	-
09.	Doxycycline	-	-	08	04 (50.0)	18	06 (33.3)	-	-
10.	Erythromycin	-	-	08	05 (62.5)	18	17 (94.4)	-	-
11.	Fluoroquinolone	-	- (85.0)	-	-	-	-	62	R
12.	Gentamicin	303	013 (04.29)	-	- (40.0-46.0)	18	01 (05.6)	-	-
13.	Imipenem	-	-	-	- (83.3)	18	12 (66.6)	-	-
14.	Kanamycin	-	- (80.0)	08	04 (50.0)	-	-	-	-
15.	Macrolides	-	-	-		-	-	62	R
16.	Nalidixic acid	336	133 (39.6)	08	02 (25.0)	-	-	-	-
17.	Nitrofurantoin	-	02.0-21.0	-	50.0-78.0	18	06 (33.3)	-	-

Contd. Table 42.								
12. Gentamicin	303	013 (04.29)	-	- (40.0-46.0)	18	01 (05.6)	-	-
18. Oxytetracycline	-	- (93.0)	-	-	-	-	-	-
19. Penicillin-G	010	010 (100)	10	09 (90.0)	18	18 (100)	-	-
20. Polymyxin	-	-	-	-	-	-	62	R
21. Rifampicin	-	-	-	- (100)	18	18 (100)	-	-
22. Streptomycin	66	04 (06.1)	-	- (77.14)	18	10 (55.6)	-	-
23. Sulfonamides	-	-	-	-	18	13 (72.2)	62	R
24. Sulfamethoxazole	-	-	-	- (60.0)	-	-	-	-
25. Tetracycline	467	270 (57.8)	-	93.0-97.2	18	06 (33.3)	62	R
26. STX /CM	356	154 (43.3)	-	- (80.0)	-	-	-	-
27. Vancomycin	-	-	-	-	18	16 (88.9)	-	-

STX = Trimethoprim-sulfamethoxazole CM = Cotrimoxazole R = Resistant
SS-1 = Sources- Apparently healthy, sick, and dead broiler, layer, and domestic birds; ducks, and geese; Apparently healthy Japanese quails, broiler meat; newly hatched chicks from broiler and layer flocks; SS-2 = Apparently healthy, sick, and dead layer & broiler chickens, litter & feed samples from broiler farms; Apparently healthy pigeons of LBMs, farms & village; Apparently healthy pigeons of LBMs, farms & villages; Apparently healthy Japanese quail; Poultry slaughter's hand & poultry residual container of poultry- slaughterhouses; broiler meat; newly hatched chicks from broiler & layer flocks; SS-3 = Layer poultry; SS-4 = Layer poultry D-1= Dhaka, Gazipur, Mymensingh, Chattog 8ram, Rajshahi, Sylhet and Sherpur, D-2 = Dhaka, Gazipur, Sherpur, Mymensingh and Chattogram, D-3 = Dhaka, D-4= Narayangonj
*Errors in published antibiogram results as R and S or bar diagrams without data and some need to purchase options caused incomplete analysis

Approximately, 29 types of antimicrobials have been used against mixed infections of Pasteurella sp. and *Bacillus* spp, *Staphylococcus* spp., *Campylobacter jejuni*, and *Campylobacter coli* in poultry birds reared under farming systems and approximately eight anti-bacterial resistant (ABR) bacterial species have been reported in different species of poultry birds in Bangladesh (Table 43).

Table 43. Antibiotic resistance status (in %) of bacterial pathogens reported in poultry and other birds in Bangladesh[18]

S/N Antibiotics	*Pasteurella* spp. + *Bacillus* spp. 252		*Staphylococcus* spp. 237,252,253			*Campylobacter jejuni* 254!,255		*Campylobacter coli* 254!,255	
	No. of samples	Mean (%) SS-5, D-5	No. of samples	Mean (%) SS-6, D-6		No. of samples	Mean (%) SS-7, D-7	No. of samples	Mean (%) SS-7, D-7
01. Ampicillin	-	-	125	125 (100)	24 (R)	22	22 (100)	9	9 (100)
02. Amoxicillin	-	-	125	107 (85.6)	24 (R)	-	58.0-66.0	-	43.0-61.0
03. Aminoglycosides	-	-	-	-	-	-	-	-	
04. Azithromycin	-	-	-	-	-	22	03 (13.6)	9	1 (11.1))
05. Carbapenems	-	-	-	-		-	-	-	
06. Cephalexin	-	-	120	46 (38.3)	-	-	-	-	
07. Chloramphenicol	-	-	-	-		22	0	9	0
08. Ciprofloxacin	-	-	120	93 (77.5)	-	22	10 (45.5))	9	2 (22.2)
09. Clindamycin	-	-	-	-		-	-	-	
10. Doxycycline	-	-	120	106 (88.3)	-	-	-	-	
11. Erythromycin	22+20	R	-	-	-	22	13 (59.6)	9	7 (77.8)
12. Fluoroquinolone	-	-	-	-	-	-	-	-	-
13. Gentamicin	-	-	120	020 (16.7)	-	22	0	8	2 (22.2)
14. Imipenem	-	-	-	-		-	-	-	-
15. Kanamycin	-	-	125	124 (99.2)	-	-	-	-	-
16. Macrolides	-	-	-	-	-	-	-	-	-
17. Nalidixic acid	-	-	-	-	-	22	17 (77.3)	9	4 (44.4)
18. Nitrofurantoin	-	-	-	-	-	22	12 (54.5)	-	-
19. Norfloxacin	-	-	-	-	-	-	25.0-54.5	9	6 (66.7)
20. Oxytetracycline	-	-	120	119 (99.2)	-	-	-	-	-
21. Penicillin-G	-	-	-	-	-	-	-	-	-
22. Polymyxin	-	-	-	-	-	-	-	-	-
23. Rifampicin	-	-	-	-	-	-	-	-	-
24. Streptomycin	-	-	-	-	-	22	02 (09.00)	9	0
25. Sulfonamides	-	-	-	-	-	-	-	-	-
26. Sulfamethoxazole	22 + 20	R	-	-	-	-	-	-	-
27. Tetracycline	22 + 20	R	5	5(100)	-	22	16 (72.7)	9	6 (66.7)
28. STX/CM	22 + 20	R	-	-	-	-	-	-	
29. Vancomycin	-	-	-	-	-	-	-	-	
30. MDR	-	-	-	-	-	49.0-86.4	-	42.0-100	

STX = Sulfamethoxazole-Trimethoprim CM = Cotrimoxazole R = Resistant (Quantitative data not available)
MDR = Multidrug resistant SS = Sample source D = Districts 254! = Multidrug resistant

SS-5 = Apparently healthy Japanese quails; SS-6 = Apparently healthy Japanese quails, frozen chicken rinse, newly hatched chicks from broiler and layer flocks; SS-7 = Hatcheries, broiler farms, and live bird markets (LBMs); broiler meat
D-5 = Mymensingh; D-6 = Mymensingh, Gazipur, Chattogram; D-7 = Mymensingh, Gazipur, Tangail

Antimicrobial-resistant *Escherichia coli* in poultry

A bacteriological study isolated 101 pathogenic *E. coli* strains from 279 dead or sick broiler and layer chickens of different ages which were screened to determine phenotypic expression of antimicrobial resistance against 13 antibiotics. Of 101 pathogenic *E. coli* isolates, more than 55% were resistant to at least one or more of the tested compounds, and 36.6% of the isolates showed multiple- drug-resistant phenotypes.[238]

A total of 17 research articles on prevalence and antimicrobial-resistant *E. coli* in poultry published from 18 out of 64 districts in Bangladesh have been reviewed. The prevalence of *E. coli* ranged from 24.3 to 100% and the isolates showed resistance to 14 antimicrobial classes and 45 different antimicrobial agents (Tables 44 & 45). The MDR *E. coli* in poultry was reported in 14 articles, including a 100% MDR in nine articles and a 92.7% combined percentage of MDR *E. coli* isolates. Twenty-four different AMR genes encoding resistance to different antimicrobials have been reported in *E. coli* isolates.[256] The presence of MDR *E. coli* and their corresponding resistance genes in poultry and poultry environments is an alarming issue for all health communities in Bangladesh.

Table 44. Prevalence of anti-microbial resistant *E. coli* in poultry with their resistance phenotypes & genotypes in Bangladesh

S/N	District	Study year	Published year	Poultry types	Sample types	No. of samples	PCR +ve/ Isolates	Resistance Phenotype (DDT)	Genotype (PCR)	MDR	ESBL	Ref. No.
01.	BD	-	2011	B & L	Feces	279	101	0 =	-	Yes	-	238
02.	Dhaka	2012	2016	Broiler	Feces	40	11	1=	blaTEM	Yes	DDST, PCR	238
03.	Jessore	2013	2018	Broiler	C swabs	08	05	2 =	-	Yes	-	239
04.	Sylhet	2014	2015	Broiler	CS, LS	100	42	3 =	-	Yes	-	240
05.	MGS	2015	2015	Broiler	Dressed	60	50	4 =	-	Yes	-	029
06.	Chattogram	2016	2019	Broiler	C swabs	60	37	5 =	blaTEM, tetA, sulII	Yes	-	241
07.	Mymensingh	2017	2018	Broiler	C swabs	65	54	6 =	qnrS	-	-	257
08.	JTKN	2017	2018	Broiler	Dressed	70	17	7 =	-	Yes	-	242
09.	Chittagong	2017	2020	Broiler	CS, ES	300	146	8 =	tetA, tetB & tetC	-	-	243
10.	Unknown	2017	2020	Layer	F,C,PP, ES	-	104	9 =	9 genotypes	Yes	PCR	027
11.	NNM	2017	2020	Layer	Multiple	-	392	10 =	-	Yes	-	244,258
12.	DR	2018	2019	Broiler	C swabs	400	400	11=	6 genotypes	Yes	-	259
13.	Mymensingh	2018	2019	Broiler	C swabs	60	44	12 =	mcr-3	-	-	260
14.	MT	2018	2020	Turkey	F, IC	55	55	13 =	tetA	Yes	-	261
15.	DSMCR	2019	2020	Chicken	FCM	133	86	14 =	blaTEM, blaCTX-M1	Yes	DDST, PCR	242
16.	Mymensingh	2019	2020	Layer	F,IC,EY,A	99	82	15 =	-	Yes	-	251
17.	SMSH	2020	2020	Chicken, Broiler	CMS -	600 300	381 197	16 =	9a genotypes Layer	Yes -	PCR	262 184
18.	MG	2019	2022	Broiler	CS,FS,HW	150	114	17 =	-	Yes	-	263
19.	7 districts Environment	-	-	Chicken		725 250	98% 78%	18 =	-	Yes	-	264

DDT = Disk diffusion test; PCR = Polymerase chain reaction; MDR = Multiple drug resistance; CS = Cloacal swabs
LS = Liver samples; ES = Environmental samples; F = Feces, C = Cecum
PP = Poultry pen; IC = Intestinal contents; FCM = Frozen chicken meat; A = Air
CMS = Chicken meat swabs; FS = Farm sewage; HW = Hand washes; DDST = Double disk synergy test
ESBL = Extended-spectrum beta-lactamase; B & L = Broiler & layer
MGS = Mymensingh, Gazipur & Sherpur; JTKN = Jamalpur, Tangail, Kishoreganj & Netrokona
NNM = Narsingdi, Narayanganj & Manikganj; DR = Dhaka & Rajshahi; MT = Mymensingh & Tangail
DSMCR = Dhaka, Sylhet, Mymensingh, Chattogram & Rajshahi; SMSH = Sylhet, Moulvibazar, Sunamganj & Habiganj
MG = Mymensingh & Gazipur; 7 districts = Name not mentioned
9 genotypes = mcr-1, blaCTX-M-1, blaCTX-M-9, blaTEM, blaOXA-1, blaOXA-47, qnrB, qnrS, and
6genotypes = tetA, tetB, blaTEM, aadA1, ereA and dfrA1
9a genotypes = tetA, Sull, aadA1, ereA, aac-3-IV, cm1A, catA1, blaSHV & CITM

0 = TE = Tetracycline (45.5%), STM = Sulfamethoxazole-trimethoprim (26.7%), NA = Nalidixic acid (25.7%), AMP = Ampicillin (25.7%), S = Streptomycin (20.8%), CIP = Ciprofloxacin (12.9%), C = Chloramphenicol (8.9%), NFT = Nitrofurantoin (2.0%) and GEN = Gentamicin (2.05%).
1= AMX = Amoxicillin, TE, STM, NFT, CIP & LEV = Levofloxacillin
2 = AMP, CL = Colistin , E = Erythromycin , NEO = Neomycin & P =Penicillin
3 = GEN, E, P, CPX = Cephalexin, AMX & NA

4 = AMX, AZM = Azithromycin, CIP, E, GEN, NOR = Norfloxacin, S & TE
5 = AMP, CRO = Ceftriaxone, TE, STM, GEN, CL, C, CIP, NA & E
6 = PLX = Pefloxacin, OFX = Ofloxacin, MOX = Moxifloxacin, GAT = Gatifloxacin & LEV
7 = AMX, AZM , E , GEN, NOR, S & TE
8 = OXT = Oxytetracycline & CIP
9 = AMP, TE, FOX = Cefoxitin, CRO, CTX = Cefotaxime, CAZ = Ceftazidime, CFM = Cefixime , FEP = Cefepime, CIP, NA, GEN, STM, NFT & TAZ = Tazobactam
10 = DOX = Doxycycline, AMP, TE, NFT, CIP, NA, FOX, IMP = Imipenem, GEN, C, SUL = Sulfonamide, AZM, & PB = Polymyxin B
11 = AMP, TE, S, CIP, E, STM, CL, GEN & LEV
12 = ERT = Ertapenem, MEM = Meropenem, IMP & CL
13 = LEV, E , GEN, C, CIP, S, MEM & TE
14 = CIP, NA, LEV, NOR, GAT = Gatifloxacin, PLX, OFX, CPX, CE = Cephradin, CXM = Cefuroxime, CEC = Cefaclor, CAZ = Ceftazidime, CRO, CTX, FEP = Cefepime, FOX, AMP, AMC =Amoxiclav, TAZ = Tazobactam, IMP, MEM, CL, PB, AZN = Aztreonam, GEN, TOB = Tobramycin, AMK = Amikacin, S, NEO, TE, OXT, DOX, STM, TIG = Tigecycline, C & AZM
15 = AMP, TE, C, E, EN = Enrofloxacin, NOR, CIP, S, CL & GEN
16 = STM, E, TE, S, AMP, C and GEN
17 = LEV, CIP, CAZ, CRO, CTX, AMC, CL, DOX, IMP & MEM
18 = CIP, AMP, TE, TMP (Trimethoprim), GE, FQ (Fluoroquinolones class), SUL

Table 45. Phenotypic and genotypic antimicrobial resistance profiles of *E. coli* sourced from poultry in Bangladesh

S/N	Antibiotics used	No. of isolates	Resistant No. (%)	References
A. Penicillins and beta-lactamase inhibitors				
01.	Amoxicillin	206	187 (90.78)	240,242,268
02.	Ampicillin	987	953 (96.56)	27,241,245,259,262,267
03.	Penicillin	47	047 (100)	29,30
04.	Tazobactam	100	065 (65.0	27,242
05.	Cephalexin	86	040 (46.5)	242
06.	Amoxiclav	200	059 (29.5)	242,263
07.	Cephalaxin	42	042 (100)	240
08.	Ceftriaxone	251	030 (11.95)	27,241,242,263
09.	Cefotaxime	114	089 (78.1)	27,242
10.	Ceftazidime	114	002 (01.8)	27,242
11.	Cefixime	14	013 (92.9)	27,242
12.	Cefepime	100	074 (74.0)	27,242
13.	Cephradine	86	043 (50.0)	242
14.	Cefuroxime	86	037 (43.0)	242
15.	Cefaclor	86	013 (15.1)	242
B. Carbapenems				
10.	Imipenem	327	148 (45.26)	240,258, 260,263
02.	Ertapenem	114	029 (65.9)	258
03.	Meropenem	299	153 (51.17)	240,242,260,263
C. Fluoroquinolones				
01.	Ciprofloxacin	1014	737 (72.68)	27,240,242,245,258,262, 265-268
02.	Levofloxacin	684	478 (69.88)	240,242,245,257,262,266
03.	Nalidixic acid	293	228 (77.82)	27,240,241,242,258
04.	Norfloxacin	189	059 (31.22)	242,258,268
05.	Gatifloxacin	123	050 (40.65)	241,242
06.	Moxifloxacin	18	010 (55.6)	235
07.	Pefloxacin	104	087 (83.65)	235,242
08.	Ofloxacin	104	059 (56.73)	235
09.	Enrofloxacin	86	020 (55.6)	242
D. Aminoglycosides				
01.	Neomycin	91	029 (31.87)	239,242
02.	Gentamycin	1232	421 (34.17)	27,235,240-242, 245, 258,261,262, 267,268
03.	Streptomycin	1025	758 (73.95)	235,242,245,261, 262, 267,268
04.	Tobramycin	86	007 (08.1)	242
05.	Amikacin	86	015 (17.4)	242
E. Tetracyclines				
01.	Tetracycline	1201	1025 (85.35)	27,241,242,245,258, 261,262, 266-268
02.	Oxytetracycline	183	177 (96.72)	242,265
03.	Doxycycline	314	238 (75.80)	242,258,263
F. Macrolides				
01.	Erythromycin	1023	938 (91.69)	239,240-242,245,261, 262,267,268
02.	Azithromycin	267	074 (27.72)	242,258,268
G. Polymyxins				
01.	Colistin	826	260 (31.48)	27,239,241,242,245, 260,263,267
02.	Polymyxin B	200	016 (08.0)	242,258
H. Phenicols				
01.	Chloramphenicol	709	332 (46.83)	241,242,258,261,262,
I. Sulfonamides/ Foliate pathway inhibition				
01.	SXT	929	740 (79.66)	27,241,242,245,262,266
02.	Sulfonamide	114	051 (44.7)	258
J. Cephamycins				
01.	Cefoxitin	214	092 (42.99)	27,242,258
K. Nitrofurans				
01.	Nitrofurantoin	139	078 (56.11)	27,258,266,
L. Monobactams				
01.	Aztreonam	86	001 (01.2)	242
M. Glycylcyclines				
01.	Tigecycline	86	002 (02.3)	242

SXT = Sulfamethoxazole-Trimethoprim

Prevalence of ABR bacteria in dairy and other animals

Different species of anti-bacterial resistance (ABR) bacteria have been reported from domestic food and wild animal sources in different districts in Bangladesh (Table 46). MDR zoonotic bacterium *E. coli* carried tetA and SHV resistance genes isolated from mastitis-affected cows, milkers' hands, and different components of the farm environment that developed resistance against different antimicrobials including azithromycin (100%). In addition to *E. coli*, the milk of mastitis-affected cows also contained different antibiotic-resistant bacterial

pathogens including *Bacillus* spp., *Streptococcus* spp., *Staphylococcus* spp., *Klebsiella* spp., *Enterobacter* spp., and *Shigella* spp. which developed resistance against several antibiotics (Table 46).

The disposal of farm waste directly into the environment contributes to ABR bacteria pollution and ultimately poses a health hazard to both farm animals and humans.[18,30] The MDR foodborne zoonotic bacteria *Salmonella* spp. carrying tetA and SHV resistance genes which have been reported from cow dung, milk, milkers' hands, and dairy farm environments with resistance against several antibiotics (Table 46,47). It has been reported that the dissemination of antibiotic-resistant bacteria including *Salmonella* spp., *Staphylococcus* spp., and *Yersinia* spp. in wild Irrawaddy squirrels (Table 46,47).[269,275] Contamination of the animal source food products by ABR bacteria with resistance against different antibiotics has also been reported (Table 46,47).[270]

Table 46. Antibiotic resistance status (Range, mean, %) of bacterial pathogens reported in dairy and other animals in Bangladesh[18]

S/N	Antibiotics	*Escherichia coli* R1* No. of isolates	Mean (%) SS-1, D-1	*Salmonella* spp.R2* No. of isolates	Mean (%) SS-2, D-2	*Bacillus* spp. R3 No. of isolates	Mean (%) SS-3, D-3	*Streptococcus* spp. R4 No. of isolates	M (%) SS-5, D-4	*Staph.* spp. R5 No of isolates	Mean (%) SS-5 D-5
01.	Ampicillin	152	103 (67.76) (25.7-91.89)	143	139 (97.2)	67	52 (77.6) 60.0-84.0	30	21 (70.0)	99	81 (81.82) (73.0-100)
02.	Amoxicillin	50	33 (66.00) (70.0-92.0)	50	046 (92.0)	67	30 (44.78)	30	27 (90.0)	-	(42.0-100)
03.	Amoxicillin-CA	78	47 (60.26)	-	-	-	-	-	-	212	115 (54.25)
04.	Azithromycin	316	316 (100)	136	136 (100)	-	-	-	-	-	-
05.	Cephalexin	54	14 (53.8)	07	05 (71.4)	-	-	-	-	39	24 (61.53)
06.	Chloramphenicol	370	138 (37.30)	136	43 (31.6)	31	06 (19.35)	-	-	56	2 (57.14) (50.0-58.0)
07.	Ciprofloxacin	604	70 (11.59)	136	19 (14.0	37	18 (48.65)	-	-	201	100 (49.75)
08.	Colistin sulfate	-	-	7	02 (28.6)	-	-	-	-	39	21 (53.85)
09.	Doxycycline	84	62 (73.81)	-	-	61	33 (54.10) 60.0-84.0)	30	13 (43.33)	86	62 (72.02) 73.0-88.0
10.	Ertapenem	180	120 (66.7)	143	72 (50.4)	-	-	-	-	-	-
11.	Erythromycin	321	283 (88.17) 83.0-88.9	143	125 (87.4)	31	19 (61;29) 60.0-84.0 ()	-	-	211	55 (26.07)
12.	Gentamicin	317	73 (23.03)	136	09 (06.6)	37	29 (78.38)	-	-	214	51 (23.83)
13.	Imipenem	234	46 (1966)	136	018 (13.2)	31	02 (06.45)	-	-	56	10 (17.86)
14.	Kanamycin	180	59 (32.78)	136	39 (28.7)	-	-	-	-	-	-
15.	Memopenem	180	49 (27.22)	136	31 (22.8)						
16.	Metronidazole	05	05 (100)	-	-	06	06 (100)	-	-	-	-
17.	Nalidixic acid	54	46 (85.19)	-	-	31	23 (74.19) 60.0-84.0	-	-	-	-
18.	Neomycin	180	61 (33.89)	136	47 (34.6)	-	-	-	-	-	-
19.	Nitrofurantoin	54	32 (59.26)	-	-	-	-	-	-	56	28 (50.00) 50.0-58.0
20.	Oxacillin	-	-	-	-	-	-	-	-	145	81 (55.86)
21.	Oxytetracycline	180	142 (78.9)	143	124 (86.7)	-	-	-	-	184	56 (30.43)
22.	Penicillin-G	05	05 (100)	-	-	06	06 (100)	-	-	10	02 (20.0)
23.	Rifampicin	-	-	-	-	-	-	-	-	30	21 (70.0)
24.	Streptomycin	113	60 (53.1) 47.4-100	-	-	36	27 (75.00) 70-100	30 -	21 (70.0) -	- -	70.0-100 -
25.	Tetracycline	312	251 (80.45) (89.4-100	143	120 (83.9) 28.6-86.8	-	-	-	-	118	70 (59.32) 30.8-88.0
26.	Trimethoprim	05	05 (100)	-	-	06	06 (100)				
27.	SXT	78	41 (52.56)	-	-	-	-	-	-	184	56 (30.43)
28.	Vancomycin	-	-	-	-	-	-	-	-	56	12 (21.43)

- = Data not available SXT = Sulfamethoxazole- Trimethoprim- CM = Cotrimoxazole R = Resistant (Quantitative data not available)
SS = Sample source D = District CA = Clavulanic acid=
SS-1 = Cattle of intensive and free-range farming systems, cow dung, milk, milkers' hand wash, soil, water, and vegetables of dairy farms, milk from mastitis-affected cows, feces of goats, wild Irrawaddy squirrels.
SS-2 = Cow dung, milk, milkers' hand wash, soil, water, and vegetables of dairy farms, wild Irrawaddy squirrels
SS-3 = Milk from mastitis-affected cows SS-4 = Milk from mastitis-affected cows
SS-5 = Milk from mastitis-affected cows, wild Irrawaddy squirrels
D-1 = Dhaka, Mymensingh, Chattogram, Sirajgonj, Satkhira, Rajshahi, Cox's Bazar and Bandarban
D-2 = Mymensingh, Cox's Bazar and Bandarban D-3 = Dhaka, Chattogram, Gazipur, Mymensingh, Sylhet, Satkhira, Rajshahi
D-4 = Mymensingh, Rajshahi

D-5 = Dhaka, Chattogram, Gazipur, Mymensingh, Satkhira, Rajshahi, Cox's Bazar, and Bandarban
*tetA and SHV resistance genes are present among the AMR E. coli isolates
Reference No. R1 = 29,30, 271-275 R2 = 18,265 R3 = 30,271,276 R4 = 271 R5 = 31,271, 272,275-277

Antimicrobial resistance (AMR) pattern of bovine clinical mastitis (CM) pathogens by disk diffusion method of the six bacteria obtained from 221 CM isolates (*S. aureus* 56, *E. coli* 54, *Klebsiella* spp. 42, *Enterobacter* spp. 26, *Bacillus* spp. 31 and *Shigella* spp. 12; total = 221) for 12 commonly used antibiotics from nine different groups/ classes are presented in Table 48.

Bacteriological examination of 56 samples comprising milk (n = 40), water (n = 10), and feces (n = 6) showed an overall 21 (37.5%) positive for *Vibrio cholerae* and 17 (30.35%) other Vibrio species. Prevalence of *V. cholerae* was recorded as 13 (32.5%) in milk, 4 (40.0%) in water, and 4 (66.67%) in feces. The isolated *V. cholerae* were found resistant to erythromycin, azithromycin, and ampicillin (Table 47) and all of the *V. cholerae* isolates were found to be multidrug-resistant.[278]

Table 47. Antibiotic resistance status (in %) of bacterial pathogens reported in dairy and other animals in Bangladesh[18]

S/N Antibiotics	*Yersinia* spp. [275]		Clinical mastitis [31] (Table 48)		*P. aeruginosa* [279]		*Vibrio cholerae* [278]		Unidentified [18,30]	
	No. of isolates	Mean (%) SS-6, D-6	SS-7, D-7		No. of isolates	Mean %) SS-8, D-8	No. of isolates	Mean (%) SS-9, D-9	No of samples	Mean (%) SS-10 D-10
01. Ampicillin	-	-	-	-	2	R	21	11 (52.38)	15	01 (06.67)[54]
02. Amoxicillin	24	17 (69.2)	-	-	2	R	-	-	-	-
03. Aminoglycosides	-	-	-	-	-	-	-	-	-	-
04. Azithromycin	-	-	-	-	-	-	21	16 (76.9)	-	-
05. Carbapenems	-	-	-	-	-	-	-	-	-	-
06. Cephalexin	24	13 (53.8)	-	-	-	-	-	-	-	-
07. Chloramphenicol	-	-	-	-	-	S	-	-	-	
08. Ciprofloxacin	-	07.7	-	-	-	S	-	-	15	06 (40.0)
09. Clindamycin	-	-	-	-	-	-	-	-	-	-
10. Colistin sulfate	24	13 (53.9)	-	-	-	-	-	-	-	-
11. Doxycycline	-	-	-	-	-	-	-	-	15	04 (26.67)
12. Ertapenem	-	-	-	-	-	-	-	-	-	-
13. Erythromycin	-	-	-	-	-	I	21	20 (95.23)	15	08 (53.3)
14. Fluoroquinolone	-	-	-	-	-	-	-	-	-	-
15. Gentamicin	24	04 (15.4)	-	-	-	S	-	-	57	R31
16. Imipenem	-	-	-	-	-	-	-	-	-	-
17. Kanamycin	-	-	-	-	-	I	-	-	57	R31
18. Macrolides	-	-	-	-	-	-	-	-	-	-
19. Nalidixic acid	-	-	-	-	-	-	-	-	15	15 (100)
20. Nitrofurantoin	-	-	-	-	-	-	-	-	-	-
21. Oxacillin	-	-	-	-	-	-	-	-	15	15 (100)
22. Oxytetracycline	-	-	-	-	2	R	-	-	-	-
23. Penicillin-G	-	-	-	-	-	-	-	-	-	-
24. Polymyxin	-	-	-	-	-	-	-	-	-	-
25. Rifampicin	-	-	-	-	-	-	-	-	-	-
26. Streptomycin	-	-	-	-	-	-	-	-	57	R31
27. Sulfonamides	-	-	-	-	-	-	-	-	-	-
28. Sulfamethoxazole	-	-	-	-	-	I	-	-	-	-
29. Tetracycline	24	11 (46.2)	-	-	2	R	-	-	15	15 (100)
30. SXT/ CM	24	07 (30.8)	-	-	-	-	-	-	-	-
31. Vancomycin	-	-	-	-	-	-	-	-	-	-

Kleb., Enter & Shig. = Klebsiella, Enterobacter & Shigella;
CM = Cotrimoxazole;
SS = Sample source;
I = Intermediately sensitive;
SS-6 = Wild Irrawaddy squirrels;
SS-8 = Pus from abscess of cattle;
SS-10 = Feces & waste-water of dairy farms and veterinary clinics, and bovine livers sold at retail meat shops;
D-6 = Cox's Bazar and Bandarban;
D-8 &9 = Mymensingh;
SXT = Sulfamethoxazole -Trimethoprim;
R = Resistant (Quantitative data not available);
D = District; S = Sensitive;
R = Resistant
SS-7 = Milk from mastitis-affected cows;
SS-9 = Milk from cows, water, and feces from the farm environment;
D-7 = Dhaka, Mymensingh, Chattogram, Gazipur and Sylhet;
D-10 = Dhaka and Chattogram

Table 48. Antibiotic resistance pattern of bacteria (No., % of isolates) associated with bovine clinical mastitis[31]

S/N	Antibiotics	*S. aureus* (n = 56)	*E. coli* (n = 54)	*Klebsiella* spp. (n = 42)	*Enterobacter* sp. spp. (n = 26)	*Bacillus* spp. (n = 31)	*Shigella* spp. (n = 12)
01.	Ampicillin (AMO)	48 (85.71)	42 (77.78)	36 (85.71)	24 (92.30)	25 (80.64)	10 (83.33)
02.	Doxycycline (DOX)	49 (87.50)	46 (85.18)	39 (92.86)	22 (84.61)	26 (83.87)	10 (83.33)
03.	Tetracycline (TCN)	46 (82.14)	50 (92.59)	38 (90.48)	24 (92.30)	11 (35.48)	12 (100)
04.	Ciprofloxacin (CIP)	28 (50.00)	22 (40.74)	18 (42.86)	08 (30.77)	13 (41.94)	04 (33.33)
05.	Imipenem (IMP)	10 (17.86)	12 (22.22)	11 (26.19)	05 (19.23)	02 (06.45)	03 (25.00)
06.	Chloramphenicol (CHL)	32 (57.14)	34 (62.96)	23 (54.76)	18 (69.23)	06 (19.35)	06 (50.00)
07.	Gentamycin (GEN)	22 (57.14)	23 (42.60)	21 (50.00)	04 (15.38)	23 (74.19)	05 (41.67)
08.	Nalidic acid (NAL)	-	46 (85.18)	36 (85.71)	20 (76.92)	23 (74.19)	12 (100)
09.	Nitrofurantoin (NIT)	28 (50.00)	32 (59.25)	30 (71.42)	12 (46.15)	-	04 (33.33)
10.	Cefoxitin (CFX)	14 (25.00)	14 (25.00)	12 (28.57)	08 (30.77)	-	02 (16.67)
11.	Vancomycin (VAN)	12 (21.42)	-	-	-	06 (19.35)	-
12.	Erythromycin (ERY)	41 (73.21)	-	-	-	19 (61.29)	-

Multidrug resistance (MDR)

Although bacteria resistant to individual antibiotics were observed earlier, one of the first reports of MDR bacteria was of Shigella resistant to sulfonamides, streptomycin, chloramphenicol, and tetracycline in Hong Kong in 1955.[280] Property of a bacterial pathogen that is resistant to two or more antimicrobial agents.[10] MDR bacteria with extreme resistance against antibiotics recommended for use in both animals and humans have been reported and been being a potential public health hazard in Bangladesh.[18] Recent studies in Bangladesh have reported increased incidence of multi-drug resistance *E. coli*, *Salmonella* spp., and *Shigella* spp. in different human and environmental samples.[125]

Methicillin-resistant *S. aureus* (MRSA) also called oxacillin-resistant *S. aureus* (ORSA) is associated with a prominent reason for higher morbidity and mortality in burn patients causing a variety of infections. Out of 180 samples tested from burn wound-infected hospitalized patients, 80 were infected with *S. aureus*. The antibiotic-resistant pattern showed that 22.5% of the isolates were resistant to oxacillin and the results of multiple drug results are presented in Table 49. More than 250,000 people get injured due to burn and of them, more than 3000 die each year in Bangladesh.[220] The frequency of MRSA occurrence in burn wounds and its antibiotic profile recorded in this study are alarming. Regular monitoring of the drug resistance profile of the pathogen and rapid diagnosis for MRSA detection would be required for effective therapy management of burn wounds.

Table 49. Multiple drug resistance status of *S. aureus* (n=80) collected from burn unit of DMCH[220]

No. of drugs	List of resistant drugs	Resistant isolates, %
Two	AML + E	72.5
Three	AMl + E + AZ	70.0
Five	AML + E + AZ + CIP + LEF	42.5
Seven	AML + E + AZ + CIP + LEF + NA + CFM	37.5
Eight	AML + E + AZ + CIP + LEF + NA + CFM + OX	25.0
Nine	AML + E + AZ + CIP + LEF + NA + CFM + OX + TE	17.5
Ten	AML + E + AZ + CIP + LEF + NA + CFM + OX + TE + GM	07.5
Eleven	AML + E + AZ + CIP + LEF + NA + CFM + OX + TE + GM + CLX	05.0

AML = Amoxicillin
E = Erythromycin
AZ = Azithromycin
CIP = Ciprofloxacxin
LEF = Levofloxacin
NA = Nalidixic acid
CFM = Cefixime
OX = Oxacillin
TE = Tetracycline
GM = Genamicin
CLX = Cloxacillin

It appears that the MDR bacteria with extreme resistance against antibiotics recommended for use in both veterinary and human medicine have been reported and have been a potential public health hazard in Bangladesh. Execution of extensive AMR surveillance in human and veterinary medical practices and awareness-building programs for stakeholders along with the strengthening of the laboratory capacities for effective containment of AMR emergence and dissemination in the livestock health sector in Bangladesh.
The MDR bacteria are rarely confined to a specific region and any region with a high prevalence of ABR bacteria can serve as a reservoir from which resistant strains can migrate to other parts of the world via

humans, animals, agricultural products, water, and others.[3]

The review results would provide a reference for future works and to guide policymakers and prescribers towards adopting the best strategy to lower the extent of ABR, as well as to mitigate the problems resulting from increasing resistance. The world faces an antibiotics pipeline and access crisis. There is an inadequate research and development pipeline in the face of rising levels of resistance, and an urgent need for additional measures to ensure equitable access to new and existing vaccines, diagnostics, and medicines.[12]

One Health Approach of AMR

Antibiotic-resistant bacteria (ARB) is a complex global issue associated with serious threats to the health of humans, livestock, and their shared environment. It is a global issue at the human-livestock-environment interface, providing suitable conditions for the rapid spread and evolution of bacteria. These bacteria are released into the environment from the feces of humans and livestock and can disrupt the normal environmental flora, potentially acting as a reservoir before reintroduction into the livestock-human cycle. Accordingly, all these three domains- livestock, humans, and environment are deeply interconnected and changes in one domain can have far-reaching effects on the others. Therefore, the 'One Health' approach is highly justified to reduce the impact of ARB on these three domains to ensure the efficacy of antibiotics.

The antimicrobial resistance bacteria or genes circulate in fragile ecosystems and disseminate into the human food chain through direct or indirect ways (Fig. 1). AMR in bacteria can be achieved in several ways including the inherent capability of natural resistance by certain bacteria, genetic mutation, or acquired resistance through their surroundings.[5] The AMR has been recognized in both human and veterinary medicine, but this phenomenon has been developed at the human-animal-wildlife-environmental interface and subsequently, the resistance gene or the bacteria get entry into the human food chain.[5] A great majority of antimicrobial classes are used in both humans and livestock including domestic animals, birds, and farm fishes. For pet animals, antimicrobial uses are broadly similar to those in humans. Accordingly, the 'One Health' approach is a significant concept to get insights into this AMR problem (Fig.1).

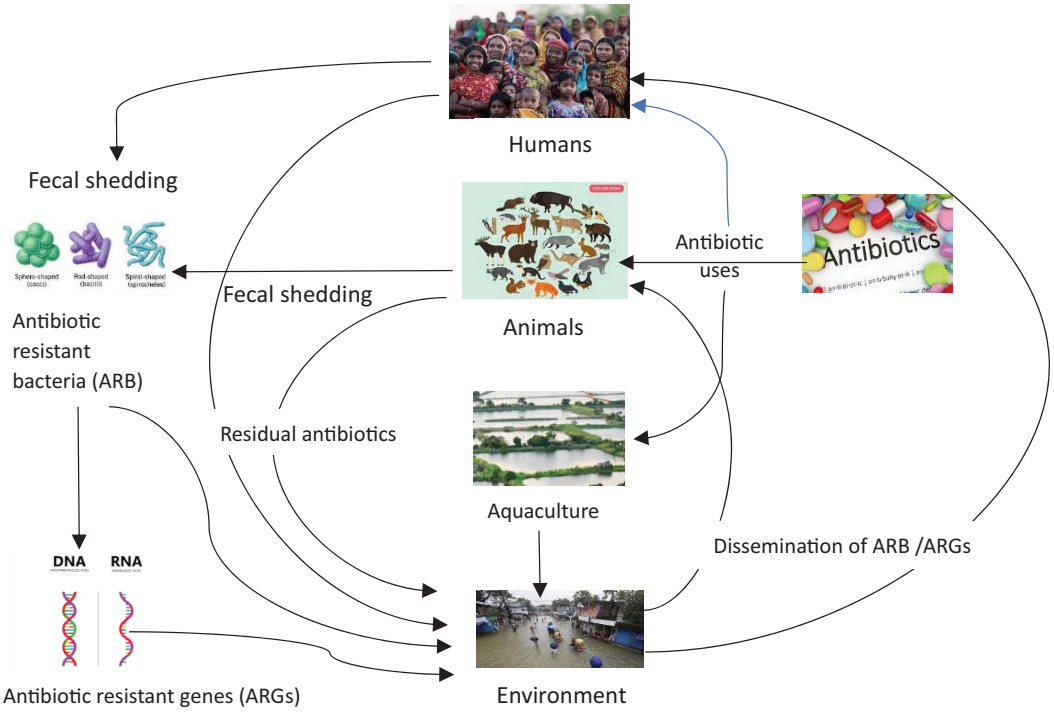

Fig. 1. Schematic diagram for dissemination of ARB / ARGs in 'One Health' perspective

The dynamic interactions between humans and livestock, along with their shared environments, likely serve as important routes for human exposure to antibiotic-resistant pathogens, especially in a setting with inadequate sanitation infrastructure, limited access to safe water, and poor hygienic practices.[281] ESBL-producing *E. coli* prevalence has been reported to be 67.5% in humans, 68.0% in poultry, and 92.5% in wastewater samples, and humans, poultry, and wastewater isolates shared common resistance genes (bla_{CTX}-M-1, qnr, and bla_{TEM}).[230] Bidirectional transmission of antibiotic resistance between humans, poultry, and the environment is likely in these community settings, underlying the importance of 'One Health' mitigation strategies.

Coordinated global action to address AMR

The overall prevalence of antimicrobial resistance in livestock has been reported to be progressively increased from 4.44% during the 2005-2010 period (13,14) to 42.22% during 2011 to 2014 (15-33) and 53.33% during the 2015-2019 period (34-57).[5]

Most of the antibiotics currently in clinical use have been reported to be resistant against pathogens except for only a few effective antibiotics in the pipeline that have caused antibiotic resistance is a global health emergency. Many of the same microbes infect animals and humans, as they share the ecosystem they live in. The 'One Health' approach to these shared pathogens necessitates studying the interactions of people, domestic animals, wildlife, plants, and the environment. Drug-resistant microbes can be transmitted between animals and humans through direct contact between animals and humans or through contaminated food, so to effectively contain it, a well-coordinated approach in humans and animals is required. Efforts by just one sector cannot prevent or eliminate the problem, thus, professionals with a range of expertise in different sectors including public health, animal health, plant health, and the environment should join forces to support 'One Health' approaches.[282]

Antibiotic resistance (ABR) is recognized as a 'One Health' challenge because of the rapid emergence and dissemination of resistant bacteria and genes among humans, animals, and the environment on a global scale.[281,283] However, very limited studies have integrated all three components of the 'One Health' spectrum to understand the dynamics of transmission and the prevalence of community-acquired resistance in humans and animals.[281,283]

The AMR is a complex problem that requires sector-specific actions in the human health, food production, animal, and environmental sectors, and a coordinated approach across these sectors.

'One Health' refers to an integrated, unifying approach that aims to achieve optimal and sustainable health outcomes for people, animals, and ecosystems. It recognizes that the health of humans, domestic and wild animals, plants and the wider environment are closely linked and interdependent. The 'One Health' approach to preventing and controlling AMR brings together stakeholders from relevant sectors to communicate and work together in the design, implementation, and monitoring of programs, policies, legislation, and research to mitigate AMR and attain better health and economic outcomes.[17]

Environment plays a key role in the development, transmission, and spread of AMR. Therefore, the response must be based on a 'One Health' approach, recognizing that humans, animals, plants, and the environment are interconnected and indivisible, at the global, regional, and local levels, from all sectors, stakeholders, and institutions. Prevention is at the core of the action needed to halt the emergence of AMR and the environment is a key part of the solution.[11]

Global and National Action Plans (NAPs) to tackle antimicrobial resistance (AMR) have been instigated and coordinated through the tripartite alliance of the WHO (World Health Organization), FAO (Food and Agricultural Organization), and OIE/WOAH (World Organization for Animal Health). All countries are now tasked with implementing NAPs on AMR through multisectoral work to ensure comprehensive surveillance, monitoring, and policy implementation across human, animal, and environmental domains.

To coordinate the 'One Health' global response to AMR, WHO works closely with the FAO, UNEP, and WOAH. These 4 organizations are known as the Quadripartite. A quadripartite joint secretariat is hosted by WHO to drive multi-stakeholder engagement in AMR.[15]

International, national, and local approaches have been advised for the control and prevention of antimicrobial resistance. Rational use of antimicrobials, regulation of over-the-counter availability of antibiotics, improving

hand hygiene, and improving prevention and control are the major recommended approaches. A thorough understanding of resistance mechanisms and innovation of new antimicrobial drugs and vaccines would be required. A multidisciplinary, collaborative, regulatory approach is demanded for combating antimicrobial resistance.[284]

Global Antimicrobial Resistance and Use Surveillance System (GLASS)

The WHO GLASS was launched in 2015 to foster AMR surveillance and inform strategies to contain AMR. The system started with surveillance of AMR in bacteria causing common human infections and has expanded its scope to include surveillance of antimicrobial consumption (AMC), invasive fungal infections, and a One Health surveillance model relevant to human health. To meet future challenges, it is a continuous evolution to enhance the quality and representativeness of data to inform the AMR burden accurately.

GLASS provides a standardized approach to the collection, analysis, and sharing of AMR data by countries. Glass is supported by WHO Collaborating Centers, involving strong commitment from participating countries and close collaborations with AMR regional networks. As of the end of 2022, 127 countries, territories, and areas participate in Glass.

Pathogens under GLASS surveillance

Pathogens currently included in Glass-AMR are *Acinetobacter* spp., *E. coli*, *Klebsiella pneumoniae*, *Neisseria gonorrhoeae*, *Salmonella* spp., *Shigella* spp., *Staphylococcus aureus*, and *Streptococcus pneumoniae*. The Acinetobacter genus comprises many species that can be divided into the *Acinetobacter baumannii* group (pathogenic) and non-baumannii group (low pathogenic-environmental). *A. baumannii* group, are intrinsically resistant to many antimicrobial agents. Colistin is usually the only effective antibacterial, but with an increase in colistin use, colistin resistance is emerging, mostly among carbapenem-resistant *A. baumannii* strains which have been classified by the WHO priority pathogens (Table 50).

Table 50. WHO priority level of bacterial pathogens with their resistance pattern

WHO priority level	Bacteria species	Antimicrobial resistance pattern
Priority 1: Critical	*Acinetobacter boumonnii*	Carbpenem-resistant
	Pseudomonas aeruginosa	Carbpenem-resistant (CR)
	Enterobacteriaceae*	CR, 3rd generation cephalosporin-resistant
Priority 2: High	*Enterococcus faecium*	Vancomycin-resistant
	Staphylococcus aureus	Methicillin-resistant, Vancomycin intermediate & R
	Helicobacter pylori	Clarithromycin-resistant
	Campylobacter spp.	Fluoroquinolone-resistant
	Salmonella spp.	Fluoroquinolone-resistant
	Neisseria gonorrrhoeae	3rd generation cephalosporin-resistant Fluoroquinolone-resistant
Priority 3: Medium	*Streptococcus pneumoniae*	Penicillin non-susceptible
	Haemophilus influenzae	Ampicillin-resistant
	Shigella spp.	Fluoroquinolone-resistant Fluoroquinolone-resistant

*Enterobacteriaceae include *Klebsiella pneumoniae*, *E. coli*, *Enterobacter* spp. *Serratia* spp., *Proteus* spp., *Providebcia* spp., *Morganella* spp.

AMR surveillance market

The global antimicrobial resistance surveillance market in terms of revenue was estimated to be worth US $ 5.9 billion in 2023 and is poised to reach $ 7.7 billion by 2028, growing at a CAGR of 5.6% from 2023 to 2028. Growth in this market is majority driven by factors such as the growing prevalence of infections caused by drug-resistance pathogens, innovations in diagnostic technologies, and growing government initiatives to combat AMR species. The growing number of epidemic outbreaks caused by drug-resistance pathogens, such as methicillin-resistant *Staphylococcus aureus* (MRSA), Vancomycin-resistant Enterococcus (VRE), Multi-drug-resistance *Mycobacterium tuberculosis* (MDR-TB), and Carbapenem-resistant Enterobacteriaceae (CRE) gut bacteria is also propelling the demand for antimicrobial resistance surveillance solutions.[285]

Risk factors associated with antibiotic-resistant bacteria (ARB)

ARB is dangerous because some variants remain permanently resistant, following an upward trend that reduces treatment options and also delays treatment for patients thus posing a primary threat to animal and public health and resulting, (a) increased risk of severe, extended illness or death, (b) long duration of antibiotic uses may cause severe side effects of drugs, (c) longer hospital stays, (d) more medical appointments and (e) increased medical costs. The misuse and overuse of antimicrobials in humans, animals, and plants are the main drivers in the development of drug-resistant bacteria.[12] In another report, six main risk factors were suggested to be associated with ARB which have been linked to: ① Overprescription of antibiotics, ② Patients not finishing the entire antibiotic course, Overuse of antibiotics in livestock and fish farming, ④ Poor infection control in health care setting, ⑤ Poor hygiene and sanitation and ⑥ Absence of new antibiotics being discovered.[286] AMR occurs when microorganisms and parasites change over time and no longer respond to drugs. This makes infections harder to treat and increases the risk of disease spreading severe illness and death. However, some risk factors causing ARB in human and animal health, and some preventive measures are suggested (Table 51).[287]

Table 51. Factors causing ARB in human and animal health and some preventive measure.[287]

S/N	Risk factors of antibiotic resistance	Some proposed preventive measures
A.	**Human health**	
1.	Uses of antibiotics for primary viral infection	1. Should not prescribe or take any antibiotics for viral infection.
2.	Patients are not taking the full course of antibiotics and interrupt their treatment when they feel better.	2. Patients should take their full course of antibiotics even if they feel better.
3.	Patients should take self-medication and misuse of antibiotics	3. Banning the sale of antibiotics in pharmacies without a prescription but health service facilities need to provide at community levels.
4.	Occasionally, physicians are made overprescription of unnecessary antibiotics include broad-spectrum.	4. Physicians should not prescribe any over-prescription with unnecessary antibiotics.
5.	Poor hygienic practices in hospitals and clinics including hand-washing and changing gloves.	5. Need to be improved the hygienic practices at the hospital and clinic levels
6.	Avoid using date expired and counterfeit antibiotics	6. Avoid to use of date-expired and counterfeit antibiotics at all levels.
B.	**Livestock health**	
1.	Overusing antibacterials in animal feeds for growth and disease control.	1. Establishing guidelines for prudent usage.

Measures against antibiotic resistance

The WHO has identified AMR as one of the biggest global health threats facing humanity. As bacteria evolve and become resistant to existing antibiotics, the challenge is growing. Some estimates suggest that without reversing this trend, AMR could lead to 10 million deaths a year by 2050. To avoid this, there is a need to ensure a continuous pipeline that delivers new, innovative antibiotics to treat patients with infections that have become resistant to existing antibiotics. However, the current antibiotic pipeline is not sufficient to protect against increasing resistance. Accordingly, some tools like diagnostics for infections or pipeline AMR detection, for measuring and monitoring antibiotic consumption (e.g. surveillance tools), and for guiding medical doctors and veterinarians in selecting suitable antibiotics. In addition, the food chain plays a potentially major role in the transmission of resistant bacteria as well as resistance genes from animals to humans and thus needs to ensure food safety.[288] Some approaches are suggested to improve the situation:

① Discovery of new antibiotics

Recently some antibiotics have been discovered including Teixobactin which has bactericidal activity against *S. aureus, Clostridium difficile*, and *Bacillus anthracis*,[289] Halicin, which showed bactericidal activity against a broad spectrum of pathogenic and resistant bacteria.[290] Another article has reported Dynobactin, which demonstrated potent bactericidal activity against dangerous Gram-negative bacteria resistant to other antibiotics.[291] However, some challenges include economic, regulatory, and scientific barriers that hinder the discovery and development of effective antibiotics to combat bacterial infections.

A-economic challenges (limited financial incentives) and long development timelines- the high cost and low profitability, lengthy and expensive processes of developing new antibiotics make it less attractive for investment from pharmaceutical companies.[292] C-Scientific challenges- antibiotic resistance- the prevalence of a high rate of antibiotic-resistant bacteria poses a significant challenge in the development of new antibiotics.[293]

② **Antibiotic adjuvants**

Antibiotic adjuvants are compounds that do not directly kill bacteria but instead enhance an antibiotic's effectiveness by inhibiting resistance mechanisms. For example, β-lactamase inhibitors are small-molecule antibiotic adjuvants. β-lactamase inhibitors, when combined β-lactam antibiotics, have been used successfully for over 30 years to treat Gram-positive and Gram-negative infections.[294] The exploitation of antibiotic adjuvants is a cost-effective therapy to combat antibiotic resistance by conjugating with ineffective antibiotics.[295]

③ **Nano antibiotics**

Nanoscale antibiotics, which consist of pure antibiotic molecules between 1 and 100 nm in size or antibiotic molecules physically attached to nanoparticles, represent one beneficial use of nanotechnology.[296,297] The uses and benefits of nanoscale antibiotics have been suggested by reengineering antibiotics at the nanoscale and this new antimicrobial approach revives the arsenal of available medications by making them effective against various clinically important pathogens.

④ **Plants** produce secondary metabolites, including alkaloids, flavonoids, phenolics, quinones, tannins, coumarins, terpenes, lectins, and saponins. These secondary metabolites exhibit antimicrobial activity against various microorganisms.[298]

⑤ **Bacteriophages**

Bacteriophages are innovative elements that could combat microbial resistance.[299] This technique has been applied in humans and animals to treat various bacterial diseases and has shown positive effective results. These bacterial pathogens include *Shigella dysenteriae*,[300] *Vibrio cholera*,[300] *Pseudomonas aeruginosa*,[280] *C. difficile,*[301] Vancomycin-resistant *E. faecium*,[302] β-lactam-producing *E. coli*,[303] imipenem-resistant *P. aeruginosa*,[303] *Acinetobacter baumannii,*[304] *E. coli*,[305] MDR *S. aureus*,[306] unclassified bacterial dysentery,[300] *S. typhi* [307] and anti-biotic resistant *P. aeruginosa*.[308]

⑥ **Miscellaneous methods**

Since the discovery of new antibiotics is challenging, it is crucial to develop ways to prolong the lifespan of existing antimicrobials. Many unsuccessful attempts have been made toward breaking such resistance through antibiotic-resistance breakers, reversibility of antibiotic resistance, chemical modifications or the addition of other conjugated compounds.

Recent research showed that while antibiotic reduction or discontinuation can be valuable in preventing future resistance, it does not reverse resistance that has already occurred.[309] Antibiotic resistance breakers (ARBs) can combat bacterial resistance via several mechanisms like enhancing the uptake of antibiotics, obstructing the efflux of the drug, signaling pathways, preventing the modification of both drug and target sites, and formation of biofilm.[310,311] The effective ARBs should possess one or more characteristics: (a) they should have direct antibacterial action even though they are not employed in clinical settings as antibiotics, (b) they may improve antibiotic effectiveness and/or counteract drug resistance mechanisms, (c) they may aid in the clearance of the infection by interacting with host targets to trigger host defense mechanisms, such as encouraging autophagy or blocking pro-inflammatory toll-like receptors (TLRs) or encouraging autophagy.[312] A new approach to lighting antibiotic resistance could help to prevent diseases by making bacteria vulnerable to treatment again. Antibiotic-resistant bacteria have a host of different proteins in their arsenals that neutralize antibiotics. To function properly, these resistance proteins have to be folded into the right shapes. It has been suggested that by targeting disulfide bond formation and protein folding, it is possible to reverse antibiotic resistance across several major pathogens and resistance mechanisms.[313]

Photodynamic inactivation (PDI) can break antimicrobial resistance, since it potentiates the effect of antibiotics, and induces oxidative stress in microorganisms through the interaction of light with a photosensitizer. PDI showed an innovative feature for modifying the degree of bacterial sensitivity to antibiotics according to dosages, thus reducing resistance and persistence of microorganisms from standard and clinical strains. A reduction in the degree of antimicrobial resistance through photooxidative action combats antibiotic

failure has been suggested.[314] Scientists have developed a new small molecule that can suppress the evolution of antibiotic resistance in bacteria and make resistant bacteria more susceptible to antibiotics. An inhibitory of the SOS response can suppress the evolution of antibiotic resistance in bacteria (ox.ac.uk/nws). Although theoretically these methods are attractive, the antibiotic-resistance breakers / the reversibility of resistance has proven difficult to use in clinical practice[315]

CONCLUSIONS

This article has reviewed various aspects of antimicrobials, their history, mechanisms of action, and resistance in the field of human and veterinary medicine. Antibiotics have diverse applications in different fields, a 'One Health' approach on zoonotic bacterial pathogens with their antibacterial resistance status, and some suggestions are made to combat the resistance problem. Up-to-date (up to 2023) published reports on ABR and MDR status in different species of bacteria isolated and identified from samples collected from humans, animals, and poultry birds have been reviewed in Bangladesh. This review recorded some findings and observations which include, mostly similar patterns of high prevalence of ARB and MDR of bacterial pathogens in both the human and veterinary medical samples in Bangladesh. A significant gap in ABR and MDR reports in both human and veterinary medicine has been observed, with only such data being published from six, eight and 18 districts out of 64 districts in human, animals and poultry bird samples respectively which means that such data from 58 districts in humans, 56 districts in aniamls and 46 districts in birds are not yet been published from Bangladesh. Many published reports on the sensitivity and resistance status of the isolated bacterial pathogens in both human and veterinary medical samples had gaps in the methodological data which included resistance testing methods, guidelines for the interpretation of sensitivity, and source of infection that made it difficult to make comparisons and interpretations. However, a 'One Health' approach would be required for the standardization of surveillance methodology and continuous nationwide surveillance simultaneously both in human and veterinary medical fields because most of the isolated bacterial pathogens have zoonotic importance. The development of antibiotic resistance can be prevented by minimizing unnecessary prescribing and overprescribing of antibiotics, the correct use of prescribed antibiotics, and good hygiene and infection control practices. There is a continuous need for iterative cycles of antibiotic discovery and development to deal with the selection of resistant pathogens that emerge as the therapeutic application of an antibiotic becomes widespread. There are four pillars and two fundamental steps that have been suggested to overcome barriers faced by people and health systems in addressing AMR which include: (a) prevention of infections, (b) access to essential health services, (c) timely, accurate diagnosis, and (d) appropriate, quality-assured treatment. The pillars are supported by the two fundamental steps: effective governance, awareness and education; and strategic information through surveillance and research. Extensive research efforts need to be continued to expand the understanding of the genetic diversity, epidemiology, evolution, and therapeutic management of MRSA infections in both humans and livestock.

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Reviews do not need any ethical approvals or informed consent.

CONFLICTS OF INTEREST

The author declares no conflict of interest.

REFERENCES

01. Hutchings MI, Truman AW and Wilkinson B (2019). Antibiotics: past, present and future. *Current Opinion in Microbiology* 51: 72-80 [doi: 10.1016/j.mib.2019.10.008]

02. IHME (2019). The burden of antimicrobial resistance (AMR) in Bangladesh. The University of Washington. healthdata.org/sites/default/files/flies/Project/GRAM/Bangladesh_0.pdf

03. Ahmed I, Rabbi MB and Sultana S (2019). Antibiotic resistance in Bangladesh: A systematic review. *International Journal of Infectious Diseases* 80: 54-61 [doi: 10.1016/j.ijid.2018.12.017]

04. Hoque R, Ahmed SM, Naher N, Islam MA, Rousham EK, Islam BZ and Hassan S (2020). Tackling antimicrobial resistance in Bangladesh: A scoping review of policy and practice in human, animal and environment sectors. *PLoS ONE* 15(1): e0227947 [doi: 10.1371/journal.pone.0227947]

05. Khan SA, Imtiaz MA, Sayeed MA, Shaikat AH and Hassan MM (2020). Antimicrobial resistance pattern in domestic animal-wildlife-environmental niche via the food chain to humans with a Bangladesh perspective; a systemic review. *BMC Veterinary Research* 16, 302 [doi: 10.1186/s12917-020-02519-9]

06. Rahman MR, Islam F, Rahman MA, Bashar SB, Rjfat RH, Saha BC and Paran MS (2021). Antibiotic resistance situation in Dhaka, Bangladesh: a review. *International Journal of Basic and Clinical Pharmacology* 10 (5): 584-590 [doi: 10.18203/2319-2003.ijbcp20211659]

07. van Duijkeren E, Schink AK, Roberts MC, Wang Y and Schwarz S (2018). Mechanisms of bacterial resistance to antimicrobial agents. *Microbiology Spectrum* 6: [doi: 10.1128/microbiolspec.arba-0019-2017]

08. Chis AA, Rus LL, Morgovan C, Arseniu AM, Frun A, Vonica-Tincu AL, Gligor FG, Muresan ML and Dobrea CM (2022). Microbial resistance to antibiotics and effective anti-biotherapy. *Biomedicines* 10 (5), 1121 [doi: 10.3390/biomedicines10051121]

09. WHO (2017). WHO publishes list of bacteria for which new antibiotics are urgently needed. https://www.who.int/news/item/27-02-2017-who-publishes-list-of-bacteria-for-which-new-antibiotics-are-urgently-needed

10. World Bank (2017). Final Report- Drug Resistance Infections: A threat to our economic future (March 2017).chrome-extension://efaidnbmnnibpcajpcglclefindmkaj/https://documents1.worldbank.org/curated/en/323311493396993758/pdf/final-report.pdf

11. UN (2023). Antimicrobial resistance: a global threat. https://www.unep.org/topics/chemicals-and-pollution-and-health/antimicrobial-resistance-globalthreat#:~test=According%20to%20recent%20 estimate%2C%20in,poverty%20in%20the%20next%20decade

12. WHO (2023). Antimicrobial resistance. who.int/news-room/fact-sheets/detail/antimicrobial-resistance#

13. ARC (2022). Antimicrobial Resistance Collaborators- Global burden of bacterial antimicrobial resistance in 2019: a systematic analysis. The Lancet; 399 (10325): p629-655 [doi: 10.1016/S0140-6736(21)02724-0]

14. Hamers RL, Dobreva Z, Cassini A, Tamara A, Lazarus G, Asadinia KS, Burzo S, Olaru ID, Dona D, Emdin F, Weezenbeek KV and Bertagnolio S (2023). Global knowledge gaps on antimicrobial resistance in the human health sector: A scoping review. *International Journal of Infectious Diseases* 134: 142-149 [doi: 10.1016/j.ijid.2023.06.004]

15. WHO (2023). People-centred approach to addressing antimicrobial resistance in human health. http://www.who.int/publications/i/item/9789240082496

16. O'Neill J (2016). Review on antimicrobial resistance- Tackling drug-resistant infections globally. amr-review.org

17. World Bank (2023). Drug Resistance Infections: A threat to our economic future (March 2017). https:www.worldbank.org/en/topic/health/publication/drug-resistant-infections-a-threat-to-our-economic-future

18. Al Amin M, Hoque MN, Siddiki AZ, Saha S and Kamal MM (2020). Antimicrobial resistance situation in animal health of Bangladesh. *Veterinary World* 13(12): 2713-2727 [doi: 10.14202/vetworld.2020.2713-2727]

19. Zhang Z, Zhang Q, Wang T, Wang T, Xu N, Lu T, Hong W, Penuelas J, Gillings M, Wang M, Gao W and Qian H (2022). Assessment of global health risk of antibiotic resistance genes. *Nature Communications* 13, 1553 [doi: 10.1038/s41467-022-29283-8]

20. Deekshit VK and Srikumar S (2022). To be, or not to be- The dilemma of silent antimicrobial resistance genes in bacteria. *Journal of Applied Microbiology* 133: 2902-2914 [doi: 10.1111/jam.15738]

21. Murray CJL, Ikuta KS, Sharara F and Swetschinski L (2022). Global burden of bacterial antimicrobial resistance in 2019: a systematic analysis. *The Lancet* 399 (10325): 629-655 [doi: 10.1016/S0140-6736(21)02724-0]

22. Orubu ESF, Zaman MH, Rahman MT and Wirtz VJ (2019). Veterinary antimicrobial resistance containment in Bangladesh: Evaluating the national action plan and scoping the evidence on implementation. *Journal of Global Antimicrobial Resistant* 21: 105-115

23. Sihombing B, Bhatia R, Srivastava R, Aditama TY, Laxminarayan R and Rijal S (2023). Response to antimicrobial resistance in South-East Asia Region. www.thelancet.com Vol 18 November 2023

24. Akond MA, Alam S, Hassan SM and Shirin M (2009). Antibiotic resistance of *Escherichia coli* isolated from poultry and poultry environment of Bangladesh. *International Journal of Food Safety* 11 : 19-23

25. 14. Begum K, Reza TA, Haque M, Hossain A, Hassan FK, Hasan SN, Aktrer N, Ahmed A and Barua U (2010). Isolation, identification and antibiotic resistance pattern of *Salmonella* spp. from chicken eggs, intestines and environmental samples. *Bangladesh Pharmacological Journal* 13: 23-27

26. Poole K (2005). Efflux-mediated antimicrobial resistance. *Journal of Antimicrobial Chemotherapy* 56(1): 20-51 [doi: 10.1093/jac/dki171]

27. Amin MB, Sraboni AS, Hossain MI, Roy S, Mozmader TAU, Unicomb L, Rousham EK and Islam MA (2020). Occurrence and genetic characteristics of mcr-1 positive colistin-resistant *Escherichia coli* from poultry environments in Bangladesh. *Journal of Global Antimicrobial Resistant* 22: 546-552 [doi: 10.1016/j.jgar.2020.03.028]

28. Alam SB, Mahmud M, Akter R, Hasan M, Sobur A, Nazir KHMNH, Noreddin A, Rahman T, El-Zowalaty ME and Rahman M (2020). Molecular detection of multidrug-resistant Salmonella species isolated from broiler farm in Bangladesh. *Pathogens* 9, 201 [doi: 10.3390/pathogens9030201]

29. Hasan B, Sandegren L, Melhus A, Drobni M, Hernandez J, Waldenstrom J, Alam M and Olsen B (2012). Antimicrobial drug-resistant *Escherichia coli* in wild birds and free-range poultry, Bangladesh. *Emerging Infectious Diseases* 18(12): 2055-2058 [doi: 10.3201/eid1812.120513]

30. Ahmed S, Hossain MI, Hossain T, Islam KR, Rahman MB and Hossain MA (2013). The Central Cattle Breeding and Dairy Farm, Bangladesh waste contributes to the emergence and spread of aminoglycoside-resistant bacteria. *Advances in Biosciences and Biotechnology* 4 (2A): 278-282 [doi: 10.4236/abb.2013.42A038]

31. Hoque MN, Istiaq A, Clement RA, Gibson KM, Saha O, Islam OK, Abir RA, Sultana M, Siddiki AMAMZ, Crandall KA and Hossain MA (2020). Insights into the resistome of bovine clinical mastitis microbiome, a key factor in disease complication. *Frontiers Microbiology* 11: 860 [doi: 10.3389/fmicb.2020.00860]

32. Kabir H, Hasan MK, Akter N, Tassdik H, Islam MF, Jannat H, Tutul AH, Akter O, Ara R, Islam MD, Mahmud S, Akter M and Mitra DK (2023). Antibiotics administration without prescription in Bangladesh. *International Journal of Infectious Diseases Regions* 7: 11-17 [doi: 10.1016/j,ijregi.2023.03.001]

33. Newton PN, Green MD and Fernandez FM (2010). Impact of poor quality medicines in the developing world. *Trends Pharmacological Science* 31: 99-101 [doi: 10.1016/j.tips.2009.11.005]

34. Irfan M, Almotiri A, and AlZeyadi ZA (2022). Antimicrobial resistance and its drivers- A review. *Antibiotics* (Base). 11 (10):1362 [doi: 10.3390/antibiotics11101362]

35. SCIPAGE (2024). What are the drivers of antimicrobial resistance? https://typeset.io/questions/what-are- drivers-of-antimicrobial-resistance-zeplabjrfg

36. IEDCR (2023). National antimicrobial resistance (AMR) surveillance report, Bangladesh 2016-2023. Institute of Epidemiology, Disease Control & Research (IEDCR). chromeextension://efaidnbmnnnibpcajpcglclrfindmkaj/ https://dashboard.iedcr.gov.bd/amr/upload/ amr_report_2016-23

37. Zhang R, Eggleston K, Rotimi V and Zeckhauser RJ (2006). Antibiotic resistance as a global threat: evidence from China, Kuwait and the United States. *Global Health* 2:6 [doi: 10.1186/1744-8603-2-6]

38. Amin VP, Dhanani M, Patel J, Dhawan A, Mahesh G, Chenna VSH, Kyada S, Dekhne and Desai HD (2023). Burden of bacterial antimicrobial resistance in the United States in 2019: A systematic analysis. *Open Forum Infectious Diseases* 10(Suppl 2): ofad500.1855 [doi: 10.1093/ofid/ofad500.1855)

39. Saga T and Yamaguchi K (2009). History of antimicrobial agents and resistant bacteria. *Journal of the Japan Medical Association* 52: 103-108

40. Ali MH, Reshad RAI, Rahman MM and Miah MF (2023). Antimicrobial resistance: understanding the mechanism and strategies for prevention and control. *Journal of Advanced Biotechnology and Experimental Therapy* 6(2): 468-482 [doi: 10.5455/jabet.2023.d142]

41. Bush K and Bradford PA (2016). β-lactams and β-lactamase inhibitors: an overview. *Cold Spring Harbor Perspectives in Medicine* 6(8): a025247

42. Davies J and Davies D (2010). Origins and evaluation of antibiotic resistance. *Microbiology and Molecular Biology Reviews.* 74(3): 417-433 [doi: 10.1128/MMBR.00016-10]

43. Ramirez MS and Tolmasky ME (2010). Aminoglycosides modify enzymes. *Drug Resistance Update.* 13 (6): 151-171 [doi: 10.1016/j.drup.2010.08.003]

44. Li XZ, Nikaido H and Poole K (1995). Role of mexA-mexB-oprM in antibiotic efflux in *Pseudomonas aeruginosa. Antimicrobial Agents and Chemotherapy* 39(9): 1948-1953

45. Nguyen F, Starosta AL, Arenz S, Sohmen D, Donhofer A and Wilson DN (2014). Tetracycline antibiotics and resistance mechanisms. *Biological Chemistry* 395 (5): 559-575 [doi. 10.1515/hsz-2013-0292]

46. Ruiz J (2003). Mechanisms of resistance to quinolones: target alterations, decreased accumulation and DNA gyrase protection. *Journal of Antimicrobial Chemotherapy* 51(5): 1109-1117 [doi: 10.1093/jac/dkg222]

47. Nikaido H (2009). Multidrug resistance in bacteria. *Annual Review of Biochemistry* 78: 119-146 [doi: 10.1146/annurev.biochem.78.082907.145923]

48. Casanova NG, Ruiz MS and Bellido JLM (2017). Mechanisms of resistance to daptomycin in *Staphylococcus aureus. Revista Espanola Quimioterapia* 30 (6): 391-396

49. Nam EY, Yang SJ, Klim ES, Cho JE, Park KH, Jung SI, Yoon N, Kim DM, Lee CS, Jang HC, Park Y, Lee KS, Kwak YG, Lee JH, Park SY, Hwang JH, Kim M, Song KH and Kim HB (2018). Emergence of daptomycin-nonsusceptible methicillin-resistant *Staphylococcus aureus* clinical isolates among daptomycin-naïve patients in Korea. *Microbial Drug Resistance* 24(5): 534-541 [doi: 10.1089/mdr.2017.0212]

50. Gardete S and Tomasz A (2014). Mechanism of vancomycin resistance in *Staphylococcus aureus. Journal of Clinical Investigation* 124 (7): 2836-2840 [doi: 10.1172/JC168834]

51. Thakur SD, Levett PN, Horsman GB, Dillon JAR (2018). High levels of susceptibility to new and older antibiotics in *Neisseria gonorrhoeae* isolates from Saskatchewan (2003-15): time to consider point-of care or molecular testing for precision treatment? *Journal of Antimicrobial Chemotherapy* 73(1): 118-125 [doi: 10.1093/jac/dkx333]

52. Martinez JL and Baquero F (2002). Interactions among strategies associated with bacterial infection: pathogenicity, epidemicity, and antibiotic resistance. *Clinical Microbiology Reviews* 15 (4): 647-679 [doi. 10.1128/CMR.15.4.647-679.2002]

53. Dinos GP, Athanassopoulos CM, Missiri DA, Giannopoulou PC, Vlachogiannis IA, Papadopoulos GE, Papaioannou D and Kalpaxis DL (2016). Chloramphenicol derivatives as antibacterial and anticancer agents: historic problems and current solutions. *Antibiotics* 5 (2), 20 [doi: 10.3390/antibiotics5020020]

54. Leclercq R (2002). Mechanisms of resistance to macrolides and lincosamides: nature of the resistance elements and their clinical implications. *Clinical Infectious Diseases* 34 (4): 482-492 [doi. 10.1086/324626]

55. Leclercq R and Courvalin P (2002). Resistance to macrolides and related antibiotics in Streptococcus pneumoniae. *Antimicrobial Agents Chemotherapy* 46(9): 2727-2734 [doi: 10.1128/AAC.46.9.2727-2734.2002]

56. Smieja M (1998). Current indications for the use of clindamycin: a critical review. *Candian Journal of Infectious Diseases* 9(1): 22-28 [doi: 10.1155/1998/538090]

57. Tsiodras S, Gold HS, Sakoulas G, Eliopoulos GM Wennersten C, Venkataraman L, Moellering RC, and Ferraro MJ (2001). Linezolid resistance in a clinical isolate of *Staphylococcus aureus. The Lancet* 358 (9277): 207-208 [doi: 10.1016/S0140-6736(01)05410-1]

58. Skold O (2000). Sulfonamide resistance: mechanisms and trends. *Drug Resistance Update* 3(3): 155-160 [doi: 10.1054/drup.2000.0146]

59. Grobbelaar M, Louw GE, Sampson SL, Helden PDV, Donald PR and Warren RM (2019). Evolution of rifampicin treatment for tuberculosis. *Infection, Genetics and Evolution* 74: 103937 [doi: 10.1016/j.meegid.2019.103937]

60. Shoemaker DM, Simou J and Roland WE (2006). A review of daptomycin for injection (Cubicin) in the treatment of complicated skin and skin structure infections. *Therapeutics and Clinical Risk Management* 2(2): 169-174 [doi: 10.2147/tcrm.2006.2.2.169]

61. Hamel M, Rolain JM and Baron SA (2021). The history of colistin mechanisms in bacteria: progress and challenges. *Microorganisms* 9(2): 442 [doi: 10.3390/microorganisms9020442]

62. da Cunha BR, Fonseca LP and Calado CRC (2019). Antibiotic discovery: where have we come from, where do we go? Antibiotic (Basel): 8(2): 45 [doi: 10.3390/antibiotics8020045]

63. Garcia-Bustos V, Navalon MDC and Lleti MS (2022). Resistance to beta-lactams in Gram-negative bacilli: relevance and potential therapeutic alternatives. *Revista Espanola de Quimioterapia* 35 (Suppl 2): 1-15 [doi: 10.37201/reqs02.01.2022]

64. Chin KW, Tiong HLM, Luang-In V and Ma NL (2023). An overview of antibiotic and antibiotic resistance. *Environmental Advances* 11: 100331 [doi: 10.1016/j.envadv.2022.100331]

65. NZG (2023). New Zealand Government- Antibiotics and antimicrobial resistance- a timeline. sciencelearn.org.nz/interactive-timeline/15-antibiotics-and-antimicrobial-resistance-a-timeline

66. Walsh C (2000). Molecular mechanisms that confer antibacterial drug resistance. *Nature* 406: 775-781

67. Morier D (2023). Antibiotic resistance. britannica.com/science/antibiotic-resistance

68. ReAct (2023). How do antibiotics work? https://www.reactgroup.org/toolbox/understand/antibiotics/ how-do-antibiotics-work/

69. Kapoor G, Saigal S and Elongavan A (2017). Action and resistance mechanisms of antibiotics: A guide for clinicians. *Journal of Anaesthesiology Clinical Pharmacology* 33: 300-305 [doi: 4103/joacp.JOACP 349 15]

70. Neu HC and Gootz TD (1996). *Medical Microbiology*. 4th edn., The University of Texas Medical Branch at Galveston, USA [ncbi.nim.nih.gov/books/NBK7986/#

71. Rollins DM and Joseph SW (2000). Basic mechanisms of antibiotic action and resistance. science.umd.edu/classroom/bsci424/Chemotherapy/AntibioticMechanisms.htm

72. Hooper DC (2001). Mechanisms of action of antimicrobials: focus on fluoroquinolones. *Clinical Infectious Diseases* 32: S9-S15 [doi: 10.1086/319370]

73. Reygaert WC (2018). An overview of the antimicrobial resistance mechanisms of bacteria. *AIMS Microbiology* 4: 482-501 [doi: 10.3934/microbiol.2018.3.482]

74. Creative Biolabs (2024). Mode of actions and targets for antibacterial drugs. creative-biolabs.com/drug-discovery/therapeutics/mode-of-actions-and-targets-for-antibacterial-drugs.html#

75. Cho H, Uehara T and Bernhardt TG (2014). Beta-lactam antibiotics induce a lethal malfunctioning of the bacterial cell wall synthesis machinery. *Cell* 159(6): 1300-1311 [doi: 10.1016/j.cell.2014.11.017]

76. Malik M, Zhao X and Drlica K (2006). Lethal fragmentation of bacterial chromosomes mediated by DNA gyrase and quinolones. *Molecular Microbiology* 61: 810-825 [doi: 10.1111/j.1365-2958.2006.05275.x]

77. Shree P, Singh CK, Sodhi K, Surya JN and Singh DK (2023). Biofilms: understanding the structure and contribution towards bacterial resistance in antibiotics. *Medical Microbiology* 16, 100084 [doi: 10.1016/j.medmic.2023.100084]

78. Vicens Q and Westhof E (2003). RNA as a drug target: the case of aminoglycosides. *ChemBioChem* 4: 1018-1023 [doi: 10.1002/cbic.200300684]

79. Brodersen DE, Clemons WM, Carter AP, Morgan-Warren RJ, Wimberly BT and Ramakrishnan V (2000). The structural basis for the action of the antibiotics tetracycline, pactamycin and hygromycin B, on the 30S ribosomal subunit. *Cell* 103: 1143-1154 [doi: 10.1016/S0092-8674(00)00216-6]

80.Tensol T, Lovmar M and Ehrenberg M (2003). The mechanism of action of macrolides, lincosamides and streptogramin B reveals the nascent peptide exit path in the ribosome. *Journal of Molecular Biology* 330: 1005-1014 [doi: 10.1016/S0022-2836(03)00662-4]

81. Syroegin EA, Flemmich L, Klepacki D, Vazquez-Laslop N, Micura R and Polikanov YS (2022). Structural basis for the context-specific action of the classic peptidyl transferase inhibitor chloramphenicol. *Nature Structural and Molecular Biology* 29: 152-161 [doi: 10.1038/s41594-022-00720-y]

82. Foti C, Piperno A, Scala A and Giuffre O (2021). Oxazolidinone antibiotics: chemical, biological and analytical aspects. *Molecules* 26(14), 4280 [doi: 10.3390/molecules26144280]

83. Capasso C and Supuran CT (2014). Sulfa and trimethoprim-like drugs-antimetabolites act as carbonic anhydrase, dihydropteroate synthase and dihydrofolate reductase inhibitors. *Journal of Enzyme Inhibition and Medicinal Chemistry* 29 (3): 379-387 [doi: 10.3109/14756366.2013.787422]

84. Munita JM and Arias CA (2016). Mechanisms of antibiotic resistance. *Microbiology Spectrum* 4(2): [doi: 10.1128/microbiolspec.VMBF-0016-2015]

85. Dever LA and Dermody TS (1991). Mechanisms of bacterial resistance to antibiotics. *Arch Internal Medicine* 151(5): 886-895 [doi: 10.1001/archinte.1991.00400050040010]

86. Cesur S and Demiroz AP (2013). Antibiotics and the mechanisms of resistance to antibiotics. *Medical Journal of Islamic World Academy of Sciences* 21(4): 138-142

87. Zhang F and Cheng W (2022). The mechanism of bacterial resistance and potential bacteriostatic strategies. *Antibiotics* 11(9), 1215 [doi: 10.3390/antibiotics11091215]

88. Future Learn (2023). What are the mechanisms of antimicrobial resistance? https://www.futurelearn.com/info/courses/antimicrobial-resistance/0/steps/92121

89. Anon. (2023). What clinicians should know about antibiotic resistance and its mechanisms? *Global Alliance for Infections in Surgery.* https://infectioninsurgery.org/what-clinicians-should-know-about- antibiotic-resistance-and-its-mechanisms/

90. Ali MH, Reshad RAI, Rahman MM and Miah MF (2023). Antimicrobial resistance: understanding the mechanism and strategies for prevention and control. *Journal of Advanced Biotechnology and Experimental Therapy* 6(2): 468-482 [doi: 10.5455/jabet.2023.d142]

91. Cloeckaert A, Zygmunt MS and Doublet B (2017). Editorial: Genetics of acquired antimicrobial resistance in animal and zoonotic pathogens. *Frontiers in Microbiology* 8: 2428 [doi: 10.3389/fmicb.2017.02428]

92. Kang HK and Park Y (2015). Glycopeptide antibiotics: structure and mechanisms of action. *Journal of Bacteriology and Virology* 45 (2): 67-78

93. Darby EM, Trampari E, Siasat P, Gaya SM, Alav I, Webber MA and Blair JMA (2023). Molecular mechanisms of antibiotic resistance revisited. *Nature Reviews Microbiology* 21: 280-295 [doi: 10.1038/s41579-022-00820-y]

94. Sodhi KK, Singh CK, Kumar M and Singh DK (2023). Whole-genome sequencing of *Alcaligenes* sp. Strain MMA: insight into the antibiotic and heavy metal resistance genes. *Frontiers in Pharmacology* 14: 1144561-1144611 [doi: 10.3389/fphar.2023.1144561]

95. Fernandez B, Maria AE, Llambias C, Jordana-Lluch E, Oliver A and Macia MD (2023). Mechanisms of antibiotic resistance in *Pseudomonas aeruginosa* biofilms. *Biofilm* 5, 100129 [doi: 10.1016/j.biofilm.2023.100129]

96. Hirsch J and Klostermeier D (2021). What makes a type IIA topoisomerase a gyrase or a Topo IV? *Nucleic Acid Research* 49 (11): 6027-6042 [doi: 10.1093/nar/gkab270]

97. Fabrega A, Madurga S, Giralt E and Vila J (2009). Mechanism of action of and resistance to quinolones. *Microbial Biotechnology* 2(1): 40-81 [doi: 10.1111/j.1751-7915.2008.00063.x]

98. Peschel A, Vuong C, Otto M and Gotz F (2000). The D-alanine residues of *Staphylococcus aureus* teichoic acids after the susceptibility to Vancomycin and the activity of autolytic enzymes. *Antimicrobial Agents and Chemotherapy* 44(10): 2845-2847 [doi: 10.1128/AAC.44.10.2845-2847.2000]

099. Dzidic S, Suskovic J and Kos B (2008). Antibiotic resistance mechanisms in bacteria: biochemical and genetic aspects. *Food Technology and Biotechnology* 46 (1): 11-21

100. Hasan CM, Dutta D and Nguyen ANT (2021). Revisiting antibiotic resistance: mechanistic foundations to evolutionary outlook *Antibiotics* 11(1), 40 [doi: 10.3390/antibiotics11010040]

101. Patel Y, Soni V, Rhee KY and Helmann JD (2023). Mutations in rpoB that confer rifampicin resistance can alter levels of peptidoglycan precursors and affect β-lactam susceptibility. *Microbiology* 14: e03168-22 [doi: 10.1128/mbio.03168-22]

102. Halawa EM, Fadel M, Al-Rabia, Behairy A, Nouh NA, Abdo M, Olga R, Fericean L, Atwa AM, El-Nablaway M and Abdeen A (2023). Antibiotic action and resistance: updated review of mechanisms, spread, influencing factors, and alternative approaches for combating resistance. *Frontiers in Pharmacology* 14: 1305294 [doi: 10.3389/fphar.2023.1305294]

103. Strateva T and Yordanov D (2009). *Pseudomonas aeruginosa*- a phenomenon of bacterial resistance. *Journal of Medical Microbiology* 58(9): 1133-1148 [doi: 10.1099/jmm.0.009142-0]

104. Beceiro A, Tomas M and Bou G (2013). Antimicrobial resistance and virulence: a successful or deleterious association in the bacterial world? *Clinical Microbiology Reviews* 26 (2): 185-230 [doi: 10.1128/CMR.00059-12]

105. Randall CP, Mariner KR, Chopra I and O'Neill AJ (2013). The target of daptomycin is absent form *Escherichia coli* and other Gram-negative pathogens. *Antimicrobial Agents and Chemotherapy* 57(1): 637-639 [doi: 10.1128/AAC.02005-12]

106. Hawkey PM (2003). Mechanisms of quinolone action and microbial response. *Journal of Antimicrobial Chemotherapy* 51: 29-35 [doi: 10.1093/jac/dkg207]

107. Redgrave LS, Sutton SB, Webber MA and Piddock LJV (2014). Fluoroquinolone resistance: mechanisms, impact on bacteria, and role in evolutionary success. *Trends Microbiology* 22: 438-445 [doi: 10.1016/j.tim.2014.04.007]

108. Huovinen P, Sundstrom L, Swedberg G and Skold O (1995). Trimethoprim and sulfonamide resistance. *Antimicrobial Agents and Chemotherapy* 39 (2): 279-289 [doi: 10.1128/aac.39.2.279]

109. Vedantam G, Guay GG, Austria NE, Doktor SZ and Nichols BP (1998). Characterization of mutations contributing to sulfathiazole resistance in *Escherichia coli*. *Antimicrobial Agents and Chemotherapy* 42: 88-93 [doi: 10.1128/aac.42.1.88]

110. Pfeifer Y, Cullik A and Witte W (2010). Resistance to cephalosporins and carbapenems in Gram-negative bacterial pathogens. *International Journal of Medical Microbiology* 300: 371-379 [doi: 10.1016/j.ijmm.2010.04.005]

111. Bush K and Brandford PA (2016). β-lactams and β-lactamase inhibitors: an overview. *Cold Spring Harbor Perspectives in Medicine* 6 (8): a02527 [doi: 10.1101/cshperspect.a025247]

112. Grossman TH (2016). Tetracycline antibiotics and resistance. *Cold Spring Harbor Perspectives in Medicine* 6(4): a025387 [doi: 10.1101/cshperspect.a025387]

113. Chopra I and Roberts M (2001). Tetracycline antibiotics: mode of action, applications, molecular biology, and epidemiology of bacterial resistance. *Microbiology and Molecular Biology Reviews* 65(2): 232-260 [doi: 10.1128/MMBR.65.2.232-260.2001]

114. Piddock LJV (2006). Clinically relevant chromosomally encoded multidrug resistance efflux pumps in bacteria. *Clinical Microbiology Review* 19(2): 382-402 [doi: 10.1128/cmr.19.2.382-402.2006

115. Webber MA and Piddock LJV (2003). The importance of efflux pumps in bacterial antibiotic resistance. *Journal of Antimicrobial Chemotherapy* 51(1): 9-11 [doi: 10.1093/jac/dkg050]

116. Du D, Wang-Kan X, Neuberger A, van Veen HW, Pos KM, Piddock LJV and Luisi BF (2018). Multidrug efflux pumps: structure, function and regulation. *Nature Reviews Microbiology* 16: 523-539 [doi: 10.1038/s41579-018-0048-6]

117. Thakur V, Uniyal A and Tiwari V (2021). A comprehensive review on the pharmacology of efflux pumps and their inhibitors in antibiotic resistance. *European Journal of Pharmacology* 903: 174151 [doi: 10.1016/j.ejphar.2021.174151]

118. DZIF (2023). Resistance gene. https://www.dzif.de/en/glossary/resistance-gene#:

119. Jian Z, Zeng L, Xu T, Sun S, Yan S, Yang L Huang Y, Jia J and Dou T (2021). Antibiotic resistance genes in bacteria: occurrence, spread, and control. *Journal of Basic Microbiology* 61 (12): 1049-1070 [doi: 10.1002/jobm.202100201]

120. Safain KS, Bhuyan GS, Hasib SH, Islam MS, Mahmud-Un-Nabi AM, Sultana R, Tasmin S, Noor FA, Sarker SK, Islam MT, Rahat A, Leung DT, Domman LD, Manzoor F, Anwar S, Bhuiyan MAM, Chowdhury EK, Qadri SS, Qadri F and Mannoor K (2021). Genotypic and phenotypic profiles of antibiotic-resistant bacteria isolated from hospitalized patients in Bangladesh. *Tropical Medicine and International Health* 26(7): 720-729 [doi: 10.1111/tmi.13584]

121. Kester JC and Fortune SM (2014). Persisters and beyond: mechanisms of phenotypic drug resistance and drug tolerance in bacteria. *Critical Review of Biochemistry and Molecular Biology* 49(2): 91-101 [doi: 10.3103/10409238.2013.869543]

122. Tacconelli E, Cataldo MA, Dancer SJ, De Angelis G, Falcon M, Frank U, Kahlmeter G, Pan A, Petrosillo N, Rodriguez-Bano J, Singh N, Venditti M, Yokoe DS and Cookson B (2014). ESCMID guidelines for the management of the multidrug-resistant Gram-negative bacteria in hospitalized patients. *Clinical Microbiology and Infection* 20: 1-55 [doi: 10.1111/1469-0691.12427]

123. Chowdhury F, Mah-E-Muneer S, Bollinger S, Sharma A, Ahmed D, Hossain K, Hossain MJ, Rahman M, Vanderende D, Sen D, Mozumder P, Khan AA, Sarker M, Smith RM, Styczynski A and Luvsansharav U (2023). Prevalence of colonization with antibiotic-resistant organisms in hospitalized and community individuals in Bangladesh, a phenotypic analysis: findings from the antibiotic resistance in communities and hospitals (ARCH) study. *Clinical Infectious Diseases* 77: S118-124 [doi: 10.1093/cid/ciad254]

124. Ahmed D, Hoque A, Elahi MSB, Endtz HP and Hossain MA (2012). Bacterial aetiology of diarrhoeal diseases and antimicrobial resistance in Dhaka, Bangladesh, 2005-2008. *Epidemiology and Infection* 140: 1678-1684 [doi: 10.1017/S0950268811002135]

125. Sharif N, Ahmed SN, Khandaker S, Monifa NH, Abusharha A, Vargas DLR, Diez IDT, Castilla AGK, Talukder AA, Parvez AK and Dey SK (2023). Multidrug resistance pattern and molecular epidemiology of pathogens among children with diarrhea in Bangladesh, 2019-2021. *Scientific Reports* 13:14975 [doi: 10.1038/s41598-023-41174-6]

126. Sharif N, Nobel NU, Sakib N, Liza SM, Khan ST, Billah B, Parvez AK, Haque A, Talukder AA and Dey SK (2020). Molecular and epidemiologic analysis of diarrheal pathogens in children with acute gastroenteritis in Bangladesh during 2014-2019. *The Pediatric Infectious Disease Journal* 39: 580-585 [doi: 10.1097/INF.0000000000002637]

127. Das R, Nasrin S, Palit P, Sobi RA, Sultana A, Khan SH, Haque MA, Nuzhat S, Ahmed T, Faruque ASG and Chisti MJ (2023). *Vibrio cholerae* in rural and urban Bangladesh, findings from hospital-based surveillance, 2000-2021. *Scientific Reports* 13, 6411 [doi: 10.1038/s41598-023-33576-3]

128. Sin MP, Hasan MZ and Forsberg BC (2023). Change in economic burden of diarrhea in children under-five in Bangladesh: 2007 vs. 2018. Journal of Global Health [doi: 10.7189/jogh.13.04089]

129. Garbern SC, Chu TC, Gainey M, Kanekar SS, Nasrin S, Qu K, Barry MA, Nelson EJ, Leung DT, Schmid CH, Alam NH and Levine AC (2021). Multidrug-resistant enteric pathogens in older children and adults with diarrhea in Bangladesh: epidemiology and risk factors. *Tropical Medicine and Health* 49,34 [doi: 10.1186/s41182-021-00327-x]

130. Rahman MA, Paul PR, Hoque N, Islam SS, Haque AKMZ, Sikder MH, Matin A, Yamasaki S and Kabir SML (2021). Prevalence and antimicrobial resistance of Campylobacter species in diarrheal patients in Mymensingh, Bangladesh. *BioMed Research International* Article ID 9229485 [doi: 10.1155/2021/9229485]

131. Ahmed D, Nahid MA, Sami AB, Halim F, Akter N, Sadique T, Rana MS, Elahi MSB and Rahman MM (2017). Bacterial etiology of bloodstream infections and antimicrobial resistance in Dhaka, Bangladesh, 2005-2014. *Antimicrobial Resistance and Infection Control* 6, 2 [doi: 10.1186/s13756-016-0162-z]

132. Ahmed D, Ud-Din AI, Wahid SU, Mazumder R, Nahar K and Hossain A (2014). Emergence of bla TEM type extended-spectrum beta-lactamase-producing *Salmonella* spp. in the urban area of Bangladesh. *ISRN Microbiology* 715310

133. Islam QT, Siddiqui MMR, Raz F, Asrafuzzaman M and Amin MR (2014). Patterns of antimicrobial resistance among intensive care unit patients of a private medical college hospital in Dhaka. *Bangladesh Journal of Medicine* 25(2): 47-51 [doi: 10.3329/bjmed.v25i2.2525088]

134. Ahmed F, Raj AY, Nahar L and Hasan Z (2018). Antimicrobial resistance of bacterial pathogens in a neonatal intensive care unit. *Bangabandhu Sheikh Mujib Medical University Journal* 11: 25-28 [doi: 10.3329/bsmmuj.v11i1.35133]

135. Ahsan ASMA, Fatema K, Barai L, Faruq MO, Ahmed F, Saha DK, Saha M, Nazneen S, Hamid T and Zabeen N (2016). Prevalence and antimicrobial resistance pattern of blood isolates in patients of septicemia in ICU: single center observation. *Bangladesh Critical Care Journal* 4: 100-104 [doi:10.3329/bccj.v4i2.30025]

136. Akram F, Pietroni MAC, Bardhan PK, Bibi S and Chisti MJ (2014). Prevalence, clinical features, and outcome of Pseudomonas bacteremia in under-five diarrheal children in Bangladesh. *International Scholarly Research Notices.* Article ID 469758 [doi: 10.1155/2014/469758]

137. Akter S, Ferdousi RS and Siddiqua M (2017). Bacterial isolates and antimicrobial susceptibility in children with acute diarrhea at Ibn Sina Medical College, Bangladesh. *Journal Kedokteran Dan Kesehatan Indonesia* 8(2): 80-86 [doi: 10.20885/JKKI.Vol8.Iss2.art2]

138. Akter S, Shamsuzzaman SM and Jahan F (2014). Community-acquired bacterial pneumonia: aetiology, laboratory detection and antibiotic susceptibility pattern. *Malays Journal of Pathology* 36(2): 97-103. PMID 25194532

139. Arifeen SE, Saha SK, Rahman S, Rahman KM, Rahman SM, Bari S, Naheed A, Mannan I, Seraji MHR, Ahmed NU, Hassan MS, Huda N, Siddik AU, Quasem I, Islam M, Fatema K, Al-Emran H, Brooks WA, Baqui AH, Breiman RF, Sack D and Luby SP (2009). Invasive pneumococcal disease among children in rural Bangladesh: results from a population-based surveillance. *Clinical Infectious Diseases* 48 (suppl.2): S103-113 [doi: 10.1086/596543]

140. Begum YA, Talukder KA, Azmi IJ, Shahnaij M, Sheikh A, Sharmin S, Svennerholm AM and Qadri F (2016). Resistance pattern and molecular characterization of enterotoxigenic *Escherichia coli* (ETEC) strains isolated in Bangladesh. *PLoS ONE* 11 (7): e0157415 [doi: 10.1371/journal.pone.0157415]

141. Shahriar M, Hossain M and Kabir S (2010). A survey on antimicrobial sensitivity pattern of different antibiotics on clinical isolates of *Escherichia coli* collected from Dhaka City, Bangladesh. *Journal of Applied Science and Environmental Management* 14(3): 19-20

142. Khan AI, Huq S, Malek MA, Hossain MI, Alam MM, Talukder KA, Faruque ASG, Salam MA and Sack DA (2004). Shigella serotypes among hospitalized patients in urban Bangladesh and their antimicrobial resistance. *Epidemiology and Infection* 132(4): 773-777 [doi:10.1017/ S0950268804002134]

143. Mahbubur R, Shoma S, Rashid H, El Arifeen S, Baqui AH, Siddique AK, Nair GB and Sack DA (2007). Increasing spectrum in antimicrobial resistance of Shigella isolates in Bangladesh: resistance to 482-492 [azithromycin and ceftriaxone and decreased susceptibility to ciprofloxacin. *Journal of Health Population Nutrition* 25(2): 158-167 [PMID: 17985817]

144. Sac RB, Rahman M, Yunus M and Khan EH (1997). Antimicrobial resistance in organisms causing diarrheal diseases. *Clinical Infectious Diseases* 24: S102-S105 [doi: 10.1093/clinids/24.supplement-1.s102]

145. Ud-Din AIMS, Wahid SUH, Mazumder R, Nahar K and Hossain A (2014). Emergence of blaTEM type extended-spectrum β-lactamase producing *Salmonella* spp. in the urban area of Bangladesh. *International Scholarly Research Notices* Article ID 715310 [doi: 10.1155/2014/715310]

146. Nuzhat S, Das R, Das S, Islam SB, Palit P, Haque MA, Chakraborty S, Khan SH, Ahmed D, Alam B, Ahmed T, Chisti MJ and Faruque ASG (2022). Antimicrobial resistance in shigellosis: A surveillance study among urban and rural children over 20 years in Bangladesh. *PLoS ONE* 17 (11): e0277574 [doi: 10.1371/journal.pone.0277574]

147. Biswas M, Roy DN, Tajmim A, Rajib SS, Hossain M, Farzana F and Yasmen N (2014a). Prescription antibiotics for outpatients in Bangladesh: a cross-sectional health survey conducted in three cities. *Annals of Clinical Microbiology and Antimicrobials* 13 (1): 15 [doi: 10.1186/1476-0711-13-15]

148. Biswas M, Roy MN, Manik MIN, Hossain MS and Tapu SMTA, Moniruzzaman M and Sultana S (2014). Self-medicated antibiotics in Bangladesh: a cross-sectional health survey conducted in the Rajshahi City. *BMC Public Health* 14, 847 [doi: 10.1186/1471-2458-14-847]

149. Uddin MS, Hoq MI, Ali MS, Rahman MM and Islam KMS (2017). Antibiotic resistance pattern of *Salmonella* spp. isolated from stool samples of hospitalized diarrheal patients in Bangladesh. *Asian Journal of Medicine and Biological Research* 3(4): 534-538 [doi: 10.3329/ajmbr.v3i4.35346]

150. Brooks WA, Hossain A, Goswami D, Sharmeen AT, Nahar K, Alam K, Ahmed N, Naheed A, Nair GB, Luby SP, and Breiman RF (2005). Bacteremic typhoid fever in children in an urban slum, Bangladesh. *Emerging Infectious Diseases* 11: 326-329 [doi: 10.3201/eid1102/040422]

151. Khanam F, Sayeed MA, Choudhury FK, Sheikh A, Ahmed D, Goswami D, Hossain ML, Brooks A, Calderwood SB, Charles RC, Cravioto A, Ryan ET and Qadri F (2015). Typhoid fever in young children in Bangladesh: clinical findings, antibiotic susceptibility pattern and immune responses. *PLoS Neglected Tropical Diseases* 9(4): e0003619 [doi: 10.1371/journal.pntd.0003619]

152. Chiou C, Lauderdale T, Phung DC, Watanabe H, Kuo J, Wang P, Liu Y, Liang S and Chen P (2014). Antimicrobial resistance in *Salmonella enterica serovar Typhi* isolates from Bangladesh, Indonesia, Taiwan and Vietnam. *Antimicrobial Agents and Chemotherapy* 58: 6501-6507 [doi: 10.1128/aac.03608-14]

153. Chakraborty S, Mohsina K, Sarker PK, Alam MZ, Karim MIA and Sayem SMA (2016). Prevalence, antibiotic susceptibility profiles and ESBL production in *Klebsiella pneumoniae* and *Klebsiella oxytoca* among hospitalized patients. *Periodicum Biologorum* 118 : 53-58 [doi: 10.18054/pb.2016.118.1.3160]

154. Dutta S, Hassan MR, Rahman F, Jilani MSA and Noor R (2013). Study of antimicrobial susceptibility of clinically significant microorganisms isolated from selected areas of Dhaka, Bangladesh. *Bangladesh Journal of Medical Science* 12: 34-42 [doi: 10.3329/bjms.v12i1.13351]

155. Haque ME, Shahriar M, Haq A, Gomes BC, Hossain MM, Razzak MA and Mazid MA (2011). Prevalence of β-lactamase-producing and non-producing methicillin-resistant *Staphylococcus aureus* in clinical samples in Bangladesh. *Journal of Microbiology and Antimicrobials* 3 (5): 112-118

156. Hossain MD, Ahsan S and Kabir MS (2014). Antibiotic resistance patterns of uropathogens isolated from catharized and non-characterized patients in Dhaka, Bangladesh. *Tzu Chi Medical Journal* 26: 127-131 [doi: 10.1016/j.tcmj.2014.06.003]

157. Haque R, Akter ML and Salam MA (2015). Prevalence and susceptibility of uropathogens: a recent report from a teaching hospital in Bangladesh. *BMC Research Notes* 8, 416 [doi: 10.1186/s13104-015-1408-1]

158. Yasmeen BHN, Islam S, Islam S, Uddin MM and Jahan R (2015). Prevalence of urinary tract infection, its causative agents and antibiotic sensitivity pattern: a study in Northern International Medical College Hospital, Dhaka. *Northern International Medical College Journal* 7(1): 105-109 [doi: 10.3329/nimcj.v7i1.25704]

159. Nazme NI, Al-Amin A, Jalil F, Sultana J and Fatema NN (2017). Bacteriological profile of urinary tract infection in children of a tertiary care hospital. *Bangladesh Journal of Child Health* 41(2): 77-83 [doi: 10.3329/bjch.v41i2.36102]

160. Rahman SR, Ahmed MF and Begum A (2014). Occurrence of urinary tract infection in adolescent and adult women of shanty town in Dhaka City, Bangladesh. *Ethiopian Journal of Health Science* 24: 145-152 [doi: 10.4314/ejhs.v24i2.7]

161. Saha S, Rahman S, Hassan FMN, Sarker S, Islam K, Saha, Alam B, Sultana N, Rahman KMT, Sumi SS, Islam F and Hasan S (2015). Antimicrobial resistance in uropathogen isolates from patients with urinary tract infections. *Biomedical Research and Therapeutics* 2: 263-269 [doi: 10.7603/s40730-015-0011-3]

162. Sanjee SA, Karim ME, Akter T, Parvez MAK, Hossain M, Jannat B and Parvin S (2017). Prevalence and antibiogram of bacterial uropathogens of urinary tract infections from a tertiary care hospital of Bangladesh. *Journal of Scientific Research* 9: 317-328 [doi: 10.3329/jsr.v9i3.31677]

163. Islam MA, Islam MR, Khan R, Amin MB, Rahman M, Hossain MI, Ahmed D, Asaduzzaman M, and Riley LW (2022). Prevalence, etiology and antibiotic resistance patterns of community-acquired urinary tract infections in Dhaka, Bangladesh. *PLoS ONE* 17(9): e0274423 [doi: 10.1371/journal.pone.0274423]

164. Rahman B, Islam MR, Sultana R, Alam ST, Mehjabin T, Bushra NNH, Moniruzzaman SM, Hossain MI, Rashna SN and Uddin MA (2023). Determination of the antibiotic susceptibility pattern of Gram-positive bacteria causing urinary tract infection in Dhaka, Bangladesh. Biomedical and Biotechnology Research Journal 7 : 432-437 [doi: 10.4103/bbrj.bbrj_159_23]

165. Ullah B, Ahmed S, Shahariar M and Yesmine S (2016). Current trend of antibiotic resistance in lower respiratory tract infections (LRTIs): An experience in a teaching hospital in Bangladesh. *Bangladesh Pharmacology Journal* 19(1): 85-91 [doi: 10.3329/bpj.v19i1.29243]

166. Roy S, Ahmed MU, Uddin BMM, Ratan ZA, Rajawat M, Mehta V, and Zaman SB (2017). Evaluation of antibiotic susceptibility in wound infections: A pilot study from Bangladesh. *F1000 Research* 6: 2103 [doi: 10.12688/f1000research.12887.1]

167. Nobel FA, Ahammad H, Saha SR, Asaduzzaman M, Nashra A, Jebin RA, Zahan Y, Kamruzzaman M, Babu G and Islam MJ (2024). Determination of multi-drug resistance profile of isolated Gram-positive and Gram-negative bacteria from clinical pus samples in Bangladesh. *Journal of Advanced Biotechnology and Experimental Therapeutics* 7(1): 178-189 [doi: 10.5455/jabet.2024.d16]

168. Jobayerh M, Rahman M, Akter N, Shareef N, Rana RA and Shamsuzzaman SM (2021). Organisms isolated from wound swabs and pus with their antibiotic susceptibility pattern in a tertiary care hospital of Bangladesh. *Bangladesh Medical Research Council Bulletin* 47 (2): [doi: 10.3329/bmrcb.v47i2.57777]

169. Haque S, Ahmed A, Islam N and Haque FKM (2024). High prevalence of multidrug-resistant bacteria in the trachea of intensive care units admitted patients: evidence from a Bangladeshi hospital. *Antibiotics* 13 (1), 62 [doi: 10.3390/antibiotics13010062]

170. Haque R and Salam MA (2010). Detection of ESBL-producing nosocomial Gram-negative bacteria from a tertiary care hospital in Bangladesh. *Pakistan Journal of Medical Science* 26(4): 887-891

171. Khan SA, Feroz F and Noor R (2013). Study of extended-spectrum-lactamase-producing bacteria from urinary tract infections in Bangladesh. *Tzu Chi Medical Journal* 25 (1): 39-42 [doi: 10.1016/j.tcmj.2013.01.008]

172. Jobayer M, Afroz Z, Nahar SS, Begum A, Begum SA and Shamsuzzaman SM (2017). Antimicrobial susceptibility pattern of extended-spectrum beta-lactamases producing organisms isolated in a tertiary care hospital, Bangladesh. *International Journal of Applied and Basic Medical Research* 7: 189-192 [doi: 10.4103/ijabmr.IJABMR-28-16]

173. Begum S, Salam MA, Alam KF, Begum N, Hassan P, and Haq JA (2013). Detection of extended-spectrum β-lactamase in *Pseudomonas* spp. isolated from two tertiary care hospitals in Bangladesh. *BMC Research Notes* 6(1): 7 [doi: 10.1186/1756-0500-6-7]

174. Rahman M, Khan AH, Shahjahan M, Paul DK and Hassan P (2005). Antibiotic susceptibility and R-plasmid mediated drug resistance in *Staphylococcus aureus*. *Medical Journal of Islamic World Academic of Science* 15(3): 111-116

175. Hasan R, Acharjee M and Noor R (2016). Prevalence of vancomycin-resistant *Staphylococcus aureus* (VRSA) in methicillin-resistant *S. aureus* (MRSA) strains isolated from burn wound infections. *Tzu-Chi Medical Journal* 28: 49-53 [doi: 10.1016/j.tcmj.2016.03.002]

176. Islam TAB and Shamsuzzaman SM (2015). Prevalence and antimicrobial susceptibility pattern of methicillin-resistant, vancomycin-resistant and panton-valentine leucocidin positive *Staphylococcus aureus* in a tertiary care hospital Dhaka, Bangladesh. *Tzu Chi Medicial Journal* 27(1): 10-14 [doi: 10.1016/j.tcmj.2014.12.001]

177. Alam FM, Tasnim T, Afroz S, Alam ARM, Afroze N, Khatun A, Setu SK and Saleh AA (2023). Epidemiology and antibiogram of clinical *Staphylococcus aureus* isolates from tertiary care hospitals in Dhaka, Bangladesh. Avicenna *Journal of Clinical Microbiology and Infection* 9(4): 137-147 [doi: 10.34172/ajcmi.2022.3391]

178. Safain KS, Bhuyan GS, Rasnim S, Hasib SH, Sultana R, Islam MS, Mahmud-Un-Nabi MA, Sarker SK, Noor FA, Rahat A, Bhuiyan MAM, Islam MT, Manzoor F, Anwar S, Leung D, Quadri SS, Quadri F and Mannoor K (2020). Situation of antibiotic resistance in Bangladesh and its association with resistance genes for horizontal transfer. *The Preprint Server for Biology* bioRxiv2020.04.06.027391[doi: 10.1101/2020.04.06.027391]

179. Sutradhar KB, Saha A, Huda NH and Uddin NH (2014). Irrational use of antibiotics and antibiotic resistance in southern rural Bangladesh: perspectives from both the physicians and patients. *Annual Research Review Biology* 4(9): 1421-1430

180. Nahar S, Mukhopadhyay AK, Khan R, Ahmad MM, Datta S, Chattopadhyay S, Dhar SC, Sarker SA, Engstrand L, Berg DE, Nair GB and Rahman M (2004). Antimicrobial susceptibility of *Helicobacter pylori* strains isolated in Bangladesh. *Journal of Clinical Microbiology* 42(10): 4856-4858 [doi: 10.1128/jcm.42.10.4856-4858.2004]

181. Aftab H, Miftahussurur M, Subsomwong P, Ahmed F, Khan AA and Yamaoka Y (2016). *Helicobacter pylori* antibiotic susceptibility patterns in Bangladesh: emerging levofloxacin resistance. *Journal of Infection in Developing Countries* 10(3): 245-253 [doi: 10.3855/jidc.7713]

182. Hasan MS, Sultana M and Hossain MA (2019). Complete genome arrangement revealed the emergence of a poultry-origin superbug *Citrobacter portucalensis* strain NR-12. *Journal of Global Antimicrobial Resistant* 18: 126-129 [doi: 10.1016/j.jgar.2019.05.031]

183. Hoque R, Ahmed SM, Naher N, Islam MA, Rousham EK, Islam BZ and Hassan S (2020). Tackling antimicrobial resistance in Bangladesh: A scoping review of policy and practice in human, animal and environment sectors. *PLoS ONE* 15(1): e0227947

184. Betterhealth (2023). Antimicrobial-resistant bacteria. betetrhealth.vic.gov.au/health/conditions andtreatment/antibiotic-resistant-bacteria

185. Friedman ND, Temkin E and Carmeli Y (2016). The negative impact of antibiotic resistance. *Clinical Microbiology and Infection* 22: 416-422 [doi: 10.1016/j.cmi.2015.12.002]

186. WHO (2023). The proportion of bloodstream infection due to methicillin-resistant *Staphylococcus aureus* (MRSA) (%) [indicator) https://data.who.int/indicators/i/5DD9606

187. Hasanpour AH, Sepidarkish M, Mollalo A, Ardekani A, Almukhtar M, Mechaal A, Hosseini SR, Bayani M, Javnian M and Rostami A (2023). The global prevalence of methicillin-resistant *Staphylococcus aureus* colonization in residents of elderly care centers: a systematic review and meta-analysis. *Antimicrobial Resistance and Infection Control* 12, 4 [doi: 10.1186/s13756-023-01210-6]

188. van Loo I, Huijsdens X, Tiemersma E, de Neeling A, van de Sande-Bruinsma N, Beaujean D, Voss A and Kluytmans J (2007). Emergence of methicillin-resistant *Staphylococcus aureus* of animal origin in humans. *Emerging Infectious Diseases* 13(12): 1834-1839 [doi: 10.3201/eid1312.070384]

189. Turner NA, Sharma-Kuinkel BK, Maskarinec SA, Eichenberger EM, Shah PP, Carugati M, Holland TL and Flowler VG (2019). Methicillin-resistant *Staphylococcus aureus:* an overview of basic and clinical research. *Nature Reviews Microbiology* 17: 203-218 [doi: 10.1038/s41579-018-0147-4]

190. Ejaz M, Syed MA, Jackson CR, Sharif M and Faryal R (2023). Epidemiology of *Staphylococcus aureus* non-susceptible to vancomycin in South Asia. *Antibiotics* (Basel): 12(6): 972 [doi:10.3390/antibiotics12060972]

191. Islam TAB and Shamsuzzaman SM (2015). Prevalence and antimicrobial susceptibility pattern of methicillin-resistant, vancomycin-resistant, and panton-valentine leukocidin-positive *Staphylococcus aureus* in a tertiary care hospital Dhaka, Bangladesh. *Tzu Chi Medical Journal* 27(1): 10-14 [doi: 10.1016/j.tcmj.2014.12.001]

192. Shahriar M, Shahid S, Katha KK, Nasreen W and Bhuiyan MA (2012). Vancomycin sensitivity of clinical isolates of Staphylococcus aureus from patients in Dhaka City, Bangladesh. *Bangladesh Pharmacology Journal* 15: 159-163 [doi: 10.3329/bpj.v15i2.12582]

193. Haque N, Aung MS, Paul SK, Bari S, Ahmed S, Sarker SR, Roy S, Nasreen SA, Mahmud MC, Hossain MA et al. (2019). Molecular epidemiological characterization of methicillin-susceptible and resistant *Staphylococcus aureus* isolated from skin and soft tissue infections in Bangladesh. *Microbial Drug Resistance* 25: 241-250 [doi: 10.1089/mdr.2018.0123]

194. Taz KA, Jobayer M and Shamsuzzaman SM (2019). Nasal colonization of methicillin-resistant *Staphylococcus aureus* among healthcare providers in a tertiary care hospital, Bangladesh. *Mymensingh Medical Journal* 28: 627-633 [PMID: 31391436]

195. Roy S, Barman TK, Hossain MA, Paul SK, Haque N, Ahmed S, Nasreen SA, Hossain MS, Sarker SR, Kubayashi N and Laskar N (2017). Molecular characterization of methicillin-resistance *Staphylococcus aureus* (MRSA) from different tertiary care hospitals in Bangladesh. *Mymensingh Medical Journal* 26: 37-44 [PMID: 28260753]

196. Parvez MAK, Ferdous RN, Rahman MS and Islam S (2018). Healthcare-associated (HA) and community-associated (CA) methicillin-resistant *Staphylococcus aureus* (MRSA) in Bangladesh- Source, diagnosis and treatment. *Journal of Genetic Engineering and Biotechnology* 16(2): 473-478 [doi: 10.1016/j.jgeb.2018.05.004]

197. Afroz S, Kobayashi N, Nagashima S, Alam MM, Hossain AB and Rahman MA (2008). Genetic characterization of *Staphylococcus aureus* isolates carrying Panton-Valentine leucocidin genes in Bangladesh. *Japanese Journal of Infectious Diseases* 61(5): 393-396 [doi: 10.7883/yoken.JJID.2008.393]

198. Rahman MM, Amin KB, Rahman SMM, Khair A, Rahman M, Hossain A, Rahman AKMA, Parvez MS, Miura N and Alam MM (2018). Investigation of methicillin-resistant *Staphylococcus aureus* among clinical isolates from humans and animals by culture methods and multiplex PCR. *BMC Veterinary Research* 14: 300 [doi: 10.1186/s12917-018-1611-0]

199. Giri S, Ghimire A, Mishra A, Acharya K, Kuikel S, Tiwari A and Mishra SK (2023). Prevalence of methicillin-resistant *Staphylococcus aureus* carriage among healthcare workers in South Asia in non-outbreak settings: A systematic review and meta-analysis. *American Journal of Infection Control* 51: 184-193 [doi: 10.1016/j.ajic.2022.06.001)

200. Hossain MA, Shamsuzzaman AKM, Musa AKM, Ahmed R and Tariquzzaman M (2002). Antimicrobial susceptibility pattern of *Staphylococcus aureus* isolated at Mymensingh Medical College Hospital. *Bangladesh Medical Review* 28: 9-12

201. Islam T, Kubra K and Chowdhury MMH (2018). Prevalence of methicillin-resistant *Staphylococcus aureus* in hospitals in Chittagong, Bangladesh: A threat of nosocomial infection. *Journal of Microbiology and Ultrastructure* 6(4): 188-191 [doi: 10.4103/JMAU.JMAU_38_18]

202. Islam MA, Alam MM, Uddin MS, Kobayashi N and Ahmed MU (2011). Detection of methicillin-resistant *Staphylococcus aureus* (MRSA) from animal and human origin in Bangladesh by polymerase chain reaction. *Bangladesh Journal of Veterinary Medicine* 9(2): 161-166

203. Khatun R, Hasan SS, Khatun N and Akter S (2023). Prevalence of methicillin-resistant *Staphylococcus aureus* with their susceptibility pattern and their association of Panton-Valentine leucocidin gene in a tertiary care hospital in Bangladesh. *Fortune Journal of Health Sciences* 6: 160-166 [doi: 10.26502/fjhs.111]

204. Haq JA, Rahman MM, Asna SMZH, Hossain MA, Ahmed I, Haq T and Morshed MAHG (2005). Methicillin-resistant *Staphylococcus aureus* in Bangladesh- a multicentre study. *International Journal of Antimicrobial Agents* 25(3): 276-277 [doi: 10.1016/j.ijantimicag.2005.01.004]

205. Islam MA, Alam MM, Choudhury ME, Kobayashi N and Ahmed MU (2008). Determination of minimum inhibitory concentration (MIC) of cloxacillin for selected isolates of methicillin-resistant *Staphylococcus aureus* (MRSA) with their antibiogram. *Bangladesh Journal of Veterinary Medicine* 6: 121-126 [doi: 10.3329/bjvm.v6i1.1350]

206. Tasnim A, Shamsuzzaman AKM, Alam MS, Ferdose J and Khan FA (2020). Phenotypic and genotypic isolation of MRSA from burn wound infected patients at a tertiary care hospital in Bangladesh. *Bangladesh Journal of Infectious Diseases* 7: 12-17 [doi: 10.3329/bjid.v7i1.48671]

207. Yusuf MA, Islam KMS, Shamsuzzaman AKM, Ahmed I and Sattar AA (2013). Burden of infection caused by methicillin-resistant *Staphylococcus aureus* in Bangladesh: a systematic review. *Global Advanced Research Journal of Microbiology* 2(11): 213-223

208. Jinnah F, Chowdhury K, Begum J, Sohail M, Rahman MT and Ahmed S (1998). Multi-resistant *Staphylococcus aureus* isolated from wound swabs of diabetic patients. *Journal of Infectious Diseases and Antimicrobial Agents* 15(1): 15-18

209. Iqbal J, Rahman M and Kabir MS (1999). Ciprofloxacin resistance among community-derived methicillin-resistant *Staphylococcus aureus* (MRSA) strains. *Southeast Asian Journal of Tropical Medicine and Public Health* 30 (4): 779-780 [PMID: 10928376]

210. Rahman M, Hossain M, Talukder MAS, Shahriar M and Zakaria M (2002). Prevalence of β-lactamase-producing methicillin-resistant *Staphylococcus aureus* and antimicrobial sensitivity pattern. *Pharmaceutical Journal* 12 (2): 1-5

211. Shamsuzzaman AKM, Paul SK, Mahmud MC, Musa AKM and Hossain MA (2007). Emerging antimicrobial resistance amongst common bacterial pathogens in Mymensingh Medical College Hospital. *Bangladesh Journal of Medical Microbiology* 01 (01): 4-9 [doi: 10.3329/bjmm.v1i1.20488]

212. Khan AH, Shamsuzzaman AKM, Paul SK, Alam MM and Mahmud C (2007). Antimicrobial susceptibility and coagulase typing of MRSA strains at Mymensingh Medical College. *Bangladesh Journal of Medical Microbiology* 1(2): 56-60 [doi: 10.3329/bjmm.v1i2.21510]

213. Ahmed S, Hossain MA, Shamsuzzaman AKM, Sumona AA, Bagum Z, Zahan NA, Musa AKM, Mahmud MC, Nahar K, Ahmed SSU, Huda SAN and Ahmed MU (2008). Aerobic bacterial pattern in puerperal sepsis. *Bangladesh Journal of Medical Microbiology* 2(1): 22-27

214. Kawsar NM, Mondal MEA, Khan NK, Jubaida N, Chowdhury JP and Khan L (2008). Antimicrobial susceptibility patterns of beta-lactamase-producing *Staphylococcus aureus. Journal of Armed Forces Medical College of Bangladesh* 4(2): 14-17

215. Barai L, Fatema K, Haq JA, Faruq MO, Ahsan ASMA, Morshed MAHG and Hossain MB (2010). Bacterial profile and antimicrobial resistance pattern in an intensive care unit of tertiary care hospital in Dhaka. *Ibrahim Medical College Journal* 4(2): 66-69

216. Alam MM, Uddin MS, Kobayashi N and Ahmed MU (2011). Detection of methicillin-resistance Staphylococcus aureus (MRSA) from animal and human origin in Bangladesh by polymerase chain reaction. Bangladesh. *Journal of Veterinary Medicine* 9(2): 161-166

217. Begum R, Towhid ST, Monirizzaman M, Mia Z and Islam MA (2011). Study of *Staphylococcus aureus* from clinical samples in Savar, Bangladesh. *Research Journal of Microbiology* 6(12): 884-890 [doi=jm.2011.884.890]

218. Murshed M, Kamar S, Malek MA, Haque M and Akhter N (2011). A comparative study of surgical site wound infection in Dhaka Medical College Hospital and Holy Family Red Crescent Medical College and detection of MRSA. *Osmani Medical Teachers Association Journal* 10(1): 36-41

219. Shahidullah MS, Yusuf MA, Khatun Z, Ara U and Mitul MT (2012). Antibiotic sensitivity pattern of bacterial isolates from different clinical specimens: experience at NICVD, Dhaka. *Cardiovascular Journal* 5(1): 67-72 [doi: 3329/cardio.v5i1.12276]

220. Islam MS, Ahmed MF and Rahman SR (2013). Incidence of methicillin-resistant *Staphylococcus aureus* in burn unit, Dhaka Medical College Hospital, Bangladesh. *Advances in Microbiology* 3, 38163 [doi: 10.4236/aim.2013.36066]

221. Hussain K, Rahman M, Nazir KHMNH, Rahman H and Khair A (2016). Methicillin-resistant *Staphylococcus aureus* (MRSA) in patients of community-based medical college hospital, Mymensingh, Bangladesh. *American Journal of Biomedical and Life Sciences* 4(3): 26-29 [doi: 10.11648/j.ajbls.20160403.11]

222. Rahman MA (2020). Methicillin-resistant *Staphylococcus aureus* (MRSA): prevalence and antimicrobial sensitivity pattern among outdoor and indoor patients Dhaka City Hospital Bangladesh. *Journal of Clinical Immunology and Microbiology* 1(2): 1-9 [doi: 10.46889/JCIM.2020.1203]

223. Rahman MA, Raton KA and Hossain MA (2021). Methicillin-resistant *Staphylococcus aureus* (MRSA): prevalence and antimicrobial sensitivity pattern among outdoor and indoor patients Dhaka City Hospital Bangladesh. *American Journal of Microbiological Research* 9: 9-13 [doi: 10.12691/ajmr-9-1-2]

224. Roy S, Aung MS, Paul SK, Nasreen SA, Haque N, Mazid R, Khan MS, Barman TK, Arafat P, Sathi FA, Nila SS, Jahan A, Urushibara N, Kawaguchiya M, Ohashi N and Kobayashi N (2023). Genetic characterization of methicillin-resistant/susceptible *Staphylococcus aureus* (MRSA/MSSA) and *Staphylococcus argenteus* clinical isolates in Bangladesh: Dominance of ST6-MRSA-IV/t304 and detection of cfr/fexA in ST8-MSSA/t008. *International Journal of Infectious Diseases Regions* 10: 132-139 [doi: 10.1016/J.ijregj.2023.12.006]

225. Roy K, Islam MS, Paul A, Levy S, Talukder M, Sobur MA, Ballah FM, Khan MSR and Rahman MT (2022). Molecular detection and antibiotyping of multi-drug resistant *Enterococcus faecium* from healthy broiler chickens in Bangladesh. *Veterinary Medicine and Science* 8: 200-210 [doi. 10.1002/vms3.669]

226. Ahmed MO and Baptiste KE (2018). Vancomycin-resistant enterococci: a review of antimicrobial resistance mechanisms and perspectives of human and animal health. *Microbial Drug Resistance* 24(5): [doi: 10.1089/mdr.2017.0147]

227. Banu S, Rahman MT, Ahmed S, Khatun R, Ferdous SS, Hosen B, Rahman MM, Ahmed T, Cavanaugh JS and Heffelfinger JD (2017). Multidrug-resistant tuberculosis in Bangladesh: results from a sentinel surveillance system. *International Journal of Tuberculosis and Lung Disease* 21: 12-17 [doi: 10.5588/ijtld.16.0384]

228. Kundu S, Marzan M, Gan SH and Islam MA (2020). Prevalence of antibiotic-resistant pulmonary tuberculosis in Bangladesh: A systematic review and meta-analysis. *Antibiotics* 9(10): 710 [doi: 10.3390/antibiotics9100710]

229. Kock R, Daniels-Haardt I, Becker K, Mellmann A, Friedrich AW, Mevius D, Schwarz S and Jurke A (2018). Carbapenem-resistant Enterobacteriaceae in wildlife, food-producing, and companion animals: a systematic review. *Clinical Microbiology and Infection* 24: 1241-1250 [doi: 10.1016/j.cmi.2018.04.004]

230. Rousham EK, Asaduzzaman M, Mozmader TIMAU, Amin MB, Rahman M, Hossain MI, Islam MTR, Mahmud ZH, Unicomb L and Islam MA (2021). Human colonization with extended-spectrum beta-lactamase-producing E. coli about animal and environmental exposures in Bangladesh: An observational One Health study. *Environmental Health Perspective* 129: 37001 [doi: 10.1289/EHP7670]

231. Imam T, Gibson JS, Foysal M, Das SB, Gupta SD, Fournie G, Hoque MA and Henning J (2020). A cross-sectional study of antimicrobial usage on commercial broiler and layer chicken farms in Bangladesh. *Frontiers in Veterinary Science* 7: 576113 [doi: 10.3389/fvets.2020.576113]

232. Al Masud A, Rousham EK, Islam MA, Alam MU, Rahman M, Al-Mamun A, Sarker S, Asaduzzaman M and Unicomb L (2020). Drivers of antibiotic use in poultry production in Bangladesh: Dependencies and dynamics of a patron-client relationship. *Frontiers Veterinary Sciences* 7: 78 [doi: 10.3389/fvets.2020.00078]

233. 24. Islam KS, shiraj-Um-Mahmuda S and Hazzaz-Bin-Kabir M (2016). Antibiotic usage patterns in selected broiler farms of Bangladesh and their public health implications. *Journal of Public Health Developing Countries* 2(3): 276-284

234. Ferdous J, Sachi S, Al Noman SZ, Hussani YAS and Sikder MH (2019). Assessing farmers' perspective on antibiotic usage and management practices in small-scale layer farms of Mymensingh district, Bangladesh. *Veterinary World* 12(9): 1441-1447 [doi: 10.14202/vetworld.2019.1441-1447]

235. Dey RK, Khatun MM, Islam MA and Hossain MS (2013). Prevalence of multidrug-resistant *Escherichia coli* in pigeons in Mymensingh, Bangladesh. *Microbes and Health* 2(1): 5-7 [doi: 10.3329/mh.v2i1.17254]

236. Saifuddin AKM, Islam SKMA and Anwar MN (2016). Molecular characterization and antimicrobial resistance patterns of *Salmonella* spp. and *Escherichia coli* of laying chicken. *Microbes and Health* 5(1): 4-6 [doi: 10.3329/mh.v5i1.31189]

237. Shahjada Z, Hussain K, Islam MM, Majumder S, Hasan I, Rahman M and Saha S (2017). Bacteria causing omphalitis in newly hatched chicks from broiler and layer flocks and their antibiotic profiles. *International Journal of Natural and Social Science* 4(2): 73-81

238. Hasan B, Faruque R, Drobni M, Waldenstrom J, Sadique A, Ahmed KU, Islam Z, Parvez MBH, Olsen B and Alam M (2011). High prevalence of antibiotic resistance in pathogenic *Escherichia coli* from large and small-scale poultry farms in Bangladesh. *Avian Diseases* 55(4): 689-692 [doi: 10.1637/9686-021411-Reg.1]

239. Jakaria A, Islam MA and Khatun MM (2012). Prevalence, characteristics and antibiogram profiles of *Escherichia coli* isolated from apparently healthy chickens in Mymensingh, Bangladesh. *Microbes and Health* 1(1): 27-29

240. Sarker MS, Mannan MS, Ali MY, Bayzid M, Ahad A and Bupasha ZB (2019). Antibiotic resistance of *Escherichia coli* isolated from broilers sold at live bird markets in Chattogram, Bangladesh. *Journal of Advanced Veterinary and Animal Research* 6(3): 272-277 [doi: 10.5455/javar.2019.f344]

241. Talukdar PK, Rahman M, Rahman M, Nabi A, Islam Z, Hoque MM, Endtz HP and Islam MA (2013). Antimicrobial resistance, virulence factors and genetic diversity of *Escherichia coli* isolates from household water supply in Dhaka, Bangladesh. *PLoS ONE* 8 (4): e61090 [doi: 10.1371/journal.pone.0061090]

242. Parvin M, Talukder S, Ali M, Chowdhury EH, Rahman M and Islam M (2020). Antimicrobial resistance pattern of *Escherichia coli* isolated from frozen chicken meat in Bangladesh. *Pathogens* 9(6): 420 [doi: 10.3390/pathogens9060420]

243. Singh A, Khan MSR, Saha S, Hassan J and Roy U (2012). Isolation and detection of antibiotic sensitivity pattern of *Escherichia coli* from ducks in Bangladesh and Nepal. *Microbes and Health* 1(1): 6-8

244. Al-Salauddin AS, Hossain MF, Dutta A, Mahmud S, Islam MS, Saha S and Kabir SML (2015). Isolation, identification and antibiogram studies of Salmonella species and *Escherichia coli* from broiler meat in some selected areas of Bangladesh. *International Journal of Basic and Clinical Pharmacology* 4 (5): 999-1003 [doi:10.18203/2319-2003.ijbcp20150881]

245. Dutta A, Islam MZ, Barua H, Rana EA, Jalal MS, Dhar PK, Das A, Das T, Sarma SM and Biswas SK (2020). Acquisition of plasmid-mediated colistin resistance gene mcr-1 in Escherichia coli of livestock origin in Bangladesh. *Microbiological Drug Resistant* 26(9):1058-1062 [doi: 10.1089/mdr.2019.0304]

246. Ahmed MM, Rahman MM, Mahbub KR and Wahiduzzaman M (2011). Characterization of antibiotic-resistant *Salmonella* spp. isolated from chicken eggs of Dhaka city. *Journal of Scientific Research* 3 (1): 191-196 [doi: 10.3329/jsr.v3i1.6109]

247. Rahman MM, Hossain MK, Akter MR and Hasam SM (2011). Characterization and antibiogram study of Salmonella serovars isolated from duck, quail, and pigeon in Dinajpur district of Bangladesh. *International Journal of Sustainable Agricultural Technology* 7: 23-29

248. Ahmed S, Siddique MA, Rahman M, Bari ML and Ferdousi S (2019). A study on the prevalence of heavy metals, pesticides microbial contaminants, and antibiotic resistance pathogens in raw salad vegetables sold in Dhaka. *Bangladesh Heliyon* 5: e01205 [doi: 10.1016/j.heliyon.2019.e01205]

249. Mahmud MS, Bari ML and Hossain MA (2011). Prevalence of Salmonella serovars and antimicrobial resistance profiles in poultry of Savar area, Bangladesh. Foodborne Pathogens and Diseases 8(10): 1111-1118 [doi: 10.1089/fpd.2011.0917]

250. Parvej MS, Nazir KHMNH, Rahman MB, Jahan M, Khan MFR and Rahman M (2016). Prevalence and characterization of multi-drug resistant *Salmonella enterica serovar gallinarum biovar pullorum* and *gallinarum* from chicken. *Veterinary World* 9: 65-70 [doi: 10.14202/vetworld.2016.65-70]

251. Nandi SP, Sultana M and Hossain MA (2013). Prevalence and characterization of multidrug-resistant zoonotic *Enterobacter* spp. in poultry of Bangladesh. *Foodborne Pathogens and Diseases* 10(5): 420-427 [doi: 10.1089/fpd.2012.1388]

252. Sultana S, Islam MA, Khatun MM and Nasrin S (2012). Multidrug-resistant Bacteria in the respiratory tract of apparently healthy quails. *Microbes and Health* 1(2): 46-49 [doi: 10.3329/mh.v1i2.14088]

253. Islam NN, Akter M, Farzana Z, Kader AJB, Uddin I, Siddiki AMAMZ and Kamaruddin KM (2014). Detection of *Staphylococcus aureus* in frozen chicken rinse through bacteriological and nuc gene-specific PCR methods and their drug resistance patterns in Southern Chittagong, Bangladesh. *Research Journal of Microbiology* 9(5): 251-264

254. Neogi SB, Islam MM, Islam SKS, Akhter AHMT, Sikder MMH, Yamasaki S and Kabir SML (2020). Risk of multidrug-resistant *Campylobacter* spp. and residual antimicrobials at poultry farms and live bird markets in Bangladesh. *BMC Infectious Diseases* 20, 278: 1-14 [doi: 10.1186/s12879-020-05006-6]

255. Kabir S, Sumon MH, Amin MM and Yamasaki S (2014). Isolation, identification and antimicrobial resistance patterns of Campylobacter species from broiler meat sold at KR market of Bangladesh Agricultural University campus, Mymensingh. *Journal of Agriculture and Food Technology* 4(4): 1-17

256. Islam MS, Hossain MJ, Sobur MA, Punom SA, Rahman AMMT and Rahman MT (2023). A systematic review on the occurrence of antimicrobial-resistant Escherichia coli in poultry and poultry environments in Bangladesh between 2010 and 2021. *BioMed Research International*, Article ID 2425564 [doi: 10.1155/2023/2425564]

257. Mahmud S, Nazir KNH and Rahman MT (2018). Prevalence and molecular detection of fluoroquinolone-resistant genes (qnrA and qnrS) in *Escherichia coli* isolated from healthy broiler chickens. *Veterinary World* 11: 1720-1724 [doi: 10.14202/vetworld.2018.1720-1724]

258. Saha O, Hoque MN, Islam OK, Rahman M, Sultana M and Hoassin MA (2020). Multidrug-resistant avian pathogenic *Escherichia coli* strains and association of their virulence genes in Bangladesh. *Microorganisms* 8: 1135 [doi: 10.3390/microorganisms8081135]

259. Al Azad MAR, Rahman MM, Amin R, Begum MIA, Fries R, Husna A, Khairalla AS, Badruzzaman ATM, El Zowalaty ME, Lampang KN, Ashour HM and Hafez HM (2019). Susceptibility and multidrug resistance patterns of *Escherichia coli* isolated from cloacal swabs of live broiler chickens in Bangladesh. *Pathogens* 8 (3): [doi: 10.3390/pathogens8030118]

260. Sobur MA, Levy S, Haque ZF, Nahar A, Zaman SB and Rahman MT (2019). Emergence of colistin-resistant *Escherichia coli* in poultry, house flies, and pond water in Mymensingh, Bangladesh. *Journal of Advanced Veterinary and Animal Research* 6: 50-53 [doi: 10.5455/javar.2019.f311]

261. Tawyabur M, Isla MS, Sobur MA, Hossain MJ, Mahmud MM, Paul S, Hossain MT, Ashour HM and Rahman TM (2020). Isolation and characterization of multidrug-resistant *Escherichia coli* and *Salmonella* spp. from healthy and diseased turkeys. *Antibiotics* 9(11): 770 [doi: 10.3390/antibitics9110770]

262. Rahman MM, Husna A, Elshabrawy HA, Alam J, Runa NY, Badruzzaman ATM, Banu NA, Al Mamun M, Paul B, Das S, Rahman MM, Mahbub-E- Elahi ATM, Khairalla AS and Ashour HM (2020). Isolation and molecular characterization of multidrug-resistant *Escherichia coli* from chicken meat. *Scientific Reports* 10,21999 [doi: 10.1038/s41598-020-78367-2]

263. Mandal AK, Talukder S, Hasan MM, Tasmin ST, Parvin MS, Ali MY and Islam MT (2022). Epidemiology and antimicrobial resistance of Escherichia coli in broiler chickens, farm workers, and farm sewage in Bangladesh. *Veterinary Medicine and Science* 8: 187-199 [doi: 10.1002/vms3.664]

264. Ibrahim N, Boyen F, Mohsin MAS, Ringenier M, Berge AC, Chantziaras I, Fournie G, Pfeiffer D and Dewulf J (2023). Antimicrobial resistance in Escherichia coli and its correlation with antimicrobial use on commercial poultry farms in Bangladesh. *Antibiotics* 12 (9), 1361 [doi: 10.3390/antibiotics12091361]

265. Sobur MA, Sabuj AAM, Sarker R, Rahman AMMT, Kabir SML and Rahman MT (2019). Antibiotic-resistant *Escherichia coli* and *Salmonella* spp. associated with dairy cattle and farm environment having public health significance. *Veterinary World* 12 (7): 984-993[doi: 10.14202/vetworld.2019.984-993]

266. Parvez AKM, Marzan M, Liza SM, Mou TJ and Azmi IJ (2016). Prevalence of inhibitor-resistant beta-lactamase-producing *Escherichia coli* in human and poultry origin of Bangladesh. *Journal of Bacteriology and Parasitology* 7: 2 [doi: 10.41722155-9597.1000271]

267. Levy S, Islam MS, Sobur MA, Talukder M, Rahman MB, Khan MFR and Rahman MT (2020). Molecular detection of avian pathogenic *Escherichia coli* (APEC) for the first time in layer farms in Bangladesh and their antibiotic resistance patterns. *Microorganisms* 8(7): 1021 [doi: 10.3390/microorganisms8071021]

268. Akter F, Amin MR, Osman KT, Anwar MN, Karim MM and Hossain MM (2012). Ciprofloxacin-resistant Escherichia coli in hospital wastewater of Bangladesh and prediction of its mechanism of resistance. *World Journal of Microbiology and Biotechnology* 28: 827-834

269. Hasan B, Olsen B, Alam A, Akter L and Melhus A (2015). Dissemination of the multidrug-resistant extended-spectrum-lactamase-producing Escherichia coli O25b-ST131 clone and the role of house crow (*Corvus splendens*) foraging on hospital waste in Bangladesh. *Clinical Microbiology Infect*ion 21(11): 1000e1-4

270. Rana E (2017). Antibiotic resistance, microbial and morphological changes of the marketed bovine liver at different time interval from Chittagong, Bangladesh: A public health concern. *Research & Reviews: Journal of Veterinary Sciences* 3(1): 16-23

271. Siddiki S, Samad M, Saha S, Badiuzzaman M and Islam M (2019). Comparison of bacterial pathogens associated with different types of bovine mastitis and their antibiotic resistance status in Bangladesh. *Journal of Veterinary Medical and One Health Research* 1(1): 17-27 [doi: 10.36111/jvmohr.2019.1(1).0002]

272. Rahman MT, Islam MS and Hasan M (2013). Isolation and identification of bacterial agents causing clinical mastitis in cattle in Mymensingh and their antibiogram profile. *Microbes and Health* 2(1): 19-21 [doi: 10.3329/mh.v2i1.17258]

273. Rahman MSR, Uddin MN, Nain Z and Karim MM (2019). Screening for microbial load and antibiotic resistance pattern in *Escherichia coli* isolated from paper currency circulating in Kushtia, Bangladesh. *International Journal Research in Medical Science* 7(4): 1161-1165

274. Islam K, Ahad A, Barua M, Islam A, Chakma S, Dorji C, Uddin MA, Islam S and Ahsan ASML (2016). Isolation and epidemiology of multidrug-resistant Escherichia coli from goats in Cox's Bazar, Bangladesh. *Journal of Advanced Veterinary and Animal Research* 3(2): 166-172 [doi: 10.5455/javar.2016.c147]

275. Jalal MS, Islam MZ, Dutta A, Dhar PK, Das A, Hasan MM, Barua H, Biswas PK and Ahad A (2019). Antibiotic-resistant zoonotic bacteria in Irrawaddy squirrel (*Callosciurus pygerythrus*). *Veterinary Medicine and Science* 5(2): 260-268 [doi: 10.1002/vms3.138]

276. Haque ME, Islam MA, Akter S and Saha S (2014). Identification, molecular detection and antibiogram profile of Bacteria isolated from California mastitis test-positive milk samples of crossbred cows of Satkhira district in Bangladesh. *GSTF International Journal of Veterinary Science* 1(1): 59-63 [doi: 10.5176/0000-0003_1.1.8]

277. Hoque M, Das Z, Rahman A. Haider M and Islam M (2018). Molecular characterization of Staphylococcus aureus strains in bovine mastitis milk in Bangladesh. International Journal of *Veterinary Science and Medicine* 6(1): 53-60 [doi: 10.1016/j.ijvsm.2018.03.008]

278. Islam KI, Kabir SL, Saha S and Khan M (2013). Prevalence and antimicrobial resistance patterns of Vibrio cholerae from Bangladesh Agricultural University dairy farm. *International Journal Medical Science and Biotechnology* 1(3): 13-25

279. Hossain M, Saha S, Rahman M, Singha J and Mamun A (2013). Isolation, identification and antibiogram study of *Pseudomonas aeruginosa* from cattle in Bangladesh. *Journal of Veterinary Advances* 3(7): 180-185 [doi: 10.5455/jva.20130717123841]

280. Watanabe T (1966). Infectious drug resistance in enteric bacteria. The New England Journal of Medicine 275 (16): 888-894 [doi: 10.1056/NEJM196610202751607]

281. Rousham EK, Unicomb L and Islam MA (2018). Human, animal and environmental contributors to antibiotic resistance in low-resource settings: integrating behavioral, epidemiological and 'One Health' approaches. *Proceedings of the Royal Society B* 285: [doi: 10.1098/rspb.2018.0332]

282. TGHN (2023). Antimicrobial Resistance (AMR). One Health- The Global Health Network (TGHN). https://amr.tghn.org/resources/onehealth/#:~:text=One%20Health%20Health%20is%20an%20approach,how%20One%20Health%impacts%20AMR

283. Rousham E, Unicomb L, Wood P, Smith M, Asaduzzaman M and Islam MA (2018). Spatial and temporal variation in the community prevalence of antibiotic resistance in Bangladesh: an integrated surveillance study protocol. *BMJ Open* 8:e023158 [doi: 10.1136/bmjopen-2018-023158]

284. Uchil RR, Kohli GS, Katekhaye VM and Swami O (2014). Strategies to combat antimicrobial resistance. *Journal of Clinical and Diagnostic Research* 8(7): ME01-ME04 [doi: 10.7860/JCDR/2014/8925.4529]

285. Anon. (2024). Antimicrobial resistance surveillance market. https://www.marketsandmarkets.com/ Market-Report/antimicrobial-resistance-surveillance-market-21323165.html?gad_source=1&gclid=Cj0KCQjwqexBhCo ARIsAFgBlet-UkkDJFZGUZ6ZDceeuANvnl_CKztCgfgJBFVNEuP_S5GunDDNK DkaAoZAEALw-wcB

286. Duong A and Jaelin M (2015). 6 factors that have caused antibiotic resistance. infectioncontrol.tips/2015/11/18/6-factors-that-have-caused-antibiotic-resistance/

287. Halawa EM, Fadel M, Al-Rabia MW, Behairy A, Nouh NA, Abdo M, Olga R, Fericean L, Atwa AM, El-Nablaway M and Abdeen A (2023). Antibiotic action and resistance: updated review of mechanisms, spread, influencing factors, and alternative approaches for combating resistance. *Frontiers in Pharmacology* 14: 1395294 [doi: 10.3389/fphar.2023.1305294]

288. Bergspica I, Kaprou G, Alexa EA, Prieto-Maradona M and Alvarez-Ordonez A (2020). Identification of risk factors and hotspots of antibiotic resistance along the food chain using next-geneartion sequencing. *EFSA Journal* 18(S1): e181107 [doi: 10.2903/j.efsa.2020.e181107]

289. Piddock LJV (2015). Teixobactin, the first of a new class of antibiotics discovered by Chip technology? *Journal of Antimicrobials and Chemotherapy* 70(10): 2679-2680 [doi: 10.1093/jac/dkv175)

290. Stokes JM, Yang K, Swanson K, Jin W, Cubillos-Ruiz A, Donghia NM, MacNair CR, French S, Carfrae LA, Bloom-Ackemann Z, Tran VM, Chiappino-Pepe A, Badran AH, Andrews IW, Chory EJ, Church GM, Brown ED, Jaakkola TS, Barzilay R and Collins JJ (2020). A deeo learning approach to antibiotic discovery. *Cell* 180(4): 688-702 [doi: 10.1016/j.cell.2020.01.021]

291. Miller RD, Linishi A, Modaresi SM, Yoo BK, Curtis TD, Lariviere PJ, Liang L, Son S, Nicolau S, Bargabos R, Morrissette, Gates MF, Pitt N, Jakob RP, Rath P, Maier T, Mayutin AG, Kaiser JT, Niles S, Karavas B, Ghiglieri M, Bowman SEJ, Rees DC, Hiller S and Lewis K (2022). Computational identification of a systemic antibiotic for Gram-negative bacteria. *Nature Microbiology* 7(10: 1661-1672 [doi: 10.1038/s41564-022-01227-4]

292. Clardy J, Fischbach MA and Walsh CT (2006). New antibiotics from bacterial natural products. *Nature Biotechnology* 24: 1541-1550 [doi: 10.1038/nbt1266]

293. McDevitt D and Rosenberg M (2001). Exploiting genomics to discover new antibiotics. *Trends Microbiology* 9(12): 611-617 [doi: 10.1016/S0966-842X(01)02235-1]

294. Melander RJ and Melander C (2017). The challenge of overcoming antibiotic resistance: an adjuvant approach? *ACS Infectious Diseases* 3(8): 559-563 [doi: 10.1021/acsinfecdis.7b00071]

295. Ahmad A, Hussain S, Mehmood R, Rana A and Mustafa G (2023). Antibiotic resistance breakers and nano-antibiotics in mediating antimicrobial resistance.intechopen.com/online-first/87561[doi: 10.5772/intechopen. 111761]

296. Soares S, Sousa J, Pais A and Vitorino C (2018). Nanomedicine: principles, properties and regulatory issues. *Frontier Chemistry* 6: 360-415 [doi: 10.3389/fchem.2018.00360]

297. Singh CK and Sodhi KK (2023). The emerging significance of nanomedicine-based approaches to fighting COVID-19 varients of concern: A perspective on the nanotechnology's role in COVID-19 diagnosis and treatment. *Frontiers in Nanotechnology* 4: 1-13 [doi: 10.3389/fnano.2022.1084033]

298. Gupta PD and Birdi TJ (2017). Development of botanicals to combat antibiotic resistance. *Journal of Ayurveda and Integrative Medicine* 8(4): 266-275 [doi: 10.1016/j.jaim.2017.05.004]

299. Shree P, Singh CK, Sodhi KK, Surya JN and Singh DK (2023). Biofilms: understanding the structure and contribution towards bacterial resistance in antibiotics. *Medicine in Microbiology* 16, 100084 [doi: 10.1016./j.medmic.2023.100084]

300. Chanishvili N and Sharp R (2008). Bacteriophage therapy: experience from the Eliava Institute, Georgia. *Microbiology Australia* 29: 96-101 [doi: 10.1071/ma08096)

301. Meader E, Mayer MJ, Steverding D, Carding SR and Narbad A (2013). Evaluation of bacteriophage therapy to control *Clostridium difficile* and toxin production in an in vitro human colon model system. *Anaerobe* 22: 25-23 [doi: 10.1016/j.anaerobe.2013.05.001]

302. Biswas B, Sankar A, Paul W, Paul B, Trostel AN, Powell B, Carlton R and Merril CR (2002). Bacteriophase therapy rescues mice bacteremic from a clinical isolate of vancomycin-resistant *Enterococcus faecium*. *Infection and Immunity* 70: 204-210 [doi: 10.1128/iai.70.3.1664-1664.2002]

303. Wang J, Hu B, Xu M, Yan Q, Liu S, Zhu X, Sun Z, Reed E, Ding L, Gong J, Li QQ and Hu J (2006). Use of bacteriophage in the treatment of experimental animal bacteremia from imipenem-resistant Pseudomonas aeruginosa. *International Journal of Molecular Medicine* 17(2): 309-317 [doi: 10.3892/ijmm.17.2.309]

304. Yuan Y, Wang L, Li X, Tan D, Cong C and Xu Y (2019). Efficacy of a phage cocktail in controlling phage resistance development in multidrug-resistant *Acinetobacter baumannii. Virus Research* 272, 197734 [doi: 10.1016/j.viruses.2019.197734]

305. Pouillot F, Chomton M, Blois H, Courroux C, Noelig J, Bidet P, Bengen E and Bonacorsi S (2012). Efficacy of bacteriophase therapy in experimental sepsis and meningitis caused by a clone 025b:H4-st131 *Escherichia coli* strain producing CTX-M-15. *Antimicrobial Agents and Chemotherapy* 56(7): 3564-3575 [doi: 10.1128/AAC.06330-11]

306. Fish R, Kutter E, Wheat G, Blasdel B, Kutateladze M and Kuhl S (2016). Saint Peter, hospital family and medicine residency. England: Fish 2016.

307. Kutateladze M and Adamia R (2008). Phase therapy experience at the Eliava Institute. *Medical Maladies Infections* 38 (8): 426-430 [doi: 10.1016/j.medmal.2008.06.023]

308. Wright A, Hawkins CH, Anggard EE and Harper DR (2009). A controlled clinical trial of a therapeutic bacteriophage preparation in chronic otitis due to antibiotic-resistant *Pseudomonas aeruginosa:* A preliminary report of efficacy. *Clinical Otolaryngol* 34(4): 349-357 [doi: 10.1111/j.1749-4486.2009.01973.x]

309. Herbener SJ (2023). Reducing antibiotics does not reverse antimicrobial resistance. alltech.com/blog/ reducing-antibiotics-does-not-reverse-antimicrobial-resistance#

310. Dubey KK, Indu and Sharma M (2020). Reprogramming of antibiotics to combact antimicrobial resistance. *Archiv der Pharmazie* 353 (11): e2000168

311. Liu Y, Li R, Xiao X and Wang Z (2019). Antibiotic adjuvants: an alternative approach to overcome multi-drug resistant Gram-negative bacteria. *Critical Reviews in Microbiology* 45(3): 301-314

312. Brown D (2015). Antibiotic resistance breakers: can repurposed drugs fill the antibiotic discovery void? *Nature Reviews Drug Discovery* 14(12): 821-832

313. Duncan C (2022). Scientists discover new approach to fighting antibiotic resistance. imperial.ac.uk/news/234060/scientists-discover-new-approach-to-fighting-antibiotic-resistance/

214. Soares JM, Yakovlev VV, Blanco KC and Bagnato VS (2023). Recovering the susceptibility of antibiotic-resisatnt bacteria using photooxidatve damage. *Microbiology* 120 (39): e2311667120 [doi: 10.1073/pnas.2311667120]

315. Sundqvist M (2014). Reversibility of antibiotic resistance. *Upsala Journal of Medical Science* 119(2): 142-148 [doi: 10.3109/03009734.2014.903323]