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Antimicrobial Drug Resistance: A Systematic Review and Assessment of Resistant Pathogen Infection Prevention and Control

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ABSTRACT

A significant proportion of antibacterial drug prescriptions in both inpatient and outpatient healthcare are inappropriate. Sub-therapeutic use of antibiotics during therapy does not destroy the causative pathogen or resolve clinical symptoms but enhances the emergence of resistant organisms. Prescription and dispensing procedures based on diagnoses, microbiology reports, guidelines and recommendations for drug use and the knowledge of local resistance patterns determine to some extent the clinical benefits that may result from the administered drug. Antibacterial consumption patterns are not usually driven by changes in demographic and disease patterns. Economic, cultural and microbiological factors form the basis for the use of antimicrobials. Differences in the extent of disease, the pathogenicity of the infecting organism, the effectiveness of cellular and humoral immunity and the period before therapy are initiated all influence the outcome of treatment. The variety of patients and infections lead to diverse variations in both the pharmacokinetics and pharmacodynamics profiles of antimicrobial drugs. Therefore, most government health system models are usually interventions to compensate for the market's reluctance to ensure the inclusion of the most vulnerable groups. Inequalities in antibacterial access are preventable through proper policies that address socioeconomic inequalities. The multifactorial nature of antimicrobial resistance demands the expertise and resources of the different service chains as well as comprehensiveness in policy coordination and integration. Therefore, antimicrobial stewardship is needed in training programs for health professionals to reduce the improper use of antimicrobials.

KEYWORDS

Antimicrobial therapy, infections, drug resistance, vaccine, pathogen transmission, pathogen adaptive mechanism, resistant microbes

INTRODUCTION

Globally, access to health care, drugs use practices, preferences of healthcare providers and patients and the variation between knowledge and practice reflect local medication policies. In societies where regulations are stringent regarding infection prevention through good animal husbandry, bio-security and the use of alternative measures (vaccines), there are occasions when infections and diseases occur.

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Tackling infections, diseases and overall well-being are core to the long-term economic development of nations. Antimicrobial drug resistance is a phenomenon that evolves through cell mutation, natural selection, or abrupt changes (acquisition of pathogenicity) in the environment. It is exacerbated by lifestyle changes, which might have devastating effects on ancestral beneficial microbes. It disseminates via multiple processes, such as genetic material exchange and, more likely, through plasmid transmission[1]. This exchange of genetic material and plasmid transmission leads to the transfer of resistant determinants between microorganisms[2]. Other means include a non-food mechanism (contact with the infected animals), food mechanisms (eating contaminated food) and treating infections in crops. Land application of antibiotic-laced manure releases antibiotics to the terrestrial environment, groundwater and genetic-resistant determinants in the food chain, humans and animals[3,4]. Food animals are not only vehicles of antimicrobial pathogen transmission, but also help in the propagation, selection and spread of resistant microbes and resistant genes[5]. Sub-therapeutic use of antibiotics in animal feed and water leads to quicker growth and improved feed efficiency[6,7] but results in increased antimicrobial resistance[8].

The goals of therapy are to destroy the causative pathogen, stimulate the resolution of clinical symptoms and inhibit the emergence of resistant organisms[9]. The causative agents of infectious diseases are microorganisms (viruses, bacteria, fungi and protozoa) that exist in water, air and soil. Poor infection control practices, inadequate sanitation and inappropriate food-handling encourage the spread of antimicrobial resistance. The survival of the propagules is dependent on the dose of the therapeutic agent received[10,11]. Thus, microbial infection therapy management efficiencies affect the spread of resistant pathogens. Therapy management that is based on reducing the amount of inoculum produced within a community is vulnerable to increased regional inoculum loads. It may cause microbial imbalances that enhance the risk of infection by multidrug-resistant organisms[12]. The administration of antimicrobials to livestock can result in the emergence of antimicrobial-resistant microbes and the selection of resistant veterinary pathogens[13]. Antimicrobial therapy can induce transient inhabitants of the host to become resistant. Antimicrobial agents might also increase the number of transfer genes from the increased pool of resistant cells[14] thereby playing a key role in the introduction of resistance determinants that have the potential to transfer to the commensal microbiota[15].

Resistance increases the chance that a patient receives inadequate therapy and thus further increases the risks and costs associated with nosocomial infection[16]. The rise of antimicrobial resistance (AMR) is being accelerated by excessive or inappropriate antibacterial and antifungal use (stewardship), while millions of people currently live without reliable access to such products. Both issues are closely interlinked as the need to enhance access where necessary must be balanced with that of ensuring optimal and appropriate use. The huge burden of severe antimicrobial resistance is exacerbated by the lack of clinics and hospitals to diagnose and appropriately treat microbial infections and the widespread availability of antimicrobial drugs without prescription. The monitoring, control and prevention of antimicrobial resistance are challenging. Resistant microbes are versatile, resilient and dangerous human pathogens that make some microbial infection treatments most challenging.

BARRIERS TO RESISTANT PATHOGEN INFECTION PREVENTION AND CONTROL

ANTIMICROBIAL USE STRATEGIES

A significant proportion of antimicrobial use in both inpatient and outpatient healthcare is inappropriate[17,18]. Difficulty inappropriate antimicrobial agent selection is due to a lack of diagnostic facilities, lack of basic drug information knowledge, high out-of-pocket payment expenditures and experience of the professional contributor. Table 1 outlines the differences between appropriate and inappropriate antimicrobial use.

Table 1: Differences between appropriate and inappropriate antimicrobial use[18]

Appropriate	Inappropriate
Antimicrobial drug inhibits microbial growth and the dosage is appropriately adjusted for serum levels	Choice of drug can inhibit microbial growth, but the dosage is not appropriately adjusted for serum levels
Serum levels are determined before and drugs inhibit microbial growth. Patients who had renal insufficiency received nephrotoxicand drugs and infections therapy require high doses	Choice of drug can inhibit microbial growth but share rum levels not determined
Appropriate drug administered with appropriate dose	Choice of the drug is appropriate, but the loading dose is unknown
Appropriate choice of drug and duration of therapy appropriately chosen	Appropriate choice of drug, but the duration of therapy chosen inappropriate
Appropriate choice of drug, dosage altered for patient's current level of renal or hepatic function	Appropriate choice of drug, but dosage not altered for patient's current level of renal or hepatic function
Appropriate choice of drug with appropriate dosage	Appropriate choice of drug, but the dosage inappropriate
Antimicrobial agents are effective against causative pathogens. Based on culture and susceptibility tests or for empiric therapy-on the identity of the expected pathogen and its predicted susceptibility	Antimicrobial agents are not effective against causative pathogens
Antimicrobial agents are not toxic or allergic	Antimicrobial agent is toxic or allergic
Antimicrobial agent is needed for therapy. Clinical circumstances and microbiologic data warrant drug coverage provided by a particular agent	Antimicrobial agent is not needed for therapy. Patient had no evidence of infection
An inexpensive antimicrobial agent effectively inhibited causative pathogen proliferation	Choice of antimicrobial agents is unnecessarily expensive. A substantial difference in cost is not accompanied by a significant therapeutic advantage
Deteriorating clinical status of patient checked by an antimicrobial agent. Drugs had activity against the identified or suspected pathogens	Choice of an antimicrobial agent does not prevent the deteriorating clinical status of the patient. Drugs with redundant coverage were employed

CONFLICTS OF INTERESTS AND HEALTH SYSTEMS

Health services are provided by a variety of organizations and health professionals, including medical practitioners, nurses, allied and other health professionals, hospitals, clinics, pharmacies and government and non-government agencies. Together, they deliver a wide range of services, from public health and preventive services in the community to primary health care, emergency health services, hospital-based treatment in public and private hospitals and rehabilitation and palliative care. These health services are supported by many other agencies. The research and statistical bodies provide information for disease prevention, detection, monitoring, diagnosis, treatment, care and associated policy, consumer and advocacy groups contribute to public debate and policy development and universities and health services (among others) contribute to the training of health professionals. Voluntary and community organizations and agencies also make important contributions, including raising money for health services and research, running educational and health promotion programs, coordinating voluntary care and funding and delivering a range of health services. However, human entanglement with social, political and economic environments affects the optimal performance of the health systems.

COMPARATIVE ECONOMICS OF ANTIMICROBIAL AGENTS' COSTS

The affordability of antimicrobial drugs is a challenge. The general pattern in world pharmaceutical market sales is that wealthier countries have access to varieties of antimicrobials while low-income ones are limited (Fig. 1). The huge burden of severe antimicrobial resistance is exacerbated in some regions, by a lack of quality antimicrobials to appropriately treat microbial infections among others. Limited access to antimicrobials in resource-deficient countries, especially least-developed countries markup has high markup costs that unnecessarily inflate the prices of essential medicines. These include distribution costs, import tariffs, port charges, importers' margins, value-added taxes on medicines and high margins in the wholesale and retail components of the supply chain.

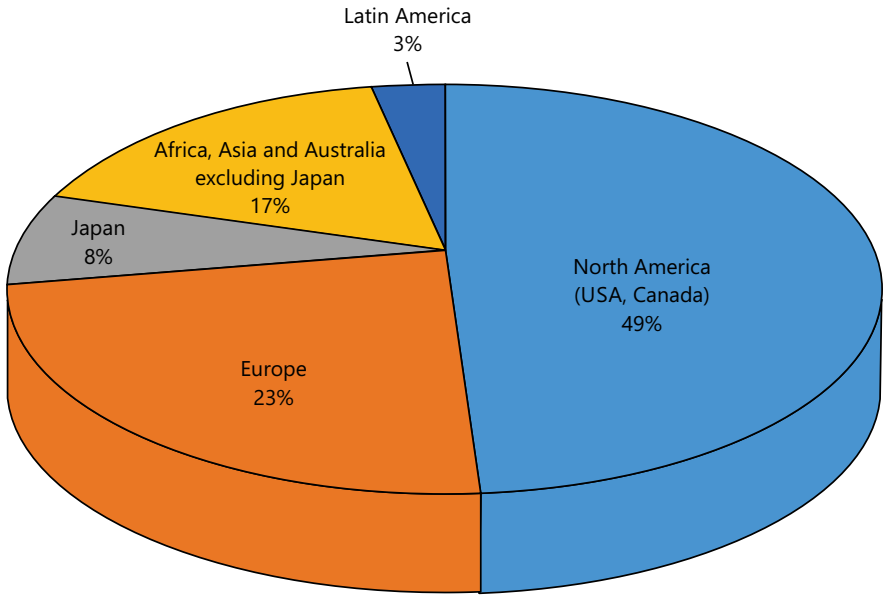

Fig. 1: Breakdown of the World Pharmaceutical Market-2018 Sales[19]

Economic, cultural and microbiological factors form the basis for the use of antimicrobials in both ambulatory and inpatient settings. Thus, antimicrobial drug costs vary across the globe. Driven by changes in demographic disease patterns, the introduction of new and expensive drugs. Income (per capita GDP), population age structure and epidemiological needs, technological progress and variation in medical practice, health system characteristics (service provision, health financing, external funds, provider payment mechanisms and the increase of relative prices of some services vis-à-vis other goods and services in the economy) influence cost differentials[20]. Other factors include an increase in microbial infections, a rise in the number of prescriptions per recipient per year (patients with multiple illnesses chronically use multiple drugs), higher antimicrobial drugs prices and the introduction of new, more expensive antimicrobials. Thus, to mitigate the apparent unfair allocation of antimicrobial development costs, governments, as the largest public guarantors of prescription drugs for low-income, elderly and disabled persons, impose drug cost regulations. However, such regulations must balance the demands of a public that expects constant advances in medical technology against the financial needs of the pharmaceutical companies that conduct research and produce life-saving drugs. Foreign price regulations have vast impacts on the producer-state drug market.

Minimising antimicrobials costs: Antimicrobial agents are among the most frequently prescribed drugs. In animal health products for commercial livestock, feed additives, in agriculture as prophylactics or growth-promoting agents. In a tertiary care facility, antimicrobials may account for over 40% of the pharmacy's drug acquisition costs. The use is significantly increasing daily with escalating drug acquisition costs. As a result, this class of drugs is targeted for increased scrutiny during an era of expenditure reduction.

The high cost of antimicrobial drugs has accelerated the development of containment strategies. This includes education, formulary restriction (i.e., mandatory approval of certain restricted antibiotics by clinical pharmacists or infectious diseases specialists), pharmacy justification, formulary substitution, early switch from intravenous to oral delivery, computer surveillance and multidisciplinary approaches. The strategies are used to implement guidelines and antimicrobial-control programs to reduce costs and limit the emergence and spread of antimicrobial-resistant organisms[21].

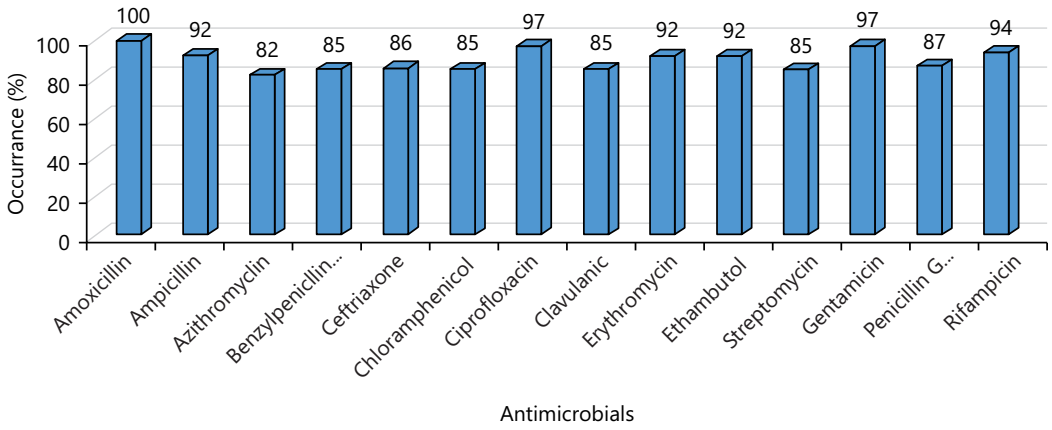

Fig 2: Most common antimicrobials in lists of essential medicines[22]

Antimicrobial essential drugs: The WHO essential medicines list (Fig. 2) is used by many nations as a guide to developing their lists. The lists include information on which antimicrobials to use for common infections, as well as for more serious conditions. This is to ensure the availability of the required antibiotics and the appropriate prescription of antibiotics for a specific infection, further enhancing treatment outcomes and reducing the development of antimicrobial resistance.

Essential antimicrobial drugs are cost-effective tools for fighting microbial infections. They have intense health influence, increase health system effectiveness, as well as increase the cost-effectiveness of pharmaceutical expenditure. The list is intended for all stakeholders involved in managing antimicrobial resistance and ensures that all antimicrobials are used appropriately in human and veterinary medicine.

State-financed subsidy programs: The state may finance the procurement of antimicrobials by the elderly or disabled individuals who do not qualify for health insurance benefits but who nonetheless meet mandated income guidelines. Antimicrobial supply partnerships between governments and pharmaceutical companies facilitate and pool product demand/costs globally, tiered pricing structures or donations/discounts. Donations can be helpful in the short period, especially where shortages exist and for the poorest populations, but are not sustainable. Such collaborations may lead to lower prices while maintaining incentives for companies to continue to make needed products.

Voluntary budget cap for antimicrobials: The government and the pharmaceutical industry agreed on a voluntary budget cap for antimicrobials as a means of controlling costs. This budget cap ensures that the pharmaceutical industry pays back the percent excess over antimicrobial expenses. However, this repayment may apply to expenses between a certain percentage. Those expenses outside these confines are not subject to return.

Therapeutic or prophylactic antimicrobials pattern: The reduction in the incidence of infection and resistance may be achieved by a combination of different drugs[23]. The cost of treatment is an important factor to be considered in deciding the drug combinations. The cost of antimicrobials imposes an enormous burden on the patient as well as the health care system. Many researchers consider the economic aspect of antimicrobial therapy to be an important cost component of cesarean section[23]. Therefore, the treatment plan in Caesarean Section could reflect the following antimicrobial combination[23].

- A = Cephradine+Metronidazole
- B = Third-generation Cephalosporin+Metronidazole
- C = Amoxycillin+Metronidazole+Gentamicin
- D = Ciprofloxacin+Metronidazole
- E = Cephradine+Metronidazole+Gentamicin
- F = Amoxycillin+Metronidazole+Gentamicin

Table 2: Therapeutic interchanges[24]

Original drug and dose	Substituted drug and dose
Ampicillin 250-500 mg q6h po	Amoxicillin 250-500 mg q8h po
Cephalothin 1-2 g q4h IV	Cefazolin 1-2 g q8h IV
Clindamycin 600 mg q6h IV	Clindamycin 600 mg q8h IV
Vancomycin 125 mg q6h po	Metronidazole 500 mg q8h po

IV Intravenously, po Orally

Programmed therapeutic substitutions: This policy involves the substitution of a drug (cephalosporins with quinolones) with an equivalent (change to a different class of agent) usually to employ a less expensive regimen for a costly one. When an antimicrobial in the programmed list is ordered by a physician, the drug is substituted by a therapeutic equivalent (Table 2). The substitution is effected immediately and physicians are informed of the switch through the patient's medical records. The advent of broad-spectrum antimicrobial agents had made such a technique popular.

Antimicrobial restriction policy: In this policy, very expensive antimicrobial drugs are labeled as restricted drugs. Restricted drug use is allowed only if for an approved indication for a specified period. The indications are printed on the restricted drug order form, which had to be completed and signed by the prescribing physician before the release of the drug by the pharmacy. The forms are reviewed daily by the pharmacy personnel and served as a quality assurance activity safeguarding appropriate antimicrobials prescription. As with other antimicrobials, specified therapy duration is also in effect to encourage reassessment of the need for further therapy with the restricted drugs.

This section will focus on restriction policies that require the approval of a designated physician or clinical pharmacist for the use of certain agents. Several innovative methods of justification have been utilized to control antibiotic usage. These are manifested in a variety of restriction and approval mechanisms, such as direct communication with the pharmacy, antibiotic order forms (written justification), implementation of control categories and automatic stop orders. These processes may or may not involve an infectious diseases physician's added approval or consultation. These strategies are probably the most onerous to prescribing physicians, yet they stand as some of the more effective methods of controlling the antimicrobial budget.

Enforcing a restricting policy can be difficult, particularly in hospitals that have rotating house staff.

Parenteral to oral conversion: This strategy requires the listing of specific antimicrobials available in parenteral and oral forms with appropriate pharmacokinetic properties and bioavailability profiles. Oral administration of such agents is considered an alternative to the parenteral route if a patient can swallow and had a functioning gastrointestinal tract. Whenever parenteral drugs are ordered, a yellow sticker giving the cost and dosage details of the oral formulation is affixed to the chart as a reminder to the physician that oral treatment should be considered.

Computer surveillance: The user computer may be the ultimate method for antimicrobial surveillance and education. The unique feature of computerized surveillance is the opportunity for instant feedback, education and a seamless adjustment in the preference for a certain agent(s)[25]. Drug utilization review can be performed efficiently when a computerized ordering system forms the basis of the database. A computer-assisted antimicrobial order-entry program can select a specific drug and designate its purpose for use. When prompted, the computer informs the physician if a restricted antimicrobial has been ordered. There are also programmed dosing selections. Combining the ordering data within vitro susceptibility information from the clinical microbiology laboratories allows for rapid feedback to prescribers.

Multidisciplinary control programs: The use of a multidisciplinary antimicrobial utilization committee that involves input from various hospital services like infectious diseases, clinical pharmacy, infection control and nursing could particularly aid the proper administration of drugs. There were two major components of the system. The first was based on consultation by infectious disease physicians for empirical therapy, focusing on cases of unreasonable empiricism. The second was streamlining by an antimicrobial specialist. Streamlining involved simplifying the antimicrobial regimen, switching to oral antimicrobials early in the course of therapy, or shortening therapy.

NATURAL HISTORY OF ANTIMICROBIAL RESISTANCE IN COLONIZING ORGANISMS WITHOUT ANTIMICROBIAL THERAPY

High microbiota richness, evenness, diversity and metabolic adaptation of microbes in an ecosystem ensure their stability both as non-pathogenic and pathogenic organisms. Microbes rapidly alter their physiology and cellular activities through metabolic modifications to enhance their fitness under varying conditions, allowing their persistence and circulation between environments and also the nature of their pathogenesis[26]. This stable microbial diversity counteracts the spread of resistance by resisting the mobilization of resistance genes, mutations, horizontal gene transfer, selection and transmission of resistance between environments. The stability of the microbiota, especially during nutritional challenge conditions allows the use of resources more efficiently[27,28]. Coping with stress (environmental fluctuations that perturbs homeostasis) in an organism's life requires adaptation to changes in the environment that maintains an inner balance at the molecular level (suitable physiological adaptations). This adaptation can be achieved through inter-and intracellular communication involving the building blocks of life, DNA, RNA and proteins (enzymes, aminoglycoside modification enzymes, including N-acetyl transferases, O-phosphotransferases and O-adenyltransferases). These molecules are activated upon exposure to harsh conditions.

Exposing microbial communities to different selective agents or mixtures, affect the stability and resilience of the microbiome to biological invasions. Long-term persistence of stress might lead to increased stabilization of microbial populations that might persist for years[29-31]. In the adhering state, the pathogens may be more resistant than cells in the planktonic state[32].

Antimicrobial-resistant pathogens are also transmitted through aerosols (droplets generated when talking, sneezing, coughing, or vomiting). Foodborne pathogens can be transferred and survive on currency, utensils and fabrics. The pathogen may be covered with a thin layer of organic matter that aids its survival, e.g., utensils and equipment covered with food soil. The pathogen may be protected from environmental stress and death by mucus, sputum, face, blood, milk, or chicken broth for long periods. Death rates vary for different species of microbes. Entero-viruses are resistant to physicochemical inactivation and must be removed by vigorous friction applied during hand washing or drying.

Identical resistance genes found in many different genetic contexts indicate that these pathogens can bypass host restrictions imposed on a given mobile element. Specific genetic determinants and several interdependent factors spanning human and animal health, pharmaceuticals, food and agriculture, environment, trade and finance contribute to antimicrobial resistance pathogens survival, adaptation outside the host, or subsequent transmission, making it one of the most complex public health challenges globally.

ANTIMICROBIAL RESISTANCE AND REDUCED FITNESS IN MICROORGANISMS

Antimicrobial resistance determinants are typically acquired through and located on mobile genetic elements (MGE), allowing their horizontal transfer to other strains (pathogens, commensal, or even environmental) or even across bacteria from different taxa. Genes in naturally resistant environmental bacteria are vertically inherited, shared by most isolates of the same species, often encoded by the

chromosome and usually immobile. The genomic changes underlying the acquisition of resistance unique mutation can occur in phage integrase (int), Sensor Histidine Kinase (cpxA), ATP-dependent serine endopeptidase La (lon), cytochrome c-type Biogenesis Protein (ccmF), ATP-dependent DNA helicase (dinG), iron Sulphur Protein Assembly (hscA) and the 16S-23S rRNA internal transcribed spacer (ITS) regions of the genome. The DNA-damaging chemicals or irradiation increase the proportion of mutants in a population. This gives different adaptive outcomes to microbes in new environments because of the increased mutation supply in a population. The level of fitness obtained in an environmental transition through a controlled response may not be as high as that possibly available in a mutant present in the population. The new environment can either reduce or increase the growth rate, in either case, the response in the new environment will change patterns of gene expression as well as the fitness of the mutants.

In every environment, microbial cells vary in size and chemical composition. These phenotypic alterations are usually triggered through specific environmental conditions and population dynamics[33]. A mutant present in a large population with a growth advantage in the new environment can become highly enriched depending on its fitness increase. Given a large enough fitness difference, mutations in a gene can become large populations within a short time. In even more extreme selections, such as for high-level antibiotic resistance, survivors will be solely from the selection and multiplication of resistant mutants over all phases of adaptation.

Environments with a wide range of microbial exposures like houseplants, traditional farms and regularly aired spaces maintain higher diversity in resistance genes compared to strong microbial control environments (intensive care units and industrially used clean rooms). Increased confinement and cleaning are associated with a loss of diversity.

ANTIMICROBIALS HALF-LIVES AND RESISTANCE DEVELOPMENT IN PATHOGENS AND NORMAL FLORA

Antimicrobial compounds can influence cellular processes (differentiation, migration, proliferation and apoptosis), thereby featuring pleiotropic physiological or pathophysiological effects on the host. The use of antimicrobial drugs can lead to the emergence of resistant pathogens either by mutation or by horizontal gene transfer. These compounds can also negatively affect the development of microbes, e.g., the inactivation of a regulatory protein (repressor protein/receptor protein). Drug-induced resistance mutation depends significantly on already existing mutants at appreciable levels in the population at the time point when the pathogen population is first exposed. However, when no drug-resistance mutations exist before treatment initiation, mutations may emerge by chance from the population. Thus, mutation and immigration can lead to appreciable levels of drug-resistance mutations in pathogen populations not exposed to drugs, particularly when selection against these mutations is weak. Once the first resistant strain has appeared in the local population, it is subject to selection by drugs, depending on specific pharmacodynamics and pharmacokinetics. Antimicrobial compounds, therefore, provide a mutual link between the host-microbiome compositional and functional configuration. The type, composition and concentration of antimicrobial compounds coupled with the host sensor molecules repertoire orchestrate the net physiological response at a given physiological context.

ANTIMICROBIALS SELECTION TENDENCY FOR RESISTANCE

Antimicrobials are the only drug class whose use influences not just the patient being treated but the entire ecosystem, with potentially profound consequences. Each drug class has significant therapeutic limitations, ranging from toxicity to drug resistance to limited routes of administration. The excessive and indiscriminate use of antimicrobial compounds in both human and veterinary practices leads to the emergence and dissemination of resistant organisms that endanger their efficacy. antimicrobial compounds as well cause a high abundance of resistance genes, including those in human pathogens[33].

Resistance genes have occurred for aminoglycoside, glycopeptide, macrolide and tetracycline[34]. There is a link between antimicrobial consumption and resistance[35]. However, antimicrobial drug resistance profiles vary between developed and developing countries. High consumption of antimicrobial agents and resistance, predisposes to cross-resistance to all classes of drugs and thus masks the effects of antimicrobial use and resistance for other classes of drugs.

Antimicrobial agents may produce an apparent increase in biodiversity or at least the emergence of new taxons whose presence was minor before antimicrobial-induced stress if the most predominant species present in the microbiome are susceptible and hence inhibited by such concentrations. Cross-transmission studies indicate that isolates from humans, farm animals, companion animals and rodents are morphologically and developmentally similar, differing in host specificity, pre-manifest and manifest periods and pathogenicity[36]. Resistance manifestations are leading to continuous changes in recommendations for antimicrobial therapy. Thus, resistance manifestations are leading to continuous changes in recommendations for antimicrobial therapy[37].

Fluoroquinolone resistance is commonly associated with point mutations in DNA gyrase (gyrA, gyrB) and topoisomerase IV (parC, parE) genes. Mutations within the Quinolone Resistance-Determining Regions (QRDRs) of these genes can occur spontaneously or with the intentional application of selective pressure. Methicillin-resistant strains occur in community-acquired infections. Non-typhoidal salmonella infections in humans are multidrug-resistant. *Staphylococcus aureus* has developed resistance to most classes of antimicrobial agents like erythromycin, clindamycin and tetracycline. By destroying penicillin by penicillinase, S. *aureus* became resistant to penicillin.

Antimicrobials and biocides impose stress on microorganisms during prophylactic or therapeutic uses as well as in animal growth promotion.

Antimicrobial consumption pattern:

β-lactam/inhibitor constituting	19.2%
Fluoroquinolones	15%
Third-generation cephalosporins	11%
Aminoglycosides	9%
Carbapenems	3.6%

Antimicrobial resistance pattern:

A. baumannii third-generation cephalosporins	88%
Fluoroquinolones	86%
Aminoglycosides	80%
β-lactam/inhibitor combinations	80%
Carbapenems	74%

PHARMACOKINETIC AND PHARMACODYNAMIC FACTORS THAT DETERMINE AN ANTIMICROBIAL MAXIMUM EFFICACY AND MINIMUM EMERGENCE OF RESISTANCE

The pharmacokinetic and pharmacodynamic profiles of various antimicrobial agents are different. Some compound inhibition/elimination capacity depends on the drug peak concentration and some work best at dosing intervals of 50 to 70% drug concentration. Therefore, while some antimicrobial compounds are given in bolus doses once daily to achieve high peak values and low average values (to reduce toxicity), others may work better when they are given by continuous infusion[38]. Pharmacodynamic studies provide a rational basis for antimicrobial dosing in animals[39]. It can determine optimal therapeutic regimens to reduce the carriage of resistant organisms. Short bursts of therapy followed by long intervals impose selective pressure on cells[40,41]. Appropriate prescription of antimicrobials may slow the rate at which resistance becomes widespread throughout a community.

Pharmacokinetic-pharmacodynamic (PKPD) gives the association between dose, concentration, desired effects and side effects of a drug. The PKPD ascertains the concentration that leads to the desired effect and the dosing regimen that will result in the target concentration range. The exposure of pathogens to antimicrobial drug concentrations below the minimal inhibitory concentrations (MICs) during therapy may encourage the emergence of resistance especially in drugs with time-dependent killing mechanisms.

High doses academically lead to higher peak serum drug concentrations. Under-dosing presents treatment failures and antimicrobial resistance. Drug administration at higher doses seems superior to the more frequent administration at the same dose but may present side effects.

Drug distribution and elimination: Electrochemical gradient mechanisms drive the uptake of numerous metabolites and xenobiotics against a concentration gradient including amino acids, peptides, vitamins, metals, salts, nucleic acids, drugs and environmental toxins.

Administered drugs' absorption, distribution and metabolism are affected by environmental, systemic and genetic factors before the drug reaches the target site[42]. The extent of the agent-induced Iterations in the microbiota depends on:

- Spectrum of the agent
- Dosage and duration of treatment
- Route of administration
- Pharmacokinetic and pharmacodynamics properties of the agent

The use of higher doses could lead to either an increase or a decrease in drug clearance. Saturable renal tubular reabsorption can lead to higher concentrations. Antimicrobial compound administration in patients with renal failure, the trans-intestinal elimination can increase substantially, thereby decreasing drug levels[38].

Drug resistance revolves around the reduction in the intracellular concentration of active drugs by such mechanisms as the downregulation of equilibrative nucleoside transporter (ENT1), mutation of drug-activating salvage enzymes and increased expression of drug efflux transporters[43].

Total body clearance: Drugs are metabolized in the gastrointestinal tract, lungs, kidneys and brain. However, drug metabolism is majorly done in the liver. Renal excretion plays a pivotal role in terminating the biological activity of some drugs, particularly those that have small molecular volumes or possess polar characteristics, such as functional groups that are fully ionized at physiologic pH. Most drugs would have a prolonged duration of action if termination of their action depended solely on renal excretion. Individuals with compromised liver function may rely on intestinal metabolism for drug elimination. Compromise of intestinal metabolism of certain drugs can also result in a significant elevation of their plasma levels and clinically relevant drug-drug interactions. This may greatly limit the bioavailability of orally administered drugs alternative routes of administration must be used to achieve therapeutically effective blood levels.

Volume of distribution: Antimicrobial drugs are not bonded to protein, concentrations diffused into extravascular tissue, lipid-soluble concentration and the volume of blood flow determines the volume of antimicrobial agent distribution in an organism. The amount of free drugs present in serum governs the level of drugs in tissues since the maximal concentration of free drugs in tissue cannot exceed the level of free drugs in serum.

Protein binding: The human and animal innate immune system is comprised of cells and proteins which can recognize molecular patterns common to invading microorganisms[44]. These systems selectively recognize invading microbial endotoxins (lipopolysaccharides and lipo-oligosaccharides) and unique surface glycolipids. These molecules affect the elimination of viable microbes and their remnants before significant multiplying and dissemination ensue. Microbes secrete proteins that facilitate their attachment and circumvention and/or suppression of the host's immune system to successfully provide an opportunity for disease transmission. The effector complex constitutes the structural part of machinery responsible for contact and communication with the host. Then the innate immune cells recognize the specific molecular patterns derived from pathogens that secrete a cocktail of effector proteins (enzymes) whose expression correlates with distinct phases of colonization. These effector proteins or their mimics exploit existing antagonistic interactions in the host hormone signaling networks, thereby dampening their immunity. Pathogen-Associated Molecular Patterns (PAMPs) are derived from microorganisms and recognized by Pattern Recognition Receptors (PRRs) found on innate immune cells as well as many epithelial cells. Toll-Like Receptors (TLRs) are germline-encoded PRRs that play a central role in host cell recognition and responses to microbial pathogens.

Pathogenic bacteria use arginine for self-preservation. Arginase produced by bacteria can also compete with iNOS of host cells for arginine, thereby inhibiting the NO production and facilitating evasion of the host defense system[45]. The competition between arginase and iNOS is reported to affect the outcome of infection of several pathogenic bacteria by modulating the NO production[46]. As a survival strategy, *Helicobacter pylori* releases its arginase to downregulate eukaryotic NO production to evade the host immune response[45]. Arginase is implicated in bacterial infection caused by *Mycobacterium tuberculosis*[47].

Bioavailability: Many chemicals require the activation of electrophilic intermediates to exert their effects[48]. However, if detoxified, these reactive species cannot react but functionally modify nucleophilic moieties on the peptidoglycan molecules.

Metabolizing enzymes and drug transporters which are critical determinants of drug efficacy and toxicity show significant differences based on gender, age, race/ethnicity, genetics (polymorphisms) and a variety of external factors (such as diet and lifestyle). For instance, transporters in the gastrointestinal tract affect drug absorption by increasing uptake (uptake transporters) or by limiting drug absorption (efflux transporters).

Macrolides target areas on the ribosomal RNA in this organism. Modification of the target site, resulting from methylation of ribosomal RNA, confers resistance to the entire Macrolide-Lincosamide-Streptogramin B (MLSB) family of antibiotics. This form of resistance is mediated by by-products of the germ genes and can be inducible (i.e., activated on exposure to the antibiotic) or constitutive (i.e., expressed at all times).

MATHEMATICAL MODELLING AND THRESHOLD RESISTANCE RATES

Interpreting the current patterns of evolution and spread of resistant pathogens as well as addressing the issue of how best to manage antibiotic resistance in both the healthcare and community settings requires simple and complex mathematical models of the key biological processes.

Mathematical models are used in pharmacokinetics to study drug absorption and elimination kinetics. The mathematical integration of the serum concentration-time curve (surface area) and the peak concentration (C_{max}) reveals the capacity of any antimicrobial compound ability to inhibit microbial growth. The effect of an antibiotic on the target pathogen usually correlates with the concentration of the drug in the habitat

of the pathogens. Antibiotics may be administered either orally, intramuscularly or intravenously and the eventual concentration of active drug at the site of infection will be determined by the dose, the route of administration and the dosage regimen. Dosage regimens are designed to maintain drug concentrations at therapeutic levels and must balance issues of both toxicity and efficacy.

EFFECTIVE ANTIMICROBIAL RESISTANCE PREVENTION AND CONTROL

The management of infections caused by pathogens is an enduring challenge worsened by the complexity of chains in the healthcare system. These diverse chains with diverse financing, contractual and regulatory arrangements as well as associated incentive structures, produce unintended effects on the healthcare systems like reduced use of cost-effective drug therapies, resulting in declines in health status, substitution of less effective, more toxic or more expensive antimicrobial agents and increased utilization of costly physician or institutional care (e.g., hospitals and nursing homes). Effective antimicrobial resistance control requires planning of supply, the funding of research and innovation, the regulation and training of medical and pharmaceutical professions and the establishment and control of medical and pharmaceutical standards.

PRESCRIBING AND DISPENSING ANTIMICROBIAL DRUGS

The responsible recommendation and subsequent provision of drug therapy to attain certain consequences that improve patient's quality of life by clinicians is known as prescription and dispensing respectively. These procedures are common in healthcare but important. They determine to some extent the clinical benefits as well as the adverse effects that may result from the administered drug. However, lapses in these procedures, resulting in treatment failures and increased healthcare costs. The manifestations of treatment failures may result from inappropriate prescription to patients with definite contraindications or renal failure, complications of hypovolaemia and electrolyte disturbances. Clinicians may also prescribe antimicrobial drugs to treat microbial infections, using inadequate criteria for diagnosis of infections that potentially have a different microbial etiology, unnecessarily prescribing expensive, broad-spectrum agents and not following established recommendations for using chemoprophylaxis.

The variety of patients and infections lead to diverse variations in both the pharmacokinetics and pharmacodynamics profiles of antimicrobial drugs. These variations result in diverse drug-drug interactions, drug-disease interactions, prescribing and dispensing and adverse drug reactions. Therefore, the prescription and dispensing of antimicrobial agents require that the clinicians are skilled in the selection of agents based on the characteristics of the infection to their pathogens and susceptibilities, sites of infection, drug absorption, distribution and elimination, comorbidities and a consideration of the benefits versus the risks of antimicrobial therapy. Antimicrobial agents are essential in the therapy of microbial infections but the right treatments should be delivered to the right patient at the right time. The heterogeneity of the health statuses of patients generalizes prescribing and dispensing decisions across the entire patient population very complicated. Prescribing, dispensing and administering antimicrobials in practice needs to start from an honest appraisal of the modest benefits achieved by such treatment. The achievement of such is not simple. It requires a willingness to address complex and sometimes controversial scientific, medical and economic issues.

Prescription of antimicrobial agents: Based on diagnoses, microbiology reports, guidelines and recommendations for antimicrobial drug use and the knowledge of local resistance patterns, the following categorization of prescription patterns is known. The variations reflect differences in the characteristics of the patient being treated, pathogens identified or suspected, prescribers' characteristics (fund of knowledge, ability and willingness to apply this knowledge), the severity of infection, expectations of patients and their families, local availability of drugs, promotional efforts of the pharmaceutical industry and economic and legal considerations.

Prescription when no antimicrobial drug therapy is justified: A common misconception that the use of antimicrobials supersedes other, more basic therapies encourages the use of antimicrobial agents as substitutes for the careful use of diagnostic measures. However, antimicrobials differ both in their mechanism of action as well as in the spectrum of microorganisms inhibited. Beta-lactam antibiotics target the bacterial cell wall, aminoglycosides, tetracyclines and macrolides all inhibit translation, fluoroquinolones disturb the DNA gyrase, rifampicins target the RNA polymerase. Thus, infections require a specific class of antimicrobial agents for effective treatment. The choice of drug is based on the results from AMR testing on a case-by-case basis, but usually on treatment procedures. This necessitates continuous changes in antimicrobial therapy[37] including generic substitution to reduce pharmaceutical expenditures[49].

Antimicrobials are recommended in several cases where the specific microbe responsible for the infection cannot be ascertained largely because clinicians cannot make a precise diagnosis. Non-infectious or nonbacterial syndrome, treatment of colonization or contamination, duration of therapy longer than necessary, adjustment not made promptly, redundant antimicrobial coverage, the spectrum of activity not indicated are some of the reasons for the unnecessary use of antimicrobial agents. Non-specific infection prevention even during high-risk periods contributes to the emergence of antimicrobial resistance. Unnecessary overuse of antimicrobials, in addition to imposing a burden on a scarce resource, modifies the ecological balance negatively, giving rise to more and more resistant strains of microorganisms[23]. It is, therefore, likely that most antimicrobial use could be evaded without negative consequences[50]. However, without suitable diagnostic support, clinicians will prescribe antimicrobials just in case their patients might have a bacterial infection, to protect themselves from litigation or to satisfy patient demands.

Inappropriate prescription for a specific condition requiring drug therapy: Diagnostic uncertainty and prescribing by inexperienced physicians. Appropriate therapy guidelines for microbial infections support using stringent clinical criteria for diagnosis to identify specific microbes[51]. Effective interventions to reduce inappropriate prescribing include clinician and patient education, audit-and-feedback, academic detailing, communication training, rapid diagnostics, clinical decision support and delayed prescriptions.

Multi-ingredient formulations/generic combination prescriptions: Prescription of a combination of an antimicrobial drug as a blanket cover for disease-causing microbes in a single episode of infection, without any diagnostic test, is not only unnecessary but also unethical. Prescribing such combinations exposes a patient to higher risks of adverse drug reactions and also increases the chances of drug resistance.

Prescription of suboptimal antimicrobial therapy to treat antimicrobial responsive conditions, interval, duration or route of administration is appropriate

Non-prescription of available, safe and effective drugs

Prescription of appropriate drugs with the improper route of administration, dosages and duration of treatment: Appropriate drug prescription by age group is usually based on national guidelines for diagnoses for which national guidelines could be used to recommend specific antibiotic prescribing rates. Regional variability may be used to produce estimates of appropriate drug prescriptions for diagnoses for which guidelines could not be used to recommend specific prescribing rates.

Prescription of unnecessary expensive drugs: Physicians' prescribing practices may be influenced by socioeconomic factors and the pharmaceutical industry's marketing techniques that include giving incentives to physicians to prescribe certain drugs. As well hospital funding arrangements, which rely on maximising drug sales profits also contribute. Rational prescribing would destroy the revenue base of hospitals, further degrading service quality.

Prescription of less expensive, less toxic, narrower spectrum antimicrobial, choice, route, duration of treatment and dosage being appropriate: Rational therapy calls for the prescription of less-costly single-ingredient drugs more often than costlier combination agents.

Dispensing and administration of antimicrobial agents: For patients to receive antimicrobials appropriate to their clinical needs, in doses that meet individual requirements for an adequate period, the Dispensers are required to label the drug packages of the dispensed drugs with drug name, quantity to be taken and when to be taken. Also, side effects, precautions/interactions/contraindications, the risks of not taking the medicine and storage. The inclusion of all basic necessary dispensing parameters may guarantee its appropriate interpretation. The following dispensing techniques may be encountered.

Appropriate dispensing of prescription: Antimicrobial drugs though administered in form of injectables, tablets, bolus, drench and bath/wash or added to feed and drinking water, are different from all other drug groups since their effects spread far beyond individual patients. Therefore, their prescription for a disease condition considers pharmacological, physiological and anatomical factors, metabolic function, receptor, life span and size in determining dosages, frequencies, or routes of administration.

Body size is important in the rate of distribution of compounds. Smaller animals turn over their blood volumes faster than the bigger ones do. The ratio of blood volume decreases with increasing body weight. Smaller animals have a relatively larger surface area than larger animals[52]. Therefore, small animals excrete compounds more rapidly than larger animals in a rather systematic manner.

The effective minimum and safely administered maximum dosages or dose ranges of drugs given to animals necessitates that lower dose is by intravenous (IV) route while higher doses are by intramuscular (IM) or subcutaneous (SQ) route. Each mode of drug administration has volume limitations. All the prescribed drugs are supplied with appropriate dispensing information. Pharmacists screen prescriptions for possible prescribing errors and significant drug interactions. Pharmacists can discontinue, or change therapy on a patient's behalf. Dispensers explain drug use to the patients. The counseling activities of pharmacists have a vital bearing on patient compliance.

Inappropriate dispensing of prescription: Prescription not dispensed according to prescription. Error in dispensing including inadequate labeling to educate patients on the appropriate mode of use for dispensed drugs, not educating patients about the potential side effects of the drugs and other precautionary measures, for example, whether the drug should be taken with or without food or storage conditions.

Dispensing without prescription or diagnosis: A lag in the ratio between healthcare professionals and the population, limited access to healthcare centers, socio-cultural beliefs, relatively high cost of hospital treatment, previous experience of treatment of the same symptoms and limited controls on the sale or advertisement of antimicrobials create opportunities for misinformation and misperceptions that can exacerbate improper use[53]. Other factors include pressure from patients who believe that antimicrobials cure every ailment, similar drugs taken in the past for similar symptoms and dispensers being more concerned and occupied with serving commercial interests (making sales) than providing appropriate healthcare. Due to the commercial and competitive nature of community pharmacy businesses, pharmacists dispensed broad-spectrum antibiotics without even being requested[54].

Self-antimicrobial medication has many adverse effects and can lead to many problems, including the global emergence of multi-drug resistant pathogens, drug addiction, masking of malignant and potentially fatal diseases, the hazard of misdiagnosis, problems relating to over and under dosage, drug interactions (hypersensitivity, anaphylaxis) and misfortunes relating to the side effect profile of specific antimicrobials.

It may be justifiable during urgent situations. It can aid in the treatment of minor microbial infections that do not require medical consultation and hence reduce the pressure on medical services mostly in disadvantaged societies with limited healthcare resources[55]. Thus, self-medication accompanied by appropriate training on appropriate drug use could mitigate against resistance to pathogens, wastage of resources, prevention and treatment of some minor pathological conditions at an affordable cost as well as minimize serious health hazards with adverse drug reactions and prolonged morbidity.

Dispensing low-quality antimicrobials/poor storage: Low-quality drugs and poor storage facilities influence the inability of physicians to prescribe and administer appropriate drugs for specific infections. Low-quality diagnostic reagents also make it difficult to determine the specific disease pathogens. The identification and detection of microbes in a patient's sample are essential for the optimal antimicrobial therapy of an infected patient and as well for the consequent determination of the appropriate antimicrobial therapy. Many classes of antimicrobials used in food-producing animals have analogs to human therapeutics and are therefore capable of selecting for similar resistance phenotypes.

MEDICAL EDUCATION

Deficiencies in physicians' knowledge of appropriate prescription of antimicrobials encourage the development of resistance. Education is an important strategy in the antimicrobial control program. Educating health professionals on the appropriate prescription and dispense of drugs could be done by direct interaction, either through discussion about the drug order or via a more formal educational program. Another technique could be through the review of the physician's prescribing pattern. Formal educational programs intended to alter antimicrobial prescribing patterns could be through conferences, lectures, audio-visual packages, clinical pharmacy consultations, drug utilization evaluations, hospital newsletters, dissemination of independent sources of information and the development of clinical guidelines or pathways. One-on-one instruction by a utilization expert is also effective. High-quality educational materials from pharmaceutical companies could improve prescribing in a variety of settings. However, educational materials, when used alone-including drug therapy guidelines, protocols, drug bulletins, self-education curricula, or commercially prepared and attractive brochures-may affect knowledge but have little or no effect on the prevalence of inappropriate prescribing practices. Prescribing performance retrospective feedback communicated by influential physicians, tutorials conducted by senior physicians and computerized reminders. However, education as a technique to minimize antimicrobial resistance is limited since the complex interaction of emotional, philosophical and microbiological (pathogenic) factors that contribute to physicians' decision-making processes might not be available at such sessions.

SERVICE INTEGRATION AND COORDINATION OF HEALTHCARE VALUE AND SUPPLY CHAINS

Antimicrobial resistance control requires the implementation of coherent policies from health care value (Consumers, fiscal intermediaries, providers, product intermediaries, manufacturers) and supply chains (health product suppliers, health service suppliers, health product distributors, financial dealers, institutional clients, consumers) that can contribute to, reinforce or improve the performance of each other. Multidimensional public problems like antimicrobial resistance, apart from coordination of the respective chain actors and implementation of coherent policies, also involve the process of making strategic and administrative decisions that would achieve the control of antimicrobial resistance occurrence (policy integration). It means that there are instruments for the various chains to execute actions in an integrated logic. The drug list adopted by the health insurance authority aims to contain the escalation of drug expenditure and improve the rational use of drugs through economically indirect restriction of prescription drugs. The capping policy adjusts the hospital revenue structure by controlling drug expenditure and rising labor costs, which gives hospitals the incentive to provide more medical services instead of overusing drugs.

DOSING AND DURATION

In human or veterinary patients, antimicrobial-dosing regimens are designed to affect the complete eradication of the disease-causing pathogens from the patient system. Antimicrobial compounds act on specific microbial targets. These compounds prevent the cross-linking of enzymes in the peptidoglycan layer of microbial cell walls and inhibit the chain elongation of 23S rRNA and associated proteins in the peptidyl transferase center of the ribosome. The compounds also inhibit DNA gyrase and the related enzyme topoisomerase IV in the mid-catalytic cycle responsible for DNA repair or replication[56]. Administration of low doses, targets mainly endothelial cells rather than diseased cells[57]. Therefore, designing optimal dosage schedules for antimicrobials is critical to achieving therapeutic success and preventing resistance emergence.

Therefore, for microbial infections, it is reasonable to establish the effect of rapid high drug concentration in serum and consequent high concentration in tissue, as well as prolonged administration of antimicrobial agents at low concentrations. High concentrations of antimicrobial drugs in serum have therapeutic advantages in the treatment of endocarditis and urinary tract infections. High drug concentrations in serum reflect only the amount present at a particular point in time and may not indicate the effective antimicrobial level of the drug in the infected tissues. It is the concentration of drugs at the site of infection that is the determinant of successful therapy.

Antimicrobials doses in oral or intravenous solutions (tablets/capsules, creams/ointments, eye drops/ointments and liquids) vary widely from individual to individual in their peak serum concentrations as well as mean biological half-life in healthy adults and pediatric populations. Dose, duration and time are important to the onset of treatment in minimizing the total amount of drug needed to effect a clinical cure and avoid the selection of resistant strains. Therefore, administering either the largest tolerable dose or the smallest clinically effective dose depends on the relative positions of the hazard curve and the therapeutic window[58]. Non-compliance with the recommended dosing schedule by patients with dose-limiting toxicity may not be harmful in terms of efficacy and resistance dynamics. Missing several days of treatment by several orders of magnitude affects the resistance. Make-up doses may not reverse the effects of missed doses. In pulsed dose schedules, the pre-existence of resistant cells may delay the time of progression of diseases by impeding the growth of resistant cells. However, when pre-existing resistant cells are absent, a schedule with a pulse is an unfavorable choice as the probability of developing resistance increases because of treatment breaks, during treatment breaks, sensitive cells resume proliferation, potentially leading to the development of resistance. Therefore, patients administered high-dose pulsed therapy once a week plus low doses during the remaining days would derive the most benefit in terms of preventing or delaying the progression of the disease because of resistance[59].

The pathophysiology of infections and the kinetics of microbes killed by antimicrobial agents reveal that the difference between a chemotherapeutically effective dose and a toxic dose in certain antimicrobial agents is very small. This is due to the difference in the pharmacokinetics and pharmacodynamics data of patients. Such data include host factors (gender, age, pregnancy, obesity, hepatic and renal function, etc.), environmental factors (concomitant drugs, supplements, food, alcohol consumption and smoking etc.), disease factors (cancer, cachexia, inflammation and diabetes mellitus etc.) and genetic factors (genetic variants and epigenetic factors). The impact of pharmacotherapeutic options is critical for antimicrobial optimization and hence antimicrobial resistance prevention. Thus, the individual response can result in adverse drug reactions, drug-drug interactions and drug-disease interactions.

CLINICAL IMPLICATIONS OF RESISTANCE PATHOGEN DETECTED *IN VITRO*

The development of new antimicrobial agents requires sound clinical microbiology laboratory reports concerning efficacy and toxicity. *In vitro* assay, the likelihood of successful infection treatment with a specific antimicrobial agent together with biosafety studies with animal and controlled human trials, are indispensable to supporting and validating the use of specific antibiotics as antibacterial agents. Hence, *in vitro* time-kill, kinetic studies give information on the effect of different dosing regimens, altered clearance, infection site, protein binding and starting inoculum size among others. In vitro-based systems are closed (batch reactor-like) systems, in which there is no flow into or out of the reactor during the experiment. As a consequence, changes occur in the environment during the experiment (e.g., nutrients become depleted and signaling molecules accumulate etc.), unless the fluid is regularly replaced.

In vitro based assays are fairly cheap as only small volumes of reagents are required, they provide the opportunity to perform a large number of tests simultaneously. This attribute makes it ideal for screening purposes. Therefore, they can be used to evaluate the effect of co-administration of antibiotics on pathogens, determine the influence of matrix components, distinguish biofilm-deficient mutants from biofilm-forming wild-type strains, screen for the antimicrobial and anti-biofilm effects of various antibiotics, disinfectants, chemicals (including quorum sensing inhibitors) and plant extracts. It permits investigators to easily vary multiple parameters including the composition of growth media, incubation temperatures, humidity, presence or absence of shear stress and O_2 and CO_2 concentrations. However, since immunological factors encountered in the in vivo situation are missing, the *vitro* response does not always reflect the clinical response. Treatment is then modified according to the laboratory results and the clinical response.

In vitro resistance studies, organisms may be sequentially passed repeatedly in the presence of the test drug sub-inhibitory concentrations. Resistance development is compared to other topical antibiotics for several species. The bactericidal effect of antibiotics that has resistant pathogens suggest that such drugs cannot be translated into appropriate therapeutic and clinical options for the prophylactic treatment of microbial infections. *In vitro*, antibiotic resistance findings are clinically relevant to the selection of systemic antibiotics to be potentially employed in therapy since antibiotics ineffective in vitro against major pathogens under ideal laboratory test conditions with planktonic microbial cells are unlikely to be of much therapeutic benefit during *in vivo* administration. However, *in vitro* microbiology laboratory analysis may assist health specialists in reducing the risk of therapeutic failure inherent with empirically prescribed systemic antibiotic therapy by identifying pathogens with either predictable antibiotic vulnerability patterns or which display *in vitro* resistance to antibiotics under consideration for *in vivo* use[60]. This approach will help limit overall patient exposure to antibiotics, reduce the development of harmfully altered microbial populations at non-oral body sites and lower the risk of increased antibiotic resistance in the human microbiome.

IMPACT OF ORAL VERSUS INJECTABLE THERAPY ON RESISTANCE

Drugs are most administered intravenously, intramuscularly or orally. However, facial lacerations and puncture wounds may require topical antibiotic agents while contaminated intraoral puncture wounds and lacerations which has an increased risk of infection and should require systemic antibiotics. In therapy situations where higher tissue penetration is essential to achieving a cure, higher doses are needed for oral therapy than for injection, to achieve the same effective antibiotic concentration in the target sites[61]. Significant concentrations of orally administered drugs in organs increase with increasing dose and the presence of infection[62]. However, drug toxicity is significantly more common with parenteral therapy than with oral therapy. The oral regimen is associated with significantly less hepatic and renal drug toxicity than the parenteral regimen. Substantial differences in efficacy are present among both injectable and oral administration but no significant differences in safety between injectable and oral treatments. The route of administration as well may not affect the efficacy of the cure rates[63]. There could be a significant difference in efficacy between drug classes.

Oral administration of antibiotics enhances resistance development in host gut microbiota. The emergence of endogenous resistant populations is prominent when antibiotics were introduced orally. Growth of antimicrobial resistance (magnitude and timing) in gut microbiota is directly associated with drug application dosage and delivery approach[64]. The difference in antimicrobial resistance between oral and intravenous routes varies with drug type due to the difference in drug excretion routes. Ampicillin is excreted mainly by the renal route[64], therefore, gut microbiota will have minimum drug exposure if delivered by injection. Rapid destruction in the stomach of ampicillin makes it imperative to appropriately higher doses to effective therapy. However, tetracycline is excreted via both the kidney (glomerular filtration) and the GI tract (biliary elimination and directly)[64].

The increase in the number of microbial strains which are resistant to therapy and the subsequent rise in treatment failures necessitate finding a substitute or a modification of the treatment routine. To increase therapeutic benefit and decrease the adverse effects (e.g., resistance, allergic reactions, drug interactions and side effects) in animals, oral administration via feed and drinking water are limited to the animal needing treatment, dosage and duration of treatment compiled with, maintain homogenous distribution of the drug so that each animal obtains the required therapeutic dose for treating the disease following the veterinary prescription and drug delivery systems suitable for the proposed treatment. Severe microbial infection symptoms in patients necessitate parenteral therapy[65]. A regular injection dosing schedule adherence help maintains microbial suppression and diminishes the risk of microbial rebound and potential development of resistance.

IMPACT OF VACCINES ON ANTIMICROBIAL RESISTANCE AND THE CARRIAGE OF RESISTANT STRAINS

A microorganism may have several subtype strains with subtle variations. Gram-negative bacteria possess a high number of resistance virulence traits. This makes it able to mediate a high level of antibody immunity during infections. Gram-positive bacteria which lack this outer layer are more vulnerable to antibiotics. Genetic flexibility and stochastic variations of bacterial properties are the keys to their success as human pathogens enabling them to adapt to any site of infection. In addition, their relatively large genome encodes a high number of virulence factors which makes the development of effective therapy strategies challenging. Therefore, vaccines are developed multivalent to induce immune responses against multiple targets on a pathogen. But an organism's response to vaccination is influenced by age, sex, genetics and the adaptive immune system. The immune system is influenced by nutrition[66]. Vaccines require immune responses. Aside from the influence of nutrition, age, sex, genetics and sanitation, the vaccine can effectively reduce the transmission and circulation of infectious microbes, including antimicrobial-resistant strains. That is, vaccination enables a specific immune response at the beginning of the infection as well as prevents an individual from ever developing an infection which could reduce overall antibiotic utilization. Studies had shown that vaccines can significantly avert millions of days of antibiotic therapy annually[67].

Widespread and systematic vaccination can virtually eliminate diseases and the resulting resistance. Vaccines protect the vaccinated individual by direct immunization and can protect others through indirect immunization if the overall vaccination rate is high enough. Long-term immunity is conferred by the maintenance of antigen-specific immune effectors and/or by the induction of immune memory cells that may be sufficiently efficient and rapidly reactivated into immune effectors in case of pathogen exposure. Epidemiological Studies had shown that vaccines covering more strains reduced antibiotic needs[68], the invasive pneumococcal disease caused by the pneumococcal serotypes and transmission of these strains to siblings and adults[68], drug-resistant *Streptococcus pneumoniae*[68]. Vaccines also induce elevated virus-specific antibody levels and potent neutralization activity against the ancestral virus and Delta variant[69]. Thus, vaccines can serve as an effective tool for reducing disease caused by drug-resistant strains as a complement to the rational use of antibiotics.

Vaccination does not disrupt the composition, diversity, or stability of the microbial community. However, the diversity and composition of the resident microbiota influence the development of protective immunity to oral vaccines. Diverse microbiota raises a more protective immune response to oral vaccines against intestinal pathogens. The immune system exerts its influence on the microbiota, both innate and adaptive immune components are modified by microbial composition[66]. Considerable discrepancies from vaccination observed from different parts of the world are due to microbiota composition in humans[66].

CONCLUSION

Microbes can acquire antimicrobial-resistant genes from other microbes by sharing the same environment. This hinders the identification and implementation of cost-effective risk management measures. Gene duplication facilitates evolution in organisms. Vaccination and inappropriate, inadequate or sub-therapeutic antibiotics therapy does not destroy or disrupt the composition, diversity, or stability of the causative pathogen nor the resolution of clinical symptoms. However, vaccines and antibiotics can be used as complementary tools to produce synergistic gains in microbial infections and resistance control.

SIGNIFICANCE STATEMENT

This study discovers that resistance genes are much more widespread in environmental non-pathogenic microbial populations. Some are geographically ubiquitous while some are environmentally determined, with restricted geographical and seasonal patterns. Thus, their export to different environments may cause a long-time lapse (usually years) due to somatic mutagenesis, increased cell proliferation and production of pro-mutagenic metabolites that can persist for years. It is therefore hoped that this study will influence the formulation and coordination of antimicrobial resistance measures to mitigate antimicrobial resistance across human, veterinary, agriculture and environmental sectors. There is a need for interventions that could account for the downstream impacts of treatment decisions mediated by the ecology of multidrug-resistant organisms. Effective policies should take into account circulating multidrug-resistant organisms' populations and the network of drug-mediated interactions among them. This is to increase health care options (infectious diseases treatment, chemotherapy, surgery, transplantations, etc.) to profit the economies of states.

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