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Review article

INFECTIOUS DISEASES AND ANTIMICROBIAL RESISTANCE: CURRENT CLINICAL DEVELOPMENTS AND UPDATE

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Abstract: Four years into the most virulent disease outbreaks of our generation—where COVID-19 became the most widely discussed infection, claiming millions of lives and leaving countless others suffering from long-term symptoms—host-pathogen interactions has never been more significant. This interplay between hosts and pathogens, alongside evolving risks of emerging infectious diseases, has been exacerbated by the exponential growth of human activities. This review focuses on host-pathogen interactions, the fight against antimicrobial resistance, the current status of antimicrobial usage, and alternative strategies to address this global health crisis.

Keywords: Infectious diseases, host-pathogens interactions, microbial drug resistance, drug design, vaccine development.

INTRODUCTION

The causative agents of infectious diseases are bacteria, viruses, fungi, and parasites that threaten humans, animals, and plants (1). Once inside the host, pathogens employ various mechanisms to cause disease and trigger immune response. Due to their high replication and tissue invasion rates, microbes and fungi cause symptoms within the host. The ever-changing dynamics of genomes in interphase between plants and the corresponding pathogen agents are the backbone of their interactions (2).

The initial step in the host-pathogen interaction starts at the point of entry into the host organism and ends at the final stage of transmission (3). Biochemical interactions occur at every step, enabling the pathogen to exploit energy and resources that facilitate replication. The cell-specific tropism of pathogens is controlled by molecular mechanisms that allow them to modify host cells and their environment (4). Over time, an evolutionary biological arms race has resulted in pathogens adopting evasion strategies to survive (1). A deeper understanding of the molecular basis of host-pathogen interactions is essential for identifying future diagnostic and therapeutic targets to combat harmful agents (5).

In 2019, 13.7 million people worldwide died from syndromes caused by infectious diseases, with 5.2 million cases coinciding with non-communicable diseases. Of these, 3 million deaths occured among children under five years old. Globally, respiratory and bloodstream bacterial infections were the leading causes of death (6).

The rise in antimicrobial resistance (AMR) continues to pose serious challenges to the effective treatment of many infections (7). While some vaccines exist, their effectiveness against all strains remain partial. Since the 1940s, antibiotics have been instrumental in combating microbial infections, but their use has also had unintended detrimental effects on human and animal health (8). The indiscriminate use of antibiotics has led to global problems, with resistance arising from genetic adaptations in microbes exposed to residual concentrations of antibiotics (9).

According to a 2014 World Health Organization report (10), deaths attributed to antimicrobial resistance could increase from 700,000 annually to 10 million by 2050. Key factors contributing to this resistance include a lack of public awareness about antimicrobial-resistant bacteria, poor health conditions, environmental influences, dietary practices involving genetically modified products, increasing cases of infectious disorders, and a decline in the discovery of new antimicrobials by pharmaceutical companies (11). In fact, research and development in the pharmaceutical industry have dwindled over the years as companies cut corners in their efforts to develop novel products, resulting in reduced efficacy.

Host-pathogen interactions

The term “host-pathogen interactions” primarily describes disease-causing microbes, though not all microbes are pathogenic to all hosts. These interactions

encompass how a pathogen thrives within its host across molecular, cellular, organismal, or population levels. Historically, the concept dates back to Filippo Pacini's work in the 1600s, with its roots traced more formally to 1884 (12).

The interaction between a pathogen and its host is determined by the type of relationship involved. The three main categories of symbiotic relationships are commensalism, mutualism, and parasitism (13). The RNA sequencing data from an infected host has helped to uncover the rewiring of the interactome and the relative fitness of the pathogen during infection.

The total cost of developing a novel antibiotic in ten years on a marketing pipeline is estimated to be $1.7 billion (14). As the monetary reward is very low, there is little impetus for pharmaceutical companies to develop new medicines. To bring novel agents into the market requires push incentives, such as grants and pull ones that are awarded upon successful regulatory approval, independent of actual usage (15). There are calls for multiple pull incentives on a global scale with the United Kingdom responding with a pilot subscription business model, while the United States has implemented the PASTEUR Act (16).

Non-antibiotic approaches to mitigate antimicrobial-resistant pathogens

With the increasing rate of antimicrobial resistance, the onus of responsibility lies on looking for alternatives to avert this global dilemma for pharmaceuticals as it is getting to a crisis point (17) (Table 1). The prospective application of unconventional techniques (18) is the use of bacteriophages (19), antimicrobial peptides (AMPs) (20) or ribosomal synthesized peptides (21), antibiotic adjuvants (22), poop transplants and probiotics (23).

As there is a pressing need to find novel antibiotics, scientists and policy makers are looking at other angles to tackle the resistance problem (24). Plasma-activated

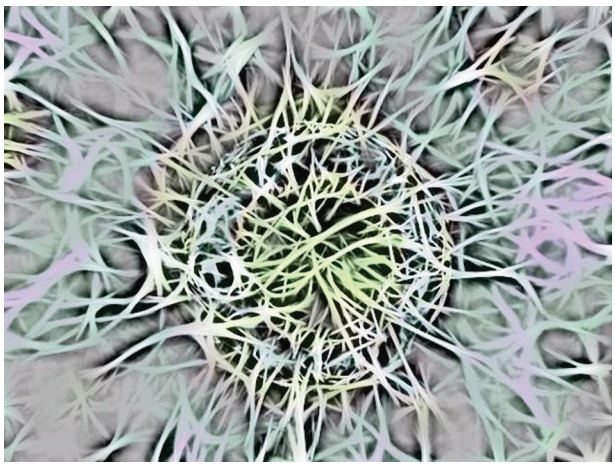

Figure 1. *Structure of an infectious pathogen with varying dendritec cells (personal communication)*

water (aka as a washing process), when enriched with oxygen and nitrogen derivatives that are chemically unstable, otherwise called free radicals and reactive forms is being considered as a potential new disinfectant (25). If bacteria are exposed to these radicals, they are effectively killed. A biochemical researcher, Katharina Richter, and her colleagues from the University of Adelaide in Australia are studying how fast plasma-activated water can heal infected wounds with methicillin-resistant *Staphylococcus aureus* (MRSA) versus untreated wounds (26). They are also investigating its potential as a supplement to intravenous antibiotics. Their findings suggest that plasma-activated water enhances wound infection elimination more quickly, with promising results for MRSA treatment (25).

Though bacteria are unicellular in nature, they can form communities and help each other to evade drugs and antiseptics (27). One mechanism by which they do this is by biofilm formation (28). These biofilms protect individual cells with approximately 80% of chronic infections in humans being attributed to biofilm-producing bacteria (29). Gallium, a metallic element, disrupts bacterial iron uptake, essentially starving mi-

Table 1. *Alternative non-antibiotic strategies to prevent antimicrobial resistance and classes of nanoparticles for antimicrobial chemotherapy (modified from (17))*

Alternative non-antibiotic strategies	**Classes of nanoparticles**
Vaccines	Inorganic and metallic nanoparticles
Stem cell AMPs	Polymeric nanoparticles (PNPs)
Immuno therapy/Antibody-antibiotic conjugates	Liposomes
CRISPR/Cas9 edits	Nanoemulsions
Nanobiotics/Enzybiotics	Nanostructured lipid carriers (NLCs)
Fecal microbiota transplantation (FMT)	Solid lipid nanoparticles (SLNs)
Phage therapy	Mesoporous silica nanoparticles (MSNPs)
Probiotics/Microbial therapies	Biomimetic nanoparticles (BNPs)

crobes of nutrients. Scientists are investigating gallium-laced drugs to combat biofilms, as demonstrated in research at the University of Manchester, UK, where gallium-based compounds reduced bacterial growth by up to 87% (30). Similar studies at Shanghai JiaoTong University, China, showed that gallium could dissolve MRSA biofilms, making it possible to kill the bacteria with just one-tenth of the typical antibiotic dose (31).

An ideal antibiotic should possess three key features: solubility, the ability to bind readily to bacteria, and the ability to penetrate cell membranes (32, 33). Designing antibiotics that meet these criteria remains a challenge. To address this, researchers are now using large digital libraries to predict these properties, screening existing compounds for the necessary characteristics (34). However, further research is required to develop a model that integrate these properties and improves cell permeability.

Application of nanobiotics in infectious diseases

Nanotechnology provides a brilliant alternative in the treatment of drug-resistant infections (35). Antimicrobials can be delivered using nanomaterials, or the nanomaterials themselves can contain drugs (36). Nanoparticles with enhanced antibacterial, antiviral, and anticancer efficacy, due to reduced toxicity, are emerging as potential drug candidates for future applications (37). These days, clinical infectious disease specialists use an increasing array of tools in their practice to harness unique features that are related to nanotechnology. Such procedures involve rapid and point-of-care diagnostic assays, antibiotics and their delivery vectors, vaccines, and materials for the purification of food and water (38).

The key benefits of nano-based drug delivery systems include reduced irritant reactions, improved bioavailability, and enhanced penetration within the body owing to their small particle size, which allows for intravenous and other routes of administration.

Nanoformulations based on lipids, namely nanoemulsions, liposomal compositions, and solid lipid nanoparticles (SLNs), are commonly used to transport antibacterial drugs (39). The targeted delivery of antibiotics directly to bacteria could be done through lipid nanoparticles fused with cell membranes (40). The liposomes, which are delivery vectors for drugs, can extend the duration of circulation and facilitate cellular absorption, thereby overcoming the resistance to antibiotics (41). The low cytotoxicity of solid lipid nanoparticles (SLNs) (42), nanostructured lipid carriers (NLCs) (43) and nanoemulsions (44) make them suitable as drug-delivery systems. These systems differ primarily in their core composition. SLNs consist of a solid support in a crystalline state, while NLCs have a lipid matrix that combines solid liquid lipids, making them a more advanced generation of lipid-based drug delivery systems (45).

The merits of nanotechnology include a stable release in a controlled manner, lipophilic molecules infiltrated into different layers, solubility, bioavailability enhancement, drug encapsulation with low-cost biocompatible and biodegradable polymers, and improvement in the effectiveness of various treatments. However, there are disadvantages involving toxicity characteristics when using different additives/polymers, side reactions and lack of standardized regulatory protocols (46).

Averting resistance to drugs through innovations

Drug resistance is a noted phenomenon in several pathogens that cause infectious diseases, namely tuberculosis, nosocomial infections, malaria, and acquired immunodeficiency syndrome (AIDS). New strains of the human immunodeficiency virus (HIV) that are resistant to antiretroviral drugs have also been reported (47). These strains therefore require the development of novel therapeutic drugs (48) (Table 2).

Table 2. *List of infectious diseases and corresponding replicates per condition (48)*

Disease	Replicates
Campylobacteriosis	1
Dengue	1
Hepatitis A	1
Pertussis	2
Salmonellosis	1
Influenza	3
Measles	7
Brucellosis	2
COVID-19	7
Scarlet fever	2
Western equine encephalitis	2
Diphtheria	5
Saint Louis encephalitis	4
Poliomyelitis	5
Typhoid	8
SARS	4
Japanese encephalitis	3
MERS	1
Typhus	1
Smallpox	6
Yellow fever	2
Cholera	14
Lassa fever	4
AIDS	1
Tuberculosis	2
Meningococcal meningitis	3
Ebola	2
Plague	10

Machine intelligence (MI) and structure-guided approaches have been applied in designing immunogens for the development of vaccines against SARS-CoV-2 and other disease-causing agents (49). The approach uses bioinformatics to identify genes associated with specific pathogens, allowing for the determination of key features that provide specificity for antigen binding, making them potential targets for vaccines (50). New candidates are being synthesized and tested in vivo through reverse vaccinology (51). Additionally, clinical research and trials can be streamlined and monitored by leveraging MI or artificial intelligence (AI) (52).

Interestingly, new strategic approaches to treat viral, bacterial and parasitic infections are being explored these days. While weakened versions of whole pathogens have been applied, vaccines now also include mRNA (53) or plasmid DNA (54) which has been applied to target parasitic infections, such as malaria. In 2017, the European Economic Area (EEA) approved the use of bezlotoxumab to combat *Clostridium difficile* and recurrent cases (55).

The World Health Organization (WHO) is leading a global effort to tackle antimicrobial resistance. Although most physicians recognize the severity of the problem, many still underestimate it in their own hospitals, continuing to prescribe antibiotics inappropriately. Strategic efforts to combat this global challenge include educating the public, raising awareness about inappropriate prescribing among general practitioners through continuous professional development (CPD), engaging pharmaceutical companies in research and development of new antimicrobials, and adopting innovative treatment strategies enabled by technological advancements. The five strategic objectives include: a) enhancing knowledge and understanding of antimicrobial resistance; b) strengthening science through monitoring and research; c) reducing infection rates; d) maximizing the use of antimicrobial agents; and e) advocating for long-term investments to meet the needs of all countries, including investment in new drugs, diagnostic tools, vaccines, and further actions (inspired from: https://infectionsinsurgery.org/5-strategies-to-combat-antibiotic-resistance-in-healthcare/).

Though still in its early stages, a new mechanism for killing bacteria is being explored through the use of antibody-antibiotic conjugates (AACs) (56). This technique involves AAC binding to bacteria, which are then internalized by host cells. Once inside, the unconjugated AAC kills the bacteria. This novel combination immunotherapy strategy, when used alongside conventional therapy, could yield promising results for combating more resilient pathogens.

What is the current development that has happened with antimicrobial resistance?

The alarming rate of antimicrobial resistance (AMR), as reported by the WHO Global Antimicrobial Resistance and Use Surveillance System (GLASS) in 2022, highlights the prevalence of resistant bacterial pathogens (57). The median rates reported in 76 countries were 42% for *Escherichia coli* resistant to third-generation cephalosporins and 35% for *Staphylococcus aureus* resistant to methicillin. In urinary tract infections caused by *E. coli*, one in five cases showed reduced treatment effectiveness with antibiotics like ampicillin, co-trimoxazole, and fluoroquinolones, making it more difficult to treat common infections. Since 1990, there have been at least 1 million deaths annually associated with antimicrobial resistance, and by 2050, more than 39 million lives are expected be lost, according to the Global Research on Antimicrobial Resistance (GRAM).

There were high levels of resistance against critically important antibiotics by a common intestinal bacterium, *Klebsiella pneumoniae*. Based on the Organization for Economic Cooperation and Development (OECD) projections, there will be a two-fold increase in resistance by 2035, stressing the urgent necessity for robust antimicrobial management practices and strengthened supervision worldwide (inspired from: https://www.who.int/news-room/fact-sheets/detail/antimicrobial-resistance).

Drug resistance among fungi

Drug-resistant fungal infections are also on the rise as WHO monitors their magnitude and impact on public health. These infections can be difficult to treat, particularly in patients with other diseases such as AIDS (inspired from: https://www.who.int/news-room/fact-sheets/detail/antimicrobial-resistance).

Drug resistance among HIV, *Mycobacterium tuberculosis* bacteria, and *Plasmodium malariae* parasites

Resistance to HIV drugs occurs due to modifications in its genome, which impair the ability of antiretrovirals (ARV) to block the virus replication. The transmission of this resistance could occur when people are first infected or it is acquired as a result of compliance problems with treatment or drug interactions. WHO is recommending that nations should conduct investigations on the resistance to HIV drugs for careful selection of an optimized regimen for ARV prevention and therapy (inspired from: https://www.who.int/news-room/fact-sheets/detail/antimicrobial-resistance).

Tuberculosis is an important contributing factor to the resistance to antibiotics. Multidrug-resistant tuberculosis disease (MDR-TB) is a type caused by germs not reactive to a combination of two antibiotics, isoniazid and rifampicin, these are the first-line treatments most effective for TB. Resistance to second-line therapies further limits treatment options, posing a public health emergency (inspired from: https://www.who.int/news-room/fact-sheets/detail/antimicrobial-resistance).

Drug-resistant parasites pose a significant threat to malaria treatment and control. For uncomplicated *Plasmodium falciparum* cases, artemisinin combination therapies are the first-line treatments used in many countries with endemic malaria. In the Greater Mekong Subregion, resistance to this antibiotic or its partner drug has been observed since 2001. In the eastern Mediterranean region, resistance to Fansidar (sulfadoxine and pyrimethamine), a partner drug, has led to treatment failures in some countries, prompting a shift to alternative combination therapies. On the African continent, mutations associated with artemisinin partial resistance have been noticed in a number of countries (inspired from: https://www.who.int/news-room/fact-sheets/detail/antimicrobial-resistance).

Since November 2023, 178 nations have developed national action plans on antimicrobial resistance (AMR) in alliance with a Global Action Plan (GAP). Worldwide, the tracking progress of an AMR action plan could be captured through cross-sectoral actions like the annual Tracking AMR Country Self-Assessment Survey (TrACSS) that was initiated in 2016 with previously published work on https://www.amrcountryprogress.org/.

Excess usage of antibiotics

One of the major issues with antibiotics is their overuse or misuse in treating infections in humans, animals, and plants (58). Bacteria can mutate, altering their cell walls to resist antibiotics or breaking them down, while some strains can share their antimicrobial resistance genes. Misuse or poor compliance with prescribed antibiotics provides a pathway for resistance to spread, allowing microbes to multiply and evolve.

How governments handle outbreaks?

The major objective in managing an outbreak is to safeguard public health by identifying the source, causes of infection, and transmission dynamics, then implementing control measures to contain further spread or recurrence. A secondary goal is to refine outbreak management, using evidence from infection sources, transmission and actions, taken, and improving training for better future responses. For example, the UK Health Security Agency (UKHSA) is responsible for reporting international health treats to the WHO under the International Health Regulations of 2005. Incidents meeting the definition of a serious cross-border health threat are also be reported to the EU Commission.

Every responsible government must take the outbreak of any infection seriously, given its potential impact on domestic and global health. It should not be dismissed due to the leader's ego, religious beliefs, national reputation, or desire to protect their image internationally. In such cases, collaboration with the World Health Organization (WHO) is crucial to effectively reduce the spread, transmission and containment of the infection. Unfortunately, some global leaders, including autocrats and dictators, prioritize their personal or political agendas over the well-being of their people and the international community, which undermines global peace, security, and health.

The confusion surrounding the COVID-19 outbreak remains unresolved, with full clarity in the chain of events leading to the pandemic still uncertain. Given the mishandling of the situation and the resulting loss of lives, it is essential for any government—regardless of its cultural, religious, geographical, or political background—to be transparent and cooperate fully with the World Health Organization (WHO) in managing outbreaks. This cooperation is vital for identifying the origin, modes of transmission, and effective containment strategies. Collaborating with WHO will mobilize global expertise to reduce transmission and limit the spread of infections worldwide.

CONCLUSION

Antimicrobial resistance will continue to pose a serious challenge to the healthcare system worldwide as long as both emerging and re-emerging infectious diseases persist. The problem could be controlled through the development of novel antimicrobials, strategic use of existing antibiotics, application of innovative technologies, and minimizing artificial host-pathogen interactions that drive cross-border transmissions.

Health is paramount and a fundamental human right. With the global population increasing and compounded by environmental catastrophes, authoritarian regimes, human cruelty, wars, populist extremism, and fascism, these factors are driving forces behind future infectious disease outbreaks. The ability to effectively address these challenges may be hindered by these forces. The role of irresponsible dictators and autocratic leaders—who disregard humanity and dismiss scientific expertise—cannot be underestimated.

COVID-19 has significantly reshaped global working conditions, with many companies, organizations, institutions, and government bodies transitioning to remote or hybrid work models for their employees, establishing these as the new standard.

As health authorities, clinicians and pharmaceutical companies tackle the crisis of antimicrobial resistance, vaccines may offer potential solutions, provided that side effects in certain groups of individuals are carefully monitored.

Novel recombinant vaccine technologies have been crucial in minimizing the use of antimicrobial combinations. One of the most significant ways to prevent them is being. achieved by vaccines. There are a few at the mid-stage of their clinical development by pharma companies against pathogenic bacteria that are deadly, namely *Clostridium difficile* (phase III), *Mycobacterium tuberculosis* (phase II), Group B *Streptococcus* (phase II) and *Staphylococcus aureus* (phase II) (inspired from: https://iris.who.int/bitstream/handle/10665/359172/9789240052451-eng.pdf?sequence=1).

The unnecessary prescription and overuse of antibiotics can be avoided by healthcare professionals. Instead, patients should be educated on proper hygiene practices to reduce the spread of diseases and minimize infections to the greatest extend possible.

Applications of genomics screening, as a fundamental tool in infectious disease studies and drug development, have played a prominent role in understanding host-pathogen interactions, including those of viruses such as Zika, Dengue and SARS-CoV-2 viruses.

In tropical regions affected by malaria, governments could make significant progress by utilizing all available resources to address sanitation, approve appropriate hygiene methods, and ensure effective drainage systems, especially during rainy periods, to minimize breeding opportunities for *Plasmodium falciparum*. This strategic combination, along with medical treatments, would help reduce the mortality rate in both children and adults in these regions. Ultimately, it comes down to accountability and the willingness to improve the health and quality of life for the affected populations.

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Note: Artificial intelligence was not utilized as a tool in this study.

Sažetak

INFEKTIVNE BOLESTI I ANTIMIKROBNA REZISTENCIJA: TRENUTNI KLINIČKI RAZVOJ I NAJNOVIJA DOSTIGNUĆA

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Četiri godine nakon jedne od najvirulentnijih epidemijskih bolesti naše generacije—u situaciji u kojoj je COVID-19 postao infekcija o kojoj se najviše diskutuje, koja je odnela milione života i ostavila bezbroj drugih ljudi sa dugoročnim simptomima—interakcije domaćin- patogen nikada nisu bile značajnije. Odnos između domaćina i patogena, zajedno sa rastućim rizicima od novih zaraznih bolesti, dodatno je pogoršan eksponencijalnim rastom ljudskih aktivnosti. Ovaj rad se fokusira na interakcije domaćin-patogen, borbu protiv rezistencije na antibiotike, trenutni status upotrebe antibiotika, kao i alternativne strategije za rešavanje ove globalne zdravstvene krize.

Ključne reči: Infektivne bolesti, interakcije domaćin-patogen, rezistencija na antibiotike, dizajn lekova, razvoj vakcina.

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