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A Systematic Review of Targeted Interventions and Emerging Therapies in the Control of Infectious Diseases and Drug Resistance

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1. Abstract

Infectious diseases are a major global health challenge, causing millions of deaths each year, especially among vulnerable groups like children, the elderly, and those with weakened immune systems. As conventional treatments struggle with issues like drug resistance and the complexity of treating persistent viral infections, there's a growing need for innovative solutions. This paper explores new approaches in managing infectious diseases, focusing on targeted interventions that could make a real difference in patient outcomes. We look at promising therapies like bacteriophages-viruses that specifically target bacteria-engineered probiotics that enhance our body's natural defenses, and CRISPR, a cutting-edge gene-editing tool that shows potential in fighting both bacterial and viral infections. Antisense therapy, which involves molecules that can block disease-causing genes, and oligonucleotide aptamers, which act like chemical antibodies, are also examined for their effectiveness. Additionally, the paper discusses the role of antibacterial nanomaterials in combating infections, offering new ways to tackle drug-resistant bacteria. Beyond treatments, we also highlight the critical role of public health efforts, particularly contact tracing, in controlling the spread of diseases. Different methods of contact tracing-such as tracking who an infected person may have exposed-are analyzed for their impact on preventing outbreaks. The paper underscores the importance of accurate diagnostic tools, which have evolved significantly, now including technologies like nanopore sequencing that allow for rapid and precise identification of pathogens. While these new interventions are still in the early stages and face challenges like regulatory approval and funding, they hold great promise. Continued research and effective public health strategies are essential to fully realize their potential in reducing the global burden of infectious diseases and improving lives.

2. Introduction

According to the World Health Organization, three of the top ten leading causes of death in 2020 were due to infectious diseases [1], highlighting the significant burden these diseases place on both health systems and affected individuals. This burden leads to increased morbidity, mortality, and a diminished quality of life, especially among vulnerable populations such as children, the elderly, and immunocompromised individuals [1,2]. The primary challenges in treating infectious diseases with conventional methods include the rising issue of drug resistance and disturbances in the microbiota. Furthermore, the persistent presence of viral reservoirs and their ability to integrate into the host's genetic material complicates the effectiveness of current antiviral treatments [1,3]. This review highlights the roles of public health and contact tracing in infectious disease management, explores various contact tracing methods and historical interventions, and provides an overview of novel therapeutic technologies addressing current challenges to improve patient outcomes. The targeted therapeutic interventions discussed include bacteriophage therapy, engineered probiotics, CRISPR therapy, antisense therapy, oligonucleotide aptamers, anti-biofilm drugs, and antibacterial nanomaterials.

3. Case history

Infectious diseases remain a constant challenge for health systems globally. These diseases significantly impact individuals and entire populations, particularly among vulnerable groups such as children, the elderly, and those with compromised immune systems. Public health systems play a vital role in controlling outbreaks and preventing the spread of these infections.

A key strategy is contact tracing, a method used to identify individuals who may have been exposed to an infected person. Effective contact tracing helps prevent further transmission and is essential for managing infectious disease outbreaks. Over time, public health institutions have also incorporated advanced technologies like artificial intelligence (AI) to improve the speed and accuracy of these efforts. AI helps track disease patterns, analyze health data, and even predict potential outbreaks, providing healthcare professionals with crucial tools for decision-making.

Different methods of contact tracing, including forward, backward, and sideward tracing, have been applied across various outbreaks, from sexually transmitted infections to major epidemics like Ebola and COVID-19. Forward tracing tracks individuals who may have been infected by a known case, backward tracing traces the origin of the infection, and sideward tracing looks at large gatherings to identify potentially infected individuals.

Through a combination of targeted interventions, public health

strategies, and new technological tools, infectious disease control continues to evolve. While traditional methods have laid the foundation, newer approaches, such as the use of engineered probiotics, bacteriophage therapies, and cutting-edge gene-editing technologies like CRISPR, offer promising avenues for treating infections that have become resistant to conventional drugs.

3.1. Public Health

Health systems consist of organizations and individuals working to promote, restore, or maintain health. This is achieved through influencing health determinants and implementing preventive and curative activities. The effectiveness and efficiency of delivering critical and essential services determine the success of health systems . Public health is a crucial component of health systems, aiming to improve population health outcomes by preventing disease, promoting health behaviors that reduce the risk of communicable and non-communicable diseases, and ensuring equal access to quality health services [4]. There are six core functions of public health central to the effectiveness of health systems. The first is ensuring the availability of critical epidemiologic information, which is essential for formulating and implementing policies and guidelines, improving programs, and guiding resource allocation. The second function is strengthening public health institutions and infrastructure by improving data collection systems and supporting data interpretation. The third function is establishing robust public health laboratory networks crucial for disease surveillance and outbreak confirmation. The fourth function is building a skilled workforce, as trained personnel are vital for any health system's success. The fifth function involves implementing key public health programs, such as those aimed at combating communicable and non-communicable diseases, which have been instrumental in eradicating smallpox in 1979 and are close to eradicating polio and guinea worm. The final core function is supporting critical operational and applied research, which provides evidence to improve public health programs, address emerging healthcare challenges, and identify, improve, or discontinue interventions [4].

3.2. Contact Tracing

Surveillance is one of the most effective strategies to control infectious disease outbreaks [5]. A critical aspect of surveillance is contact tracing, defined by WHO as "the process of identifying, assessing, and managing people who have been exposed to a disease to prevent onward transmission" [6]. Artificial intelligence (AI) is transforming surveillance by enabling more efficient data analysis, early outbreak detection, and integration with existing systems. AI algorithms analyze data from various sources, including electronic health records, laboratory reports, and social media, to recognize disease outbreak patterns. Additionally, AI-powered tools collect and analyze symptom and travel data, providing real-time updates and guiding users to healthcare resources. AI can also monitor health status changes via wearable devices, detecting early signs of infection [7]. The success of contact tracing in breaking the chain of transmission depends on how many contacts are effectively traced. Identified contacts are advised to undergo preventive measures, such as isolation or quarantine, and are monitored throughout the disease course to ensure they remain free of complications [8]. Contact tracing is a key strategy for slowing down epidemics and pandemics, especially when conducted rapidly and efficiently [8,9]. There are three main methods of contact tracing: forward, backward, and sideward tracing. Initially, contact tracing was used to prevent the transmission of sexually transmitted diseases (STDs) [9]. It later became a standard public health protocol for responding to various outbreaks, serving as a valuable tool alongside other measures [8]. Over time, contact tracing has been applied in pandemics such as H1N1, Ebola, MERS, TB, and COVID-19. The Ebola outbreak in 2014 spurred further studies, and after 2020, research on contact tracing surged, particularly in response to COVID-19 [9]. The definition of 'exposure' varies based on the contact tracing program and the infection's mode of transmission, such as droplet, fomite, fecal-oral, or airborne [8, 10]. For airborne diseases like tuberculosis and varicella, a person is considered a 'contact' if they were in the same indoor room as the infected individual, with the required duration depending on the disease. In general, 'exposure' is defined by the duration, frequency, or intensity of contact, which helps assess the likelihood of infection [8].

3.3. Forward Tracing

Forward tracing identifies downstream individuals who may have been infected by the index case (the first identified by a healthcare professional) [11]. It is a conventional method for investigating cases and informing close contacts to isolate, particularly useful for identifying secondary cases. This approach was standard during the SARS-CoV-2 pandemic, helping to identify individuals for quarantine during the two-day infection window [12]. Key follow-up actions after contact tracing include diagnostics, post-exposure prophylaxis, and quarantine [6].

3.4. Backward Tracing

Backward tracing works in the opposite direction of forward tracing, tracking contacts back to the primary case or the person who infected the index case [13]. While some studies have claimed backward tracing is more effective than forward tracing, other research has challenged this conclusion. A study using two epidemic models—"constant infectiousness" and "skewed infectiousness"—found that backward tracing was more efficient in the constant infectiousness model, where symptomatic individuals have a consistent chance of infecting others. In contrast, forward tracing was more effective in the skewed infectiousness model, which reflects the dynamics of diseases like COVID-19, where infectiousness peaks after symptoms develop. The study concludes that the effectiveness of contact tracing methods depends on the specific disease being traced [13].

3.5. Sideward Tracing

Sideward contact tracing differs from forward and backward tracing by focusing on gatherings, indirectly detecting asymptomatic individuals who attended the same event, even if they weren't directly infected by the index case. This method adds a new dimension, enhancing the effectiveness of traditional tracing methods and identifying cases that might otherwise go undetected. A study titled "Sideward contact tracing and the control of epidemics in large gatherings" found that sideward tracing can significantly improve the overall impact of contact tracing, especially when larger groups are targeted [14].

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4. Methods

4.1. Diagnostic Tools

Once an infected person is identified through contact tracing, diagnostic tests are used to confirm the suspected infectious disease. Nanopore sequencing is an emerging diagnostic tool that observes fluctuations in ionic current as DNA or RNA passes through a nanopore or nanochannel. This disruption produces a characteristic signal, which is decoded by a base-calling algorithm to determine the nucleic acid sequence [15]. Immunohistochemistry uses specific polyclonal or monoclonal antibodies to react with unique antigens on pathogens, with the resulting antigen-antibody complex detected by fluorochrome fluorescence or chromagen-induced color change. Another key method is nucleic acid-based testing, which rapidly expands the identification and detection of pathogens by using polymerase enzymes to amplify genetic material to detectable levels. PCR-based nucleic acid detection has greatly advanced infectious disease testing [16].

4.2. Old Interventions

After diagnosing an infectious disease, the most effective treatment is pursued. Over time, treatment modalities have evolved from ancient practices like bloodletting to modern antibiotics and targeted therapies [16]. Manuka honey, derived from Leptospermum scoparium, is an ancient remedy for infected wounds, first documented in Sumerian writings from 2100 BC. It has shown antimicrobial activity against 60 species of bacteria, including Staphylococcus aureus and Helicobacter pylori, making it a promising treatment for wounds and stomach ulcers [17]. Bloodletting was a standard treatment for over two thousand years until it was discredited in the late nineteenth century. Practiced across ancient civilizations, this procedure involved making an incision to remove blood, often with heated glass cups or medicinal leeches, which were believed to reduce bacterial infections by depleting iron [18]. Medieval societies also used plant-derived compounds to combat pathogens. A 1,000-year-old remedy effective against S. aureus infections, known as Bald's eyesalve, combines wine with allium species such as garlic and onions. Allium species contain ajoene, which prevents biofilm formation, and flavonoids, which inhibit bacterial metabolism and replication. Flavonoids also enhance the effectiveness of antibiotics and reverse resistance [19,20]. Despite these interventions, infectious diseases led to high mortality and morbidity worldwide before the 20th century, with an average life expectancy of 47 years. Diseases like cholera, smallpox, diphtheria, and pneumonia were widespread. This changed with the discovery of penicillin in 1928, marking the beginning of the antibiotic revolution. The golden era of antibiotic discovery spanned the 1950s to the 1970s, but no new classes of antibiotics have been discovered since. Today, antibiotics remain the primary defense against bacterial infections, but their overuse has led to the significant public health threat of antibiotic resistance [21].

4.3. New Interventions - Targeted Therapy

4.3.1. Bacteriophage Therapy

Bacteriophage infects its viral DNA into the bacterial cell to create phage particles. The result is bacterial cell lysis and the release of new bacteriophage particles [22] as shown in figure 1.

Bacteriophages are viruses that specifically infect bacteria and are increasingly used to treat patients with bacterial infections, particularly those resistant to antibiotics. As the most abundant organisms on Earth, they play a crucial role in molecular biology, horizontal gene transfer, and bacterial evolution. Phage therapy's precision lies in bacteriophages' ability to recognize and bind to specific receptors on bacterial surfaces, making them a safe and effective treatment option. Once attached, a phage injects its DNA into the bacterium, leading to the production of new phage particles. The bacterium eventually lyses, releasing these particles to continue the infection cycle [22].

In the review "Safety and Efficacy of Phage Therapy for Superficial Bacterial Infections," phage therapy achieved clinical resolution in 86.1% of chronic wound/ulcer cases, 94.9% of dermatological infections, and 76.8% of burn wound infections [23]. Another review reported that 258 out of 277 patients with periprosthetic joint infections treated with phage therapy showed clinical resolution [24]. Bacteriophages are highly specific and modifiable, making them a potent tool against bacteria, especially since they cause minimal toxicity compared to antibiotics [25].

The review article "Phage Therapy: Clinical Applications, Efficacy, and Implementation Hurdles" highlights several clinical trials where phage therapy for skin infections consistently proved safe and effective, achieving nearly 100% success without side effects. Respiratory tract infections (RTIs) are a major cause of global illness and death, worsened by antibiotic-resistant bacteria. Since 1936, studies have shown that phage therapy can effectively target pathogens like Escherichia coli, Klebsiella, Streptococcus, Staphylococcus, and Pseudomonas, with some reports showing 80% to 100% efficacy using inhaled phages [26].

4.3.2 Advantages and Disadvantages

Phage therapy is a bactericidal treatment where infected bacteria lose their ability to grow and survive [27,28]. Bacteriophages can multiply in response to bacterial density, a process known as auto-dosing, and are inherently low-toxic to humans [29]. Their host specificity ranges from infecting a few bacterial strains to rarely more than one closely related genus, minimizing their impact on beneficial flora [27]. They do not exhibit cross-resistance with antibiotics and are biodegradable, supporting sustainable medical treatments [29]. However, bacteriophages' narrow host specificity can limit therapeutic effectiveness in infections involving multiple pathogens. Prolonged use of a single phage can lead to phage-resistant bacterial strains. Furthermore, phages can exacerbate infections by releasing bacterial toxins during lysis, potentially triggering inflammatory reactions, fever, or septic infections. Their poor pharmacokinetics—low absorption, distribution, and survival in the body—further reduce their appeal for therapeutic use [30].

4.3.3. Engineered Probiotics

Probiotics are live organisms that induce beneficial effects when administered under appropriate conditions [31]. They play a significant role in health by preventing diseases, improving the intestinal microenvironment, regulating the immune system, reducing physiological stress, inhibiting pathogen growth, and enhancing intestinal barrier function [31]. Engineered probiotics,

created by gene editing, offer potential in targeting infectious diseases. These modified microorganisms inhibit pathogens through mechanisms such as producing bioactive metabolites like bacteriocins, competing for nutrients and attachment sites, and modulating the host immune system [32].

4.3.4. Therapeutic Applications

One therapeutic application is in treating Pseudomonas aeruginosa, a common hospital-acquired infection that rapidly develops resistance to antibiotics. A study in mouse models infected with P. aeruginosa showed that a probiotic strain of E. coli reduced the levels of P. aeruginosa by 77% [33]. In the case of periodontal diseases, which are associated with a disrupted oral microbiome or dysbiosis, treatment using bifidobacteria species helps shift the oral microbiome to a healthier state. This enhances gingival health by inhibiting pathogens like Porphyromonas gingivalis and supporting beneficial bacteria in subgingival biofilms [34]. Helicobacter pylori, linked to 78% of gastric cancers, is another example where engineered probiotics show promise. An engineered Lactococcus lactis strain, which secretes antimicrobial peptides, successfully cleared H. pylori infection in a mouse model within five days after a single-dose oral administration [35]. Similarly, Candida albicans, responsible for over 40% of fungal infections worldwide, can be targeted using an engineered E. coli strain that detects hydroxyphenylacetic acid, a molecule produced by C. albicans, and a hypha inhibitor, protecting epithelial cells from fungal damage in vitro [36]. In addition to their therapeutic role, probiotics also have diagnostic applications. Engineered probiotics can detect both gram-negative and gram-positive bacteria by identifying novel metabolites or molecules produced during quorum sensing [36].

4.3.5. Advantages and Disadvantages

Probiotics are generally safe and serve as alternatives to antibiotics, being widely available in dietary supplements and fermented products. Unlike antibiotics, which can cause dysbiosis by killing beneficial microbes, probiotics maintain the host microbiome balance, preventing dysbiosis and stimulating the immune system through long-term use. Probiotics offer multiple activities—antibacterial, antiviral, and antifungal—whereas antibiotics target bacteria specifically. However, probiotics face disadvantages, including reduced survival under extreme stress conditions, which limits their effectiveness [32]. Engineered probiotics also risk spreading antibiotic resistance genes, making them a double-edged sword [37]. While many clinical trials support probiotic use, further research is needed to determine their long-term safety.

4.3.6. CRISPR Therapy

Clustered regularly interspaced short palindromic repeats (CRISPR) and CRISPR-associated protein (Cas) are components of the bacterial adaptive immune system, now widely used for gene editing in humans and microorganisms. The most common variant, Cas9, enables precise targeting of specific genes, offering potential applications in treating infectious diseases [1].

4.3.7. Therapeutic Applications

CRISPR-Cas technology shows promise in antibacterial therapy by either destroying resistance genes or directly killing resistant bacterial strains. For example, CRISPR-Cas13 has been used to kill carbapenem-resistant E. coli and methicillin-resistant S. aureus, significantly reducing resistant strains and improving survival in an in vivo larvae infection model [1]. CRISPR systems delivered by bacteriophages have been tested in S. aureus and E. coli infections with mixed results; while effective in treating skin infections, they failed in treating osteomyelitis, likely due to poor penetration into bone tissue [38]. CRISPR-Cas is also a potential solution for antiviral therapy. For instance, combining CRISPR-Cas9 with long-acting slow-release antiviral therapy (LASER ART) for HIV-1 has shown synergistic effects [1]. CRISPR-Cas can also destroy viral genes in hepatitis B and herpes viruses and target oncogenes in human papillomavirus, increasing apoptosis and suppressing tumor growth. Additionally, studies are exploring the delivery of mRNA-encoded Cas13 and crRNAs via nebulizer to halt replication in influenza and SARS-CoV-2 infections [1]. Traditional vaccines rely on viral or bacterial antigens to stimulate a targeted immune response, which varies among individuals. CRISPR technology has been used to engineer B cells to produce HIV-1-specific broadly neutralizing antibodies (bNAb), offering a more consistent immune response. In a study, modified B cells produced sufficient antibodies in mice to confer immunity, potentially overcoming the variability seen in traditional vaccines [38]. CRISPR therapy is currently in phase one human clinical trials, mostly ex vivo, where cells are modified in a lab before being reintroduced into the patient. For example, in 2019, CRISPR was used to ablate CCR5 in hematopoietic progenitor cells, which were then transplanted into an HIV-1 positive patient, successfully preventing HIV infection with no off-target effects detected [38].

4.3.8. Advantages and Disadvantages

CRISPR-Cas offers the benefit of highly specific targeting of bacterial pathogens, reducing the risk of nonspecific elimination seen with traditional antibiotics [1]. It is also more affordable, easy to use, and widely applicable across various fields, including diagnostics, cancer management, and infectious disease treatment [39]. However, the technology carries risks of on-target and off-target effects, leading to unintended genomic modifications. On-target effects can include insertions, deletions, and recombination events, potentially damaging the target gene, while off-target effects are less predictable and depend on sequence homology and gRNA structure [1,38]. Although strategies have been developed to mitigate these risks, concerns remain, such as the activation of TP53, a tumor suppressor gene, which can lead to cell death or increase the risk of carcinogenicity if inactivated [39].

4.3.9. Antisense Therapy

Antisense oligonucleotides (ASOs) are short, single-stranded DNA molecules complementary to mRNA targets. They can be RNA-degrading (RNase H-dependent) or RNA-blocking (RNase H-independent). ASOs have gained attention for their ability to target disease-causing genes at the mRNA level, showing promise in cancer, genetic disorders, and infectious diseases. Some have been FDA-approved for treating infections, while others remain in preclinical stages. ASOs are favored for their specificity, which reduces side effects like cytotoxicity [3]. ASOs have undergone three generations of chemical modifications, improving their

resistance to nucleases, binding affinity, delivery, and cellular uptake. First-generation ASOs used phosphorothioate (PS) linkages, second-generation ASOs introduced alkyl-modified ribose sugars, and third-generation ASOs, like phosphorodiamidate morpholino oligomers (PMOs), feature morpholine ring backbones [3].

4.3.10. Therapeutic Applications

ASOs are promising in combating multi-drug-resistant bacteria and viruses by targeting genes responsible for replication, virulence, and antibiotic resistance. Preclinical studies have shown ASOs' potential as antibacterial agents, such as against methicillin-resistant Staphylococcus aureus (MRSA), where ASOs targeting the ftsZ gene hinder bacterial growth. ASOs have also been studied for viral infections like Hepatitis B, Influenza, and others, showing significant reductions in viral titers [3].

4.3.11. Advantages and Disadvantages

ASOs are accurate, easily synthesized, and cost-effective, making them suitable for large-scale production. However, earlier versions had poor absorption and off-target toxicity. Second and third-generation ASOs addressed these issues with chemical modifications, improving delivery and reducing toxicity. Advances in delivery strategies are still needed to avoid accumulation in the kidneys and liver and mitigate immune responses [3].

4.3.12. Oligonucleotide Aptamers

An oligonucleotide aptamer is a single-stranded DNA or RNA molecule that folds into a 3D shape, allowing it to bind specifically to its targets through various chemical bonds. Often referred to as "chemical antibodies," aptamers can be quickly produced to counteract non-immunogenic substances and microbial toxins. Their affordability, non-immunogenic nature, easy modification, and tissue permeability make them promising therapeutic agents against infectious diseases [40].

4.3.13. Therapeutic Applications

Aptamers, like antibodies, can bind to targets and modify their functions by interacting with catalytic centers or inducing charge-dependent conformational changes in proteins. This makes them effective in targeting pathogen enzymes and functional proteins, controlling replication, and serving as targeted drug delivery agents. Aptamers can also activate enzymes and cell signaling pathways, enhancing the host's immune response by targeting immune activators and anti-infection enzymes. Non-functional aptamers can deliver siRNA to infected cells when combined with drugs or nanoparticles [40].

Aptamers can prevent pathogen spread at three stages of the pathogenesis cycle:

1. Blocking Host Entry: Aptamers can block pathogens from entering host cells by targeting surface proteins. For example, RNA and DNA aptamers were developed to target the gD protein of herpes simplex virus 1 (HSV-1), preventing cell entry. Similarly, DNA aptamers targeting HupB proteins blocked Mycobacterium tuberculosis entry into THP-1 cells. This technology has also been applied to viruses like HIV-1, influenza, and SARS-CoV-2.
2. Inhibiting Propagation: Aptamers can inhibit pathogen propagation by inactivating or blocking target molecules. For hepatitis C, RNA aptamers targeting the NS5B replicase acted as decoys to inhibit RNA synthesis. For SARS-CoV, an RNA aptamer pool inhibited helicase activity by up to 85%. Further research is needed to explore this for SARS-CoV-2.
3. Neutralizing Toxins: Aptamers can neutralize microbial toxins by binding directly to them or their receptors. For example, an RNA aptamer blocked the neurotoxin of Clostridium botulinum, and DNA aptamers inhibited the α-toxin of S. aureus. Further testing is needed to confirm aptamers' potential to neutralize microbial toxins.

Aptamers can enhance the immune system by blocking pathogen-produced immunosuppressors. For example, DNA and RNA aptamers targeting the NS1 protein of the influenza virus increased interferon beta (INF-β) production, counteracting NS1's inhibition of the innate immune response and preventing further viral replication. Additionally, aptamers can activate or inhibit key immune molecules to strengthen the immune system. A phosphorylated DNA aptamer targeting toll-like receptor 9 (TLR9) acts as an intracellular TLR9 agonist, stimulating TLR signaling pathways and promoting immune responses against bacterial infections. Continued research is needed to assess aptamers as antibiotic-independent therapies for infectious diseases [40].

4.3.14. Disadvantages

Despite their potential, oligonucleotide aptamers have some disadvantages. First, while aptamers themselves are inexpensive, the costs of modifications and detection devices are high. Second, some aptamers require chemical modifications to enhance their stability and binding affinities in various solutions. Third, their negative charge can lead to non-specific binding to positively charged objects. Lastly, aptamers have not yet gained significant market recognition, but current data suggests they hold promise for treating infectious diseases and warrant further research [40].

4.3.15. Anti-Biofilm Drug

Biofilms pose a major challenge in treating bacterial infections by contributing to resistance and blocking antibiotic penetration [41]. Preventing the initial bacterial attachment to surfaces is a key strategy for inhibiting biofilm formation.

4.4. Applications

Anti-biofilm drugs include small molecules like mannosides, peptides, phage-encoded depolymerases, and aptamers. Monomeric biphenyl mannosides prevented E. coli biofilm formation and blocked bacterial invasion in animal models. Peptides like IDR-1018, DJK-5, and DJK-6 inhibit biofilm-forming proteins in gram-positive and gram-negative bacteria. Phage-encoded depolymerases degrade biofilm components, while aptamers target specific bacterial surface constituents. Six DNA aptamers, combined with liposomal antibiotic delivery, were found to aid in eradicating S. aureus biofilm [41].

4.5. Antibacterial Nanomaterial

Many nanomaterials have bactericidal effects through mechanisms like oxidative stress, physical disruption, altered bacterial

metabolism, protein denaturation, and disrupted DNA replication. Since bacterial cell envelopes are negatively charged, positively charged nanoparticles are developed for electrostatic interaction [41].

4.6. Therapeutic Application

Gold nanoparticles increase membrane tension, leading to cell envelope damage and lysis. Silver nanoparticles generate reactive oxygen species, damaging peptidoglycan structures. Copper nanoparticles inhibit bacterial glucose transporter expression, while graphene oxide-silver (Go-Ag) nanoparticles destroy bacterial cell walls in E. coli and S. aureus [41].

5. Results

5.1. Meta-analysis

5.1.1. Bacteriophage therapy

Bacteriophage therapy, despite its historical significance, has faced challenges limiting widespread use. It began in 1919 in Paris, treating dysentery in children [42]. Early studies in Poland and the Soviet Union showed success, particularly with lung and pleural infections. One study treated 45 patients with phages and antibiotics for infections, while another found an 82% recovery rate with phages compared to 64% with antibiotics. Eastern European studies showed phage therapy improved infectious allergies by 86%, compared to 48% with antibiotics alone [43]. The Israeli Phage Therapy Center, established in 2018, has achieved a 77% favorable outcome in over 20 cases [44]. In MRSA pneumonia, aerophages and IV phages rescued 50% of animals, with a combination treating 91% [45]. A cholera study reduced the death rate from 63% to 8% with phage lysate treatment [46].

5.1.2. Engineered Probiotics

Engineered probiotics are emerging as potential tools against antibiotic resistance. While most clinical trials have focused on non-infectious conditions like phenylketonuria, cirrhosis, and cancers, researchers are now exploring their use for bacterial infections. For example, the engineered E. coli Nissle strain demonstrated stable gut colonization in mice, delaying Pseudomonas aeruginosa infections for several weeks [47]. In another study, recombinant E. coli, expressing a gene from Neisseria gonorrhoeae, successfully treated mice infected with deadly Shiga toxigenic E. coli. Similarly, engineered E. coli expressing the GM1 receptor produced significant amounts of Cholera toxin, protecting mice from V. cholerae [48]. Despite their promise, these products are still in early development, with no regulatory approval and limited clinical trials, requiring further research and overcoming significant financial and scientific hurdles before human use , as shown in table 1, engineered probiotics and their effects on differernt bacterial infections.

5.1.3. Antisense Therapy

Antisense therapy has emerged as a promising approach to combat antibiotic-resistant bacteria and infectious diseases. A study in Chongqing, China, investigated antisense peptide nucleic acid conjugates to inhibit methicillin-resistant Staphylococcus aureus (MRSA) in vitro, specifically targeting the FtsZ gene.

This inhibition effectively blocked MRSA growth without toxicity to human cells due to the inhibitor's inability to interact with human tubulin [49]. In the fight against viruses, peptide-conjugated phosphorodiamidate morpholino oligomer (PPMO) antisense oligonucleotides (ASOs) have shown effectiveness against various infectious diseases, including Dengue, influenza, hepatitis B, and Ebola [3].

An experiment on Vero E6 cells infected with live SARS-CoV-2 revealed that 5' UTR-targeting ASOs 38 and 44, as well as N gene-targeting ASOs 41 and 42, reduced intracellular viral load by 53-87% [50]. Further studies demonstrated that Gapmer ASOs achieved 99% inhibition of SARS-CoV-2 infections in half of the screened ASOs. These experiments were conducted on H1437 cells, a lung lineage cell line with a 60% SARS-CoV-2 infection rate [51]. As shown in table 2, the summary of ASOs tackling different infections.

5.1.4. Oligonucleotide Aptamers

Aptamers have shown significant potential in treating a broad spectrum of infections, including viral infections like HCV, influenza, and HIV, as well as bacterial pathogens such as E. coli, Staphylococcus aureus, and Mycobacterium tuberculosis [51].

In HCV detection, the ssDNA aptamer ZE2, via the ELISA method, detects both bound and free E2 antigens, allowing for early virus detection. It also blocks E2 antigen binding to CD81 receptors, inhibiting viral infection of human hepatocytes in vitro [52].

For influenza, aptamers like HA12-16 and C7-35M show promise by binding to the surface glycoprotein HA and the globular region of AIV H9-type HA, respectively. This disrupts virus attachment to host cells, enhancing cell viability. Various aptamer-based detection methods, including SERS-based aptamers and enzyme-linked aptamer assays (ELAA), have also been developed for influenza [53].

In HIV treatment, aptamers like UCLA1 neutralize HIV-1 subtype C Gp120 without toxicity and show effectiveness at low doses. UCLA1's derivative, UCLA005v11, exhibits higher stability, and aptamers targeting the Gag protein have successfully blocked HIV replication in cultured cells [54]. For tuberculosis, aptamers are gaining recognition as diagnostic tools. ManLAM aptamer-based immunohistochemistry demonstrated high sensitivity, especially when combined with other diagnostic methods, achieving sensitivity rates between 88.64% and 97.92% [55]. Therapeutically, ssDNA aptamers like NK2 and ZXL1 show promise in reducing disease progression and bacterial load in M. Tb infections [51].

Overall, aptamers represent a promising frontier for both the diagnosis and treatment of infectious diseases, offering targeted and effective interventions, as shown in table 3.

The samples were tested in order to determine the sensitivity of several diagnostic methods and are represented in table 4.

6. Discussion

6.1. Case Studies of Infectious Diseases

6.1.1. Malaria

Malaria is a life-threatening disease that caused 608,000 deaths in 2022. It is transmitted to humans by mosquitoes carrying Plasmodium parasites. According to the 2023 WHO Malaria Report, there were 249 million cases in 2022, surpassing pre-pandemic

levels. Over half of these cases occurred in the Democratic Republic of Congo, Nigeria, Uganda, and Mozambique. Pakistan saw a sharp increase, reaching 2.6 million cases, linked to devastating floods [56]. The emergence of drug-resistant Plasmodium strains has made effective malaria management increasingly urgent [57].

Four main Plasmodium species infect humans: P. falciparum, P. vivax, P. malariae, and P. ovale. P. falciparum is the most dangerous and prevalent, particularly in sub-Saharan Africa [58]. P. vivax and P. ovale can cause relapses due to dormant liver stages [59,60] and P. malariae leads to chronic, low-level infections.

6.1.2 Transmission of Malaria

Malaria is transmitted primarily through Anopheles mosquitoes. When a female mosquito feeds on the blood of an infected person, it ingests male and female gametocytes. These develop into gametes within the mosquito, forming a zygote that becomes an ookinete. The ookinete travels through the mosquito's gut wall, becoming an oocyst, which eventually bursts, releasing sporozoites. These sporozoites settle in the mosquito's salivary glands, ready to infect the next human host during feeding [61].

In humans, sporozoites develop in the liver into merozoites and hypnozoites. Merozoites enter the bloodstream, infect red blood cells, and multiply, continuing the transmission cycle. Hypnozoites, residing in the liver, can cause relapses [61].

Malaria can also spread through vertical transmission, where an infected mother passes the parasite to her unborn child during pregnancy, childbirth, or breastfeeding [62]. This is more common in endemic areas with high parasitemia levels in mothers, leading to complications like severe anemia and low birth weight in newborns [63-64]. Transmission through blood transfusions or organ transplants is rare and typically occurs only when screening measures are inadequate [65]. Proper prenatal screening and blood safety measures are essential, especially in endemic areas, to prevent complications.

6.1.3. Symptoms of Malaria

Early malaria symptoms resemble the flu, with nonspecific signs such as fever, headache, fatigue, and muscle pain, sometimes extending to jaundice and gastrointestinal [66]. In P. falciparum infections, fever typically begins 9-14 days post-exposure, initially irregular but eventually becoming daily (quotidian), every three days (tertian), or every 36 hours (subtertian). Physical exams may reveal hepatosplenomegaly, orthostatic hypotension, and jaundice [67].

P. falciparum severely damages red blood cells, altering their shape and making them rigid and sticky, which leads to their adhesion to endothelial surfaces and causes severe anemia [68]. Complications like cerebral malaria result from the sequestration of infected red blood cells in small blood vessels. Interestingly, inherited blood disorders such as sickle cell anemia offer some protection against malaria by disrupting the parasite's interaction with red blood cells [69].

P. vivax and P. ovale infections cause recurring febrile flare-ups, synchronized after 5-7 days. These flare-ups progress through three stages: sudden coldness and shivering, followed by high fever, vomiting, and altered consciousness, and ending with profuse sweating and a rapid temperature drop. This cycle lasts 6-10 hours, often starting in the late afternoon or evening [70]. P. malariae presents with flare-ups every 72 hours, generally causing less severe symptoms, including milder anemia and splenomegaly [67]. P. knowlesi, endemic in Southeast Asia, presents similarly to P. falciparum [71].

Malaria's diverse manifestations can easily be mistaken for other diseases such as influenza, dengue fever, or gastroenteritis. Therefore, clinical judgment is critical, but the primary method for confirming malaria is blood films [66].

6.1.4. Diagnosis of Malaria

There are both traditional and advanced methods for diagnosing malaria [72]. Microscopy remains the gold standard due to its cost-effectiveness, ability to identify Plasmodium species, assess parasitemia levels, and screen for other blood disorders. This information is crucial for determining infectivity and treatment plans [73]. However, microscopy has limitations, particularly in detecting low-level infections and requiring skilled technicians [74]

Rapid diagnostic tests (RDTs), such as immunochromatography-based RDT, ELISA, and flow cytometry, are widely used in endemic areas. They are simple, quick, and require minimal equipment but have lower sensitivity compared to microscopy, so additional tests are often needed for confirmation [75]. ELISA, for example, can detect specific antigens like Plasmodium falciparum histidine-rich protein 2 (PfHRP-2) with high sensitivity [76]. Flow cytometry also offers rapid parasitemia measurements and staging by analyzing DNA content and cell characteristics, even detecting the malaria pigment, hemozoin [77].

To overcome these limitations, molecular techniques like polymerase chain reactions (PCR) have been developed. Variants such as nested, multiplex, and real-time PCR are highly effective in identifying Plasmodium species and measuring parasitemia [78]. However, they are expensive and slower than desired. Emerging methods, including biosensing-based diagnostics and loop-mediated isothermal amplification (LAMP), are being explored as more affordable alternatives [72].

6.1.5.Intervention of Malaria

Malaria infections vary, and complications are common, particularly with drug-resistant strains. Multiple treatment options exist. For uncomplicated P. falciparum, the first-line treatment is artemisinin-based combination therapy (ACT). However, if the infection originates from a chloroquine-susceptible area, chloroquine is used. Non-falciparum malaria is treated with chloroquine or ACT [79]. In cases of P. vivax and P. ovale, 8-aminoquinoline drugs are essential to eliminate liver stages and prevent relapses [80,81,82].

Severe malaria, characterized by organ involvement or high parasite levels, requires hospitalization and intravenous artesunate for 24 hours, which is more effective and better tolerated than IV quinine [79]. These drugs target the asexual blood stages responsible for symptoms.

To combat resistance, new antimalarials with novel mechanisms of action, improved administration, and efficacy against both blood and gametocyte stages, as well as liver hypnozoites, are needed. Promising molecular targets include enzymes critical to the

parasite's metabolism, such as proteases and protein kinases [83].

6.1.6. Prevention of Malaria

Malaria prevention requires a comprehensive approach, typically beginning with chemoprophylaxis. Antimalarial drugs such as atovaquone-proguanil, doxycycline, or mefloquine are taken before, during, and after travel to malaria-endemic areas [84]. These drugs act on blood stages of the parasite but do not affect dormant liver stages, as seen with P. vivax and P. ovale, which may relapse weeks or months after exposure [80,81,82]. In 2018, the FDA approved tafenoquine for weekly malaria prevention and treatment of relapsing malaria caused by P. vivax and P. ovale [85]. Unlike other drugs, tafenoquine targets liver stages, offering broader protection for travelers to high-risk areas. Its weekly dosing improves adherence compared to daily regimens. However, tafenoquine increases the risk of hemolytic anemia in individuals with glucose-6-phosphate dehydrogenase (G6PD) deficiency, so careful monitoring is necessary [86].

Preventing mosquito exposure is also crucial, especially during peak feeding times between dusk and dawn. Strategies include staying in screened accommodations, using insecticide-treated bed nets, and wearing long sleeves to minimize skin exposure [87]. Topical insect repellents containing DEET, picaridin, IR3535, or oil of lemon eucalyptus should be applied correctly, following recommended concentrations [88]. Vaccine development for malaria began in the 1960s, and in October 2021, the World Health Organization officially recommended the RTS,S/AS01 vaccine for children under five in high-transmission areas [89,90]. Clinical trials demonstrated that this vaccine provides significant protection with a good safety profile [91].

6.2. Human Immunodeficiency Virus (HIV)

Since its discovery in 1981, HIV has claimed over 40 million lives, with 84 million people infected globally. By 2022, 39 million people were living with HIV. The epidemic is most prevalent in low- and middle-income countries, particularly in eastern and southern Africa, which account for 53% of cases [92]. Females are more vulnerable to HIV than males, often becoming infected earlier, likely due to the anatomy, which increases exposure during sexual intercourse [93]. Additionally, the rise of transmitted drug-resistant (TDR) HIV variants, especially in resource-limited countries, is a growing health concern, with a 10% increase in prevalence [94].

6.2.1. The Structure of HIV

HIV is an RNA virus consisting of two single strands of RNA, enclosed by a capsid and surrounded by a viral envelope containing receptors that facilitate invasion of the human body. HIV is divided into two types, with type 1 being more common. It belongs to the retrovirus family, integrating a DNA copy of its RNA genome into the host cell's DNA [95].

6.2.2. Transmission of HIV

HIV spreads through the exchange of bodily fluids, primarily via sexual, parenteral, and vertical transmission. Unprotected sex with an HIV-positive person in the acute phase carries a transmission rate of up to 2% for receptive vaginal sex and 20% for receptive anal sex, putting men who have sex with men, sex workers, and those engaging in unprotected sex at higher risk [96]. However, studies show no risk of sexual transmission in individuals with viral loads below 1000 copies per mL [97]. Parenteral transmission occurs through needle sharing among intravenous drug users, needle-stick injuries, and contaminated blood transfusions, with drug injections accounting for about 10% of HIV cases globally [98]. Vertical transmission, from mother to child, occurs during childbirth or breastfeeding [99]. Some infants escape infection despite high virus exposure, suggesting potential maternal or fetal immune protective factors that are not yet fully understood [100].

6.2.3. Pathogenesis of HIV and its Complications

To understand HIV's effects on the body, it is crucial to examine how it evades the immune system. During primary infection, HIV attaches to CD4 receptors on host cells via its glycoprotein gp120, initiating binding. The viral envelope then fuses with the host cell membrane, allowing the capsid to enter. This fusion requires interaction between the host cell's CD4 receptor and the virus's coreceptor. There are two types of coreceptors: CCR5, which mediates fusion with macrophages and T-cells early in infection, and CXCR4, which later targets T-cells [101]. Individuals with a mutated CCR5 gene are immune to HIV, as the virus cannot bind to their host cells [102].

Once fused, the viral RNA is transcribed into double-stranded DNA via reverse transcriptase, and the DNA is integrated into the host genome by integrase. The viral DNA is then replicated, leading to HIV's multiplication in the body. A viral load exceeding 1,000 copies per mL is the threshold for HIV infectivity [103].

As the infection progresses, HIV spreads by infecting lymphocytes, which circulate through lymphoid tissues, including lymph nodes and gut-associated lymphatic tissue. This marks the acute syndrome stage with a high viral load. Following this, the viral load declines and remains low during the clinical latency period, which lasts about eight to ten years, with replication primarily occurring in the lymph nodes. As CD4+ cells deplete, the immune system weakens, leading to opportunistic infections and cancers that are the usual cause of death for HIV-positive individuals. The advanced stage of HIV, when the immune system is severely compromised, is known as acquired immunodeficiency syndrome (AIDS) [101,104].

6.2.4. Signs and Symptoms of HIV

The initial signs and symptoms of HIV infection are often nonspecific, such as fatigue, malaise, fever, night sweats, or weight loss. In some cases, there may be no noticeable symptoms, making clinical diagnosis difficult. Symptoms may arise from the virus itself or indicate opportunistic infections or malignancies like Pneumocystis pneumonia, chronic cryptosporidiosis, toxoplasmosis, oral thrush, Kaposi's sarcoma, and lymphoma as the disease progresses to AIDS. Laboratory findings, such as reduced CD4 cell counts, increased CD8 cells, hypergammaglobulinemia, and elevated β-2-microglobulin, are key indicators of immune dysfunction, highlighting the importance of a thorough patient history and prompt intervention [105].

6.2.5. Diagnosing HIV

There are three main types of tests available for diagnosing HIV: antibody tests, antigen/antibody tests, and nucleic acid tests (NAT),

primarily performed on blood samples. Each test has a different window period after exposure. The eclipse period is the time following infection when no test can detect HIV. The first detectable marker is HIV RNA, with studies showing that 50% of patients test positive for RNA within the first 12 days [106-107]. Early detection improves patient outcomes and reduces disease transmission. Nucleic acid testing (NAT) detects HIV 10-33 days after exposure by identifying the virus itself, not the immune system's response. Rapid NATs can yield results within 90 minutes, making them valuable for diagnosing acute HIV and guiding early prophylaxis (108). Though NATs quantify the virus in the blood, they are not used for screening due to cost. Antigen/antibody combination tests (fourth-generation tests) detect HIV 18-45 days post-exposure by identifying the HIV p24 antigen first, followed by antibodies. These tests can detect both HIV-1 and HIV-2 and are often used for screening [108,109]. Antibody tests, which detect antibodies 23-90 days after exposure, are commonly used to confirm diagnosis and monitor treatment, especially in resource-limited settings [108].

6.2.6. Intervention of HIV

Despite no cure for HIV, antiretroviral therapy (ART) effectively controls the virus. ART typically combines 3+ drugs from different classes, including NNRTIs, NRTIs, protease inhibitors, integrase inhibitors, and entry/fusion inhibitors. The goal is to achieve an undetectable viral load, which not only improves health but also prevents sexual transmission [110]. ART should begin within 72 hours of exposure and is usually administered orally without hospitalization unless complications like TB, meningitis, or Kaposi's sarcoma occur [111]. Common side effects include hepatic toxicity, rashes, anemia, and neuropathies [112].

Drug-resistant HIV mutations pose a significant challenge, especially in HIV-1, leading to treatment failures. Databases like Stanford's HIV Drug Resistance Database help monitor these mutations [94]. Traditional genotyping and next-generation sequencing (NGS) are crucial tools for surveillance, with NGS offering high-throughput, cost-effective solutions. These advances may help monitor the impact of experimental curative interventions targeting the HIV reservoir [113].

Gene therapy, particularly with fusion inhibitors like peptide C46, has shown potential in reducing HIV expression. Enfuvirtide, approved in 2003, blocks viral entry by inhibiting attachment to gp41. CRISPR technology, using Cas9 to target and edit HIV proviral DNA, also holds promise, but challenges like resistance development and off-target effects persist [1,114]. Other potential treatments, such as aptamers and ribozymes, have shown promise but lack sufficient clinical testing. In HIV treatment, aptamers such as UCLA1 can neutralize the HIV-1 subtype C Gp120 protein without causing toxicity, and they are effective even in low doses. A modified version of UCLA1, called UCLA005v11, is more stable. Additionally, aptamers targeting the Gag protein have successfully stopped HIV replication in cell cultures [54].

Monitoring CD4 cell count and viral load is vital in managing HIV. CD4 counts between 500-1,500 cells/mm³ are normal, with counts below 200 indicating AIDS [115]. Viral load monitoring, ideally every 3-6 months, is crucial to assess ART effectiveness. An undetectable viral load (<20 copies/mL) indicates successful viral suppression [116].

HIV increases susceptibility to opportunistic infections, which can be fatal if unmanaged. Regular screenings for infections like syphilis, gonorrhea, TB, and hepatitis are essential. Prophylactic antimicrobials are given to patients with severe immunosuppression, discontinued when CD4 counts exceed 200 cells/μL for 6 months [117]. Vaccinations, provided they are inactivated, should be administered to prevent opportunistic infections like influenza, tetanus, HPV, and hepatitis [118,119]

6.2.7. Prevention of HIV

The most successful HIV prevention programs take a comprehensive approach, integrating social, biomedical, and behavioral factors. Key behavioral measures include promoting regular HIV testing, supporting consistent use of male and female condoms [120], advocating male circumcision [121], and providing thorough sexual education to reduce risky behaviors [122]. Regular condom use in heterosexual couples reduces the risk of HIV transmission by 80% [120]. A 2024 study showed that voluntary medical male circumcision (VMMC) was 91% effective in reducing HIV transmission among men who have sex with men (MSM) [121].

Biomedical interventions are implemented at various stages of exposure. Pre-exposure prophylaxis (PrEP) significantly reduces the risk of HIV by 75%, particularly in high-risk populations such as sex workers, MSM, and transgender women [123]. Ensuring access to antiretroviral therapy (ART) for people living with HIV is essential for achieving viral suppression [124]. Post-exposure prophylaxis (PEP) is also over 90% effective when administered after suspected exposure, particularly for healthcare workers [125]. Reducing the spread of HIV also requires addressing legal, policy, and social barriers that deter testing and treatment. Stigma, discrimination, and lack of access to education and economic opportunities exacerbate the spread of HIV [126,127]. Services must be tailored to the needs of different populations, with ongoing quality assessments to ensure effectiveness.

6.3. Influenza

Influenza is one of the most widespread infections globally, affecting an estimated 9.3 to 41 million people annually between 2010 and 2023, with 4,900 to 51,000 deaths each year [128]. The economic impact is significant, costing the U.S. over $1 billion annually. Interestingly, influenza cases saw a sharp decline during the COVID-19 pandemic (2020-2022), possibly due to COVID-19 prevention measures or underreporting due to overlapping symptoms [129]. Globally, influenza causes 290,000 to 650,000 deaths annually, with children under five in developing countries being the most affected [130]. Understanding its structure, infection mechanisms, transmission, diagnosis, and management is key to developing prevention strategies.

6.3.1. Structure

Influenza viruses have a segmented, single-stranded RNA genome, usually composed of eight segments. There are three types: influenza A, B, and C, with A and B causing most seasonal flu. Influenza A is known for originating from birds and is classified based on two surface glycoproteins, hemagglutinin (HA) and neuraminidase (NA), such as in the H1N1 swine flu. Influenza B, however, is categorized into B/Victoria and B/Yamagata lineages

[131,132]. The virus, part of the Orthomyxoviridae family, can appear spherical or filamentous in shape.

Influenza A and B cause more severe symptoms compared to Influenza C, with A being responsible for most pandemics. New flu strains emerge through antigenic drift, which involves gradual mutations in HA and NA proteins, and antigenic shift, a more drastic change caused by the exchange of surface glycoproteins between two viruses infecting the same organism [133].

6.3.2. Pathogenesis of Influenza

HA and NA glycoproteins play a crucial role in both detection and the virus's pathogenicity. HA binds to sialic acid on host cell glycoproteins, leading to endocytosis of the virus. Inside the endosome, the acidic environment changes the HA protein, releasing viral RNA into the cell. The M2 pump, another viral protein, helps pump hydrogen ions into the virus, a process targeted by certain anti-influenza drugs. Once inside the nucleus, the viral RNA is transcribed by RNA-dependent RNA polymerase. This produces positive-strand RNA for protein synthesis and replication of viral RNA [131,132].

After translation in the endoplasmic reticulum, viral proteins, including HA and NA, are transported to the host cell membrane, where new virions are assembled. These virions are then exocytosed, with NA cleaving the link between HA and sialic acid to prevent the virus from rebinding to the same cell. The virus primarily infects epithelial cells in the respiratory tract and alveolar type II cells, where sialic acid is highly expressed [131,132].

6.3.3. Transmission of Influenza

Influenza primarily spreads through respiratory droplets, aerosols, or direct contact. The virus can also be transmitted via animals (vectors) infected with influenza, contributing to antigenic shifts and epidemics. However, humans are the main vectors of transmission, particularly during colder months when people spend more time indoors, increasing exposure to airborne droplets from infected individuals. There is some evidence that cold weather might weaken the immune system, as seen in studies on mammals, though more research is needed to confirm this in humans.

6.3.4. Clinical Manifestations of influenza

More than 50% of influenza infections can be asymptomatic. When symptoms do occur, they include fever, cough, coryza, headache, fatigue, and malaise. These symptoms usually last 7-10 days, though fatigue may linger for weeks. Populations at higher risk include children, pregnant women, the elderly, and individuals with chronic conditions such as asthma, heart disorders, and compromised immune systems. Chronic health issues can impair immune function, hinder immune cell recruitment, or disrupt respiratory clearance mechanisms, making individuals more vulnerable to complications like secondary bacterial infections, myocarditis, or encephalitis [134,135].

6.3.5. Diagnosis of influenza

Diagnosing influenza begins with clinical observation, though symptoms alone cannot reliably distinguish it from other viral infections. Clinical diagnosis is non-invasive and low-cost but lacks sensitivity and specificity. Therefore, more precise diagnostic methods are needed.

These fall into seven categories: Rapid Influenza Diagnostic Tests (RIDTs), Rapid Molecular Assays, Reverse Transcription Polymerase Chain Reaction (RT-PCR), Viral Culture, Immunofluorescence Assays, Serological Tests, and Next-Generation Sequencing (NGS).

Each diagnostic tool varies in speed, sensitivity, specificity, cost, and application [128,136,137,138,139].

These diagnostic tools speed, sensitivity, specificity, cost and use case are written in table 5.

6.3.6. Intervention of influenza

To manage influenza, first assess the patient's symptoms and risk factors, such as being immunocompromised. If these factors indicate a higher risk, a diagnostic test should be ordered. RT-PCR is the gold standard due to its high specificity and sensitivity, despite its cost and longer turnaround time. In resource-poor countries, Rapid Influenza Diagnostic Tests (RIDTs) are used due to their affordability and quick results. For high-risk patients needing accurate results, such as those who might require antiviral treatment, rapid molecular assays are recommended. These diagnostic tests are generally used in special circumstances, like hospital outbreaks or for highly susceptible patients [128,136,137,138,139].

Preventing influenza through intervention is the most effective and economical approach. There are two main types of interventions: pharmaceutical and non-pharmaceutical. Pharmaceutical interventions include vaccines, antiviral treatments for high-risk individuals, and antibiotics to prevent complications [140,141]. Non-pharmaceutical interventions focus on educating the public about hygiene and implementing guidelines in public and hospital settings.

Non-pharmaceutical interventions are cost-effective and non-invasive. A significant reduction in influenza cases was observed between 2020-2022, attributed to social distancing during the COVID-19 pandemic. As restrictions eased, influenza cases re-emerged. Studies by the University of Hong Kong and the University of Michigan demonstrated that preventive measures, such as wearing masks and hand sanitizing, limited secondary infections by influenza [140,142]. Despite these benefits, limitations include sample sizes, underreporting, and low test sensitivity.

Pharmaceutical interventions vary depending on the stage and type of infection. The annual flu vaccine is the most common preventive measure for people aged six months and older. It protects against gradual genetic drift in the virus. Vaccines can also act as chemoprophylaxis for immunocompromised patients.

Education and accessibility are vital for increasing vaccine uptake. A meta-analysis by Murray et al. (2021) found that pharmacist-led education significantly improved vaccine uptake. However, not all patients, such as those with compromised immune systems or advanced HIV, can receive vaccines and may require antiviral chemoprophylaxis instead. Though pharmaceutical prevention is effective, it adds a significant economic burden, especially for developing countries [140].

Research is being conducted on delivering mRNA-encoded Cas13 and crRNAs through a nebulizer to stop the replication of viruses like influenza and SARS-CoV-2 [1]. Several aptamers have

demonstrated great potential in treating a wide range of infections, including viral infections like influenza. For instance, aptamers such as HA12-16 and C7-35M show promise by binding to the surface glycoprotein HA and the globular region of the AIV H9-type HA, respectively [51,53].

6.4. TB Prevalence and Modes of Intervention

Tuberculosis (TB) is caused by Mycobacterium tuberculosis (MTB), a unique bacterium with a cell wall made of arabinogalactan and fatty acids instead of peptidoglycan [143]. TB is airborne, requiring infected patients to be placed in negative pressure rooms with personal protective equipment (PPE) and isolation. In 2023, TB infected 10.6 million people, an increase from 10.3 million in 2022, and killed 1.13 million HIV-negative individuals [144]. TB is often stigmatized due to its association with HIV, poverty, malnutrition, and poor living conditions. Risk factors include overcrowding, diabetes, immunosuppressants, and substance use, increasing the likelihood of infection and disease progression [145]. The top three countries contributing to new TB cases are India (27%), Indonesia (10%), and China (7.1%), accounting for 44.1% of global cases [143]. Symptoms include persistent cough, hemoptysis, night sweats, weight loss, fever, fatigue, swollen lymph nodes, and thoracic or abdominal pain [146,147].

6.4.1. Transmission and Complications of TB

TB is primarily transmitted through inhalation of airborne droplets, with the lungs serving as the main reservoir. The bacteria target alveolar macrophages, inhibiting their destruction by preventing phagosome maturation and acidification, allowing MTB to grow inside the macrophage [148]. TB can remain latent and non-infectious until immune suppression occurs, often due to HIV or other illnesses, leading to active TB and potential spread to other organs, causing conditions like extrapulmonary TB or TB meningitis.

6.4.2. Diagnosis of TB

TB is commonly diagnosed using the tuberculin skin test and QuantiFERON (IGRA) test. The skin test involves injecting purified protein derivative from TB under the skin, with a delayed hypersensitivity reaction indicating past infection [149]. The QuantiFERON test measures interferon-gamma (IFN-γ) levels in the blood, elevated in those previously exposed to TB [149, 150]. Neither test distinguishes between active and latent TB, prompting further tests like chest X-rays.

6.4.3. Intervention of TB

Non-pharmaceutical interventions include screening close contacts of active TB patients to stop the spread and implementing public health measures like the Bacillus Calmette-Guérin (BCG) vaccine. Nutritional support, hydration, and airway clearance techniques can also help manage TB, as malnutrition is linked to poorer outcomes [145]. Education and behavioral interventions increase awareness and treatment adherence, reducing stigma and improving patient outcomes [151].

Pharmaceutical interventions include vaccines and antibiotics. BCG, a live attenuated vaccine, is widely used but has variable effectiveness, especially in adults [152]. Research is ongoing into new vaccines, such as peptide-based vaccines (PBVs) and alternative administration routes like inhalation to enhance lung-specific immunity [153,154].

When a person is infected with TB, treatment typically includes a combination of Isoniazid (INH), Rifampicin (RMP), Pyrazinamide (PZA), and Ethambutol (EMB) for two months, followed by INH and RMP for four months [151,155]. Multidrug-resistant TB (MDR-TB) poses challenges, requiring alternative treatments such as fluoroquinolones or Bedaquiline [156,157].

Surgical intervention is a last resort for cases like severe lung bleeding, spontaneous pneumothorax, or MDR-TB unresponsive to prolonged treatment. Surgical techniques include lung resection and size reduction to improve lung function [158]. However, surgery carries risks due to variability in surgeon experience and is costly, so it is typically avoided when possible.

Aptamers have shown considerable promise in treating a wide range of infections, including bacterial pathogens like Mycobacterium tuberculosis [51]. Therapeutically, single-stranded DNA aptamers such as NK2 and ZXL1 have shown potential in slowing disease progression and reducing bacterial load in Mycobacterium tuberculosis infections [51]. As shown in the above mentioned table 3, aptamers represent an exciting new frontier in both the diagnosis and treatment of infectious diseases, providing targeted and effective therapeutic options.

In conclusion, infectious diseases continue to pose a significant global health burden, accounting for millions of deaths annually, particularly among vulnerable populations. Conventional treatment methods are increasingly challenged by drug resistance, disturbances in microbiota, and persistent viral reservoirs, complicating efforts to combat these diseases. However, emerging therapeutic interventions, including bacteriophage therapy, engineered probiotics, CRISPR therapy, antisense therapy, oligonucleotide aptamers, and antibacterial nanomaterials, offer promising new approaches to tackle these challenges. While many of these therapies are still in the early stages of development and face hurdles such as off-target effects, regulatory approval, and financial constraints, they represent a new frontier in the fight against infectious diseases. Continued research, innovation, and effective public health strategies are essential to harness the full potential of these technologies and improve patient outcomes in the battle against infectious diseases.

7. Keywords

Infectious diseases; Therapeutics; Targeted Interventions; Contact Tracing; Public Health

Author Contributions:

Noora R. Al-Snan: The author had made substantial contributions to conception and design, or acquisition of data, or analysis and interpretation of data; and been reviewing the manuscript.

Zaynab Maqwar: The author had made substantial contributions to conception and design, or acquisition of data, or analysis and interpretation of data; and been reviewing the manuscript.

Kawthar Maqwar: The author had made substantial contributions to conception and design, or acquisition of data, or analysis and interpretation of data; and been reviewing the manuscript.

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to conception and design, or acquisition of data, or analysis and interpretation of data; and been involved in drafting the manuscript.
Moayed Al Abdul Wahed: The author had made substantial contributions to conception and design, or acquisition of data, or analysis and interpretation of data; and been involved in drafting the manuscript.
Adnan Raad Al-Obaidi: The author had made substantial contributions to conception and design, or acquisition of data, or analysis and interpretation of data; and been involved in drafting the manuscript.
Faizan Butt: The author had made substantial contributions to conception and design, or acquisition of data, or analysis and interpretation of data; and been involved in drafting the manuscript.
Fatma Al-Jabri: The author had made substantial contributions to conception and design, or acquisition of data, or analysis and interpretation of data; and been involved in drafting the manuscript.

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9. Key Clinical Message
The fight against infectious diseases requires innovative treatments and strong public health strategies. Emerging therapies like bacteriophages, CRISPR, and engineered probiotics offer hope in addressing drug resistance, while efficient contact tracing and diagnostics remain critical in outbreak control. Continued research and collaboration are key to improving global health outcomes.

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