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The Significance of Vaccines in Mitigating Emerging Infectious Diseases: A Comprehensive Review

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Abstract

The global rise in emerging infectious diseases presents significant challenges to public health, exacerbated by issues such as antimicrobial resistance (AMR). Vaccination remains a pivotal strategy in preventing the spread of these diseases, yet its role is often underappreciated in the context of rising drug resistance.This review synthesizes current literature on the effectiveness of vaccines and immunotherapeutic approaches in controlling emerging infectious diseases. It analyzes data from clinical studies, epidemiological reports, and the impact of vaccination on AMR trends, particularly in regions severely affected by infectious diseases.Findings indicate that vaccines significantly reduce the incidence and severity of diseases such as tuberculosis, malaria, and COVID-19. Furthermore, immunotherapy, including monoclonal antibodies, demonstrates potential in enhancing host immunity against multidrug-resistant pathogens. Despite advancements, the ongoing rise of AMR, particularly in low- and middle-income countries, poses a considerable threat to the efficacy of existing vaccines and treatments.Vaccination and immunotherapeutic strategies are essential components in the fight against emerging infectious diseases and AMR. Continued investment in vaccine development and implementation is critical to mitigate the impact of these evolving health threats. Future research should focus on innovative vaccine technologies and strategies to enhance public health responses in vulnerable populations.

Keywords: *Vaccination, Emerging Infectious Diseases, Antimicrobial Resistance, Immunotherapy, Public Health.*

Introduction

The incidence of emerging diseases in humans has significantly increased in recent years (1). Notwithstanding the availability of several preventative, control, and treatment strategies, infectious illnesses continue to be a leading global public health issue, causing millions of deaths annually. Infectious illnesses continually jeopardize global health and economics, necessitating ongoing investigation, study, and

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enhancement in this domain (2,3). Regrettably, India is seeing one of the highest rates of age-standardized infectious illness mortality in South Asia (4).

Moreover, the progress achieved in combating these diseases is significantly jeopardized by the development of antimicrobial resistance (AMR) (5). Resistance to existing antimicrobials has emerged as a significant public health issue in the 21st century, jeopardizing the effective diagnosis and treatment of a growing array of diseases caused by various pathogenic microorganisms that have become resistant to widely utilized antimicrobials. The growing problem of antimicrobial resistance requires robust regulation and action, since it is as critical as other global challenges like climate change (6,7). Approximately 700,000 individuals worldwide succumb annually to drug-resistant infections caused by the phenomenon of antimicrobial resistance (AMR); without effective intervention, an additional 10,000,000 are projected to perish, resulting in an estimated global economic loss of almost $100 trillion in the near future. India is a global leader in the use of human antibiotics, which substantially contributes to the development of antimicrobial resistance (AMR). The issue of antimicrobial resistance (AMR) in India is exacerbated by the excessive use of antibiotics, insufficient knowledge, improper diagnostic practices, cross-infections, inadequate healthcare infrastructure, and other contributing factors.

Recent study reports indicate a rise in multidrug-resistant (MDR) strains linked with pathogenic microbial species during the COVID-19 pandemic (8–11). The majority of patients have a mild SARS-CoV-2 infection; nevertheless, co-infection has been shown to heighten a patient's vulnerability to severe illnesses by undermining their immune system (12). A variety of causes contribute to the increase of multidrug-resistant (MDR) pathogenic bacteria, with the increasing use of potent antibiotic therapies in COVID-19 patients with little risk of secondary or co-infection being especially associated with this issue. The prevalence of pathogenic organisms during this epidemic might be mitigated by quality assessment, proactive infection control strategies, suitable treatment, and optimum antibiotic use in accordance with antimicrobial stewardship guidelines (13).

Therefore, the advancement of novel approaches and procedures is essential to tackle the issue of increasing antimicrobial resistance (AMR). The systematic investigation and development of potential molecular and genetic methodologies to enhance the immune system's efficacy for sustained human health are essential for the prevention and management of the escalating worldwide issue of infectious illnesses impacting people (14–18). Immunotherapeutic approaches in immunocompromised persons provide an innovative way to enhance host defenses and are thus essential in addressing the escalating problem of antimicrobial resistance caused by various opportunistic infections. Recent developments in the treatment of illnesses like as AIDS, malaria, tuberculosis, and most recently, COVID-19, have rendered immunotherapeutic techniques more significant in the broader context of disease prevention and control. This is due to the extensive use of immunotherapy in cancer treatment. Immunotherapy treatments modulate the host's innate and adaptive immune responses (Figure 1), proving effective against several pathogenic microbial illnesses (19–22).

Figure 1. Diagrammatic illustration of the targeting process for various pathogenic agents/organisms via the activation of immune responses and the overarching processes of innate and adaptive immunity.

This review emphasizes notable advancements in immunotherapies, such as vaccines and monoclonal antibody-based therapies, as treatment strategies for various human microbial infections (bacterial and fungal). These approaches present an appealing method to enhance host defenses and address the escalating issue of antimicrobial resistance (AMR).

- *Human Microbial Diseases and The Increasing Antimicrobial Resistance*

Infectious illnesses in humans are induced by many pathogenic microorganisms, including fungus, bacteria, and viruses. Pathogenic organisms have effectively developed several resistance mechanisms that allow them to evade the effects of antimicrobials and antivirals. Many of these species have acquired resistance to almost all existing treatment modalities as a result (23). A thorough understanding of the methods used

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by these organisms to initiate resistance is essential for developing new ways to combat this longstanding issue. The prevalence of resistant bacterial species in human illnesses continues to rise significantly. This encompasses germs originating from the community and those responsible for illnesses inside the healthcare sector (24-26). Nearly all bacterial species, including those responsible for the most common human illnesses, have heightened medication tolerance rates. Severe infections caused by drug-resistant bacterial strains have poor treatment responses, often leading to adverse outcomes such as increased complication rates, higher associated costs, elevated mortality rates, and prolonged hospital stays (27–29).

The current situation presents a significant danger to the healthcare system, since the proliferation of multidrug-resistant bacterial pathogens correlates closely with the growth of antibiotic-resistant microorganisms. The Centers for Disease Control and Prevention (CDC) reports that millions of illnesses and thousands of deaths occur annually in the United States due to antimicrobial-resistant bacterial species. Furthermore, in the last decade, there has been a notable and continuous reduction in the availability of approved antibacterial agents, resulting in a critical situation that can only be addressed by the creation of new antimicrobials (30).

The issue of *Vibrio cholera* drug resistance to several medicines is escalating markedly in developing countries, with a notable increase in global cholera cases associated with multidrug-resistant *V. cholera* being observed (31, 32). Likewise, the gram-positive bacteria *Mycobacterium tuberculosis* is the causative agent of the lethal infectious illness tuberculosis (TB), which disseminates mostly by aerosolized cough droplets and predominantly impacts the lungs (33, 34). Furthermore, *Pseudomonas aeruginosa* is a gram-negative pathogenic bacterium that causes several acute and chronic nosocomial infections, including severe respiratory infections in individuals with compromised immune systems (35,36). Another significant human harmful bacterium is *Staphylococcus aureus* is a gram-positive, facultative anaerobe that often forms irregular clusters like grapes (37). Skin and soft tissue infections, bacterial endocarditis, pleuropulmonary infections, and infections associated with medical equipment are all attributable to S. Infections caused by aureus may vary in severity from mild to deadly (37). Likewise, various nosocomial and community-acquired infections, including urinary tract infections, pneumonia, liver abscesses, surgical site infections, and bloodstream infections, may be caused by the pathogenic bacterium Klebsiella pneumoniae, especially in immunocompromised individuals (38, 39). Gram-positive enterococci are intestinal commensals that are facultative anaerobes, capable of enduring various stressful and unfavorable conditions (40).

Despite the identification of over 200 unique enterococci species, the majority of enterococcal infections in people are attributable to just two species, *E. Faecalis* and *E. faecium* (40). The most detrimental species is *E. Faecalis*, despite its increased resistance to several antibiotic therapies, may lead to severe illness and mortality, especially in immunocompromised individuals. Typically, these bacteria pose little threat to healthy individuals; nevertheless, they may induce endocarditis, bacteremia, and catheter-associated urinary tract infections in immunocompromised patients (41). Regrettably, there is a limited availability of medicines to address the rapidly growing multidrug-resistant bacterial infections (42). The overuse of antibiotics, inappropriate prescriptions, reduced medication supply, and several other variables have been recognized as contributors to the emergence of antibiotic resistance concerns. Bacteria, despite their intrinsic tolerance, may develop or acquire antibiotic resistance via many ways. Antibiotic resistance in bacteria encompasses two categories of resistance mechanisms: natural (intrinsic and induced) and acquired. Intrinsic resistance pertains to bacterial species that are naturally resistant to a certain class of antibiotics, and it is evident that this kind of resistance is independent of previous antibiotic exposure (43, 44). Exposure to therapeutic levels of antibiotics may activate genes that generate natural resistance in bacteria (45). Two distinct mechanisms may lead to acquired resistance: DNA transfer or mutations associated to replication in the cell's DNA.

Conversely, fungal infections are gradually escalating as a significant global issue (46). The extensive use of diverse antifungals in agriculture and medicine is responsible for the significant rise in the prevalence of resistant infections caused by pathogenic fungus (47). The most difficult illnesses to treat in individuals today are those caused by human pathogenic fungus. Many of these fungal infections impact immunocompromised persons, including those with AIDS, diabetes, cancer treatment recipients, those undergoing therapy for autoimmune illnesses, or those on other advanced medications (48, 49). Research

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indicates that about 1,000,000 persons die annually due to serious illnesses caused by diverse pathogenic fungi. Over 90% of deaths linked to invasive fungal infections are caused by the *Candida*, *Cryptococcus*, and *Aspergillus* species (50, 51). Fungal disorders may vary in severity from superficial infections to severe acute illnesses (52).

Invasive fungal infections, especially invasive candidiasis, are among the most common causes of pathogenic fungal-related mortality and morbidity in hospitals. Invasive candidiasis, caused by *Candida* species, is classified into two types: superficial and deep tissue. Approximately 200 species of the genus *Candida* are identified, with 15 recognized as pathogenic to humans. The predominant species of *Candida* associated with Candidiasis include *Candida albicans*, *Candida parapsilosis*, *Candida glabrata*, *Candida tropicalis*, and *Candida krusei*. In many medical environments, *Candida albicans* is a prevalent human fungal pathogen; nevertheless, in many regions, infections caused by non-albicans species constitute over 50% of bloodstream infections (candidemia). *Candida auris*, a significant nosocomial fungal disease that has emerged in several regions globally, was initially discovered in Japan in 2009 and has reduced susceptibility to the key antifungal agents. In the context of severely sick individuals, elevated death rates are seen *C. auris* infections have been recorded (53, 54).

The ubiquitous filamentous fungus *Aspergillus* causes Aspergillosis, which presents clinically in several forms. Notwithstanding contemporary medical progress, Aspergillosis remains a significant fungal illness, with incidence rates among immunocompromised individuals escalating fast and an expanding epidemiology. Numerous species exist within the *Aspergillus* genus; nonetheless, Aspergillus. fumigatus, succeeded by other species, namely: *A. flavus*, *A. niger*, *A. nidulans*, among others, is the predominant causative agent of Invasive Aspergillosis and other pulmonary infections (55, 56). Conversely, there are more than 30 distinct species of *Cryptococcus*, which are distributed across the environment. *Cryptococcus neoformans* and *C. gatti* represents two principal species that often induce Cryptococcal Meningitis in humans (57, 58). As a result, therapy options for these disorders are severely restricted owing to the limited variety of antifungal agents, such as azoles, among others.

- *Immunotherapy and Its Classifications*

Infectious pathogens effectively create a conducive environment inside the host, alter host metabolic processes to meet their nutritional requirements, and suppress host defenses by changing regulatory pathways, akin to cancer progression (59). Numerous host elements within the immune system influence therapy results and affect disease progression or regression. Immunotherapy is defined as any treatment method that targets or influences the immune system (60). For instance, in the context of microbial diseases, particularly fungal infections, the use of monoclonal antibodies (MAbs) generated by Hybridoma technology presents a substantial therapeutic alternative for antibody-mediated immunity (61–64). Immunotherapy aims to eliminate sick cells from the host by using the host's innate and adaptive immune systems. To address inflammatory and autoimmune illnesses such as cancer, immune responses are either produced, enhanced, or repressed as necessary. Immunotherapy may be classified as either antigen-specific or nonspecific. Specific immunotherapy focuses on directing the immune system toward a particular tumor or fostering tolerance to a specific allergen, whereas non-specific immunotherapy seeks to enhance the general immunological response of the host. Specific immunotherapy encompasses four main categories: cancer vaccine treatment, allergen-specific immunotherapy, antibody-based immunotherapy, and adoptive immunotherapy. Cancer vaccine treatment and allergen-specific immunotherapy are proactive modalities. Conversely, antibody-based immunotherapy and adoptive immunotherapy are considered passive strategies (65). Active immunotherapy enhances the patient's immune response and induces the production of specific immune effectors (antibodies and T cells), whereas passive immunotherapy entails the infusion of ex vivo-generated immunological components (antibodies, immune cells) into patients (66).

- *Immunotherapies For Human Bacterial Infections*

The identification of antibiotic agents is among the most important breakthroughs in contemporary medicine. Patients undergoing chemotherapy, those with chronic diseases, or those who have had difficult

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surgery have been effectively safeguarded from infections. The overuse and misuse of antibiotics have led to a rise in the emergence of multidrug-resistant bacterial infections, sometimes referred to as "superbugs" (67). Superbugs are now estimated to result in around 700,000 deaths annually globally, with projections suggesting this figure might escalate to 10 million by 2050. The lack of viable therapeutic options beyond antibiotic medicines is the primary concern surrounding these rapidly evolving superbugs (68). The only therapeutic interventions available in these situations to halt the propagation of the virus and its associated complications are regular patient separation for quarantine and excision of the afflicted area (69). Despite the continuous development of novel antimicrobial compounds, the majority exhibit similar mechanisms of action to current medications, rendering the onset of antimicrobial drug tolerance seems inevitable (70–72). The problem in the pathogenic bacterial organism is exacerbated by the existence of persister cell subpopulations, which are vulnerable to low drug concentrations and often lead to disease resistance (73). Consequently, it is essential to integrate a diverse array of effective therapeutic options with standard antibiotic therapy to mitigate the illness burden generated by several antibiotic-tolerant organisms (74).

In contemporary medical practice, immunotherapy has emerged as a prevalent option for addressing several autoimmune and oncological disorders. A deeper understanding of immune suppression during bacterial infections may uncover novel therapeutic targets to enhance host immunological responses for pathogen elimination and the treatment of life-threatening illnesses. Recent findings have shown that immunological malfunction and evasion are prevalent features of both cancer and chronic pathogenic bacterial infections (66).

- *Immunotherapy Using Monoclonal Antibodies*

To tackle newly developing bacterial infections, monoclonal antibodies (MAbs) are receiving more attention (75). Antibody profiles in latent Tuberculosis infection that enhance Fc-mediated immune effector functions and facilitate macrophage destruction of intracellular bacteria highlight the protective role of these antibodies, indicating their substantial involvement in immunomodulation during TB infection (76). Nonetheless, efforts to develop Mtb-protective monoclonal antibodies have so far proven unproductive. Regarding *Pseudomonas aeruginosa* and *Staphylococcus*. Numerous customized monoclonal antibodies targeting aureus have progressed to clinical testing. MEDI3902, a bispecific IgG1 antibody produced by AstraZeneca PLC, targets *P. aeruginosa*'s PcrV protein (which induces host cell cytotoxicity) and Pslexopolysaccharide (which facilitates colonization and tissue adhesion) for the treatment of pneumonia in high-risk patients (77). Moreover, the targets are ubiquitous among *P. aeruginosa* strains globally and may enable extensive coverage (78). When administered as an adjunct treatment to people with methicillin-resistant *S. pneumonia* caused by methicillin-resistant *Staphylococcus aureus* (MRSA), AR-301, a monoclonal antibody with the ability to neutralize alpha-toxin (a virulence factor), conferred protection against host cell damage controlled by alpha-toxin (79). Additionally, MEDI4893, an innovative long-acting monoclonal antibody targeting alpha-toxin, is now in a phase II clinical study and provides effective immunoprophylaxis for *S. aureus* infection including the maintenance of serum concentrations after intravenous infusion in healthy individuals (80).

- *Immunotherapy Using Vaccines*

The causal agent of tuberculosis (TB) and the primary contributor to mortality linked with infectious diseases is Mycobacterium tuberculosis (Mtb) (81). The only approved tuberculosis vaccine, *Bacillus* Calmette-Guérin (BCG), reliably protects against the most severe extrapulmonary forms of pediatric tuberculosis but provides little protection against pulmonary tuberculosis in adults (82). Furthermore, despite its extensive usage as a tuberculosis vaccine, its ineffectiveness in halting existing tuberculosis infections underscores the need for novel strategies. The ideal tuberculosis vaccine must demonstrate superior efficacy in disease prevention compared to BCG and inhibit the transmission of *Mycobacterium tuberculosis* by averting the onset of the illness (83). Nevertheless, several tuberculosis vaccines developed historically have failed to achieve this objective. The therapeutic efficacy of BCG in infants and adults with HIV-1 infection was not enhanced by the MVA85A vaccine. Some new vaccine ideas are now in clinical trials or have just completed them, with varied degrees of success. The M72:AS01E subunit vaccine comprises the immunogenic fusion protein (M72) derived from two M. The tuberculosis antigens combined

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with the GlaxoSmithKline adjuvant AS01E shown a 49.7% efficacy in eliciting immunity against TB illness in HIV-negative individuals with latent TB infection, indicating significant promise for this vaccine (84,85).

Conclusions and Future Perspectives

Immunotherapy-based solutions may significantly enhance future therapies for autoimmune illnesses, infectious diseases, and cancer. The potential of immunotherapy to revolutionize cancer treatment has generated significant interest in using analogous techniques to address many pathogenic microbial diseases, including fungal and bacterial infections in humans. Despite encouraging first findings in preclinical models, there is less study on the efficacy of these techniques in translating to human illness within a clinical context. Currently, there are a limited number of clinical studies for infectious disorders among the almost 1,700 immunotherapy trials underway (2).

Given the looming issue of antibiotic resistance, immunotherapy may fulfill a significant unmet need for supplementary or alternative therapies to antimicrobials. Future research should focus on the use of preclinical results in the treatment of human infectious disorders, ensuring that there is no risk of exacerbating the condition. This study must examine the interplay between immunotherapies and traditional antimicrobial treatments, since immunotherapy has often been shown to disrupt or even enhance medication tolerance. Due to their ease of development and implementation, checkpoint and cytokine inhibitors seem to be especially feasible. As these inhibitors approach the expiration of their patent protection and the treatment costs significantly decrease, they will become more feasible. The use of immunotherapy for the treatment of various microbial illnesses continues to present several unanswered issues that must be addressed in the near future via enhanced preclinical and appropriate clinical investigations (74).

In an effort to surpass the limitations of conventional chemotherapeutics, such as efficacy, cytotoxicity, and the rising issue of drug resistance, immunotherapeutic approaches are particularly promising (17, 18). It has become evident that addressing several infectious illnesses requires a multifaceted approach, like to most therapies for any ailment. The optimal amalgamation of procedures that will provide the most favorable patient outcomes must be included in forthcoming pre-clinical and clinical research. To achieve the eradication of diseases such as tuberculosis or malaria, a combination of several immunotherapeutic techniques with standard alternative therapies must be included (17, 19). This method, which prioritizes optimal clinical outcomes, facilitates the development of medicines characterized by high specificity and selectivity, so ushering in the age of precision medicine (18, 20–23).

The employment of phage display libraries for extensive antibody fragment screening, progress in molecular methodologies to optimize and augment antibody stability and efficacy (thereby reducing dosage), identification of appropriate expression hosts, and enhancement of cell culture conditions, among other factors, have collectively resulted in decreased costs of monoclonal antibody therapies, consequently increasing accessibility to these treatments. These developments have facilitated the approval and increased utilization of therapeutic antibodies, surmounting many obstacles that previously hindered their extensive use (18, 24). The use of novel vaccination techniques, such as DNA, mRNA, and viral vector vaccines, presents options that may lead to more rapid and cost-effective vaccine development processes, mitigating the limitations of previous peptide-based vaccinations (18, 22, 26).

The capacity to tackle pharmaceutical safety issues arising from systemic immunotherapy is shown by the concurrent evolution of customized delivery systems and improvements in vehicle technology, which may augment options for experimental treatments. Consequently, improvements in immunotherapy are increasingly seen as attractive alternatives for the treatment of several infectious disorders. Consequently, these diverse immune therapies are emerging as compelling strategies for the prevention and treatment of human pathogenic microbial infections. Monoclonal antibodies and vaccinations are gaining importance as therapy methods. Monoclonal antibodies (MABs) have been used in the treatment of a wide array of medical situations, including autoimmune disorders, cancer, and several other ailments. These

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immunotherapies exhibit remarkable adaptability owing to their distinctive and selective characteristics, and in the next years, they will benefit the public and enhance medical treatment.

The persistent COVID-19 pandemic is a significant global medical challenge. Consequently, this has resulted in unparalleled progress in the formulation of therapies and vaccinations across several countries. There is a clear need for capacity development, and the available resources should focus on addressing these needs in a manner pertinent to the country's priorities. The advancement of novel treatments should focus on repurposing existing medications or using vaccinations, which may be rapidly used to address emergent infectious diseases (22). Nonetheless, socioeconomic disparities continue to have a substantial influence on access to preventive and therapeutic medications. The higher prevalence of infectious diseases in medium and low-income nations underscores this point. Moreover, infectious illnesses disproportionately adversely affect indigenous and low-income populations in affluent countries (25). The advancement of diverse immunotherapeutic techniques will facilitate the eradication of numerous infectious illnesses in the near future, supplemented by financial backing to promote innovation and coordinate worldwide initiatives. These initiatives should occur at the local level within healthcare facilities, educational institutions, and other enterprises (11).

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أهمية اللقاحات في الحد من الأمراض المعدية الناشئة: مراجعة شاملة

الملخص

الخلفية :يمثل الارتفاع العالمي في الأمراض المعدية الناشئة تحديات كبيرة للصحة العامة، تتفاقم بسبب قضايا مثل مقاومة مضادات الميكروبات (AMR). تظل التطعيمات استراتيجية محورية في منع انتشار هذه الأمراض، ومع ذلك غالبًا ما يُستهان بدورها في سياق تزايد مقاومة الأدوية.

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الطرق :تجمع هذه المراجعة بين الأدبيات الحالية حول فعالية اللقاحات والأساليب المناعية في السيطرة على الأمراض المعدية الناشئة. كما تحلل البيانات من الدراسات السريرية والتقارير الوبائية وتأثير التطعيم على اتجاهات مقاومة مضادات الميكروبات، لا سيما في المناطق التي تتأثر بشدة بهذه الأمراض.

النتائج :تشير النتائج إلى أن اللقاحات تقلل بشكل كبير من معدل الإصابة وشدة الأمراض مثل السل والملاريا وكوفيد-19. علاوة على ذلك، تظهر العلاجات المناعية، بما في ذلك الأجسام المضادة أحادية النسيلة، إمكانيات واعدة في تعزيز المناعة ضد الممرضات المقاومة للأدوية. على الرغم من التقدم المحرز، يشكل الارتفاع المستمر لمقاومة مضادات الميكروبات، خاصة في البلدان منخفضة ومتوسطة الدخل، تهديدًا كبيرًا لفعالية اللقاحات والعلاجات الحالية.

الاستنتاج :تُعد استراتيجيات التطعيم والعلاج المناعي مكونات أساسية في مكافحة الأمراض المعدية الناشئة ومقاومة مضادات الميكروبات. يعد الاستثمار المستمر في تطوير وتنفيذ اللقاحات أمرًا ضروريًا للتخفيف من تأثير هذه التهديدات الصحية المتزايدة. ينبغي أن تركز الأبحاث المستقبلية على تقنيات لقاح مبتكرة واستراتيجيات لتعزيز الاستجابات الصحية العامة في الفئات السكانية الأكثر عرضة للخطر.

الكلمات المفتاحية :التطعيم، الأمراض المعدية الناشئة، مقاومة مضادات الميكروبات، العلاج المناعي، الصحة العامة.