Inactivated, Live Attenuated and mRNA Vaccines in Comparative Perspective and Future Directions

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Abstract. Vaccination remains one of the most effective strategies for controlling infectious diseases, with an estimated 86.9 million child deaths averted between 1990 and 2019 through routine immunization programs. Among existing platforms, inactivated vaccines, live attenuated vaccines, and mRNA vaccines have demonstrated distinct contributions to global health. Inactivated vaccines are historically well established and provide a favorable safety profile, yet their immunogenicity is relatively weak and often requires booster doses. Live attenuated vaccines mimic natural infection and induce comprehensive and long-lasting immunity, although they present risks for immunocompromised populations and demand strict cold-chain maintenance. mRNA vaccines have transformed the field by enabling rapid design and scalable production, offering strong humoral and cellular responses, but they remain constrained by stability issues, storage conditions, and production costs. These differences shape their roles in childhood immunization schedules, outbreak response, and vaccination strategies for vulnerable groups. This review aims to systematically evaluate the principles, advantages, and limitations of inactivated, live attenuated, and mRNA vaccines, and to highlight their potential in guiding future vaccine innovation and public health policy.

Keywords: Inactivated vaccines, live attenuated vaccines, mRNA vaccines, public health, immunization strategies.

1. Introduction

Vaccines are biological preparations that induce specific immune responses and establish immunological memory to prevent infectious diseases, enabling the human body to respond rapidly upon re-exposure to pathogens, thereby reducing the risk of illness or mitigating symptoms [1]. Epidemiological evidence indicates that routine immunization between 1990 and 2019 averted approximately 86.9 million deaths in children under five years of age, with classic vaccines such as those for diphtheria, tetanus, pertussis (DTP), and measles playing crucial roles in controlling common infectious diseases [2]. In the context of the COVID-19 pandemic and emerging infectious diseases like mpox, the demand for efficient and rapidly adaptable vaccine platforms has become increasingly urgent. The primary technological platforms include inactivated and live attenuated vaccines. Inactivated vaccines employ physical or chemical methods (e.g., heat) to kill the pathogen, preserving its antigenicity while eliminating its replicative capacity. The immune response is primarily humoral, often relatively weak and requiring multiple booster doses (e.g., inactivated poliovirus vaccine, influenza vaccine). Live attenuated vaccines use artificially weakened strains to mimic natural infection, capable of inducing more comprehensive and durable protection. However, they raise safety concerns in immunocompromised individuals and require stringent cold-chain transportation (e.g., measles, varicella vaccines) [3].

In recent years, nucleic acid (mRNA) vaccines have been widely deployed. These vaccines deliver mRNA encoding pathogen antigens into the body, utilizing host cells to synthesize the target protein, thereby simultaneously activating both humoral and cellular immunity. They also allow rapid adaptation to viral variants (e.g., mpox mRNA vaccine) [4]. Regarding safety, inactivated vaccines are generally the most controllable, followed by mRNA vaccines, while live attenuated vaccines must be used cautiously in immunocompromised individuals. In terms of immunogenicity and durability, live attenuated vaccines perform the strongest, mRNA vaccines are intermediate, and inactivated vaccines are relatively weaker. Concerning accessibility and supply chain feasibility, inactivated vaccines have relatively lenient storage conditions, live attenuated vaccines often require

approximately -20°C cold chain, and some mRNA formulations need ultra-cold storage around -70°C. This review aims to systematically compare the immunogenicity, safety, and applicable scenarios of these three vaccine types, assess their potential in childhood immunization programs, emerging infectious diseases, and special populations, and provide an evidence-based foundation for vaccine development strategies and public health policies.

2. Inactivated Vaccines

As one of the oldest vaccine technologies, the core principle of inactivated vaccines is to completely destroy the pathogen's replicative ability through physical or chemical means while retaining the key antigenic structures that elicit an immune response. Common inactivation methods include heat treatment, formaldehyde solution fixation, or chemical modification with β-propiolactone. These methods effectively render viruses or bacteria non-infectious. For example, β-propiolactone inactivates by disrupting viral nucleic acid structures while minimizing damage to surface protein antigenicity. Upon administration, the inactivated pathogens are recognized and processed by antigen-presenting cells, primarily activating B lymphocyte-mediated humoral immunity to produce specific neutralizing antibodies. While this mechanism effectively prevents infection, the lack of intracellular replication of a live pathogen makes it difficult to activate strong T-cell immune responses, resulting in limited immune durability.

Among representative vaccines, the widespread use of the Inactivated Poliovirus Vaccine (IPV) has reduced global polio cases by over 99% [2]. World Health Organization (WHO) data from 2022 reported only 30 cases of wild poliovirus infection globally, demonstrating IPV's comprehensive coverage of the three poliovirus serotypes and its high safety profile, making it a cornerstone of the "Polio Eradication Initiative." The influenza inactivated vaccine updates its antigenic components annually based on WHO predictions of circulating strains. It can reduce hospitalization risk by 40%-60% in the elderly and those with chronic conditions [5]. For instance, the adjustment of the 2023-2024 Northern Hemisphere vaccine to target influenza A(H1N1) and A(H3N2) strains significantly curbed seasonal outbreaks. Another significant example is the hepatitis A inactivated vaccine. Since its introduction in 1996, the incidence of hepatitis A in the United States has decreased by over 95% [6]. Its two-dose regimen achieves long-term herd immunity in endemic areas and is particularly suitable for travelers and high-risk occupational groups.

The core advantage of inactivated vaccines lies in their safety: the non-replicating pathogen makes them suitable for pregnant women, the elderly, and immunocompromised individuals. Their production process leverages mature cell culture and inactivation techniques, allowing easy scaling. Most products remain stable for 2-3 years at 2-8°C, reducing cold chain transportation costs. However, their limitations are also notable: weaker immunogenicity leads to faster waning antibody titers, often necessitating primary immunization followed by booster doses. Furthermore, their efficacy against intracellular pathogens or highly variable viruses is limited, and they struggle to induce cytotoxic T-cell responses, impairing the clearance of already infected cells. Recent research has explored overcoming these drawbacks through novel adjuvants, multi-epitope antigen design, and combination with other platforms, but overall improvement remains constrained. Future directions will focus on how to further enhance immunogenicity while maintaining high safety.

3. Live Attenuated Vaccines

Live attenuated vaccines are created by artificially reducing the virulence of a pathogen while retaining its ability to replicate limitedly within the host. Traditional methods include serial passage of the pathogen in non-natural host cells or genetic engineering to delete virulence genes. These vaccines mimic the natural infection process. After replication in local tissues, they release antigens, simultaneously activating CD4+ helper T cells, CD8+ cytotoxic T cells, and B cells, forming a comprehensive barrier involving mucosal, humoral, and cellular immunity. This characteristic often

allows for the establishment of long-lasting immune memory after a single dose and significantly reduces pathogen transmission at the population level.

A classic representative of this technology is the Measles, Mumps, and Rubella (MMR) combination vaccine. In regions with vaccination coverage exceeding 80%, measles mortality has declined by 99% [2]. The Americas became the first continent to eliminate measles in 2016, a success attributed to a seroconversion rate of over 95% after a single dose and lifelong immune memory. The live attenuated varicella (chickenpox) vaccine induces VZV-specific T-cell responses, leading to a 90% reduction in childhood varicella incidence and a 70–90% decrease in the risk of herpes zoster in older adults [7]. Similarly, rotavirus live attenuated vaccines have shown outstanding performance, reducing severe rotavirus diarrhea by 80-90% in high-burden countries in Africa and Asia, preventing nearly 200,000 child deaths annually [8].

The core advantage of live attenuated vaccines lies in the strength and durability of the immune response; most provide protection for 10 years or even a lifetime after a single dose and can interrupt pathogen transmission. However, their limitations focus on safety: they can cause vaccine-associated diseases in immunocompromised individuals (e.g., AIDS patients) and carry a very low risk of reversion to virulence; additionally, their high chemosensitivity requires storage and transportation at -20°C, making them susceptible to failure due to cold chain interruptions in tropical regions. Recent research explores using gene editing technology to enhance the stable inactivation of virulence genes and developing lyophilized or thermostable formulations to further improve their safety and accessibility [9].

4. mRNA Vaccines

mRNA vaccines represent a major breakthrough in third-generation vaccine technology. Their core involves encapsulating mRNA sequences encoding key pathogen antigens within lipid nanoparticles (LNPs). The LNPs deliver the mRNA into the cytoplasm via membrane fusion, where host ribosomes translate it into the target protein (e.g., the SARS-CoV-2 spike protein). These endogenously produced antigens are then presented via both Major Histocompatibility Complex (MHC) class I and II pathways, simultaneously activating CD8+ T cell-mediated cellular immunity and B cell-mediated humoral immunity, creating a dual defense mechanism [4].

In practical application, COVID-19 mRNA vaccines progressed from sequence design to first administration in just 11 months. Clinical trials showed a 95% efficacy against the original strain [10]. By 2021, over 2 billion doses were administered globally, reducing the risk of severe disease by 89-95% [11]. For emerging outbreaks, mpox mRNA vaccines targeting viral envelope proteins like A29L and A35R have been designed. Animal models showed a 40-fold increase in neutralizing antibody titers after a single dose, enabling a rapid response to the multi-country outbreak in 2022 [12]. Furthermore, influenza mRNA vaccines have entered Phase III clinical trials. Their advantage lies in encoding the hemagglutinin proteins of four influenza strains simultaneously, with early data suggesting antibody responses superior to traditional inactivated vaccines [13].

The platform's core advantage is its "programmability" – when key viral mutations arise, the mRNA sequence can be updated in mere weeks without changing the production process. It also induces high-titer neutralizing antibodies and a Th1-biased T-cell response. However, significant technical bottlenecks remain: some early products required ultra-cold storage and transport (-70°C for Pfizer's BNT162b2, stable for only 2 weeks between -25°C and -15°C). Rare risks like myocarditis (incidence ~1 in 10,000 in adolescents) require long-term monitoring [14]. The cost of LNP raw materials and patent barriers make the per-dose cost 5-10 times higher than that of inactivated vaccines [15].

5. Challenges and Future Directions

Production and storage/transportation bottlenecks remain major obstacles to the equitable global distribution of vaccines. The stringent cold chain requirements for early mRNA products (e.g., -20°C for Moderna, -70°C for Pfizer) were difficult to meet in Africa and other resource-limited areas. Reports indicate that in many low-income and middle-income countries, standard cold chain capacity at 2–8°C remains limited or unreliable, resulting in frequent vaccine stock-outs and interruptions in supply chains [16]. While live attenuated vaccines can remain stable at -20°C, they still face the risk of cold chain failure in areas with unreliable electricity. In contrast, inactivated vaccines can be stored long-term at 2–8°C, making them more suitable for routine immunization, but their scaled production requires high-level biosafety laboratories (e.g., BSL-3 for SARS-CoV-2 culture), limiting production flexibility [17].

The response to emerging infectious diseases highlights the differences between platforms. mRNA vaccines enabled a rapid response during COVID-19. Moderna completed the design of a candidate vaccine just 42 hours after the viral gene sequence was published, quickly moving to clinical trials [4]. Inactivated vaccines, constrained by the need for large-scale virus culture and inactivation cycles, had a slower development pace. The attenuation and safety assessment for live attenuated vaccines require even longer timelines [3]. Establishing a "prototype pathogen vaccine library" pre-emptively stocking broad-spectrum candidate vaccines for viral families is a future necessity [18].

Vaccination strategies for special populations require individualized consideration. The elderly are often prioritized for highly immunogenic mRNA vaccines or adjuvanted inactivated vaccines (e.g., Fluad for influenza) to compensate for weakened immune responses. Immunocompromised individuals are contraindicated for live attenuated vaccines due to the risk of severe infection and should receive inactivated or mRNA alternatives. Pregnant women are recommended inactivated vaccines (e.g., Tdap), while data on mRNA vaccine safety in mid-to-late pregnancy is gradually accumulating [19].

Future development focuses on two main areas. Firstly, overcoming storage and transport limitations, such as freeze-dried mRNA vaccines funded by DARPA that remain stable at 40°C for 6 months, showing potential to revolutionize cold chain logistics [20]. Secondly, developing multivalent vaccines against multiple pathogen threats, like Moderna's mRNA-1073 combining COVID-19 and influenza antigens, and Pfizer's RSV mRNA vaccine entering Phase III trials. Additionally, novel adjuvants and mucosal delivery systems hold promise for enhancing immunogenicity and potentially expanding vaccine use in children and the elderly.

6. Conclusion

This review systematically compares the technological principles and immunological characteristics of inactivated, live attenuated, and mRNA vaccines. Inactivated vaccines are suitable for broad populations due to their high safety profile but possess weaker immunogenicity. Live attenuated vaccines induce potent and durable immune responses but are limited by potential virulence reversion and cold chain dependence. mRNA vaccines excel with their rapid development platform and potent immune activation but face challenges related to storage/transport costs and the need for long-term safety monitoring. Looking ahead, vaccine technology development will focus on breaking through these bottlenecks. This includes optimizing immunogenicity and safety through novel adjuvants and genetic engineering, developing formulations stable at ambient or elevated temperatures to improve accessibility, and exploring innovative strategies like multivalent vaccines and mucosal delivery. These advancements are poised to play a greater role in responding to emerging infectious diseases and enhancing global vaccine equity.

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