NOTATION TRENDPLUS PUBLISHING
WHERE IDEAS MEET IMPACT

Volume-1, Issue 1, August 2026, Page No- 156-195
Journal of Pharmaceutical Innovations and Therapeutic Horizons (JPITH)

Comparative Efficacy of mRNA and Conventional Vaccines Against Viral Diseases: A Systematic Literature Review

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Article Received: 03-05-2026

Revised Version: 19-06-2026

Accepted: 08-07-2026

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Abstract: The rapid development and deployment of mRNA vaccines during the COVID-19 pandemic has prompted a critical need to systematically compare their efficacy and safety against conventional vaccine platforms across various viral diseases. This systematic literature review aims to synthesize and critically evaluate evidence on the comparative performance of mRNA and conventional vaccines, focusing on mechanisms of action, clinical outcomes, and future applications. We conducted a comprehensive search of peer-reviewed literature, applying predefined inclusion and exclusion criteria to identify studies that directly compared these vaccine types or reported robust efficacy data for individual platforms. Our analysis reveals that mRNA vaccines consistently induce potent humoral and cellular immune responses, often exceeding those of conventional platforms in terms of neutralizing antibody titers and T-cell activation; however, this superior immunogenicity is frequently accompanied by a higher incidence of transient reactogenicity. Conventional vaccines, including inactivated and viral vector formulations, demonstrate advantages in storage stability and lower manufacturing costs, and they remain highly effective, particularly against endemic viral diseases. The results further indicate that mRNA technology offers unparalleled flexibility for rapid antigen design, enabling swift adaptation to emerging pathogens, while conventional platforms benefit from decades of safety data and established production infrastructure. We conclude that no single platform universally outperforms the other; rather, the optimal choice depends on specific viral threats, target populations, and logistical constraints.

Keywords: mRNA vaccines, Conventional vaccines, Viral diseases, Vaccine efficacy, Systematic literature review

Introduction

The past can demonstrate the unflagging battle against infectious diseases that has faced mankind, with Edward Jenner's smallpox vaccine and the eventual eradication of rinderpest being just two significant events. Only a few vaccines have actually been used over the last 100 years and they have proved safe and effective, including live-attenuated viruses, inactivated whole pathogens, protein-subunit vaccines and toxoid vaccines (Plotkin, 2014). The conventional definition of 'vaccine' is one based on the idea of attenuation or inactivation—these vaccines have been hugely successful in blocking diseases such as polio, measles, Hepatitis B, for example, and have thus saved millions of lives every year (Plotkin, 2005). Developing them, however, is a time consuming and lengthy process, taking 10 years or more to reach licensure. These time scales were not appropriate in a quickly spreading pandemic, particularly the 2009 H1N1 influenza pandemic and the 2014-2016 Ebola outbreak as evidenced in Fineberg (2014).

As an unprecedented international health crisis, COVID-19, caused by the SARS-CoV-2 virus, surfaced at the end of 2019, the researchers had to create a vaccine in a few months instead of years. It was during this crisis that for the first time a new class of vaccines came into use – messenger RNA (mRNA) vaccines (Chaudhary et al., 2021). Vaccines based on mRNA teach a cells to produce an antigen, sparking a robust and specific immune response, versus being required to take an antigenic protein or an attenuated pathogen. The development of this technology, particularly in the field of immunotherapeutics for cancer has been developed over a number of years and was quickly translated into the field of infectious disease prophylaxis (Jackson et al 2020). What was created was the fastest vaccine producing in the history of the world, and with the first mRNA-based COVID-19 vaccines approved as emergency use vaccines within one year of the genome of the virus being sequenced. It is a remarkable achievement that has changed the paradigm in vaccinology and raised a number of interesting questions on the advantages and disadvantages of this new platform as opposed to the conventional, traditional way.

mRNA vaccines have proven to be effective during COVID-19 pandemic, but the relative effectiveness and safety of mRNA vaccines compared to traditional vaccines in a broader range of viral diseases is not yet fully understood and addressed. While the literature is rich, it is not all-inclusive, and there were very few studies that made direct and controlled comparisons between platforms or specific diseases (Kavikondala et al., 2024). Moreover, at this stage of the technology frontier the first generation of mRNA vaccines have been effective but so far not the most attractive; but a better version might be available. More recent are the designs of selfamplifying RNA (saRNA) and the multivalent formulations, which can potentially offer enhanced durability and extent of protection (Bloom et al., 2021). But traditional platforms are not equally rigid; there are some new additions, types of delivery, that are being introduced to increase immunogenicity, speed up the development process and improve the result (Ghattas et al., 2021). There is therefore a critical research gap in pulling together all this fast-evolving evidence, so that one can compare specific attributes of this vaccine individually and comprehensively with a balanced, evidence-based synthesis for future vaccine development strategies, public health policy and pandemic preparedness planning.

The aim of this SLR is, therefore, to help fill this gap with the objective of presenting a comprehensive, structured and critical comparison of the comparative efficacy and safety of the mRNA vaccines and the conventional vaccines against viral diseases. This work is important in a number of ways. First of all, it doesn't only have to do with COVID-19 and they need to be checked on their performance pertaining to various viral diseases like influenza virus, rabies virus, emerging viral diseases like Zika, Nipah etc. The broader context offers us the advantages of today's platform's nitrogen in the general context. Second, this review examines the mechanisms whereby this explains the clinical discrepancies that have been observed, such as induction of innate immune activation, the production of long-lived

B-cell and T-cell memory, and others. Third, third key challenges to realizing impact are carefully considered by the platform such as manufacturability, thermostability and costs, which may be more of a challenge than immunogenicity. Last but not least, the review might provide a direction for future research and development, with focus on how hybrid approach or synergic could help with the greatest benefits in oncology and veterinary field.

The systematic approach taken (literature search, literature screening, data extraction) is briefly summarized in section 2 of this paper. General characteristics of the research are summarised initially in Section 3, which gives an overview of the overall trend in the research literature, before more detailed analysis of how each of the different types of nanoparticle-based therapeutics for the various viruses may work and the delivery systems used in each case, and clinical efficacy in these cases. We then discuss the therapeutic applications for oncology, an next generation platform design, extension to emerging pathogens and veterinary applications, and finally we compare the advantages and disadvantages and perspectives on the future development. In Section 4 our findings are discussed and conclusions about them drawn; gaps in the evidence base and suggestions for further research are identified. Finally, the paper summarizes the main insights and meaning for the future of vaccinology in section 5.

Methodology

The selection of literature and literature review are carried out according to Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement (Page et al., 2021). The review protocol was developed a priori to guarantee a rigorous, transparent and reproducible process in identifying, screening and synthesizing the relevant evidence.

Review Protocol

The search of four main electronic biomedical and life science databases was conducted, utilizing their respective strengths, in order to get a comprehensive, multi-disciplinary bibliography. It was chosen as the primary database because PubMed is a complete database of biomedical peer-reviewed articles, and much research and clinical trials of vaccines have been published in these journals. ScienceDirect was selected because of its excellent collection of articles in full text from life and health science journals and its ability to "dive" into article metrics that would provide a better break-out of the research that has been published in quality life and health science journals. The addition of Web of Science has been made possible by its breadth of coverage of scientific topics such as immunology, virology and biotechnology and its coverage of conference proceedings and quality, international scientific journals. To ensure no major studies were missed, a complementary search of Scopus, which extends to over 20 disciplines and has good citation tracking facility, was completed. Finally, grey literature, preprints, and other publications were found via a more involved search process by using Google Scholar, another search engine.

A literature search for literature was conducted iteratively and ideas were gathered using a combination of MeSH terms, keywords and Boolean operators to increase the sensitivity and specificity in the search. Search questions focused on identification of research studies that have comparative results on mRNA vaccines and traditional vaccine platforms (inactivated, live-attenuated, subunit, or viral vector vaccines) for a variety of viral diseases and with specific emphasis on efficacy, effectiveness and immunogenicity outcomes, for each of the databases. Each database was used with these keywords:

1. Search in PubMed: "mRNA vaccines"[MeSH] OR "mRNA vaccine"[TIAB] OR "messenger RNA vaccine"[TIAB] AND ("Vaccines, Inactivated"[MeSH] OR "Vaccines, Attenuated"[MeSH] OR "Vaccines, Subunit"[MeSH] OR "conventional vaccine"[TIAB] OR

"inactivated vaccine"[TIAB] OR "live-attenuated vaccine"[TIAB] OR "Virus Diseases"[MeSH] OR "viral disease"[TIAB] OR "virus infection"[TIAB] OR "Efficacy"[TIAB] OR "Effectiveness"[TIAB] OR "Immunogenicity"[TIAB] NOT ("Review"[Publication Type] OR "Meta-Analysis"[Publication Type] OR "Systematic Review"[TIAB])

2. Boolean operators may be used with these keywords.The following keywords have been consistently used to create a logical expression, which can be combined using boolean operators: 'TS=((mRNA vaccine OR messenger RNA vaccine) AND (conventional vaccine OR inactivated vaccine OR live-attenuated vaccine OR subunit vaccine) AND (efficacy OR effectiveness OR immunogenicity) AND (viral disease OR virus) NOT TS=((review OR meta-analysis OR systematic review))'.
3. Search: Scopus: 'TITLE-ABS-KEY(("mRNA vaccine" OR "messenger RNA vaccine") AND ("conventional vaccine" OR "inactivated vaccine" OR "live-attenuated vaccine" OR "subunit vaccine") AND ("efficacy" OR "effectiveness" OR "immunogenicity") AND ("viral disease" OR "virus")) AND NOT TITLE-ABS-KEY("review" OR "meta-analysis" OR "systematic review")'
4. Identify articles on the efficacy of conventional vs mRNA vaccines.MedChem overload in the twenty-first century is an evolving digital challenge that demands a reimagined approach, which can take the form of selecting specific keywords for "mRNA vaccine" search results.Articles related to mRNA vaccines are frequently found in MedChem overload in the twenty-first century, and a reimagined approach involves selecting certain keywords in mRNA vaccine search results.
5. In order to be included, the article/research must contain all these combination keywords: mRNA vaccine OR message/ messenger/ mRNA-based vaccine AND conventional vaccine OR inactivated vaccine OR live-attenuated vaccine OR protein subunit vaccine OR viral vector vaccine AND efficacy OR effectiveness OR immunogenicity OR protection AND viral disease OR virus OR SARS-CoV-2 OR influenza OR Ebola OR Zika OR Zika virus NOT review AND NOT survey AND NOT meta-analysis

A subset of original research articles was provided, and clinical trials only were included with the use of filters specific to the database used (cases, reviews, and meta-analyses, as well as cases reports were not included).

Research Questions

To guide systematic collection and collation of evidence, we created the following general research questions, that closely fit the topical themes of results. Questions were formulated to be more than just efficacy measures—looking to the fundamental truths in the biology, technology, and practice of mRNA and conventional vaccine strategies. The first question is aimed at revealing the underlying mechanism, whereby asking which is more antigen presenting to the immune system than the other, with mRNA platforms compared to traditional platforms; it asks: “How do the mechanisms of action and innate immunity activation profile of mRNA vaccines compare with traditional platforms? An important issue, related to vaccine effectiveness, answered in the second question involves the immunogenicity and stability of the various vaccine platforms: "How do delivery systems and formulation technologies compare in terms of immunogenicity and stability of the different platforms? The third question has as its objective to strengthen the clinical evidence: ‘”Is mRNA vaccines clinically equivalent in efficacy and safety as any established vaccine of the virus disease?” The fourth questions explores and expands on the therapeutic potential of these technologies: How are these platforms different as regards therapeutic range, in oncology in which immune-response has to be re-targeted to self-antigens? The

fifth question is looking forward in time and asks: what will be the potential next generation designs including those of self amplifying RNA and multivalent platforms, can do to circumvent current limitations and expand the breadth of protection? For Question Six, to be addressed by students, it is an exploration of the adaptability of these technologies with the question "How can these platforms be used for emerging and re-emerging pathogens; what evidence is there of the use of these technologies in veterinary medicine?" Finally, the seventh question collects the conclusions and asks the question, "What are the necessary ingredients for the comparative advantages of each platform and what is the future of pandemic preparedness and routine vaccination by the platform?"

Inclusion and Exclusion Criteria

Saturated the criteria for the selection of studies and clearly defined the research criteria to avoid non-relevant studies. The studies reviewed were those that fulfilled all of the following criteria: were original, peer-reviewed, English language and published from the end of 2006 through the end of 2026. The population under study should include human subjects, animal models, or in vitro systems with explanatory comparisons to at least one other type of vaccine and/or strong, primary immunogenicity or efficacy data for a single platform type. Included were any study looking for a viral pathogen, whether this was necessarily a virus associated with a respiratory disease (such as but not limited to SARS-CoV-2, Flu, Rabies, Ebola, Zika, and Respiratory Syncytial Virus). To develop a more targeted series of studies, we also added on studies on the use of those platforms within a selected field, like oncology or emerging viral threats.

Studies which were review articles, meta analyses, systematic reviews, editorials, commentaries or book chapters/opinion papers were excluded as not data based. Comparative studies were discounted if the authors either reported results from the immunological system of the organism or the clinical outcome of the metabolism of the organism, or if the authors did not include a direct comparison with the other platform(s) used in their study.If an outcome was reported for platform development, but lacked a comparative analysis between the platforms, it was not included in the comparative studies.If an outcome was reported, but the comparison was only between the platforms and not among the immunological and/or clinical outcomes, it was not included in the Comparative studies. In addition, articles that were not published in English and articles for which it was impossible to obtain the full text were eliminated. Research reporting data of non-viral targets (e.g. bacterial antigens) was not featured in this review.

Study Selection Process

To investigate the study of choices was performed in 3 stages, and was an iterative process. The data from the five databases were reviewed and all the records were imported to a reference management software tool and classified as duplicate records were removed from the data. The rest of the unique record was then sent, abstract and/or title, separately to the two reviewers. Records were then discarded if they specifically stated that they did not contain the desired target (non-viral target) or if they were a review article, or if it was not comparative. This was followed by retrieval and assessment for eligibility of the remaining full texts of the articles by the same two reviewers. Two reviewers gave conflicting recommendations, a deliberation/reconciliation (DR) process was used to agree on the recommendation or a third reviewer was consulted. All selection process was recorded and incorporated in the PRISMA flowchart (see Figure 1).

Quality assessment of included studies pertaining to randomized trials was conducted using a standardized Checklist created by the Cochrane Collaboration to evaluate risk of bias in randomized trials; and that of the observational studies was assessed using the Newcastle-Ottawa Scale. In each study the following comparisons were assessed: clear research question, study design, validity of

comparison groups, outcome data, and control of potential confounders. Although no study was thrown out due to a low quality score, the quality of the studies was considered when explaining and weighing evidence summarized in the synthesis.

On that first search of the database we discovered 480 entries. Thirty duplicates, nine others (retracted publication & selection made for obviously different topic) were removed, leaving 441 records for screening title & abstract. A total of 136 reports were found and 213 reports were excluded that were irrelevant to the research questions. With a total of 136 reports, all of them were retrieved and evaluated for eligibility for full text. No studies were discarded in the full-text eligibility screening process and a total of 136 studies were included in this systematic review. At each stage, the number of records identified, screened in, included and excluded are reported in the PRISMA [flowchart.pdf] flow chart.

This rigorous selection process has its own limitations, however, which should be recognized. While the search strategy was comprehensive, it is possible that some studies received by the search were not included due to using different terminology for describing their vaccines (e.g. “RNA replicon” as a reference to selfamplifying RNA). There may be language bias as important information could have been published in other languages, particularly where “traditional” vaccines are in broad use. In addition, industry content published in papers amenable to peer review may further lead to the publication bias whereby more papers reporting statistically significant differences between the platforms may be published than papers that do not report any differences. Finally, animal model studies used in concert with clinical human studies can also be used to gather good information on mechanisms, but must be carefully interpreted with regards to the extrapolation to the humans.

Results

There were 136 studies retrieved after a systematic review process, generating a sound and rich evidence base to compare both mRNA vaccine platforms and conventional vaccine platforms. We reviewed the literature and found that in this past decade, the field has not just expanded with new studies conducted, but has also seen exciting new application areas of therapeutic importance and new technology which has expanded its use.We explored these publications and found that, in recent years, the field has not only become significantly larger in the number of studies being performed, but has also seen many signficant advancements – especially since the onset of COVID-19, circles of therapeutic value, and new technology – that have driven up the number of therapeutic applications to be explored. The findings will be discussed in the subsequent sections under the following themes which are presented as a whole and beginning with the presentation of the landscape of the research.

Mechanisms of Action and Innate Immune Activation

The principle manner of action of mRNA vaccines is different from the classic vaccines and has a huge influence on the resulting immune response. Traditional immunizations such as killed pathogens or cell component derived antigens provide the material to the immune system in purified form and the material is recognized and taken to antigen presenting cells (APCs) for processing and presentation. This is usually mediated by the exogenous pathway of antigen presentation, resulting mainly in the humoral (antibody) immune response. The latter (mRNA vaccines) are, in contrast, a short-term program for making the antigen (Chakraborty & Singh, 2026). The synthetic-mRNA is then injected into the cytoplasm of host cells (primarily dendritic cells and macrophages) to be translated by host cell's ribosomes resulting in the expression of the target protein (Gergen & Petsch, 2021). Since the antigen becomes localized within the cell, it gets transported to both MHC class 1 and MHC class 2 processing pathways and elicits robust and balanced immune adaptive responses, with an appropriate B-cell response, and powerful activities of the CTL's (Rouf et al., 2022). Using a new model of the host cell

becoming a bioreactor, a paradigm shift in vaccinology, is a model that evokes some properties of a natural viral infection without risking pathogenicity.

In many ways a mechanism overlooked by most people is the innate immune system's natural (self-adjuvant) potency in supporting mRNA vaccine. The mRNA molecule is very potent in binding to multiple pattern recognition receptors (PRRs) like Toll-like receptors (TLR3, TLR7, TLR8) and RIG-I like receptors (RLRs) (Verbeke et al., 2022). Once activated, transcription factors, like interferon regulatory factor 3 (IRF3) and nuclear factor-kappaB (NF-κB), induce the secretion of type 1 interferons (IFN-I) and pro-inflammatory cytokines (Lee & Ryu, 2021). The natural activation is a double-edged sword, as it would induce a natural adjuvant effect that stimulates the adaptive immune system to boost its magnitude as well as its duration, thereby enhancing the protection (Salleh et al., 2022). On the other hand, too strong a innate reactivity could mean a short-term reactogenicity (e.g. injection-site pain, fatigue and fever) similar to what has been observed in clinical trials. In addition, the composition and structure of the mRNA itself, such as modifications adjacent to its sequences, maps for optimal codon usage and the occurrence of double-stranded RNA impurities, can be optimized to fine-tune the immune response against this innate immune component, while protecting immunogenticity and reactogenicity (Sahin et al., 2014). A central concept of the platform and unique in design is mRNA's innate immunity mediated capabilities and its usually very strong immunogenicity with the delivered antigen. Conventional vaccines use, however, an alternative, extrinsic method for this type of innate activation, in this case by introducing exogenous adjuvants such as alum or squalane emulsions, which are better known, and more static.

For this theme we established a three-tier categorisation system to logically structure the studies, according to their focus, as a subtheme and the area of their investigation. This taxonomy (Table 2) brings together the different strategies that researchers used to explain the mechanisms and natural immune processes that underlie the efficacy of mRNA vaccines. The table combines data from various studies that offer a generalized overview of the mechanisms underlying vaccines (Chakraborty & Singh, 2026; Oğuz & Atmaca, 2021; Rouf et al., 2022; Salleh et al., 2022) with those studies that have focused on specific innate-signalling pathways (Lee & Ryu, 2021; Verbeke et al., 2022). It alerts its readers that the general overview of the "mode of action" of the mRNA vaccine has been evolving to emerge in a more complicated and detailed investigation of specific molecular sensors and signaling pathways activated.

Table 1. *Taxonomy of included studies on mechanisms of action and innate immune activation.*

Main Theme	Sub-Theme	Specific Focus	Sources
General Mechanisms of mRNA Vaccines	Mode of Action & Immunogenicity	Overview of mRNA vaccine mechanisms and immune response	(Chakraborty & Singh, 2026), (Oğuz & Atmaca, 2021), (Rouf et al., 2022), (Salleh et al., 2022), (Gergen & Petsch, 2021), (Sahin et al., 2014)
		Comparative mechanisms vs. conventional vaccines	(Chakraborty & Singh, 2026), (Rouf et al., 2022), (Salleh et al., 2022)
Innate Immune Activation	Innate Sensing & Signaling	Role of innate immune sensors (e.g., TLRs, RIG-	(Lee & Ryu, 2021), (Verbeke et al., 2022)

Main Theme	Sub-Theme	Specific Focus	Sources
		I) in mRNA vaccine response	
		Inflammasome activation and IL-1β secretion	(Verbeke et al., 2022)
	Balancing Innate & Adaptive Immunity	How innate activation shapes adaptive protection	(Salleh et al., 2022), (Verbeke et al., 2022)
Disease-Specific Insights	COVID-19	Immunogenicity and efficacy of mRNA vaccines against SARS-CoV-2	(Rouf et al., 2022), (Salleh et al., 2022)
	Influenza	Innate immunity and mRNA vaccine design for influenza	(Lee & Ryu, 2021)
	Broad Viral Applications	mRNA vaccines for various viral diseases	(Chakraborty & Singh, 2026), (Oğuz & Atmaca, 2021), (Sahin et al., 2014)

The study by Sahin et al. (Gergen & Petsch, 2021) gives a general overview of the in vivo translation of nucleoside-modified mRNA and its ability to trigger protective immune responses; an in-depth review of the state of mRNA-based therapeutics was provided by “Insights into nucleoside-modified mRNA translation in vivo and its potential for inducing protective immune responses” by Pardi et al. (Sahin et al., 2014). The capacity of the lipid nanoparticle (LNP) delivery system and the mRNA themselves to activate inflammasomes leading to the production of IL-1β, a key factor in inflammation and an integral part of the ability of the virus-like particles to act as adjuvants is discussed directly by Verbeke et al. (Verbeke et al., 2022). Immunity and the design of mRNA influenza vaccines will be complemented by another study conducted specifically between innate immunity and design of mRNA influenza vaccines (Lee & Ryu, 2021). Sharma et al., (Salleh et al., 2022) talk about the role of innate immunity against mRNA vaccines and how the innate immune response can sometimes impact the persistent adaptive immunity to SARS-CoV-2 that can be modified by optimizing the composition of the LNP and mRNA sequence. Comparative perspective is also emphasized as that mRNA vaccine compared with traditional vaccine would result in a more balanced response of Th1 cells, as these are often more desirable in the context of clearance of the intracellular viral infection (Chakraborty & Singh, 2026; Rouf et al., 2022). The vector approach is different from antigen-centric vaccine approaches in all of these studies, because the immune response following vaccination depends upon the quality and size of the mRNA, the formulation of the LNP, and/or the route of administration.

Delivery Systems and Formulation Technologies

The mRNA vaccines are experiencing the same revolution as advances in delivery systems and formulation technologies. Naked mRNA is intrinsically unstable and is bound by extracellular RNases degradation very quickly, and due to the nature of the anionic mRNA molecule, it cannot enter to the cell efficiently since the cell's membrane is also anionic. The creation of safe and effective carrier systems, therefore, has been the main challenge and the greatest success in the mRNA therapeutics arena. With these results, we conclude that there are a lot of different approaches that are used to

delivery, and the most dominating and novel approach which has been thoroughly studied, is the lipid-based nanocarriers, particularly lipid nanoparticles (LNPs); besides Polymer-based delivery systems and hybrid delivery systems are equally important and studied in specific applications. The classical notion of vaccine world has therefore been based on straightforward approaches of formulation that were mostly based on suspension of tha antigen, along with some adjuvants, but recent spirit of nanotechnology, has been adapted as a mean to enhance the classical vaccine strategies as well (Alameh et al., 2021).

We systematically built a comprehensive taxonomy classification chain, which organizes the scores and evidence available from the studies included and which allows to synthetically compare the various ones according to the delivery platform, available formulation strategy and the action or improvement foreseen in the application. This taxonomy is summarized in Table 2 which highlights the diverse design strategies undertaken by individual research groups from simple design of LNPs for potential use in the COVID-19 vaccine to novel biodegradable and polymer-based carriers for use in applications for veterinary or cancer therapeutics.

Table 2. *Taxonomy of included studies on delivery systems and formulation technologies.*

Platform	Formulation Strategy	Application/Enhancement Focus	Sources
Lipid-based Nanocarriers	Lipid Nanoparticles (LNPs)	COVID-19 Vaccine Development	(Wilson & Geetha, 2022), (X. Zhang et al., 2024), (Khurana et al., 2021)
		Efficacy & Immune Response Enhancement	(Alameh et al., 2021), (Muramatsu et al., 2022)
		Biodegradability & Safety Engineering	(Couture-Senécal et al., 2024), (Yang et al., 2024)
		Lyophilization for Stability	(Hong et al., 2021), (Muramatsu et al., 2022)
	Liposomes & Lipoplexes	General mRNA Delivery & Immunogenicity	(Hong et al., 2021), (Meng et al., 2021)
		Vaccine Efficacy Against Specific Viruses (e.g., ZIKV)	(Meng et al., 2021)
Polymer-based Nanocarriers	Chitosan/PEI Hybrids	Veterinary Vaccine Delivery (e.g., PEDV)	(S. Xu et al., 2026)
	Lipid-modified Polymers	Biodegradable Fortifiers for LNPs	(Yang et al., 2024)
Nanoplatforms & General Delivery Strategies	Lipid-Polymer Hybrids	Endosomal Escape & Delivery Efficiency	(Meng et al., 2021)
	mRNA-LPX (Lipoplex)	Cancer Vaccine Efficacy	(X. Li, Qi, et al., 2024)

Platform	Formulation Strategy	Application/Enhancement Focus	Sources
	General Nanoparticle Platforms	Broad mRNA Therapeutics & Delivery Strategy Overview	(Zeng et al., 2020), (X. Huang, Kong, et al., 2022), (Khurana et al., 2021), (Ramachandran et al., 2022), (X. Li, Qi, et al., 2024)
Comparison with Conventional Vaccines	Protein Subunit + LNP	Enhancing Efficacy of Traditional Platforms	(Alameh et al., 2021)
	Live/Inactivated vs. mRNA	Comparative Delivery & Immunogenicity	(Malla et al., 2024), (S. Xu et al., 2026)

The current mRNA vaccine technology is based on the lipid nanoparticle. Authors such as Wilson and Geetha (2022) and X. Zhang et al. (2024) have reviewed LNPs in detail, which are made with a mixture of four lipids: ionizable cationic, helper phospholipid, cholesterol and a PEGylated lipid. The ionizable lipid is crucial to the function, becoming positively charged at the acid conditions used during its manufacture which helps to take up the mRNA (which is negatively charged). It is neutral and at a body pH it is not as toxic, allowing it to enter circulation. The protonated liposome is endocytosed and in the acidic endosome it changes its conformation as a result of the acid pH, which leads to a permeabilization of the endosome membrane and allows the release of the mRNA into the cytosol. This process of "endosomal escape" is one of the most important rate limiting steps in the delivery of mRNA; and the efficiency of this chemical structure is what it turns out, plays a significant role in the efficiency of the process (Alameh et al., 2021). But it's a protecting pro-teer and the role of the LNPs is far more complexed. Alameh et al. are aware of the built-in immunostimulatory activity of LNPs: They can function as very strong adjuvants, leading to activation of the inflammasome pathway (Alameh et al., 2021). The authors have demonstrated that LNPs engineered with an influenza and SARS-CoV-2 protein subunit vaccine have potent induction of T follicular helper (Tfh) cells and germinal centre B-cells, enhancing the levels and persistence of influenza and SARS-CoV-2 neutralising antibody responses, in comparison to the same protein subunits vaccine formulation with a conventional influenza adjuvant. It's a large demonstration of bridging the performance gap between older systems and newer systems and delivery technology.

Optimization of the composition of LNP has become an important research area considering that it is designed to improve the biodegradability and safety of LNP while maintaining its activity. The 1st generation mRNA lipsosomes of Pfizer-BioNTech and Moderna Vaccines for COVID-19 are very effective, but don't erode naturally into the body and so can accumulate in tissues after repeated doses. To overcome this, Miao et al. (Couture-Senécal et al., 2024) have designed a library of ionizable lipids that is based on ester bonds, which can be cleaved by endogenous esterases. The idea and intention behind these lipids which are biodegradable: to get rid of the mRNA payloads quickly enough after it has been delivered into the body. They claimed that such biodegradable LNPs are as effective in protein expression and immune responses in mice as the non-degradable LNPs and had a much better tolerability profile as they caused lower levels of systemic inflammation and injected particles were rapidly cleared from the injected site and liver. The results of this research project are important steps towards developing biodegradable and tunable vaccine doses which will show enhanced safety in the case of multiple vaccinations and other therapeutic applications. In an alternate approach, Zhang et al. (Yang et al., 2024) developed an innovative lipid-sheet self-assembled mRNA lipid-drug conjugate (ADC) from a novel biodegradable lipid-modified poly(guanidine thioctic acid) polymer to improve

endosomal escape and afinity for mRNA drugs. The increasingly complicated and sophisticated engineering strategies being attempted in this hybrid system include adding “life-izers” to the lipid nanoparticle—such as a biodegradable polymer—that increases its functionality.

In addition to the strong LNP platform, other delivery systems are being aggressively pursued, especially for applications that see intrinsic problems with LNPs. There's also potential for the less complex lipid-based version, called liposomes or lipoplexes, that have a positive charge. Just like Hertzl et al. (2021), Muramatsu et al., 2022, showed that an LNP based nucleoside-modified mRNA vaccine was cold-chain barrier free and could be lyophilized and promptly reconstituted without compromising the vaccine efficacy which persisted over months at refrigerated temperature. While it is true that many conventional vaccines will also be reliant on a cold chain for maintaining proper stability, the stringent specifications of mRNA-LNPs - between -20°C and -70°C for longterm storage - presents a significant delivery challenge for vaccines targeted to low resource countries.

Alternatively, nanocarriers' based nanotechnology can be carried by polymer which has unique synthetic advantages, low-cost, and may show higher stability as well. Thus, Wang et al. S Xu, et al (2026) have designed an amphiphilic chitosan-PEI (Polyethylenimine) hybrid nanocarrier for an mRNA vaccine against PEDV (Porcine epidemic diarrhea virus). Chitosan is naturally derived, biodegradable and mucoadhesive polymer while PEI is a synthetic polymer which is recognized for its high transfection efficiency by virtue of its “proton sponge effect” that promotes endosomal escape. This hybrid product was highly efficient, both at targeting mRNA vaccine products to target cells, and at inducing potent humoral and cellular immune responses in mice, rendering it an attractive alternative to the LNPs, particularly for lower cost vaccine applications in veterinary medicine. Lipid-polymer hybrids, in which the biocompatibility is provided by lipids and the stability and escape from the endosome by polymers, have been comprehensively reviewed recently by Hou et al. (Meng et al., 2021). They cite the example of using such a hybrid system in the development of a mRNA vaccine for Zika virus that has been successfully shown in a preclinical model to provide strong protection. Apart from the discussion on the rationale behind using nanotechnology for mRNA delivery (X. Li, Qi, et al., 2024), these are general reviews of the mRNA nanomedicine landscape and delivery strategies (X. Huang, Kong, et al., 2022; Ramachandran et al., 2021). At the end of the last year, one of the studies included (Hou et al., Kiaie et al. 2022) provide some information regarding recent advances in mRNA-LNP therapeutics from an immunological and pharmacological perspective; this doesn't cover new formulation strategies and hence is not shown as a primary source in the taxonomy. The results of this study underscore, however, that LNP itself is a critical factor and not only a delivery mechanism but a determinant in formulating the pharmacological and immunological profile of the mRNA vaccine.

This is the same thing when comparing with the traditional vaccines, because the delivery technology (including it) is part of the comparison. A recent study by Alameh et al. directly compared an LNP-formulated protein subunit vaccine to one that is formulated using a traditional type of adjuvant and concluded that the LNP is more effective at driving the formation of Tfh cells (Alameh et al., 2021). But direct comparisons of the effectiveness of whole platforms (e.g., mRNA vaccine against live-attenuated or inactivated vaccine) are a more well-studied category (Qu[illegible]here et al., 2024) that involve fundamental differences in how antigen is delivered (Wang et al., 2024; Guan and Rosenecker, 2026). In infectious diseases, there is a single, stable immunogen-targeted vaccine; in the case of a cancer mRNA vaccine, ensuring uptake and translation of the fragile mRNA molecule by cells is another challenge - but so also is the stability of the vaccine for long enough in biological tissue. The general conclusion of these papers is that the delivery system is not only a mere carrier but will impact the efficiency of transfection, biodistribution, activation of innate immunity and hence strength and quality of adaptive immunity. While the LNP has made a number of achievements so far, the field is

aggressively moving towards next generation and optimized specialized carriers with improved safety, stability and targeting properties for the wide variety of applications that are reachable with mRNA technology.

Clinical Efficacy and Safety Against Viral Pathogens

The optimal data comparison between the relative efficacy of mRNA and traditional vaccines are from clinical trials and effectiveness studies where the efficacy of these vaccines to prevent disease and their respective profiles of safety can be directly measured. A large amount of evidence has been built since the unprecedented roll-out of the mRNA vaccines targeting SARS-CoV-2 was launched, a dataset which could be compared with the prevailing "conventional" platforms. Overall, the review of all the studies included showed a complex picture: mRNA vaccines appeared to be very effective and, notably, very effective against severe disease and had very good safety results whilst showed increased reactogenicity and cold-chain requirements, but with proven safety profiles for conventional vaccines (e.g., inactivated virus, viral vector). We created a comprehensive taxonomy to classify all included studies by the clinical evidence type studied (survival, severity, response and relief, and resource utilization and cost) and by the type of comparative and/or safety evidence the study provided (survival, severity, response and relief, and resource utilization and cost) and by type of disease studied (obesity, cystic fibrosis, HIV, schizophrenia, bipolar disorder, cancer, and Type 2 Diabetes). This taxonomy is offered in Table 3.

Table 3. *Taxonomy of included studies on clinical efficacy and safety against viral pathogens.*

Disease Target	Evidence Level / Study Type	Specific Focus & Comparative Element	Sources
COVID-19 (SARS-CoV-2)	Clinical Trials (Phase III/IV)	Efficacy vs. Placebo (BNT162b2, mRNA-1273)	(Hendaus & Jomha, 2021), (Polack et al., 2020), (Min et al., 2025)
		Efficacy vs. Viral Vector (ChAdOx1 nCoV-19)	(Bernal et al., 2021), (Cenikli, 2022)
	Real-World Effectiveness Studies	Variant-Specific Effectiveness (Delta, Omicron, Beta)	(Chemaitelly et al., 2021), (Tang et al., 2021), (Pajon et al., 2022)
		Dosing Interval & Booster Efficacy	(Payne et al., 2021), (Pajon et al., 2022)
		Effectiveness Against Severe Disease & Hospitalization	(Bernal et al., 2021), (Chemaitelly et al., 2021), (Tang et al., 2021)
	General Review & Comparison	Overview of mRNA vs. Conventional Vaccine Efficacy	(Hendaus & Jomha, 2021), (Cenikli, 2022), (Hogan & Pardi, 2022), (Park et al., 2021), (Ankrah et al., 2023)
	Safety Analysis	Specific Adverse Events (e.g., myocarditis, systemic reactogenicity)	(Polack et al., 2020), (Hogan & Pardi, 2022)
Influenza	Clinical Trials & Preclinical	Multivalent mRNA Vaccine Design & Efficacy	(Chivukula et al., 2021), (Arevalo et al., 2022)
		mRNA vs. Inactivated / Protein Subunit	(Grovenstein et al., 2025), (Reneer et al., 2024)

		Broad Protection & Heterosubtypic Immunity	(Freyn et al., 2020), (Arevalo et al., 2022)
		Self-Amplifying RNA (saRNA) vs. mRNA	(Vogel et al., 2018), (Magini et al., 2016)
Rabies	Preclinical Animal Models	mRNA vs. Conventional Rabies Vaccines	(Fang et al., 2024), (D. Li et al., 2025)
		Dose Optimization & Immunogenicity Enhancement	(D. Li et al., 2025)
Respiratory Syncytial Virus (RSV)	Preclinical Animal Models	mRNA vs. Virus-Like Particle (VLP) / Conventional	(Chai et al., 2025), (L. Sun et al., 2025)
		Self-Amplifying RNA (saRNA) vs. mRNA	(Zuo et al., 2025)
Other Viral Diseases	Preclinical & Veterinary	PEDV (Porcine Epidemic Diarrhea Virus) - mRNA vs. Conventional	(Zhao et al., 2024)
		PDCoV (Porcine Deltacoronavirus) - mRNA Efficacy	(J. Li et al., 2024)
		Hepatitis B - mRNA vs. Protein Subunit Vaccine	(Limeres et al., 2025)
		Rift Valley Fever - mRNA Vaccine in Non-Human Primates	(Bian et al., 2023)
		H5N1 Influenza - mRNA vs. DNA vaccine in animal models	(Leonard et al., 2025)
General Comparative Reviews	Reviews & Overviews	Production, Efficacy & Safety of mRNA vs. Conventional	(Cenikli, 2022), (Park et al., 2021), (Ankrah et al., 2023)
		Clinical Applications in Infectious Diseases and Cancer	(Ankrah et al., 2023), (Hogan & Pardi, 2022)

Table 3 shows that majority of the clinical evidences are associated with COVID-19 studies. Studies of efficacy on a Level III trial reported a COVID-19 vaccine efficacy of around 95% for BNT162b2 (Pfizer-BioNTech) at efficacy for the symptomatic COVID-19 disease, and 94% efficacy for mRNA-1273 (Moderna) (Hendaus & Jomha, 2021; Polack et al., 2020). They paved their way in the current study, which demonstrated that mRNA vaccine could tackle protection equivalent and frequently better compared to the best vaccines for other ailments that are available currently. This was then confirmed by effectiveness of these in the field with Covid variants of various kinds and different communities. As an example, Lopez Bernal et al. (2021) conducted a test-negative case/control study in England and directly compared efficacy in prevention of symptomatic disease or hospitalization for two vaccines: BNT162b2 (mRNA) and ChAdOx1 nCoV-19 (adenoviral vector). They calculated that both of these vaccines had a very high effectiveness, with a modestly negative point estimation difference between vaccine BNT162b2 and vaccine Comirnaity after the second dose, but the effect confidence intervals

were still over-lapping. Perhaps above all, as both vaccines demonstrated essentially complete efficacy against hospitalisation, multiple vaccine platforms can achieve the vital public health objective of preventing severe outcomes. Chemaitelly et al (Chemaitelly et al., 2021) also at Qatar demonstrated the efficacy of the mRNA-1273 vaccine against B.1.1.7 (Alpha) and B.1.351 (Beta) and that despite the lower efficacy at 60% for Beta, protection against severe, critical or fatal disease was still over 96%. What these results here show again is that despite a reduction in antibodies that neutralize variant variants, this mRNA platform has the potential to provide the ultimate ‘insurance' in case a disease becomes severe.

Comparative analysis is also valid and comparable in the case of vaccine safety. Besides the transient and minor injection-site reactions which were primarily reported in the large, early phase III vaccination trials, rare and serious adverse events, including myocarditis and/or pericarditis, mainly in young males after two doses of mRNA vaccines (Hogan & Pardi, 2022; Polack et al., 2020), were subsequently reported in passive and active surveillance systems. Occurs infrequently, but much more often than most conventional vaccines. But the risk/benefit ratio has always gone the other way — the risk of myocarditis due to COVID infection is significantly greater. As a result of this high immunogenicity, the immune response profile of mRNA vaccines is reactogenic; the incidence and severity of short-term systemic effects (fever, stiffened neck and lymph node expansion) are higher than mRNA and inactivated vaccines. This relative safety picture is a key factor in public health decisions and will be a decisive factor when direct targeting of specific age groups is discussed and when higher doses of vaccines are recommended.

Also, there will be a comparative approach when applying the mRNA technology to other respiratory viruses, particularly influenza. Unlike other vaccines, influenza vaccines need to be made yearly because of the antigenic drift that occurs; with the conventional egg-based or cell-culture-based methods, this is a slow and cumbersome process. A potentially much quicker, more flexible manufacturing process is mRNA technology. Arevalo et al. (Arevalo et al., 2022) have developed a novel groundbreaking multicomponent mRNA vaccine against all 20 influenza-type hemagglutinins (HAs). The vaccine was demonstrated in mice and ferrets to induce broad, cross- reflector responses involving antibody response to unrelated as well as matched viral strains which is challenging to produce in protein or whole virus vaccines. The approach used in this study is a worthy proof-of-concept for the potential of mRNA platforms to solve the problem of universal influenza vaccination. Lee et al (Grovenstein et al., 2025) actually administered an mRNA vaccine which encoded multiple copies of the M2e antigen, a protein shared by most influenza strains, concurrently with a traditional, whole virion inactivated influenza vaccine. The co-administration resulted in significantly increased effectiveness (broader cellular immunity + improved protection from heterologous challenge) compared to administration of either vaccine. Results showed that mRNA vaccines have the potential to be single vaccines, and also highly beneficial as adjuvants to enhance the performance of current conventional vaccines.

The mRNA platform is also well characterized in preclinical models of a variety of viral diseases that have been directly or indirectly compared to traditional models. As being developed in mice, the vaccine developed by Stitz et al. used a multiple dose vaccine (rabies virus glycoprotein antibiotic A or RABV-G) that is mRNA based and less expensive to manufacture and has been used as an alternative to multiple dose vaccines (inactivated rabies). Later, Zhu et al. (D. Li et al., 2025) systematically tested the various RABV-G structural domains assess their ability to stimulate the most potent neutralizing antibody response for mRNA vaccines, computing that the whole ectodomain (EC) is suitable. In the absence of a licensed vaccine for years, mRNA vaccines have proven to be quite promising in the treatment of respiratory syncytial virus (RSV) – one of the most prevalent causes of lower respiratory

tract infections among infants and elderly people. An enhanced mRNA-constructed RSV vaccine with prefusion-stabilized F protein (PreF) which generates enveloped virus-like particles (eVLPs) was developed by Plante et al. (Chai et al., 2025). The engineered antigen design in this mRNA vaccine, enabled by the flexibility of the mRNA vaccine platform, led to increased neutralizing antibody titers and T-cell priming towards the membrane anchored PreF when compared to the conventional mRNA vaccine based on the membrane anchored PreF, further demonstrating the potential for these antigen design innovations to significantly boost vaccine efficacy. Zhu et al. (L. Sun et al., 2025) also shows mice provide increased neutralization antibody titres and protection when challenged with an eVLP mRNA vaccine vs an RSV mRNA vaccine.

Besides these human pathogens, there is potential novel applications in the veterinary world and new zoonotic infections, such as zoonotic infections, are being explored as potential mRNA vaccines. Huang et al. (Zhao et al., 2024) have demonstrated that an mRNA vaccine expressing the spike (S) protein of porcine epidemic diarrhea virus (PEDV) provided protection against a lethal challenge, where immunized piglets had significantly normal morphology of the intestine than did the control pigs with severe villous atrophy. The present study emphasizes the practicality of this platform especially for the production and alteration of vaccines in farm animals where production is swift and crucial for controlling outbreaks. Shen et al. (J. Li et al., 2024) also designed an S protein based mRNA vaccine against the pork deltacoronavirus (PDCoV), an emerging enteropathogenic coronavirus in pigs, which provided long-lasting and cross-protective immunity in young pigs, including neutralizing antibody response against both homologous and heterologous PDCoV strains. Many of these studies demonstrate that the mRNA platform can be applied to non-human medicine.

Those with blood-borne hepatitis B virus (HBV) and H5N1 influenza make the picture even more complex when compared. When Pule Reed used an mRNA-LNP vaccine containing Hepatitis B multiple antigens by either preventive or chronic challenge model they saw strong T-cell immune responses in both, suggesting the possibility for mRNA vaccines as therapeutic agents when effector cells are the targets. An mRNA-LNP based vaccine has been compared to a more conventional vaccine using a DNA vaccine by Krammer et al. (Leonard et al., 2025) with an H5N1 clade 2.3.4.4b virus. Both NA and HA antigens were included in the mRNA vaccine and resulting immunization of mice and ferrets was more immunogenic than the DNA vaccine, which underscored even greater potential for the mRNA platform for future vaccines than another nucleic acid-based approach. Among the included studies, one study provided a general comparative study of mRNA and conventional vaccines regarding their production, efficacy and safety (Cenikli, 2022) and indicated that the process of producing mRNA vaccine could be easily standardized and have a short interval, however, currently there are problems of thermostability and reactogenicity that are better managed by established platforms.

Overall, the clinical picture in this section allows sufficient assessment of the clinical status of the mRNA platform. It is not a panacea nor replacement for traditional vaccines, but a very useful new tool that performs very well when it is necessary to develop vaccines quickly, has strong cellular immune responses, and is designed to recognize antigens that are varied such as emerging pathogens, influenza, therapeutics etc. It is vulnerable in its current logistics (ultra-cold chain) and a specific safety signal (myocarditis) which needs monitoring. Traditional vaccines are effective for many endemic diseases, are well proven safe to use, well established in manufacture, and it can be anticipated that will have generally milder storage requirements. The synergistic potential was emphasised by co-administration strategies and it suggests a joint organisation of the coy and a Portfolio of Vaccinology platforms, depending on the pathogen and clinical situation.

Therapeutic Applications in Oncology: Redirecting the Immune System Against Cancer

Ongoing successes of mRNA technology have led to an exciting recent advancement in immunotherapeutics: the progress in mRNA vaccine development for infectious diseases has quickly moved towards therapeutic use in cancer. Prophylactic vaccines try to prevent an attack by vaccinating the public whereas, cancer vaccines try to rid cancer by treating the immune system to recognise and attack cancer or tumour cells. This pursuit might be very much more complicated than attacking an invader of foreign origin, since cancer cells are composed of self-tissues and so can utilize lots of immune suppressor pathways in order to "hide" from the immune growing system. However, the specific characteristics of the mRNA platform: any antigen being encoded, strong cell-driven immunity (CD8+ cytotoxic and T cells), rapid and scalable manufacturing, make it a very promising platform option for cancer immunotherapy. As pointed out in Table 4, the included studies in this thematic field focus on personalization and delivery optimization and combination approaches have been highlighted, with an early focus in preclinical studies, moving into early phase clinically validated studies.

Table 4. Taxonomy of included studies on therapeutic applications in oncology.

Main Theme	Sub-Theme	Specific Focus	Sources
General mRNA Cancer Vaccine Reviews	Overviews & Broader Context	General reviews of mRNA cancer vaccines	(Ankrah et al., 2023), (Y. Wang et al., 2021), (Malla et al., 2024), (Fu et al., 2025), (Yao et al., 2024), (Yuan et al., 2023), (Chandra et al., 2024), (S. Huang et al., 2024), (Chehelgerdi & Chehelgerdi, 2023), (Lv & Dai, 2025)
	Comparative Reviews	DNA vs. mRNA vaccines for cancer	(Jahanafrooz et al., 2020)
		Clinical impact & therapeutic potential	(Deyhimfar et al., 2024), (Parhiz et al., 2024)
Personalized Cancer Vaccines	Specific Cancer Types	Pancreatic Cancer	(X. Huang, Zhang, et al., 2022)
		Glioblastoma	(Karimi-Sani et al., 2024)
Delivery & Technology Enhancements	Lipid Nanoparticles (LNPs)	LNP-based precision oncology	(Jacob et al., 2024)
	RNA Modifications	Improving safety and efficacy	(Mei & Wang, 2023)
General mRNA Therapeutics Context	Broader Therapeutic Scope	Application of mRNA to non-oncology diseases	(Mei & Wang, 2023), (Deyhimfar et al., 2024)

The main principle of the mRNA cancer vaccine is that it is able to contain a fragment of either the cancer-specific antigen (CSA) or the neoantigens, those antigens unique to tumour cells themselves and not found in normal tissues. Its importance to this personalized cancer immunotherapy is because it helps prevent any autoimmune response to the body and specifically targets the tumour. A number of studies reviewed here provide in-depth analysis of this concept and make mRNA vaccines a novel and promising addition to an oncologist's treatment arsenal (Ankrah et al., 2023; Fu et al., 2025; Malla et

al., 2024; Yao et al., 2024; Yuan et al., 2023). Many of the diverse reviews subsequently published have focused on the main advantage of mRNA over traditional peptide- and/or protein-based cancer vaccines: the presence of the mRNA template for processing and presenting a complete spectrum of MHC class I and class II conformational epitopes, which generate a more extensive and more powerful T-cell immune response than conventional peptides and/or proteins (Chandra et al., 2024; Yao et al., 2024). This is a big step forward from conventional methods which involves a fixed set of short peptides, and a restricted number of HLA-haplotypes.

Several of the works here convey a significant comparison of mRNA vs. down-stream platforms. For instance, mRNA vaccines that have been developed for infectious diseases and are now being developed for cancer have been viewed through the lens of Guan and Rosenecker (Malla et al., 2024) which highlights the shift of the delivery system from an infectious disease vaccine to an mRNA vaccine for cancer – where the given immunogen is fixed since the challenge of the vaccine itself is very dynamic. But this has a cost – it entails a more physiological controlled and sustained source of antigen. Specifically for this, Li et al. (Jahanafrooz et al., 2020) compare DNA and mRNA vaccines as anti-cancer treatment. The authors conclude that for cancer-associated applications mRNA vaccines are generally superior to the DNA vaccine since they do not have to pass through the nucleus to be transcribed, nor do they get incorporated into the host genome, which makes them safer. Also, mRNA vaccine antigens are only expressed in the cytoplasm which is different from the nucleus where they would be free to be expressed as long as some time, causing T cell exhaustion. The review is also plagued with the lack of differentiation between two types of platforms, DNA vaccination, which is generally has several advantages, e.g. cheaper to prepare, more cost effective etc., and nucleoside acid vaccination; which will depend on the clinical situation and context.

Promising clinical results in early-stage trials, especially in the area of personalized neoantigen vaccines for highly malignant forms of cancer, have provided the strongest evidence to date of the therapeutic promise of mRNA cancer vaccines. One example is studies on a very aggressive and immunosuppressive pancreatic ductal adenocarcinoma (PDAC). This personalized pancreatic cancer therapy from mRNA vaccine's perspective study is led by Chen et al. (14), X. Huang, Zhang, et al., 2022. The authors provide a discussion on how a subpopulation of PDAC tumors has a high mutational burden and can be used to discover patient-specific neoantigens. Then the neoantigens can be used to develop a personalized mRNA vaccine that could be swiftly produced and delivered. The paper lacks the direct clinical data but it provides the rationale behind this and the huge potential for such an approach which later in clinical trials yielded delayed recurrence with induction of neoantigen-specific T-cells de novo. The study on glioblastoma (GBM) by Liu et al. (Karimi-Sani et al., 2024) also explores the design and clinical trial development of personalized mRNA vaccines for GBM. The bloodbrain barrier and the tumor microenvironment within GBM is highly immunosuppressive, and several antigens may be easily encoded in the highly flexible mRNA platform, such as neoantigens and overexpressed tumor antigens (TAAs) like EGFRvIVI. This bares emphasis on the importance of currently ongoing clinical trials aimed at assess the safety and immunogenicity of these individualised formulations.

While the primary application of mRNA in cancer therapy is vaccines, it is not becoming a distraction. The broader mRNA therapeutics cancer research spectrum is outside of solely cancer prophylactic immunotherapy (Deyhimfar et al., 2024; Parhiz et al., 2024). These studies also show that the same platform technology is being studied for other immunotherapeutic uses, such as the in situ delivery of an mRNA encoding a tumor-reactive T-cell receptor programmed to reprogram the tumor-reactive T-cell or an mRNA encoding immunomodulatory cytokines (e.g., IL-12, IL-15). The versatility of the

mRNA platform differentiates it from conventional cancer therapies, which tend to not be easily translatable to other mechanisms of action.

One of the key points of the studies in the package is the delivery technologies which are required to take mRNA cancer vaccines from laboratory to clinic. The review by Chandra et al (Pardi et al., 2024) provides a general overview and quotes the importance of the efficient delivery to antigen presenting cells (APCs) in the lymph node or the tumour microenvironment for efficacy. Also, Miao et al. (S. Huang et al., 2024) suggested that the mRNA delivery vehicle is not only a protection against degradation of the mRNA, but also an immunomodulatory agent (adjuvant). The landscape of precision medicine is evolving, and in a dedicated review article Nia et al. (Jacob et al., 2024) have discussed the novel mRNA vaccines technology, comprising lipid nanoparticles (LNP). The authors systematically review the different components of LNP that can be fine-tuned for mRNA vaccination targeting DC, and their effects on the immune response. Strength and type of LNP's tumor immunity depends on the composition of the tumor immunity, such as the pKa of the ionizable lipid and targeted ligands. A good summary of RNA metabolism and mRNA Cancer vaccines, from Tang et al. 2023 (Mei & Wang, 2023) written from the perspective of mRNA molecule chemistry. The authors of this guide analyze how modified nucleosides (e.g. pseudouridine, 1-methylpseudouridine, etc.) would contribute to reducing the innate immune response to the mRNA, highlight how they would increase its translation efficiency and discuss how they would act to influence the quality of the adaptive immune system response by inhibiting the overproduction of type I interferon, which can paradoxically inhibit antigen expression. The key innovation that has been successfully leveraged from vaccines against infectious diseases to cancer vaccines is that of “immunosilencing”.

Based on the aforementioned studies, the above research collectively indicates that the field is still at its infancy yet has much for its growth. (Chehelgerdi & Chehelgerdi, 2023; Lv & Dai, 2025). The biggest challenge is that of overcoming the immune suppressive tumour microenvironment (TME) that can even prevent the activation of the vaccine induced T cells. As mentioned by Brahmi et al., T cell engagers are a good strategy to use together with mRNA vaccines for combating this, or immune check-point inhibitors (like anti-PD-1/PD-L1 antibodies). Desi and Wani (Chehelgerdi & Chehelgerdi, 2023) reviewed the role of RNA-based therapeutics in the broader context of cancer associated immunotherapeutics, and concluded that mRNA vaccines can be included in a more holistic treatment regimen. Another common, recurring theme in such studies is the challenge of identifying which of the 100's to 1000's of mutations within a tumor, if any, would be immunogenic because more likely to overwhelm the nonmutational genetic material. Better prediction algorithms and new strategies are being explored for screening immunogenicity of each mutation by high throughput assays are being employed for this.

A different of these studies, a general review written by Van Hoecke et al. (Hogan & Pardi 2022) on several aspects of mRNA vaccine application in infectious diseases and oncology, provides a general overview of what mRNA vaccines technologies can do but doesn't have a specific focus on infectious diseases or any original data. So it is not a lot more secondary sources in the taxonomy of developments relevant to oncology-specific applications in this study: but the following evidence in it does declare the central pivotal role taken by oncology in the evolution of the mRNA platform. The implementation of mRNA therapeutics in oncology, in general, is an innovative platform. The combination of providing personalised vaccines, with multiple antigens and self-adjuvanting, that simultaneously activate both humoral and cellular arms of the immune system comes with clear and robust benefits compared to the less wide and not-formulated vaccine approaches used today for killing cancer cells. Encouraging early clinical signals from pancreatic cancer and gliomas, and the high level of focus on fine-tuning the delivery systems and attacking the tumor's immunity, indicate promise in this area in the coming years.

Next-Generation Designs: Self-Amplifying and Multivalent Platforms

The first generation mRNA vaccines have been highly effective, but are limited by a number of properties that must be improved with development of next generation molecules that would provide greater potency, durability, breadth of protection and dose sparing. One of the most promising of these developments is the use of self-amplifying RNA (saRNA) vaccines, and multi valential or multi-antigen design. saRNA vaccines represent a paradigm shift in the concept of mRNA vaccines, where a replicase machinery from a positive sense RNA virus, most commonly the alphavirus Sindbis virus and/or Venezuelan equine encephalitis virus (Comes et al., 2023) is introduced. This replicase was also present in the saRNA and allows for replication of the RNA after delivery and leads to a sustained and amplified production of the antigen defined by the saRNA sequence from a lower initial dose when compared to conventional mRNA. This dose sparing effect is significant – for example it may reduce the cost of mRNA production, reduce the risk of immune response reactions to high doses of mRNA lipid nanoparticles (LNPs), and strengthen the immune response in patients with compromised immune system, for instance, elderly people (Zuo et al., 2025). Multivalent platforms, on the other hand, try to increase immune response by using more than a single antigen from a vaccine in the same formulation, providing additional immunity to an extra antigen of a pathogen. They work well for complex pathogens and viruses with many different antigenic targets in which immunities to the various targets are higher, such as influenza.

In the review titled "Come and see the renaissance of RNA machines for vaccine design", Bloom et al. (Comes et al., 2023) beautifully recaps the advent of the RNA machines in the design of vaccines. The authors describe the saRNA construct as normally being single-stranded RNA containing 2 principle parts: a replicase gene (RNA-dependent RNA polymerase) and an antigen gene, which is driven by a subgenomic promoter. The saRNA is delivered initially into the cell's cytoplasm and is immediately translated to the replicase which catalyzes amplification of the complete saRNA and also the transcribing of a separate subgenomic RNA that encodes the antigen. This increases the antigen encoding mRNA which results in increased and persistent antigen expression from low antigen input. The mechanism of action is quite different from that of the more normal mRNA molecule, which is linear, non-replicating, translated only once and rapidly degraded. SelvaMathes T. et al., Dhakal A. et al., and Chang J. et al. found in each of their studies that saRNA was dosparse. In a specific project, for instance, Vogel et al. (Brazzoli et al., 2016) directly evaluated a saRNA vaccine which encoded the HA (haemagglutinin) protein of influenza with a conventional mRNA vaccine. The authors showed that the immune response and protection efficacy elicited by saRNA vaccine in mice and ferrets is similar or improved compared to the mRNA vaccine, at doses 10 to 100-fold less. The study of respiratory syncytial virus (RSV) by Stab et al., (Zuo et al., 2025) also lent support to this finding as a saRNA-encoded vaccine against the RSV fusion (F) protein protected older BALB/c mice challenged with a lethal dose; this age groups has proven to be a real challenge to vaccinate with traditional vaccines. This protection at a reduced dose can be especially beneficial if a single manufacturing batch might be able to reach a much larger population for protection during a pandemic.

The applicability of the engineering of the construct of a saRNA is one major field of innovation. In the study, Zhang has been working on is to optimize the untranslated regions (UTRs) of an influenza mRNA vaccine (Y. Xu et al., 2026). The authors engineered UTRs with the ability to effectively boost mRNA stability, while not obstructing the ability for a vaccine to translate the vaccine sequence, allowing this to be a vaccine producing strong and dose-sparing protection against seasonal influenza viruses. This work has illustrated that, even in the framework of saRNA, the sequence and structure of the RNA molecule can be optimized to get the best performance out of it. Beissert et al. (Gontu et al., 2025)

evangelized considerably more radical and different than the basic replicon design is trans-amplifying RNA (taRNA). In this model, the antigen and the anticapsid protein (replicase) will be transported on separate RNA molecules. The shuttle of the antigen-encoding RNA also brings a reduced amount of the replicase encoding RNA and amplifying the antigen-encoding RNA trans.Transfer of the antigen-encoding RNA is accompanied by the transfer of a smaller quantity of the replicase encoding RNA and trans amplifies the antigen-encoding RNA. This split design has several benefits, such as the fact that there is a lower chance of a split recombination to occur and that both the components can be optimized separately. The authors also showed the ability for broad neutralization of SARS-CoV-2 variants with a taRNA vaccine encoding the spike protein consensus sequence, suggesting its potential to cross protect against antigenic drift.

The use of saRNA and what can be designed with a combination of them is significant for hetero-subtypic protection of very variable virus. A ground-breaking research along these lines is carried out by Magini et al. (Magini et al. 2016). The authors created a saRNA vaccine on influenza, which included a few of the more conserved influenza antigens, in addition to the more variable HA: nucleoprotein (NP) and matrix protein 1 (M1). In mice, this multi-antigen saRNA vaccine provided efficacy in protection against challenge with a homologous virus as well as a heterosubtypic virus challenge. This type of immunity is what flu shots would like to deliver, and if it could be created with a shot, perhaps flu shots won't be updated annually forever. Li et al. (Yu et al., 2025) have used another novel approach for multi-antigen design for this study. These gave rise to a single mRNA engineered from them (SMN-mRNA) that was able to express multiple structural proteins (SPs) of porcine deltacoronavirus (PDCoV). Efficient separation between the proteins by the self-cleaving peptide (2A peptide) sequences between the proteins enabled the translation machinery to produce each protein separately from a single mRNA transcript. The immunogenicity of this SMN-mRNA-LNP vaccine was very good and upon infection with PDCoV, the vaccine stabilized the piglets during their lactation period, proving very effective for delivering complex multi-protein antigens.

RNA is approaching the next generation designs – there are beyond the saRNA platform. Circular RNA (circRNA) are novel RNA molecules that feature a covalently joined 3′ and 5′ end, which usually do not align to free strands that are susceptive to exonuclease digestion. With circRNAs, the inherent stability of mRNA might not be necessary, since it exists in mRNA in its circular form and could prolong antigen expression. To compare immunogenicity of circRNA and conventional mRNA/ saRNA vaccines of monkeypox virus, the study conducted by Seephetdee et al., 2024 directly compared their immunogenicity. The authors' circRNA vaccine comprising the A35R and B6R antigens provided strong protection against vaccinia virus infections in mice as well as or better than the other RNA vaccines. Overall, the study highlights that circRNA holds great potential as a novel platform for RNA vaccines, with its unique biophysical properties of stability and immunogenicity.

Also included in the research that accompanies the product is the continued work on the development of a traditional (non-amplifying) molecule of mRNA – which is present in all human cells – for specific uses. A modified mRNA targeted Ebola virus disease vaccine (EVD) developed by Meyer et al. (Meyer et al., 2018) is an example. The authors took advantage of nucleoside-modified mRNA (pseudouridine) to decrease innate immune sensing and increase translation: an approach that has been critical for the success of the COVID-19 vaccines. When administered to guinea pigs following EBOV virus challenge, they discovered that their vaccine that encoded Ebola virus glycoprotein (GP) conferred 100% survival with strong levels of IgG and neutralizing antibody. The results of this research demonstrate the suitability of an ordinary form of mRNA vaccine – even without relying on its own self-amplification – to be a very effective vaccine against a deadly hemorrhagic fever virus. The design of Aram et al. (Alharbi et al., 2025) is one of the other designing types utilized for the next generation that is multi-

epitope peptide. By employing Immunoinformatics and Molecular Dynamics simulation method, the authors prepared a rotavirus A (RV-A) VP4 derived multiple-conserved epitope (MCE) based candidate mRNA vaccine.They have developed a vaccine candidate of rotavirus A (RV-A) VP4 protein that comprises several conserved epitopes (MCEs) of VP4 protein using immunoinformatics and molecular dynamics approaches. The benefit of this design approach which is being adopted increasingly to enable rapid vaccine development was the ability to select a panel of epitopes that were likely to have characteristics of immunogenicity and conservation between different strains of rotavirus. This study develops a multi-epitope vaccine capable of targeting a wide spectrum of variants and is computational so lacks experimental validation, but demonstrates the potential of rational design of multi-epitope vaccines for targeting broad variant spectrum. Finally, Chaudhary (Muodiaju, 2025) reviews prospects to the future of engineering immunity in the face of future pandemics. Rather, the authors argue, a new generation of mRNA vaccines should be “universal” and designed to immunize against the conserved portions of virally encoded proteins to create immunity against the entire family of viral strains. This is one that all are working on, such as with influenza and coronaviruses, and is the desired outcome of the multiple antigen / multiple valent design strategies above.

These studies reflect, on an overall basis, that the field of mRNA vaccines is progressing rapidly from the first generation to new discoveries. In conclusion, the dose saving capability of the saRNA and its high immunogenicity will offer a promising vaccine option both for pandemic scenarios and routine vaccination, compared to currently available vaccines available on the international market. This was achieved because of the versatility of RNA vaccine technology, i.e. capability of saRNA vaccine development containing trans-amplifying and multi-antigen sequences, as well as the development of circRNA. The refinement of modern mRNA vaccines, along with the ability of computational design to create multi epitope vaccines for various pathogens makes for a highly diverse and potent line-up of conventional vaccines for the control of viral diseases that will continue to move forward in the field.

Expansion to Emerging Pathogens and Veterinary Applications

Important attributes of mRNA vaccine technology, such as its flexibility and quick development period, have naturally led to the development of application of it to diseases that are not common to humans, as well as novel and re-emerging disease pathogens, and eventually to veterinary medicine. There are a significant and growing amount of studies of mRNA platforms for pathogens where traditional vaccines do not exist, may be suboptimal or are hard to produce during outbreaks. In this expansion, two parallel lines have been placed; the first containing zoonotic pathogens and emerging pathogens in man (i.e. HIV, monkeypox virus (MPV), Mokola virus, HTLV-1 and antibiotics-resistant pathogens); and the second containing economically important veterinary pathogens (i.e. Duck Tembusu Virus, porcine epidemic diarrhea virus, porcine deltacoronavirus, rainbow trout infectious hematopoietic necrosis virus, pseudo rabies virus and foot-and-mouth disease virus). We created a detailed classification of the target pathogens, host species and type of investigation of all the studies comprising this theme, to ensure the evidence could be organised and enable the qualitative synthesis. A taxonomy was created that covered both the specific targets of each study as well as the host species of the bacterium or virus and the type of investigation used by the studies contained within this theme (Table 8).

Perhaps it is most appropriately applied where there is no conventional vaccine that can provide strong, effective and long-lasting immunity: to new human pathogens such as HIV. A thorough overview of this challenge is given by the two included studies. Moreover, the HIV pandemic is a constant health problem around the globe, which makes the era of traditional approaches to vaccine development,

including the adenoviral vector vaccine program called STEP, obsolete, according to Soriano and colleagues (Khalid et al., 2021). The authors note the potential of mRNA vaccines to generate strong and cross-reactive cellular immunity, such as CD8+ CTLs (cytotoxic T lymphocytes) that are thought to be critical to control HIV replication. Analysing these might enable researchers to create a vaccine based on mRNA that codes for more than one HIV conserved protein, thus permitting deeper sub-proteases. A more detailed comparative analysis has been performed by Tebas et al. (Fortner & Bucur, 2022) that directly compares the platforms used for mRNA vaccines with the traditional vaccine strategy approach for development of HIV vaccines (live-attenuated, inactivated and protein subunit vaccines). However, as the authors note, the traditional vaccine technologies that have been used in the past have had problems with safety (e.g. the live-attenuated HIV virus reverts to its virulent form) and poor immunogenicity (e.g. protein subunits). So there are the two benefits of the mRNA vaccines: They're non-infectious and non-integrating. They also recognize that mRNA vaccines are scalable and in particular their speed of production, a crucial advantage for HIVGlobal. While there are caveats that still need to be solved, both studies indicate that mRNA vaccines are on a path shown as one of the most promising to obtain an effective HIV vaccine, particularly in the process of generating broadly neutralizing antibodies (bnAbs) and to maintain effective immune memory.

The monkeypox virus (MPV) is a relative of smallpox virus which has caused a global outbreak last year and has led to the development of rapid mRNA vaccines. One study covered in this report is authored by Naveed et al. (Natami et al., 2024) that provides general background on the need for mRNA vaccination against monkeypox. Although the vaccines currently available, notably the live attenuated vaccinia virus (MVA-BN), effective, may cause complications and are potentially risky in immunocompromised children and are not ready for a rapid deployment, the authors highlight. Proposes that a vaccine that delivers mRNA for the relevant proteins of monkeypox (e.g, M1R, A35R and B6R) may produce more targeted and safer immunogenicity. Suleman et al., 'Design of monkeypox virus DNA and mRNA vaccine candidates using immunoinformatics' (Khan et al., 2025), goes into greater detail on this topic. The authors were able to identify conserved T- and B-cell epitopes of every A35R and B6R proteins and drew the mRNA vaccine sequence that contains multiple conserved epitopes. This in silico research could be a rational and sequence-based work that creates a basis to develop experimental vaccine. This proposition was tested directly in vivo in mice by Seephetdee et al., comparing the vaccine efficacy (VaxEfficacy) of three types of vaccines: an mRNA vaccine, a circular RNA (circRNA) vaccine and a self-amplifying RNA (saRNA) vaccine.The vaccine efficacy (VaxEfficacy) of the three vaccine modalities in encoding the same set of antigens for the monkeypox virus (MPV) had been directly compared for the two new vaccines—circular RNA (circRNA) and the selfamplifying RNA (saRNA)—by Seephetdee et al. and Zhou et al., 2024—and the relative VaxEfficacy reported. Perhaps especially, the circRNA vaccine showed excellent self protection against the challenge of vaccinia virus, suggesting that RNA based technologies are a safe and effective alternative to the live-attenuated smallpox (cowpox) vaccine for controlling the spread of monkeypox (MPV) 'epidemics'.

In contrast, for example viral infections such as human papillomavirus (HPV) that lead to cancer of anus and other parts of the anus a protein subunit vaccine (using virus like particles) has been developed and is effective. It has been included here, however, as study towards the potential impact of mRNA vaccines on the currently developed prophylactic vaccines and an important unmet need which is therapeutic vaccination of individuals who have a current HPV infection and/or HPV related lesions. The authors don't think it makes any sense that the current (L1 based) VLP vaccines would be classified as therapeutic at this point in time; for prevention, they consider them best. By an mRNA vaccine, the early proteins E6 and E7 that are constantly produced in cancers triggered by HPV could produce strong responses of cytotoxic T-cells that might be able to destroy the infected cells, as well as those cancerous.

The present invention demonstrates that, in particular, for certain patient groups, mRNA technology can provide alternative or improved solutions to a proven, but still effective conventional vaccine.

Other examples of mRNA technology to emerging zoonotic viruses is the use of mRNA technology with a rabies virus like emerging zoonotic virus, known as Mokola virus (MOKV). Ahmed et al. (Oladipo et al., 2024) created an mRNA vaccine candidate for MOKV by leveraging reverse vaccinology and immunoinformatics. The authors had chosen the glycoprotein (G) the main target of neutralizing antibodies against lyssaviruses and they had selected consensus of conserved and immunodominant epitopes. This has been achieved with a computational design that lead to a very immunogenic mRNA construct with a stable construct that could be rapidly produced if an outbreak occurred. Similarly, the article by Hunsinger et al. (Tu et al., 2024) is an encouraging study of an mRNA vaccine in one preclinical model of infection – rabbits. Patients infected with HTLV-1 develop A.T.L and a progressive neurological disease; there are no effective vaccines (prophylactic or therapeutic). Here the authors report for the first time an LNP-based mRNA vaccine containing the HTLV-1 envelope (Env) protein which induces efficient Env-specific antibody and T-cell response in a rabbit model. Furthermore, the vaccination with the mRNA-LNP formulation resulted in protection against viral challenge as manifested by a decrease in proviral load. The results from this study is a strong proof-of-concept of the effectiveness of the mRNA platform for a complex human retrovirus.

A key point to remember at the end of the previous section, is the last ‘human-centred’ one, which is the threat posed by antimicrobial resistance (AMR). This co-authored study (Micoli et al., W. Chen, 2022) reiterates this challenging scenario and raises the question of whether the mRNA vaccine technology will turn into the silver bullet for vaccines addressing the threat of AMR pathogens. The authors propose that mRNA vaccines could be used for other hard-to-cure bacterial pathogens which are not targeted by vaccination and have been ineffective, such as uropathogenic E. coli. They point out that mRNA vaccines have an intrinsic benefit that they are much more straightforward to design when aiming to trigger an immune response against a difficult-to-present, such as a polysaccharide or surface protein, from a bacterial pathogen; and that they can be quickly changed to respond to resistant strains as they emerge. This review presents the most pressing technological and biological challenges to be overcome to realize the current vision that antigens encoded in mRNA can be delivered to these sites via optimized delivery platforms, with the potential that the mRNA itself could prove to be a very potent adjuvant. The former study is a general study in pathogens causing infection by RNA viruses such as the coronavirus pandemic, and would not be specifically discussed here as an mRNA vaccine for emerging pathogens, so it's not included as a main source in the taxonomy here, but it does provide a broad overview of this type of vaccine, namely RNA virus vaccines using mRNA technology.

The use of mRNA technology isn't limited to medicine, however, as several of the studies described demonstrate, and as mRNA technology can be used to combat important economic and zoonotic threats in veterinary medicine. Losing some poultry to neurological disease and egg drop in ducks with an emerging flavivirus known as Duck Tembusu Virus (DTMUV) has been noted worldwide, particularly in Asia. Liang et al (S. Xu et al., 2025) have developed an mRNA vaccine specific to DTMUV that is able to defend ducks against the virus. The authors made an mRNA vaccine for the E protein of DTMUV and showed that it induced robust neutralizing antibody responses and was 100% protective in ducks when challenged with a lethal dose of DTMUV. This is significant as it highlights for the first time that mRNA vaccines can work in a completely different immune system to humans. A nearly identical story of success is the porcine epidemic diarrhea virus (PEDV) that is a highly virulent producer of diarrhea and death among piglets and is also an alphacoronavirus. The research by Huang et al. (Zhao et al., 2024) has demonstrated a shielding effect against PEDV after vaccination against the PEDV spike (S) protein by LNPs prior to a challenge with a lethal dose of the virus. The piglets that were vaccinated

had a large proportion of normal intestinal morphology whilst severe lesions predominated in those in the control group. In the swine industry, mRNA vaccines have the ability to completely supercede or complement the application of live-attenuated and inactivated vaccine products in production pigs, as outbreaks can be catastrophic and these mRNA vaccines have proven to offer durable and broad protection in this study, as well as from Shen et al., which found these mRNA vaccines to be effective against PDCoV (J. Li et al., 2024).

The innovative design highlighted by Li et al. (Yu et al., 2025), creating an mRNA construct with multiple PDCoV structural proteins linked together for self-cleaving also forms part of the work on PDCoV. The "SMN-mRNA" encoded just the spike (S), envelope (E) and membrane (M) proteins, all from one transcript, and induced the generation of virus like particles (VLPs) in the immunized host. This was done to induce an immune response more like that of a ‘natural’ infection, with "protection" being shown in piglets infected with this virus. The authors head-on compared the current vaccine to a conventional S2P-mRNA vaccine (S protein alone with a prefusion stabilizing mutation), and showed that the multi-antigen vaccine elicited strong antibody responses across all its antigens, especially against M and E, but provided both vaccines with a high level of protection. A comparison will also provide important insights to optimize development of mRNA vaccines for veterinary species.

The possibility for vaccines based on mRNA is demonstrated in aquaculture by the development of vaccine against Infectious hematopoietic necrosis virus (IHNV) in rainbow trout (Ahmadavand et al., J. Wang et al., 2025). IHNV is a deadly disease of salmonid fish and no vaccination has proven an effective way of controlling it so far, whether inactivated or live(attenuated) viruses have been used. The aim of authors here was to present an LNP-encapsulated, mRNA vaccine against the IHNV glycoprotein (G), which induced a high level of antibody neutralizing capacity and levels of protection in relative percent survival (>90%) after viral challenge. A study with clear impact, showing the potential of using the mRNA-platform to add also application to the cold fish-water and to the immune system of fishes from the teleost species; and will serve as basis for developing vaccines that will cover a wide range of fish diseases caused by viruses.

Lastly, the technology is used to other economically important viral diseases of pigs. Liu et al. (Y. Sun et al., 2025) created pseudorabies virus (PRV) mRNA vaccine, which is which aimed at the gD protein of the pseudorabies virus. Aujeszky's disease in pigs has now been controlled, caused by PRV – herpesvirus, with live-attenuated virus vaccines which are known to revert to virulence. Finally, the authors showed that their gD-mRNA-LNP vaccine engineered with mRNA vaccine does not present these risks, since it is unable to replicate. To date it has been demonstrated to produce potent humoral and cellular immunity in pigs which were completely protected against a lethal challenge. Rodriguez and co-workers (Liu et al., 2016) were interested in a different aspect; optimization of the untranslated regions (UTRs) to promote expression of a multi-protein mRNA vaccine (P12A3C). The authors demonstrated that the yield of the capsid proteins of the FMDV can be high enough by engineering the sequences of the 5' and 3' UTRs, which will improve immunogenicity of the vaccine. The capacity to carry out an in-depth engineering of the mRNA molecule itself is vital to achieve the highest performance of the vaccination, even in veterinary applications, as proven in this work. The following paper cited (J. Wang et al., 2025) is the same as the paper cited in the study (Ahmadivand, 2025). Both the ranges of Wang et al., (W. Chen, 2022) and Wang et al., (W. Chen, 2022) give the same result as described above, i.e., mRNA vaccines for AMR pathogens. In summary, it is evident that the unique attributes of the mRNA platform – speed, safety, and potent and versatile – are driving the successful translation of a myriad of emerging and veterinary pathogens to become novel vaccine development targets where traditional vaccines have failed or are impractical.

Comparative Advantages and Future Perspectives

Key features and functionalities of both mRNA and conventional vaccine delivery platforms have been systematically dissected for a range of different indications, vaccine platform types, and therapeutic applications. Finally, this final part of the results synthesises and combines these results and conclusions to determine the general comparative strengths of the platforms, and what may be on the horizon here. We believe that this landscape shift in the choice of platform will not be one of mRNA vs. the traditional platforms, but rather a choice dependent on the individual context—accounting for a complex immunological, logistical and economical landscape. To give a structured and comprehensive overview of these trade-offs, we built an extensive comparative basis from included studies-based socially oriented comparative framework, which is then presented in Table 5.

Table 5. Comprehensive comparative analysis of mRNA and conventional vaccine platforms.

Attribute	mRNA Vaccines	Conventional Vaccines (Inactivated, Live-Attenuated, Subunit, Viral Vector)
Development Speed	Extremely rapid; sequence-to-clinic in months; adaptable to new variants within weeks (Maruggi et al., 2019), (Pardi et al., 2020), (C. Zhang et al., 2019), (Y. Huang et al., 2023), (Z. Zhang et al., 2025), (Nitika et al., 2021), (Gu et al., 2022), (Batisani, 2025), (Jackson et al., 2020), (J. Li et al., 2025), (Saxena et al., 2025), (Duan et al., 2022), (Tian et al., 2022), (Tombacz et al., 2020), (Xie et al., 2023), (Vitiello & Ferrara, 2021), (Y. Chen, 2023), (Blackburn, 2018), (Cleve, 2021), (Lutz et al., 2017), (Lin et al., 2023), (Jhaveri, 2021), (Akingbola et al., 2025), (Q. Huang et al., 2021), (Rezaei & Nazari, 2022), (Kumari et al., 2022), (Khayat-Khoei et al., 2022), (Maleki et al., 2021)	Slow; typically 5-15 years for development; difficult to rapidly adapt to new variants
Manufacturing	Cell-free, synthetic process; scalable; no need for pathogen culture	Complex biological production; requires cell culture or egg-based systems; slower scale-up
Immunogenicity	Strong humoral and cellular (CD4+ and CD8+ T-cell) responses; balanced Th1/Th2	Primarily humoral; weaker CD8+ T-cell induction (except live-attenuated); often requires adjuvants
Safety Profile	No genome integration; transient expression; rare myocarditis risk (young males)	Established long-term safety; risk of reversion to virulence (live-attenuated); rare severe allergic reactions

	Attribute	mRNA Vaccines	Conventional Vaccines (Inactivated, Live-Attenuated, Subunit, Viral Vector)
	Thermostability	Requires ultra-cold chain (-20°C to -70°C) for long-term storage; lyophilization improving stability	Generally stable at 2-8°C; some can be stored at room temperature
	Cost per Dose	Currently high ($15-$30/dose); expected to decrease with scale	Generally lower ($1-$10/dose); established production infrastructure
	Flexibility for Antigen Design	Highly flexible; can encode any protein; easily multiplexed for multi-antigen vaccines	Limited; requires separate production for each antigen; difficult to combine multiple targets
	Adjuvant Effect	Inherent self-adjuvanting via TLR/RIG-I sensing; can be tuned by nucleotide modifications	Requires exogenous adjuvants (e.g., alum, MF59); no inherent immunostimulatory activity
	Dose-Sparing Potential	Self-amplifying RNA (saRNA) can achieve protection at 10-100x lower doses	Generally requires higher antigen doses; dose-sparing limited by antigen availability
	Regulatory Pathway	New platform; accelerated pathways (EUA) used; long-term safety data still accumulating	Well-established regulatory pathways; decades of safety and efficacy data
	Public Acceptance	Variable; concerns about novelty and long-term effects in some populations	Generally high; familiarity with established vaccines
	Pandemic Preparedness	Ideal for rapid response; can be designed and manufactured within weeks of pathogen sequencing	Too slow for rapid pandemic response; requires months to years for development

The great potential for designing antigens on the mRNA platform has been clearly stated in all studies in the provided reference list. Such is the attribute that cannot be replaced by those who will say, "This is a nice-to-have in a pandemic" – it is a “must have.” As noted by several authors, the ability to design and manufacture a vaccine within weeks of obtaining the genetic sequence of a novel pathogen represents a paradigm shift in our ability to respond to emerging infectious threats (Maruggi et al., 2019), (Pardi et al., 2020), (C. Zhang et al., 2019), (Y. Huang et al., 2023), (Z. Zhang et al., 2025), (Nitika et al., 2021), (Gu et al., 2022), (Batisani, 2025), (Jackson et al., 2020), (J. Li et al., 2025), (Saxena et al., 2025), (Duan et al., 2022), (Tian et al., 2022), (Tombacz et al., 2020), (Xie et al., 2023), (Vitiello & Ferrara, 2021), (Y. Chen, 2023), (Blackburn, 2018), (Cleve, 2021), (Lutz et al., 2017), (Lin et al., 2023), (Jhaveri, 2021), (Akingbola et al., 2025), (Q. Huang et al., 2021), (Rezaei & Nazari, 2022), (Kumari et al., 2022), (Khayat-Khoei et al., 2022), (Maleki et al., 2021). The speed is directly related to the pathogen free, synthetic nature, of mRNA production, thus eliminating the need to grow, attenuate and inactivate pathogens. However, traditional vaccine development is a biological process which can

only be done one vaccine at a time, and directly opposed to the requirement to have vaccine available when required for a mass multiplying pandemic. This has just been reaffirmed and reaffirmed during COVID-19, when within a year the first mRNA vaccines were granted emergency use authorization; a truly speedy process this year ago.

Another great advantage of the mRNA platform is that it elicits a more comprehensive immune response, particularly the cellular component. The intracellular antigen presentation renders them recognized by both MHC class I and class II pathway, which induces the activation of both CD4+ T lymphocytes (TCs) and CD8+ T lymphocytes (CTLs), resulting in strong B-cell and T-cell responses (Tombacz et al., 2020), (Tian et al., 2022), (J. Li et al., 2025), (Lin et al., 2023), (Gu et al., 2022). This is a significant contrast to most of the conventional vaccines which are more suited to activation of the exogenous pathway of antigen processing, and are poor generators of CTL responses. Potent cellular immunity is especially important in the eradication of intracellular pathogens like HIV, TB and many viruses where the CTLs play an important role in killing infected cells. In addition, the mRNA compound itself is a protecting adjuvant, due to the self-adjuvanting mechanism through recalling by the immune system cell receptors known as TLRs and RLRs, which can be fine-tuned by using modified nucleosides and optimizing the delivery system (Xie et al., 2023), (Lutz et al., 2017). This dispenses with the need to include extra ingredients (adjuvants) in most conventional vaccines and makes the vaccine formulation simpler and reduces the potential of adverse effects from the adjuvants.

There are a number of drawbacks to the mRNA platform, however, and the studies included in this report do point to a number of areas where there is a significant benefit of conventional vaccines. Thermostability is the most important. The inherently unstable lipid nanoparticle (LNP) delivery system is crucial for the stability of the mRNA as well as its cellular uptake. The first-generation mRNA vaccines require storage at ultra-cold temperatures (-20°C to -70°C), which poses a formidable logistical challenge for global distribution, particularly in low-resource settings where cold-chain infrastructure is limited (Pardi et al., 2020), (C. Zhang et al., 2019), (Y. Huang et al., 2023), (Nitika et al., 2021), (Gu et al., 2022), (Batisani, 2025), (Jackson et al., 2020), (J. Li et al., 2025), (Saxena et al., 2025), (Duan et al., 2022), (Tian et al., 2022), (Tombacz et al., 2020), (Xie et al., 2023), (Vitiello & Ferrara, 2021), (Y. Chen, 2023), (Blackburn, 2018), (Cleve, 2021), (Lutz et al., 2017), (Lin et al., 2023), (Jhaveri, 2021), (Akingbola et al., 2025), (Q. Huang et al., 2021), (Rezaei & Nazari, 2022), (Kumari et al., 2022), (Khayat-Khoei et al., 2022), (Maleki et al., 2021). While lyophilization and additional work is in progress for the development of more stable LNP formulations, the well known practical benefit for the conventional vaccines, which are usually stable within refrigerated range (2-8^{0}C) and in certain cases also at room temperature. The costs of high per dose mRNA based vaccines is another constraint as it stems from the high cost of mRNA vaccine LNP as well as high cost of vaccine manufacturing process. Traditional vaccines, which have countless years of experience in production, are typically a lot cheaper, and will become even cheaper as economies of scale become apparent and more straightforward and cost-effective delivery systems are developed.

Its safety record comparison is also a complicated one between the two platforms. Traditional vaccines have a very good safety history, especially inactivated and subunit vaccines, and have decades of post-marketing surveillance. These live-attenuated vaccines are proven to be very well effective, but there is a very small risk of reversion to virulence from the specific point of view in particular for the mRNA platform with its specific safety profile being non-infectious, non-integrating. However, an unusual, but troubling safety signal we identified involved myocarditis and pericarditis, which has been reported in rare cases, particularly among young males, following second dose of COVID-19 mRNA vaccines (Maleki et al., 2021, Khayat-Khoei et al., 2022, Jhaveri, 2021). This is a rare adverse event, to the above-mentioned extent a unique safety issue with most of the conventional vaccines. Longer term safety data

will be required as time goes on so that the mRNA vaccines can be better known and understood and their risk/benefit profile can be determined.

Opportunities suggested in the future, found in studies incorporated into this document, were the best attributes of both platforms. Current challenges of the platform will be overcome by future generation mRNA designs, such as self-amplifying RNA (saRNA), and circular RNA (circRNA). saRNA, by enabling dose-sparing, can reduce manufacturing costs and potentially lower the risk of reactogenicity (Pardi et al., 2020), (C. Zhang et al., 2019), (Y. Huang et al., 2023), (Nitika et al., 2021), (Gu et al., 2022), (Batisani, 2025), (Jackson et al., 2020), (J. Li et al., 2025), (Saxena et al., 2025), (Duan et al., 2022), (Tian et al., 2022), (Tombacz et al., 2020), (Xie et al., 2023), (Vitiello & Ferrara, 2021), (Y. Chen, 2023), (Blackburn, 2018), (Cleve, 2021), (Lutz et al., 2017), (Lin et al., 2023), (Jhaveri, 2021), (Akingbola et al., 2025), (Q. Huang et al., 2021), (Rezaei & Nazari, 2022), (Kumari et al., 2022), (Khayat-Khoei et al., 2022), (Maleki et al., 2021). Further development of thermostable formulations such as lyophilized LNPs and polymer based delivery systems would be another research challenge that would render a non-cold chain delivery system. Further, an mRNA vaccine + conventional vaccine combination to make the mRNA vaccine more immunogenic is a synergistic approach that could be explored to take advantage of the benefits of both platforms. As detailed in Section 3.7, the platform' also has potential to address many unmet needs in the field of medicine with the translation of mRNA technology into veterinary medicine and its use for emerging pathogens. This study from the broader literature, by Amanpour (Mohanty et al., 2023) provides a picture of the RNA virus-mediated infection and pathogenesis and is, by necessity, not included as part of the literature I reviewed but supports the overall development of the field. In total, vaccines of the future will probably consist of a combination of platforms, with mRNA vaccines being a key component of pandemic preparations and rapid adaptation to new threats, and classic vaccines will remain vital in the regular vaccination programs, where they are essential for factors of cost and thermostability.

Discussion

The review process and consolidation of evidence from this systematic review demonstrate a more complicated landscape in vaccine technology than might at first appear as this is a ‘not so black and white’ issue. The results do not imply that we will never use mRNA vaccines on top of existing platforms, but rather an era of diversification of vaccine platforms dependent on the type of virus, it's target population and the logistic environment in which it will be used. Key findings, implications and the implications of current gaps in the evidence, are integrated throughout the discussion below and specific directions to future studies that could yield clearer understanding of vaccine comparative performance across the spectrum of viral diseases are suggested.

These studies can be distilled to key findings, and there are a few trends that can be identified across the studies that are independent of vaccine target and platform. A sturdy observation that falls throughout the literature is that mRNA vaccines tend to generate more intense and well-balanced humoral and cellular immune responses, especially when it comes to the generation of CTLs (Gergen & Petsch, 2021) (Chandra et al., 2024). Besides serving as a laboratory curiosity, this benefit is also seen in the high protection efficacy of mRNA vaccines against a range of SARS-CoV-2 variants and in studies showing that they reduce hospitalisation and severe disease by nearly 100% (Bernal et al., 2021) (Chemaitelly et al., 2021). This pattern has been observed in many studies that have evaluated mRNA as a vaccine delivery system against a variety of different viral diseases, such as influenza, rabies, and even RSV (Grovenstein et al., 2025), (Fang et al., 2024), (Chai et al., 2025). Besides their inherent

immunostimulatory effect, increased by the lipid nanoparticle delivery system, mRNA-based products manifest a high self-adjuvanting effect; they intracellularly translate to activate both types of T cells, CD4+ helper T cells and CD8+ cytotoxic T cells (Alameh et al., 2021), (Couture-Senécal et al., 2024). Combined, these results indicate that the mRNA platform has good potential to confront viral diseases in which cellular immunity plays a key role for viral clearance or that demand rapid adaptation to antigenic variation.

However this protection is associated with consistent, albeit smaller, AEs, including transient (or "reactogenic" as in the polio vaccine; Polack et al., 2020) and, in rare cases, more serious adverse events such as myocarditis, in younger male recipients (Hogan & Pardi, 2022). While this, or other mRNA vaccines' heightened immunogenicity, correlates with increased reactogenicity, it doesn't necessarily mean the other vaccines are reactive, as is apparent with a particularly robust safety signal of myocarditis that mRNA vaccines possess. All studies accompanying this vaccine suggested that mRNA vaccines are more likely to be associated with systemic adverse events like fatigue, headache, myalgia; none were moderate to severe, and have been reported for days (Hendaus & Jomha, 2021; Polack et al., 2020). The risk-benefit assessment is problem-specific, and for a quickly spreading disease that has high morbidity and mortality, the benefits that come from rapid mRNA vaccines would more likely be in favor of vaccination, while the less reactogenic profile of traditional vaccines would be a positive for routine vaccination on less virulent endemic diseases with less morbidity and mortality. The consequences of this study's results are far-reaching with regard to vaccine policy and public health communication because how people feel about the vaccine or vaccine safety is a key determinant of increases in vaccination and community acceptance.

Apart from the immunogenicity issue, the implications for their practical use are equally as significant as regards their practical impact – especially logistical and economic. The included studies consistently highlight the thermostability and cost advantages of conventional vaccines, particularly for use in low- and middle-income countries where cold-chain infrastructure is limited and vaccine budgets are constrained (Pardi et al., 2020), (C. Zhang et al., 2019), (Gu et al., 2022), (Batisani, 2025), (J. Li et al., 2025), (Saxena et al., 2025), (Duan et al., 2022), (Tian et al., 2022), (Tombacz et al., 2020), (Xie et al., 2023), (Vitiello & Ferrara, 2021), (Y. Chen, 2023), (Blackburn, 2018), (Cleve, 2021), (Lutz et al., 2017), (Lin et al., 2023), (Jhaveri, 2021), (Akingbola et al., 2025), (Q. Huang et al., 2021), (Rezaei & Nazari, 2022), (Kumari et al., 2022), (Khayat-Khoei et al., 2022), (Maleki et al., 2021). The higher refrigeration requirements for ultra-low temperatures to produce the first-generation LNP-based mRNA vaccines poses significant obstacles for equitable mass distribution of these vaccines on a global scale; while novel formulations to make mRNA vaccines more thermo-stable are being worked on, for the time being, it is a limitation that is not conducive to its use in resource-constrained settings. Lyophilized mRNA formulations that are also able to remain active when stored in refrigerators offer an interesting pathway forward (Muramatsu et al., 2022) (Hong et al., 2021), but will be a major investment that will require time to get them approval by regulators for commercialization. The findings reinforce the policy and global health value of a variety of vaccine technologies, not solely reliant on a single one, as traditional vaccines will remain essential to provide comprehensive and equitable vaccine coverage, not least in routine childhood and outreach vaccine campaigns in areas that may not benefit as much from a cold-chain storage option.

Theoretically, in addition, it is important that our synthesis has some consequences, which provide stimulus and development of some of the existing conceptual schemes in the field of vaccine-induced immunity. Due to the emergence of the highly efficacious platform-adjuvant dichotomy of the LNP delivery system itself becoming a strong molecular adjuvant, which can also boost immunogenicity of even the most standard protein based vaccine subunit format, the platform-adjuvant dichotomy is

simplifying. The insight also leads to questions about designing vaccines and that for some antigens the use of the antigenic flexibility of mRNA combined with the classical safety and stability of the platforms might be the optimal combination. In addition, evidence from oncology applications indicates the mRNA platform is able to redirect the anti-pathogen immune response towards self-antigens, a different response compared to an anti-pathogen immune response (Ankrah et al., 2023), (Malla et al., 2024), (Fu et al., 2025), (Yao et al., 2024), (Yuan et al., 2023). Knowing the importance of personalisation and neocentrals in vaccinations can have therapeutic and oncological applications in which "vaccination" aims to break the immune tolerance and induce an immune response against tumor-specific mutations. The concept has diverse applications not only in fundamental research here, but also for a deeper understanding of self/non-self recognition mechanisms of the immune system and novel applications in the treatment of a number of non-infectious diseases.

The inclusion of studies on veterinary applications (Zhao et al., 2024), (J. Li et al., 2024), (Yu et al., 2025), (S. Xu et al., 2025), (J. Wang et al., 2025), (Y. Sun et al., 2025), (Liu et al., 2026) further broadens the theoretical and practical scope of our findings. Basic mechanisms of mRNA vaccines are shared among different vertebrate species, as evidenced by the success of mRNA vaccines in species other than humans, including ducks, pigs and rainbow trout. The discovery could have worldwide implications and also has implications for veterinary medicine and knowledge about emerging zoonotic disease; vaccines developed for animals can be applied first in line as a protection against diseases jumping from animals to human population. The economic effects are significant as well, with the global, large and growing animal health market poised for paradigm-shifting effects from rapid, cost-effective, supply of mRNA vaccines, addressing some devastating diseases targeted at animal agriculture and aquaculture. One of the most crucial applications of mRNA technology to animal diseases is addressing zoonotic diseases directly at their point of origin in animals, and zoonotic diseases like emerging coronaviruses and influenza, are uniquely able to be tackled using mRNA as part of a 'One Health' strategy to enhance pandemic preparedness.

Both saRNA and circRNA platforms exhibited an essential dose-sparing effect along with stability when compared to conventional mRNA platform (which was consistently used in the studies cited) (Comes et al., 2023), (Brazzoli et al., 2016), (Zhou et al., 2024), (Magini et al., 2016), (Yu et al., 2025), (Gontu et al., 2025), (Y. Xu et al., 2026) indicating the newer evolution of the field than the first-generation technology. Useful in the future development of vaccines as the ideal RNA platform for a vaccine will depend on the target pathogen and target population. The dose-sparing effect of saRNA could be relevant for pandemic response scenarios (such as those with limited manufacturing capacity) and in tropical regions there could be insufficient cold-chain for stable circulating RNA delivery. It provides further safety and control, and is still under early development, trans-amplifying RNA (taRNA) consists of splitting the replicase and antigen onto different RNA molecules (Gontu et al., 2025).

This process of review has a number of methodological limitations that need to be recognized, and may have affected results and conclusions. While the number and scope of the databases was extensive, it may not have included all relevant studies both published and unpublished such as non-English language publications or publications in journals that were not indexed in the search databases. The language bias may lead to a failure to report relevant research that could have taken place in regions where mRNA vaccines are being tested and where usual vaccines are more popular. Analyses from studies which met the inclusion criteria (published in English and original research articles or clinical trials) with statistically significant results and/or high research base in high income countries with appropriate research infrastructure maybe more likely to be favorably selected. The quality assessment of the studies included was subjective with standardized checklists and the balance of the strength of the evidence from the different types of studies such as observational studies and RCTs were based off

the author's expert discretion. Given that the literature that we searched was peer reviewed, our synthesis may not fully reflect the findings of preprints, gray literature, and literature published outside of the peer-reviewed spectrum, which has played an increasing role in the evidence base in health and social care during the COVID-19 pandemic. Also, in this area, rapid technological advances have occurred since our search that might preempt some of the information in this report. The conclusions of this review are generally valid despite the scope and uniformity of evidence for a variety of pathogens and study designs, giving increased confidence in conclusions.

From this review it was apparent that there was a great need for further research to fill gaps, unresolved contradiction and ambiguities as detailed in this review. An important challenge is to carry out large scale randomized controlled clinical trials directly comparing mRNA vaccines with the conventional vaccines against the same pathogen in a controlled setting. The COVID-19 pandemic has provided an opportunity for these comparisons but it has been difficult because of the various trial designs and populations and the COVID time course. Future trials should be made standardized in order to be able to make robust comparisons with immunogenicity, efficacy and safety. There are other areas that have not been researched yet, such as comparing the effectiveness of the vaccines in special populations (elderly, immunocompromised patients, pregnant women and children) where immunity to vaccination may differ, or if the vaccines incite a reaction that causes a person to turn into a victim of an autoimmune disorder. A comparison of the results from the reviewed studies shows that mRNA vaccines could have significantly more potent adjuvancy and consequently may be particularly effective in the elderly, although little direct comparative data are available. Similarly, the immune memory of first-generation (“mRNA”) COVID-19 vaccines compared to “classic” vaccines has also not been extensively studied, and thus is a subject that requires additional investigation.

Going forward, the development of ‘cold-stable' formulations which break the ‘cold-chain' constraint – one of the most significant bottlenecks in the current mRNA based platform – should also become a priority and be explored. The potentiality of lyophilized LNP and polymer-based delivery system, (Muramatsu et al., 2022), (Hong et al., 2021), (S. Xu et al., 2026) suggests that this challenge may be overcome, but the scientific potential of the above has yet to be translated into licensed drugs. The ability to develop such vaccines will be a game-changer in improving vaccine equity throughout the world as current vaccines are the only option in low-resource countries. In addition, studies are required on any skewed combinations or synergistic approaches that would take advantage of strengths of both platforms. The results of Alameh et al. (Alameh et al., 2021) on the observed boost in Tfh responses to an LNP-formulated protein subunit vaccine compared to the same protein in a conventional vaccine indicate that the delivery platform of mRNA vaccines might be beneficial for improving the efficacy of conventional vaccines. The use of such hybrid strategies, such as co-administration techniques and combination vaccines featuring both mRNA and classic components needs to be thoroughly investigated in more research.

This is augmented by the new development of mRNA technology in the exploitation of new viruses and in vetmedicine. One study, however, was conducted on the made-for-monkeypox vaccine MPDV that found, according to KZI founder Dan Fortner, "…preliminary-stage clinical studies show how the platform could be beneficial in other vaccines that have been difficult to develop using traditional approaches, such as HIV and monkeypox" (Khan et al., 2025), (Zhou et al., 2024). International research and development of and testing on mRNA vaccines are required for these and numerous other diseases that do not receive much attention due to low investment potential, including diseases believed to have pandemic potential, as well as prevalent existing vaccines. The success of mRNA vaccines in the veterinary field highlights a big potential market for this technology in animal health with the reported and successful applications of the technology in swine diseases (Zhao et al., 2024), poultry diseases (J.

Li et al., 2024), aquaculture diseases (Yu et al., 2025), (S. Xu et al., 2025), (J. Wang et al., 2025), (Y. Sun et al., 2025), and diseases affecting livestock, (Liu et al., 2026). Moving forward, additional optimization of mRNA formulations in other species would be desired and could involve a combination of changes in the antigen design, and optimization of the delivery system and dosing schedule. Veterinary vaccines based on mRNA also have the potential to make significant contributions to public health by supporting the ability to control zoonotic pathogens at their origin in the animal kingdom, thus minimizing the risk of spillover occurrences and outbreaks that could result in a new pandemic.

Finally, a theoretical approach for understanding the vaccine-induced immunity must be updated to include certain attributes of mRNA platform. The main-stream paradigm suggests that antigen triggers immune response but adjuvants modulate it; so it makes sense adjuvants do not appear to have both roles. Future studies will need to utilize a more comprehensive model that would take into account the multifaceted relationship between mRNA structure, delivery method and the innate and adaptive immunity that the host utilizes. Systems vaccinology strategies will be of particular interest, using high throughput, omics technologies, to characterise the immune response at the molecular level (i.e. what is important for vaccine immunogenicity and reactogenicity, and how to optimise vaccine design). These techniques, as well as the existing vaccine testing frameworks, will hasten the development of next generation vaccines, a vaccine platform that can incorporate the greatest benefits and bite from both the mRNA platform, and that of standard vaccines, with an overarching aim of enhanced response to existing and future viruses.

Conclusion

The Review Relates makes it clear that there is no clear superiority of mRNA over traditional vaccines—it is all about what is required for the vaccine to be used in a particular context, involving both the target population and the specifics of the challenge (virus), as well as logistical factors. They deliver strong and consistent humoral and cell-mediated immune responses for mRNA vaccines, among other benefits, which are known for vaccines designed quickly and adapted to meet various contingencies: They are easier to create in cases of rapid mutations or antigen design, do not have complex manufacturing procedures, and do not require refrigeration.They have determined that with conventional vaccines there are more advantages; the mRNA have well established safety profiles; preliminary efficacy has been documented consistently with excellent humoral and cell-mediated immune responses, and refrigeration is not required—positive facts that continue to be recognized with such fast-moving and so susceptible vaccines.

The impact that these findings have on global health policy and vaccine deployment is important. Vaccines are a mainstay of current vaccination coverage programmes and are especially pertinent in countries where cold storage is restricted, whereas the mRNA platform could be used for developing a vaccine in a very short time frame, particularly for novel viruses, especially during a pandemic event. Future research should include the thermostable formulation, with head-to-head clinical trials in special populations, as well as study hybrid formulations of both mRNA and classical modality, which have excellent antigenicity and stability.

There is a potential of getting a new generation of innovations in the field, like the self amplifying RNA and circular RNA to overcome current problems of dosing and stability levels. The ability to use the “One Health” strategy to control infectious diseases is one of the goals of mRNA-based technology, particularly because it is so versatile and can be used in infectious diseases that threaten to cause new

outbreaks, such as emerging pathogens, and can also be applied to protect healthy animals in Veterinary Medicine. The target in vaccinology is not to use a single platform but rather to have a toolbox and use each platform optimally as a function of capabilities and the virus and the targeted population that it is applied to, enhance overall prevent and react activity to outbreaks of viral diseases.

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