



Review article

Clinical advancements in mRNA vaccines against viral infections

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ABSTRACT

Over the last decade, mRNA vaccines development has shown significant advancement, particularly during the COVID-19 pandemic. This comprehensive review examines the efficacy of pivotal vaccines against emerging COVID-19 variants and strategies for enhancing vaccine effectiveness. It also explores the versatility of mRNA technology in addressing other infectious diseases such as influenza, respiratory syncytial virus, HIV, cytomegalovirus, Ebola, Zika, Rabies, and Nipah viruses. The analysis includes safety and clinical progress of mRNA vaccines and evaluates their potential in combination vaccine strategies. Additionally, it addresses challenges related to delivery and scalability while highlighting opportunities for future advancements in the field. Recent advances in mRNA optimization, biomaterial-based delivery and thermostable designs offer promising solutions. It is essential to gain insights into the evolving landscape of mRNA vaccine technology to maximize its vital role in addressing diverse viral threats, advancing vaccinology and enhancing public health preparedness for future pandemic.

1. Introduction

The use of messenger RNA (mRNA) in medical research can be traced back to 1961 when scientists first uncovered its pivotal role in protein synthesis [1]. A significant milestone in the field occurred in 1984, when Krieg and Melton successfully generated functional mRNA in a controlled laboratory setting [2]. During the 1990s, researchers embarked on preclinical investigations for in vitro synthesis of mRNA for different applications such as protein therapies, gene editing and vaccination strategies for addressing cancer and infectious diseases [3–6]. Since the early time of its discovery, the main emphasis was to discover the structural and functional characteristics of mRNA, as well as its metabolic processes within eukaryotic cells. Major milestones of mRNA research and its implication in vaccine development are given in Fig. 1. Researchers were dedicated to unraveling the complexities of mRNA, laying the groundwork for investigating the potential of mRNA to produce specific proteins. This involved utilizing the protein synthesis machinery, either in vitro or in vivo within transfected cells [7–9].

Unlike plasmid DNA and viral vectors, mRNA transcripts show superior transfection efficiency and lower toxicity. In the cytoplasm, mRNA undergoes translation while DNA therapeutics require nuclear

entry for transcription, and their efficacy depends on the breakdown of the nuclear envelope during cellular division [6]. Moreover, mRNA has advantageous features to treat diseases through protein expressions, leading to enhanced therapeutic efficacy [27]. Another advantage is that mRNA is non-infectious and non-integrating thus eliminates the risk of insertional mutagenesis [28]. Translation of encoded proteins ensures prolonged expression in contrast to transient protein therapeutics [29,30]. Additionally, in vitro production of synthetic mRNA has proven to be a simple and cost-effective process.

Clinical use of mRNA has been difficult due to its limited half-life, innate vulnerability to enzymatic degradation, and tendency to induce undesirable immune responses. Overcoming major obstacles and accomplishing game-changing breakthroughs have characterized the shift from fundamental mRNA research to real-world applications. Advances in mRNA engineering, such as chemical changes like replacing uridine with pseudouridine [16], sequence optimization [31,32], and purification techniques [33], have significantly increased mRNA stability, decreased immunogenicity, and increased translational efficiency. But even with these developments, mRNA's negative charge, vulnerability to RNases, and difficulty entering the anionic cell membrane made it a significant challenge to deliver into cells. To combat

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this, researchers created a variety of specialized carriers, such as polymeric nanoparticles, lipid-polymer hybrid nanoparticles, and lipid nanoparticles (LNPs) [34–37]. These carriers enabled effective intracellular delivery by shielding mRNA from enzymatic degradation and facilitating its passage through several biological barriers [38–40]. As delivery systems advanced, scientists found that mRNA could stimulate humoral and cellular immunity, which makes it a promising vaccine platform [28]. The quick development and effectiveness of mRNA vaccines during the COVID-19 pandemic was made possible by these scientific advancements taken together, indicating the technology's potential for use in vaccines and treatments in the future [41].

Several mRNA vaccine candidates for COVID-19 are being tested for pre-clinical trials and 43 of them are in the stage of clinical evaluations as of March 30, 2023 (enlisted in Table 1). More importantly, according to the WHO report, 7 of these candidates have entered phase 3 trials [42]. This shows the continued and promising use of mRNA technology for addressing pandemic. The success of mRNA COVID-19 vaccines, exemplified by those developed by Moderna and BioNTech/Pfizer has not only been crucial in combating the pandemic but has also prompted advancements in mRNA-based technology for a range of viral infections. Support by national health and regulatory agencies, and participation of volunteer has facilitated comprehensive clinical trial studies, revealing the potential of mRNA vaccines across diverse infections.

In this review, we have provided a brief overview of recent developments made in mRNA vaccines for a broad range of viral infections. In context of COVID-19, an overview of efficacy of pivotal vaccines has been summarized, highlighting the strategies opted to boost the efficacy by utilizing emerging variants. Beyond COVID-19, the review explores the extensive efforts made for the development of mRNA vaccines for diverse infections including influenza, respiratory syncytial virus, HIV, cytomegalovirus, Ebola, Zika, Rabies and Nipah viruses. Additionally, we have addressed challenges and opportunities associated with mRNA-based technology in vaccine development, aiming to contribute to better understanding of this field for preventing future pandemics.

2. COVID-19 mRNA vaccines

In the race against COVID-19, leading vaccine companies have showcased their innovative approaches to vaccine development. Phase I

trials of Moderna's mRNA-1273 vaccine, which employ nucleoside-modified mRNA encoding for SARS-CoV-2 S-2P, formulated in LNP technology, demonstrated strong immune responses in adults and also extended its efficacy for older adults (NCT04283461) [43]. The 100- μ g dose selected from these trials showed a remarkable 94.1 % efficacy against SARS-CoV-2 and a convincing 100 % efficacy against severe COVID-19 in Phase 3 trials [23,44]. Furthermore, age-specific trials involving adolescents aged 12 to 17 years (NCT04649151) and children aged 6 to 11 years (NCT04796896) have shown no serious adverse events and immune responses were robust and noninferior to young adults, indicating the vaccine's safety and effectiveness across diverse age groups [45,46]. Meanwhile, BioNTech and Pfizer's evaluation in assessing four COVID-19 vaccine candidates resulted in the selection of BNT162b2, a nucleoside-modified mRNA encoding for SARS-CoV-2 spike, featuring two proline mutations to stabilize prefusion state [47]. In a global trial, BNT162b2 demonstrated an outstanding efficacy of 95 % against COVID-19 among individuals aged 16 years or higher, with minimal adverse events [24]. Additionally, this vaccine has demonstrated a robust immune response and remarkable 100 % efficacy in preventing COVID-19 in adolescents aged 12 to 15 years, with validated safety and efficacy across this age group [48].

Exploring an alternative approach, CureVac's unmodified mRNA COVID-19 vaccine (CVnCoV) encountered challenges with a suboptimal efficacy of 48.2 % in a phase 2b/3 trial (NCT04652102), significantly less than the effectiveness observed in vaccines developed by Moderna and Pfizer/BioNTech [49]. Possible factors responsible for decreased effectiveness of CVnCoV includes emergence of multiple variants of SARS-CoV-2, lower dosage of vaccine (12 μ g) and lower translation efficiency of unmodified RNA [50]. Overcoming this setback, 2nd generation vaccine (CV2CoV) has demonstrated enhanced immune response in preclinical studies and progressed to phase 1 trial (NCT05260437). Such diversity in advancements of COVID-19 vaccines is the reflection of continuous efforts to combat the pandemic by adopting multiple strategies, where each approach contributes to significant insights into the global vaccination endeavor.

Despite this progress, there are still issues with the declining efficacy of COVID-19 mRNA vaccines in older adults, especially regarding the duration of protection against serious outcomes like hospitalization and death. The adaptability of mRNA vaccines has proven crucial in

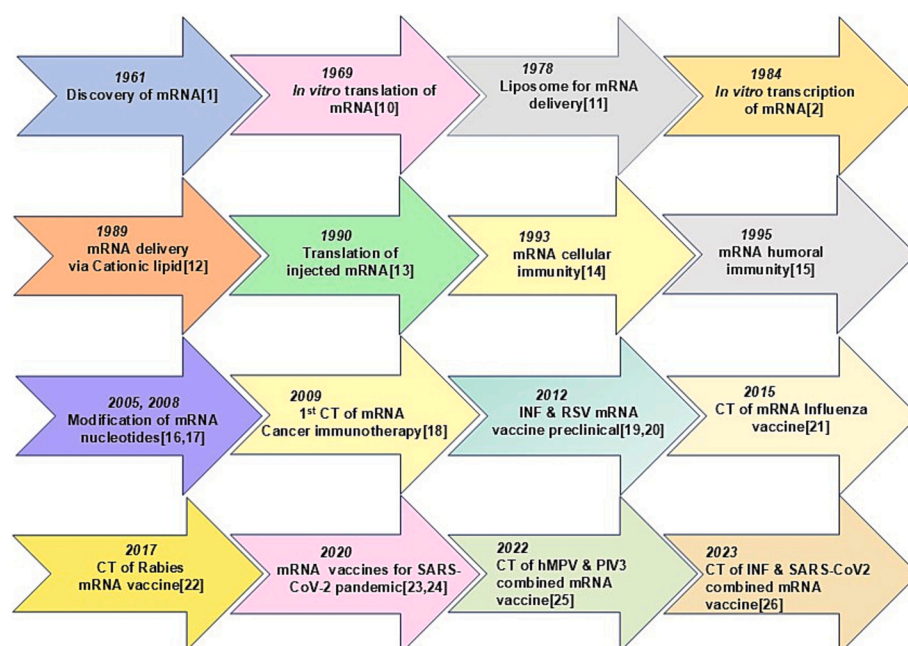


Fig. 1. Timeline of major discoveries for mRNA vaccine developments [1,2,10-26].

Table 1
Clinical trials of mRNA vaccines against viral infections (Excluding COVID-19).

Product Name	Antigen/protein	Infectious Disease	Population	NCT Number (status)	Phases	Sponsor
mRNA-1010	Seasonal quadrivalent HA of Influenza A (H1N1,H3N2) and Influenza B (Yamagata Lineage, Victoria Lineage)	Influenza A & B strains	Adult, Older adult	NCT05415462 (Completed) NCT05566639 (Active, not recruiting) NCT05827978 (Recruiting)	3	ModernaTX, Inc.
mRNA-1440 (VAL-506440)	HA sequence of H10N8	Influenza A	Adult	NCT03076385 (Completed)	1	ModernaTX, Inc.
mRNA-1851 (VAL-339851)	HA sequence of H7N9	Influenza A	Adult	NCT03345043 (Completed)	1	ModernaTX, Inc.
mRNA-1030, mRNA-1020	HA and NA of influenza A and B strains	Influenza A & B strains	Adult, Older adult	NCT05333289 (Completed)	1, 2	ModernaTX, Inc.
mRNA-1011.1, mRNA-1011.2, and mRNA-1012.1	Seasonal quadrivalent HA & additional HA sequences of H3N2, and H1N1	Influenza	Adult	NCT05827068 (Completed)	1, 2	ModernaTX, Inc.
Quadrivalent influenza modRNA vaccine (qIRV)	Seasonal quadrivalent HA of influenza	Influenza	Adult, Older adult	NCT05052697 (Completed) NCT05540522 (Active, not recruiting)	1, 2 3	Pfizer
PF-07852352, PF-07836391, PF-07836394, PF-07836395, PF-07836396, PF-07867246, PF-07871987, PF-07914705 and PF-07915048	Self-amplifying Ribonucleic acid vaccine (SaRNA) against Influenza	Influenza	Adult	NCT05227001 (Completed)	1	Pfizer
MRT5407 MRT5410 MRT5413	Seasonal quadrivalent HA of Influenza	Influenza	Adult, Older adult	NCT05553301 (Active, not recruiting) NCT05624606 (Active, not recruiting) NCT05650554 (Active, not recruiting)	1, 2	Sanofi Pasteur
mRNA NA vaccine	Monovalent NA of influenza	Influenza	Adult, Older adult	NCT05426174 (Active, not recruiting)	1	Sanofi Pasteur
H3 mRNA / LNP Vaccine	Monovalent HA sequence of H3N2	Influenza	Adult, Older adult	NCT05829356 (Active, not recruiting)	1	Sanofi Pasteur
CVSQIV	Seasonal quadrivalent HA of influenza	Influenza	Adult, Older adult	NCT05252338 (Completed)	1	CureVac
Flu mRNA (GSK4382276A)	Multivalent seasonal influenza vaccine against four strains	Influenza	Adult, Older adult	NCT05823974 (Recruiting)	1, 2	GlaxoSmithKline
RSV mRNA LNP CL-0059, RSV mRNA LNP CL-0137	RSV mRNA vaccine formulated with 2 different LNPs	Respiratory Syncytial Virus	Adult, Older adult	NCT05639894 (Active, not recruiting)	1, 2	Sanofi Pasteur
mRNA-1345	Stabilized prefusion F glycoprotein of RSV	Respiratory Syncytial Virus	Adult, child Adult, Older adult Pregnant woman, Infant Child	NCT04528719 (Active, not recruiting) NCT05127434 (Active, not recruiting) NCT06143046 (Recruiting) NCT06097299 (Recruiting)	1 2,3 2 2	ModernaTX, Inc.
mRNA-1644	OD-GT8 60mer of HIV	HIV	Adult	NCT05414786 (Active, not recruiting)	1	IAVI
mRNA-1644, mRNA-1644v2-Core	eOD-GT8 60mer and boost Core-g28v2 60mer of HIV	HIV	Adult	NCT05001373 (Active, not recruiting)	1	IAVI
mRNA-1574 (BG505 MD39.3 mRNA, BG505 MD39.3 gp151 mRNA, BG505 MD39.3 gp151 CD4KO mRNA)	HIV trimer	HIV	Adult	NCT05217641 (Active, not recruiting)	1	NIAID
mRNA-1647	CMV pentamer complex and gB protein	Cytomegalovirus Infection	Adult Adult Child, Adult	NCT05105048 (Completed) NCT04232280 (Completed) NCT05085366 (Recruiting)	1 2 3	ModernaTX, Inc.

(continued on next page)

Table 1 (continued)

Product Name	Antigen/protein	Infectious Disease	Population	NCT Number (status)	Phases	Sponsor
mRNA-1647, mRNA-1443	CMV pentamer complex, gB protein, Phosphoprotein 65 T antigen	Cytomegalovirus Infection	Adult	NCT03382405 (Completed)	1	ModernaTX, Inc.
mRNA-1893	Pre-membrane and envelope glycoproteins of ZKV	Zika Virus	Adult Adult, Older adult	NCT04064905 (Completed) NCT04917861 (Active, not recruiting)	1 2	ModernaTX, Inc.
mRNA-1325	Pre-membrane and envelope glycoproteins of ZKV	Zika Virus	Adult	NCT03014089 (Completed)	1	ModernaTX, Inc.
RG SAM (CNE) vaccine (GSK3903133A)	Rabies virus glycoprotein G	Rabies Virus	Adult	NCT04062669 (Completed)	1	GlaxoSmithKline
RNAActive (CV7201)	Rabies virus glycoprotein G	Rabies Virus	Adult	NCT02241135 (Completed)	1	CureVac
mRNA vaccine (CV7202)	Rabies virus glycoprotein (RABV-G)	Rabies Virus	Adult	NCT03713086 (Completed)	1	CureVac
mRNA-1653	Fusion proteins of hMPV & PIV3	Human Metapneumovirus & Human Parainfluenza virus type 3	Adult Child, Adult	NCT03392389 (Completed) NCT04144348 (Completed)	1	ModernaTX, Inc.
mRNA-1944	mRNA encoding for anti-Chikungunya virus monoclonal antibody, CHKV-24	Chikungunya Virus Infection	Adult	NCT03829384 (Completed)	1	ModernaTX, Inc.
mRNA-1388 (VAL-181388)	Full native structural polyprotein (C-E3-E2-6k-E1) that is naturally processed into C and E proteins of CHKV	Chikungunya Virus	Adult	NCT03325075 (Completed)	1	ModernaTX, Inc.
mRNA-1189	EBV envelope glycoproteins (gH, gL, gp42, gp220)	Epstein-Barr Virus Infection	Child, Adult	NCT05164094 (Recruiting)	1	ModernaTX, Inc.
mRNA -1215	Secreted pre F/G of NiV	Nipah Virus Infection	Adult	NCT05398796 (Active, not recruiting)	1	NIAID

addressing immune waning, especially for populations at higher risk. It has been demonstrated that booster doses greatly improve immunity in older adults, offering sustained protection [51]. Although both vaccines (mRNA-1273, BNT162b2) offered strong protection, real-world data and meta-analyses have shown that mRNA-1273 has been more successful in preventing hospitalizations and infections in adults 65 and older. [52,53]. With few instances of severe health events after vaccination, the safety profile of mRNA vaccines is still favorable. Because the majority of side effects are self-limiting and do not require medical attention, older adults can continue using them. [54]. Sustained immunity and a decrease in severe COVID-19 outcomes in this susceptible population require timely booster doses and ongoing surveillance.

Strategies addressing the impact of emerging variants further enlightened the complexity in the landscape of vaccine development. Several investigations have highlighted the importance of booster doses, variant-specific formulations and heterologous vaccination in the development of effective vaccines against evolving strains [55–57]. Importantly, BNT162b2 and mRNA-1273 trials have revealed a decline in efficacy against emerging variants and emphasized the necessity of booster doses especially against omicron variants [58–60]. The exploration of self-amplifying mRNA exemplified by ARCT-154 has introduced the significance of booster dosage for enhancing immune response [61]. To address the dominance of Omicron variants in 2022, Moderna and Pfizer/BioNTech have investigated the efficacy of booster vaccinations employing their original vaccines and sequence-updated design to align with circulating variants.

A phase 3 trial has revealed that bivalent Omicron BA.1 adapted BNT162b2 boosters as well as monovalent BA.1 exhibited superior neutralizing activity against Omicron BA.1 compared to the original BNT162b2, with both monovalent and bivalent BA.1 being non-inferior to the original vaccine [62]. Similar findings were reported for the bivalent mRNA-1273.214 booster incorporating ancestral Wuhan-Hu-1 and omicron B.1.1.529 [BA.1]. Bivalent elicited superior neutralizing antibody responses against Omicron variants BA.4/5 [63]. Other

findings have also highlighted the significance of bivalent vaccines in achieving enhanced protection against COVID-19 variants [64,65]. Bivalent vaccination in Korea has revealed significantly enhanced immunity during COVID-19 circulation [66]. Furthermore, bivalent categories targeting different Omicron variants have shown sustained prevention for up to six months [67]. Recognizing the significance of bivalent vaccines, FDA has allowed the use of Moderna and Pfizer-BioNTech COVID-19 bivalent formulations as single booster doses [68]. Recent findings of antibody evasion and additional spike mutations in Omicron and the emergence of subvariants (SARS-CoV-2 BQ and XBB) have raised challenges in the ongoing battle against the evolving virus [69]. Therefore, it is crucial for the updated vaccines to possess the capability to induce cross-protective immunity against emerging variants. Clinical study for the XBB.1.5 vaccine has demonstrated a safety profile aligned with previous vaccines, with recipients exhibiting robust neutralizing antibody titers against various variants such as XBB.1.5, XBB.1.16, EG.5.1, FL.1.5.1, and BA.2.86 [70]. Keeping in consideration of the prevalence of XBB.1.5 subvariant, Moderna and Pfizer/BioNTech have updated their vaccines targeting XBB.1.5. subvariant and received FDA approval [71]. Recently CDC has issued guidelines to utilize updated vaccines for individuals equal to or higher than 6 months for enhancing protection during the fall and winter [72]. In parallel efforts to improve COVID-19 vaccines, researchers are actively developing a refrigerator-stable version, exemplified by Moderna mRNA-1283, a next-generation candidate currently in a Phase 3 trial, aiming to facilitate easier distribution and administration in developing countries [73,74].

The pandemic demonstrated that mRNA vaccines are viable for treating a variety of difficult diseases by validating their safety, effectiveness, and scalability in the real world. As we learn more about immune responses, ongoing research is broadening the development of mRNA vaccines. Innovative approaches to delivery system optimization are expanding the potential of mRNA beyond SARS-CoV-2 [75,76]. saRNA is also being investigated to increase the efficacy of mRNA

vaccines. Adopting this strategy, vaccines that target other infectious diseases may benefit from lower dosages and possibly longer-lasting immune responses [77]. Developing vaccines for a wider range of diseases, including those that affect low- and middle-income countries, is made possible by the cost-effectiveness of mRNA vaccine production [78,79].

3. mRNA vaccines beyond COVID-19

Progress in developing two mRNA vaccines for coronavirus, Moderna's mRNA-1273 and Pfizer/BioNTech's BNT162b2, has triggered the exploration of mRNA vaccines against viral infections beyond COVID-19. Ongoing research involves early-phase clinical investigations of mRNA vaccines designed to target influenza, respiratory syncytial virus, HIV, cytomegalovirus, Ebola, Zika, Rabies, and Nipah virus (summarized in Table 1). These endeavors signify the expanding potential of mRNA vaccine technology in revolutionizing preventive measures against a broad spectrum of infectious agents.

4. Influenza virus mRNA vaccine

The emergence of new influenza strains demand for the urgent need of vaccines with precise antigen design and rapid scalable manufacturing. Fortunately, mRNA vaccines offering these essential attributes, stand as a promising technology to effectively combat emerging threats from influenza and various pathogens. Before the onset of the COVID-19 pandemic, extensive efforts were devoted to design mRNA vaccines for influenza, these vaccines have been subjected to both preclinical and clinical trials. The phase 1 clinical trials of the first mRNA influenza vaccines, utilizing chemically modified mRNAs encoding full-length hemagglutinin glycoproteins from H10N8 (NCT03076385) and H7N9 (NCT03345043) strains within an LNP delivery system, demonstrated safety and robust immunogenicity. The trials, which were carried out in Germany and the US, produced favorable immune responses against the H10N8 and H7N9 influenza viruses, and no significant side effects were noted. While the H7N9 vaccine produced 1:40 HAI titers in 36 %, 93 %, and 90 % of participants at doses of 10, 25, and 50 µg, respectively, and humoral responses to the H7N9 vaccine persisted for six months after immunization, the H10N8 vaccine produced HAI titers of 1:40 or higher in 100 % of participants at the 100 µg dose [21]. For influenza vaccines, many manufacturers use the mRNA platform by combining several mRNA sequences that encode different influenza antigens into a single vaccine formulation. The mRNA-1010 influenza vaccine, which encodes hemagglutinin proteins from A/H1N1, A/H3N2, and B/Yamagata and B/Victoria lineages, has shown an acceptable safety and tolerability in phase1/2 trials (NCT04956575). In comparison to the approved vaccine Afluria, it demonstrated strong T-cell responses, long-lasting humoral responses, and greater hemagglutination inhibition titers for influenza A strains [80]. These promising results paved the path for the advancement of multiple seasonal quadrivalent influenza vaccines through phases 1/2 clinical trials (NCT05650554, NCT05252338, NCT05823974). The mRNA-based multivalent vaccines offer more comprehensive and efficient protection against influenza by concurrently targeting multiple virus strains. To address the challenge posed by highly mutating influenza virus, researchers are investigating vaccine candidates with multiple hemagglutinin antigens to achieve broader coverage of circulating strains. Examples include pentavalent and hexavalent vaccines mRNA-1011/1012 (NCT05827068), which generated strong antibody responses, comparable to mRNA1010. These vaccines provided immunity to added A/H3N2 strains, indicating the inclusion of an additional antigen did not compromise response to other strains, therefore offering protection against diverse influenza viruses. mRNA-LNP vaccines like [81]. Further advancement in influenza vaccine candidates, such as mRNA-1020 and mRNA-1030 (NCT05333289), including both hemagglutinin (HA) and neuraminidase (NA) antigens, essential proteins in the

influenza virus lifecycle, thereby reducing the potential for antigenic escape. Recently, the leading influenza mRNA-1010 vaccine, have demonstrated encouraging outcomes in phase 3 trials (P301 NCT05415462, P302 NCT05566639, P303 NCT05827978) [82]. When compared to Fluarix, an authorized quadrivalent inactivated influenza vaccine, the interim analysis of the revised formulation (P303) revealed greater HAI titers and seroconversion rates for all four strains. [83]. The ongoing development of mRNA-1010 as a possible seasonal influenza vaccine candidate is supported by these encouraging findings. Researchers are working to create a universal influenza vaccine by utilizing the mRNA vaccine platform [84]. Evaluating the long-term safety profile of mRNA influenza vaccines in real world settings is crucial for future advancement. Additionally, extending research to encompass vulnerable people such as children, elderly people and individuals having compromised immunity is essential. By systematically addressing these gaps in knowledge, the scientific community can refine vaccine strategies to meet the unique immunological challenges posed by different age groups and their respective.

5. Respiratory syncytial virus mRNA vaccine

In order to combat respiratory infection caused by syncytial virus (RSV), several vaccine candidates based on pre-F protein are being investigated. For instance, mRNA-1777 and mRNA-1172 for adults and mRNA-1345 for children and adults have shown advancements. Phase 1 study of mRNA-1777 in younger and older adults has exhibited a favorable safety profile with all administered doses. Furthermore, mRNA-1777 demonstrated robust humoral and cellular immune responses against RSV [85]. These promising results provide a foundation for further research on mRNA-based prefusion F vaccines. The subsequent development of mRNA-1172 after sequence optimization showed enhanced immunogenicity compared to mRNA-1777 in pre-clinical studies [86]. The mRNA-1345 has undergone sequence modification and codon optimization, this leads to better translation and immunogenicity. The phase 1 clinical study showed safety and efficacy in adults against both A and B subtypes of RSV, with effects lasted for six months [87]. Expanding upon the positive findings of the phase 1 clinical trial, the following phase 2–3 results of mRNA-1345 has shown efficacy of 83.7 % and 82.4 % against RSV-associated lower respiratory tract disease (LRTD) with at least 2 or 3 symptoms and 3 or more symptoms respectively. Furthermore, vaccine has shown efficacy of 68.4 % against acute respiratory disease associated with RSV among individuals aged 60 or higher. Crucially, this protection extended across RSV subtypes A and B with consistent efficacy observed in various subgroups distinguished by age and coexisting conditions [88]. This approach holds potential for preventing RSV infection in susceptible adult populations, addressing a critical unmet medical need, particularly in older adults facing higher morbidity and mortality risks associated with severe RSV infections. The FDA designated mRNA-1345 with breakthrough therapy against RSV-LRTD among individuals aged 60 or higher [89].

Recent analysis of mRNA-1345 in Canada's elderly population have revealed encouraging economic benefits by lowering health care costs associated with RSV [90]. People of all ages who need to be vaccinated should be protected by an optimal RSV vaccine that can elicit extremely effective immune responses. Its phase 1 trial among children aged 5–24 months (NCT05743881) and among RSV-seropositive children aged 12–59 months (NCT04528719) are ongoing to determine its tolerability and safety. Prior research on RSV vaccination in naive infants has demonstrated the risk of increased hospitalization, mortality, and enhanced respiratory disease (ERD) after RSV infection [91]. In RSV-naive children, ERD is linked to the production of antibodies with low avidity and decreased neutralizing activity, which causes heightened inflammatory reactions [92]. mRNA vaccines have the potential to address infants' Th2-biased immunity and inadequate interferon responses, but the technology is still in its infancy. A balanced immune response in infants is a major challenge that needs more research, and

the long-term effects on the developing immune system are still unclear. To guarantee the development of a safe and effective mRNA-based RSV vaccine for children, robust age-stratified studies and comprehensive regulatory evaluations are essential. In order to reduce the risk of ERD and prevent severe RSV disease in newborns, maternal vaccination offers a promising substitute.

6. HIV mRNA vaccine

Advancements in mRNA vaccines against COVID-19 has inspired to apply this strategy for HIV vaccine. Phase 1 trial of mRNA-1574, an HIV vaccine incorporating HIV trimer mRNA can be regarded as pioneer work to develop mRNA vaccine for HIV infection. In particular, the HVTN 302 trial (NCT05217641) is investigating 3 potential candidates including i) BG505 MD39.3 mRNA, ii) BG505 MD39.3 gp151 mRNA and iii) BG505 MD39.3 gp151 CD4KO mRNA. All of these trimer mRNA vaccine candidates encode for different but closely related stabilized spike protein and also tailored to ensure that none of them can induce HIV infection [93]. These trimer designs are based on native-like BG505 MD39 trimer as reported in Steichen et al.'s work in Immunity [94]. The exploration of a germline-targeting vaccine strategy essential for creating an effective HIV-1 vaccine is in its early stages. Promising candidates, including, eOD-GT8 60mer mRNA vaccine (mRNA-1644) and the Core-g28v2 60mer mRNA vaccine (mRNA-1644v2-Core) are in development phase. Following the foundation laid by IAVI G001, two phase 1 clinical trials, IAVI G003 (NCT05414786) and IAVI G002 (NCT05001373) are advancing in parallel. IAVI G003, conducted at four US sites, is focused on evaluating safety and efficacy of eOD-GT8 60-mer (mRNA-1644). Meanwhile, IAVI G002, taking place in South Africa, is being assessed for safety and efficacy of Core-g28v2 60-mer (mRNA-1644v2-Core) and eOD-GT8 60-mer (mRNA-1644). Regarding HIV vaccines, the ongoing phase 1 trial of mRNA-1644 and mRNA-1574 are a promising development. Although they are still in their infancy, mRNA vaccines give hope to the decades-long search for a successful HIV vaccine. Researchers are combining various mRNA vaccine components and investigating sequential immunization strategies to direct the immune response toward the production of effective bnAbs and CD8⁺ T cell responses against HIV. These responses are induced through distinct pathways, and both might be important for optimal protection from HIV infection [95]. As demonstrated by the short timeframe from concept to clinical trials of HIV mRNA vaccines, this advancement highlights the substantial potential of mRNA technology to expedite HIV vaccine development.

7. Cytomegalovirus mRNA vaccine

Harnessing the advantage of targeting key cytomegalovirus (CMV) proteins simultaneously, mRNA-1647 vaccine has been developed which is composed of six distinct mRNAs [96]. These mRNAs encode two important CMV surface proteins: five membrane-bound pentamer complex and one membrane-bound glycoprotein B (gB). Both pentamer complex and gB are necessary to initiate CMV infection. The mRNA-1647 can elicit immune system against both proteins, demonstrating potential of mRNA vaccines to address complex viral challenges by targeting multiple proteins simultaneously. Phase 1 and 2 studies showed functional antigen-specific responses, supporting the vaccine ability to prevent CMV infection (NCT05105048; NCT04232280). Phase 2 showed effectiveness at 50, 100, and 150 µg, indicating safety and eliciting robust, persistent antibody responses. These results led to the selection of 100-µg mRNA-1647 in phase 3 trial (NCT05085366), for evaluating safety and efficacy of vaccine to prevent CMV infection in 16 to 40 years of female [96].

8. Ebola mRNA vaccine

In the ongoing efforts to combat the Epstein-Barr virus (EBV), mRNA-

1189 has been developed as a candidate for an EBV vaccine. This formulation is designed to stimulate the immune response against EBV envelope glycoproteins that play an important role in viral attachment with B-cells and epithelial cells. The mRNA-1189 contains four mRNAs encoding gp220, gp42, gH and gL packed within lipid nanoparticles (LNPs). Phase 1 study of mRNA-1189 is underway to check its efficacy for adults aged between 12 and 30 (NCT05164094). This research represents a significant step in developing EBV vaccine.

9. Zika virus mRNA vaccine

Diverse approaches have been introduced for the development of mRNA vaccine for Zika virus, mRNA-1325 and mRNA-1893 are known as 1st and 2nd generation of vaccines for Zika virus. The mRNA-1325 and mRNA-1893 encode prME derived from Micronesia 2007 and RIO-U1 isolate of Zika virus respectively. Phase 1 studies of mRNA-1325 (NCT03014089) and mRNA-1893 (NCT04064905), have been conducted to assess safety and immunogenicity in healthy adults with and without flavivirus seropositivity. The findings indicated that the mRNA-1325 vaccine has acceptable safety but anti-Zika virus antibody response was low. In contrast, mRNA-1893 induced robust neutralizing antibodies. Therefore mRNA-1893 vaccine has emerged as a potential candidate for prevention of infection caused by Zika virus [97]. Currently, a phase 2 trial of mRNA-1893 is underway to explore the vaccine's safety and efficacy comprehensively across various participants (NCT04917861).

10. Rabies virus mRNA vaccine

In 2017, prophylactic mRNA vaccine CV7201 (NCT02241135) encoding the rabies virus glycoprotein and formulated with the cationic protein protamine was assessed in phase 1 trial. Diverse doses and schedules, along with intradermal and intramuscular administration methods using either needle-syringe or needle-free devices, were employed. CV7201 exhibited general tolerability, but the generation of sufficient immune responses was dependent upon the administration mode, particularly necessitating intradermal or intramuscular delivery with specialized devices [22]. Subsequent to the progress in mRNA vaccine technology, another candidate vaccine, CV7202 (NCT03713086) incorporating the identical mRNA antigen as CV7201, encapsulating in lipid nanoparticles demonstrated the elicitation of rabies neutralizing antibody responses with remarkably low mRNA quantities [98]. This initial study represented a significant venture into uncovering the capabilities of mRNA technology for vaccine development against Rabies infection.

11. Nipah virus mRNA vaccine

Phase 1 clinical trial for Nipah virus vaccine mRNA-1215 (NCT05398796) has been conducted. This Nipah mRNA vaccine encodes prefusion F protein covalently bonded with G (Pre-F/G) of NiV Malaysian strain. Currently undergoing assessment in Phase 1 trial with a specific focus on pandemic preparedness. It represents the first investigation to investigate safety and efficacy among healthy individuals aged 18 to 60 years.

12. Combination mRNA vaccines

Exploring the potential of combinatorial mRNA vaccines is highly desired to effectively combat acute viral respiratory diseases in a single injection, while synergistically strengthening coverage rates. Combination vaccines hold promise for enhancing health outcomes at reduced costs driven by factors such as increased compliance, improved uptake, reduced vaccine administration expenses, and enhanced consumer convenience. Meanwhile, mRNA vaccines demonstrate the capability to integrate various antigens within a single vaccine. Recently research focus on individual mRNA vaccines particularly COVID-19, seasonal flu

and RSV is shifting toward their combination. The mRNA-1653 is one of the leading candidates of combination vaccine, it is composed of mRNA encoding F proteins of hMPV and PIV3. Results obtained from the Phase 1 trial have demonstrated that mRNA-1653 meets the safety requirements as well as increased neutralizing titers against hMPV and PIV3 (NCT03392389, NCT04144348). These findings are encouraging to cope with respiratory infections induced by hMPV and PIV3 viruses using combination vaccines [25].

Among the pool of candidates undergoing clinical development, mRNA-1083 (NCT05827926) is another emerging candidate for combination vaccine, undergoing a phase 1/2 trial as an investigational candidate designed to prevent both influenza and COVID-19. This vaccine has demonstrated similar or higher inhibition of hemagglutination compared to licensed quadrivalent influenza vaccines. Additionally, it has exhibited SARS-CoV-2 neutralizing antibody like Spikevax bivalent booster [26]. As a significant milestone, mRNA-1083 combination vaccine has progressed to phase III trial as pioneer to combat respiratory infections. Another candidate of combination vaccine composed of Spike proteins of wild SARS-CoV-2, Omicron sublineages BA.4/BA.5 and hemagglutinin of four influenza strains has been progressed to stage of clinical trial phase 1/2 to access its potential against influenza and COVID-19 (NCT05596734). Initial finding has demonstrated safety profile and immunogenicity in line with approved standards for vaccines targeting influenza and SARS-CoV-2.

13. Challenges and opportunities of mRNA vaccines

The mRNA vaccine platform provides innovative solutions for immunization against various infectious diseases. Remarkable success has been shown by mRNA vaccines in the rapid development of COVID-19 vaccines. However, challenges persist in term of efficacy, as mRNA vaccines may experience reduced effectiveness against highly mutating viruses. For example, mRNA vaccines based on wild S protein have exhibited reduced effectiveness for mutant strains like Beta, Delta, and Omicron occasionally resulting in breakthrough infections [59]. To address this, there is a critical need for the prompt design and screening of antigens to update vaccine in accordance with circulating viral strains, ensuring that mRNA vaccines remain effective against evolving strains. The flexibility of mRNA may enable prompt responses to novel variants of pathogens, reducing the time needed to develop vaccines during outbreaks. Furthermore, encoding multiple antigens in a single dose holds promise for treating a wide range of infections, and mRNA vaccines offer a flexible and quick development process in comparison to traditional vaccine platforms. A major challenge of mRNA vaccines is the requirement of the relatively high doses to generate robust immune responses. Self-amplifying mRNA vaccines with replicon genes allow expansion of mRNA offering a possible solution by sustained antigen levels and effective immune responses even at lower dosage [99]. Even low doses of the saRNA can elicit strong neutralizing antibody titers and T cell responses, according to findings on the COVID-19 vaccine, highlighting their potential as affordable and dose-sparing vaccination options [100,101]. Future studies should address the innate immune response triggered by saRNA and the requirement for precise dosage to avoid cytotoxicity [102,103].

Furthermore, the vaccine-induced immune response may be reduced with passage of time since immune system's memory of the virus fades [104]. While this reduction is a common feature across various vaccines, the unique mechanism of action intrinsic to mRNA vaccines implies a potentially accelerated rate of decline [105]. Booster vaccination are very important to boost immunity and providing protection against life-threatening infections [106,107]. The genetic polymorphisms can affect how long vaccine-induced immunity lasts, with particular gene variants linked to a higher risk of breakthrough infections. A better understanding of these genetic variations can result in customized vaccination plans that maximize immune responses and improve vaccine efficacy [108]. Precision-focused strategies, such as mix-and-match approaches

and booster dose interval optimization, have the potential to improve the overall efficacy and durability of vaccines. To ensure long-term efficacy, these targeted efforts are basically necessary to advance our knowledge of mRNA vaccines.

Regarding safety, mRNA based COVID-19 vaccines are in general safe and effective, with few exceptions of mild side effects observed among individuals. Rare instances of significant adverse events, such as anaphylaxis [109], myocarditis [110], pericarditis [111] and thrombosis with thrombocytopenia syndrome [112], necessitate in depth insight and monitoring following immunization to determine the unknown components of mRNA vaccines responsible for these events. The mRNA vaccines have been associated to acute adverse reactions, including cytokine storms and anaphylaxis, which are often attributed to components like polyethylene glycol (PEG) and lipid nanoparticles (LNPs). These reactions are linked to the release of inflammatory cytokines, such as IL-1 β and IL-6, leading to heightened immune responses in some individuals [113]. Alternative LNP formulations, like trehalose glycolipids, have shown promise in lowering the toxicity and side effects of traditional LNPs while preserving vaccine effectiveness [114]. Adjuvant integration into mRNA vaccine nanoparticles is essential for obtaining balance between minimizing side effects and promoting effective immune stimulation. Adverse reactions are linked to excessive immune activation, which can be avoided with careful component design [115]. Assessing the safety and effectiveness of mRNA COVID-19 vaccines in immunocompromised individuals remain challenging requiring further investigation. The ongoing emergence of new mRNA therapies adds complexity and a comprehensive evaluation of mRNA vaccine effectiveness among immunocompromised individuals is still ongoing [116,117].

Innovations in mRNA optimization and its delivery through biomaterials represent a significant advancement to overcome challenges faced by the mRNA therapies such as mRNA instability and low delivery efficiency. One of the unique advantages of mRNA vaccine is encapsulation of multiple mRNA antigen in LNP formulation in a simplified way. In contrast, traditional vaccine technologies require multistep approach based on antigen-specific operations. However, mRNA technology streamlines the process by utilizing the same unit of operation for multiple antigens. Further investigations are necessary to determine the number of antigens that can be simultaneously delivered through mRNA-LNP vaccines. Despite outstanding success, the storage conditions and shipping temperatures of mRNA vaccines still need attention of the scientific community as evident during the COVID-19 pandemic. Although, the ultra-cold storage was feasible in developed countries, it has posed considerable challenges for low and middle-income countries, contributing to global vaccine inequalities. To improve the stability of mRNA vaccines, researchers are investigating novel formulations and delivery systems. For instance, mRNA/LNP complexes' thermostability has increased when conventional helper lipids are combined with the imidazole-modified lipid DOG-IM4 [118]. Similar to this, adding mannose modifications to lipid nanoparticles maintains the vaccine's characteristics and targeting specificity even after lyophilization, a procedure used for long-term storage. This modification ensured that the vaccine will stay immunogenic and stable at 4 °C for at least 24 weeks [119]. Additionally, efforts are underway for the development of a microneedle patch format for thermostable covid-19 mRNA vaccines [120,121]. Overcoming these challenges involves not only solving temperature constraints but also tackling bottlenecks in supplies and manufacturing infrastructure to achieve widespread vaccine access.

As mRNA technology continue to evolve, the hope is that next-generation mRNA vaccines will overcome the existing challenges and be more widely used for treating and preventing infectious diseases. To address this, ongoing research efforts are essential to extend our understanding of the underlying immunological mechanisms that enable the induction of responses against multiple antigens. Recently published studies of multivalent influenza vaccines suggest that mRNA multivalent approach is not only feasible but also effective, with no observed

instances of immune interference [122]. The plethora of clinical studies for mRNA vaccines demonstrate that soon mRNA might compete with or possibly replace the conventional vaccine platforms. Hesitancy toward mRNA vaccines, however, is still a major problem, because of their novelty. The innovation of mRNA technology has been shown to reduce the chances of vaccine acceptance by 14.2 %. However, because peer vaccination rates increase willingness to vaccinate, it has been revealed that societal conformity plays a significant role in lowering vaccine hesitancy. Addressing public concerns through education and utilizing social conformity could be key strategies for improving vaccine coverage and fostering trust in mRNA technology [123].

14. Conclusion

In conclusion, proven ability of mRNA vaccines against COVID-19 represents a breakthrough in vaccine development demonstrating longstanding challenges faced by traditional technologies, including scalability, adaptability and speed of development. The versatility and adaptability of mRNA technology positions it as a pivotal tool in combating pandemics and endemic diseases worldwide. Safety and efficacy of mRNA vaccines for COVID-19 proven by clinical trials and mass vaccination has been useful in preventing millions of deaths reflecting profoundly global impact of mRNA vaccines. Beyond COVID-19, mRNA vaccines hold transformative potential for addressing diverse infectious diseases, exemplifying a global shift of technology to address emerging threats. It is highly desired to develop mRNA vaccines stable in refrigerator for easier distribution and administration specifically in developing countries. The anticipated success of existing mRNA candidates and ongoing development, along with steady global manufacturing, underscores the profound impact of mRNA technology on vaccinology, with potential broad and meaningful benefits for global public health.

CRediT authorship contribution statement

Munazza Fatima: Writing – original draft, Investigation, Formal analysis, Data curation. **Pil-Gu Park:** Writing – review & editing, Writing – original draft, Formal analysis. **Kee-Jong Hong:** Writing – review & editing, Funding acquisition, Formal analysis, Conceptualization.

Declaration of competing interest

The authors declare no conflicts of interest.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.clim.2024.110424>.

Data availability

No data was used for the research described in the article.

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