The mRNA vaccine platform: A novel tool for the rapid development of vaccines against respiratory viral infections

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What is the rationale for mRNA-based vaccines and their design?

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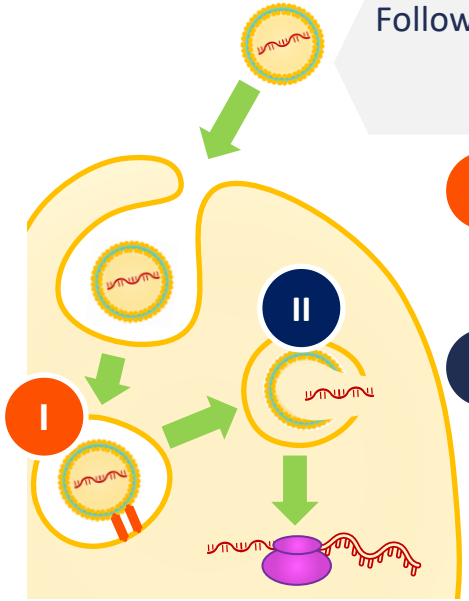
How do mRNA vaccines work?

mRNA vaccines: Innate and adaptive immune responses



After endosomal release, vaccine mRNA is translated into protein(s) by ribosomes

Following endocytosis and endosomal release, mRNA vaccines invoke cellular and humoral immune responses

I Innate immunity

TLR activation

IFN-I
- 'Self-adjuvant' effect
- Innate antiviral responses

II Adaptive immunity

mRNA-derived antigens

CD4⁺ T cells
- Cytokine production supporting cell-mediated and humoral immune responses

CD8⁺ T cells
- Elimination of infected cells by cytotoxic mechanisms

B cells
- Antibody secretion

IFN-I, type I interferon; mRNA, messenger RNA; TLR, toll-like receptors.

Fang E, et al. *Signal Transduct Target Ther*. 2022;7:94.

Characteristics of mRNA vaccines

Advantages[1,2]

- Rapid development of modified versions
- Optimal antigen expression
- Elicit humoral and cellular adaptive immunity
- No live pathogens required
- *'Self-adjuvant'* effect

Caveats[1,2]

- Severe reactions to polyethylene glycol
- Potential risk of myocarditis in selected groups
- Cold chain transportation and storage required

1. Rzymski P, et al. *J Med Virol*. 2023;95:e28572; 2. Zhang C, et al. *Front Immunol*. 2019;10:594.

How do the design of the mRNA sequence and its structure affect vaccine efficacy and safety?

mRNA sequence design features and functions

↑ Protein expression

Coding region for vaccine candidate sequence for gene or antigen of interest

Codon composition may be modified to optimize:

- Translation efficiency
- mRNA abundance
- Protein folding
- Antigen stability/immunogenicity

5′ cap

3′ poly(A) tail

↑ mRNA stability

- Initiates translation
- Regulates processing
- Shields from innate immunity
- Protects from exonucleases

↑ mRNA half-life and stability

- Ribosome recognition
- Translational machinery recruitment
- Structural folding

↑ mRNA stability

- Stabilizes and promotes translational efficiency
- Tail length is proportional to translational efficiency

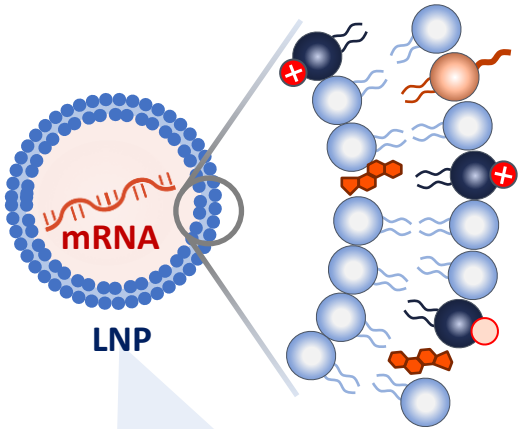
A, adenosine; G, guanine; mRNA, messenger RNA, P, phosphate; UTR, untranslated region.

Kim SC, et al. *Mol Cellular Toxicol*. 2022;18:1–8.

What delivery strategies have been used for mRNA vaccines and how do they affect their efficacy and safety?

Lipid nanoparticles: Structural features and functionality

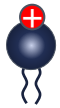
LNPs comprise four lipid components:



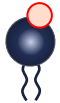
- Nanoscale vesicle simulates cell membrane phospholipid bilayer
- Encapsulates mRNA

Ionizable

Charged



Neutral



- Essential LNP components
- Mediates mRNA binding within LNP central core
- Ionizable property confers functional properties:
  - **Charged:** Facilitates endosomal escape
  - **Neutral:** Aids safe and stable delivery

Helper

- Supports LNP bilayer
- Promotes endosomal fusion
- Determines target organ specificity

Cholesterol

- Confers LNP stability
- Promotes endosomal fusion
- Aids vaccine complex uptake

PEGylated

- Reduces LNP aggregation
- Minimizes non-specific uptake by immune cells
- Determines circulation rate and immune cell uptake

LNP, lipid nanoparticle; mRNA, messenger RNA; PEG, polyethylene glycol.

Fang E, et al. *Signal Transduct Target Ther*. 2022;7:94.

What is the current clinical trial and real-world evidence for mRNA-based COVID-19 vaccines?

Prof. Dr. med. Oliver Cornely

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Scientific Director, Clinical Trials Centre
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How might mRNA vaccine platforms offer ongoing protection as new variants emerge?

Updated mRNA vaccines

- Omicron and its sublineages are now the dominant circulating variants worldwide[1]
- Studies show vaccine effectiveness tended to be lower against BA.2 and especially against BA.4/5, compared with BA.1[1]

	Bivalent: Original + omicron BA.1	Bivalent: Original + omicron BA.4/BA.5	Monovalent: Omicron XBB.1.5
BNT162b2	• Phase III (4th dose), NCT04955626[2] • Age: >55 years • Monovalent or bivalent omicron BA.1-adapted vaccines elicited neutralizing activity against BA.1 superior to the original BNT162b2 vaccine	• Phase II/III (4th dose), NCT05472038[3] • Age: >55 years • Bivalent BA.4/BA.5 vaccine elicited greater neutralizing responses against BA.5- and BA.2-derived sublineages than the original BNT162b2 vaccine	• Regulatory applications submitted to the FDA and EMA. Availability 2023–24[4,5]
mRNA-1273	• Phase II/III (4th dose), NCT04927065[6] • Age: ≥18 years • Bivalent BA.1-containing vaccine elicited neutralizing antibody responses against BA.1 superior to the original mRNA-1273 vaccine	• Phase II/III (4th dose), NCT04927065[7] • Age: ≥18 years • Bivalent BA.4/BA.5 vaccine elicited neutralizing antibody responses against BA.4/BA.5 superior to the original mRNA-1273 vaccine	• Regulatory applications submitted to the FDA and EMA. Availability: 2023–24[4,5]

Monovalent and bivalent vaccines were efficacious against ancestral strains and the emerging variants studied, with no evident safety differences from the original vaccines

EMA, European Medicines Agency; FDA, US Food and Drug Administration. 1. Feikin DR, et al. *Vaccine*. 2023;41:2329–38; 2. Winokur P, et al. *N Engl J Med*. 2023;388:214–27; 3. Zou J, et al. *N Engl J Med*. 2023;388:854–7; 4. FDA. 2023. Available at: www.fda.gov/media/169591/download (accessed 11 July 2023); 5. ECDC-EMA. 2023. Available at: www.ema.europa.eu/en/documents/other/ecdc-ema-statement-updating-covid-19-vaccines-composition-new-sars-cov-2-virus-variants_en.pdf (accessed 11 July 2023); 6. Chalkias S, et al. *N Engl J Med*. 2022;387:1279–91; 7. Chalkias S, et al. *medRxiv*. 2022;DOI:10.1101/2022.12.11.22283166.

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What are the key safety considerations surrounding mRNA-based COVID-19 vaccines?

Safety considerations with mRNA vaccines[1,2]

Contraindication[1,2]

Hypersensitivity to active substance or excipients

Frequently reported AEs (≥10%)

(Adult/adolescent dosages)

- Injection site pain/swelling[1,2]
- Injection site erythema[2]
- Fatigue[1,2]
- Headache[1,2]
- Myalgia[1,2]
- Chills[1,2]
- Arthralgia[1,2]
- Fever[1,2]
- Diarrhoea[1]
- Axillary swelling/tenderness[2]
- Nausea/vomiting[2]

Incidence of AEs varied by age ranges of study cohorts[1,2]

Warnings and precautions[1,2]

↑ risk of myocarditis and pericarditis

- Can develop within a few days after vaccination, primarily within 14 days
- More common after the second dose and in younger males

Risk of serious AEs

Interim surveillance data following 11,845,128 doses of mRNA vaccines[3]

- Events per 1,000,000 person-years (RR and 95% CI) days 1–21 vs days 22–42 post vaccination:
  - Ischaemic stroke: 1612 vs 1781 (0.97; 0.87–1.08)
  - Appendicitis: 1179 vs 1345 (0.82; 0.73–0.93)
  - Acute myocardial infarction: 935 vs 1030 (1.02; 0.89–1.18)
  - Myocarditis/pericarditis: 132 vs 107 (1.18; 0.79–1.79)

AE, adverse event; CI, confidence interval; EMA, European Medicines Agency; mRNA, messenger RNA; RR, adjusted rate ratio; SmPC, summary of product characteristics.

1. EMA. Elosmeran SmPC. Available at: www.ema.europa.eu/en/medicines/human (accessed 11 July 2023); 2. EMA. Tozinameran SmPC. Available at: www.ema.europa.eu/en/medicines/human (accessed 11 July 2023); 3. Klein NP, et al. *JAMA*. 2021;326:1390–99.

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What are the current guidelines and recommendations for COVID-19 vaccination, and how do you apply them in clinical practice?

WHO SAGE guidance: Roadmap updates in March 2023

Interim **recommendations for primary series and booster doses** updated based on the latest evidence for current dominant Omicron circulation and high population-level immunity

Key updates*

New priority-use groupings	Reduced from 4 to 3 strata
Specific guidance by priority-use group	Adjusted recommendations for primary series and boosters
During pregnancy	Additional booster if last dose given >6 months ago, ideally to be administered by mid-second trimester
Frontline health workers	Additional booster 12 months after the last dose
Healthy children and adolescents	Consider primary series based on country-specific context (disease burden; costs; other health programme priorities)

*Recommendations in this Roadmap will be updated should the epidemiology or vaccine characteristics change.
WHO, World Health Organization; SAGE, Strategic Advisory Group of Experts on Immunization.
WHO. 2023. Available at: www.who.int/publications/i/item/WHO-2019-nCoV-Vaccines-SAGE-Roadmap (accessed 07 July 2023).

What is the future of mRNA-based vaccines for protecting against respiratory infections?

Prof. Ann R Falsey

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What have we learned from COVID-19 vaccination on the potential for mRNA-based vaccines in the prevention of respiratory diseases?

mRNA vaccines: Advantages and caveats

Advantages

- Efficacy confirmed for vulnerable persons and across a wide range of ages
- Modifiable platform permitting adaptions to emerging variants
- Extensive real-world dataset
- Acceptable safety profile

Caveats

- Rare but serious AEs
- Limited duration of protection
- Reduced efficacy against emerging variants of concern

Logistical challenges

Thermostability and ultracold storage requirements present challenges with cold-chain supply, notably in low-income regions

AE, adverse event.

Echaide M, et al. *Int J Mol Sci.* 2023;24:5944.

What novel mRNA vaccines against respiratory pathogens are in development?

Novel mRNA vaccines against respiratory pathogens

EBV

	Cohort age
mRNA-1189 NCT05164094 (Phase I)	18–30 yrs
mRNA-1195 NCT05831111 (Phase I)	18–55 yrs

RSV

	Cohort age
mRNA-1345	
NCT05127434 (Phase II/III)	≥60 yrs
NCT05330975 (Phase III)	≥50 yrs

Influenza

	Cohort age
mRNA-1110	
NCT05415462 (Phase III)	≥18 yrs
NCT05566639 (Phase III)	≥50 yrs
NCT05827978 (Phase III)	≥18 yrs
PF-07252220	
NCT05540522 (Phase III)	≥18 yrs

hMPV + PIV3

	Cohort age
mRNA-1653	
NCT04144348 (Phase Ib)	18–49 yrs 12–59 mos

Trial status:*

- Recruiting
- Active, not recruiting
- Completed

*Trial status as of 27 June 2023.

EBV, Epstein–Barr virus; hMPV, human metapneumovirus; mo, month; mRNA, messenger RNA; PIV3, parainfluenza virus type 3; RSV, respiratory syncytial virus; yr, year.

ClinicalTrials.gov. Available at: https://clinicaltrials.gov/ according to specific trial number (accessed 27 June 2023).

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What developments in the design of mRNA vaccines could optimize efficacy and safety?

Potential mRNA vaccine design developments

Further mRNA design developments[1]

Self-amplifying RNA

- Enhanced antigen expression at lower doses
- Long-term duration of immunity

Multivalent vaccines[2,3]

Universal vaccines

- Could provide protection against antigenically variable viruses[2]

Combined vaccines against different pathogens[3]

Improvements in storage requirements[4]

Freeze-drying

- Could allow storage at higher temperatures for a prolonged period

Novel routes of administration[5]

Intranasal delivery

- Could potentially lead to a more robust protective mucosal immune response

mRNA, messenger RNA.

1. Fang E, et al. *Signal Transduct Target Ther*. 2022;7:94; 2. Arevalo CP, et al. *Science*. 2022;378:899–904; 3. August A, et al. *Open Forum Infect Dis*. 2022;9:ofac206; 4. Meulewaeter S, et al. *J Control Release*. 2023;357:149–60; 5. Rzymski P, et al. *J Med Virol*. 2023;95:e28572.

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In your opinion, what are the most promising applications of mRNA vaccines in the near future?

Addressing health care challenges in adult RSV

Healthcare challenges associated with RSV in older adults are increasingly recognized[1]

RSV

- Substantial morbidity and mortality[1,2]
- Acute functional decline that may become prolonged[3]

FDA-approved vaccines for prevention of RSV-associated LRTD in adults aged ≥60 years[2,5,6]

- **RSVPreF3**
- **RSVPreF**

} Recombinant pre-fusion F protein

Risk factors for severe RSV disease:

- Chronic comorbidities (e.g. lung, CV)[2]
- Immunocompromised status [2]
- Frailty [2]
- Advanced age [2]
- LTCF residency [2,4]

RSV vaccines in phase III trials in adults[7]

mRNA-1345	mRNA based	NCT05330975 NCT05127434
Ad26.RSV.preF	Viral vector (AdV)	NCT04908683
MVA-BN-RSV	Viral vector (MVA-BN)	NCT05238025

Prophylactic RSV vaccination may prevent morbidity in older adults at risk for severe disease[2]

AdV, adenovirus; CV, cardiovascular; FDA, US Food and Drug Administration; LTCF, long-term care facility; LRTD, lower respiratory tract disease; mRNA, messenger RNA; MVA-BN, smallpox and monkeypox vaccine modified vaccinia Ankara-Bavarian Nordic; PI, prescribing information; preF, pre-fusion F protein; RSV, respiratory syncytial virus.

1. Hill-Ricciuti A, et al. *Infect Control Hosp Epidemiol.* 2023;44:433–9; 2. Melgar M, et al. *MMWR.* 2023;72:793–801; 3. Branche AR, et al. *Influenza Other Respir Viruses.* 2022;16:1151–60; 4. Pérez SN, et al. *Open Forum Infect Dis.* 2023;10:ofad111; 5. FDA. RSV vaccine, adjuvanted PI. Available at: www.fda.gov/media/167805/download (accessed 24 July 2023); 6. FDA. RSV vaccine PI. Available at: www.fda.gov/media/168889/download (accessed 24 July 2023); 7. ClinicalTrials.gov. Available at: www.clinicaltrials.gov/ according to specific trial number (accessed 26 July 2023).

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