Safety and efficacy of mRNA vaccines: a mechanistic and public health perspective

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mRNA vaccines represent a transformative advance in vaccinology, combining rapid development timelines, scalable manufacturing, and strong immunogenicity with a favourable safety profile. Global deployment of mRNA vaccines during the COVID-19 pandemic provided an unprecedented real-world evaluation of this platform, with billions of doses administered across diverse populations. In this Review, we critically examine the safety and efficacy of mRNA vaccines from mechanistic, preclinical, clinical, and public health perspectives. We outline the biological basis of mRNA vaccines, including their transient cytoplasmic expression, lack of genomic integration, and rapid clearance, distinguishing them clearly from other gene therapies. We synthesise evidence on vaccine components, manufacturing quality controls, and regulatory standards that underpin safety, alongside data from randomised trials, post-authorisation surveillance, and active pharmacovigilance systems. We also review real-world effectiveness across age groups, pregnancy, and populations that are immunocompromised, along with the effects on transmission. Last, we address public perception and vaccine confidence, and discuss implications for next-generation mRNA vaccines, including strategies to reduce reactogenicity, improve breadth and durability of immunity, enhance global access, and support sustainable public trust. Together, the accumulated evidence affirms mRNA vaccines as a safe, effective, and adaptable platform with enduring relevance for future infectious disease prevention and public health preparedness, and for the treatment of cancer and autoimmunity.

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Introduction

The development of mRNA vaccines represents one of the most major scientific achievements of the 21st century, built upon decades of foundational research into RNA biology, lipid nanoparticle delivery, and vaccinology.[1,2] Before the COVID-19 pandemic, mRNA vaccine technology had been explored primarily in preclinical and early clinical studies targeting infectious diseases, such as influenza and Zika, and in oncology immunotherapy.[2] Despite promising data, widespread application was restricted by challenges in mRNA stability, delivery efficiency, and large-scale manufacturing. The global health crisis in 2020 catalysed extraordinary collaboration between academia, industry, and regulatory agencies, leading to the focused development, authorisation, and deployment of mRNA vaccines against SARS-CoV-2. These vaccines showed high efficacy and favourable safety profiles in large efficacy trials and subsequently in real-world settings, establishing mRNA as a clinically validated vaccine platform.[3,4] As mRNA vaccines continue to evolve, maintaining public confidence in their safety and efficacy is paramount.[5,6] The widespread dissemination of misinformation and the politicisation of vaccine discourse threaten to erode trust in science-based medicine. Sustained confidence depends on transparent, evidence-driven communication of safety data, supported by rigorous preclinical and clinical evaluation, continuous pharmacovigilance, and clear differentiation from unrelated technologies, such as gene therapy. This Review aims to critically assess the safety of mRNA vaccines by integrating mechanistic, preclinical, clinical, and pharmacovigilance evidence. We seek to clarify biological and manufacturing foundations of mRNA vaccines, evaluate real-world safety outcomes, and reinforce the central role of scientific evidence in sustaining global vaccine confidence.

Mechanism of action of mRNA vaccines

mRNA vaccines function by delivering a strand of synthetic mRNA into the cytoplasm of a person's cells, where it is translated by ribosomes to produce the encoded antigenic protein, such as the SARS-CoV-2 spike protein.[7] Notably, one advantage of mRNA vaccines is that the platform easily enables expression of and immunity to multiple antigens, including up to 20 influenza antigens in a single vaccine.[8] Once synthesised, the antigen is recognised by antigen-presenting cells, which stimulate both cellular immunity, including helper and cytotoxic T-cell responses, and humoral immunity, including B cells that generate neutralising antibodies that provide durable protection against infection (figure 1). This transient expression of a non-self protein mimics natural infection without introducing live or whole inactivated pathogens, thereby achieving immunisation by endogenous antigen production.[2]

Historically, several experts (including Cullis, and Karikó and Weissman) have referred to mRNA

Search strategy and selection criteria

We searched PubMed from Jan 1, 2000, to Dec 1, 2025, using the following search terms: "messenger RNA", "mRNA", "self-amplifying RNA", "vaccines", "lipid nanoparticles", "mRNA vaccines", and "COVID-19". We also searched for ongoing clinical trials on ClinicalTrials.gov. Potentially relevant articles in English were identified and reviewed, and we included research articles, reviews, clinical studies, conference abstracts, and case reports.

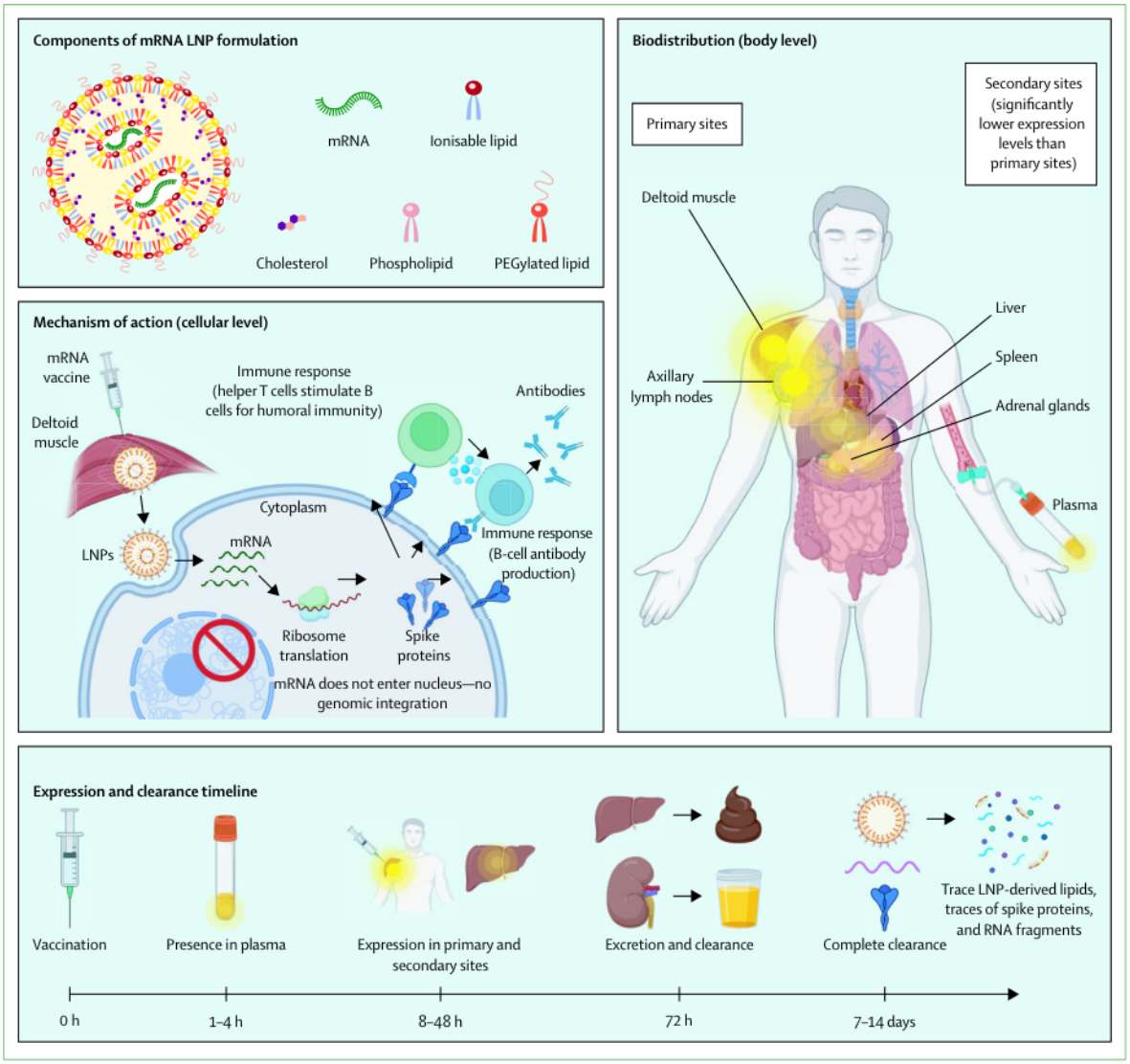


Figure 1: **Schematic of mRNA lipid nanoparticle components, mechanism of action, biodistribution, and expression and clearance timeline for mRNA vaccines**
LNP=lipid nanoparticle. PEG=polyethylene glycol.

technologies as forms of gene therapy.[9,10] However, modern regulatory definitions differentiate between these modalities based on mechanism and intent. The modern definition of gene therapy specifies the deliberate and permanent alteration of a patient's genome for therapeutic purposes.[11] While both gene therapies and nucleic acid vaccines deliver genetic material to cells, the biological goals are clearly distinct. Gene therapies aim to correct defective genes or restore missing host proteins required for survival, often with durable or integrating expression systems.[12,13] In contrast, mRNA vaccines deliver transient instructions for the production of a pathogenic or tumour-associated antigen to elicit immune protection.[14–16] For instance, circulating spike proteins after mRNA COVID-19 vaccination are detectable for approximately 7 days, a duration consistent with transient immune stimulation rather than persistent expression.[17]

The distinction between viral and non-viral vectors further illustrates the unique pharmacology of mRNA vaccines. Adenoviral vector vaccines, such as ChAdOx1 nCoV-19 and Ad26.COV2, use attenuated, non-replicating viruses that deliver DNA to the nucleus, whereas mRNA vaccines encapsulate RNA in lipid nanoparticles that remain cytoplasmic.[18] Although adenoviral vectors theoretically carry low risk of genomic integration, empirical studies show that these vectors remain episomal and do not integrate into host DNA.[19,20] Consequently, both viral vector and mRNA-based COVID-19 vaccines result in temporary, non-integrating

protein expression consistent with vaccine classification, that would not be considered as gene therapy when applying current definitions.

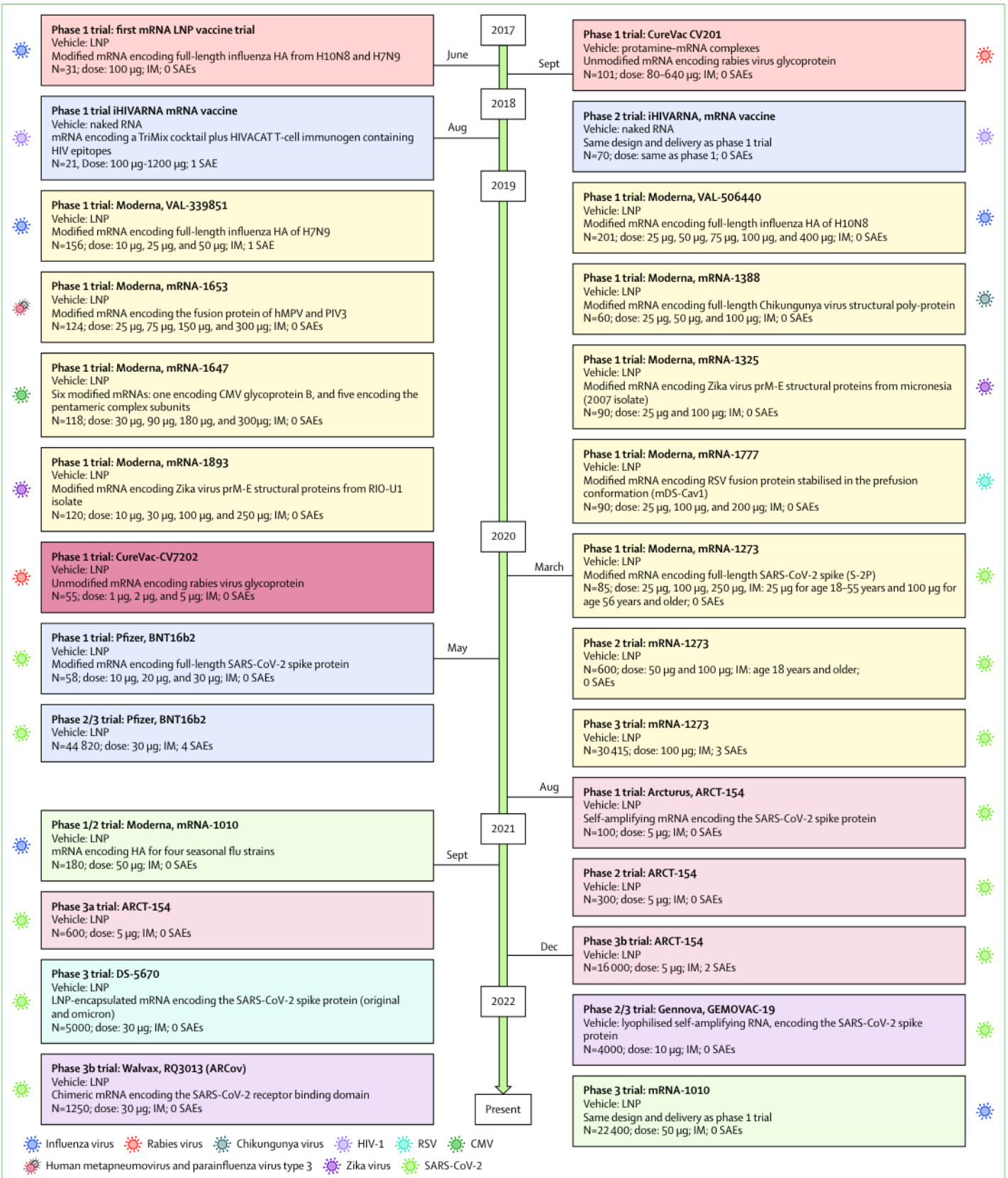
Pharmacokinetic and biodistribution studies show that after intramuscular injection, mRNA lipid nanoparticle vaccines remain largely localised to the injection site, with limited distribution to secondary organs, such as the liver, spleen, adrenal glands, and ovaries in preclinical models.[21] These findings are based on conservative preclinical models using doses exceeding human equivalents to identify potential toxic effects. Even under such conditions, any local or systemic immune-induced changes resolved completely within 3 weeks.[21] Both RNA and lipid components of the vaccines undergo rapid clearance via renal and hepatic pathways; when radiolabelled, the lipid nanoparticles were excreted within 72 h via urine and faeces[22] and both RNA and lipid metabolites are cleared within 168 h in rodent models.[23] Persistence in blood versus lymphoid organs differed in vaccinated human participants; residual mRNA was detectable in plasma for up to 14 days post-vaccination in 37% of participants,[24] whereas mRNA and spike antigens were detectable in ipsilateral axillary lymph nodes for up to 60 days post-vaccination.[25] The SARS-CoV-2 pandemic and mRNA vaccines have enabled a new understanding of human immunology, including longitudinal lymph node sampling,[26] characterisation of the duration of plasma cells in bone marrow,[27] and the characterisation of long-lasting germinal centre reactions.[28] While the duration of antigen detection has not been well characterised for other types of vaccines, these long-lasting germinal centre reactions might enable effective vaccine responses against infections for which no vaccine currently exists, such as HIV-1, which relies on broadly neutralising antibodies.[29–31] Collectively, these data show that mRNA vaccines are characterised by transient biodistribution, rapid clearance, and short-lived antigen expression, which are features that underpin their favourable safety profile. Further evidence from repeated high-dose studies and real-world observations, and an interesting report of an individual who received 217 vaccinations against SARS-CoV-2 without adverse events, underscore the excellent tolerability of the platform.[32] 130 vaccinations were documented by the public prosecutor whereas 108 vaccinations were individually recorded and partially overlap with the prosecutor-confirmed vaccinations. Of note, a hyper-vaccinated individual did not report any vaccination-related side-effects.[32]

Vaccine components and manufacturing considerations

mRNA vaccines are composed of lipid nanoparticles that encapsulate a strand of synthetic mRNA encoding a target antigen. The mRNA serves as the active pharmaceutical ingredient, while the lipid nanoparticle acts as a delivery vehicle that enables cellular uptake and protects the RNA from degradation. Lipid nanoparticles typically consist of four components: an ionisable lipid that enables RNA complexation and endosomal escape, a phospholipid that contributes to the bilayer structure, cholesterol that enhances membrane stability, and a polyethylene glycol (PEG)-conjugated lipid that confers stability.[33] The distinction between cationic and ionisable lipids is central to understanding the safety and tolerability of mRNA lipid nanoparticle formulations. Early gene delivery systems relied on permanently cationic lipids, which possess a constant positive charge that interacts strongly with negatively charged cellular membranes, resulting in cytotoxicity and inflammatory responses in vivo.[34–36] In contrast, the lipids used in the BNT162b2 (ie, ALC-0315)[37] or mRNA-1273 (ie, SM-102)[38] COVID-19 vaccines are ionisable cationic lipids designed to mitigate this issue. These molecules are neutrally charged at physiological pH but acquire a positive charge in acidic environments; for example, during formulation or within endosomes.[39] Ionisable lipids have consistently shown reduced cytotoxicity and improved tolerability compared with permanently cationic lipids,[40] representing a key advancement in the clinical translation of mRNA vaccines.

mRNA vaccines and other in-vitro transcribed mRNAs typically contain modified ribonucleotides, causing desired increased stability and decreased innate immune responses, and in the case of vaccines, results in reduced reactogenicity.[41] COVID-19 mRNA vaccines specifically include N^1-methylpseudouridine to achieve these effects.[42–44] In addition, N^1-methylpseudouridine can result in a +1 frameshifting at ribosome slippery sequences, thus producing off-target proteins that can also induce an immune response, with both B-cell and T-cell responses detected.[45] To date, no specific adverse outcomes have been associated with the N^1-methylpseudouridine in mRNA COVID-19 vaccines and phase 4 studies are prospectively following recipients. The introduction of specific mutations into the slippery site sequences has been shown to reduce +1 frameshifting, and work is ongoing to further optimise sequences included in new mRNA vaccines and other therapeutics to reduce these effects.

The final COVID-19 mRNA vaccine products include mRNA, lipid nanoparticles, and additional salts and sucrose.[46] In addition to the vaccine ingredients, the manufacturing process is integral to the safety of mRNA vaccines.[47] The manufacturing of mRNA vaccines begins with in vitro transcription, wherein an mRNA is synthesised using RNA polymerase from a linear DNA template.[48] Two good manufacturing practice processes have been used to generate this DNA template: PCR amplification and plasmid amplification in *Escherichia coli*.[3] While PCR-based methods are suited for small-scale production, plasmid amplification enables large-scale manufacturing.[49] Following in vitro transcription, residual DNA is removed enzymatically by



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DNase digestion, leaving only trace amounts in the final product. These impurities, including DNA, double-stranded RNA, proteins, and endotoxins, are routinely quantified, with regulatory assays ensuring compliance with established safety thresholds.[50,51] Regulatory agencies such as WHO and the US Food and Drug Administration (FDA) stipulate that residual DNA in biologics should be fewer than 200 base pairs in length and less than 10 ng per vaccine dose, as measured by quantitative PCR.[52,53] Empirical analyses of mRNA COVID-19 vaccines have shown that DNA residues are well lower than these limits;[54] batches of both BNT162b2 or mRNA-1273 were frequently tested by regulators and independent accredited laboratories for the presence of DNA throughout the pandemic, and universally found to be within this limit.[55,56] Multiple studies have subsequently confirmed these findings.[57,58] Importantly, decades of research on plasmid DNA vaccines further demonstrate the negligible risk of genomic integration or oncogenic transformation.[59–61] Lastly, mRNA integrity is crucial for ensuring both efficacy and safety. Studies have shown that the commercial BNT162b2 or mRNA-1273 vaccines retained more than 95% of their intact mRNA, even following a freeze–thaw cycle, confirming the molecular stability of distributed vaccine batches.[62] High mRNA integrity and adherence to regulatory standards for DNA impurities underpin the robust safety profile of mRNA lipid nanoparticle vaccines.

Preclinical and clinical safety evidence

Adverse events

COVID-19 and other mRNA vaccination programmes have been rigorously monitored with passive and active surveillance approaches. COVID-19 mRNA vaccines showed immunogenicity and safety in animal models, and no evidence of developmental or reproductive toxic effects.[63–66] Serious adverse events were detected in phase 3 clinical trials for BNT162b2 and mRNA-1273 with similar frequency in mRNA-vaccinated and placebo control groups; the pivotal trials enrolled a total of almost 75 000 individuals, with around 50% of participants receiving either the BNT162b2 or mRNA-1273 vaccine (figure 2).[3,89] Established infrastructure in many countries was key to providing comprehensive and rapid adverse event monitoring following immunisation surveillance, including passive reporting to public health bodies, analysis of administrative databases, active surveillance studies, and clinical and research networks targeting specific populations. Regular review, analysis, and dissemination of data collected via these infrastructures enabled early detection and evaluation of safety signals across jurisdictions, including anaphylaxis, myocarditis and pericarditis, thromboembolic events, and Bell's palsy (table).

Figure 2: **Progression of mRNA vaccine trials, including the type of RNA, indication, delivery platform, dose, trial size, and associated SAEs with time[67–88]**

CMV=cytomegalovirus. HA=haemagglutinin. IM=intramuscular injection. LNP=lipid nanoparticle. RSV=respiratory syncytial virus. SAE=serious adverse event.

Anaphylaxis

Soon after vaccine implementation, cases of severe anaphylaxis were reported following first doses of BNT162b2 and mRNA-1273 vaccines, at rates up to 10 per 1 000 000 vaccine receivers in the USA.[105] In a systematic review, the estimated rate of anaphylaxis was 2·3–8 per 1 000 000 COVID-19 mRNA vaccine recipients, and was similar for BNT162b2 and mRNA-1273 vaccines.[106] PEG in the lipid nanoparticle was initially believed to be the most likely trigger of anaphylaxis, although further studies have not confirmed a role for anti-PEG IgE in these events.[107] A systematic review reported a risk of recurrent severe allergic reactions after rechallenge with a COVID-19 mRNA vaccine of only 4·9%.[107,108] Moreover, patients with a history of anaphylaxis to PEG-asparaginase—a chemotherapeutic agent commonly associated with hypersensitivity reactions that have been attributed to PEG—were shown to tolerate mRNA vaccines, further indicating that anti-PEG responses are unlikely to be responsible as a trigger for anaphylaxis following mRNA vaccination. Alternatively, the lower molecular weight of PEG used in mRNA vaccines might reduce cross-reactivity, compared with the higher molecular weight molecules present in other medications, or that these reactions might not be IgE-mediated.[107,109,110] Allergist assessment and vaccination under supervision can support safe revaccination of individuals with severe allergic reactions after COVID-19 mRNA vaccination.[107,111,112]

Myocarditis and pericarditis

Cases of myocarditis and pericarditis after COVID-19 mRNA vaccination were first detected from passive surveillance in Israel, the USA, and Canada in 2021. Subsequent analyses of post-market surveillance data confirmed an increased risk of myocarditis and pericarditis greater than background rates 0–21 days following COVID-19 mRNA vaccination, peaking within 0–7 days.[113,114] Risk factors include male sex, age 12–29 years, receipt of first and second doses 30 days or fewer apart (*vs* ≥56 days), and 100 µg dose mRNA-1273 versus BNT162b2 vaccine.[113,115,116] The risk of myocarditis and pericarditis was highest after dose two, but was also increased after the first and third doses. The relative risk of myocarditis and pericarditis following COVID-19 mRNA vaccination was significantly lower than with SARS-CoV-2 infection and did not alter the risk–benefit assessment of vaccination.[113,117] Surveillance of XBB.1.5-adapted vaccines has not identified a significantly elevated risk.[118] Patients with vaccine-associated myocarditis had lower rates of hospitalisation, intensive care unit admission, and death than those with non-vaccine associated myocarditis.[119] However, a subset of

	Vaccine	Common reactogenicity*	Serious adverse events
mRNA	Pfizer–BioNTech (BNT162b2)[3,90–92]	Pain at injection site (~75%); fatigue (~48%); headache (~40%); muscle pain (~25%)	Myocarditis and pericarditis: risk—12·6 cases per million (second dose); highest in males age 18–29 years. Anaphylaxis: risk—4·7 cases per million doses.
mRNA	Moderna (mRNA-1273)[89,91,92]	Pain (~80%); fatigue (~70%); headache (~65%); muscle pain (~61%)	Myocarditis and pericarditis: risk—35·6 cases per million (second dose). Anaphylaxis: risk—2·5 cases per million doses.
Self-amplifying RNA	Arcturus (ARCT-154)[93,94]	Pain (~70%); fatigue (~55%); headache (~38%); muscle pain (70%)	Myocarditis and pericarditis: risk—0 cases per 17 000 participants (note, trial n=<20 000; larger surveillance required to confirm rare risks).
Protein	Novavax (NVX-CoV2373)[95,96]	Pain (~35%); fatigue (~35%); headache (~40%); muscle pain (~40%)	Myocarditis and pericarditis: risk—1 case in 15 187 participants (note, likely viral myocarditis rather than vaccine-related).
Viral vector	AstraZeneca (ChAdOx1 nCoV-19)[97–100]	Pain (~25%); fatigue (~13·7%); headache (~8%); swelling (~4·7%)	Myocarditis and pericarditis: risk—0 reported. TTS: risk—5 cases in 130 000 vaccinated participants. GBS: 38 cases in 10 million people.
Viral vector	Johnson & Johnson–Janssen (Ad26.COV2.S)[101–104]	Pain (~45%); fatigue (~35%); headache (~35%); swelling (~15%)	Myocarditis and pericarditis: risk—68 cases from 1·33 million doses. TTS: risk—60 cases from 17 million doses. GBS: 12 cases from 7 million doses.

TTS=thrombosis and thrombocytopenia. GBS=Guillain–Barré syndrome. *Including age 16–55 years and 55 year and older groups.

Table: **Comparison of reactogenicity and serious adverse events between COVID-19 vaccination platforms**

patients report persistent symptoms with or without abnormalities on cardiac imaging beyond 12 months, suggesting long-term follow-up of COVID-19 vaccine-associated myocarditis is warranted.[120–123]

Thromboembolic events

Thrombosis with thrombocytopenia syndrome was reported with COVID-19 viral vector vaccines in 2021 sparking intense surveillance and research.[99,124] Thrombosis with thrombocytopenia syndrome has not been associated with mRNA vaccines.[114] Similarly, thromboembolic events, a known complication of SARS-CoV-2 infection, have not been associated with mRNA vaccination.[114,118]

Bell's palsy

Phase 3 randomised clinical trials for COVID-19 mRNA vaccines reported an imbalance of Bell's palsy between vaccinated and placebo groups.[89,125] Post-market surveillance did not detect a consistent pattern of increase in Bell's palsy after mRNA vaccination, and the National Academy of Medicine report favoured rejection of a causal association based on the body of evidence.[114,126,127]

Immunogenicity and efficacy

Effectiveness across populations

COVID-19 vaccines were designed to elicit primarily neutralising antibodies against the SARS-CoV-2 spike protein. Initial efficacy of both vaccines was greater than 90% after two doses in phase 3 clinical trials,[3,89] with good correlation between antibody responses and clinical efficacy data.[128] Both BNT162b2 and mRNA-1273 also showed some efficacy after only one dose, when non-neutralising antibodies and moderate T-helper 1-cell responses were detectable, in the absence of neutralising antibodies, suggesting the importance of other immunological mechanisms of protection, which might include T cell-mediated mechanisms that are generally harder to measure.[129–131] Later systems immunology studies confirmed the ability of mRNA vaccines to elicit very high antibody responses, in addition to polyfunctional $CD4^+$ and $CD8^+$ T-cell responses after the second dose.[41] The second dose in particular induced enhanced innate immune responses, which were primarily due to stimulation of inflammatory monocytes and plasma IFN-γ responses,[41] and corresponded with the reactogenicity of these vaccines in the first few days after vaccination.[3,89]

Numerous analyses and systematic reviews have been published on the effectiveness of COVID-19 vaccines throughout the pandemic. In one comprehensive analysis of 68 published studies, mRNA vaccines had a pooled effectiveness of 87% (95% CI 84–90) against any documented infection, 93% (95% CI 89–95) against hospitalisation, and 94% (95% CI 88–97) against mortality at 14–42 days after vaccination.[132] Protection was particularly high in periods with less intense circulation of SARS-CoV-2, and reduced in periods of more intense circulation, consistent with so-called leaky protection.[133] Protection was lower for vaccination with the ancestral strain vaccine against the omicron variant (67% [95% CI 53–77] against infection and 72% [95% CI 58–81] against hospitalisation), and with time (48% [95% CI 31–62] against infection and 80% [95% CI 64–88] against hospitalisation) by 224–251 days post-vaccination.[132] Ongoing evolution of the SARS-CoV-2 virus and waning immunity have led to the recommendation of ongoing booster doses for high-risk groups, annually in many countries.

Additional studies have confirmed good protection in various populations, including children and adolescents,

pregnant individuals, and immunocompromised populations. In one analysis of 14 studies in children and adolescents, the vaccine effectiveness against omicron infection was 51% (95% CI 22–68) and 61% (95% CI 41–80), respectively in these age groups, which are similar estimates to the adult studies.[134] Another analysis of 14 studies reported a 69% (95% CI 41–84) lower probability of infection, and 85% (95% CI 79–90) lower probability of hospitalisation in pregnant women who had received a COVID-19 vaccine in pregnancy, compared with unvaccinated individuals.[135]

Transmission prevention and real-world effectiveness

The effect of COVID-19 vaccines on reducing transmission has primarily been via the reduction of asymptomatic and symptomatic infection, thus, the onwards spread of SARS-CoV-2 to susceptible individuals, rather than eliciting true sterilising immunity at the mucosal surface. Early studies showed that COVID-19 vaccination resulted in a decreased duration of viral shedding plus a reduced viral load.[136,137] Vaccination with the ancestral strain reduced transmission of the aplha variant more than the delta variant.[138] More recent household transmission studies conducted by the US Respiratory Virus Transmission Network Study Group have shown that immunity from COVID-19 vaccination with or without previous infection results in a reduced risk of transmission, with protection from secondary infections highest (relative risk reduction 19% [95% CI 7–30]) in the setting of hybrid immunity (ie, vaccination and previous infection). The greatest protection occurred when the last immunising event was 6 months or less (*vs* >6 months) before a subsequent SARS-CoV-2 exposure, with a relative risk reduction of 31% (95% CI 17–43).[139] While these data are encouraging, the best protection is achieved by direct vaccination, rather than reliance on indirect protection with the vaccination of close contacts.

Surveillance and post-market pharmacovigilance

Post-market pharmacovigilance is essential for monitoring the safety of mRNA vaccines beyond clinical trials, capturing real-world data on rare adverse events, long-term effects, and population-level effects. Both passive and active surveillance systems have been used to detect, evaluate, and respond to safety signals. These approaches have been pivotal in addressing concerns of vaccine safety during the COVID-19 pandemic, while countering misinformation in an era of declining public health infrastructure.[140,141] Post-market pharmacovigilance for mRNA COVID-19 vaccines has involved extensive passive and active surveillance systems globally, confirming a favourable safety profile with benefits outweighing risks, even after billions of doses were administered. mRNA COVID-19 vaccine developers conducted post-marketing surveillance to satisfy regulatory requirements, and submitted extensive safety datasets to authorities, such as the FDA, European Medicines Agency, and WHO.[142] In parallel, independent academic groups, national public health agencies, and international research networks have conducted large-scale real-world surveillance and meta-analyses to independently verify and extend these findings.[143,144]

Passive surveillance relies on voluntary reporting from health-care providers, patients, and manufacturers to systems, such as the Vaccine Adverse Event Reporting System (VAERS) in the USA, EudraVigilance in Europe, and WHO's VigiBase. The strengths of passive surveillance include broad accessibility, low cost, and the ability to detect novel or rare signals that might not emerge in controlled trials, such as initial reports of myocarditis following mRNA vaccination;[145] for instance, passive systems facilitated early identification of anaphylaxis.[146] However, there are several limitations of passive surveillance. Under-reporting, estimated at 1–10% for serious events, can introduce bias, as motivated individuals could over-report perceived issues, while milder events go unnoticed.[147] Causality assessment is challenging without denominators for incidence rates.[148] False narratives in mRNA COVID-19 vaccine pharmacovigilance have emerged from the misinterpretation of unverified signals in passive systems such as VAERS, where spontaneous reports are misused to suggest causality without accounting for coincidences, background rates, or the lack of verification, leading to widespread disinformation that erodes public trust and vaccine uptake.[149]

Active surveillance involves proactively gathering data from predefined populations, such as cohort studies or electronic health records, to calculate precise incidence rates and evaluate causality, controlling for confounders, such as age and comorbidities. This approach has been instrumental in affirming the safety of updated mRNA COVID-19 vaccines. For instance, a 2025 Danish nationwide cohort study involving 1 million vaccinated adults assessed 29 adverse events of special interest, including cardiovascular, thrombotic, neurological, and autoimmune conditions, and found no significant risk increases in the 28-day post-vaccination period.[150] Similarly, a US self-controlled case series analysis of 244 494 adults receiving XBB.1.5-containing mRNA vaccines evaluated 15 adverse events of special interest and identified a significant association only with anaphylaxis, with no elevated risks for other outcomes.[151] Strengths of active surveillance include its statistical rigour, ability to provide real-world effectiveness, and capacity for rapid signal validation, as shown in these studies of variant-adapted formulations. Limitations, however, encompass high resource demands, limited sample size to evaluate very rare adverse events following immunisation occurring in less than 1–10 per million people, and potential biases from health care-seeking patterns or residual confounding.

Public perception, vaccine hesitancy, and misinformation

Hesitancy around vaccines is not a new occurrence, although it has become increasingly politicised and is experiencing what is characterised as the social amplification of risk—with the public amplifying the scale of vaccine risks and spreading these perceptions widely, prompting unfounded fears with negative effects on vaccine uptake.[152] Notably, vaccine hesitancy is defined as the oppositional attitude towards getting vaccinated despite the availability of vaccines, although some people who are hesitant still accept vaccines,[153] and can be mitigated using social conformity[154] and gentle persuasion.[155] Alongside this exaggeration of risk, is a realm of misinformation about vaccines, how they are made, and their ingredients.[156] Particular anxieties have arisen around mRNA vaccines, and more recently self-amplifying RNA.[157,158] Vaccine hesitancy is increasingly volatile, particularly in the context of rapidly spreading digital media and new modes of artificial intelligence, influencing vaccine intent.[159,160]

Vaccine hesitancy was already a growing issue before the COVID-19 pandemic, with WHO calling out vaccine hesitancy as being the one of the "top ten global health threats" in 2019.[161] During the COVID-19 pandemic, when anxieties around vaccines escalated, whole populations were searching for vaccine information online and many, particularly those with young children, were exposed to negative media around vaccines, which they were not previously aware of. 52 (94%) of 55 countries had a decline in vaccine confidence during the COVID-19 pandemic as reported in the UNICEF 2023 State of the World's Children Report.[162]

There were multiple reasons for the accelerated decline in vaccine confidence during the pandemic, including anxieties around the newness of the vaccines, the unprecedented speed in which these brand-new vaccines became available, concerns about safety, and growing discontent with COVID-19 vaccine mandates, with multiple boosters during the course of the pandemic. Risk communications expert, Peter Sandman, identified key characteristics that matter to public confidence.[163] Among them are numerous points highly relevant to mRNA vaccine acceptance, namely: is it voluntary, is it natural, is it familiar (or unfamiliar), and importantly, can I trust you (ie, the regulator, the health professional, the vaccine producer)? One 2023 study mapping global sentiments around mRNA, via an analysis of nearly 750 000 tweets, found widespread negative sentiment and a global lack of confidence in the safety, effectiveness, and trustworthiness of mRNA vaccines and therapeutics, with frequent discussions of severe vaccine side-effects, rumours, and misinformation.[164] We have an opportunity to build confidence and have clear information on the urgent need for trust building, before introducing more new mRNA vaccines and therapeutics.[165,166]

Implications for future mRNA vaccine development

mRNA technology has the potential to transform vaccine development, but considerable challenges remain. The success of COVID-19 vaccines has driven investment in emerging infectious diseases; however, sustainable markets beyond pandemics are essential. The mRNA-1349 respiratory syncytial virus (RSV) mRNA vaccine marked the first licensing of an mRNA vaccine for another infectious disease,[167] opening broader applications, with multiple indications, including mPox, HIV, Varicella-zoster virus, norovirus, and *Mycobacterium tuberculosis*, now in clinical trials.[168] While safe and effective in older adults and children aged 12–59 months,[169] higher rates of severe RSV were observed in RSV-naive infants aged 5–7 months, prompting regulatory review.[170] Recent studies also show that mRNA vaccines can be effective against seasonal influenza. The relative efficacy of the modRNA vaccine as compared with the standard quadrivalent inactivated virus vaccine (FLUZONE) against influenza-like illness was 34·5% (95% CI 7·4–53·9), meeting the threshold for both non-inferior and superior.[171] Broader adoption will depend on demonstrating efficacy and effectiveness across strains and age groups while reducing reactogenicity compared with existing vaccines.[172] However, mRNA vaccines are not a panacea for all diseases, as seen with the failure of mRNA-1647 against congenital cytomegalovirus.[173]

These examples highlight key barriers to broader access and acceptance. Reactogenicity and safety concerns remain central challenges. Reactogenicity arises from innate immune sensing of RNA and inflammatory responses to delivery systems, such as lipid nanoparticles. Modified nucleotides can reduce innate recognition and reactogenicity,[174] but not eliminate it, leaving scope for further innovation. Dose is another important factor, particularly for multivalent vaccines, such as seasonal influenza, where higher doses increase the risk of systemic reactions. Dose-sparing approaches, including self-amplifying RNA, might help address this problem. Systemic reactions—fever, chills, malaise, and musculoskeletal pain—are more common in younger individuals (age 16–55 years, although for myocarditis there is a greater risk in those aged 12–29 years) assuming the same dose and are associated with rare adverse events, including myocarditis or pericarditis (particularly in young men), hyperinflammatory syndromes, and autoimmune flare-ups.[175] Strategies that restrict vaccine exposure to the injection site and draining lymph nodes without compromising efficacy, or dose-reduction could reduce these risks.

Delivery systems strongly influence inflammatory responses and biodistribution. New lipid nanoparticle formulations using less inflammatory ionisable lipids and tissue-targeting components are under development.[176] Replacing PEGylated lipids is a priority and addresses the rising prevalence of anti-PEG antibodies,

which could accelerate nanoparticle clearance and reduce effectiveness.[176] The effect of these changes on intramuscular vaccine potency remains uncertain, especially as many advances originate from intravenous RNA therapeutics. While lipid nanoparticles dominate the field, alternative platforms, such as biodegradable charged polymers, are being explored.[177]

Despite their success, mRNA vaccines reveal inherent immunological limitations. mRNA vaccines induce rapid but transient antigen expression, generating strong short-term antibody and memory B-cell responses, yet are less effective at producing long-lived plasma cells in bone marrow.[178] Immunity wanes, needing boosters that shift antibody responses towards IgG4 (ie, from 0·04% to 19·27%), an isotype that neutralises the virus but is less effective at Fc-mediated clearance.[179] Repeat doses of non-mRNA vaccines being studied currently against HIV, malaria, and pertussis also increase IgG4 concentrations.[180] Although mRNA vaccines offer proven protection, the importance of this IgG4 shift toward non-inflammatory functions remains unclear; it might be balanced by Fab functions or T cells and could reduce immunopathology. Intramuscular mRNA vaccines induce limited mucosal immunity, reducing their ability to prevent infection and transmission. Next-generation platforms aim to address these limitations. While the rapid induction of immunity renders the platform perfectly suited to a pandemic setting, or the case of seasonal vaccination where short-term protection is sufficient, longer lasting immunity would be desirable for endemic infections where years or decades of protection is the goal. Circular RNAs and self-amplifying RNA enable prolonged antigen expression, with early clinical evidence showing more durable immune responses.[181] Additional strategies include adjuvanted formulations, RNA-encoded adjuvants, and mucosal delivery approaches targeting the respiratory or gastrointestinal tract.[182,183] Although there was an initial surge in trials of infectious disease vaccines, 11% of current trials are focused on cancer vaccines,[168] including encouraging advances in personalised RNA neoantigen vaccines[184] and development of in vivo CAR-T therapy.[185] 30% of clinical trials are also focused on mRNA therapeutics, with advances in rare diseases (eg, propionic acidaemia)[186] and success in gene therapy with mRNA gene editing to treat carbamoyl phosphate synthetase 1 deficiency.[187]

Global access to mRNA vaccines remains a major challenge. Early mRNA vaccines required ultra-cold storage, complicating distribution in low-resource settings. Stability has improved with formulation advances, lyophilisation, and spray drying, but production costs remain high—several times those of traditional vaccines.[188] Cost reductions via manufacturing optimisation, dose-sparing technologies, and initiatives (eg, the Medicines Patent Pool and WHO mRNA Technology Transfer Programme)[189] combined with strengthened regulatory capacity in low-income and middle-income countries (LMICs), will be crucial. Addressing these challenges is essential for mRNA vaccines to move beyond pandemic use and to realise their full public-health potential. Market penetration remains uncertain and costing US$85–290 per dose,[190] mRNA vaccines are currently unaffordable for most LMICs. The mRNA Technology Transfer programme could help to address this issue by supporting technology transfer and manufacturing in LMIC settings.[189]

Conclusions and future directions

The cumulative evidence from mechanistic studies, randomised trials, and extensive post-authorisation surveillance shows that mRNA vaccines are both safe and highly effective. mRNA vaccine mechanism of action and transient cytoplasmic mRNA translation without genomic integration, coupled with rapid clearance of both RNA and lipid components, underpins a favourable safety profile that is distinct from gene therapy and persistent viral vector platforms. Across billions of administered doses, serious adverse events have been rare, well characterised, and consistently outweighed by the substantial protection conferred against severe disease, hospitalisation, and death. Effectiveness has been shown across age groups, in pregnancy, and in populations that are immunocompromised, establishing mRNA vaccines as a clinically validated and adaptable platform.

The COVID-19 pandemic underscored the crucial role of science-driven public health policy. Rapid vaccine development and deployment were made possible by decades of foundational research, robust regulatory frameworks, and coordinated global surveillance systems. Where transparent communication and evidence-based decision making were prioritised, public health benefits were maximised. Conversely, misinformation and erosion of trust highlight the fragility of vaccine confidence and the necessity of sustained investment in scientific literacy, regulatory credibility, and pharmacovigilance.

Looking forward, continued vigilance is essential. Ongoing safety monitoring, long-term follow-up of rare adverse events, and iterative improvements in vaccine design should remain priorities as mRNA technologies expand to new pathogens and indications. Equally important is clear, proactive communication of evidence to clinicians, policy makers, and the public. Strengthening global surveillance infrastructure, manufacturing capacity, and equitable access, particularly in LMICs, will be crucial to ensure that the full public health potential of mRNA vaccines is realised beyond pandemic settings.

Contributors

All authors contributed to the literature search, manuscript outline and content, writing and review of the manuscript writing, and final manuscript approval.

Declaration of interests

AKB serves on the scientific advisory board for Replicate Bioscience, Genvax Technologies, and Pasture Biosciences; has been an investigator on projects funded by Pfizer, Replicate Biosciences, and Rocket Science

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Health; and has served as an expert witness for a disciplinary hearing. BJC has consulted for AstraZeneca, Fosun Pharma, GSK, Moderna, Novavax, Pfizer, Roche, and Sanofi Pasteur. HJL received grants from GSK, Moderna, and the Gates Foundation unrelated to this manuscript; received payment for honoraria for lectures at Rice University (TX, USA), UNC (NC, USA), and Rockefeller University (NT, USA); received support for attending the Asia Pacific Immunization Summit and the Examining Board for Helsinki and Oslo PhD candidates; serves on the board of directors of PATH; and consults for the Gates Medical Research Institute. KAT received grants from the Canadian Institutes of Health Research , the Public Health Agency of Canada, and Coalition for Epidemic Preparedness Innovations unrelated to this Review; and has served as a Voting Member of the National Advisory Committee on Immunization. MS received grants from GSK, Merck, Moderna, Pfizer, and Sanofi–Pasteur unrelated to this work; and served as Chair and Deputy Chair of two data and safety monitoring boards for COVID-19 vaccine trials. RJS has consulted for Sanofi–Pasteur.

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