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Review

Evidence-based assessment of safety and mechanistic questions Related to mRNA COVID-19 Vaccines

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ABSTRACT

Messenger RNA (mRNA) COVID-19 vaccines have been administered globally at unprecedented scale and have demonstrated strong effectiveness against severe disease, hospitalization, and death. Extensive safety monitoring across randomized clinical trials, national surveillance systems, and global pharmacovigilance programs has consistently supported a favorable benefit–risk profile for these vaccines. Despite this evidence, a range of questions and mechanistic hypotheses continue to circulate, including assertions of increased risk of malignancies, autoimmune diseases, and all-cause mortality, as well as proposed mechanisms involving product-related impurities (e.g. DNA contamination), biodistribution and antigen persistence, non-canonical translation (e.g. ribosomal frame-shifting), and immune modulation.

This targeted narrative review synthesizes nonclinical, clinical, pharmacoepidemiologic, and regulatory evidence relevant to these mechanistic and safety related questions. Published literature, regulatory assessments, and surveillance data were qualitatively evaluated in the context of biological plausibility, methodological rigor, and consistency across independent data sources.

Across the body of evidence, findings do not support increased long-term mortality, malignancy, autoimmune disease, genotoxicity or other long-term safety issues attributable to mRNA COVID-19 vaccination. On the contrary, several large population-based studies have reported lower all-cause mortality among vaccinated individuals. Residual DNA levels are within established regulatory limits when measured using validated methods, and no credible mechanism supports genomic integration. Biodistribution studies demonstrate expected localization to the injection site and lymphoid tissues with no persistence. Immunologic findings, including IgG4 subclass responses, have not been associated with impaired protection in real-world vaccine effectiveness studies.

Collectively, the evidence supports the safety and effectiveness of mRNA COVID-19 vaccines. Ongoing surveillance and rigorous evaluation remain essential to inform public health policy. Importantly, vaccine safety questions should be assessed using transparent, structured frameworks that systematically weigh benefits, harms, quality of evidence, values, and feasibility.

1. Introduction

COVID-19 vaccination programs have had a profound global impact, with vaccination against SARS-CoV-2 estimated to have prevented approximately 2.5 million deaths worldwide [1]. To date, billions of COVID-19 vaccine doses have been administered globally, accompanied by an unprecedented level of safety and effectiveness monitoring across multiple countries and health systems [2–101]. As SARS-CoV-2 continues to evolve and circulate endemically, evidence from these extensive surveillance efforts continues to support vaccination with updated COVID-19 vaccines as the most effective strategy to prevent severe disease, complications, and serious outcomes for at risk-populations, a position consistently reinforced by the World Health Organization [102,103].

Messenger RNA (mRNA) COVID-19 vaccines were enabled by decades of public and private research in mRNA biology, immunology, and vaccine technology, including foundational work on lipid nanoparticle delivery and nucleoside-modified mRNA designed to reduce innate immune activation [104]. National Institutes of Health (NIH) scientists and Moderna began collaborating on adaptable mRNA vaccine design

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approaches in 2016 [105]. Following publication of the SARS-CoV-2 genetic sequence in January 2020, this groundwork supported rapid progression into clinical evaluation, with the first NIH-led Phase 1 trial dosing of mRNA-1273 beginning in March 2020 [4], and early BioNTech/Pfizer clinical dosing beginning in April 2020 [5]. Following successful phase 1/ 2 studies, manufacturers conducted large phase 3 randomized placebo-controlled safety and efficacy trials [2,3] following extensive feedback from NIH, COVID-19 Prevention Network (COVPN) and regulatory authorities including U.S, Food and Drug Administration (FDA) and European Medicines Agency (EMA). Operation Warp Speed accelerated timelines primarily by enabling manufacturing scale-up in parallel with ongoing clinical trials, while maintaining required safety and regulatory review standards [106]. mRNA COVID-19 vaccines, including BNT162b2 (Comirnaty; BioNTech/Pfizer) and mRNA-1273 (Spikevax; Moderna) were authorized by multiple regulatory authorities worldwide based on robust safety and efficacy demonstrated in pivotal Phase 3 randomized clinical trials, the gold standard for evaluating vaccine efficacy and safety [2,3].Following authorization, these findings have been reinforced through large post-authorization safety studies and active pharmacovigilance under continuous regulatory oversight [46–101].

To ensure consistent product quality and performance throughout global distribution, mRNA vaccines are manufactured with processes that are compliant with current Good Manufacturing Practices [107.108] and are comprehensively characterized using validated analytical assays and quality controls, in alignment with International Council for Harmonization (ICH) guidelines [109–114].

Building on this foundation, a broad and growing body of real-world evidence across multiple countries, populations, seasons, and circulating variants has consistently demonstrated robust protection against severe disease, hospitalization, and death [6–46], alongside a favorable safety profile [46–101]. Recent U.S. observational studies further demonstrate sustained effectiveness of updated formulations, including meaningful protection against COVID-19 related hospitalization and medically attended disease during the 2024–2025 season [45]. A recently published France national cohort study including the entire adult population aged 18–59 years (28 million) used a national health records system to review COVID-19 vaccination outcomes with nearly four years of follow up. Results showed that mRNA COVID-19 vaccination was associated with a 74% reduction in the risk of death from severe COVID-19 and a 25% lower risk of all-cause mortality, with no increase in deaths from major conditions such as cardiovascular disease or cancer [46]. Collectively, these data demonstrate that updated mRNA COVID-19 vaccines provide effective protection against contemporary SARS-CoV-2 variants, supported by extensive post-authorization safety monitoring and without evidence of increased long-term mortality risk.

Despite the extensive body of clinical trial and real-world evidence establishing the safety profile of mRNA COVID-19 vaccine, theoretical safety questions related to off-target effects of mRNA vaccines continue to circulate. These include speculations on increased malignancy risk, alterations in immune responses, effects on all-cause mortality purportedly linked to hypothetical questions on levels of residual DNA, biodistribution of vaccine components, and immune modulation, among related topics. Such questions have been amplified by social media, often with selective presentation of the evidence. At the September 2025 Advisory Committee of Immunization Practices (ACIP) meeting, members asserted many of these questions as facts [115]. While ongoing scientific inquiry is appropriate, several statements presented during the meeting reflect misinterpretation of observational data, rely on studies with acknowledged methodological limitations, or incompletely characterize established biological and regulatory standards.

The objective of this review is to identify and synthesize the published evidence regarding the safety of mRNA COVID-19 vaccines, with particular attention to questions concerning their biological mechanisms of action. The scope of the review was informed by questions raised during the September 2025 ACIP meeting and COVID-19 Work Group Terms of Reference [115, 116]. This narrative review synthesizes comprehensive scientific evidence, integrating nonclinical data, randomized clinical trial results, pharmacoepidemiologic analyses, and global post-authorization safety surveillance, together with benefit–risk evaluations conducted by regulatory authorities.

2. Methods

A targeted narrative literature review was conducted to identify and synthesize published evidence relevant to the safety of mRNA COVID-19 vaccines, with particular attention to questions regarding biological mechanisms of action. The scope of the review was informed by questions raised during the September 2025 ACIP meeting [115]. Relevant publications were identified through focused searches of peer-reviewed biomedical literature databases, including PubMed and Embase. Search strategies prioritized terms related to mRNA vaccines' mechanisms of action, biodistribution, immunologic responses, safety and effectiveness outcomes across nonclinical, clinical, and pharmacoepidemiologic or real-world settings. Searches were limited to articles published in English. In addition, reference lists of key publications were reviewed manually to identify additional relevant sources. Relevant regulatory assessments, safety communications, and publicly available reports from global health authorities and regulatory agencies were also reviewed to contextualize scientific findings, manufacturing standards and safety standards.

Retrieved publications were reviewed qualitatively. Safety-related findings were assessed in the context of biological plausibility, methodological rigor, consistency across independent data sources, and relevance to the proposed mechanisms of action.

Data from Moderna-sponsored studies were included when relevant to the review objectives and were evaluated alongside external published evidence. Where available, findings from independent health authorities, nationwide surveillance systems, and recent data were prioritized. This review was intended to summarize and contextualize the existing body of evidence rather than to conduct a formal systematic review, meta-analysis, or graded assessment of evidence strength.

3. Safety of COVID-19 Vaccines

3.1. COVID-19 vaccine safety concerns stem from unexpected Biological activities of mRNA gene therapy, raising questions about potential pathogenic mechanisms and HRP [115] cardiovascular, thrombotic, neurologic, immunologic, and other severe adverse events [116]

COVID-19 vaccines have undergone one of the most intensive safety monitoring to date [2–5,46–101]. In the United States (US), Food and Drug Administration (FDA) and Centers for Disease Control and Prevention (CDC) vaccine safety programs have evaluated at least 65 prespecified outcomes, investigated multiple potential signals, and conducted several epidemiologic studies, some ongoing [54]. Additionally, tree-based data mining within the Vaccine Safety Datalink (VSD) assessed over 60,000 potential adverse events within 70 days after vaccination across primary, booster, and bivalent booster doses [54]. No new safety concerns were identified beyond very rare events (<1 event/10,000 doses) already reflected in the label, including myocarditis/pericarditis, allergic reactions, and commonly observed local and systemic reactogenicity [54,117].

The safety of COVID-19 vaccines has also been rigorously monitored by global health authorities [118–122]. Several national health systems have published population-wide studies of the impact of these vaccines [14,28,46,55,56]. A recent publication in *JAMA* by the Health Ministry of France leveraged a universal health record for the national health system covering all individuals in the French population aged 18 to 59 years, including 23 million vaccine recipients and 6 million unvaccinated controls for the 4 years since vaccination started in 2021. The study found no association between mRNA COVID-19 vaccination and

increased long-term all-cause mortality; rather, vaccination was associated with a 25% lower overall risk of death, consistent with sustained protection against severe COVID-19 and its complications [46]. Similar large-scale follow-up studies from the UK and Nordic countries have not identified any long-term safety concerns in population-wide, national health systems [55,56].

Moderna has conducted comprehensive safety assessments of its COVID-19 vaccines across clinical development and real-world use, including evaluation of more than 60,000 participants in pre-licensure placebo-controlled efficacy trials and post-licensure studies involving over 13 million vaccinated individuals [123]. Ongoing pharmacovigilance includes spontaneous adverse event reporting and aggregate safety analyses [52]. Domestic and international post-authorization observational studies of mRNA-1273 [57–61] identified known very rare (<1 case per 10,000 doses) risks of myocarditis and pericarditis, (particularly in younger males) and anaphylaxis, and have not identified new or unexpected safety concerns. To date, no cases of vaccine-associated myocarditis have been observed with mRNA-1283 (mNexspike; Moderna), which does not include the full spike protein, after approximately 5 million doses administered [124]. The very low risks of myocarditis and pericarditis are reflected in prescribing information [117,125].

Regulatory review by the U.S. Food and Drug Administration continues to confirm the favorable benefit–risk profile of Moderna's COVID-19 vaccines, as reflected in approval of the 2025–2026 LP.8.1–containing vaccine formulations [117,125]. mRNA-1273 has been approved in more than 70 countries including the UK, Germany, Australia, Canada and Japan [126].

3.2. *Cancers have been reported in mRNA-vaccinated individuals in temporal association with immunization based on 38 case reports and 96 cases of pancreatic duct adenocarcinoma outcomes vs IgG4 [115]*

Theoretical concerns that mRNA COVID-19 vaccination could increase risk of cancer [115] are not supported by available epidemiologic evidence. More than 6 billion doses of mRNA COVID-19 vaccines have been administered globally over approximately 5 years [123,127]; no increased risk of cancer has been identified across multiple independent large-scale surveillance systems [46,52,54]. Isolated case reports, including small case series (e.g., 38 cases), do not provide sufficient evidence to infer causality, particularly when considered alongside consistent findings from multiple large-scale epidemiologic analyses demonstrating no increased cancer risk.

A large epidemiologic study demonstrated that individuals vaccinated with at least one dose of an mRNA COVID-19 vaccine had had lower all-cause mortality, with reductions observed across major causes of death, including cancer and cardiovascular disease. Importantly, cancer mortality was numerically lower (769 versus 853 deaths per million individuals) indicating no excess cancer risk associated with vaccination [46].

These conclusions are aligned with assessments by global regulatory authorities. According to the FDA, “Pharmacovigilance data in hundreds of millions of individuals also indicate no evidence indicative of genotoxicity [128].” Likewise, the European Medicines Agency (EMA) concluded that “the mRNA used in COVID-19 vaccines does not interfere with our genetic code…. mRNA does not enter the cell's nucleus where our DNA is kept…. No side effects linked to gene mutations, such as cancer, have been observed after vaccination with mRNA vaccines [129].”

3.3. *All-cause death [116]*

In a large population-based study of approximately 28 million adults in France, individuals who received at least one dose of a COVID-19 vaccine had a 25% (weighted hazard ratio, 0.75 [95% CI, 0.75–0.76]) lower risk of death from any cause compared with those who remained unvaccinated. Investigators concluded that a causal association between mRNA COVID-19 vaccination and excess long-term mortality was not observed, underscoring the safety of these vaccines. This study represents the largest assessment to date of long-term mortality following mRNA COVID-19 vaccination in the general adult population [46].

Consistent with these findings, the CDC reported that adverse event reporting rates in Vaccine Adverse Events Reporting System (VAERS) remain below background rates observed in the US population and that self-controlled analyses conducted within VSD found no increase in all-cause, non–COVID-19 mortality following vaccination [54]. Similarly, a nationwide study in Norway showed lower all-cause mortality rate adjusted IRR 0.42 [95% CI, 0.41 to 0.43] in vaccinated than unvaccinated in individuals 65 years and older [56] and a large multinational European postmarketing safety study across Denmark, Norway, Spain and the United Kingdom found no increased risk of sudden death or death from any cause following vaccination with mRNA COVID-19 vaccines [61].

3.4. *Risk of autoimmune disease, including Guillain-Barré syndrome [116]*

Theoretical concerns about increased risk for autoimmune disease following mRNA COVID-19 vaccination are not substantiated by results across randomized trials [2,3,130–134] or from large population studies [47,82,94,135–138].

A broad spectrum of autoimmune and immune-mediated conditions that are considered adverse events of special interest has been evaluated following mRNA COVID-19 vaccination, including neurologic (e.g., Guillain-Barré syndrome, encephalitis), hematologic (e.g., immune thrombocytopenia, Kawasaki disease), hepatic (e.g., autoimmune hepatitis), cutaneous (e.g., vasculitis, single-organ cutaneous vasculitis), arthritis, multisystem inflammatory syndrome, and endocrine conditions (e.g., thyroiditis, diabetes) [SPEAC Brighton Collaboration] [98].

Across clinical development, no imbalance in autoimmune events was observed between vaccine and control groups [2,3,130–134], and routine post authorization safety monitoring through the end of 2023 identified no concerning patterns across any mRNA-1273 strain formulations [51,92]. In postmarketing safety surveillance, Moderna has systematically evaluated multiple immune-mediated outcomes. Pooled analyses across databases did not demonstrate an increased risk. Importantly, subgroup analyses among individuals with preexisting autoimmune or inflammatory conditions showed a safety profile consistent with that of the overall population [59].

Routine pharmacovigilance activities evaluating a broad range of autoimmune conditions identified no evidence of new or emerging safety concerns following administration of original or updated mRNA-1273 formulations [52]. Reported events have largely consisted of rare case reports or small case series rather than widespread or consistent findings, underscoring the rarity of these conditions [139].

Consistent with these findings, large-scale surveillance systems have not identified increased risks for key autoimmune outcomes [47,135–138]. A joint CDC/FDA analysis encompassing approximately 487 million administered vaccine doses found no increased risk for Guillain-Barré syndrome following mRNA COVID-19 vaccination [62].

4. DNA impurities

4.1. *Assertion: Moderna vaccine exceeds residual DNA limits by ~112 to 627-fold [115]*

DNA is an indispensable component of the manufacturing of virtually every biological medicine [140]. In mRNA vaccine manufacturing, DNA is used as the template for in vitro transcription, determining the nucleotide sequence of the synthesized mRNA. DNA is subsequently degraded enzymatically and removed during multiple purification steps [141]. In the interest of ensuring product quality, health authorities

have established regulatory standards for residual DNA present in vaccines (for example, measles mumps and rubella (MMR), influenza, and COVID-19 vaccines) and other injectable biological medicines. These standards are grounded in established regulatory practice and supported by extensive experience across many biological products. FDA and WHO guidelines stipulate that residual DNA is to be controlled to levels lower than 10 ng per dose and fragmented to pieces smaller than the size of a functional gene, approximately 200 base pairs [142,143]. All of Moderna's vaccines adhere to these guidelines.

Reports that assert the presence of excessive DNA in mRNA COVID-19 vaccines rely primarily on non-validated fluorometry methods [144–147]. These methods dramatically over-report the level of DNA present in an mRNA vaccine because they cannot accurately distinguish between DNA and the main components of the vaccine, the mRNA and lipids [148]. The methodology of these studies has been refuted by researchers and regulators. The Paul-Ehrlich-Institut (PEI, Germany's vaccines and biomedicines regulator) concluded that "the data and studies on suspected contamination of COVID-19 mRNA vaccines circulating in the public are based on methodological deficiencies [149,150]." The Therapeutic Goods Administration (TGA, Australia's medicines regulator) stated, "These reports are based on studies conducted by a small number of laboratories that have attempted to investigate the amount of DNA in COVID-19 vaccines…these recent studies fail to apply the required scientific rigor expected in pharmaceutical testing. As such, the results are not robust or reliable and are creating confusion and unsubstantiated concern regarding the safety of vaccines [140]." When using validated methods capable of accurately differentiating between DNA and mRNA, the levels of DNA present in vials of Moderna's COVID-19 vaccine were confirmed to be lower than the thresholds established in FDA and WHO guidelines (10 ng per dose) [148,151].

Health authorities have executed independent measurements of DNA levels in commercial batches of mRNA COVID-19 vaccines, including mRNA-1273. The TGA (Australian regulator) has confirmed [151] that the amount of DNA in all mRNA-1273 batches tested was significantly below the limit of 10 ng per dose (Supplemental Table 1). Similarly, results of testing from PEI (German regulator) were consistent with those reported by Kaiser et al. [150].

4.2. Assertion: no safety considerations or guidelines for LNP-enveloped DNA impurities have been established by regulatory agencies [115]

It is incorrect to assert that regulatory agencies have not considered the safety and guidelines of residual DNA in the context of LNP-formulated mRNA vaccines. Product safety is established by manufacturers and regulatory authorities based on review of preclinical safety studies, large placebo-controlled clinical trials (Phase 1, Phase 2, and Phase 3), and post-approval safety studies previously listed. These establish the safety profile of the product, in alignment with applicable harmonized regulatory guidelines [152–158].

The validation of the manufacturing process and controls, as well as release testing performed on each lot against established specifications, ensure that every batch of the product is of consistent quality and, therefore, that the established safety profile based on clinical, preclinical and safety studies remain applicable. This is rigorously assessed by manufacturers and independently by regulators for compliance with cGMP [107,108] prior to the approval of any new product, and throughout its commercial lifecycle. The US FDA has stated "The agency has taken into account the totality of the mRNA COVID-19 vaccine product, including the lipid nanoparticles, as it reviewed the manufacturers' specifications for residual DNA fragments present [128]."

4.3. Concerns due to known DNA integration and gene activation/disruption by SV40 promoter/enhancer sequences [115]

There is no plausible mechanism by which mRNA vaccines could lead to disruption of the genome [128,159]. The integrity of the genome is maintained by a multitude of mechanisms, each of which prevents perturbation by mRNA vaccines or residual DNA [160–162]. Speculation about DNA disruption caused by residual DNA in mRNA vaccines would similarly apply to every medicine that uses DNA in its manufacturing process, virtually all biological medicines, including therapeutic antibodies and insulin. These concerns are not substantiated by fundamental biological science or real-world observations by regulatory authorities. The Australian TGA stated, "There has been no evidence of mRNA vaccines or biological medicines used in Australia resulting in integration of residual DNA into human DNA genome. This includes products such as recombinant insulin, which are injected multiple times a day for life-long treatments [140]." The US FDA stated that "On first principle, it is quite implausible that the residual small DNA fragments located in the cytosol could find their way into the nucleus through the nuclear membrane present in intact cells and then be incorporated into chromosomal DNA… Pharmacovigilance data in hundreds of millions of individuals also indicate no evidence indicative of genotoxicity [128]."

Additionally, assertions have been made that mRNA vaccines contain an SV40 promoter/enhancer sequence. The DNA templates used to manufacture mRNA-1273 and mRNA-1283 do not contain any SV40-related sequences.

5. Biodistribution

5.1. Assertion: COVID-19 mRNA vaccine biodistribution studies did not use commercial product [115]

Moderna has conducted a biodistribution study using mRNA-1273 (Spikevax) in male and female Sprague Dawley rats [163]. This study was conducted following interactions with the FDA and other global health authorities and was performed in accordance with applicable international guidance, including the World Health Organization (WHO) guidelines on the nonclinical evaluation of vaccines and mRNA vaccines and the International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use [152,154–158]. Detailed biodistribution datasets, such as those contained in the mRNA-1273 biodistribution study, have been reviewed by multiple regulatory agencies worldwide, including the US FDA, and have been considered sufficient to support licensure of multiple mRNA vaccines. In the case of mRNA-1273, such data have enabled regulatory approval in more than 70 countries [126]. These detailed study reports and datasets are reviewed by health authorities as part of regulatory submissions, but they are not typically accessible to the public. Therefore, statements asserting that a biodistribution study with mRNA-1273 has not been conducted by Moderna, based solely on the observation that they were not included in the FDA Summary Basis for Regulatory Action or EMA Assessment Report, are inaccurate. To enhance public understanding, biodistribution data for mRNA-1273 were recently submitted for review in a peer review journal and made available as preprint [163].

5.2. Assertion: Biodistribution data did not show confinement to site of injection. Distribution included draining lymph nodes, liver spleen heart, brain, lungs, and blood and can cross the blood-brain barrier [115]

Moderna biodistribution data have been shared with regulatory authorities, including the FDA, and were recently submitted for review in a peer review journal and made available as a preprint to describe where mRNA vaccine components travel in the body following intramuscular injection [163]. These studies examined three different mRNA products including mRNA-1273, a candidate cytomegalovirus (CMV) vaccine (mRNA-1647), and a reporter mRNA (NPI-luciferase). All three were injected into rats at doses much higher than those used in humans (more than 130 times higher after accounting for body weight), representing a conservative and extreme estimate of how much vaccine components

and produced proteins could be present after vaccination [163].

The tissues with the highest amounts of vaccine components were the injection site, associated draining lymph nodes, and spleen. There was minimal distribution to other organs, representing only a small fraction of exposure relative to the injection site. Vaccine components cleared rapidly (within 48 h in serum and within 2 weeks in tissues) and SARS-CoV-2 Spike protein was cleared within 5 days. Furthermore, there was no observed accumulation of vaccine components in blood or tissues following repeat dosing of mRNA-1273 [163]. Licensed adjuvanted protein and viral-vector vaccines, as well as BNT162b2, show similar biodistribution patterns following intramuscular administration in rodent and rabbit models [164–168].

As established in scientific literature low-level and sporadic detections in gross organs are best explained by residual intravascular content following tissue perfusion, as complete clearance of all capillary blood is not achievable even in ideal experimental conditions. When sporadic and close to a validated assay's limit of detection, these observations are generally regarded as experimental contamination [169,170].

5.3. *Assertion: Spike protein from mRNA COVID-19 vaccine has been reported to persist for up to 706 days [115]*

Moderna characterized vaccine-encoded spike protein kinetics in a SARS-CoV-2–naïve model, enabling unambiguous assessment of clearance in the absence of prior or subclinical infection, which cannot be ruled out in human studies. This study evaluated the kinetics of spike protein under a dosing paradigm of 2 dose administrations, one month apart, reflecting the most frequent prime–boost interval used for mRNA-1273. In pharmacodynamic analyses of circulating spike protein following mRNA-1273 administration, serum concentrations peaked approximately 24 h post-dose (TEmax), representing the time of maximum observable pharmacodynamic effect. Concentrations declined rapidly thereafter, with an effective serum half-life of approximately 18 h. Quantifiable levels in blood were only observed up to 3 days following the first dose and up to 7 days following the second dose. Modeling of first-order elimination kinetics demonstrated greater than 98% elimination within 5 days post-dose, consistent with rapid systemic clearance [163].

Assertions of spike protein persistence for months after vaccination are not supported by the broader scientific evidence. Two studies that have often been cited to argue the persistence of spike protein following vaccination were based on small non-random cohorts with self-reported symptoms [171,172]. Importantly, both studies were limited by the inability to control for whether detected spike protein originated from vaccination or from any prior, intercurrent, or immediate SARS-CoV-2 infection. The authors themselves acknowledge that the methodological limitations confound interpretation and stated that “The study generates hypotheses regarding the underlying pathobiology of this condition… however, this study is early-stage and requires replication and validation. We emphasize the critical task of discerning between meaningful results and random fluctuations in the data [171].” At present, no validated assays are capable of distinguishing spike protein derived from natural infection from Spike antigen expressed following mRNA COVID-19 vaccination.

6. Other topics

6.1. *Assertion: N1-methylpseuouridine (nucleoside-modified mRNA) instructs cells to produce off-target proteins due to ribosomal slipping [115]*

Ribosomal frameshifting is a well-established, naturally occurring phenomenon in protein synthesis. During normal translation, as ribosomes read RNA in three-nucleotide codons, occasional low-frequency shifts in the reading frame (+1 or − 1) can occur, resulting in production of alternative amino acid sequences [173,174]. Low-level ribosome frameshifting occurs routinely in human cells, and several layers of biological mechanisms contribute to robust tolerance of this phenomenon [175]. Frameshifting is also observed during natural viral infections and following administration of other well-established vaccines, including live attenuated viral vaccines such as MMR [173,174]. Thus, the presence of any low-frequency frameshifting does not imply toxicity or clinical risk.

Assertions that nucleoside-modified mRNA containing N1-methylpseudouridine (m1Ψ) may cause elevated rates of ribosomal frameshifting are based on a study that assessed two reporter mRNA sequences in a transformed cancer cell line [176]. This publication also noted the potential for T cell responses against frameshifting-derived proteins, although these responses were low and were also reported with a viral vaccine (non-mRNA) in the same study. The conclusion that mRNA modification can lead to increased frameshifting remains contested, with more recent studies employing high-resolution ribosome tracking finding no measurable impact of mRNA modification [177]. These results are consistent with a larger body of data finding that modified mRNA maintains the high translation fidelity of unmodified mRNA [178].

6.2. *Assertion: COVID-19 vaccination, especially multiple doses, can lead to immune changes (e.g., IgG4 class switching, production of anti-idiotype antibodies, low long-term IgG fc glycosylation and sialyation levels, persistent cytokine changes, reduction in circulating memory and effector CD4T cells, and increases in TNF TNFα+ CD8 T cells) which could lead to long term consequences, including risk of persistent and/or recurring infections. [115]*

Adaptive immune responses induced by mRNA COVID-19 vaccines are specific to the SARS-CoV-2 spike antigen. Assertions that repeated mRNA vaccination causes non-specific suppression or long-lasting reprogramming of innate or adaptive immunity and increase risk of persistent, recurrent infection and potentially cancer are not supported by clinical or epidemiological evidence. In one of the cited papers suggesting such changes, the authors (Föhse et al), acknowledged the limitations stating “… without a defined minimal clinically important difference, it is not known whether these will translate to clinically relevant impacts on human health [179].” Another study cited to support claims that increased IgG4-positive cell infiltration may be associated with poorer outcomes in pancreatic ductal adenocarcinoma did not evaluate SARS-CoV-2–specific IgG4 antibodies and did not assess immune responses related to vaccination [180].

It has been asserted that increased ratios of SARS-CoV-2–specific IgG4 relative to IgG1 and IgG3 antibodies, or alterations in IgG Fc glycosylation and sialylation following repeated mRNA vaccination, impair protective immunity [181,182]. However, extensive year-over-year real-world effectiveness data across multiple seasons and variant-updated formulations consistently demonstrate that repeated (i.e.) booster doses of mRNA COVID-19 vaccines continue to confer protection against COVID-19, particularly in preventing severe COVID-19 outcomes including hospitalization and death, despite viral evolution [8–28,31,33,39,40,45].

Mechanistic immunology studies further indicate that functional antibody responses are preserved following repeated mRNA vaccination. Although spike-specific IgG4 antibodies increase following repeated doses, overall antibody functionality against SARS-CoV-2 remains robust. Fc-mediated effector functions, including antibody-dependent cellular phagocytosis, neutrophil phagocytosis, and complement deposition, are overall maintained post vaccination, including data with our own mRNA-1273 vaccine [183,184]. More specifically, we conducted an analysis, where we evaluated the kinetics of IgG subclasses post mRNA-1273 primary series (1st and 2nd doses) and post booster dose (3rd dose) in healthy adults age 18 and above. We demonstrated that SARS-CoV-2 spike-specific IgG4 antibodies, purified from

vaccinated individuals and evaluated in a binding assay with a chaotropic agent, exhibited higher affinity for the SARS-CoV-2 spike protein post-boost compared to pre-boost, suggesting affinity maturation. In addition, the purified IgG4 antibodies were potently neutralizing in an in vitro assay [183].

7. Conclusion

mRNA COVID-19 vaccines have been evaluated extensively through nonclinical studies, large randomized clinical trials, and what is likely the largest global body of real-world evidence accumulated for any medical product over five years of use. Across these data sources, the vaccines have consistently demonstrated strong effectiveness in preventing severe COVID-19 outcomes, including hospitalization and death, alongside a favorable and well-characterized safety profile. Independent regulators across the US, Europe, Canada, UK, Australia, Switzerland, Japan, South Korea, Taiwan, as well as many others, have repeatedly reviewed all available data and confirmed that the benefits of vaccination far exceed the risks for the indicated populations. Ongoing evaluation of vaccine safety and effectiveness remains an annual public health objective, generating updated evidence through national and multinational surveillance systems. In this context, several population-level analyses, including a recent nationwide cohort study, have reported lower all-cause mortality among vaccinated individuals, including reductions in cardiovascular and cancer-related deaths, without identification of new safety signals.

Scientific inquiry is integral to the advancement of knowledge; however, conclusions should be grounded in the totality and quality of available evidence. Findings derived from validated, reproducible assays should be weighed more heavily than those based on non-validated or methodologically limited approaches. Similarly, population-scale epidemiologic analyses conducted across multiple countries provide stronger inference than isolated case reports or small uncontrolled series. Accordingly, conclusions should be articulated transparently and evaluated through independent peer review.

This targeted review synthesized data from a range of study designs and settings to evaluate proposed mechanisms of action and related safety concerns. Collectively, the evidence lends additional credence to the conclusion that mRNA COVID-19 vaccines are safe and effective, while underscoring the importance of ongoing scientific inquiry and transparent evaluation of emerging data as central to evidence-based decision-making.

A limitation of this work is its narrative design, which did not include formal systematic identification, quantitative synthesis, or graded certainty assessment of all available evidence. Additionally, the review places greater emphasis on Moderna-sponsored trials and data, reflecting the authors' familiarity with mRNA-1273 and access to new datasets. While efforts were made to incorporate broader evidence across mRNA COVID-19 vaccines, the scope and depth of analysis may not be uniform across products. Nonetheless, this review is particularly relevant in the context of recent safety assertions that were not accompanied by structured evaluation within established evidence-to-recommendation frameworks. Future efforts should include rigorous, systematic reviews with formal grading of evidence quality and certainty to support more definitive conclusions across mRNA COVID-19 vaccines. Importantly, public health policy decisions should be guided by structured and transparent frameworks, such as the CDC's established Evidence to Recommendations (EtR) framework, which integrates systematic evidence review with assessments of benefits, harms, values, and feasibility to inform sound policy decisions.

CRediT authorship contribution statement

Woo Yun Sohn: Writing – review & editing, Writing – original draft, Visualization, Validation, Supervision, Resources, Project administration, Methodology, Investigation, Funding acquisition, Formal analysis, Data curation, Conceptualization. **Susan M.G. Goody:** Writing – review & editing, Writing – original draft, Visualization, Validation, Supervision, Resources, Project administration, Methodology, Investigation, Funding acquisition, Formal analysis, Data curation, Conceptualization. **David W. Reid:** Writing – review & editing, Writing – original draft, Visualization, Validation, Supervision, Resources, Project administration, Methodology, Investigation, Funding acquisition, Formal analysis, Data curation, Conceptualization. **Darin K. Edwards:** Writing – review & editing, Writing – original draft, Visualization, Validation, Supervision, Resources, Project administration, Methodology, Investigation, Funding acquisition, Formal analysis, Data curation, Conceptualization. **Veronica Urdaneta:** Writing – review & editing, Writing – original draft, Visualization, Validation, Supervision, Resources, Project administration, Methodology, Investigation, Funding acquisition, Formal analysis, Data curation, Conceptualization. **Brian P. Doyle:** Writing – review & editing, Writing – original draft, Visualization, Validation, Supervision, Resources, Project administration, Methodology, Investigation, Funding acquisition, Formal analysis, Data curation, Conceptualization. **Walter L. Straus:** Writing – review & editing, Writing – original draft, Visualization, Validation, Supervision, Resources, Project administration, Methodology, Investigation, Funding acquisition, Formal analysis, Data curation, Conceptualization. **Carole Henry:** Writing – review & editing, Writing – original draft, Visualization, Validation, Supervision, Resources, Project administration, Methodology, Investigation, Funding acquisition, Formal analysis, Data curation, Conceptualization. **Bishoy Rizkalla:** Writing – review & editing, Writing – original draft, Visualization, Validation, Supervision, Resources, Project administration, Methodology, Investigation, Funding acquisition, Formal analysis, Data curation, Conceptualization.

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Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: Woo Yun Sohn reports a relationship with Moderna, Inc. that includes: employment and equity or stocks. Susan M G Goody reports a relationship with Moderna, Inc. that includes: employment and equity or stocks. David W Reid reports a relationship with Moderna, Inc. that includes: employment and equity or stocks. Darin K Edwards reports a relationship with Moderna, Inc. that includes: employment and equity or stocks. Veronica Urdaneta reports a relationship with Moderna, Inc. that includes: employment and equity or stocks. Brian P Doyle reports a relationship with Moderna, Inc. that includes: employment and equity or stocks. Walter L Straus reports a relationship with Moderna, Inc. that includes: employment and equity or stocks. Carole Henry reports a relationship with Moderna, Inc. that includes: employment and equity or stocks. Bishoy Rizkalla reports a relationship with Moderna, Inc. that includes: employment and equity or stocks. If there are other authors, they declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.vaccine.2026.128394.

Data availability

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

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