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The Novelty of mRNA Vaccines and Potential Harms: A Scoping Review

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Review

The Novelty of mRNA Vaccines and Potential Harms: A Scoping Review

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Abstract: Pharmacovigilance databases are showing evidence of injury in the context of the COVID-19 modified mRNA shots. According to recent publications, adverse event reports linked to the mRNA COVID-19 products largely point to the spike protein as an aetiological agent of adverse events, but we propose that the platform itself may be culpable. To assess the safety of current and future mRNA vaccines, further analysis on the risks due to the platform itself, and not specifically the expressed antigen. If harm can be exclusively and conclusively attributed to the spike protein, then it is possible that future mRNA vaccines expressing other antigens will be safe. If harms are attributable to the platform itself, then regardless of the toxicity, or lack thereof, of the chosen payload therein, the platform may be inherently unsafe, pending modification. In this work, we examine previous studies of RNA-based delivery by a lipid nanoparticle (LNP) and break down the possible etiological elements of harm.

Keywords: COVID-19 vaccination; mRNA vaccines; clinical trials; safety assessment; novel technologies; spike protein

1. Introduction

Pharmaceutical and medical device approvals are based in structured approval processes and historically, the track record for approval has been adequate. However, there are many examples of over-turnings of approvals of pharmaceuticals post facto, due to emergence of oversights of particular safety factors that had occurred during the approval process [1]. The former examples represent failures in regulatory bodies to sufficiently assess safety during this process and this can be quite costly both in terms of potential economic and individual harms [2]. To put this ever-present issue into perspective, of 309 novel cardiovascular, orthopaedic and neurologic devices approved in the EU between 2005 and 2010, 73 (24%) were subject to either a safety alert or product recall [3], consistent with other reported rates [4]. Importantly, as complexities and novelties of products are increasing, approval success rates have been decreasing [5] and in the face of new drug approvals currently marred by low Phase III trial success rates (~10%), this is an issue in dire need of acknowledgement and remedy [6]. The precautionary principle dictates that caution must be exercised in the context of potential safety issues with novel drugs and technologies, and thus due to the low success rates of novel and unprecedented drugs [6–8], and the potential risks to the population, it is important to adopt the *precautionary principle* [9] when approving any pharmacological products, especially those given to large populations. COVID-19 mRNA products are novel with regard to their delivery system and their payload are the first mRNA vaccines approved for use in humans, as well as the first approved coronavirus vaccine in humans. The speed

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at which they were designed, developed, approved and administered is also unprecedented in pharmaceutical history [10] and defies traditional timelines for testing of biological products for use in humans.

To assess the novelty of COVID-19 mRNA products, we look back to the history of mRNA vaccines, which begins with experiments on in-vitro transcribed RNA, i.e. delivering RNA to a cell for expression of a protein of interest. Synthetic RNA technology has a wide variety of applications, from the delivery of small interfering RNAs (siRNAs) to reduce gene expression, or messenger RNAs (mRNAs) to encode for a protein of therapeutic value, or to encode for an antigen to stimulate an immune response, as in the strategy of mRNA vaccination.

Early attempts to express proteins from injected mRNA faced several challenges. First, bare RNA produces an inflammatory response, limiting the expression potential of the RNA, as it is broken down. Secondly, it is difficult for the bare RNA to enter through a cell membrane. These issues were addressed through the processes of pseudouridylation and encapsulation in a lipid nanoparticle (LNP) respectively. The former discovery decreased the lability of RNA, enabling it to remain in the body for longer periods of time. The latter discovery not only shielded the RNA from the host's immune response as well as RNAses, it also enabled efficient uptake by cells, where it could be efficiently translated by host ribosomes. Pseudouridine was later replaced by N1-methyl-psuedouridine, owing to its greater translation fidelity, higher expression, and better evasion of the host immune response.

LNP development was improved through two innovations, PEGylation, and the use of cationic lipids. LNP surface modifications by poly-ethylene glycol (PEG) enabled lipid nanoparticles to survive for longer lengths of time still, so that their package contents could be delivered to cells to provoke an immune response when the antigen is expressed. Another important development for LNPs is the use of cationic lipids; enabling efficient self-assembly and encapsulation of the mRNA. Cationic lipids can additionally be modified to deliver drugs to certain cell types, an important consideration when delivering mRNA.

There is a prior history of drug delivery by lipid nanoparticles (LNP), and one approved drug for the delivery of a small interfering RNA (Onpattro [11]). Questions remain pertaining to the safety of mRNA vaccines, as several assumptions on which they were rapidly approved, have been either challenged or overturned by experimental [12] and clinical evidence [13]. Quoted theoretical safety advantages were the ease of production without contamination (mRNA vaccines do not require live virus production), and lower (in theory non-existent) risks of infection or host genome integration [14]. Beforehand, concerns existed over the induction of Type I interferon responses by mRNA vaccines [15,16], which are associated with inflammation and autoimmunity [17,18].

For example, the dual assumptions that LNPs remain at the injection site, and that the mRNA degrades quickly have been shown to be false; biodistribution and bioaccumulation data indicate that LNPs can enter the bloodstream [12], and per-reviewed studies have shown durability of both mRNA and spike protein for *in vivo* [19] and up to 4 months post injection for spike protein [20]. Given the novelty of mRNA vaccines, and the increasing evidence of harm from clinical reports [13], epidemiology [21] as well as laboratory science [22], there are open safety concerns to be addressed by future research.

This review summarizes known mechanisms of harm specific to mRNA vaccines, where we examine historical data on mRNA vaccines to determine if safety signals were apparent during production or testing. Prior to the trials on COVID-19 vaccines involving tens of thousands of people, public data exists on only 285 patients administered mRNA vaccines, with the earliest trials finishing in 2018 and exhibiting high rates (>10%) of severe adverse events (Supplementary Table S1). The novelty of mRNA/LNP products must be stressed in guiding their safety assessment, as current approvals still leave many questions unanswered, and serious risks cannot be definitively ruled out based on current evidence.

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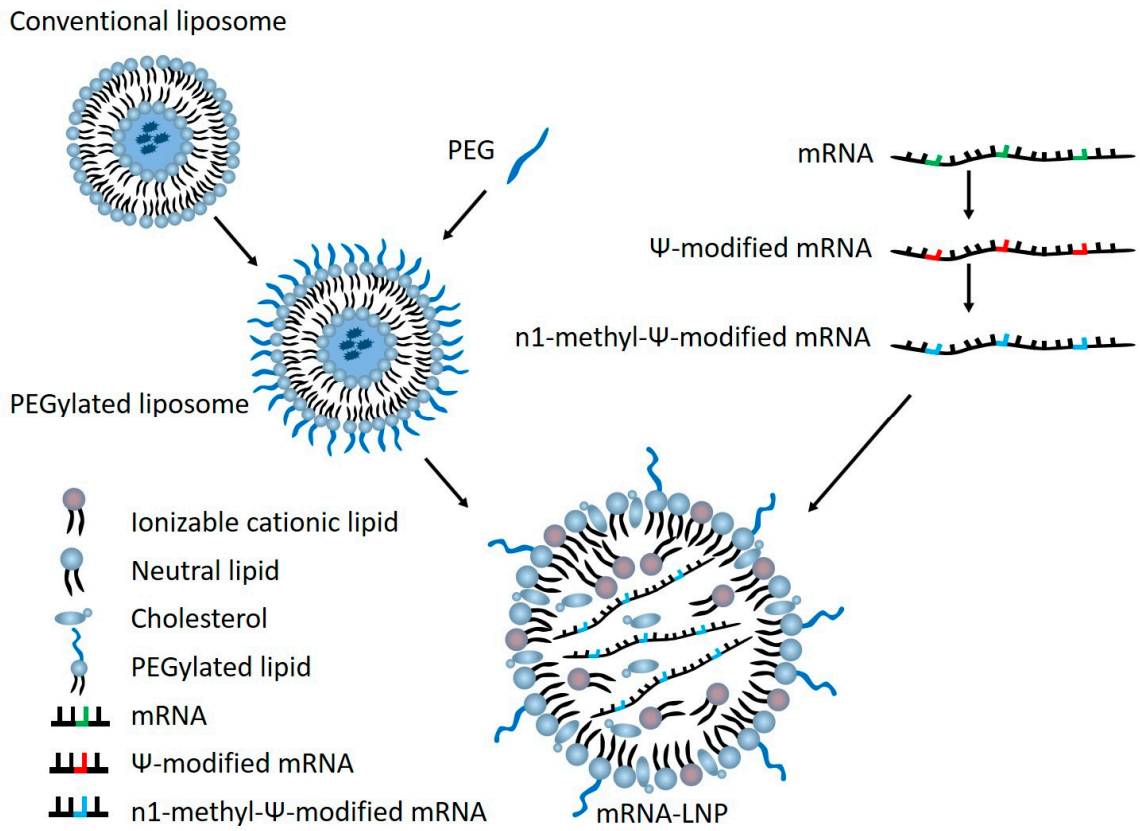

Figure 1. Overview of mRNA-LNP vaccine components.

In this review, we summarize what is known about the individual components of mRNA vaccines individually, by reviewing literature on past therapeutics. Additionally, we review the known safety impacts of mRNA vaccines prior to COVID-19, as well as other coronavirus vaccines, which while using a non-mRNA platform, inform us of safety risks when vaccinating against coronaviruses.

2. mRNA vaccine elements and potential for harm

2.1. Harms due to Lipid Nanoparticle (LNP)

Lipid nanoparticles have been used in the delivery of drugs for decades, beginning with the 1990 EU approval of the drug AmBisome (LNP-encapsulated Amphotericin B) for fungal infections [11]. In the US environment, the first LNP administered drugs were Doxil (LNP-encapsulated Doxorubicin) for Kaposi's sarcoma and Abelcet (LNP-encapsulated Amphotericin B) for asperillosis [11].

The simplest form of LNP is a liposome, which is produced endogenously. This consists merely of a lipid bilayer which separates the contents from the outside environment. While simple liposomes are detected and destroyed by the body's immune system, the addition of polyethylene glycol (PEG), which enables the liposome to evade the host's immune response and last longer in the body to deliver the encapsulated product.

While PEG is thought to be inert in the body, the injection of PEG does elicit anti-IgM antibodies, and subsequent injections are cleared faster due to this immune response [23]. Additionally, a small proportion of the population has an allergy to PEG, and injection can trigger anaphylaxis, as has happened for several people receiving COVID-19 vaccines [24–27].While PEG is thought to be inert in the body, the injection of PEG does elicit anti-IgM antibodies, and subsequent injections are cleared faster due to this immune response [e2]. Additionally, a small proportion of the population has an

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allergy to PEG[1], and injection can trigger anaphylaxis, as evidenced by multiple COVID-19 vaccine adverse event reports [24–27].

The safety of DSPC, a component of the LNP used in both the Pfizer and Moderna COVID-19 vaccines, has been studied for its safety [29]. Animal studies in mice ruled that it was likely not toxic to humans, as no clinical manifestations were present. LNPs have been claimed safe for delivery of therapeutic agents, according to a review [30].

2.2. Harms due to exogenous RNA

Foreign RNA triggers an inflammatory response, as toll like receptor (TLR) [31] and retinoic acid-inducible gene I (RIG-I) [32] are activated. Extracellular RNA exists as a pro-coagulant [33], and increases the permeability of the endothelial cells in brain microvasculature [34]. The initial reason for modification of the RNA by pseudouridinylation was to bypass activation of TLR [35]. As pseudouridinylated RNA was translated at lower fidelity than RNA [36], the nucleosides were modified to N1-methyl-pseudouridine, which brought translation fidelity to near that of RNA [37]. Foreign RNA of course triggers an inflammatory response, as a toll like receptor (TLR) [31] and retinoic acid-inducible gene I (RIG-I) [32] are activated. In fact, the initial reason for modification of the RNA by pseudouridinylation was to bypass activation of TLR [35]. As pseudouridinylated RNA was translated at lower fidelity than RNA [36], the nucleosides were modified to N1-methyl-pseudouridine, which brought translation fidelity to near that of RNA [37].

The properties of both ΨRNA and N1-mΨRNA have been studied in some depth, though questions still remain. For example, through some application of the central dogma of molecular biology, it is assumed that RNA vaccines cannot be incorporated into the genome. This statement is not supported by experiment [38], and is in fact contradicted by experiments showing reverse transcription of the Pfizer BioNTech COVID-19 mRNA vaccine into a human liver cell line [22].

ΨRNA exists in nature and comprises between 0.2% and 0.6% of uridine content in human cell lines, and has biologically significant differences from RNA [39]. While N1-mΨRNA exists in nature, and is found within the archaea [40], studies on its properties go back only as recently as 2015 [41]. Additionally, important biological differences exist between unmodified and modified RNA. For example, through some application of the central dogma of molecular biology, it is assumed that RNA vaccines cannot be incorporated into the genome. This statement is not supported by the research [38], and is in fact contradicted by experiments showing reverse transcription of the Pfizer BioNTech COVID-19 mRNA vaccine into a human liver cell line [22].

2.3. Harms due to in vitro transcribed (IVT) RNA

One level of complexity over delivery of a non-expressed RNA are therapeutics which deliver an mRNA which is expressed by the host translational system. For these applications, typically you are replacing a damaged protein of interest by supplying it exogenously. Using an LNP-mRNA platform here is better than supplying the protein itself, as a protein expressed from IVT RNA is more likely to have the correct post transcriptional modifications (and subsequent conformation) for its cell type than an exogenously supplied protein[42]. For these applications, it is typically necessary for the drug to be administered repetitively over long time periods [42,43]. With repetitive dosing, safety is very important, as even a low per-dose AE rate can compound over the many doses of the treatment.

Most studies of this therapeutic modality so far focus on drug efficacy, and limited safety data exists. In a 2021 review of non-immunologic application of mRNA, all studies using LNP-mRNA as protein replacement therapy demonstrated liver toxicity or lacked safety data [42]. Several studies also saw the development of anti-drug antibodies (ADAs) [44–46], which can deactivate the drug and prevent treatment [47–50]. Immune-mediated toxicity is also a cause for concern [51,52]. Most studies of this therapeutic modality so far focus on drug efficacy, and limited safety data exists. In a 2021

[1] According to a Canadian survey, the prevalence of vaccine allergy is 0.037%. and 0.01% of patients had an allergy to either PEG or common injectable medications containing PEG (CIMCP) [28].

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review of non-immunologic application of mRNA, all studies using LNP-mRNA as protein replacement therapy demonstrated liver toxicity or lacked safety data [42]. Several studies also saw the development of anti-drug antibodies (ADAs) [44–46], which can deactivate the drug and prevent treatment [47–50]. Immune-mediated toxicity is also a cause for concern [51,52].

With ADAs, there is also the concern of the development of cross-reactivity to endogenous proteins, which can occur if the endogenous protein possesses similar structural motifs to the protein expressed from the administered mRNA [53]. Thromboembolic events have been observed in ADA reactions [48]. Typically, ADA reactions are decreased in cases where the encoded protein is a 'self' protein, as opposed to an exogenous protein [54].

2.4. Harms of RNA vaccination

In addition to the other harms present in IVT RNAs, RNA vaccines also have the additional safety challenges of expressing an exogenous protein for the express purpose of generating an immune response and immune memory [55]. Of the RNA therapeutic systems introduced so far, the mRNA vaccines are the most complex drug-like therapeutic biologic.

Limited safety data exists on RNA vaccines against infection (Supplementary Table S1). Prior to the trials for COVID-19 vaccines, there was data on 285 patients, with the earliest trials on a non-HIV vaccine only completed in 2018. The serious adverse event (SAE) rate of these exploratory trials was 14±2% (Grade 3 or above[2]). As a comparison, a post-marketing surveillance study of influenza vaccines in the UK found an SAE rate of 0.16% [56]:, almost 100 times less than the SAE rate for mRNA vaccines.

In addition, study results that might capture long-term effects are not available, or limited. such as those mediated by the immune response with later variants of the virus. While the type of vaccination (i.e. attenuated live virus, inactivated virus, mRNA) should not have a significant impact on the IgG antibodies produced, an important consideration must be mentioned; mRNA vaccines, in encoding for a limited number of proteins (a single antigen in most cases), better enable immune escape than a broader antibody response including other proteins. Recent evidence shows a subclass switch from IgG1 to IgG4 in the context the Comirnaty mRNA product, which may have consequences with regard to cancer [57], pregnancy [58] and IgG4-related diseases [59,60]. COVID-19 mRNA vaccines are commonly used in Europe and North America; these encode specifically and exclusively for the spike (S) protein [61,62]. Since the introduction of vaccines, mutations have occurred lessening the neutralizing capacity of these vaccines [63,64].

2.5. Harms of coronavirus vaccination

In addition to the considerations on the novelty of mRNA vaccines, the C19 mRNA vaccines are also unprecedented on another quality, namely, they are the first coronavirus vaccines approved in humans. Following the 2002/2003 outbreak of SARS-CoV [65] and the 2012 outbreak of MERS-CoV [66], In addition to the considerations on the novelty of mRNA vaccines, the C19 mRNA vaccines are also unprecedented on another quality, namely, they are the first coronavirus vaccines approved in humans. Following the 2002/2003 outbreak of SARS-CoV [65] and the 2012 outbreak of MERS-CoV [66], vaccines against coronaviruses infecting humans gained more attention [67]. Coronavirus vaccines were tested in both animal models as well as human subjects [67].

One 2004 study on ferrets given a vaccine against SARS-CoV-2 showed enhanced hepatitis [68]. Animal trials on four SARS vaccine candidates in ferrets demonstrated an initial protective period against infection, followed by hypersensitivity to rechallenge with SARS-CoV. The ferrets developed histopathological changes in the lungs induced from virus challenge after all four vaccine candidates, suggesting immune mediated damage [69]. One 2004 study on ferrets given a vaccine against SARS-

[2] Event classification available at:
https://rsc.niaid.nih.gov/sites/default/files/corrected-grading-table-v-2-1-with-all-changes-highlighted.pdf

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CoV-2 showed enhanced hepatitis [68]. Animal trials on four SARS vaccine candidates in ferrets demonstrated an initial protective period against infection, followed by hypersensitivity to rechallenge with SARS-CoV. The ferrets developed histopathological changes in the lungs induced from virus challenge after all four vaccine candidates, suggesting immune mediated damage [69].

Mice given an inactivated virus later developed a pro-inflammatory pulmonary response upon challenge [70]. Furthermore, anti-spike IgG antibodies, as are produced by all of the mRNA vaccines, in addition to most other Covid-19 vaccines, are demonstrated to cause severe acute lung injury on re-exposure to the virus, suggesting a negative impact of a narrow immune response [71]. MERS-CoV vaccines have been tested in mice and rhesus macaques [72], revealing protection without visible histopathologyMice given an inactivated virus later developed a pro-inflammatory pulmonary response upon challenge [70]. Furthermore, anti-spike IgG antibodies, as are produced by all of the mRNA vaccines, in addition to most other Covid-19 vaccines, are demonstrated to cause severe acute lung injury on re-exposure to the virus, suggesting a negative impact of a narrow immune response [71]. MERS-CoV vaccines have been tested in mice and rhesus macaques [72], revealing protection without visible histopathology

Immune mediated danger from vaccines has been widely acknowledged to be an extant issue in the development of coronavirus vaccines [73–79], and is supported by current evidence [80]. During the rapid development of Covid-19 vaccines, it was an issue of concern that sufficient long-term monitoring for antibody-dependent enhancement (AD) effects be put into place [81,82]. Unfortunately, as of this writing, there is not data available on the long term impacts of Covid-19 vaccines, including effects resulting from rechallenge with the virus. Immune mediated danger from vaccines has been widely acknowledged to be an extant issue in the development of coronavirus vaccines [73–79], and is supported by current evidence [80]. During the rapid development of Covid-19 vaccines, it was an issue of concern that sufficient long-term monitoring for antibody-dependent enhancement (AD) effects be put into place [81,82]. Unfortunately, as of this writing, there is not data available on the long term impacts of Covid-19 vaccines, including effects resulting from rechallenge with the virus.

Other, more distantly related coronaviruses have veterinary vaccines available. These have been summarized in a recent review [83]. Evidence of immune dependent enhancement was present for cell culture experiments on vaccination against feline coronaviruses [84–86]. Additionally, ADE is a concern for avian infectious bronchitis virus (IBV), a coronavirus [87,88]. In IBV, suboptimal vaccination alters the evolutionary dynamics of the viruses and can contribute to the production of escape mutants [89–91]. Finding broadly neutralizing IBV vaccines remains a significant challenge for the poultry industry [92–96].Other, more distantly related coronaviruses have veterinary vaccines available. These have been summarized in a recent review [83]. Evidence of immune dependent enhancement was present for cell culture experiments on vaccination against feline coronaviruses [84–86]. Additionally, ADE is a concern for avian infectious bronchitis virus (IBV), a coronavirus [87,88]. In IBV, suboptimal vaccination alters the evolutionary dynamics of the viruses and can contribute to the production of escape mutants [89–91]. Finding broadly neutralizing IBV vaccines remains a significant challenge for the poultry industry [92–96].

Early canine coronavirus vaccines were withdrawn due to neurological symptoms [97,98], though current vaccines do not carry the same safety issues [99,100]. [99,100]. Bovine coronavirus vaccinations often fail to provide immunity against subsequent reinfections [101–103]. Immunizations against transmissible gastroenteritis virus (TGEV) in swine have historically had issues in inducing immune protection [104,105], but are widely used now. Too frequent exposure to vaccine antigens can lower the immune response against TGEV [106]. Another swine coronavirus porcine epidemic diarrhea virus (PEDV) is widely used. Extant safety concerns are minor, and mostly deal with lack of efficacy; these are summarized in a review [107]. Bovine coronavirus vaccinations often fail to provide immunity against subsequent reinfections [101–103]. Immunizations against transmissible gastroenteritis virus (TGEV) in swine have historically had issues in inducing immune protection [104,105], but are widely used now. Too frequent exposure to vaccine antigens can lower the immune response against TGEV [106]. Another swine coronavirus porcine epidemic diarrhea

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virus (PEDV) is widely used. Extant safety concerns are minor, and mostly deal with lack of efficacy; these are summarized in a review [107].

Human trials of coronavirus vaccines have also taken place prior to the approval of Covid-19 vaccines. In addition to the endemic coronaviruses which infect humans, several epidemic strains of coronaviruses have occurred in the past two decades, namely the coronaviruses associated with severe acute respiratory syndrome (SARS-CoV) in 2003 [65] and middle eastern respiratory syndrome (MERS-CoV) in 2012 [108]. These outbreaks impelled the production of coronavirus vaccine candidates, summarized in a recent review [67] (Table 1). In total, before the development of the Covid-19 vaccines, data existed on a total of 179 human participants given a SARS or MERS vaccine candidate, of which, 7 (4±2%) experienced a serious adverse event (Table 1). A human trial of 63 adults for a MERS vaccine candidate showed no severe adverse events, but infections in 36% of participants [109,110]. Human trials of coronavirus vaccines have also taken place prior to the approval of Covid-19 vaccines. In addition to the endemic coronaviruses which infect humans, several epidemic strains of coronaviruses have occurred in the past two decades, namely the coronaviruses associated with severe acute respiratory syndrome (SARS-CoV) in 2003 [65] and middle eastern respiratory syndrome (MERS-CoV) in 2012 [108]. These outbreaks impelled the production of coronavirus vaccine candidates, summarized in a recent review [67] (Table 1). In total, before the development of the Covid-19 vaccines, data existed on a total of 179 human participants given a SARS or MERS vaccine candidate, of which, 7 (4±2%) experienced a serious adverse event (Table 1). A human trial of 63 adults for a MERS vaccine candidate showed no severe adverse events, but infections in 36% of participants [109,110].

Table 1. Summary of human trials of non-covid-19 coronavirus vaccines. Adapted from [67].

Platform	Vaccine	Group	Status	Severe adverse events	NCT ID	Study
SARS Vaccine Clinical Trials						
Inactivated virus	Inactivated SARS-CoV vaccine (ISCV)	Sinovac	Phase I, completed	[0/24, 0%]	No NCT ID	[111]
DNA vaccine	VRC-SRSDNA015-00-VP	NIAID	Phase I, completed	[0/9, 0%]	NCT00099463	[112]
MERS Vaccine Clinical Trials						
DNA vaccine	GLS-5300 (INO-4700)	GeneOne Life Science/Inovio Pharmaceuticals/International Vaccine Institute	Phase I, completed	[0/75, 0%] *Infections in 36% of participants	NCT02670187	[110]
DNA vaccine	GLS-5300 (INO-4700)	GeneOne Life Science/Inovio Pharmaceuticals/ International Vaccine Institute	Phase I/IIa, completed	No results available	NCT03721718	

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Platform	Vaccine	Group	Status	Severe adverse events	NCT ID	Study
Viral vector vaccine	MVA-MERS-S	CTC North GmbH & Co. KG	Phase I, completed	[0/23,0%]	NCT03615911	[113]
Viral vector vaccine	MVA-MERS-S_DF1	CTC North GmbH & Co. KG	Phase Ib, not yet recruiting	No data	NCT04119440	[114]
Viral vector vaccine	ChAdOx1 MERS	University of Oxford	Phase I, recruiting	[1/24, 4%]	NCT03399578	[115]
Viral vector vaccine	ChAdOx1 MERS	King Abdullah International Medical Research Center/University of Oxford	Phase I, recruiting	[6/24, 25%]	NCT04170829	[116]
Viral vector vaccine	BVRS-GamVac-Combi	Gamaleya Research Institute of Epidemiology and Microbiology/Acellena Contract Drug Research and Development	Phase I/II, recruiting	No data	NCT04128059	
Viral vector vaccine	BVRS-GamVac	Gamaleya Research Institute of Epidemiology and Microbiology	Phase I/II, recruiting	No data	NCT04130594	

Studies of coronavirus vaccines have a limited number of human participants and still represent a novel technique. The recent implementation of large-scale vaccination programs for Covid-19 has greatly increased the level of data available to assess the safety of human coronavirus vaccines.

2.6. Harms of RNA vaccination with SARS-CoV-2 spike (S) antigen

There is reason to believe that vaccines encoding the spike (S) protein of SARS-CoV-2 have additional mechanisms of harm, owing to the biological impacts of S protein specifically. There is a wide literature , and it is beyond the scope of this review to cover this in significant depth. However, the addition of spike protein adds another factor in assessing the complexity of RNA vaccines. The complexity, as well as uncertainties about possible harms, are non-trivial and cannot be dismissed based on current data. This section will briefly cover some of the hypothesized mechanisms of harm from spike protein encoding mRNA vaccines and the evidence for each from a clinical/epidemiological outlook as well as any mechanistic data from laboratory work.

Several observations have been made which contradict fundamental claims of RNA vaccine safety. For example, it was assumed that the RNA was relatively labile and transient in the cell. However, studies observe spike protein and vaccine mRNA up to 4 months post-injection [19,20]. Spike protein has been shown in laboratory settings to cause inflammation [117,118], vascular damage [119], and to act as a seed for amyloid formation [120].

3. Discussion

There is limited information to make a safety assessment of mRNA vaccines. In the category of mRNA vaccines, there are patient data for 385 patients. For mRNA vaccines against an infection, there was patient data for 285 patients. The rate of serious adverse events was 64 out of 385 for the

broad category of RNA vaccines (including cancer vaccines), or 17%; restricting the definition to vaccines against infection, the rate of SAEs is 41/285 or 14%. While high levels can be expected for trials of a novel technology where dosage levels must be determined (many of these trials are phase I) [121], these findings showcase the relative immaturity of mRNA vaccination as a strategy. high levels can be expected for trials of a novel technology where dosage levels must be determined (many of these trials are phase I) [121], these findings showcase the relative immaturity of mRNA vaccination as a strategy.

The key to the reactivity of mRNA vaccines is the fact that they express a foreign antigen, for which the antigen presenting cells are marked for destruction. While the lipid nanoparticle exhibits an acute inflammatory response by itself [122–124], the trials using LNPs so far have not found a large safety signal when using LNPs to deliver small molecules, non-expressing RNAs, or RNAs for endogenous proteins. [122–124], the trials using LNPs so far have not found a large safety signal when using LNPs to deliver small molecules, non-expressing RNAs, or RNAs for endogenous proteins.

In addition to there being harms attributable to the general immune response from an LNP-RNA delivery system, there are also some harms specific to the spike protein. Several of these mechanisms are supported by laboratory experiments and clinical findings but need more investigation. Medicine is replete with cases for which safety was assumed without adequate evidence at the time, which later regretfully led to loss of health and life. mRNA vaccines are demonstrating great unintended harms, and these harms demand further investigation into mechanism, which is important for identifying treatment modalities.

Novel biomedical technologies can bring relief to a wide variety of conditions and diseases. However, their use must take into consideration their possible harms. Here, we argue that the technology is novel enough that safety concerns in current and future products cannot be definitively ruled out, and further research must be performed to ensure their safety for current and future users. Considering the lack of data on the platform itself, we recommend a robust, independent and wide-ranging safety audit of mRNA-LNP formulations and call on regulators to hold manufacturers to high safety standards; especially for products used prophylactically in the general population.

Supplementary Materials: The following supporting information can be downloaded at the website of this paper posted on Preprints.org. Table S1: Safety profile of previous LNP-mRNA products.

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