

REVIEW



## Evaluating the relationship between myocarditis and mRNA vaccination

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### ABSTRACT

**Introduction:** Inflammatory conditions affecting the heart and surrounding tissues have been recently reported following mRNA vaccination. Evaluating trends in the epidemiology of these events and possible mechanisms related to vaccination will enhance vaccine safety surveillance and inform best practices for future vaccine campaigns.

**Areas covered:** Epidemiology of the burden of vaccine-associated myocarditis are reviewed. Key summaries of available data from public health advisory bodies and vaccine safety surveillance databases are critically reviewed. The possible biological pathways for vaccine-associated heart inflammations are introduced. A critical synthesis of available information to inform vaccine recommendations and best practices is provided. The citations were selected by the authors based on PubMed searches of the literature, national vaccine safety surveillance databases and summaries from national public health bodies.

**Expert opinion:** Myocarditis may be associated with vaccination, through several biological mechanisms. Studies have shown that live viral vaccinations can act as a trigger for hypersensitivity inflammatory reactions, but further work is required to examine how the mRNA formulation may induce these autoimmune responses. Given that the risk of these adverse events is low, and the benefit of protection against disease is so great, the receipt of mRNA vaccines is recommended.

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## 1. Introduction

Surveillance and assessment of adverse events following immunization is crucial for ongoing safety monitoring of vaccines. This informs best practices for clinicians, recommendations from national health advisory bodies, and expands public knowledge about vaccine safety. Public acceptance and trust in vaccine safety is important for the success of any vaccination campaign. Recent reports have arisen of inflammatory conditions affecting the heart and surrounding tissues following the administration of mRNA vaccines against SARS-Cov-2. We will review the existing data concerning the association between these adverse events and mRNA vaccines, discuss the biological precedent for this association, and provide a critical synthesis of the literature to support an opinion of the use of mRNA vaccines.

### 1.1. Methodology

The references that were selected were those based on literature searches of the PubMed database (National Library of Medicine) and key surveillance bulletins from national public health agencies, advisory bodies, and vaccine safety databases to provide evidence to support the statements made in this narrative review.

### 1.2. Epidemiology of illness myocarditis/pericarditis following mRNA vaccines

Myocarditis is an inflammation of the heart muscle, characterized by chest pain, shortness of breath and arrhythmia [1,2]. Pericarditis, inflammation of the lining of the heart, presents with chest pain as the primary complaint [3,4] (thereafter, both conditions will be referred to by myocarditis). Myocarditis is most commonly triggered by viral infections such as Parvovirus B19, Human Herpes Virus, and Coxsackie virus which lead to an inflammatory response in the host; however, less common etiologies include exposure to other pathogens, or hypersensitivity reactions to drugs [1,2]. Both conditions have been implicated as adverse events following vaccinations [5–14]. While the clinical presentation may vary, and prognosis differ based on severity of symptoms, most cases tend to be mild and respond well to clinical management [1–4].

Cases of inflammatory heart conditions following administration of mRNA vaccines against SARS-Cov-2 have recently been reported internationally, with the highest burden observed in the United States [6,15–22]. Most cases have typically been mild, with patients' primary complaint being chest pain. Reports have been predominantly within days of vaccination, more common among younger males and more frequently reported following a second dose of the vaccine [15–19,21–25]. Consistently, all patients hospitalized with

**Article highlights**

- Myocarditis associated with the receipt of COVID-19 mRNA vaccines has been documented, with the greatest risks in young adult males and following the administration of a second dose
- While the observed numbers of myocarditis exceed expected event rates, it remains a very rare adverse events, with most cases being mild and resolved without complications
- The mechanisms by which mRNA vaccines trigger myocarditis are not well understood, but may be attributable to the antagonization of cardiomyocytes by the SARS-Cov-2 virus, or by autoimmune antibodies generated by the host which provoke hypersensitive inflammatory reactions

Despite the increased risk of myocarditis subsequent to vaccination, the risk of acute myocardial injury during the course of natural COVID-19 infection is substantially higher, which is important for assessing the vaccine benefit-risk profile

mRNA-associated myocarditis have been discharged in stable condition and responded well to clinical management, resolving the episode [15–27].

An early case review of six patients in Israel found that all patients presented with chest pain, five presented 24–72 hours following the second dose of Pfizer-BioNTech mRNA vaccine, and the sixth presented 16 days following their first dose (28). All patients had abnormal electrocardiograms, elevated C-reactive protein and troponin levels, indicative of heart inflammation. The authors conducted an observed to expected case analysis using the background rate of myocarditis during winter months in their hospital, finding a mean of 1.17 cases per month (range 0–3). As such, the presentation of 6 patients with the event within a single month far exceeded expected cases, although the chi-squared statistic was not significantly different.

A review of seven healthy adolescent males who developed acute myocarditis within four days of a second dose of the Pfizer-BioNTech COVID-19 vaccine found chest pain to be the primary complaint, with no indication of serious condition or multisystem inflammatory syndrome [19]. This study rigorously investigated alternate infectious etiologies for myocarditis, including a full respiratory pathogen panel by RT-PCR. Consistent with other reports, patients in this case series all had elevated troponin levels [23].

A case series of previously-healthy United States military service members found that 23 males presented with chest pain within four days of immunization with an mRNA COVID-19 vaccine [26]. Of these, seven patients had received the Pfizer-BioNTech vaccine, and 16 received Moderna mRNA-1273. Patients had a median age of 25 (range: 20–51), 20 presented following a second dose of vaccine, as compared to three reports after a first dose. Interestingly, the three patients reporting symptoms after a first dose all had a confirmed COVID-19 infection more than 2-months prior to the receipt of the vaccine. All patients had elevated cardiac troponin levels, and all who underwent diagnostic imaging had findings indicative of myocarditis. Alternate etiologies including viral triggers, autoimmune disease or other hypoxic condition were ruled out. All patient symptoms were resolved within one week or responding well at the time of the study's

publication. Based on a US background incidence rate of 1–10 cases per 100,000 person years within a 30-day risk window, the study found that observed numbers of myocarditis were higher than expected numbers, particularly in second doses administered to military males [26].

In the United States, a total of 1,226 myocarditis events following ~300 million mRNA vaccine doses administered have been reported to the Vaccine Adverse Events Reporting System as of 11 June 2021 (VAERS) [16,20,25,27]. This database is a spontaneous reporting system managed by the Centers for Disease Control and Prevention and the Food and Drug Administration. Based on VAERS data, there were reports of approximately 40.6 cases of myocarditis per million second doses among males and 4.2 cases per million among females have been reported as of 11 June 2021 in persons 12–29 years of age who received the mRNA COVID-19 vaccines. For persons over 30 years of age, the reporting rates were 2.4 and 1.0 per million second doses, respectively, for males and females [20]. Of 1,226 events reported between 29 December 2020 and 11 June 2021, the median age was 26 years (12–94 years) and median days before symptom onset was 3 (0–179) [16,25]. A rapid analysis by the CDC analyzes cases meeting the CDC case definition of myocarditis by chart review. Of 323 patients meeting the case criteria, the median age was 19 years (12–29 years), and significantly more males (291 males as compared to 32 females,  $p < 0.001$ ). 92% of patients presented with symptom onset within seven days following vaccination, and of those with known outcomes, 95% had been mild, resolved and discharged at the time of review. There were no observed deaths.

The CDC COVID-19 Vaccine Task Force conducted preliminary analyses of vaccine safety data using observed to expected analyses of the background rates of myocarditis. Predominantly, younger males experienced a greater number of events than females, and more so following the second dose of vaccination, consistent with other reports (Tables 1 and 2). Analysis of the observed number of events in comparison to background rates found the number of reports exceeded the expected distribution in males aged 12–29 following the first dose, and in both sexes following a second dose, between the ages of 12 and 49 (Tables 1 and 2). Crude reporting rates, per million doses, were highest in males aged 12–17 years following the second dose (66.7 events). Events reported in males were consistently higher than those reported for females, across age groups and doses. Further analysis by the CDC compared outcome events in the 21-day risk window after either dose with the rate of events in vaccinated comparators on the same calendar days. This evaluation found an adjusted rate ratio of 1.07 events (95% CI: 0.70–1.67), after adjusting for site, age strata, sex, ethnicity and calendar date. Given the inconclusive confidence interval, no signal was determined by the CDC [25]. Overall, the data suggest that more cases of myocarditis occur after a second dose, occur more frequently in males, and that clustering of symptom onset appears within the week following vaccination.

In Ontario, data on cardiac injury and inflammatory conditions following vaccination are required to be reported to Public Health Ontario and the Public Health Agency of Canada. Within Public Health Ontario's vaccine adverse events reporting system,

**Table 1.** Reports of myocarditis to VAERS following a first dose mRNA vaccination which exceeded the expected numbers of events †.

Age (yrs)	Using a 21-day risk window			Using a 7-day risk window		
	Doses administered	Expected	Observed	Doses administered	Expected	Observed
12–17	3,569,239	2–21	32	3,569,239	1–7	27
18–24	5,863,268	3–34	47	5,863,268	1–11	41
25–29	-	-	-	4,685,036	1–9	14

† table includes only males

Based on Gubernot et al. U.S. Population-Based background incidence rates of medical conditions for use in safety assessment of COVID-19 vaccines. *Vaccine*. 14 May 2021;50264-410X(21)00578–8. Expected counts among females 12–29 years adjusted for lower prevalence relative to males by factor of 1.7 (Fairweather, D. et al, *Curr Probl Cardiol*. 2013;38(1):7–46).**Table 2.** Reports of myocarditis to VAERS following a second dose mRNA vaccination which exceeded the expected numbers of events.

	Age (yrs)	Using a 21-day risk window			Using a 7-day risk window		
		Doses administered	Expected	Observed	Doses administered	Expected	Observed
Females	12–17	2,189,726	1–7	20	2,189,726	0–2	19
	18–24	5,237,262	2–18	27	5,237,262	1–6	23
	25–29	-	-	-	4,151,975	0–5	7
Males	12–17	2,039,871	1–12	132	2,039,871	0–4	128
	18–24	4,337,287	2–25	233	4,337,287	1–8	219
	25–29	3,625,574	2–21	69	3,625,574	1–7	59
	30–39	8,311,301	5–48	71	8,311,301	2–16	61
	40–49	-	-	-	8,577,766	2–16	34

Based on Gubernot et al. U.S. Population-Based background incidence rates of medical conditions for use in safety assessment of COVID-19 vaccines. *Vaccine*. 14 May 2021;50264-410X(21)00578–8. Expected counts among females 12–29 years adjusted for lower prevalence relative to males by factor of 1.7 (Fairweather, D. et al, *Curr Probl Cardiol*. 2013;38(1):7–46).

a total of 74 reports of myocarditis have been received between 13 December 2020 and 3 July 2021 [18]. Of these, 46 (62%) occurred following the Pfizer-BioNTech vaccine, whereas 28 (38%) were reported following Moderna vaccine. Events reported after the first dose were predominantly related to the Pfizer vaccine, whereas events reported following the second dose were more frequently related to Moderna (first dose: 32 events with Pfizer vaccine, 4 with Moderna; second dose: 14 events with Pfizer, 24 with Moderna). The reporting rate of acute cardiovascular injury (per 100,000 doses administered in Ontario between 13 December 2020 and 3 July 2021) was 0.6 for the Pfizer vaccine and 0.9 for the Moderna vaccine [17,18]. As of July 2<sup>nd</sup>, the Public Health Agency of Canada had received 70 reports of myocarditis following the Pfizer vaccine, and 26 reports following the Moderna vaccine – corresponding to reporting rates of 0.28 and 0.34 per 100,000 doses administered, respectively [24].

Despite accumulating data supporting the association between vaccination and inflammatory adverse reactions, national advisory bodies including the CDC, WHO Global Advisory Committee on Vaccine Safety, the Pharmacovigilance Risk Assessment Committee (PRAC) of the European Medicines Agency (EMA), and the Advisory Committee on Immunization Practice (ACIP) and the National Advisory Committee on Immunization (NACI) continue to recommend continued administration of mRNA vaccines. The benefits of preventing hospital admissions and deaths associated with COVID-19 infections continue to outweigh the potential risk of developing mild myocarditis, in all populations for which the vaccine is indicated. A benefit-risk assessment undertaken by ACIP found that per million second doses of mRNA vaccine administered in the highest risk group for myocarditis (males aged 12–29 years), a total of 11,000 cases of COVID-19 could be prevented, including 560 hospitalizations and 138 intensive care admissions [16]. The potential harms associated with these vaccinations may be 39–47

expected cases of myocarditis. It is important to note that the long-term cardiac implications of acute myocardial injury, especially when incurred at a young age, are not well known. A meta-analysis of cohort studies of suspected myocarditis in the presence of both viral infection and virus-negative patients found no significant differences in prognosis in terms of all-cause death, heart transplant, or re-hospitalization due to fatal arrhythmia and heart failure [28]. Observational studies assessing myocardial injury following COVID-19 infections found that persistent inflammation and regional fibrosis are common findings in patients recovered from viral myocarditis, and is associated with adverse outcomes [29–34]. In a study which evaluated patients 3 months following viral myocarditis, persistent inflammation was observed in 58% of cases, confirmed by biopsy [31]. Of note, adverse events were significantly more likely in patients who presented with left ventricle dysfunction, which may serve as an important predictor of prognosis [33,35,36]. Regardless of clinical symptoms at presentation, a study of 222 patients with biopsy-confirmed viral myocarditis found that late gadolinium enhancement (LGE) was a strong predictor of all-cause mortality and cardiac mortality (HR: 8.4,  $p = 0.004$ ; and HR: 12.8,  $p < 0.01$  respectively (confidence intervals not reported)) [32]. The importance of late gadolinium enhancement is demonstrated in another study of 670 patients with viral myocarditis, followed up for almost five years, which demonstrated that LGE significantly modified the risk of future cardiovascular adverse outcomes [30].

Despite the growing evidence for incomplete recovery from post-viral autoimmune dysfunction [1,28,36–39], the long-term sequelae of vaccine-driven myocarditis are less clear [14,26,40,41]. One study using large cohort data demonstrated that viral infection is associated with a much greater risk of myocarditis, as compared to vaccine-induced myocarditis [42]. This study found that Pfizer mRNA vaccination was associated with a 3-fold increase in the relative risk of

myocarditis, whereas natural infection by COVID-19 was associated with an 18-fold risk increase, which has profound implications for the benefit-risk ratio. Importantly, this study found that the highest incidence of myocarditis (10.69 cases per 100,000 persons; 95% CI, 6.93 to 14.46) was observed in males between the ages of 16 to 29 years, which mitigates some of the concerns surrounding vaccine administration to children  $\leq 18$ . Moreover, no other vaccine formulation which may be indicated in adolescent age groups appears to be readily available for use. Vaccination of children and adolescents by vaccination may be an important factor for reducing community transmission, minimizing the susceptible population to infection and reducing the opportunities for emergent variants to circulate and evolve [43,44].

The majority of myocarditis cases observed were described as mild (76%), and another 22% described as moderate in severity [41,42]. These findings are consistent with those described in another study evaluating the same vaccine and population catchment, which found 95% of myocarditis cases subsequent to Pfizer vaccination were mild [45]. These large cohort studies of the Pfizer vaccine, administered in Israel, found that in 2.5–5 million vaccinated people, 54–136 developed myocarditis. The overall risk difference between doses as 1.76 per 100,000 persons (95% confidence interval [CI], 1.33 to 2.19), suggesting that in general, administration of a second dose significantly increased the risk of myocarditis [45]. Of note, the greatest difference in risk between the first and second doses occurred in males aged 16–19 (difference, 13.73 per 100,000 persons; 95% CI, 8.11 to 19.46). One identified case was fulminant and fatal. A case report of two other cases of fulminant myocarditis following Pfizer vaccination found them characterized by systemic hyperinflammatory syndrome, very high ferritin, macrophage activation syndrome, and requiring oxygen support [46]. These cases rapidly progressed into multiorgan failure and shock, requiring mechanical cardiac support and immunosuppressive intervention to resolve. While the authors note that these are abnormally severe manifestations of disease, it remains important to consider the possible increased risks of myocardial injury related to systemic hyperinflammatory responses.

### 1.3. Epidemiology of myocarditis following other vaccinations

While myocarditis is generally an uncommon reaction to vaccination, a causal association has been found in adults receiving smallpox vaccine [5,7,8,10–14,47]. The mechanism by which the smallpox vaccine induces myocarditis is thought to be due to the infectious agent of the vaccine, that is vaccinia virus, which is live attenuated in this formulation to induce an immune response. Live attenuated vaccines are known to be more reactogenic, but this formulation differs in all aspects from the current mRNA-composed vaccines. A retrospective study of the passive surveillance Vaccine Safety Datalink in the United States examined adults who received live viral vaccines (measles-mumps-rubella vaccine, varicella vaccine, oral polio vaccine, or yellow fever vaccine) between 1996 and 2007 for

their potential association with myocarditis [8]. Of 416,629 vaccinees and a 42-day risk window, this study found 72 cases of chart-confirmed myocarditis or pericarditis. Of these, the majority of myocarditis cases were among 18–29 year-olds, and both events predominated in males (myocarditis: 79% male; pericarditis: 69% male). Upon further review by a cardiology nurse and physician, a total of 8 definitive cases were identified as myocarditis within the 42-day risk window. A self-controlled risk interval analysis found the increased risk to be 0.57 (0.07–4.51) for developing myocarditis within six weeks of live viral vaccination in adults [8]. This risk is significantly lower than the observed events following smallpox vaccination, suggesting that live vaccination itself may not be the trigger of cardiac symptoms, but perhaps the host-pathogen interaction may be implicated.

A prospective study examined the incidence of new onset cardiac symptoms following smallpox and trivalent inactivated influenza vaccination in military service members [5]. This study found that healthy unvaccinated active-duty service members experienced myocarditis at a rate of 2.6 (1.9, 2.34) events per 100,000. In smallpox-vaccinated service members, the rate of myocarditis was 7.46 (6.89, 8.48) per 100,000, corresponding to a relative risk difference of 16.11 in the vaccinated group. Individuals vaccinated against smallpox were significantly more likely to experience new onset and severe cardiac symptoms ( $p < 0.001$  for both). The relative risk of experiencing new onset chest pain was 5.1 (1.7–15.9) in smallpox vaccinees, as compared to influenza vaccinees. Relative risks of any new symptoms or severe cardiac symptoms in smallpox vaccinees were 4.0 (1.7–9.3) and 5.5 (1.9–17.5) respectively, both significant at  $p < 0.001$ . The incidence rate of vaccinia-associated myocarditis was found to be 463 per 100,000 (150–1079). The peak inflammatory period of reactogenicity occurred between 4 and 27 days post-vaccination, with most occurring on days 8–9. Inflammatory responses provoked by the vaccine were characterized by elevated IFN- $\gamma$ , TNF- $\alpha$ , IL-10 and IL-6 cytokine expression and activity. The rise in cytokine levels was observed to correlated with rising troponin levels indicative of acute heart injury, and presentation of clinical symptoms, suggesting that the pro-inflammatory cytokines may be associated [5].

An analysis of the VAERS surveillance database between 2011 and 2015 found 199 cases of myocarditis reported following immunizations [6]. Of these, 149 were attributable to smallpox vaccine. The remaining 50 cases were reported after human papillomavirus, meningitis, hepatitis A and influenza vaccines. Main reported symptoms were chest pain, allergic reactions and fever. In children aged  $< 18$  years, a statistically significant difference in reporting odds ratio was found for meningococcal vaccines (ROR: 3.55, 1.23–10.24). In adults, significant differences existed in reporting odds ratios of typhoid vaccine (ROR: 11.13, 7.73–16.03), Japanese encephalitis vaccine (ROR: 8.54, 2.7–27.01), anthrax (ROR: 25.5, 18.8–34.5) and smallpox vaccine (ROR: 71.88, 49.25–104.89). Based on this analysis, the CDC recommends continued monitoring of these signals [6].

## 2. Pathways /mechanisms of action

SARS-Cov-2 has been shown to be a highly tropic virus, able to invade and replicate within numerous cell types. The virus, responsible for COVID-19 disease, enters via the cell-surface receptor called angiotensin-converting enzyme 2 (ACE2) [48–50]. Coronaviruses are the only family of viruses which use ACE2 as a site of binding and viral entry [49]. ACE2 is an essential regulator of heart function, with impacts on myocardial contractility, antihypertrophic function, and blood pressure regulation [51–55]. ACE2 is known to be present in almost all human organs, which is proposed to influence the high tissue tropism of the virus. A study on tissue distribution of ACE2 protein found ACE2 present in endothelial cells from all arteries and veins in the tissues examined, and found high localization of the protein in arterial smooth muscle cells [50]. Studies have proposed that the high presence of ACE2 in heart tissues may lead to the exacerbation of underlying cardiac pathologies by SARS-Cov-2 infection [38,39,50]. The encoded viral surface spike protein of the mRNA vaccine, which triggers the immune response, may interact with ACE2 receptors in the host, increasing the likelihood of cardiac sensitivity or inflammatory reactions [38,39]. An potential avenue for vaccine-associated myocarditis may be a nonspecific innate inflammatory immune response, or perhaps an interaction between the encoded viral spike protein of the mRNA and an as-yet undetermined cardiac protein [21,56]. Studies have hypothesized that the antibodies generated in response to the mRNA spike protein may react with surface antibodies of the cardiomyocytes of susceptible hosts, provoking an inflammatory reaction and associated tissue damage [21,57]. Possible host genetic factors in ACE2 receptors, which vary across ethnic groups, may drive increased susceptibility to aggravated cardiovascular symptoms or the development of an inflammatory response triggering symptom onset [39,52,58].

Severe clinical manifestation of COVID-19 is characterized by the hyperactive inflammatory immune response known as a ‘cytokine storm.’ This cytokine storm causes tissue damage and activation of the coagulation cascade, increasing an individual’s risk of cardiac distress, thromboembolic events, and myocardial injury [59–61]. It is possible that the surface spike protein of SARS-Cov-2, which serves as the target for immunogenicity encoded by the mRNA vaccine, may induce immune cross-reactivity by molecular mimicry of live virus infection [56]. Molecular mimicry is a phenomenon in which there are shared peptide sequences between the immunogens of the vaccine and those naturally present in human cells. This leads to cross-activation of adaptive immune responses, leading to autoreactivity [37,56,62]. The engagement of the host inflammatory response is a crucial step of innate immune defenses against viral infection [59,60]. However, when cells are not capable of distinguishing between foreign and self-peptides, the pro-inflammatory cytokine reaction becomes dysregulated, causing immune damage to the host. The presentation of symptoms within days of receiving a second dose of mRNA vaccination suggest an immune mediated reaction in the host [56]. It is possible that genetic factors regulating the inflammasome activation,

or interferon-signaling cascade, may contribute to an individual’s risk of developing the cytokine storm responsible for triggering auto-reactive cell activity after exposure to the mRNA vaccine [58,61,63]. Heart-reactive auto-antibodies have been reported at elevated levels in patients with myocarditis [2,57,64]. These antibodies may target multiple antigens, possibly having functional effects on cardiac myocytes and contributing to the pathogenesis of vaccine-induced myocarditis.

## 3. Summary

Current evidence suggests a probably causal association between inflammatory heart conditions and the receipt of mRNA vaccines. Our review of available patient data suggest a potential hypersensitivity reaction may be linked to host autoimmune mechanisms, or exacerbations of cardiomyocyte cell function by the encoded mRNA spike protein.

In light of available data, national health advisory bodies maintain that the benefits of mRNA vaccination against COVID-19 continue to outweigh the risks of potential adverse events following immunization and hospitalizations attributable to the disease.

Existing data is predicated on pilot studies or spontaneous reporting systems; there is a lack of robust methodological investigation of this association. Further study to determine the strength of this signal and long-term prognosis is warranted.

## 4. Expert opinion

Further research on the association between mRNA vaccination and inflammatory cardiac reactions is necessary. Upon consideration of the existing evidence and possible causal mechanisms, we believe this signal to be a real association which merits further surveillance through longitudinal post-marketing studies. A key question which remains concerns optimal dosing schedules, particularly in individuals at high risk for an inflammatory or hypersensitivity reaction. To answer this question, as well as investigate the causal link between myocarditis and mRNA vaccination, continued surveillance efforts will be needed, as well as global capacity building in vaccine safety surveillance to ensure comprehensive epidemiological data. Further study to investigate the mechanism by which mRNA vaccination interacts with the cells of the cardiac and immune systems. A greater understanding of this process would improve recommendations for vaccination in individuals considered high risk, and an enhanced safety profile of the vaccine and its future uses. Mechanistic research which investigates the pathophysiology of mRNA-associated myocarditis would have meaningful implications for best clinical practices, and on the development of mRNA technologies for future candidate vaccines.

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## Author contributions

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