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COVID-19 mRNA Vaccines: Lessons Learned from the Registrational Trials and Global Vaccination Campaign

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M. Nathaniel Mead [1], Stephanie Seneff [2], Russ Wolfinger [3], Jessica Rose [4], Kris Denhaerynck [5], Steve Kirsch [6], Peter A. McCullough [7, 8]

1. Biology and Nutritional Epidemiology, Independent Research, Copper Hill, USA 2. Computer Science and Artificial Intelligence Laboratory, Massachusetts Institute of Technology, Cambridge, USA 3. Biostatistics and Epidemiology, Independent Research, Research Triangle Park, USA 4. Immunology and Public Health Research, Independent Research, Ottawa, CAN 5. Epidemiology and Biostatistics, Independent Research, Basel, CHE 6. Data Science, Independent Research, Los Angeles, USA 7. Cardiology, Epidemiology, and Public Health, McCullough Foundation, Dallas, USA 8. Cardiology, Epidemiology, and Public Health, Truth for Health Foundation, Tucson, USA

Corresponding author: M. Nathaniel Mead, mead33@me.com

Abstract

Our understanding of COVID-19 vaccinations and their impact on health and mortality has evolved substantially since the first vaccine rollouts. Published reports from the original randomized phase 3 trials concluded that the COVID-19 mRNA vaccines could greatly reduce COVID-19 symptoms. In the interim, problems with the methods, execution, and reporting of these pivotal trials have emerged. Re-analysis of the Pfizer trial data identified statistically significant increases in serious adverse events (SAEs) in the vaccine group. Numerous SAEs were identified following the Emergency Use Authorization (EUA), including death, cancer, cardiac events, and various autoimmune, hematological, reproductive, and neurological disorders. Furthermore, these products never underwent adequate safety and toxicological testing in accordance with previously established scientific standards. Among the other major topics addressed in this narrative review are the published analyses of serious harms to humans, quality control issues and process-related impurities, mechanisms underlying adverse events (AEs), the immunologic basis for vaccine inefficacy, and concerning mortality trends based on the registrational trial data. The risk-benefit imbalance substantiated by the evidence to date contraindicates further booster injections and suggests that, at a minimum, the mRNA injections should be removed from the childhood immunization program until proper safety and toxicological studies are conducted. Federal agency approval of the COVID-19 mRNA vaccines on a blanket-coverage population-wide basis had no support from an honest assessment of all relevant registrational data and commensurate consideration of risks versus benefits. Given the extensive, well-documented SAEs and unacceptably high harm-to-reward ratio, we urge governments to endorse a global moratorium on the modified mRNA products until all relevant questions pertaining to causality, residual DNA, and aberrant protein production are answered.

Categories: Public Health, Epidemiology/Public Health, Infectious Disease
Keywords: sars-cov-2 (severe acute respiratory syndrome coronavirus -2), risk-benefit assessment, cardiovascular, autoimmune, mortality, gene therapy products, serious adverse events, immunity, registrational trials, covid-19 mrna vaccines

Introduction And Background

Our understanding of coronavirus disease 2019 (COVID-19) mRNA vaccinations and their impact on mortality has evolved substantially since the first vaccine rollouts in December 2020. Early investigations indicated the potential of these biologicals for preventing severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection. Based on the first randomized controlled trials sponsored by Pfizer-BioNTech ((New York, United States (US); Mainz, Germany) and Moderna Inc. (Massachusetts, US), researchers concluded that there was a noteworthy 95% relative risk (RR) reduction of symptomatic COVID-19 [1,2]. The overlapping finding between the two trials prompted the US Food and Drug Administration (FDA) to allow the use of the COVID-19 mRNA vaccines under Emergency Use Authorization (EUA) on December 11, 2020, a decision that was followed by early unblinding and cessation of the trials [3].

Prior to the rapid authorization process, no vaccine had been permitted for market release without undergoing a testing period of at least four years, the record set by Merck & Co., Inc. (New Jersey, US) in 1967 with the development of the world's first mumps vaccine [4]. Pfizer's vaccine (BNT162b2) completed the process in seven months. Previous timeframes for phase 3 trial testing averaged 10 years [5]. Health departments have stated that 10-15 years is the normal timeframe for evaluating vaccine safety [6]. With the COVID-19 vaccines, safety was never assessed in a manner commensurate with previously established scientific standards, as numerous safety testing and toxicology protocols typically followed by the FDA were sidestepped [7,8]. Preclinical studies of the mRNA product's biodistribution and potential toxicities from repeated doses (to mimic multiple vaccinations), were circumvented to enable accelerated clinical testing

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[9]. Perhaps the most important trial benchmark obviated by the rapid authorization process was the minimum 6-12 month observation period typically recommended for identifying possible longer-term vaccine-related adverse effects (AEs) in the vaccine versus placebo groups [9].

The previously established 10-15-year timeframe for clinical evaluation of vaccines was deemed necessary to ensure adequate time for monitoring the development of AEs such as cancers and autoimmune disorders [10,11]. To be expeditious, the coordinators of Pfizer and Moderna trials prioritized symptomatic COVID-19 risk reduction over severe AEs and mortality concerns. In retrospect, this was a grave misstep. Historical accounts bear witness to instances where vaccines were prematurely introduced to the market under immense pressure, only to reveal disabling or even fatal AEs later on. Examples include the 1955 contamination of polio vaccines, instances of Guillain-Barré syndrome observed in flu vaccine recipients in 1976, and the connection between narcolepsy and a specific flu vaccine in 2009 [12-14]. Against this backdrop, it is not surprising that so many medical and public health experts voiced concerns about the COVID-19 mRNA vaccines bypassing the normal safety testing process [15-17].

Political and financial incentives may have played a key role in undermining the scientific evaluation process leading up to the EUA. Lalani and colleagues documented the major investments made by the US government well before authorization [18]. Even prior to the pandemic, the US National Institutes of Health invested $116 million (35%) in mRNA vaccine technology, the Biomedical Advanced Research and Development Authority (BARDA) had invested $148 million (44%), while the Department of Defense (DOD) contributed $72 million (21%) to mRNA vaccine development. BARDA and the DOD also collaborated closely in the co-development of Moderna's mRNA vaccine, dedicating over $18 billion, which included guaranteed vaccine purchases [18]. This entailed pre-purchasing hundreds of millions of mRNA vaccine doses, alongside direct financial support for the clinical trials and the expansion of Moderna's manufacturing capabilities. The public funding provided for developing these products through Operation Warp Speed surpassed investments in any prior public initiative [19]. Once the pandemic began, $29.2 billion (92% of which came from US public funds) was dedicated to the purchase of COVID-19 mRNA products; another $2.2 billion (7%) was channelled into supporting clinical trials, and $108 million (less than 1%) was allocated for manufacturing and basic research [18]. This profuse spending of taxpayer dollars continued throughout the pandemic: BARDA spent another $40 billion in 2021 alone [20].

Using US taxpayer money to purchase so many doses in advance would suggest that, prior to the EUA process, US federal agencies were strongly biased toward successful outcomes for the registrational trials. Moreover, it is reasonable to surmise that such extensive vested interests could have influenced the decision to prematurely halt the registrational trials. Unblinding essentially nullified the "placebo-controlled" element of the trials, eliminating the control group and thus undermining the ability to objectively assess the mRNA vaccines' safety profile and potential serious AEs (SAEs). Thus, while the accelerated authorization showcased the government's dedication to provide these novel products, it also raised concerns among many experts regarding risk-benefit issues and effectively eliminated the opportunity to learn about the potential long-range harms of the mRNA inoculations. The political pressures to rapidly deliver a solution may have compromised the thoroughness and integrity of the scientific evaluation process while downplaying and obfuscating scientific concerns about the potential risks associated with mRNA technology.

Concerns about inadequate safety testing extend beyond the usual regulatory approval standards and practices. Although we employ the terms "vaccine" and "vaccination" throughout this paper, the COVID-19 mRNA products are also accurately termed gene therapy products (GTPs) because, in essence, this was a case of GTP technology being applied to vaccination [21]. European regulations mandate the inclusion of an antigen in vaccines, but these immunogenic proteins are not intrinsic to the mRNA vaccines [22]. The GTP vaccine platform has been studied for over 30 years as an experimental cancer treatment, with the terms gene therapy and mRNA vaccination often used interchangeably [23]. This is due to the mRNA products' specific mode of action: synthetic mRNA strands, encapsulated within a protective lipid nanoparticle (LNP) vehicle, are translated within the cells into a specific protein that subsequently stimulates the immune system against a specific disease. Another accurate label would be prodrugs because these products stimulate the recipient's body to manufacture the target protein [24]. As there were no specific regulations at the time of the rapid approval process, regulatory agencies quickly "adapted" the products, generalized the definition of "vaccine" to accommodate them, and then authorized them for EUA for the first time ever against a viral disease. However, the rationale for regulating these products as vaccines and excluding them from regulatory oversight as GTPs lacks both scientific and ethical justification [21]. (Note: Throughout this review, the terms vaccines and vaccinations will be used interchangeably with injections, inoculations, biologicals, or simply, products.)

Due to the GTPs' reclassification as vaccines, none of their components have been thoroughly evaluated for safety. The main concern, in a nutshell, is that the COVID-19 mRNA products may transform body cells into viral protein factories that have no off-switch (i.e., no built-in mechanism to stop or regulate such proliferation), with the spike protein (S-protein) being generated for prolonged periods, causing chronic, systemic inflammation and immune dysfunction [25,26]. This S-protein is the common denominator between the coronavirus and the vaccine, which helps to explain the frequent overlap in AEs generated by both the infection and the inoculation [25]. The vaccine-induced S-protein is more immunogenic than its

viral counterpart; and yet, the increased antibody production is also associated with more severe immunopathology and other adverse effects [27]. The Pfizer and Moderna mRNA products contain mRNA with two modified codons that result in a version of the S-protein that is stabilized in its prefusion state [28]. This nucleoside-modified messenger RNA technology is intended to extend the synthetic mRNA's persistence in the body. When the S-protein enters the bloodstream and disseminates systemically, it may become a contributing factor to diverse AEs in susceptible individuals [25].

In this narrative review, we revisit the registrational trials and review analyses of the AEs from these trials and other relevant studies. Most of the revelations have only recently come to light, due to the past few years of extensive censorship of healthcare professionals and research scientists who challenged the prevailing narrative set forth by the vaccine enterprise [29,30]. We begin with a focus on the two randomized double-blind placebo-controlled trials that resulted in the EUA, followed by an in-depth exploration of the various adverse impacts of the mRNA inoculations, with frequent reference to the original trials. In a post-pandemic context in which the immediate urgency has subsided, exploratory narrative reviews such as this can play an important role in helping us reevaluate the scientific basis for the general public's well-founded safety concerns regarding the COVID-19 mRNA vaccinations.

Review

Revisiting the registrational trials

Early in the pandemic, US public health officials promised that the phase 3 trials would prove the COVID-19 mRNA vaccines were "safe and effective", including a reduction in severe disease, hospitalization, and death, with a secondary endpoint of preventing transmission and infection [31]. Nine vaccine manufacturers issued an unprecedented joint statement pledging not to prematurely seek regulatory review [32]. Both sets of assurances were delivered to a population already suffering from pandemic fatigue, mostly attributable to lockdowns, masking, social distancing, and other restrictions imposed by the same agencies responsible for ushering in the vaccination program. Despite the rhetoric, no large randomized double-blind placebo-controlled trials have ever demonstrated reductions in SARS-CoV-2 transmission, hospitalization, or death.

Importantly, the study designs for the pivotal trials that led to the EUA were never intended to determine whether the mRNA inoculations could help prevent severe disease or premature death [31]. This was mainly due to insufficient statistical power for assessing these outcomes [33]. (The power calculation was based solely on the reduction of COVID-19 symptoms, the primary outcome.) The limitation stemmed from the recruitment of young, healthy trial participants in the 18-55-year age group and the relatively low number of reported clinical infection cases in the intervention arms of the trials, with only eight cases in Pfizer and 11 in Moderna [1,2]. Whereas Pfizer's trial recorded just one instance of severe COVID-19, Moderna's trial reported none, leading the company to proclaim 100% efficacy against severe illness [34]. Moderna also reported one COVID-19 death, in the placebo group [2]. Thus, between the two trials, there was only one death attributed to COVID-19 among the more than 73,000 trial participants [1,2].

After announcing the trial's results, Pfizer extended its study by four months. Trial participants were unblinded by week 20, and placebo volunteers were invited to receive the mRNA vaccination. Pfizer's announcement of the efficacy of its mRNA product was based on 162 out of 22,000 placebo recipients contracting COVID-19, compared to only eight out of 22,000 vaccine recipients. None of the 162 placebo recipients who contracted COVID-19 died from the disease [35]. These numbers are too small to draw meaningful, pragmatic, or broad-sweeping conclusions with regard to COVID-19 morbidity and mortality [36].

Moreover, the 170 polymerase chain reaction (PCR)-confirmed case count diverts attention from another finding: a much larger number of cases identified during the study fell under the category of "suspected COVID-19," where individuals exhibited symptomatic COVID-19 but lacked a positive PCR test [37]. (Note: The PCR tests used in these trials were those widely accepted for detecting SARS-CoV-2 and ostensibly met certain standards of performance and reliability for accurate detection of the coronavirus.) A total of 3,410 cases of suspected, unconfirmed COVID-19 were identified, a 20-fold difference between suspected and confirmed cases. There were 1,594 such cases in the vaccinated group, and 1,816 in the placebo. When factoring in both confirmed and suspected cases, vaccine efficacy against developing symptoms drops to only 19%, far below the 50% RR reduction threshold required for regulatory authorization [37]. Even when removing cases occurring within seven days of vaccination to account for short-term vaccine reactogenicity (rather than true infections), efficacy would be a meager 29%. Any false negatives among the suspected cases would tend to further diminish the benefit. Thus, when considering both confirmed and suspected cases, vaccine efficacy appears to have been dramatically lower than the official 95% claim.

Similarly, it is important to emphasize that the "cases" being counted in the trials were PCR-positive patients with mild infections, not moderate to severe illnesses. Thus, a cough or other mild respiratory symptoms qualified as primary endpoints [38,39]. The trial's conclusion was predicated on a mere 100 of such COVID-19 "cases" recorded within the placebo group [31]. Once the trial reached this point, it was anticipated that efficacy would be declared, and participants in the placebo group would be offered the active vaccine. This was the precise scenario that transpired, with Pfizer's blinded phase concluding at two months

and Moderna's ending at three, effectively terminating the blinded randomized follow-up period and greatly limiting any risk-benefit evaluations.

The lack of ability to evaluate severe illness in the trials reflected the real-world context, namely that the likelihood of severe COVID-19, hospitalization, and dying from the infection has always been very low. Stratifying by age, the infection fatality rate (IFR) in 2021 showed an age gradient with approximately a three to four-fold increase for each decade, starting as low as 0.0003% (nearly zero) among children and adolescents, increasing to 0.5% in those aged 60-69 [40]. Even in older age groups (>70 years), the IFR varies from 1-5% depending on comorbidities and treatment access. As a basic principle, all-cause mortality (ACM) tends to increase with age. In the case of COVID-19, the presence of comorbid disease greatly modifies the influence of age on mortality [41]. For younger generations (<40 years), SARS-CoV-2 infection severity and fatality rates since 2020 have been comparable to those of influenza [42]. Even in countries that showed excess mortality in 2020, death rates among children were extremely low [43]. In Sweden, where 1.8 million children were allowed to freely attend school in 2020, zero COVID-19 deaths were recorded among them by summer 2021 [44].

Although randomized controlled trials are viewed as the gold standard for testing the safety and efficacy of medical products (due to minimizing bias), trials of limited scope can readily obscure the true safety and efficacy issues with respect to different segments of the population. In this case, the trials excluded key sub-groups, notably children, pregnant women, frail elderly persons, and immunocompromised individuals, as well as those with cancer, autoimmune disease, and other chronic inflammatory conditions [45]. Whereas the founding trials did not recruit individuals with comorbidities, vaccine recipients in the rollouts showed the actual presence of these underlying conditions. Rather than assess these well-known safety and comorbid risk concerns, the focus was narrowly placed on the potential for inflammatory lung injury as had been seen in COVID-19 patients and, many years earlier, in immunized animal models infected with SARS-CoV [46]. We are now beginning to recognize the folly of this narrow safety focus, as millions of severe and life-threatening events associated with the COVID-19 vaccines continue to be documented in the medical literature [47-51].

What did the pivotal trials reveal about overall (all-cause) mortality? After carefully analyzing the ACM for the Pfizer and Moderna trials, Benn and colleagues found 61 deaths total (31 in vaccine, 30 in placebo) and a mortality RR of 1.03 (0.63-1.71), comparing the vaccinated to placebo [52]. These findings can be interpreted as "no significant difference" or no gold-standard evidence showing these mRNA vaccines reduce mortality. The lack of significant differences in deaths between the study arms is noteworthy. The true mortality impact remains unknown in this context, and this fact alone is relevant, as it would be preferable to take a vaccine with good trial evidence of reduced mortality than to take a vaccine where trial evidence does not show convincing evidence of improved survival [53]. Similarly, a subsequent analysis of the Pfizer trial data concluded that mortality rates were comparable between vaccinated and placebo groups during the initial 20-week period of the randomized trial [54]. The fact that the mRNA vaccinations did not lead to a reduction in overall mortality implies that, if the injections were indeed averting deaths specifically attributable to COVID-19, any such reduction might be offset by an increase in mortality stemming from other causes, such as SAEs.

Even the six-month Pfizer trial failed to show any reduction in all-cause mortality [35]. Indeed, a reanalysis of the postmarketing data provided to the FDA suggests the opposite effect. The extended portion of the trial included four months of an unblinded period, in which most placebo participants crossed over to the vaccination group. During this phase, there were five additional deaths, including three in the original vaccine group and two among the placebo participants who chose vaccination [35]. When these five deaths are included as "vaccinated" deaths, the total count becomes 20 deaths in the vaccine group and 14 deaths in the placebo group, which would represent a 43% increase in deaths (not statistically significant due to small counts). In the FDA documents, however, a total of 38 deaths were reported, with 21 in the vaccine group and 17 in the placebo group, representing a 23.5% increase in all-cause deaths among those who received the two-dose primary series of BNT162b2 [55,56]. This suggests that the two placebo participants who died after mRNA vaccination were counted twice (i.e., both deaths were counted in each arm of the trial). To properly account for the five extra deaths, however, one should adjust the analysis based on person-months spent in each group. Applying this method, the total count was 36 deaths: 21 in the BNT162b2 arm and 16 in the placebo arm. Calculating the relative ACM risk, the vaccine group had a mortality rate of 0.105% (21 deaths out of 20,030), while the placebo group had a mortality rate of 0.0799% (16 deaths out of 20,030). The RR equation yielded a value of 1.3125 (95%CI 0.6851-2.5144, p=0.41), indicating a 31% higher ACM risk in the BNT162b2 group compared to the placebo group. The estimate may be considered conservative, as it does not assume that all placebo recipients chose to get vaccinated during the open-label phase of the trial.

For the Pfizer and Moderna registrational trials, Benn et al. also reported a non-significant 45% increase in cardiovascular deaths (RR=1.45; 95%CI 0.67-3.13) in the vaccine arms of the trials [52]. This outcome was consistent with numerous reports of COVID-19 vaccine-related cardiovascular pathology among both young and old segments of the population [57-63]. None of the mortality estimates from the trials are statistically significant. Nevertheless, the upward trends for both ACM and cardiovascular deaths are concerning. If the Pfizer trial had not been prematurely discontinued, and assuming death rates remain the same in both arms

as observed in the first six months, the ACM difference would reach the standard threshold for statistical significance ($p < 0.05$) at approximately 2.8 years (34 months). The p-value is 0.065 at 2.5 years and 0.053 at 2.75 years (see Appendix 1). These calculations were independently confirmed by Masterjohn [64].

Absolute risk and the "number needed to vaccinate (NNV)"

One of the often-overlooked shortcomings of the registrational trials was the final reports' exclusive focus on RR while omitting absolute risk reduction. The latter measure gives a better indication of a drug's clinical utility than the former relative measure since it is scaled by the sample size [65]. RR is the ratio of COVID-19 symptom rates in the vaccine versus placebo groups, which was reported as 95% and 94.5% for the Pfizer and Moderna products, BNT162b2 and mRNA-1273, respectively [1,2]. Absolute risk refers to the probability of an outcome (in this case, symptoms of clinical infection), based on the number of people experiencing the outcome in relation to the population at large. It is typically calculated as the number of events that occurred in a study population divided by the number of people in that population. Both types of risk estimation are required to avoid reporting bias and to provide a more comprehensive perspective on vaccine efficacy [65]. Omitting the absolute risk statistics leads to overestimation of the clinical benefits of the vaccines [66]. In contrast with the 95% RR figure, the absolute risk reductions for BNT162b2 and mRNA-1273 were 0.7% and 1.1%, respectively [67]. These estimates were derived from publicly available data that ultimately enabled EUA for the vaccines to be granted by the FDA's Vaccines and Related Biological Products Advisory Committee (VRBPAC) [68]. However, the data reviewed by the VRBPAC did not include absolute risk reduction measures, thus deviating from FDA's guidelines, which state that both approaches are crucial in order to avoid the misguided use of pharmaceuticals [69]. Again, failing to provide the absolute risk and instead fixating only on RR generally results in an overestimation of vaccine benefits. Absolute risk statistics are also valuable when assessing and comparing safety measures such as AE rates.

An absolute risk reduction of approximately 1% for the COVID-19 mRNA vaccinations meant that a substantial number of individuals would need to be injected in order to prevent a single mild-to-moderate case of COVID-19. Specifically, the NNV to prevent one case of COVID-19 would be 142 (range 122-170) for the BNT162b2 injection and 88 (range 76-104) for the mRNA-1273 injection, respectively [65]. These numbers increase with age and depending on the variant [70]. The NNV is an interpretable and salient metric for assessing real-world impact, enabling us to gauge the potential benefits derived from vaccination. For any relatively healthy population (with minimal comorbidities), the risk-benefit profile with a high NNV could easily point to excessive harms.

It is imperative to carefully weigh all potential risks associated with the COVID-19 mRNA products. Should substantial harms be linked to their use, the perceived "reward" conveyed by the NNV would necessitate a re-appraisal. For example, assuming an NNV of 119 and an IFR of 0.23% (both conservative estimates), approximately 52,000 vaccinations would be needed to prevent one COVID-19-related death. Thus, for the BNT162b2 injection, a generous estimate would be two lives saved from COVID-19 for every 100,000 courses of the biological. Given the evidence of trial misconduct and data integrity problems (see next section), we conjecture that this estimate is an "upper bound", and therefore the true benefit is likely to be much lower. Regarding potential harms, assuming 30% false-positive reports and a moderate under-reporting factor of 21, we calculate a risk of 27 deaths per 100,000 doses of BNT162b2. Thus, applying these reasonable, conservative assumptions, the estimated harms of the COVID-19 mRNA vaccines greatly outweigh the rewards: for every life saved, there were nearly 14 times more deaths caused by the modified mRNA injections (for details, see Appendix 2).

Underreporting of harms and data integrity issues

Underreporting of severe harms, including SAEs, is another important concern that often garners scant attention in the public domain. Notably, severe harms that significantly impede daily activities and quality of life are universally underreported in randomized trials, particularly in industry-sponsored studies [71]. Such AEs may be most common in mRNA-vaccinated individuals who are subsequently infected with SARS-CoV-2. While, in principle, systematic reviews of randomized trials serve as a reliable source of evidence, the reporting of serious harms is invariably missing from the drug trial reports [72]. This dearth of reporting seems exceptionally evident in the context of vaccine trials [73-75]. In the case of the COVID-19 vaccine trials, the underreporting was also situational, as participants were unblinded in the open-label phase of the Pfizer trial, and placebo recipients were offered the vaccine within only a few weeks of the EUA. The early unblinding occurred without allowing sufficient time to identify late-occurring or diagnosed harms associated with the vaccines [15]. Was this necessary, given that none of the deaths in the Pfizer trial were attributed to COVID-19 as the primary cause, and given the very low IFR for a relatively healthy population [40]?

Classen notes that the trial coordinators employed a haphazard approach to AE monitoring and thus the potential harmful impact of these biologicals on health outcomes was more substantial than is usually acknowledged [49]. Investigators prioritized the documentation of COVID-19 events while prospectively tracking patients for "solicited" AEs for a duration of approximately seven days post immunization. "Unsolicited" AEs were subsequently reported for a period of 30-60 days. Among the trial participants were individuals with limited education and elderly individuals (possibly with cognitive impairment) [49]. The

ability of such individuals to competently recognize and report serious AEs is questionable. Moreover, the original trial reports did not include data on serious non-infectious events, including fatalities, that occurred beyond the 30-60-day reporting period [49]. By contrast, COVID-19 infections were continuously monitored from the time of immunization (a form of information bias). Both Pfizer and Janssen showed leniency in recording AEs, restricting the documentation of "solicited" events to a safety cohort representing less than 20% of the overall study population. These findings align with prior studies showing that only a small proportion, generally 5%, of AEs are typically reported in pharmaceutical company-sponsored trials [76].

To make matters worse, the public was never allowed access to the registrational trials' raw data, thus precluding independent verification of AEs by the scientific community (these were revealed later on, after widespread distribution of the inoculations) [77]. Such secrecy may have enabled the industry to more easily present an inflated and distorted estimate of the genetic injections' benefits, along with a gross underestimation of potential harms.

A recent forensic analysis of Pfizer's six-month trial data revealed that many deaths in the trial occurred after the cutoff date used to create the briefing booklet reviewed by the FDA and resulting in the authorization of the vaccine; this effectively concealed mortality data from the decision-making part of the EUA process [54]. Pfizer's original application for the EUA described the trial results only up to the data cutoff date of November 14, 2020. However, deaths and other SAEs continued to occur afterward, even before the definitive VRBPAC meeting to authorize the mRNA vaccine. During the initial 33 weeks of Pfizer-BioNTech Clinical Trial CA4591001, which spanned 153 clinical trial sites in more than seven different countries, a total of 38 subjects passed away. The 38 trial subjects were listed in the Pfizer-BioNTech six-month Interim Report [35]. These events occurred in chronological order within the 33-week period commencing on July 27, 2020, and concluding on March 13, 2021. To visually represent this data, Michels et al. created a bar graph illustrating the number of subject deaths per week (Figure *1*). The number of subject deaths in both the BNT162b2 ("vaccinated") and placebo arms of the trial is depicted separately. The graph also includes a plot illustrating the cumulative number of deaths in each arm, measured at the end of each week. Solid bars represent subjects who received the BNT162b2 injection, while gray bars represent those who received a placebo, and hatched bars represent subjects who initially received a placebo but were unblinded and subsequently administered BNT162b2. Additionally, the authors included a linear graph that displays the cumulative number of deaths in each trial arm. A solid line corresponds to BNT162b2-injected subjects, while a dotted line represents the placebo group [54].

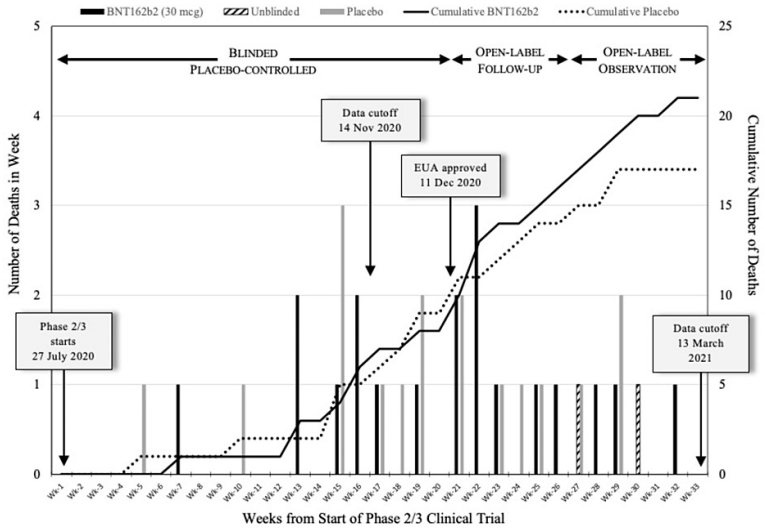

FIGURE 1: Analysis of Pfizer trial's weekly mortality over a 33-week period

This representation of the Pfizer trial by Michels et al. [54] showcases the weekly count of subject deaths from July 27, 2020, to March 13, 2021. Solid bars denote BNT162b2 recipients, gray bars signify the placebo group, and hatched bars represent previously unblinded placebo subjects who later received BNT162b2. The solid line represents the cumulative death count for the BNT162b2 group and the dotted line for the placebo group.

Notably, the unblinded placebo recipients who later received BNT162b2 are combined with the BNT162b2 "vaccine group" for this analysis [54]. To provide context, the registrational trial can be divided into three distinct periods. The first is the "Blinded placebo-controlled period," which spanned from July 27, 2020, to December 10, 2020. The second phase is the "Open-label follow-up period," encompassing the timeframe from December 11, 2020, to January 24, 2021. The final period is the "Open-label observation period," which extended from January 25, 2021, to May 13, 2021 [35,78]. The initial placebo subject death was recorded in Week 5, while the first death among BNT162b2 subjects occurred in Week 7.

The first 12 weeks of the trial saw very few deaths, likely due to ongoing enrollment of new subjects. The plots illustrating the cumulative number of deaths in both arms appear to closely align until around Week 20, after which they diverge (Figure *1*). Beyond Week 20, the rate of deaths in the placebo arm decreased and eventually stabilized by Week 30. In contrast, the number of deaths among BNT162b2 subjects continued to rise at a consistent rate. This reduced rate in the placebo arm was likely a result of the diminishing number of unvaccinated placebo subjects remaining in the trial, stemming from the unblinding and vaccination process initiated after December 11. Despite the low overall death count, it is likely that the general public's perception of the vaccines would have been far less favorable had they known that the mortality rate had continued to increase among the mRNA-vaccinated participants [54]. The data for Figure *1* by Michels et al. [54] were obtained directly from Pfizer's Six-Month Interim Report [35]. Moreover, Michels et al. [54] compared the reported number of deaths to an age-stratified estimated number based on US data from 2019 [79] and determined that Pfizer's reported number of 38 deaths is about 17% of what would be expected for the US population.

Alarmingly, drawing from Pfizer's Six-Month Interim Report, Michels and colleagues found evidence of a substantial increase in the number of deaths due to cardiovascular events in BNT162b2 vaccinated subjects that the vaccine manufacturer did not report [54]. For their published peer-reviewed analysis, the researchers were able to access the narrative reports on a few critical subjects that provided explicit notification of the subject's date of death prior to November 14, 2020 [54]. Protocol C4591001 required immediate reporting of SAEs, including death or hospitalization, within a 24-hour window, a guideline likely followed by the trial site staff. Nevertheless, Pfizer used the dates that the death was recorded in the subject's Case Report Forms, which Pfizer maintained. The Michels et al. investigation uncovered a consistent pattern of reporting delays of the date of death on subjects' Case Report Forms across the entire trial [54]. These delays were greatest in vaccinated subjects who died prior to November 14, 2020. If Pfizer

had used the actual death dates in their EUA application, two additional vaccinated subjects would have been included in the EUA application. This discrepancy was crucial, as all vaccinated subject deaths (four of four) and half the placebo deaths (two of four) were cardiac-related. The forensic analysis revealed that 75% of the deaths in vaccinated subjects and 33.3% of those in the placebo group were cardiac-related [54]. Among the 14 subjects experiencing cardiac SAEs, 11 were individuals who received the BNT162b2 vaccine, and three were from the Placebo-only trial arm, a 3.7-fold increase (OR 3.7, 95%CI 1.02-13.2, p = 0.03) [54]. It is noteworthy that neither the original trial paper by Thomas et al. nor Pfizer's Summary Clinical Safety report acknowledged or commented on this crucial safety signal [35,78].

In hindsight, the previously undisclosed observation that twice as many cardiac deaths occurred proportionately among vaccinated compared to unvaccinated subjects in the Pfizer trial would likely have prompted the FDA's reevaluation, especially considering the later accumulated data by December 10, 2020, where 17 deaths had occurred [54]. Delays in documenting these patients' fatalities in their Case Report File, coupled with the omission of the actual date of death, effectively concealed their deaths during the crucial phase of the EUA approval process, masking the cardiac SAE signal [54]. In short, the various reporting delays and omissions, if they had been openly discussed and considered by the VRBPAC, might have prolonged the authorization process. The improper reporting and insufficient scrutiny by the VRBPAC may have ultimately enabled Pfizer to manipulate the trial results and obscure the cardiac death signal. Recent in vivo animal studies demonstrate that "in isolated cardiomyocytes, both mRNA-1273 and BNT162b2 induce specific dysfunctions that correlate pathophysiologically to cardiomyopathy" [80]. In principle, then, cardiomyocytes cannot be excluded from the biodistribution of the LNP-mRNA, and every new mRNA product has the potential to cause life-threatening heart problems, including cardiomyopathy and cardiac arrest.

Beyond these omissions in SAE reporting, the official reporting of trial results was also problematic. The trial data Pfizer submitted for the EUA application revealed a puzzling trend when comparing COVID-19 incidence between the mRNA-injected and placebo groups: a striking divergence after day 12 following the first BNT162b2 dose [81,82]. While the placebo group continued to see new cases, the BNT162b2 group's infection rate abruptly halted, suggesting sudden, uniform immunity onset at day 12. Such an abrupt and complete response on day 12 contradicts biological plausibility, given that such immunological responses would realistically tend to register in a more gradual way in a group context. Moreover, Pfizer failed to provide the data for individuals receiving only one dose. Figure *2* from the same trial report [83], adapted by Palmer et al. [82], showing neutralizing antibody titers on the day of the first injection (D1) and various subsequent days, depicts the gradual rise of neutralizing antibodies to SARS-CoV-2 following the mRNA inoculation. This contradicts the notion of rapid, full clinical immunity. By day 21, after the first dose, neutralizing antibodies only slightly increased, peaking on day 28, well after most individuals would have received their second dose. This inconsistency between clinical and antibody data raises doubts about the graphic depiction of sudden immunity on day 12, casting suspicion on its validity. Figure *2* shows two charts sourced from the European Medicines Agency (EMA) assessment report on Pfizer's trial data [83].

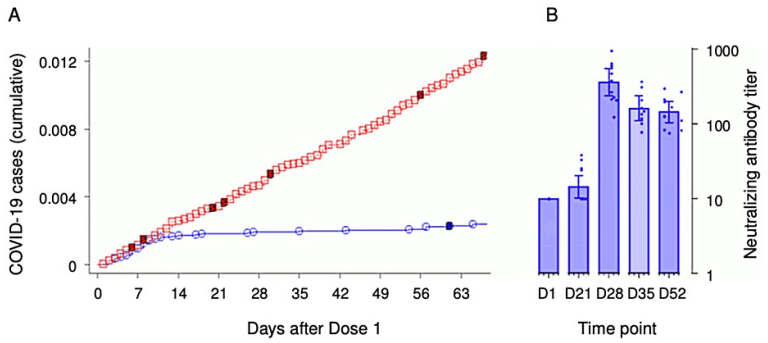

FIGURE 2: Charts illustrating Pfizer trial irregularities in reporting of COVID-19 cases and humoral immune responses (antibody titers)

This indicates an unusual pattern post day 12 following the BNT162b2 injection. While the placebo group continued experiencing cases, the BNT162b2 group showed a sudden decline in infection rates, suggesting unexpected immediate immunity.

Image source: Palmer M, et al., 2023 [82]; Reproduced under Creative Commons Attribution-NonCommercial-ShareAlike 4.0 International License (CC BY-NC-SA 4.0). Data was extracted from the European Medicines Agency (EMA) report, referencing Figures 9 (A) and 7 (B) [83].

When Pfizer's Six-Month Interim Report of Adverse Events (C4591001) revealed a total death count of 38 [35], the number seemed unexpectedly low for a clinical trial involving 44,060 participants amidst a pandemic. To investigate, Michels and colleagues estimated the anticipated deaths based on US mortality rates in 2020, presuming comparability across participating countries [54]. With 132 trial sites in the US and 80% of subjects, they estimated that 222 deaths should have occurred between July 27, 2020, and March 13, 2021, making the observed 38 deaths only 17% of the projected number. Most of the trial sites had fewer deaths than anticipated, possibly attributed to a considerable percentage of "Lost to Follow-up" subjects (4.2% of randomized subjects), including 395 unique subjects within the study period. While some sites recorded negligible losses, others exhibited substantial figures, up to 5% of the site's subjects [54]. These numbers likely contributed to the seemingly low overall death count and should have prompted increased efforts to locate these individuals. Losing track of nearly 400 study participants in the follow-up observation period could have substantially compromised the validity and generalizability of the results. The missing data can produce biased estimates, leading to invalid conclusions. This could result in a distortion of vaccine efficacy and underestimation of SAEs (including deaths), thus misrepresenting the safety profile of the mRNA products. In short, Pfizer's failure to minimize participant attrition seriously undermined the accuracy and reliability of the six-month study's conclusions.

According to a retrospective analysis by Gulbrandsen and colleagues, the Pfizer trial data showed a significant association between the mortality rate and time since the injection in both the vaccine and placebo arms [84]. A minimal number of deaths were recorded during the initial 80 days, but a significant mortality increase was observed around the 100-day mark post-injection, indicating a pattern that cannot be attributed to chance. Remarkably irregular trends are also evident in the cardiac SAEs within the trial. Nearly half of all the cardiac events manifested within the initial 50 days following the injection, despite the constant risk exposure anticipated for the first 140 days. Oddly, a dramatic surge in cardiac SAEs was observed around the 100-day mark from the first injection in both the placebo and vaccine groups, coinciding with the heightened death rate. Examining the predominant medical diagnoses before participation in the trial revealed yet another aberrant trend: all nine of the most prevalent pre-existing diagnoses were more commonly found among participants in the placebo arm. Moreover, there was a notable contrast in the ages of deceased participants between the two groups. These observed patterns were unlikely to occur randomly. The only plausible explanation that aligned with these anomalous trends was that the SAE records among vaccine recipients were altered, relocating them to the placebo arm post occurrence [84].

These concerns are further compounded by revelations concerning substandard research practices and inadequate data management in the pivotal trials. A whistleblower report by a former employee of the contract research organization responsible for enrolling patients in Pfizer's pivotal trial raises significant questions regarding data integrity and the safety of trial participants [85]. Among the trial conduct issues documented were failure to report protocol deviations, improper storage of vaccines, mislabeling of laboratory specimens, and lack of timely follow-up for patients experiencing AEs, possibly leading to underreporting. In terms of regulatory oversight, the FDA inspected only nine out of the 153 study sites involved in the Pfizer trial [86].

Finally, an unblinding of participants occurred early in the trial, potentially on a wide scale across different study sites. Participants were not presented with clear information regarding potential AEs in both trial protocols and consent forms [87]. Some parts of the consent form were misleading and merely intended to elicit participation that might not otherwise have occurred if the volunteers had been made aware that what was promised in theory or "on paper" was unlikely to happen in reality [87]. As a result, participants were not being granted truly informed consent; the potential injuries and AEs most likely to be caused by the vaccinations were never openly stated.

This lack of informed consent carried over into the real-world setting following the EUA. For example, not publicly disclosing the Pfizer trial's exclusion of pregnant women is arguably among the CDC's most egregious oversights when asserting the safety of COVID-19 vaccine administration during pregnancy [1]. The Nuremberg Code established patients' rights to voluntary informed consent in the aftermath of World War II [88]. US courts consistently support informed consent as a fundamental right for patients' autonomy [89]. Informed consent procedures must provide clear distinctions between risks that are frequently observed, risks that occur rarely, and the more obvious risk of lack of effectiveness or waning immunity, which is separate from the risk of SAEs. Whether in a clinical trial or free-living real-world setting, informed consent is essential to providing a clear understanding of the potential risks associated with receiving a genetic vaccine. Throughout the pandemic, healthcare workers were duty-bound to provide clear risk-benefit information to patients. In practice, however, informed consent was non-existent, as information sheets were blank [90], and vaccinees were never informed of potential risks beforehand.

Shifting narratives, illusions of protection

The ability to halt or greatly limit infection is generally considered essential to vaccine effectiveness. Nevertheless, the registrational trials by Pfizer and Moderna were not designed to address this issue. The endpoint of the trials was the reduction of symptoms associated with COVID-19 [1,2], even though the public was subsequently told by the CDC that the COVID-19 products would stop transmission [91]. Moreover, asymptomatic transmission was shown to be extremely minuscule [92]. Since 2021, the scientific

community has known that the COVID-19 mRNA products do not prevent either transmission or infection [93]. Even experts sponsored by the vaccine industry admitted to a maximum reduction in transmission of 61% in 2021 [94]. The Omicron subvariants are associated with a 30-50% reduction in transmission following administration of the boosters [95-97]. The benefit is incremental and transient, with protection against Omicron infection lasting only a few months [93]. Even though antibody titers against SARS-CoV-2 are higher following the injection, these levels decline faster in the mRNA recipients compared to individuals with natural infection [98]. The impact of reduced disease severity among COVID-19-vaccinated individuals on the risk of causing secondary infections has never been systematically investigated in controlled clinical trials [93].

The best evidence for the failure of the COVID-19 mRNA vaccine's ability to confer protection against COVID-19 comes from two large cohort studies of employees within the Cleveland Clinic Health System (CCHS) after the bivalent mRNA boosters became available [99,100]. In the first study (n=51,017), COVID-19 occurred in 4,424 (8.7%) during the 26-week observation period [99]. In terms of preventing infections by the three prevailing Omicron subvariants, the vaccine effectiveness was 29%, 20%, and a non-significant 4%, respectively [99]. No protection was provided when the XBB lineages were dominant. Notably, the risk of "breakthrough" infection was significantly higher among those who received the earlier vaccine, and a higher frequency of vaccinations resulted in a greater risk of COVID-19 [100]. In a second CCHS cohort study (n= 48,344), adults who were "not up-to-date" by the CDC definition had a 23% lower incidence of COVID-19 than those "up-to-date" with their vaccinations [100]. These findings are further reinforced by multiple real-world studies showing rapidly waning protection against Omicron infection after the boosters [101]. The vaccine effectiveness against laboratory-confirmed Omicron infection and symptomatic disease rapidly wanes within three months of the primary vaccination cycle and booster dose [97].

Figures *3*-*4* present the surprising findings from these two Cleveland Clinic studies. Figure *3* displays the earlier study's findings, with a cumulative incidence of COVID-19 for study participants stratified by the number of mRNA vaccine doses previously received. Day 0 was September 12, 2022, the date the bivalent vaccine was first offered to CCHS employees. Case rates were clearly increasing in tandem with greater frequency of mRNA injections [99]. Figure *4* presents another unexpected finding, this time from the second Cleveland Clinic study, with a Simon-Makuch hazard plot comparing the cumulative COVID-19 incidence in the "up-to-date" and "not up-to-date" with respect to CDC-defined vaccination status. Day zero was January 29, 2023, the day the XBB lineages of the Omicron variant became dominant in Ohio. For both charts, point estimates and 95%CIs are shown along the x-axis [100].

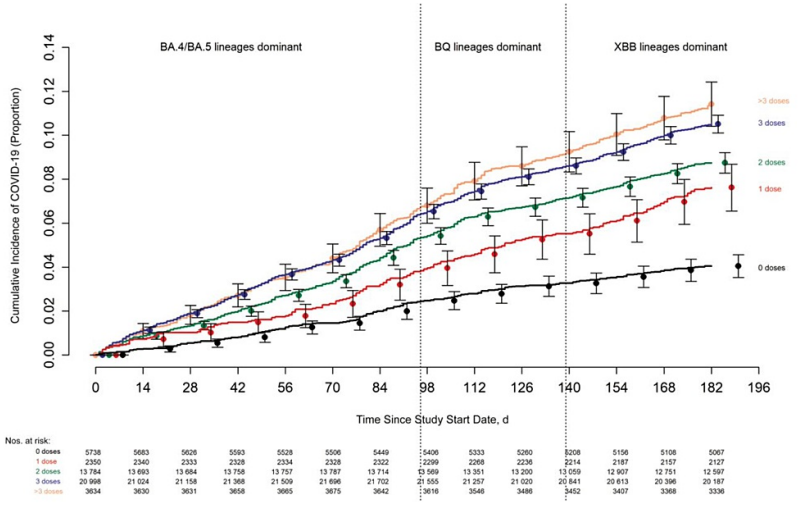

FIGURE 3: Cleveland Clinic study showing increasing COVID-19 cases with increasing mRNA vaccinations

Cleveland Clinic study demonstrating COVID-19 incidence among participants based on the number of prior mRNA vaccine doses received. The study shows rising case rates associated with increased COVID-19 mRNA vaccine doses.

Image Source: Shrestha et al., 2023 [99]; Open Access article with public sector information, licensed under the Open Government Licence v3.0 (http://www.nationalarchives.gov.uk/doc/open- government-licence/version/3/)

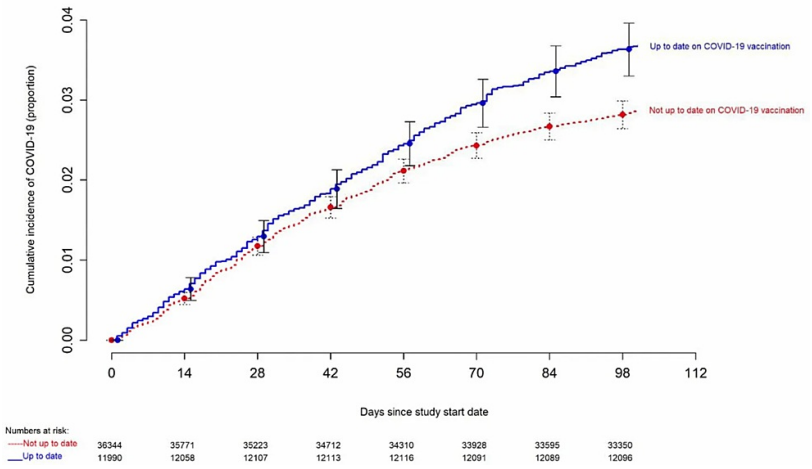

FIGURE 4: Cleveland Clinic study showing increased COVID-19 cases for subjects most "up to date" with mRNA vaccinations

Cleveland Clinic study comparing cumulative COVID-19 incidence between "up-to-date" and "not up-to-date" individuals based on CDC-defined vaccination status. The plot includes point estimates and 95% confidence intervals along the x-axis.

Image Credit: Shrestha et al., 2023 [100]; Open access, licensed under CC BY 4.0 Deed (Attribution 4.0 International)

With the product efficacy profile now firmly in question, the vaccine enterprise has embraced two narratives to justify the ongoing use of COVID-19 vaccinations. The first is that while the COVID-19 mRNA products may not block infections, these products still protect against severe disease, hospitalization, and mortality. The second narrative states that the protection associated with the mRNA inoculation, when combined with natural infection, is superior to natural infection (and thus natural immunity) alone.

The first narrative posits a counterintuitive dichotomy between the two forms of protection, protection against infection versus protection against severe disease, and seems to imply their independence. As an encapsulation of this dichotomy, a 2022 Israeli study report states that the "protection against confirmed infection appeared short-lived, whereas protection against severe illness did not wane during the study period" [102]. However, is it reasonable to contend that protection against severe illness and mortality remains intact even after the rapid decline in protection against infections? To address this issue, Ophir and colleagues conducted a meticulous analysis of prominent data from clinical trials, large observational studies from Israel, and contemporary dashboards of statistics [103]. The authors noted "multiple methodological and representational constraints, including short, and sometimes arbitrary or uneven follow-up periods, uneven exclusion criteria and COVID-19 testing levels, selection biases, and selective reporting of results. But most importantly, the documented, conditional probability of death and severe illness (i.e., the percentage of severe illness and death cases among those infected with the virus) did not differ between the treatment and the control groups of the various clinical and observational efficacy studies" [103]. The authors concluded that there was no valid evidence to substantiate the claim that getting a second COVID-19 mRNA booster effectively prevents severe illness and mortality [103].

The second alternative narrative focuses on the phenomenon of hybrid immunity, the combined protection obtained from natural infection followed by the booster. In those individuals recently exposed to SARS-CoV-2 infections, COVID-19 vaccine-induced immunity is believed to surpass natural immunity because it generates a more robust antibody response and broadens the spectrum of antibodies generated [104]. These robust, broad-based humoral responses entail the production of memory B cells at levels 5-10 times higher than those achieved through either infection or vaccination alone [105]. By now, most if not all individuals in developed countries have been infected by SARS-CoV-2. Once informed of the additional protection afforded by hybrid immunity, laypersons cognizant of having a history of infection may be more inclined to embrace ongoing boosters. Nonetheless, given the relatively low severity of Omicron, is the additional antibody production truly necessary? One also needs to consider the potential risks of this increased antibody production. Because the Omicron subvariants are constantly mutating, many of the antibodies generated by current vaccines are non-neutralizing. The potential overproduction of non-neutralizing antibodies could lead to the phenomenon of vaccine-associated enhanced disease (VAED), which is based in part on antibody-dependent enhancement [106]. To date, there have been only a few reports of mild VAED in COVID-19 vaccination in animal models and no documented cases in humans [107]. With repeated

boosters, however, VAED could eventually impact the long-term safety of the mRNA vaccinations.

In the context of hybrid immunity, the most serious immunological pitfall pertains to SARS-CoV-2 infection occurring after the COVID-19 mRNA injection, when S-protein production is already systemically increased. It was originally assumed that prior vaccination might lessen the severity of the infection and reduce the risk of severe COVID-19 illness. In the post-vaccination period, the immune system would be primed for responding more robustly to a subsequent infection within a few weeks after completing the full series. However, the opposite scenario can also unfold due to the circumvention of innate immune responses, together with the above-mentioned overproduction of non-neutralizing antibodies and inadequate protection against severe disease [108]. COVID-19 vaccinations are known to cause innate immune suppression via profound impairment in type I interferon signaling along with disruption of regulatory control of protein synthesis and cancer surveillance [26]. Excessive production of non-neutralizing antibodies could increase the risk of autoimmune reactions by cross-reacting with host tissues instead of the virus, thereby triggering inflammatory autoimmune reactions via molecular mimicry [109-111]. These mechanisms may collectively raise the risk of autoimmune inflammatory pathologies, including cancers, cardiovascular diseases, and many other diseases with a chronic inflammatory etiology [112,113]. (For a discussion of the mechanistic basis for adverse events, please see the section, “Mechanisms underlying AEs”.)

Up to this point, when considering the SAEs, we have focused primarily on those effects associated with Pfizer’s mRNA product, BNT162b2, drawing from the six-month trial data as well as the 393-page confidential document released on August 2022, revealing close to 1.6 million AEs [114]. In the context of hybrid immunity, it is important to note that the Moderna product, mRNA-1273, generates a substantially stronger immune response, resulting in lower rates of symptomatic infection and severe COVID-19 outcomes when compared to BNT162b2 [115]. Those who fixate on these infection-preventing benefits, however, may tend to overlook the potential harms: mRNA-1273 has exhibited significantly higher risks of SAEs compared to BNT162b2, according to clinical trials, survey-based studies, and a government-sponsored surveillance study [1,2,116-120]. This shows the unsavory trade-off between increased protection against Omicron infection on the one hand and a substantial risk of vaccine-induced SAEs on the other.

In a recent study of nearly five million adults, those who had a SARS-CoV-2 infection within 21 days post injection showed an eight-fold increased risk of ischemic stroke (OR=8.00, 95%CI 4.18-15.31) and a five-fold increased risk of hemorrhagic stroke when compared to vaccinees without concurrent infection (OR=5.23, 95%CI 1.11-24.64) [121]. The risk was highest for those receiving the mRNA-1273 injections. Thus, SARS-CoV-2 infection close to the time of vaccination produced a strong association with early incidence of ischemic and hemorrhagic strokes [121]. Again, with a hybrid immunity approach, the potential harms may greatly outweigh the rewards.

Natural immunity carries none of these risks and is more than sufficient against the mild virulence of Omicron subvariants. Much evidence now indicates that natural immunity confers robust, durable, and high-level protection against COVID-19 severe illness [122-126]. A large United Kingdom (UK) study of over 30,000 healthcare workers, having a prior history of SARS-CoV-2 infection, showed an 84% reduced risk of reinfection, with a median protective period of seven months [125]. In a large observational study in Israel, previously infected individuals who remained unvaccinated were 6-13 times less likely to contract the virus compared to those who were vaccinated [122]. Among 32,000 individuals within the same healthcare system, vaccinated individuals had a 27-time higher risk of developing symptomatic COVID-19 and an eight-time higher risk of hospitalization compared to their unvaccinated counterparts [122].

After recovering from COVID-19, the body harbors long-lived memory immune cells, indicating an enduring capacity to respond to new infections, potentially lasting many years [127]. Mounting evidence suggests that the training of antibodies and induction of T-cell memory resulting from repeated natural infection with Omicron can augment the mitigation of future infections [128,129]. In a recent cohort study, children who had experienced prior infection showed long-lasting protection against reinfection with SARS-CoV-2 for a minimum of 18 months [130]. Such children between the ages of five and 11 years demonstrated no decline in protection during the entire study, while those aged 12-18 experienced a mild yet measurable decline in protection over time [130]. For these younger generations in particular, natural immunity is more than sufficient and of course vastly safer than the mRNA inoculations.

Analyses of serious harms to humans

We now review what is known about the AEs and SAEs reported in the registrational trials, including data that regulatory agencies and drug safety surveillance studies revealed following the EUA. As early as 2014, Sahin and colleagues had warned of the potential dangers of the mRNA vaccine technology, specifically cautioning that the encoded antigen should be investigated for multiple disease risks [131]. Surveys show that the primary concern expressed by parents regarding their children receiving the COVID-19 vaccines is not vaccine effectiveness but rather the potential AEs [132,133]. In a survey of US parents, concerns about the unprecedented speed of the mRNA vaccines’ development (and, by implication, the rapid authorization process) were ranked just above concerns about harmful side effects [133]. The risks may vary depending on the number and frequency of COVID-19 vaccine doses. Whereas some authors have observed fewer AEs after

the second dose [134], others have reported an increased incidence [116]. Sultana et al. reported varying trends in AEs after the second dose for both mRNA products, albeit with a higher frequency of AEs following the second-dose administration of the Moderna vaccine [135].

The most compelling revelations regarding the adverse impacts of these products have come from a comprehensive re-analysis of the trial data, with a primary focus on the more serious outcomes, including fatalities. Applying rigorous methodology, Fraiman and colleagues conducted an in-depth investigation and analyzed the interim datasets for the Pfizer and Moderna trials, encompassing approximately four months of observation following the commencement of the trials [50]. SAEs were defined as events that led to any of the following outcomes: death, life-threatening conditions, inpatient hospitalization or extension of existing hospitalization, persistent or significant disability/incapacity, a congenital anomaly/birth defect, or a medically significant event based on medical judgment. The risk of vaccine-related SAEs was divided into general SAEs and AEs of special interest (AESIs), as identified by the Brighton Collaboration criteria adopted by the World Health Organization [136].

For both the Pfizer and Moderna trials combined, there were about 125 SAEs per 100,000 vaccine recipients, which translates into one SAE for every 800 vaccinees [50]. Because the trials avoided the most frail as participants, one would expect to see even higher proportions of SAEs in the population-wide rollouts. Remarkably, the Pfizer trial exhibited a 36% higher risk of SAEs in the vaccine group compared to the placebo, with a risk difference of 18.0 (95%CI 1.2-34.9) per 10,000 vaccinated; risk ratio 1.36 (95%CI 1.02-1.83). These findings stand in sharp contrast with the FDA's initial claim that SAEs reported by the two pivotal trials were "balanced between treatment groups" [15,50]. The discrepancy may be partly explained by the fact that the FDA was focusing only on individual participant data, and yet many of those individuals were experiencing multiple SAEs. Instead of analyzing individuals, Fraiman et al. focused on total SAEs to take into account the multiple, concurrent events [50]. When the SAEs were viewed collectively, the risks in the vaccine group were substantially elevated beyond those previously determined by the FDA.

For their risk-benefit assessment, Fraiman's team considered the excess risk of serious AESIs in the vaccine group versus the risk of COVID-19 hospitalization in the placebo group [50]. This analysis was based on published reports from the vaccine companies' sponsors and FDA presentations. Remarkably, according to Fraiman et al., the Pfizer trial exhibited a four-fold higher risk of serious AESIs compared to the risk of COVID-19 hospitalizations (10.1 AESIs vs. 2.3 hospitalizations per 10,000 participants, respectively), while the Moderna trial demonstrated a more than two-fold higher risk (15.1 AESIs vs. 6.4 hospitalizations per 10,000 participants, respectively) [50]. These findings indicate a much stronger degree of vaccine-related harm than initially estimated during the time of EUA. To put these findings in perspective, the official SAE rate for other vaccines is only 1-2 per million [137]. Fraiman et al.'s estimate based on the Pfizer trial data (1,250 SAEs per million) exceeds this benchmark by at least 600-fold.

Analyses of two large drug safety reporting systems in the US and Europe revealed over 7.8 million AEs reported by approximately 1.6 million individuals following COVID-19 vaccination [47]. When compared to individuals aged 18-64 years, the older age groups exhibited a higher frequency of death, hospitalizations, and life-threatening reactions, with RR estimates ranging from 1.49 (99%CI 1.44-1.55) to 8.61 (99%CI 8.02-9.23). Signals were identified for myocardial infarction, pulmonary embolism, cardio-respiratory arrest, cerebral infarction, and cerebral hemorrhage associated with both mRNA vaccines. These signals, along with ischemic strokes, were confirmed by a large disproportionality analysis [48]. In an independent risk-benefit analysis, BNT162b2 produced 25 times more SAEs than the number of severe COVID-19 cases prevented [51]. Such an uneven risk-benefit calculus reinforces the findings from the Skidmore survey, which estimated that the total number of US fatalities due to COVID-19 mRNA vaccinations in 2021 alone was 289,789 (95%CI 229,319-344,319) [138]. A physician and survey research specialist helped to validate the survey, and the sample (obtained by Dynata, the world's largest first-party data platform, based in Connecticut, US) was deemed representative of the US population [138].

Finally, autopsy studies have provided additional evidence of serious harms. In a comprehensive systematic review with full independent adjudication, 74% of autopsy findings (240 out of 325 cases), were judged to have been caused by the COVID-19 mRNA products [139]. The mean time from injection to death was 14.3 days, and the vast majority of deaths had the cardiovascular system as the single fatal organ system injury to the body. These findings are reinforced by those of a more recent adjudicated autopsy review of mRNA vaccine-induced myocarditis (28 deaths, all of which were attributed to the injections) [140] as well as a previous autopsy study of mRNA vaccine recipients that did not have the advantage of independent adjudication [141]. Based on multiple autopsy studies, German pathologists led by the late Arne Burkhardt have documented the presence of vaccine-mRNA-produced S-proteins in blood vessel walls and brain tissues through immunohistopathological-staining [142,143]. These findings help explain the wide range of well-documented COVID-19 vaccine-induced toxicities that impact the nervous, gastrointestinal, hepatic, renal, hematological, immune, and reproductive systems [25,144,145]. Post-mortem examinations are critical for identifying potential SAEs of the mRNA inoculations. However, as clinics and hospital administrations have a large vested interest in the COVID-19 vaccines' distribution, the common administrative practice of discouraging autopsies and postponing autopsy reports only serves to undermine comprehensive risk assessment, perpetuate public misconceptions regarding safety, and weaken public health policymaking [145].

Quality control issues and process-related impurities

Given the novelty of the mRNA technology used in the SARS-CoV-2 vaccines, it would be prudent to establish regular production inspection and quality assurance along with long-term safety monitoring protocols and to perform the requisite tumorigenicity, genotoxicity, neurotoxicity, immunotoxicity, and reproductive toxicity studies. The fact that no safety and toxicity studies appropriate for these gene-based or GTP products were ever performed is concerning.

A key issue that could help explain why some individuals succumb while others do not is vaccine type and batch variability. Due to the inherent instability of mRNA technology, some batches may contain extremely low levels of intact mRNA [146]. Some batches were contaminated with double-stranded RNA (dsRNA), as documented by the EMA for both the Pfizer and Moderna products [147,148]. The dsRNA has a high potential to trigger immune-inflammatory reactions such as myocarditis [149].

Quality control is central to any discussion of batch variability and process-related impurities, and yet, in practical terms, evaluating such control for individual vials is not feasible. In a paper published in 2021, Yu et al. hypothesized that variability in adverse reactions might be caused by quality differences among different batches or even different individual vials, due to variabilities in both contaminants and handling histories [150]. The requirement of maintenance at extremely low temperatures may not always be practical, and the consequences of improper handling (e.g., cold chain breaching) are not well characterized.

The issue of batch variability is further complicated by recent findings of DNA contamination in the mRNA vaccines [151]. In an analysis of multiple vials of the bivalent Pfizer and Moderna mRNA products, McKernan et al. found "high levels of DNA contamination in both the monovalent and bivalent vaccines" that were "orders of magnitude higher than the EMA's limit" of 330 nanograms of DNA per milligram of RNA [152]. The DNA process-related impurities also exceeded the safety limits of the FDA (10ng/dose).

In a follow-up attempt to disprove this claim, Buckhaults and his genomics research team examined two batches of Pfizer mRNA vials and confirmed contamination with the plasmid DNA vector that had been used as the template for mRNA vaccine production [8,153]. At a South Carolina Senate hearing, Buckhaults reported having consistently sequenced substantial quantities of plasmid DNA, 200 billion DNA fragments per vial [153].

A surprising and potentially alarming discovery was the presence of the Simian virus 40 (SV40) promoter in samples of the Pfizer vaccine, which was notably absent from the Moderna vaccine samples [151]. In October 2023, the regulatory agency Health Canada confirmed the presence of this genetic sequence in mRNA vaccine samples [154]. SV40, an oncogenic DNA virus originally isolated in 1960 from contaminated polio vaccines, induces lymphomas, brain tumors, and other malignancies in laboratory animals [155]. Immunological data from cancer patients have indicated that their sera had a higher prevalence of antibodies against SV40 compared to healthy subjects [156]. A meta-analysis based on pooling diverse data from 1,793 cancer patients identified a significant excess risk of SV40 in association with brain tumors, bone cancers, non-Hodgkin's lymphoma, and malignant mesothelioma [157]. It seems improbable, however, that SV40 exposure alone results in human malignancy, as suggested by the absence of a cancer epidemic following the distribution of SV40-contaminated polio vaccines. A more likely scenario is that SV40 functions as a cofactor in the genesis and progression of tumors, as indicated by laboratory studies revealing its cocarcinogenic potential with asbestos, an established carcinogen [158].

The SV40 promoter has found potential use as an enhancer in gene therapy treatments based on DNA plasmids. In a 2001 study on somatic gene delivery to skeletal muscle cells, it was shown that incorporation of the SV40 enhancer into DNA plasmids could increase the level of exogenous gene expression by a factor of 20 [159]. According to an insightful editorial on the implications of process-related impurities, the packaging of DNA fragments into lipid particles enhances the possibility that the DNA fragments will integrate into the human genome [160].

While absent in the vials utilized during the registrational trials, the SV40 promoter has been identified in all tested BioNTech vials drawn from batches that have been distributed to the public. On December 6, 2023, Florida's surgeon general Joseph Ladapo contacted the FDA and CDC with questions about safety assessments and the discovery of billions of DNA fragments per dose of the mRNA vaccine products [161,162]. A week later, the FDA responded in writing by citing genotoxicity studies (which are inadequate for evaluating the risk of DNA integration) and by blurring the distinction between the SV40 promoter/enhancer and SV40 proteins, erroneously treating these elements as interchangeable [162]. Because the agency has thus far failed to provide any evidence of conducting DNA integration assessments to address the risks highlighted by the agency itself back in 2007, Ladapo called for a complete halt on the use of all COVID-19 mRNA vaccines [161,162]. In a Brownstone Institute article, mRNA vaccine developer Robert Malone strongly criticized the FDA's unwillingness to evaluate the potential risks of the contaminant DNA [163].

A joint statement offered by an international expert advisory panel sponsored by the World Council for

Health included the following: “There are multiple completely undeclared genetic sequences in both Moderna and Pfizer vials, with the SV40 sequence found only in the Pfizer vials. However, latent SV40 infections in a significant portion of the population could present the same SV40 risk to Moderna recipients. Even in the absence of chromosomal integration, the DNA plasmids could generate mRNA for the S-protein toxin and other harmful proteins for prolonged and unpredictable periods of time. Integration of foreign DNA into the human genome disrupts existing natural genetic sequences; this carries further risk of disease including cancer” [164]. Due to the lack of formal and transparent assessment by regulators, the experts also noted that it is currently impossible to provide informed consent for these products, as their complete risks remain undisclosed and not fully understood.

How did such dangerous, large-scale contamination escape the scrutiny of public health officials, and were the manufacturers aware of the issue? It is important to note that the process-related impurities were absent from the COVID-19 mRNA products used in the registrational trials. Virtually all doses used in those trials originated from “clinical batches” produced using what is known as Process 1 [1]. As a post-authorization emergency supply measure for global distribution, however, a method much more suitable for mass production known as Process 2 was devised utilizing bacterial plasmid DNA [165]. The Process 2 alterations include modifications to the DNA template employed for RNA transcription, changes in the purification phase, and adjustments in the manufacturing process of LNPs [165].

Notably, batches produced using Process 2 showed significantly reduced mRNA integrity [146,166]. According to the protocol amendment, each batch of the Pfizer product manufactured using Process 2 was administered to approximately 250 participants aged 16-55 years, with subsequent comparative analyses of immunogenicity and safety carried out on 250 randomly chosen recipients of Process 1 batches [165]. As of this writing, there are no publicly available analyses comparing the safety and reactogenicity of Process 1 and 2 batches.

Another relevant concern is the potential biological impact of replacing all the uridines in the RNA molecule with N1-methylpseudouridine. This strategy is regarded as a useful way to enhance protein expression as part of mRNA therapeutics [167]. This was also considered a breakthrough innovation, since the CureVac mRNA vaccine (CureVac N.V.. Tübingen, Germany), lacking this innovation, was less effective than the Pfizer and Moderna formulations [168]. The boost in effectiveness is likely because such an alteration retards the degradation process and thus causes the mRNA to last much longer. While N1-methylpseudouridine is a natural molecule, normally it is only present as a substitute for uridine in a small percentage of the uridines in a sequence. Still to be determined is what effect the massive introduction of N1-methylpseudouridine into the cell might have on its own synthesis of new mRNA molecules [169].

In a remarkable discovery, Mulroney et al. observed that the mRNA vaccines induced antibodies in mice to proteins that could be synthesized from the mRNA code if it were frameshifted by one nucleotide. This was not seen in cells challenged with just the S-protein or in mice vaccinated with the Astra-Zeneca vaccine (AstraZeneca plc, Cambridge, United Kingdom), which is a DNA-based vaccine [170]. They suggested that it was the N1-methylpseduouridylation that caused the frameshift. Such unintended, off-target proteins have, in Mulroney et al.’s terms, “huge potential to be harmful,” in part due to potential homology with human proteins that could, in turn, induce autoimmune disease [170-172]. Based on a query of the MedDRA code “Autoimmune disorder” in the Vaccine Adverse Events Reporting System (VAERS), there was an 803% increase in autoimmune disorders per million doses administered when comparing the administration of Influenza vaccines from 2018 to 2020 with COVID-19 vaccinations from 2021 to 2023 (Figure *5*) [173]. This represents an immense safety signal. Such fundamental questions and concerns about the technology should have been addressed before the products were delivered to hundreds of millions of people [174].

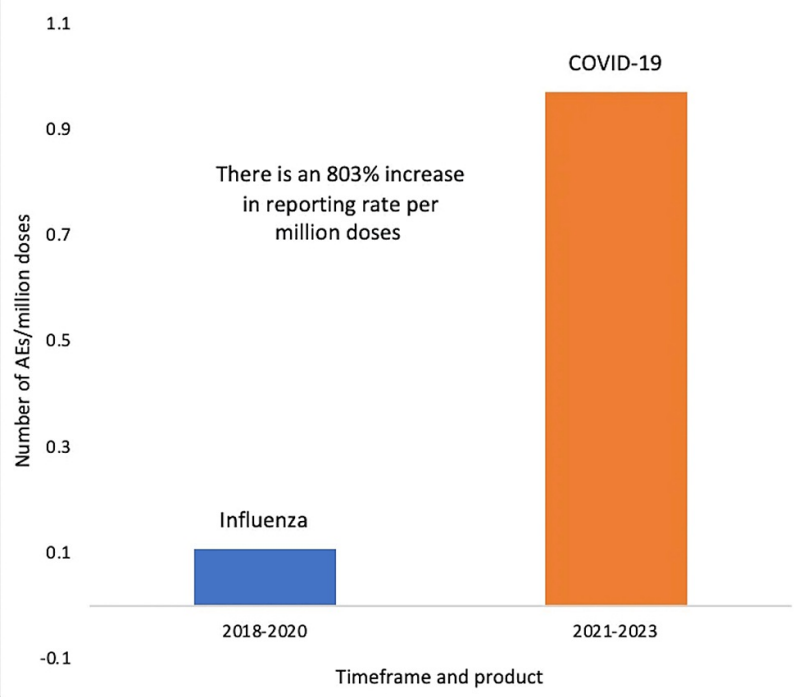

FIGURE 5: VAERS reports of autoimmune disease per million doses of COVID-19 mRNA (2021-2023) compared to Influenza (2018-2020) vaccinations

Based on a VAERS query (https://vaers.hhs.gov/) using the MedDRA code “Autoimmune disorder”, there was an 803% increase in reporting rate per million doses administered when comparing Influenza vaccines administered from 2018 through 2020 to COVID-19 mRNA injections administered from 2021 through 2023. Notably, the reports exclude individuals with a history of an autoimmune disorder.

Image credit: Jessica Rose (coauthor), [173]

Mechanisms underlying AEs

A complete discussion of the biological mechanisms that may explain the various AEs of the COVID-19 vaccines is beyond the scope of this paper. We therefore refer readers to these papers [26,175-181]. The mechanisms of molecular mimicry, antigen cross-reactivity, pathogenic priming, viral reactivation, immune exhaustion, and other factors related to immune dysfunction all reinforce the biological plausibility for vaccine-induced pathogenesis of malignant and autoimmune diseases [26, 182-185]. Both SARS-CoV-2 and the mRNA vaccines can trigger immune dysfunction along with a host of pathophysiological effects, including chronic inflammation, thrombogenesis, prion-related dysregulation, and endotheliitis-related tissue damage [180].

The mRNA vaccines offer unique mechanisms of immune activation that are quite distinct from the response to a viral infection. These mechanisms help explain the AE profile of these gene-based products. The S-protein itself is arguably the most toxic protein produced by the virus [180]. The distribution of mRNA-LNP across a diverse array of tissues facilitates the expression of S-proteins on cell surfaces across multiple cell types [186]. This, in turn, renders the target tissues susceptible to T-cell-mediated attack and subsequent destruction [109-111]. Notably vulnerable are tissues such as cardiac muscle and neuronal tissues [80,144], both characterized by limited repair and regenerative capacity. Furthermore, vascular tissues show widespread targeting and assault throughout the body [180].

Other components of the vaccines contribute to complex, poorly understood, and unpredictable AEs. These components include the lipid nanoparticles, in particular the ionizable cationic lipids, the polyethylene glycol (PEG), and various process-related impurities such as the DNA plasmids (discussed in the preceding section) recently detected by independent researchers [151,186]. Ionizable cationic lipids are known to be toxic, inducing pro-apoptotic and pro-inflammatory cascades [187]. Yet they are an essential component of the vaccines, supporting the more prolific synthesis of abundant S-protein from the mRNA.

More than three decades ago, researchers were aware of the unusual potential for synthetic cationic lipid nanoparticles to form amphiphilic aggregates, disrupt the cell membrane, induce an inflammatory response, and suppress immune function [188]. In fact, there is growing interest in an emerging new theory for immune function that can explain immune activation in the absence of overt infection. Seminal research by Matzinger and her immunogenetics research team at the US National Institute of Allergy and Infectious Diseases has pioneered the concept that immune responses are primarily driven by the need to defend against what is dangerous instead of what is foreign [189].

PEG, one of the primary adjuvant components of the COVID-19 mRNA vaccines, is believed to be a major factor in vaccine-induced anaphylactic shock, a well-established potential immediate SAE in susceptible individuals [190]. Conjugation of PEG to the nanoparticles increases its immunogenicity, causing complement activation and a subsequent acute and life-threatening reaction [191]. Furthermore, the combination of PEG with the vaccine-generated S-protein may contribute to sudden-onset pituitary disorders (pituitary apoplexy, with transition to acute hypophysitis) occurring within a week of COVID-19 vaccination [192,193]. Taieb and colleagues postulate that these vaccine components could trigger a systemic inflammatory response and circulatory problems associated with vaccine-induced thrombotic thrombocytopenia (VITT), resulting in pituitary hemorrhage or infarction [192]. Because the symptoms of pituitary apoplexy include headache, vertigo, fever, and myalgia (all common vaccine adverse reactions), the authors suspect that the actual rate of post-vaccine pituitary disorders is much higher than what has been typically recorded. In a Taiwan study, the rate of post-vaccination vertigo/dizziness appeared to be substantially higher among recipients of Moderna's mRNA-1273 compared to Pfizer's BNT162b2, with the median time to the onset of vertigo/dizziness being 12 days and six days, respectively [194].

There is a large and growing literature describing the remarkable toxic effects of the S-protein. Its persistence for up to 30 days following vaccination is of great concern [195]. The S-protein causes an acute inflammatory response, through activation of the NF-κB signaling pathway [196]. It has been shown to induce senescence in endothelial cells, and this likely contributes to the diverse vascular-related AEs [197]. Of great concern is its amyloidogenic potential, which may play a significant role in the broad spectrum of neurological symptoms [198].

Following COVID-19 mRNA vaccination, particularly in young adults, many studies have found increased risks of myocarditis and cardiac arrhythmias, in some cases leading to sudden death [57,60,140,149,199-202]. The S-protein persists in circulation in young adults who developed myocarditis post vaccination, but not in vaccinated individuals who did not develop myocarditis [202]. Vaccine mRNA was isolated in the human heart at autopsy out to 30 days [195]. Direct cardiotoxicity of the Pfizer and Moderna mRNA vaccines on rat cardiomyocytes has been documented 48 hours after the injection [80]. S-protein and active inflammation were observed upon biopsy in young individuals hospitalized with COVID-19 vaccine myocarditis [203]. Cadegiani has proposed that a surge of adrenalin is a major precipitating factor in triggering cardiac arrest in young persons who suffer cardiac arrest in the setting of clinical or subclinical myocarditis [204]. An additional cardiotoxic mechanism may involve downregulation of angiotensin-converting enzyme 2 (ACE2) receptor expression following its binding to the S-protein. This can lead to unopposed ACE expression, increased angiotensin-2 levels, inflammation, and, ultimately, apoptosis [201]. Elevated angiotensin-2 causes inflammation and oxidative stress, which are major contributing factors in the progression of cardiomyopathy [205].

Generic immune suppression emerging after repeated booster injections poses another major concern. T-cell exhaustion refers to an immunologic condition in which CD8+ T cells show a progressive loss of cytokine production and cytotoxic potential [206]. Such dysfunction is known to occur in conditions such as chronic infections, cancer, and autoimmune diseases [207,208]. After three and four doses of the COVID-19 mRNA vaccine, researchers observed a diminished T-cell response against the S-protein, associated with a class switch to IgG4 [209]. Not only does IgG4 not protect from infection, but it actively blocks other IgGs to suppress their action, leading to immunosuppression [210]. Notably, a reduced T-cell response against SARS-CoV-2 was observed one month after receiving the third and fourth doses [211]. Such T-cell exhaustion in the wake of multiple COVID-19 mRNA inoculations could help explain the findings from studies showing increased rates of COVID-19 with increased frequency of boosters [99,100].

Loacker et al. demonstrated a significant increase in the expression of programmed death ligand 1 (PD-L1) on the surface of immune cells, measured two days following the second mRNA injection [212]. The binding of PD-L1 to PD-1 found on cancer cells restricts the ability of T cells to eliminate cancer cells, thereby facilitating tumor immune evasion [213]. Elevated levels of PD-L1 on immune cells may predispose cancer patients to unfavorable outcomes, and treatments that target PD-L1 suppression (anti-PD1 blockade) are gaining traction as viable therapeutic options [214]. Rapid progression of various lymphomas has been linked to COVID-19 mRNA vaccinations [215-218], and elevated PD-L1 may play a role in this context.

Other factors related to the oncogenic and tumor-hyperprogressive potential of the COVID-19 vaccines have become a focus of intensive inquiry. A recent review by Angues and Bustos explores the hypothetical capacity of COVID-19 vaccines to activate biological mechanisms that may collectively create a microenvironment conducive to cancer progression, either accelerating existing macroscopic disease or awakening dormant micrometastases [219]. These mechanisms relate primarily to the pro-inflammatory

effects of the S-protein and LNPs, disruptions in the body's ability to generate type I interferon, and disturbances in the regulation of cellular microRNAs caused by the altered structure of mRNA within the vaccines [219]. Additionally, the COVID-19 mRNA vaccines elicit elevated concentrations of interleukin-17 (IL-17) and upregulation of Th17, thereby disrupting Th1-Th2 immunity, escalating the chronic inflammatory condition of cancer patients, and further amplifying tumor growth and progression [220-222].

Immunologic basis for vaccine inefficacy

The biomedical purpose of the COVID-19 mRNA vaccination is basically twofold: (1) to leverage the body's immune defenses against infection by SARS-CoV-2, and (2) to reduce the risk of severe disease and its consequences. Following intramuscular injection with the mRNA product, the S-protein-encoding mRNA is delivered via LNPs to human cells that generate S-proteins and/or related antigens that resemble those present on the surface of the coronavirus [25]. These antigens then stimulate the production of memory T-cells and B-cells, with the latter subsequently producing antibodies that bind to specific epitopes of the virus. Consequently, if a vaccinated individual encounters SARS-CoV-2, their immune system will mount a robust adaptive immune response in the short term, theoretically reducing the severity of the infection. This reduction in COVID-19 symptoms represents the intended clinical benefit of these biologicals.

The above explanation, however, connotes an immunologic disconnect between the systemic effects of the COVID-19 vaccination and the protection naturally afforded by lung mucosal immunity. SARS-CoV-2 is primarily an airborne virus that enters the human body via the upper respiratory tract. Thus, the immune system's first encounter with the pathogen usually occurs in the nasal passages and tonsils, inducing the production of secretory IgA antibodies in saliva, nasal fluid, tears, and other secretions within just four days of the initial exposure [223]. The virus is then successfully confined to the upper respiratory tract, resulting in either asymptomatic infection or mild symptoms such as a cough or sneeze [223]. The combination of secretory IgA and activated tissue-resident T-cells in mucosal areas can halt the infection altogether, rather than just limiting the infection and curbing disease symptoms [224]. Moreover, based on studies of SARS-CoV (the presumed predecessor to SARS-CoV-2), the cellular immunity that accompanies the initial respiratory infection may persist for up to 17 years, even without a detectable humoral component [225]. In research involving human participants who consented to exposure to the H1N1 flu virus, pre-existing mucosal IgA provided better protection against severe illness than systemic IgG [226], suggesting that high circulating IgG titers might not correlate with robust protection. The lung mucosa produces an array of innate immune factors (e.g., complement, proteases, lactoferrin, and antimicrobial peptides) that work in synchrony with secretory antibodies (sIgA and sIgM) to limit the entry of foreign microbes and particles [227]. During infection, neutrophils are the predominant responders, releasing IL-8 and elastase to enhance the recruitment of natural killer cells, monocytes, and eosinophils from the circulation [227].

Given this immunological context, it is reasonable to surmise that the natural mucosal immunity against SARS-CoV-2 and other respiratory viruses may typically lead to more comprehensive, long-lasting protection compared to the systemic immune responses elicited by the COVID-19 vaccinations. Whereas SARS-CoV-2 infection induces both mucosal and systemic immune responses, the COVID-19 mRNA vaccines, as currently administered, are ineffectual in terms of inducing mucosal immunity [227,228]. The presumed benefits of vaccine-induced immunity are further counterbalanced by the SAE risks discussed previously. It cannot be overemphasized that these risks pertain to the entire population, the vast majority of whom have the capacity to eliminate SARS-CoV-2 without succumbing to severe morbidity or premature death.

When federal officials said the COVID-19 mRNA vaccines were "safe and effective", they often added that the products were "95% effective against the infection". Nonetheless, later studies showed that any protective benefit was short-lived, with immunity waning after only a few months [229,230]. This waning effect becomes more pronounced with successive boosters [231]. There is a logical explanation for this phenomenon. First, due to viral evolution, SARS-CoV-2 variants are constantly mutating, and numerous mutations have occurred in the S-protein, the intended target for neutralizing antibodies. These mutations, mostly concentrated in the vicinity of the receptor-binding domain (RBD), create constant opportunities for the generation of new escape variants (i.e., those that evade neutralizing antibodies), thus enabling immune evasion in subsequent vaccinations. Second, confrontation with novel antigens on escape variants is associated with "original antigenic sin", the production of cross-reactive antibodies that may not be effective against the new antigen or pathogen due to prior exposure to predecessor strains [232,233]. Although cross-neutralization is a rare event, cross-reactivity in antibody binding to S-protein is common in the context of SARS-CoV-2 infection [234]. Additionally, other research indicates a degree of cross-reactivity between seasonal coronaviruses and SARS-CoV-2 [235].

When the immune system becomes entrained on preexisting SARS-CoV-2 variants, there is a progressive narrowing of the antibody response to the current, prevailing variants. This imprinting phenomenon has been demonstrated with respect to both natural infection and COVID-19 vaccination [236]. A 2021 pilot study found robust increases in humoral responses in SARS-CoV-2-naïve individuals following each dose of BNT162b2, whereas previously infected individuals showed strong humoral responses to the first dose of the mRNA injection but muted responses to the second dose [237]. Immune imprinting was also identified as the underlying factor contributing to the unanticipated decrease in the effectiveness of the bivalent COVID-19

vaccines since the "immune systems of people immunized with the bivalent vaccine, all of whom had previously been vaccinated, were primed to respond to the ancestral strain of SARS-CoV-2" [238].

At least part of the immunologic basis for COVID-19 vaccine failure can be summarized as follows. SARS-CoV-2's S-protein binds to the ACE2 receptor, creating a scenario wherein strong selective immune pressure prompts the S gene to mutate and develop viral escape mechanisms. Since the majority of SARS-CoV-2 vaccines are designed using the S-protein sequence from the initial Wuhan strain, these escape mutants can effectively evade the immune responses triggered by these vaccines. This leads to reduced effectiveness of all subsequent injections with mRNA products utilizing the original S-protein sequence [236,239,240]. Periodic COVID-19 mRNA inoculations may adversely impact viral ecology and encourage the ongoing emergence of immune escape variants (i.e., variants escaping the selective pressure via mutation) that ultimately render the vaccines ineffective. Such diminishing returns were observed in the Cleveland Clinic studies discussed earlier in this paper [99,100]. Additionally, ongoing boosters are likely to cause immune dysfunction, thereby diminishing antiviral and microbial protection while promoting autoimmune disease and accelerated cancer progression.

Given the ongoing genetic changes in SARS-CoV-2 driven by both natural viral evolution and vaccine-induced selective pressure on the immune system, it is likely that frequent COVID-19 mRNA vaccinations would need to be administered in the coming years to address new prevailing variants. However, the immune imprinting noted above could limit the ability to achieve robust protection and could potentially facilitate viral transmission even with population-wide vaccination [239]. Immune evasion by new or emerging SARS-CoV-2 variants in individuals vaccinated against former variants will continue indefinitely, due to antibody cross-reactivity and immune imprinting.

Somewhat ironically, then, the mRNA vaccines' ability to perpetuate the emergence of new variants also tends to engender the perception among the general public that a new round of boosters is necessary. This, in turn, sets up an endless vaccine-escape variant cycle, a feedback loop whereby the actions taken to address the issue (more vaccinations) inadvertently contribute to ongoing inefficacy. Mutations in the viral S-protein provide resistance against antibody responses, and this selection process underlies the larger phenomenon in which new dominant variants are emerging [241-243]. Mass mRNA inoculations result in the natural selection of highly infectious immune-evading SARS coronavirus variants that successfully bypass vaccine-induced immunity, leading to a dramatic rise in the prevalence of these variants [108].

In summary, the large-scale emergence of dominant variants was an adaptive response to the selection pressure exerted by the mass vaccination campaign, a response further heightened in immunosuppressed individuals [244]. Importantly, the immune-escape mutants are developing primarily in vaccinated individuals, not in the unvaccinated [245,246][241,242]. Mechanisms underlying vaccine-induced immune dysfunction (see preceding section) contribute further to the inefficacy. The main factors involved in COVID-19 mRNA vaccine inefficacy are summarized in Figure *6* [247].

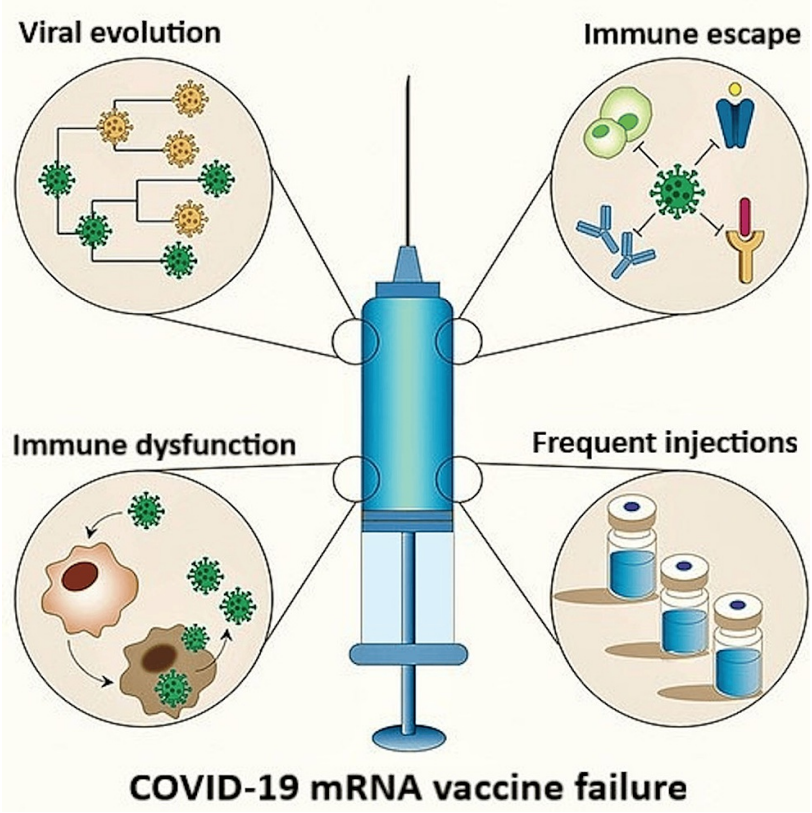

FIGURE 6: Factors contributing to COVID-19 mRNA vaccine inefficacy

COVID-19 vaccines may lose efficacy in part by inducing SARS-CoV-2 mutations that lead to new immune escape variants, thus ultimately limiting vaccine-related protection against subsequent coronavirus infections. Periodic COVID-19 mRNA injections could elicit a diverse range of mechanisms associated with immune dysfunction (mostly due to subversion of innate immunity), resulting in a heightened risk of cancers, infections, and autoimmune disorders.

Image Credit: Majumder and Razzaque, 2022 [247]; adapted with permission from authors.

Discussion

In this review, we consider alternate narratives based on a direct assessment of available data and published studies. By doing so, our intention is to foster transparency, trust, and informed decision-making, ensuring that the public's legitimate questions concerning COVID-19 vaccine safety are addressed. This approach not only contributes to the ongoing discourse surrounding safety but also paves the way for the improvement in public health strategies going forward. The ethical implications of our inquiry relate to epidemiological inequities: whereas COVID-19 has primarily afflicted the immunosuppressed, elderly, and those with multiple comorbidities, the COVID-19 vaccinations have the potential to adversely impact people of all ages, not only frail elderly individuals (the most vulnerable sub-group) but also young and relatively healthy individuals, most of whom have a near-zero risk of serious consequences from COVID-19 [40]. When we consider the likelihood of more frequent SAEs resulting from interactions between COVID-19 mRNA vaccination and subsequent SARS-CoV-2 infections, it is important to bear in mind that the Omicron subvariant infections that have been dominant since early 2022 follow a mild course and are invariably non-lethal [248]. Moreover, whereas infections by their very nature are involuntary and accidental, the mRNA injections are a choice with potentially life-threatening repercussions.

The pivotal role of randomized placebo-controlled clinical trials in assessing the efficacy of vaccines and other interventions has long been recognized within the medical and public health communities. The value of well-designed controlled trials was highlighted in a report by the WHO Ad Hoc Expert Group on the Next Steps for COVID-19 Vaccine Evaluation published in January 2021 [249]. Ensuring the credibility of observed outcomes, particularly in the context of novel experimental drugs such as modified RNA-LNP products, entails a meticulous process of randomly assigning subjects meeting various criteria to either intervention

or placebo groups. Randomization not only establishes a baseline for comparison but also facilitates the attribution of any differences in outcomes to the intervention itself. The placebo control minimizes the chances of erroneous conclusions about the intervention's effects. Although invaluable as tools for detecting safety signals, national health surveillance databases such as VAERS and Yellow Card do not meet the rigorous standards set by controlled trials, further underscoring the necessity of this approach for the assessment of medical and public health interventions.

In retrospect, the most concerning revelation from the registrational trials that led to the EUA was not the apparent overstatement of 95% efficacy, but rather the indication within those trials that the vaccines carried a significant risk of SAEs and premature death, even among a relatively healthy group of participants. Based on the extended Pfizer trial findings, our person-years estimate yielded a 31% increase in overall mortality among vaccine recipients, a clear trend in the wrong direction. Moreover, the Fraiman et al. analysis showed a significant 36% higher risk of SAEs (including deaths and many life-threatening conditions) in the vaccine group for the Pfizer trial [50]. The Michels et al. analysis found a nearly four-fold increase in cardiovascular SAEs among subjects in the Pfizer trial who received the BNT162b2 injection compared to placebo, a fact never reported to the public at the time of the rollouts in December 2020 [54]. Notwithstanding these grave concerns, the Moderna product has shown even more frequent AEs when compared to its Pfizer counterpart [116-120,135]. Both mRNA products were linked with increased risks of ischemic stroke, brain hemorrhage, acute coronary syndrome, and other conditions known to reduce life expectancy.

Against this backdrop, and, in particular, given the high NNV (~52,000 vaccinations needed to prevent one COVID-19 death), the rationale behind the FDA's decision to declare the COVID-19 mRNA vaccines "safe and effective" for worldwide distribution after only 20 weeks of observation seems dubious at best. Indeed, one might have expected the COVID-19 mRNA vaccines to have been withdrawn from the market following the Fraiman study's revelation of one SAE in 800. The 1976 swine flu vaccine was pulled after being associated with Guillain-Barré Syndrome at a rate of approximately one in 100,000 [250]. The rotavirus vaccine Rotashield was withdrawn following reports of intussusception in one or two in 10,000 vaccinees [251]. In the case of the mRNA vaccines, Fraiman's team reported their preliminary findings to both the FDA and EMA. Leaders from both agencies met with the team and provided feedback that resulted in a revised analysis [50]. Nonetheless, the regulators took no action afterward to warn the public and restrict access to the injections.

Along similar lines, the forensic analysis by Michels et al. exposed serious flaws in the methods used by the FDA, CDC, and NIH in the development and safety/efficacy evaluation of new pharmaceutical products [54]. The authors concluded that "the decision to approve the BNT162b2 mRNA vaccine by the US FDA and other international regulatory agencies was not an informed decision based on an unbiased, thorough, and transparent evaluation of the evidence intended to demonstrate that this vaccine met the criteria that it was a 'safe and effective' means of controlling the COVID-19 pandemic" [54]. Pfizer had an ethical responsibility to proactively disclose any new information that could impact the FDA's decision-making process. Their failure to do so was factually misleading. Conversely, it is reasonable to expect that all participants in the VRBPAC meeting should have been aware that the trial's mortality data from November 14, 2020, had become outdated. Remarkably, no VRBPAC members inquired about updates on AEs that transpired between the EUA data cutoff date (November 14, 2020) and the date of the meeting (December 10, 2020) [54].

According to a 393-page confidential document requested by the EMA and released in August 2022 [114], Pfizer had by that time documented approximately 1.6 million AEs covering nearly every organ system [114, 252,253]. One-third of the AEs were classified as serious. Among the many findings were 3,711 tumors, 264 categories of vascular disorders (73,542 cases total), over 100,000 blood and lymphatic disorders, 127,000 cardiac disorders (including 270 categories of heart damage in addition to myocarditis and pericarditis), 77,000 psychiatric disorders (including psychoses, depression, suicide and suicidal behaviors), and hundreds of categories of neurological disorders (696,508 cases total), many of which are considered very rare, a clear indication of grave hazards. These estimates offer a striking contrast with the official FDA document titled "Summary Basis for Regulatory Action" dated November 8, 2021, in which the review committee voted to approve the Pfizer-BioNTech product [56]. The report's entire "Risk-Benefit Assessment" section consists of a single sentence: "Considering the data submitted to support the safety and effectiveness of COMIRNATY that have been presented and discussed in this document, as well as the seriousness of COVID-19, the Review Committee is in agreement that the risk/benefit balance for COMIRNATY is favorable and supports approval for use in individuals 16 years of age and older" [56].

International analyses of excess mortality indicate that COVID-19 vaccinations may have had serious largescale consequences. In a careful study of mass vaccinations throughout Europe in 2021-2022, Aarstad and Kvitastein analyzed the potential interplay between COVID-19 vaccination coverage in 2021 across Europe and subsequent monthly excess mortality through 2022 [254]. Utilizing a well-curated dataset encompassing 31 nations, the authors applied population-weighted analyses and found the following: (a) increases in ACM during the initial nine-month period of 2022 were positively correlated with increases in 2021 vaccination distribution; and (b) each percentage point increase in 2021 vaccination coverage was associated with a 0.105% increase (95%CI 0.075-0.134) in monthly mortality during 2022. An extensive, multi-country ecological analysis by Rancourt and colleagues estimated that COVID-19 vaccination resulted

in 17 million excess deaths, with a global vaccine-dose fatality rate (vDFR) of 0.1257 ± 0.0035%, or approximately 0.1% [251]. Rancourt's 180-page report showed that the COVID-19 vaccine rollouts were synchronously followed by peaks in all-cause mortality in many countries [255,256].

While most vaccinees have an extremely low risk of COVID-19 hospitalization and death, they face a relatively high risk of SAEs (one SAE for every 800 injections) following the COVID-19 mRNA vaccination [50]. This disturbing dichotomy is most pronounced in the context of the childhood immunization programs, although in fact all ages under 40 show near-zero IFRs. Pezzullo et al. calculated median IFRs of 0.0003% at 0-19 years, 0.002% at 20-29 years, and 0.011% at 30-39 years [40]. As noted earlier, death rates among children have been extremely low even in countries showing excess mortality during the pandemic [43], and allowing children to attend school freely, as occurred in Sweden, resulted in zero COVID-19 deaths among this younger age group [44]. Given this very low risk to children, we must reject the policy of administering an experimental vaccine to these age groups. Against the (then dominant) Omicron subvariant, BA.5, the bivalent mRNA vaccines were only tested in eight mice, never in humans [257]. Following this authorization, noted vaccinologist Paul Offit, a member of the VRBPAC, wrote: "We should stop trying to prevent all symptomatic infections in healthy, young people by boosting them with vaccines containing mRNA from strains that might disappear a few months later" [237]. Based on the best available evidence, the potential risks of these mRNA inoculations have consistently outweighed the benefits for younger generations [258,259]. Consideration of a harm-to-reward calculus weighs heavily on factors like lymphomas [215-218] and heart damage [57-63] in these younger age groups. With regard to cardiac risks, prospective studies with careful assessments of potential myocardial damage have found that the risk of ambulatory young individuals developing myocarditis is about 2.5% (2500 per 100,000 recipients) for either BNT162b2 or mRNA-1273 following the second or third injections [260,261]. The 2.2% myocarditis risk in adolescent teens following the COVID-19 mRNA injection is approximately 37 times the risk associated with SARS-CoV-2 infection (0.06%) in that same age group [260,262]. Given these estimates, there is no valid reason for vaccinating this age group.

Figure 7 shows a graph based on myocarditis reports in VAERS Domestic Data as of September 29, 2023, which offers an indication of the gravity of this situation. All myocarditis reports are plotted according to age and dose (dose 1 (pink), dose 2 (green), and dose 3 (blue)). After dose two, there was a five-fold increase in myocarditis cases among 15-year-old males. Regardless of age, myocarditis cases were more frequent following dose two, which is suggestive of a causal link between myocarditis and the COVID-19 mRNA inoculations. The data depicted in the chart are further reinforced by a recent disproportionality analysis of VAERS data showing a statistically significant association between cardiovascular events and COVID-19 vaccinations [263].

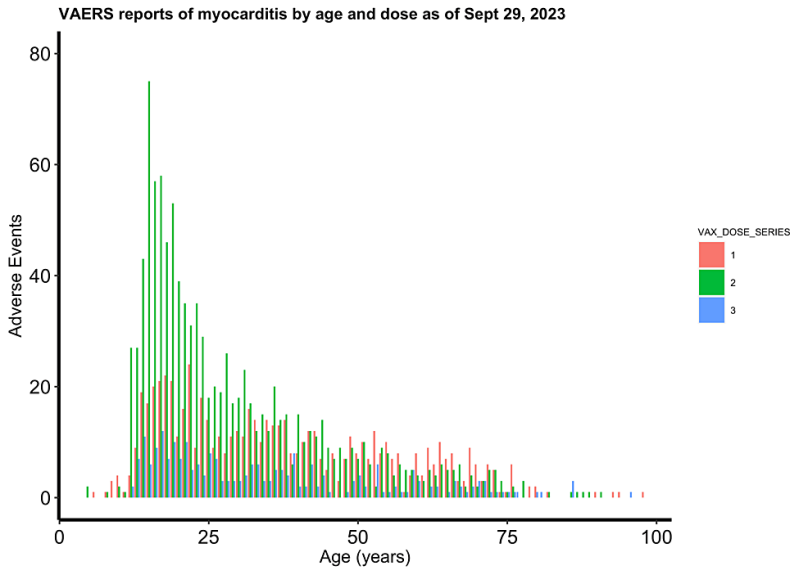

FIGURE 7: Myocarditis reports in VAERS Domestic Data as of September 29, 2023, plotted by age and dose

Dose 1: pink, Dose 2: green, Dose 3: blue

Data indicates a five-fold rise in myocarditis cases after the second COVID-19 shot for 15-year-old males, and overall, second doses were linked to more myocarditis cases [263].

VAERS: Vaccine Adverse Event Reporting System; COVID-19: coronavirus disease 2019

Image Credit: Jessica Rose (coauthor).

The adverse impacts on younger segments of the population were also reflected by the extraordinary reports from US life insurance companies for the latter half of 2021. According to the Group Life survey data, during Q3 and Q4 of 2021, the general US population experienced a 32% increase in mortality compared to 40% in the Group Life count (8% difference) [264]. Group Life Policyholders are well-employed, young, and generally healthy adults, previously dying at about one-third the rate of the US population, based on a 2016 Society of Actuaries (SOA) analysis [264]. Thus the mortality observed among the Group Life cohort in 2021 represents an inversion of previous trends. The excess deaths in the Group Life data were determined by comparing average death rates in the Group Life data from the 2017-2019 baseline, adjusted for seasonality and combined with CDC data. Between Q2 and Q3, the beginning of the second US vaccination rollout, the SOA analysis showed a 36% increase in excess mortality for ages 25-34, a 50% increase for the 35-44 age group, and a 52% increase for the 45-54 age group [264]. These numbers represent colossal and unprecedented increases in excess mortality for the 25-54 age range, with an average increase of 46% (though averaging the percentages tends to mask the severity of the impact on specific age cohorts) [264].

As mentioned above, these were younger, healthier adults, and thus it is illogical to suggest that COVID-19 had any substantial influence on mortality, especially given the extremely low IFR associated with the younger age brackets. Indeed, according to the most recent Group Life report, the excess mortality in each of the age groups applied only to “non-COVID-19” deaths; there was no excess mortality directly attributed to COVID-19 [264]. Importantly, the surge in excess mortality among the 25-54 age group was also temporally associated with the introduction of US vaccine mandates among military and hospital personnel from the summer into the fall of 2021 [265]. From March 2021 to February 2022, there were approximately 61,000 excess deaths among Americans under age 40, equivalent to all US servicemen lives lost during the Vietnam War [266]. This tragedy was never reported by any of the major US news media.

The health-related repercussions of these vaccine-related heart risks have been manifesting on the public stage since 2021. Prior to that year, the average annual number of cardiac arrests on the field for professional athletes in Europe was 29; this number has risen to 283 per year, an approximately 10-fold increase, based on the annualized rate of cardiac arrests following the vaccination program’s inception for active players aged 35 [267]. Two-thirds of the players were not resuscitated [267]. Recent research suggests there may be a genetic basis (SCN5A variants) for sudden deaths occurring within seven days of COVID-19

vaccination, regardless of vaccine type, number of doses, and underlying diseases [268]. By identifying genetic risk factors (e.g., MTHFR polymorphisms) before receiving the COVID-19 vaccine, the risks of venous thromboembolism and other vaccine-related vascular injuries can be more effectively addressed [269,270].

The World Council for Health has demanded an immediate moratorium on these novel products [164], due in part to the issue of extensive DNA contamination. On a precautionary basis, we agree with recommendations for the immediate removal of the COVID-19 vaccines from the childhood immunization schedule along with the suspension of boosters and a full investigation of the vaccine industry's and regulatory agencies' misconduct regarding safety assessments and data from the founding trials. It is unethical and unconscionable to administer an experimental vaccine to a child who has a near-zero risk of dying from COVID-19 (IFR, 0.0003%) but a well-established 2.2% risk of permanent heart damage based on the best prospective data available. Additional risks for these otherwise healthy young individuals include seizures, cancers, autoimmune disorders, and numerous other life-stealing conditions post vaccination.

Another relevant aspect of this unfolding tragedy is the untold story of reduced life expectancy. In many developed countries, the main causes of reduced life expectancy (smoking, obesity, opioid overdose, homicides, suicides, and infant mortality) are the primary causes of premature death on a population scale [271]. Nevertheless, it is also clear that several risks associated with COVID-19 vaccinations may translate into premature death in the long term. Among the poor, untreated bacterial pneumonia is a major cause of reduced life expectancy and may be further exacerbated by COVID-19 vaccination [272]. Strokes and myocarditis associated with COVID-19 vaccinations may cause premature death years after the initial event. A longitudinal study of stroke patients found that fewer than 28 days after a stroke, the risk for death was 28%; this increased to 41% at one year and 60% at five years [273]. Undiagnosed heart and clotting problems can persist asymptomatically for years. Multiple autopsy studies provide definitive evidence of serious post-injection damage to the heart, including sudden cardiac arrest and sudden death, all associated with the COVID-19 mRNA vaccines [140]. In adolescent males, however, myocarditis can have a mild outward clinical appearance yet result in severe cardiac fibrosis (scarring), with permanent damage to the heart muscle [274,275]. Such damage can eventually lead to congestive heart failure and death many years later [276]. The registrational trials were insufficient for detecting these long-range hazards, most of which only became evident after 2.5 years of follow-up observation and over a billion mRNA injections.

Also germane to this discussion is the medically intractable phenomenon known as "long COVID". After the acute phase of a SARS-CoV-2 infection, some individuals experience persistent symptoms like fatigue, brain fog, muscle pain, breathing difficulties, tingling extremities, and chest and throat discomfort for extended periods. This has come to be known as post-acute COVID-19 syndrome (PACS), a multifactorial, multisystemic condition encompassing dysautonomia, encephalitis, chronic fatigue syndrome, immune dysfunction, cardiovascular and clotting abnormalities, and impacts on multiple organ systems [277]. Specific types of PACS can be defined based on the presentation of symptoms [278,279]. Not surprisingly, because of the common denominator between infection and mRNA inoculation (the S-protein), COVID-19 vaccination produces long-term symptoms that share many features with PACS [280,281]. The condition may be triggered by an immune overreaction to the vaccine-generated S-protein [282], which has been shown to persist at least six months after the injection [283]. Vaccine-associated S-protein has been found in PACS patients [284,285]. Diexer et al. observed that 70% of PACS cases occurred in individuals who had received full COVID-19 vaccination, indicating that the injections may exacerbate PACS in most cases [286]. The group with the lowest risk of PACS was the unvaccinated individuals who contracted Omicron as their first infection. Thus, contrary to popular beliefs and media messaging, vaccinated individuals may experience more severe long-term outcomes of COVID-19 compared to the unvaccinated. Several new syndromes associated with the mRNA inoculations have been introduced that encompass conditions very similar to PACS: post-COVID-19 vaccination syndrome (PCVS), acute COVID-19 vaccination syndrome (ACVS), and post-acute COVID-19 vaccination syndrome (PACVS) [287]. It has been proposed that the forthcoming version of the International Classification of Diseases (ICD) diagnostic codes should incorporate a new code specifically for "post-COVID-19 vaccination condition, unspecified" [287].

In addition to addressing the complex, post-COVID-19 vaccine-related conditions alluded to above, it is our bioethical imperative to carefully consider other consequences of ongoing, repeated boosters. Broadly speaking, these consequences may be divided into two categories: (1) diminishing returns following the injections due to various immune-suppressive effects along with extrinsic selective pressures that ultimately accelerate viral evolution and resistance; and (2) SAEs, notably the profound suffering and premature death resulting primarily from autoimmune, neurological, malignant, and cardiovascular disorders. Consideration of both the potential immunological impacts of repeated booster doses on viral evolution and resistance alongside the risks of premature death and other SAEs is crucial for a comprehensive risk-benefit assessment of the mRNA COVID-19 vaccinations, ensuring informed public health decisions.

Based on the research presented in this narrative review, the global COVID-19 vaccination campaign should be regarded as a grave medical error. Medical errors represent a substantial threat to personal and public safety and have long constituted a leading cause of death [288-290]. Misguided political and regulatory decisions were made at the highest levels and may have been heavily influenced by financial incentives. Government agencies should have considered all reasonable treatment alternatives and deflected

pressures away from the medical-pharmaceutical industry rather than allowing population-wide distribution of experimental genetic vaccines. Had the FDA recognized the nearly four-fold increase in cardiac SAEs (including deaths) subsequently identified in the Pfizer trial's vaccine group [54], it is doubtful that the EUA would have transpired in December 2020. An in-depth investigation of the COVID-19 vaccine's long-term safety profile is now urgently needed. Despite the many striking revelations discussed in this review, most developed countries continue to advocate the ongoing adoption of COVID-19 mRNA boosters for the entire eligible population. US federal agencies still emphasize the safety of the vaccines in reducing severe illness and deaths caused by the coronavirus, despite the absence of any randomized, double-blind, placebo-controlled trials to support such claims. This reflects a bewildering disconnect between evidence-based scientific thinking and public health policy.

Conclusions

Careful, objective evaluation of COVID-19 mRNA product safety is crucial for upholding ethical standards and evidence-informed decision-making. Our narrative review concerning the registrational trials and the EUA's aftermath offers evidence-informed insights into how these genetic vaccines were able to enter the market. In the context of the two pivotal trials, safety was never assessed in a manner commensurate with previously established scientific standards either for vaccines or for GTPs, the more accurate classification of these products. Many key trial findings were either misreported or omitted entirely from published reports. The usual safety testing protocols and toxicology requirements were bypassed by the FDA and vaccine manufacturers, and the premature termination of both trials obviated any unbiased assessment of potential SAEs due to an insufficient timeframe for proper trial evaluation. It was only after the EUA that the serious biological consequences of rushing the trials became evident, with numerous cardiovascular, neurological, reproductive, hematological, malignant, and autoimmune SAEs identified and published in the peer-reviewed medical literature. Moreover, the COVID-19 mRNA vaccines produced via Process 1 and evaluated in the trials were not the same products eventually distributed worldwide; all of the COVID-19 mRNA products released to the public were produced via Process 2 and have been shown to have varying degrees of DNA contamination. The failure of regulatory authorities to heretofore disclose process-related impurities (e.g., SV40) has further increased concerns regarding safety and quality control oversight of mRNA vaccine manufacturing processes.

Since early 2021, excess deaths, cardiac events, strokes, and other SAEs have often been wrongly ascribed to COVID-19 rather than to the COVID-19 mRNA vaccinations. Misattribution of SAEs to COVID-19 often may be due to the amplification of adverse effects when mRNA injections are followed by SARS-CoV-2 subvariant infection. Injuries from the mRNA products overlap with both PACS and severe acute COVID-19 illness, often obscuring the vaccines' etiologic contributions. Multiple booster injections appear to cause immune dysfunction, thereby paradoxically contributing to heightened susceptibility to COVID-19 infections with successive doses. For the vast majority of adults under the age of 50, the perceived benefits of the mRNA boosters are profoundly outweighed by their potential disabling and life-threatening harms. Potential harms to older adults appear to be excessive as well. Given the well-documented SAEs and unacceptable harm-to-reward ratio, we urge governments to endorse and enforce a global moratorium on these modified mRNA products until all relevant questions pertaining to causality, residual DNA, and aberrant protein production are answered.

Appendices

Appendix 1

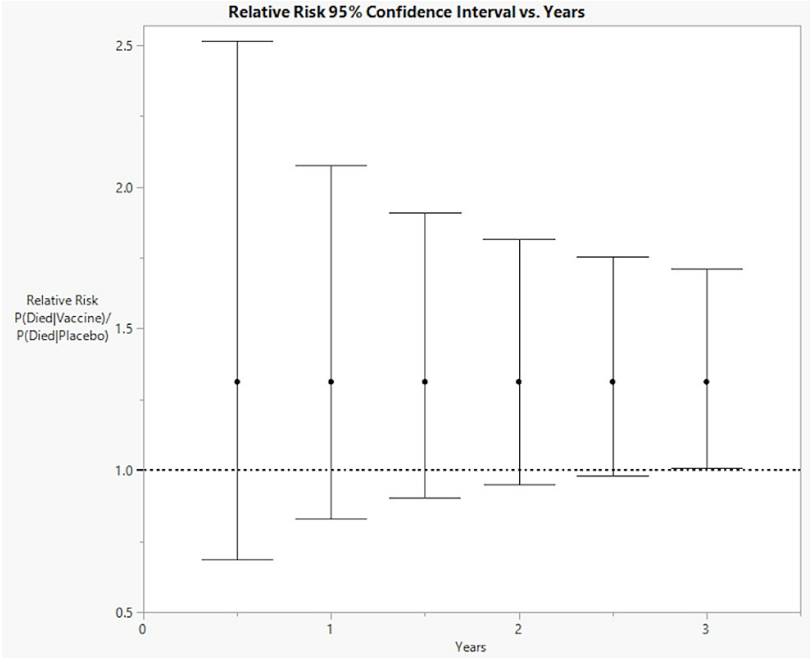

FIGURE 8: Registrational trial for Pfizer, projected three-year mortality If the six-month Pfizer trial had continued, the risk difference would reach statistical significance at 34 months, with a 31% higher mortality risk in the vaccine group compared to the placebo group

This is a transparent, quantifiable, and simple illustration of how small death rates might become statistically significantly different over time within the three-year duration originally planned for the trials. Hypothetically, if the six-month Pfizer trial had continued, assuming the relative risk of 1.31 remained constant and deaths accrued at the same rates as during the trial, then the lower limit of the 95% confidence interval would exceed one at 34 months. Stated another way, the relative risk would exhibit statistical significance ($p<0.05$) at this time, with a 31% increased mortality risk in the mRNA vaccine vs placebo groups. This calculation assumes death rates are held constant in each group and mortality is measured at six-month intervals, with p-values monotonically declining over time. Thus, assuming the mortality rates continued unchanged in both groups as observed in the initial six months, the all-cause mortality difference would have become statistically significant ($p<0.05$) around 2.8 years (34 months). At 2.5 years, the p-value was at 0.065, decreasing to 0.053 by 2.75 years.

Chart generated by biostatistician Russ Wolfinger (coauthor).

Appendix 2

Regarding potential harms, assuming 30% false-positive reports and a moderate under-reporting factor of 21, we calculate a risk of 27 deaths per 100,000 doses of BNT162b2. Thus, applying these reasonable assumptions, the estimated harms of the COVID-19 mRNA injectables outweigh the rewards by nearly 14-fold.

This mortality analysis combines two groupings of data, the first reflecting benefits, and the second reflecting harms. The first data grouping assumes one is saving lives by using the vaccine to prevent severe COVID-19 symptoms and hospitalization, based on the Pfizer and Moderna founding RCTs. The second grouping utilizes data from injury-reported databases, specifically the UK Yellow Card data as obtained by Norman Fenton and colleagues [291]. The Fenton data is “per dose” so is effectively doubled to a “course” consisting of two injections. The Excel (Microsoft Corporation, Redmond, Washington, United States) formula is based on the rules of joint probability:
P(A & B) = P(A) + P(B) - P(A)*P(B) (assuming two events are independent).
It turns out that:
P(A)*P(B) is small, so in effect, it is P(A) + P(B), which if A=B is 2*P(A).

Benefits/Rewards

Calculations for the number of lives saved per 100K vaccinations, based on most generous assumptions are

as follows:
Assuming NNV of 119 and IFR of 0.23%, about ~52,000 vaccinations would be needed to prevent one death.
Upper limit of lives saved per is 10,000*1/52,000 = 0.19 or ~0.2 or 1/5 of a life is saved for every 10,000 courses of the mRNA vaccine.
Thus, for Pfizer mRNA vaccination, ~2 lives were saved from COVID-19 for every 100,000 courses of the vaccine.

Sources informing the numbers used in this estimate: NNV to prevent a case is 119, based on data from Olliaro et al., 2021 [66], and assuming the infection-fatality ratio of COVID-19 is generously estimated at 0.23%, based on 2021 WHO data from Ioannidis: https://apps.who.int/iris/handle/10665/340124

Estimates of IFR are based on meta-analysis and NNT obtained from the Phase 3 Pfizer trial. Given evidence of RCT fraud, this estimate should be viewed as an upper bound; the true value is likely much lower (i.e., even fewer lives saved).

Risks/Harm

Lives lost per 100,000 vaccinations-calculations based on the most conservative assumptions (URF=10):
Fenton calculates 68 deaths/1,000,000 doses = 12.8 deaths per 100,000 per primary course of Pfizer, or just under 13 deaths from serious adverse events per 100,000 for each primary course of the Pfizer vaccine.
Comparing AEs to potential benefits, we calculate an excess death risk of 12.8 - 2 = ~11 deaths per 100,000 doses.
Thus, comparing the benefits to harms, at least 5 times more lives are lost than saved by the full course of Pfizer mRNA vaccinations.

Notes on the estimate: Fenton number of 12.8 indicates an excess death risk of 12.8 - 2 = ~11/100,000 comparing the adverse effects to potential benefits. Our estimate is therefore alleging about one excess death per 9,000 Pfizer courses, which seems quite plausible. This is also in line with officially reported all-cause deaths in the Pfizer trial being 15 vaccinated and 14 in unvaccinated, which is a ~7% increase, although obviously not statistically significant. If there is one excess death per 9,000 jabs, a difference of ~2 deaths in 20,000 subjects/arm in the Phase-3 trial (one observed, but could be more) would be expected. Finally, a higher URF (e.g., 21, based on Rancourt data), would yield a higher estimate

Pfizer trial data, applying the same Fenton calculation sequence and 30% false-positive reports, with a moderately conservative URF of 21: (i) Lives saved per 100,000 vaccinated (by preventing one COVID-19 death): NNV to prevent one COVID-19 case = 59,574 (95% CI 51,118-71,381). Lives saved per 100,000 vaccinated = 1.7 (95% CI 1.4-2.0); (ii) Lives lost per million: Net excess deaths per primary Pfizer course: 3,705 (95% CI 3,667-3,744). Excess death risk of 27 deaths (95% CI 26.7-27.3) per 100,000 doses of Pfizer's COVID-19 mRNA vaccine.

Moderna trial data, applying the same Fenton calculation sequence and 30% false-positive reports, but with a moderately conservative URF of 21: (i) Lives saved per 100,000 vaccinations (by preventing one COVID-19 death): NNV to prevent one COVID-19 case = 25,394 (95% CI 22,434-29,254). Lives saved per 100,000 vaccinated (by preventing one COVID-19 death) = 3.9 (95% CI 3.4-4.5); (ii) Lives lost per 100,000 vaccinations (by preventing one COVID-19 death): Net excess deaths per primary Moderna course = 9,292 (95% CI 8,864-9,764). Excess death risk of 10.8 deaths (95% CI 10.2-11.3) per 100,000 Moderna vaccine courses.

Interpretation/context: There are three important numbers to consider in these calculations: net mortality, NNV, and net excess deaths per primary course. Net mortality is the overall mortality, including deaths caused by the vaccines as well as other cause of death that could be biologically plausible given the population. In this case, however, the population is relatively healthy and "low risk" in terms of COVID-19-related mortality (relatively healthy population with no comorbid diseases at baseline), and thus any disproportionate increase in overall mortality must logically be linked with the vaccination.

The epidemiological meaning of "net excess deaths per primary (Pfizer or Moderna) course" (NEDPC) number is the net cumulative incidence of increased death expected after vaccination, within about three months of the vaccine. In our calculation, the NEDPC number is the reciprocal of the net mortality. The interpretation is in the context of the calculation, i.e., benefits versus harms, with fairly conservative assumptions made on the harm side (false-positive reports and under-reporting assumptions).

Based on the founding clinical trial timeframes, we assume that three months is the period of time in which the vaccine would either incur benefit in terms of lives saved (related to the duration of trial and/or immunity) or incur harm, as in serious adverse events related to the vaccination. In real-world observational studies, longer timeframes would likely reveal other serious adverse effects that could result in premature death.

We also assume a 30% false positive rate (very conservative) and differing underreporting factors (URFs) of

10 and 21. The underreporting range is 10-100, with the upper end based on Harvard data of Lazarus et al. [292]. Thus, the URF of 10 may be deemed extremely conservative, and the URF of 21 is modestly conservative.

Calculation of the NNV is dependent on COVID-19 prevalence, and for this, we rely on the WHO website's seroprevalence study by Ioannidis et al. [293]. Due to our use of the injury database data, the hierarchy of evidence would be considered lower than for the analyses from the papers of Fraiman et al. [50] and Classen [49], which relied only on RCT evidence.

All of our "harm data" is from the UK's Yellow Card data set, which is stratified by vaccine in Fenton's analysis [291]. While this information comes from the UK population, the trials were principally conducted in North America; nevertheless, it is unlikely that the adverse event rates would be different between the two populations.

Additional Information

Author Contributions

All authors have reviewed the final version to be published and agreed to be accountable for all aspects of the work.

Concept and design: M. Nathaniel Mead, Stephanie Seneff, Russ Wolfinger, Peter A. McCullough

Acquisition, analysis, or interpretation of data: M. Nathaniel Mead, Stephanie Seneff, Russ Wolfinger, Jessica Rose, Kris Denhaerynck, Steve Kirsch, Peter A. McCullough

Drafting of the manuscript: M. Nathaniel Mead, Stephanie Seneff

Critical review of the manuscript for important intellectual content: M. Nathaniel Mead, Stephanie Seneff, Russ Wolfinger, Jessica Rose, Kris Denhaerynck, Steve Kirsch, Peter A. McCullough

Supervision: Peter A. McCullough

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EXHIBIT B

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Innate immune suppression by SARS-CoV-2 mRNA vaccinations: The role of G-quadruplexes, exosomes, and MicroRNAs

Stephanie Seneff [a,*], Greg Nigh [b], Anthony M. Kyriakopoulos [c], Peter A. McCullough [d]

[a] Computer Science and Artificial Intelligence Laboratory, MIT, Cambridge, MA, USA, 02139
[b] Immersion Health, Portland, OR, 97214, USA
[c] Research and Development, Nasco AD Biotechnology Laboratory, Department of Research and Development, Sachtouri 11, 18536, Piraeus, Greece
[d] Truth for Health Foundation, Tucson, AZ, USA

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ABSTRACT

The mRNA SARS-CoV-2 vaccines were brought to market in response to the public health crises of Covid-19. The utilization of mRNA vaccines in the context of infectious disease has no precedent. The many alterations in the vaccine mRNA hide the mRNA from cellular defenses and promote a longer biological half-life and high production of spike protein. However, the immune response to the vaccine is very different from that to a SARS-CoV-2 infection. In this paper, we present evidence that vaccination induces a profound impairment in type I interferon signaling, which has diverse adverse consequences to human health. Immune cells that have taken up the vaccine nanoparticles release into circulation large numbers of exosomes containing spike protein along with critical microRNAs that induce a signaling response in recipient cells at distant sites. We also identify potential profound disturbances in regulatory control of protein synthesis and cancer surveillance. These disturbances potentially have a causal link to neurodegenerative disease, myocarditis, immune thrombocytopenia, Bell's palsy, liver disease, impaired adaptive immunity, impaired DNA damage response and tumorigenesis. We show evidence from the VAERS database supporting our hypothesis. We believe a comprehensive risk/benefit assessment of the mRNA vaccines questions them as positive contributors to public health.

1. Introduction

Vaccination is an endeavor to utilize non-pathogenic material to mimic the immunological response of a natural infection, thereby conferring immunity in the event of pathogen exposure. This goal has been primarily pursued through the use of both whole organism and attenuated virus vaccines. Use of fragments of virus or their protein products, referred to as "subunit vaccines," has been more technically challenging (Bhurani et al., 2018). In any event, an implicit assumption behind the deployment of any vaccination campaign is that the vaccine confers the effects of a 'benign infection,' activating the immune system against future exposure, while avoiding the health impacts of actual infection.

Much of the literature on this related to COVID-19 suggests that the immune response to mRNA-based vaccination is similar to natural infection. A preprint study found "high immunogenicity of BNT162b2 vaccine in comparison with natural infection." The authors found there to be many qualitative similarities though quantitative differences (Psichogiou et al., 2021a). Jhaveri (2021) suggests that mRNA vaccines do what infection with the virus does: "The protein is produced and presented in the same way as natural infection." The U.S. Centers for Disease Control and Prevention (CDC) makes the case based upon antibody titers generated by prior infection vs. vaccination, in addition to production of memory B cells, to argue that the immune response to vaccination is analogous to the response to natural infection (Centers for Disease Control and Prevention, 2021a). It is this similarity in the humoral immune response to vaccination vs natural infection, paired with both trial and observational data demonstrating reduced risk of infection following vaccination, that stands as the justification for the mass vaccination campaign.

Our paper summarizes the current literature on mRNA and its effects on the molecular biology within human cells. We recognize that there is a wide range of opinions in this nascent phase of mRNA technology. Given its widespread deployment ahead of basic work on so many of the

* Corresponding author.
E-mail addresses: seneff@csail.mit.edu (S. Seneff), drnigh@immersionhealthpdx.com (G. Nigh), antkyriak@gmail.com (A.M. Kyriakopoulos), peteramccullough@gmail.com (P.A. McCullough).

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mechanisms we discuss here, we believe that our work is important for providing a broad understanding of present and future reviews that relate to the burgeoning preclinical molecular work being done in this area.

In this paper, we explore the scientific literature suggesting that vaccination with an mRNA vaccine initiates a set of biological events that are not only different from that induced by infection but are in several ways demonstrably counterproductive to both short- and long-term immune competence and normal cellular function. These vaccinations have now been shown to downregulate critical pathways related to cancer surveillance, infection control, and cellular homeostasis. They introduce into the body highly modified genetic material. A preprint has revealed a remarkable difference between the characteristics of the immune response to an infection with SARS-CoV-2 as compared with the immune response to an mRNA vaccine against COVID-19 (Ivanova et al., 2021). Differential gene expression analysis of peripheral dendritic cells revealed a dramatic upregulation of both type I and type II interferons (IFNs) in COVID-19 patients, but not in vaccinees. One remarkable observation they made was that there was an expansion of circulating hematopoietic stem and progenitor cells (HSPCs) in COVID-19 patients, but this expansion was notably absent following vaccination. A striking expansion in circulating plasmablasts observed in COVID-19 patients was also not seen in the vaccinees. All of these observations are consistent with the idea that the anti-COVID-19 vaccines actively suppress type I IFN signaling, as we will discuss below. In this paper we will be focusing extensively, though not exclusively, on vaccination-induced type I IFN suppression and the myriad downstream effects this has on the related signaling cascade.

Since long-term pre-clinical and Phase I safety trials were combined with Phase II trials, then phase II and III trials were combined (Kwok, 2021); and since even those were terminated early and placebo arms given the injections, we look to the pharmacosurveillance system and published reports for safety signals. In doing so, we find that that evidence is not encouraging. The biological response to mRNA vaccination as it is currently employed is demonstrably *not* similar to natural infection. In this paper we will illustrate those differences, and we will describe the immunological and pathological processes we expect are being initiated by mRNA vaccination. We will connect these underlying physiological effects with both realized and yet-to-be-observed morbidities. We anticipate that implementation of booster vaccinations on a wide scale will amplify all of these problems.

The mRNA vaccines manufactured by Pfizer/BioNTech and Moderna have been viewed as an essential aspect of our efforts to control the spread of COVID-19. Countries around the globe have been aggressively promoting massive vaccination programs with the hope that such efforts might finally curtail the ongoing pandemic and restore normalcy. Governments are reticent to consider the possibility that these injections might cause harm in unexpected ways, and especially that such harm might even surpass the benefits achieved in protection from severe disease. It is now clear that the antibodies induced by the vaccines fade in as little as 3–10 weeks after the second dose (Shrotri et al., 2021), such that people are being advised to seek booster shots at regular intervals (Centers for Disease Control and Prevention, 2021b). It has also become apparent that rapidly emerging variants such as the Delta and now the Omicron strain are showing resistance to the antibodies induced by the vaccines, through mutations in the spike protein (Yahi et al., 2021). Furthermore, it has become clear that the vaccines do not prevent transmission of the disease, but can only be claimed to reduce symptom severity (Kampf, 2021a). A study comparing vaccination rates with COVID-19 infection rates across 68 countries and 2947 counties in the United States in early September 2021, found no correlation between the two, suggesting that these vaccines do not protect from spread of the disease (Subramanian and Kumar, 2947). Regarding symptom severity, even this aspect is beginning to be in doubt, as demonstrated by an outbreak in an Israeli hospital that led to the death of five fully vaccinated hospital patients (Shitrit et al., 2021). Similarly, Brosh-Nissimov et al. (2021) reported that 34/152 (22%) of fully vaccinated patients among 17 Israeli hospitals died of COVID-19.

The increasing evidence that the vaccines do little to control disease spread and that their effectiveness wanes over time make it even more imperative to assess the degree to which the vaccines might cause harm. That SARS-CoV-2 modified spike protein mRNA vaccinations have biological impacts is without question. Here we attempt to distinguish those impacts from natural infection, and establish a mechanistic framework linking those unique biological impacts to pathologies now associated with vaccination. We recognize that the causal links between biological effects initiated by mRNA vaccination and adverse outcomes have not been established in the large majority of cases.

2. Interferons: an overview with attention to cancer surveillance

Discovered in 1957, interferon (IFN) earned its name with the recognition that cells challenged by attenuated influenza A virus created a substance that "interfered with" a subsequent infection by a live virus (Lindenmann, 1982). IFN is now understood to represent a very large family of immune-modulating proteins, divided into three types, designated as type I, II, and III based upon the receptors each IFN interacts with. Type I IFN includes both IFN-α and IFN-β, and this type is the most diverse, being further divided into seventeen subtypes. IFN-α alone has thirteen subtypes currently identified, and each of those is further divided into multiple categories (Wang et al., 2017a). Type I IFNs play a powerful role in the immune response to multiple stressors. In fact, they have enjoyed clinical therapeutic value as a treatment option for a variety of diseases and conditions, including viral infections, solid tumors, myeloproliferative disorders, hematopoietic neoplasms and autoimmune diseases such as multiple sclerosis (Passegu and Ernst, 2009).

As a group, IFNs play exceedingly complicated and pleiotropic roles that are coordinated and regulated through the activity of the family of IFN regulatory factors, or IRFs (Kaur and Fang, 2020). IRF9 is most directly involved in anti-viral as well as anti-tumor immunity and genetic regulation (Alsamman and El-Masry, 2018; Huang et al., 2019; Zitvogel et al., 2015).

Closely related to this are plasmacytoid dendritic cells (pDCs), a rare type of immune cell that circulate in the blood but migrate to peripheral lymphoid organs during a viral infection. They respond to a viral infection by sharply upregulating production of type I IFNs. The IFN-α released in the lymph nodes induces B cells to differentiate into plasmablasts. Subsequently, interleukin-6 (Il-6) induces plasmablasts to evolve into antibody-secreting plasma cells (Jego et al., 2003). Thus, IFNs play a critical role in both controlling viral proliferation and inducing antibody production. Central to both antiviral and anticancer immunity, IFN-α is produced by macrophages and lymphocytes when either is challenged with viral or bacterial infection or encounters tumor cells (De Andrea et al., 2002). Its role as a potent antiviral therapy has been recognized in the treatment of hepatitis C virus complications (Feng et al., 2012), Cytomegalovirus infection (Delannoy et al., 1999), chronic active ebola virus infection (Sakai et al., 1998), inflammatory bowel disease associated with herpes virus infection (Ruther et al., 1998), and others.

Impaired type I IFN signaling is linked to many disease risks, most notably cancer, as type I IFN signaling suppresses proliferation of both viruses and cancer cells by arresting the cell cycle, in part through upregulation of p53, a tumor suppressor gene, and various cyclin-dependent kinase inhibitors (Musella et al., 2017; Matsuoka et al., 1998). IFN-α also induces major histocompatibility (MHC) class 1 antigen presentation by tumor cells, causing them to be more readily recognized by the cancer surveillance system (Heise et al., 2016; Sundstedt et al., 2008). The range of anticancer effects initiated by IFN-α expression is astounding and occurs through both direct and indirect mechanisms. Direct effects include cell cycle arrest, induction of cell

differentiation, initiation of apoptosis, activation of natural killer and $CD8^+$ T cells, and others (Schneider et al., 2014).

The indirect anticancer effects are predominantly carried out through gene transcription activation of the Janus kinase signal transducer and activator of transcription (JAK/STAT) pathway. IFN-α binding on the cell surface initiates JAK, a tyrosine kinase, to phosphorylate STAT1 and STAT2 (Asmana Ningrum, 2014). Once phosphorylated, these STATs form a complex with IRF9, one of a family of IRFs that play a wide range of roles in oncogene regulation and other cell functions (Takaoka et al., 2008). It is this complex, named IFN-stimulated gene factor 3 (ISGF3), that translocates to the cell nucleus to enhance the expression of at least 150 genes (Schneider et al., 2014). IRF9 has been suggested to be the primary member of the IRF family of proteins responsible for activation of the IFN-α antiproliferative effects, and that appears to be through its binding to the tumor necrosis factor-related apoptosis-inducing ligand (TRAIL) receptor 1 and 2 (TRAIL-R1/2) (Tsuno et al., 2009). IRF7 is another crucial member of the IRF family of proteins involved early in the response to a viral infection. It is normally expressed in low amounts but is strongly induced by ISGF3. IRF7 also undergoes serine phosphorylation and nuclear translocation to further activate the immune response. IRF7 has a very short half-life, so its gene-induction process is transient, perhaps to avoid overexpression of IFNs (Honda et al., 2006).

Once TRAIL is bound by IRF9, it is then able to act as a ligand for Death Receptor 4 (DR4) or DR5, initiating a cascade of events involving production of caspase 8 and caspase 3, and ultimately triggering apoptosis (Sayers, 2011). Dysregulation of this pathway, through suppression of either IFN-α or IRF9 and the resulting failure to bind TRAIL-R, has been associated with several hematologic malignancies (Testa, 2010) and has been shown to increase the metastatic potential in animal models of melanoma, colorectal cancer, and lymphoma (Finnberg and El-Deiry, 2008).

IFN-α both initiates and orchestrates a wide range of cancer suppressing roles. Dunn et al. (2005) showed that IFN-α plays an active role in cancer immunoediting, its locus of action being hematopoietic cells that are "programmed" via IFN-α binding for tumor surveillance. It is via the exceedingly complex interactions between type I IFNs and IRF7 and IRF9 in particular that a great deal of antiproliferative effects are carried out. This is evidenced by the large number of studies showing increased tumor growth and/or metastases associated with a wide number of cancer types.

For example, Bidwell et al. (2012) found that, among over 800 breast cancer patients, those with high expression of IRF7-regulated genes had significantly fewer bone metastases, and they propose assessment of these IRF7-related gene signatures as a way to predict those at greatest risk. Use of microRNA to target IRF7 expression has also been shown to enhance breast cancer cell proliferation and invasion *in vitro* (Li et al., 2015). Zhao et al. (2017) found a similar role for IRF7 in relation to bone metastases in a mouse model of prostate cancer. Regarding the anti-cancer mechanism behind IRF7 expression, Solis et al. (2006) found that IRF7 induces transcription of multiple genes and translation of their downstream protein products including TRAIL, IL-15, ISG-56 and CD80, with the noted therapeutic implications.

IRF9, too, has a central role to play in cancer surveillance and prevention. Erb et al. (2013) demonstrated that IRF9 is the mediator through which IL-6 augments the anti-proliferation effects of IFN-α against prostate cancer cells. Tian et al. (2018) found IRF9 to be a key negative regulator of acute myeloid leukaemia cell proliferation and evasion of apoptosis. It does so, at least in part, through acetylation of the master regulatory protein p53.

Both IFN-α and IRF9 are also apparently necessary for the cancer-preventative properties of a fully functional BRCA2 gene. In a study presented as an abstract at the First AACR International Conference on Frontiers in Basic Cancer Research, Mittal and Chaudhuri (2009) describe a set of experiments which show for the first time that BRCA2 expression leads to increased IFN-α production and augments the signal transduction pathway resulting in the complexing of IRF9, STAT1 and STAT2 described previously. Two years prior, Buckley et al. (2007) had established that BRCA1 in combination with IFN-γ promotes type I IFNs and subsequent production of IRF7, STAT1, and STAT2. Thus, the exceedingly important cancer regulatory genes BRCA1 and BRCA2 rely on IRF7 and IRF9, respectively, to carry out their protective effects. Rasmussen et al. (2021) reviewed compelling evidence that deficiencies of either IRF7 or IRF9 lead to significantly greater risk of severe COVID-19 illness. Importantly, they also note that evidence suggests type I IFNs play a singularly important role in protective immunity against COVID-19 illness, a role that is shared by multiple cytokines in most other viral illnesses including influenza.

As will be discussed in more detail below, the SARS-CoV-2 spike glycoprotein modifies host cell exosome production. Transfection of cells with the spike protein's gene and subsequent SARS-CoV-2 spike protein production results in those cells generating exosomes containing microRNAs that suppress IRF9 production while activating a range of pro-inflammatory gene transcripts (Mishra and Banerjea, 2021). Since these vaccines are specifically designed to induce high and ongoing production of SARS-CoV-2 spike glycoproteins, the implications are ominous. As described above, inhibition of IRF9 will suppress TRAIL and all its regulatory and downstream apoptosis-inducing effects. IRF9 suppression via exosomal microRNA should also be expected to impair the cancer-protective effects of BRCA2 gene activity, which depends on that molecule for its activity as described above. BRCA2-associated cancers include breast, fallopian tube, and ovarian cancer for women, prostate and breast cancer for men, acute myeloid leukaemia in children, and others (National Cancer Institute, 2021).

Vaccination has also been demonstrated to suppress both IRF7 and STAT2 (Liu et al., 2021). This can be expected to interfere with the cancer-protective effects of BRCA1 as described above. Cancers associated with impaired BRCA1 activity include breast, uterine, and ovarian cancer in women; prostate and breast cancer in men; and a modest increase in pancreatic cancer for both men and women (Cancer risk and BRCA1 gene, 2021).

Reduced BRCA1 expression is linked to both cancer and neurodegeneration. BRCA1 is a well-known breast cancer susceptibility gene. BRCA1 inhibits breast cancer cell proliferation through activation of SIRT1 and subsequent suppression of the androgen receptor (Zhang et al., 2016). In a study conducted by Suberbielle et al. (2015), reduced levels of BRCA1 were found in the brains of Alzheimer's patients. Furthermore, experiments with knocking down neuronal BRCA1 in the dentate gyrus of mice showed that DNA double-strand breaks were increased, along with neuronal shrinkage and impairments in synaptic plasticity, learning and memory.

Analysis detailed in a recent case study on a patient diagnosed with a rare form of lymphoma called angioimmunoblastic T cell lymphoma provided strong evidence for unexpected rapid progression of lymphomatous lesions after administration of the BNT162b2 mRNA booster shot (Goldman et al., 2021). Comparisons of detailed metrics for hypermetabolic lesions conducted immediately before and 21 days after the vaccine booster revealed a five-fold increase after the vaccine, with the post-booster test revealing a 2-fold higher activity level in the right armpit compared to the left one. The vaccine had been injected on the right side. It is worth pointing out in this regard that lymphoid malignancies have been associated with suppression of TRAIL-R1 (MacFarlane et al., 2005).

Given the universally recognized importance of optimally functioning BRCA1/2 for cancer prevention and given the central role of the TRAIL signal transduction pathway for additional cancer surveillance, the suppression of IRF7 and IRF9 through vaccination and subsequent SARS-CoV-2 spike glycoprotein production is extremely concerning for long-term cancer control in SARS-CoV-2 mRNA genetic vaccine injected populations.

3. Considerations in the design of mRNA vaccines

Over the last three decades, the mRNA technological platform aimed to develop effective and safe nucleic acid therapeutic tools is said to have overcome serious obstacles on the coded product instability, the overwhelming innate immunogenicity, and on the delivery methodologies (Pardi et al., 2018). One of the major success stories of mRNA use as a genetic vaccination tool is on the introduction of robust immunity against cancer (Van Lint et al., 2015). In addition, the potential of mRNAs to restore or replace various types of proteins in cases of rare genetic metabolic disorders like Fabry disease has offered great potential therapeutic alternatives where no other medication has proved to be successful (Martini and Guey, 2019). However, in the case of mRNA use as genetic vaccines against infectious diseases, the preliminary safety investigations seemed to be premature for a world-wide use in the general population (Pardi et al., 2018; Doulberis et al., 2021).

Although there are essential epitopes on other SARS-CoV-2 proteins where an antibody response could have provided essential immunogenicity, well known from SARS-CoV-1 (Gordon et al., 2020), the primary goal of the developers of the SARS-CoV-2 mRNA vaccines was to design a vaccine that could induce a robust antibody response exclusively to the spike glycoprotein. Such antibodies, especially IgA in the nasopharynx, should cause the invading viruses to be quickly cleared before they could invade host cells, thus arresting the disease process early on. As stated succinctly by Kaczmarek et al. (2021):

"The rationale behind vaccination is to provide every vaccinated person with protection against the SARS-CoV-2 virus. This protection is achieved by stimulating the immune system to produce antibodies against the virus and to develop lymphocytes that will retain memory and the ability to fight off the virus for a long time." However, since vaccination is given parenterally, IgG is the principal antibody class that is raised against the SARS-CoV-2 spike glycoprotein, not IgA (Wisnewski et al., 2021).

Vaccines generally depend upon adjuvants such as aluminum and squalene to provoke immune cells to migrate to the injection site immediately after vaccination. In the history of mRNA vaccine development, it was initially hoped that the mRNA itself could serve as its own adjuvant. This is because human cells recognize viral RNA as foreign, and this leads to upregulation of type I IFNs, mediated via toll like receptors such as TLR3, TLR7 and TLR8 (Karik ó et al., 2005).

However, with time it became clear that there were problems with this approach, both because the intense reaction could cause flu-like symptoms and because IFN-α could launch a cascade response that would lead to the breakdown of the mRNA before it could produce adequate amounts of SARS-CoV-2 spike glycoprotein to induce an immune response (de Beuckelaer et al., 2016). A breakthrough came when it was discovered experimentally that the mRNA coding for the spike protein could be modified in specific ways that would essentially fool the human cells into recognizing it as harmless human RNA. A seminal paper by Karikó et al. (2005) demonstrated through a series of *in vitro* experiments that a simple modification to the mRNA such that all uridines were replaced with pseudouridine could dramatically reduce innate immune activation against exogenous mRNA. Andries et al. (2015) later discovered that 1-methylpseudouridine as a replacement for uridine was even more effective than pseudouridine and could essentially abolish the TLR response to the mRNA, preventing the activation of blood-derived dendritic cells. This modification is applied in both the mRNA vaccines on the market (Park et al., 2021).

Rather prophetically, the extensive review by Forni and Mantovani (2021) has raised serious questions about the development of innate immunity by the mRNA SARS-CoV-2 genetic vaccinations. As the authors declared: "Due to the short development time and the novelty of the technologies adopted, these vaccines will be deployed with several unresolved issues that only the passage of time will permit to clarify." Subsequently, the authors recommended including certain molecules such as the long pentraxin PTX3 as representative humoral immunity markers to assess the early activation of innate immune mechanisms and the underlying reactogenicity under the BIOVACSAFE consortium protocols (Forni and Mantovani, 2021; Weiner et al., 2019). However, to the best of our knowledge these safety protocols have not been included in the assessment of induced innate immunity by the SARS-CoV-2 mRNA genetic vaccines (Mulligan et al., 2020).

In this regard, in the case of SARS-CoV-2 BNT162b2 mRNA vaccine, unlike the immune response induced by natural SARS-CoV-2 infection, where a robust interferon response is observed, those vaccinated with BNT162b2 mRNA vaccines developed a robust adaptive immune response which was restricted only to memory cells, i.e., an alternative route of immune response that bypassed the IFN mediated pathways (Mulligan et al., 2020). Furthermore, due to subsequent mutations in the SARS-CoV-2 spike protein, there is a substantial loss of neutralizing antibodies induced by the BNT162b2 mRNA vaccine compared to those conferred by the SARS-CoV-2 mutants alone (Collier et al., 2021). In that respect, as vaccine developers admit: "Vaccine RNA can be modified by incorporating 1-methylpseudouridine, which dampens innate immune sensing and increases mRNA translation *in vivo*." (Mulligan et al., 2020; Katalin Karikó et al., 2008). Bearing in mind the multiple mutations that SARS-CoV-2 develops, as for example in the Brazil outbreaks (Timmers et al., 2021), an effective immune response that prevents the spread of SARS-CoV2 mutants necessarily involves the development of a robust IFN-I response as a part of the innate immune system. This response also requires the involvement of a functional NF-κB response. Unfortunately, spike glycoprotein overexpression dismantles the NF-κB pathway responses, and this molecular event can be augmented by spike-protein-coding mRNAs (Kyriakopoulos and McCullough, 2021; Jiang and Mei, 2021).

For successful mRNA vaccine design, the mRNA needs to be encapsulated in carefully constructed particles that can protect the RNA from degradation by RNA depolymerases. The mRNA vaccines are formulated as lipid nanoparticles containing cholesterol and phospholipids, with the modified mRNA complexed with a highly modified polyethylene glycol (PEG) lipid backbone to promote its early release from the endosome and to further protect it from degradation (Hou et al., 2021). The host cell's existing biological machinery is co-opted to facilitate the natural production of protein from the mRNA through endosomal uptake of a lipid particle (Hou et al., 2021). A synthetic cationic lipid is added as well, since it has been shown experimentally to work as an adjuvant to draw immune cells to the injection site and to facilitate endosomal escape. de Beuckelaer et al. (2016) observed that "condensing mRNA into cationic lipoplexes increases the potency of the mRNA vaccine evoked T cell response by several orders of magnitude." Another important modification is that they replaced the code for two adjacent amino acids in the genome with codes for proline, which causes the spike glycoprotein to stay in a prefusion stabilized form (Wrapp et al., 2020).

The SARS-CoV-2 spike glycoprotein mRNA is further "humanized" with the addition of a guanine-methylated cap, 3′ and 5′ untranslated regions (UTRs) copied from those of human proteins, and finally a long poly(A) tail to further stabilize the RNA (Kyriakopoulos and McCullough, 2021). In particular, researchers have cleverly selected the 3′UTR taken from globins which are produced in large quantities by erythrocytes, because it is very effective at protecting the mRNA from degradation and maintaining sustained protein production (Orlandini von Niessen et al., 2019). This is to be expected, since erythrocytes have no nucleus, so they are unable to replace the mRNAs once they are destroyed. Both the Moderna and the Pfizer vaccines adopted a 3′UTR from globins, and the Pfizer vaccine also uses a slightly modified globin 5′UTR (Xia, 2021). de Beuckelaer et al. (2016) aptly summed up the consequences of such modifications as follows: "Over the past years, technical improvements in the way IVT *[in vitro* transcribed] mRNAs are prepared (5′ Cap modifications, optimized GC content, improved polyA tails, stabilizing UTRs) have increased the stability of IVT mRNAs to such extent protein expression can now be achieved for days after direct

in vivo administration of the mRNA."

However, the optimized analogue cap formation of synthetic mRNAs inevitably forces the recipient cells to undergo a cap-dependent prolonged translation, ignoring homeostatic demands of cellular physiology (Kyriakopoulos and McCullough, 2021). The cap 2'-O methylation carried out by cap 2′-O methyltransferase (CMTR1) serves as a motif that marks the mRNA as "self," to prevent recognition by IFN-induced RNA binding proteins (Williams et al., 2020). Thus, the mRNA in the vaccines, equipped with the cap 2'-O methylation motif, evades detection as a viral invasion. Furthermore, the overwhelming impetus for cells to perform a single and artificial approach to translation according to the robust capping and synthetic methylations of mRNAs in vaccines is fundamentally associated with disease progression due to differential rather than normal signaling of pattern recognition receptors (PRRs) (Leung and Amarasinghe, 2016).

The regulatory process controlling mRNA translation is extremely complex, and it is highly disturbed in the context of mRNA vaccines (Kyriakopoulos and McCullough, 2021; Leung and Amarasinghe, 2016). Briefly, the idea is for mRNA vaccines to achieve the intended goal (i.e., production of the modified spike protein) through a stealth strategy that bypasses the natural immunological response to RNA-type viral infection. Injected lipid nanoparticles containing mRNA are brought to the cell interior via endocytosis. The mRNA escapes its lipid carrier and migrates to the ribosome, where it is abundantly translated into its final protein product, following an optimized program for producing large quantities of a specific protein over an extended period of time. These modified SARS-CoV-2 spike glycoproteins then follow one of three primary pathways. Some are proteolytically degraded and fragments are bound by MHC class I molecules for surface presentation to cytotoxic T-cells. A second pathway has those same spike glycoprotein fragments bind MHC class II molecules, move to the cell surface, and activate T-helper cells. A final pathway has soluble spike glycoproteins extruded from the cell in exosomes, where they can be recognized by B-cell-activated spike-glycoprotein-specific antibodies (Chaudhary et al., 2021).

A recent early-release study has found that the mRNA in the COVID-19 vaccines is present in germinal centers in secondary lymphoid tissue long after the vaccine is administered, and that it continues to synthesize spike glycoprotein up to at least sixty days post-vaccination (Röltgen et al., 2022). This suggests that immune cells taking up the mRNA in the arm muscle migrate into the lymph system to the lymph nodes, presumably in order to expose B-cells and T-cells to the toxic antigen. The persistence of the mRNA in the lymph nodes and its sustained synthesis of SARS-CoV-2 spike glycoprotein reflect the clever engineering involved in the mRNA technology, as described above.

In the end, it is through utilization of nanolipids and sophisticated mRNA technology that the normal immune response to exogenous RNA is evaded in order to produce a strong antibody response against an exogenous RNA virus.

4. GC enrichment and potential G4 (pG4) structures in vaccine mRNAs

Recently, members of our team investigated possible alterations in secondary structure of mRNAs in SARS-CoV-2 vaccines due to codon optimization of synthetic mRNA transcripts (McKernan et al., 2021). This study has shown that there is a significant enrichment of GC content in mRNAs in vaccines (53% in BNT162b2 and 61% in Moderna mRNA-1273) as compared to the native SARS-CoV-2 mRNA (36%). The enriched GC content of mRNAs is the result of codon optimization performed during the development of the mRNAs used in SARS-CoV-2 vaccines, apparently without determining the effect on secondary structures, particularly the Guanine quadruplex (G quadruplex) formation (McKernan et al., 2021).

Codon optimization describes the production of synthetic, codon-optimized polypeptides and proteins used in biotechnology therapeutics (such as the synthetic mRNAs used for SARS-CoV-2 vaccination). The altered codon assignments within the mRNA template dramatically increase the quantity of polypeptides and/or proteins produced (Mauro and Chappell, 2014). Synonymous codon replacement also results in a change in the multifunctional regulatory and structural roles of resulting proteins (Shabalina et al., 2013). For this reason, codon optimization has been cautioned against due to its consequent changes causing perturbation in the secondary conformation of protein products with potentially devastating effects on their resulting immunogenicity, efficacy and function (Zhou et al., 2013; Agashe et al., 2013). Notably, various human diseases are the result of synonymous nucleotide polymorphisms (McCarthy et al., 2017).

In an experiment where GC-rich and GC-poor versions of mRNA transcripts for heat shock protein 70 were configured in the context of identical promoters and UTR sequences, it was found that GC-rich genes were expressed several-fold to over a hundred-fold more efficiently than their GC-poor counterparts (Kudla et al., 2006). This is partly because all of the preferred mammalian codons have G or C nucleotides in the third position. It is also well documented that AU-rich elements in the 3' UTRs can destabilize mRNA (Otsuka et al., 2019). What may be of particular concern is the fact that GC enrichment content in vaccine mRNAs results in an enhanced ability for potential G-quadruplex (pG4) formations in these structures, and this could cause onset of neurological disease (Wang et al., 2021). Remarkably, the human prion protein (PrP) genetic sequence contains multiple G4 forming motifs, and their presence may form the missing link in the initial conversion of PrP to the misfolded form, PrPsc (Olsthoorn, 2014). PrP binding to its own mRNA may be the seed that causes the protein to misfold. This observation is particularly concerning in light of the fact that the SARS-CoV-2 spike glycoprotein has prion-like characteristics (Tetz and Tetz, 2022).

On the one hand, the GC content has a key role in the modulation of translation efficiency and control of mRNA expression in mammals (Babendure et al., 2006). Especially during translation initiation, the GC content operating as a cis-acting mRNA element orchestrates the 43S ribosomal pre-initiation complex attachment and thereafter the assembly of the eukaryotic translation initiation factor 4F (eIF4F) complex. One representative example of this system in action is the regulation of α and β globin mRNA expression through their 5′ untranslated regions (5′UTRs) (Babendure et al., 2006).

On the other hand, the presence of pG4s in RNAs is implicated in cancer biology as key determinants of the regulation of G4 RNA binding proteins such as helicase (Herdy et al., 2018). Generally, the G-quadruplexes in RNAs have essential roles in a) the regulation of gene expression, b) the localization of ribonuclear proteins, c) the mRNA localization and d) the regulation of proto-oncogene expression (Fay et al., 2017).

Regarding SARS-CoV-2, relevant studies reveal overwhelming similarities between SARS-CoV-2 pG4s, including in RNA coding for SARS-CoV-2 spike glycoprotein, and those sequenced in the human transcriptome (Zhang et al., 2020). Thus, it can be inferred that synthetic mRNAs in vaccines carrying more pG4 structures in their coding sequence for SARS-CoV-2 spike glycoprotein will amplify and compound the potential post-transcriptional disorganization due to G4-enriched RNA during natural SARS-CoV-2 infection. Moreover, the cellular nucleic acid binding protein (CNBP), which is the main cellular protein that binds to the SARS-CoV-2 RNA genome in human-infected cells (Schmidt et al., 2021), binds to and promotes the unfolding of SARS-CoV-2 G4s formed by both positive and negative sense template strands of the SARS-CoV-2 RNA genome. A similar modulation of CNBP on vaccine mRNA G4s and promotion of G4 equilibrium towards unfolded conformations create favorable conditions for miRNA binding, and this will have a direct impact on miRNA-dependent regulation of gene expression (Rouleau et al., 2017).

The negative-sense RNAs are intermediate molecules produced by the replicase transcriptase complex (RTC) formed by the nonstructural proteins of coronaviruses (including SARS-CoV-2) to provide efficiency in replication and transcription (Bezzi et al., 2021; Sola et al., 2015).

This, however, introduces another potentially serious complication associated with vaccination. Co-infection with other negative sense RNA viruses such as hepatitis C (Jaubert et al., 2018) or infection by other coronaviruses contemporaneous with vaccination periods would provide the necessary machinery of RTC to reproduce negative sense intermediates from synthetic mRNAs and therefore amplify the presence of pG4s by negative sense templates. This would result in further epitranscriptomic dysregulation (Spiegel et al., 2020).

Summarizing the topic to this point, the enrichment of GC content in vaccine mRNA will inevitably lead to an increase in the pG4 content of the vaccines. This, in turn, will lead to dysregulation of the G4-RNA-protein binding system and a wide range of potential disease-associated cellular pathologies including suppression of innate immunity, neurodegeneration, and malignant transformation (Herdy et al., 2018).

Concerning the post translational dysregulation due to emergence of new G4 structures introduced by vaccination, one other important issue related to miRNA regulation and pG4s arises. In miRNA structures, hundreds of pG4 sequences are identified (Rouleau et al., 2018). In their unfolded conformation, as during binding to their respective targets in 3′ to 5′ sequences of mRNAs, miRNAs switch off the translation of their respective target mRNA. Alternatively, when in the presence of a G4 ligand, the translation of their target mRNAs is promoted (Chan et al., 2018). Moreover, a vast number of putative miRNA binding sites overlap with G4s in 3' UTRs of mRNAs as there are at least 521 specific miRNAs that are predicted to bind to at least one of these G4s. Overall, 44,294 potential G4-miRNA binding sites have been traced to possess putative overlapping G4s in humans (Rouleau et al., 2017).

As described elsewhere, during the cellular translation of vaccine mRNAs, an increased assembly of a number of RNA binding protein helicases, such as eIF4A bound to eIF4G, will occur (Kyriakopoulos and McCullough, 2021). The presence of increased pG4s in synthetic mRNAs can potentially amplify binding of RNA binding proteins and miRNAs. This form of molecular crowding of protein components (helicases) with great affinity for G4 binding (Rouleau et al., 2017) will decrease the number of RNA binding proteins binding G4s normally available for miRNA regulation. This loss of RNA binding proteins as well as miRNA availability for regulation by binding to G4s can dramatically alter the translational regulation of miRNAs present in cells and thereby disrupt essential regulation of oncogene expression. An example is the p16-dependent regulation of the p53 tumor suppressor protein (Rouleau et al., 2017; Al-Khalaf and Aboussekhra, 2018).

This process is exceedingly complicated yet tantamount to cellular homeostasis. So, again, it merits summarizing. If pG4s accumulate, as would be expected with an increased amount of GC content in the vaccine mRNA, this would have an effect of increasing potential G4 structures available during translation events and this can affect miRNA post-transcriptional regulation. This, in turn, would either favor greater expression of the oncogenes related to a range of cancers, or drive cells towards apoptosis and cell death (Weldon et al., 2018). The case study described earlier in this paper strongly supports the hypothesis that these injections induce accelerated lymphoma progression in follicular B-cells (Goldman et al., 2021).

miRNA binding recognition patterns are imperfectly complementary to their target regions, and for this reason they are referred to as "master regulators," since one miRNA affects a plethora of different targets (Rouleau et al., 2018). The multitude of pG4s in the mRNA of the vaccine would predictably act as decoys, distracting miRNAs from their normal function in regulating human protein expression. The increase in G4 targets due to the vaccine would decrease the availability of miRNAs to target human-expressed G4s for regulation of gene expression. This can result in downregulation of miRNA expression which is implicated in cardiovascular pathology (Small and Olson, 2011), onset of neurodegeneration (Abe and Bonini, 2013), and/or cancer progression (Farazi et al., 2013).

In most respects within epitranscriptomic machinery, miRNAs are involved in translation repression. One example, vital for cellular normal housekeeping, is that of Mouse double minute 2 homolog (MDM2), a physical negative regulatory protein of p53. P53 itself is considered the master regulator of the cellular tumor suppression network of genes. P16 controls the expression of many miRNAs, and, via miR-141 and mIR-146b-5p binding to MDM2 mRNA, it induces the negative regulation of MDM2, thus enabling p53 ubiquitination and promotion of cell survival upon DNA damage events (Al-Khalaf and Aboussekhra, 2018). Dysregulation of miRNAs that control MDM2 suppression of p53 would predictably lead to an increased risk to a range of cancers (Ozaki and Nakagawara, 2011).

5. Type I IFNs and COVID-19

Type I IFNs play an essential role in fighting viral infections, and deficiencies in type I IFN signaling have been associated with poor outcomes from COVID-19 in multiple studies. These cases are often associated with autoantibodies to type I IFNs. As reviewed below, type I IFNs have been used with some success in treating severe COVID-19, particularly if administered very early in the disease process. If, as argued above, the mRNA vaccines interfere with type I IFN signaling, this could lead to increased susceptibility to COVID-19 in the two weeks following the first vaccine, before an antibody response has been initiated.

Cells infected with a virus detect the presence of virus replication through a number of pattern recognition receptors (PRRs), which serve as sentinels sensing aberrant RNA structures that often form during viral replication. These receptors respond by oligomerizing and subsequently inducing type I IFNs, ultimately upregulating a large number of proteins involved in suppressing viral proliferation (Janeway and Medzhitov, 2002).

A multi-author study by researchers in Paris, France, involving a cohort of 50 COVID-19 patients with varying degrees of disease severity, revealed that patients with severe disease were characterized by a highly impaired type I IFN response (Hadjadj et al., 2020). These patients had essentially no IFN-β and low IFN-α production and activity. This was associated with a persistent blood viral load and an exacerbated inflammatory response, characterized by high levels of tumor necrosis factor α (TNF-α) and Il-6. The authors proposed type I IFN therapy as a potential treatment option. A paper by several researchers in the United States also identified a unique and inappropriate inflammatory response in severe COVID-19 patients, characterized by low levels of both type I and type III IFNs along with elevated chemokines and elevated expression of Il-6 (Blanco-Melo et al., 2020).

Type I IFNs have even been proposed as a treatment option for severe COVID-19. In a hamster model, researchers exposed hamsters to SARS-CoV-2 and induced an inflammatory response in the lungs and systemic inflammation in distal tissues. They found that intranasal administration of recombinant IFN-α resulted in a reduced viral load and alleviation of symptoms (Hoagland et al., 2021). A retrospective cohort study of 446 COVID-19 patients determined that early administration of IFN-α2b was associated with reduced in-hospital mortality. However, late IFN therapy increased mortality and delayed recovery, revealing that early administration of interferon therapy is essential for a favorable response (Wang et al., 2020a).

A surprising number of people have neutralizing autoantibodies against type I IFNs, although the underlying etiology of this phenomenon is not understood. A study using longitudinal profiling of over 600,000 peripheral blood mononuclear cells and transcriptome sequencing from 54 patients with COVID-19 and 26 controls found a notable lack of type I IFN-stimulated gene responses in myeloid cells from patients with critical disease (van der Wijst et al., 2021). Neutralizing autoantibodies against type I IFNs were found in 19% of patients with critical disease, 6% of patients with severe disease, and 0% of patients with moderate disease. Another study based in Madrid, Spain revealed that 10% of patients with severe COVID-19 disease had

autoimmune antibodies to type I IFNs (Troya et al., 2021). A multi-author study based in France found that COVID-19 mortality was significantly more frequent in patients with neutralizing autoantibodies against type I interferon than those without neutralizing antibodies (55% vs. 23%) (Chauvineau - Grenier et al., 2022). Finally, Stertz and Hale (2021) note that, whether due to autoantibodies or perhaps loss-of-function polymorphisms associated with interferon system genes, deficiencies in interferon production are associated with as many as 15% of all life-threatening COVID-19 cases.

6. Are the methylation strategies for cellular housekeeping generally omitted by vaccine mRNAs?

Methylation of mRNAs has been evolutionarily devised to control translation of transcripts and therefore expression of genes by a complex cascade of methylator (writers), de-methylator (eraser) and reader proteins. Adenosine methylation is the most abundant epitranscriptomic mRNA modification, and it occurs at multiple sites across the mRNA molecule (Zaccara et al., 2019). A key methylation of adenosine "N6-methyladenosine (m6A)" specifically in the 5′ UTR of mRNAs regulates normal cell physiology, the inflammatory response and cancer progression. The role and mechanisms of m6A in human disease is extensive, and it is excellently covered in other comprehensive reviews (Yang et al., 2020; Knuckles and Bühler, 2018). Foremost among these, the SARS-CoV-2 molecular vaccination induces cell stress conditions, as is described by the elevated NF-κB signaling after vaccination (Liu et al., 2021; Koo et al., 2010).

Under conditions of cellular stress, which can be induced by a viral infection or disease states such as cancer, m6A mediates mRNAs to undergo translation preferentially in a cap-independent way (Meyer et al., 2015). As discussed previously, this is opposite to the impact of mRNA SARS-CoV-2 vaccination, which drives cells toward a *cap-dependent* translation. Furthermore, under diversified conditions of cellular stress, there is an overwhelming induction of transcriptome-wide addition of m6A that causes an increased number of mRNAs to possess 5′UTRs enriched with m6A (Meyer et al., 2015).

Eukaryotic translation initiation factor 4E (eIF4E) is the initial mRNA cap-binding protein that directs ribosomes to the cap structure of mRNAs, in order to initiate translation into protein. The dependence on cap-dependent translation of vaccine mRNAs will consume a surplus of eIF4E availability needed to translate an unnaturally high number of synthetic mRNAs. However, cap-independent translation takes place without requiring eIF4E to be bound to eIF4F. The competition for ribosomes will shift towards the cap-independent translation of transcripts, since the mRNAs undergoing cap-independent translation are equipped, apart from internal ribosome entry sites (IRES), with special binding motifs that bind to factors that actively recruit mRNAs to the ribosome cap-independent translational enhancers (CITEs) (Shatsky et al., 2018).

Furthermore, this also means that eIF4E, which is a powerful oncogene regulator and cell proliferation modulator, will sustain its activities by this competition for an unnaturally prolonged period of time, trying to counterbalance the competition between robustly-capped mRNAs in vaccines and IRES-containing mRNAs (Kyriakopoulos and McCullough, 2021; Svitkin et al., 2005). This type of condition results in dysregulation of co-transcriptional m6A mRNA modifications and seriously links to molecular progressions of various cancers (Han and Choe, 2020), as well as creating predisposing conditions for subsequent viral infections (Svitkin et al., 2005).

We next consider the impact of mRNA-vaccination-derived SARS-CoV-2 spike glycoprotein on the cellular IFN system via massive exosome production.

7. Exosomes and MicroRNAs

An important communication network among cells consists of extracellular vesicles (EVs) that are constantly released by one cell and later taken up by another cell, which could be in a distant organ. Small vesicles known as exosomes, formed inside endosomes, are similar in size to viruses, and are released through exocytosis into the extracellular space to subsequently circulate throughout the body (Yoshikawa et al., 2019). Exosomes can deliver a diverse collection of biologically active molecules, including mRNA, microRNAs (miRNAs), proteins, and lipids (Ratajczak and Ratajczak, 2016). During a viral infection, infected cells secrete large quantities of exosomes that act as a communication network among the cells to orchestrate the response to the infection (Chahar et al., 2015).

In a collaborative effort by a team of researchers from Arizona and Connecticut, it was found that people who were vaccinated with the mRNA vaccines acquired circulating exosomes containing the SARS-CoV-2 spike glycoprotein by day 14 following vaccination (Bansal et al., 2021). They also found that there were no circulating antibodies to the spike glycoprotein fourteen days after the first vaccine. After the second vaccine, however, the number of circulating spike-glycoprotein-containing exosomes increased by up to a factor of 12. Furthermore, antibodies first appeared on day 14. The exosomes presented spike glycoprotein on their surface, which, the authors argued, facilitated antibody production. When mice were exposed to exosomes derived from vaccinated people, they developed antibodies to the spike glycoprotein. Interestingly, following peak expression, the number of circulating spike-glycoprotein-containing exosomes decreased over time, in step with the decrease in the level of antibodies to the spike glycoprotein.

Exosomes exist as a part of the mRNA decay mechanism in close association under stress conditions with stress granules (SGs) and P-bodies (PBs) (Decker and Parker, 2012; Kothandan et al., 2020). Under conditions of vaccine-mRNA-induced translation, which could be called "excessive dependence on cap-dependent translation," there is an obvious resistance to promotion and assembly of the large decapping complex (Kyriakopoulos and McCullough, 2021), and therefore resistance against physiological mRNA decay processes (Decker and Parker, 2012). This would mean that the fate of particular synthetic mRNAs that otherwise would be determined by the common cellular strategy for mRNA turnover involving messenger ribonucleinproteins (mRNPs) is being omitted (Borbolis and Syntichaki, 2015).

Furthermore, under conditions of over-reliance on cap-dependent translation by the synthetic mRNAs in SARS-CoV-2 vaccines (Kyriakopoulos and McCullough, 2021), many native mRNAs holding considerable IRES and specific methylations (m6A) in their structure will favorably choose cap-independent translation, which is strongly linked to mRNA decay quality control mechanisms (Han and Choe, 2020). In this sense, considerable deadenylated mRNA products as well as products derived from mRNA metabolism (decay) are directly linked to exosome cargoes (Borbolis and Syntichaki, 2015).

An example of dependence on cap-dependent translation is described in T-cell acute lymphoblastic leukaemia (T-ALL). Due to mechanistic target of rapamycin C (mTORC)-1 over-functioning in T-ALL, the cells are driven completely towards cap-dependent translation (Girardi and De Keersmaecker, 2015). An analogous condition is described by Kyriakopoulos and McCullough (2021). Even in this highly aggressive cancerous state, during inhibition of cap-dependent translation in T-ALL cells, there is a rapid reversion to cap-independent translation (Girardi and De Keersmaecker, 2015). Similarly, a picornavirus infection (Jang et al., 1990) drives cells towards cap-independent translation due to inhibition of components of eIF4F complex and pluralism of IRES in viral RNA.

In humans, there is an abundance of mostly asymptomatic picornavirus infections like the Safford Virus with an over 90% seroprevalence in young children and adults (Zoll et al., 2009). In either case, whether an apoptotic event due to a stress-like condition (Rusk, 2008) or an mRNA-cap-driven-like carcinomatous effect (De Paolis et al., 2021), the miRNA levels will be increased due to the increased epitranscriptomic

functioning and enhanced mRNA decay. Because of the high demand for gene expression, high levels of certain miRNAs will be expected to be contained in exosomes via P bodies (Yu et al., 2016).

Also, under conditions of overwhelming production of SARS-CoV-2 spike glycoprotein due to SARS-CoV-2 molecular vaccination, it would of course be expected that a significant proportion of over-abundant intracellular spike glycoproteins would also be exported via exosome cargoes (Wei et al., 2021).

Mishra and Banerjea (2021) investigated the role of exosomes in the cellular response of SARS-CoV-2 spike-transfected cells. They wrote in the abstract:

> "We propose that SARS-CoV-2 gene product, Spike, is able to modify the host exosomal cargo, which gets transported to distant uninfected tissues and organs and can initiate a catastrophic immune cascade within Central Nervous System (CNS)."

Their experiments involved growing human HEK293T cells in culture and exposing them to SARS-CoV-2 spike gene plasmids, which induced synthesis of spike glycoprotein within the cells. They found experimentally that these cells released abundant exosomes housing spike glycoprotein along with specific microRNAs. They then harvested the exosomes and transferred them to a cell culture of human microglia (the immune cells that are resident in the brain). They showed that the microglia readily took up the exosomes and responded to the microRNAs by initiating an acute inflammatory response. The role of microglia in causing neuroinflammation in various viral diseases, such as Human Immunodeficiency Virus (HIV), Japanese Encephalitis Virus (JEV), and Dengue, is well established. They proposed that long-distance cell-cell communication via exosomes could be the mechanism by which neurological symptoms become manifest in severe cases of COVID-19.

In further exploration, the authors identified two microRNAs that were present in high concentrations in the exosomes: miR-148a and miR-590. They proposed a specific mechanism by which these two microRNAs would specifically disrupt type I interferon signaling, through suppression of two critical proteins that control the pathway: ubiquitin specific peptidase 33 (USP33) and IRF9. Phosphorylated STAT1 and STAT2 heterodimers require IRF9 in order to bind IFN-stimulated response elements, and therefore IRF9 plays an essential role in the signaling response. The authors showed experimentally that microglia exposed to the exosomes extracted from the HEK293 culture had a 50% decrease in cellular expression of USP33 and a 60% decrease in IRF9. They further found that miR-148a specifically blocks USP33 and miR-590 specifically blocks IRF9. USP33 removes ubiquitin from IRF9, and in so doing it protects it from degradation. Thus, the two microRNAs together conspire to interfere with IRF9, thus blocking receptor response to type I interferons.

A study by de Gonzalo-Calvo et al. (2021) looked at the microRNA profile in the blood of COVID-19 patients and their quantitative variance based upon disease severity. Multiple miRNAs were found to be up- and down-regulated. Among these was miR-148a-3p, the guide strand precursor to miR-148a. However, miR-148a itself was not among the microRNAs catalogued as excessive or deficient in their study, nor was miR-590. It appears from these findings that miR148a and miR-590 and their inflammatory effects are unique to vaccination-induced SARS-CoV-2 spike glycoprotein production.

Tracer studies have shown that, following injection into the arm muscle, the mRNA in mRNA vaccines is carried into the lymph system by immune cells and ultimately accumulates in the spleen in high concentrations (Bahl et al., 2017). Other studies have shown that stressed immune cells in germinal centers in the spleen release large quantities of exosomes that travel to the brain stem nuclei along the vagus nerve (as reviewed in Seneff and Nigh (2021)). The vagus nerve is the 10th cranial nerve and it enters the brainstem near the larynx. The superior and recurrent laryngeal nerves are branches of the vagus that innervate structures involved in swallowing and speaking. Lesions in these nerves cause vocal cord paralysis associated with difficulty swallowing (dysphagia) difficulty speaking (dysphonia) and/or shortness of breath (dyspnea) (Gould et al., 2019; Erman et al., 2009). We will return to these specific pathologies in our review of VAERS data below.

HEK293 cells were originally derived from cultures taken from the kidney of a human fetus several decades ago and immortalized through infection with adenovirus DNA. While they were extracted from the kidney, the cells show through their protein expression profile that they are likely to be of neuronal origin (Shaw et al., 2002). This suggests that neurons in the vagus nerve would respond similarly to the SARS-CoV-2 spike glycoprotein. Thus, the available evidence strongly suggests that endogenously produced SARS-CoV-2 spike glycoprotein creates a different microRNA profile than does natural infection with SARS-CoV-2, and those differences entail a potentially wide range of deleterious effects.

A central point of our analysis below is the important distinction between the impact of vaccination versus natural infection on type I IFN. While vaccination actively suppresses its production, natural infection promotes type I IFN production very early in the disease cycle. Those with preexisting conditions often exhibit impaired type I IFN signaling, which leads to more severe, critical, and even fatal COVID-19. If the impairment induced by the vaccine is maintained as antibody levels wane over time, this could lead to a situation where the vaccine causes a more severe disease expression than would have been the case in the absence of the vaccine.

Another expected consequence of suppressing type I IFN would be reactivation of preexisting, chronic viral infections, as described in Section 9.

8. Impaired DNA repair and adaptive immunity

The immune system and the DNA repair system are the two primary systems that higher organisms rely on for defense against diverse threats, and they share common elements. Loss of function of key DNA repair proteins leads to defects in repair that inhibit the production of functional B- and T-cells, resulting in immunodeficiency. Non-homologous end joining (NHEJ) repair plays a critical role in lymphocyte-specific V(D)J recombination, which is essential for producing the highly diverse repertoire of B-cell antibodies in response to antigen exposure (Jiang and Mei, 2021). Impaired DNA repair is also a direct pathway towards cancer.

A paper published by Liu et al., in 2021 monitored several parameters associated with immune function in a cohort of patients by conducting single-cell mRNA sequencing of peripheral blood mononuclear cells (PBMCs) harvested from the patients before and 28 days after the first injection of a COVID-19 vaccine based on a weakened version of the virus (Liu et al., 2021). While these vaccines are different from the mRNA vaccines, they also work by injecting the contents of the vaccine into the deltoid muscle, bypassing the mucosal and vascular barriers. The authors found consistent alteration of gene expression following vaccination in many different immune cell types. Observed increases in NF-κB signaling and reduced type I IFN responses were further confirmed by biological assays. Consistent with other studies, they found that STAT2 and IRF7 were significantly downregulated 28 days after vaccination, indicative of impaired type I IFN responses. They wrote: "Together, these data suggested that after vaccination, at least by day 28, other than generation of neutralizing antibodies, people's immune systems, including those of lymphocytes and monocytes, were perhaps in a more vulnerable state." (Liu et al., 2021).

These authors also identified disturbing changes in gene expression that would imply impaired ability to repair DNA. Up to 60% of the total transcriptional activity in growing cells involves the transcription of ribosomal DNA (rDNA) to produce ribosomal RNA (rRNA). The enzyme that transcribes ribosomal DNA into RNA is RNA polymerase I (Pol I). Pol I also monitors rDNA integrity and influences cell survival (Kakarougkas et al., 2013). During transcription, RNA polymerases (RNAPs)

actively scan DNA to find bulky lesions (double-strand breaks) and trigger their repair. In growing eukaryotic cells, most transcription involves synthesis of ribosomal RNA by Pol I. Thus, Pol I promotes survival following DNA damage (Kakarougkas et al., 2013). Many of the down-regulated genes identified by Liu et al. (2021) were linked to the cell cycle, telomere maintenance, and both promoter opening and transcription of POL I, indicative of impaired DNA repair processes.

One of the gene sets that were suppressed was due to "deposition of new CENPA [centromere protein A] containing nucleosomes at the centromere." Newly synthesized CENPA is deposited in nucleosomes at the centromere during late telophase/early G1 phase of the cell cycle. This points to arrest of the cell cycle in G1 phase as a characteristic feature of the response to the inactivated SARS-CoV-2 vaccine. Arrest of pluripotent embryonic stem cells in the G1 phase (prior to replication initiation) would result in impaired self-renewal and maintenance of pluripotency (Choi et al., 2013).

Two checkpoint proteins crucially involved in DNA repair and adaptive immunity are BRCA1 and 53BP1, which facilitate both homologous recombination (HR) and NHEJ, the two primary repair processes (Zhang and Powell, 2005; Panier and Boulton, 2014). In an *in vitro* experiment on human cells, the SARS-CoV-2 full-length spike glycoprotein was specifically shown to enter the nucleus and hinder the recruitment of these two repair proteins to the site of a double-strand break (Jiang and Mei, 2021). The authors summarized their findings by saying, "Mechanistically, we found that the spike protein localizes in the nucleus and inhibits DNA damage repair by impeding key DNA repair protein BRCA1 and 53BP1 recruitment to the damage site."

Another mechanism by which the mRNA vaccines could interfere with DNA repair is through miR-148. This microRNA has been shown to downregulate HR in the G1 phase of the cell cycle (Choi et al., 2014). As was mentioned earlier in this paper, this was one of the two microRNAs found in exosomes released by human cells following SARS-CoV-2 spike glycoprotein synthesis in the experiments by Mishra and Banerjea (2021).

9. Reactivation of varicella-zoster

Type I IFN receptor signaling in $CD8^+$ T cells is critical for the generation of effector and memory cells in response to a viral infection (Kolumam et al., 2005). $CD8^+$ T cells can block reactivation of latent herpes infection in sensory neurons (Liu et al., 2000). If type I IFN signaling is impaired, as happens following vaccination but not following natural infection with SARS-CoV-2, $CD8^+$ T cells' ability to keep herpes in check would also be impaired. Might this be the mechanism at work in response to the vaccines?

Shingles is an increasingly common condition caused by reactivation of latent herpes zoster viruses (HZV), which also causes chicken pox in childhood. In a systematic review, Katsikas Triantafyllidis et al. (2021) identified 91 cases of herpes zoster occurring an average of 5.8 days following mRNA vaccination. While acknowledging that causality is not yet confirmed, "Herpes zoster is possibly a condition physicians and other healthcare professionals may expect to see in patients receiving COVID-19 vaccines" (Katsikas Triantafyllidis et al., 2021). In a letter to the editor published in September 2, 2021, Fathy et al. (2022) reported on 672 cases of skin reactions that were presumably vaccine-related, including 40 cases of herpes zoster and/or herpes simplex reactivation. These cases had been reported to the American Academy of Dermatology and the International League of Dermatologic Societies' COVID-19 Dermatology Registry, established specifically to track dermatological sequalae from the vaccines. There are multiple additional case reports of herpes zoster reactivation following COVID-19 vaccination in the literature (Psichogiou et al., 2021b; Iwanaga et al., 2021). Lladó et al. (2021) noted that 51 of 52 reports of reactivated herpes zoster infections happened following mRNA vaccination. Herpes zoster itself also interferes with IFN-α signaling in infected cells both through interfering with STAT2 phosphorylation and through facilitating IRF9 degradation (Verweij et al., 2015).

An additional case of viral reactivation is noteworthy as well. It involved an 82-year-old woman who had acquired a hepatitis C viral (HCV) infection in 2007. A strong increase in HCV load occurred a few days after vaccination with an mRNA Pfizer/BioNTech vaccine, along with an appearance of jaundice. She died three weeks after vaccination from liver failure (Lensen et al., 2021).

10. Immune thrombocytopenia

Immune thrombocytopenia is an autoimmune disorder, where the immune system attacks circulating platelets. Immune thrombocytopenic purpura (ITP) has been associated with several vaccinations, including measles, mumps, rubella (MMR), hepatitis A, varicella, diphtheria, tetanus, pertussis (DPT), oral polio and influenza (Perricone et al., 2014). While there is broad awareness that the adenovirus DNA-based vaccines can cause vaccine-induced immune thrombotic thrombocytopenia (VITT) (Kelton et al., 2021), the mRNA vaccines are not without risk to VITT, as case studies have been published documenting such occurrences, including life threatening and fatal cerebral venous sinus thrombosis (Lee et al., 2021; Akiyama et al., 2021; Atoui et al., 2022; Zakaria et al., 2021). The mechanism is believed to involve VITT antibodies binding to platelet factor 4 (PF4) and forming immune complexes that induce platelet activation. Subsequent clotting cascades cause the formation of diffuse microclots in the brain, lungs, liver, legs and elsewhere, associated with a dramatic drop in platelet count (Kelton et al., 2021). The reaction to the vaccine has been described as being very similar to heparin-induced thrombocytopenia (HIT), except that heparin administration is notably not involved (Cines and Bussel, 2021).

It has been shown that the mRNA vaccines elicit primarily an immunoglobulin G (IgG) immune response, with lesser amounts of IgA induced (Wisnewski et al., 2021), and even less IgM production (Danese et al., 2021). The amount of IgG antibodies produced is comparable to the response seen in severe cases of COVID-19. It is IgG antibodies in complex with heparin that induce HIT. One can hypothesize that IgG complexed with the SARS-CoV-2 spike glycoprotein and PF4 is the complex that induces VITT in response to mRNA vaccines. It has in fact been shown experimentally that the receptor binding domain (RBD) of the spike protein binds to PF4 (Passariello et al., 2021).

The underlying mechanism behind HIT has been well studied, including through the use of humanized mouse models. Interestingly, human platelets, but not mouse platelets, express the FcγRIIA receptor, which responds to PF4/heparin/IgG complexes through a tyrosine phosphorylation cascade to induce platelet activation. Upon activation, platelets release granules and generate procoagulant microparticles. They also take up calcium, activate protein kinase C, clump together into microthrombi, and launch a cell death cascade via calpain activation. These activated platelets release PF4 into the extracellular space, supporting a vicious cycle, as this additional PF4 also binds to heparin and IgG antibody to further promote platelet activation. Thus, FcγRIIA is central to the disease process (Nevzorova et al., 2019).

Studies on mice engineered to express the human FcγRIIA receptor have shown that these transgenic mice are far more susceptible to thrombocytopenia than their wild type counterparts (McKenzie et al., 1999). It has been proposed that platelets may serve an important role in the clearance of antibody-antigen complexes by trapping the antigen in thrombi and/or carrying them into the spleen for removal by immune cells. Platelets are obviously rapidly consumed in the process, which then results in low platelet counts (thrombocytopenia).

Platelets normally circulate with an average lifespan of only five to nine days, so they are constantly synthesized in the bone marrow and cleared in the spleen. Antibody-bound platelets, subsequent to platelet activation via Fcγ receptors, migrate to the spleen where they are trapped and removed through phagocytosis by macrophages (Crow and Lazarus, 2003). Fully one third of the body's total platelets are found in the spleen. Since the mRNA vaccines are carried into the spleen by

immune cells initially attracted to the injection site in the arm muscle, there is tremendous opportunity for the release of spike-glycoprotein-containing exosomes by dendritic cells in the spleen synthesizing spike protein. One can speculate that platelet activation following the formation of a P4F/IgG/spike protein complex in the spleen is part of the mechanism that attempts to clear the toxic spike glycoprotein.

We mentioned earlier that one of the two microRNAs highly expressed in exosomes released by human cells exposed to the SARS-CoV-2 spike glycoprotein was miR-148a. miR-148a has been shown experimentally to suppress expression of a protein that plays a central role in regulating FcγRIIA expression on platelets. This protein, called T-cell ubiquitin ligand-2 (TULA-2), specifically inhibits activity of the platelet Fcγ receptor. miR-148a targets TULA-2 mRNA and down-regulates its expression. Thus, miR-148a, present in exosomes released by macrophages that are compelled by the vaccine to synthesize SARS-CoV-2 spike glycoprotein, acts to increase the risk of thrombocytopenia in response to immune complexes formed by spike glycoprotein antigen and IgG antibodies produced against the spike glycoprotein.

11. PPAR-α, sulfatide and liver disease

As we have already stated, an experiment by Mishra and Banerjea (2021) demonstrated that the SARS-CoV-2 spike glycoprotein induces the release of exosomes containing microRNAs that specifically interfere with IRF9 synthesis. In this section we will show that one of the consequences of suppression of IRF9 would be reduced synthesis of sulfatide in the liver, mediated by the nuclear receptor peroxisome proliferator-activated receptor α (PPAR-α).

Sulfatides are major mammalian serum sphingoglycolipids which are synthesized and secreted mainly from the liver (Lu et al., 2019). They are the only sulfonated sphingolipids in the body. Sulfatides are formed by a two-step process involving the conversion of ceramide to galactocerebroside and its subsequent sulfation. Sulfatide is expressed on the surface of platelets, erythrocytes and lymphocytes. Serum sulfatides exert both anti-coagulative and anti-platelet-activation functions. The enzyme in the liver that synthesizes sulfatide, cerebroside sulfotransferase, has specifically been found to be induced by activation of PPAR-α in mice (Kimura et al., 2012). Therefore, reduced expression of PPAR-α leads to sulfatide deficiency.

PPAR-α ligands exhibit anti-inflammatory and anti-fibrotic effects, whereas PPAR-α deficiency leads to hepatic steatosis, steatohepatitis, steatofibrosis, and liver cancer (Wang et al., 2020b). In 2019, an experiment was conducted by a team of researchers in Japan on mice with a defective gene for PPAR-α (Lu et al., 2019). These mice, when fed a high cholesterol diet, were susceptible to excess triglyceride accumulation and exacerbated inflammation and oxidative stress in the liver, along with increased levels of coagulation factors. The mice also manifested with decreased levels of sulfatides in both the liver and the serum. The authors hypothesized that cholesterol overload exerts its toxic effects in part by enhancing thrombosis, following abnormal hepatic lipid metabolism and oxidative stress. They showed that PPAR-α can attenuate these toxic effects through transcriptional regulation of coagulation factors and upregulation of sulfatide synthesis, in addition to its effects in ameliorating liver disease. They proposed that therapies such as fibrates aimed at activating PPAR-α might prevent high-cholesterol-diet-induced cardiovascular disease.

Tracer studies have shown that the mRNA from mRNA vaccines migrates preferentially to the liver and spleen, reaching higher concentration there than in any other organs (Bahl et al., 2017). Thus, there is potential for suppression of IRF9 in the liver by the vaccine. IRF9 is highly expressed in hepatocytes, where it interacts with PPAR-α, activating PPAR-α target genes. A study on IRF9 knockout mice showed that these mice developed steatosis and hepatic insulin resistance when exposed to a high-fat diet. In contrast, adenoviral-mediated hepatic IRF9 overexpression in obese mice improved insulin sensitivity and ameliorated steatosis and inflammation (Wang et al., 2013).

Multiple case reports in the research literature describe liver damage following mRNA vaccines (Zin Tun et al., 2021; Dumortiera, 2022; Mann et al., 2021). A plausible factor leading to these outcomes is the suppression of PPAR-α through downregulation of IRF9, and subsequently decreased sulfatide synthesis in the liver.

12. Guillain Barré syndrome and neurologic injury syndromes

GBS is an acute inflammatory demyelinating neuropathy associated with long-lasting morbidity and a significant risk of mortality (Cr é ange, 2000). The disease involves an autoimmune attack on the nerves associated with the release of pro-inflammatory cytokines.

GBS is often associated with autoantibodies to sulfatide and other sphingolipids (Ilyas et al., 1991). Activated T-cells produce cytokines in response to antigen presentation by macrophages, and these cytokines can induce autoantibody production through epitope spreading (Vanderlugt and Miller, 2002). The antibodies, in turn, induce complement activation, which causes demyelination and axonal damage, leading to severe injury to peripheral neurons (Kuwahara and Kusunoki, 2018). The SARS-CoV-2 spike glycoprotein has been shown to bind to heparan sulfate, which is a sulfated amino-sugar complex resembling the sulfated galactose in sulfatide (Kalra and Kandimalla, 2021). Thus, it is conceivable that the spike glycoprotein also binds to sulfatide, and this might trigger an immune reaction to the spike-glycoprotein-sulfatide complex.

As described in the previous section, impaired sulfatide synthesis in the liver due to suppression of IRF9 will lead to systemic sulfatide deficiency over time. Sulfatide deficiency can have major impact in the brain and nervous system. Twenty percent of the galactolipids found in the myelin sheath are sulfatides. Sulfatide is a major component of the nervous system, found in especially high concentrations in the myelin sheath in both the peripheral and the central nervous system. Deficiencies in sulfatide can lead to muscle weakness, tremors, and ataxia (Honke, 2013), which are common symptoms of GBS. Chronic neuroinflammation mediated by microglia and astrocytes in the brain leads to dramatic losses of brain sulfatide, and brain deficiencies in sulfatide are a major feature of Alzheimer's disease (Qiu et al., 2021). Mice with a defect in the ability to synthesize sulfatide from ceramide show an impaired ability to maintain the health of axons as they age. Over time, they develop redundant, uncompacted and degenerating myelin sheaths as well as deteriorating structure at the nodes of Ranvier in the axons, causing the loss of a functionally competent axoglial junction (Marcus et al., 2006).

Angiotensin II (Ang II), in addition to its profound effects on cardiovascular disease, also plays a role in inflammation in the brain leading to neurodegenerative disease (Lanz. et al., 2010). The SARS-CoV-2 spike glycoprotein contains a unique furin cleavage site not found in SARS-CoV, which allows the extracellular enzyme furin to detach the S1 segment of the spike glycoprotein and release it into circulation (Letarov et al., 2021). S1 has been shown to cross the blood-brain barrier in mice (Rhea et al., 2021). S1 contains the receptor binding domain that binds to ACE2 receptors, disabling them. When ACE2 receptor signaling is reduced, Ang II synthesis is increased. Neurons in the brain possess ACE2 receptors that would be susceptible to disruption by S1 released from spike-glycoprotein-containing exosomes or spike-glycoprotein-producing cells that had taken up the nanoparticles in the vaccines. Ang II enhances TLR4-mediated signaling in microglia, inducing microglial activation and increasing the production of reactive oxygen species leading to tissue damage, within the paraventricular nucleus in the brain (Rodriguez-Perez et al., 2015).

Elevated levels of Ang II is a causal factor in neurodegeneration of the optic nerve, causing optic neuritis, which can result in severe irreversible visual loss (Guo et al., 2017). Multiple case reports have described cases of optic neuropathy appearing shortly after mRNA vaccination for COVID-19 (Maleki, 2021; Barone et al., 2021). Other

debilitating neurological conditions are also appearing shortly after vaccination, where a causal relationship is suspected. A case study based in Europe tracking neurological symptoms following COVID-19 vaccination identified 21 cases developing within a median of 11 days post-vaccination. The cases had diverse diagnoses including cerebral venous sinus thrombosis, nervous system demyelinating diseases, inflammatory peripheral neuropathies, myositis, myasthenia, limbic encephalitis, and giant cell arteritis (Kaulen et al., 2021). Khayat-Khoei et al. (2021) describe a case series of 7 patients, ages ranging from 24 to 64, presenting with demyelinating disease within 21 days of a first or second mRNA vaccination. Four had a prior history of (controlled) MS, while three were previously healthy.

Hearing loss and tinnitus are also well-known side effects of COVID-19. A case study involved a series of ten COVID-19 patients who suffered from audiovestibular symptoms such as hearing loss, vestibular dysfunction and tinnitus (Jeong et al., 2021). The authors demonstrated that human inner ear tissue expresses ACE2, furin and the transmembrane protease serine 2 (TMPRSS2), which facilitates viral entry. They also showed that SARS-CoV-2 can infect specific human inner ear cell types.

Another study evaluating the potential for the SARS-CoV-2 virus to infect the ear specifically examined expression of the receptor ACE2 and the enzymes furin and TM-PRSS2 various types of cells in the middle and inner ears of mice. They found that ACE2 and furin were "diffusely present in the eustachian tube, middle ear spaces, and cochlea, suggesting that these tissues are susceptible to SARS-CoV-2 infection." (Uranaka et al., 2021). Tinnitus is positively associated with hypertension, which is induced by elevated levels of Ang II (Rodrigues Figueiredo et al., 2016).

Headache is a very common adverse reaction to the COVID-19 mRNA vaccines, particularly for people who are already susceptible to headaches. In a study based on a questionnaire involving 171 participants, the incidence of headaches was found to be 20.5% after the first vaccine, rising to 45.6% after the second shot (Sekiguchi et al., 2021). A case study described a 37-year-old woman suffering from a debilitating migraine attack lasting for 11 days following the second Pfizer/BioNtech mRNA vaccine (Consoli et al., 2021).

Steroids are often used as adjunct therapy to treat migraine (Huang et al., 2013). Dexamethasone and other steroids stimulate PPAR-α receptors in the liver through the steroid receptor, thus offsetting the effects of IRF9 suppression (Lemberger et al., 1994). A theory for the origins of migraine involves altered processing of sensory input in the brainstem, primarily trigeminal neurons (Dodick and Silberstein, 2006). The trigeminal nerve is in close proximity to the vagus nerve in the brainstem, so spike-glycoprotein-carrying exosomes could easily reach it along the vagal route. Magnetic resonance imaging has revealed that structural changes in the trigeminal nerve reflecting aberrant microstructure and demyelination are a characteristic feature of people who suffer from frequent migraine headaches (Mungoven et al., 2020). A potential factor linked to either SARS-CoV-2 infection or mRNA vaccination is an excessive level of Ang II in the brainstem due to SARS-CoV-2 spike glycoprotein inhibition of ACE2 receptors. ACE inhibitors and Ang II receptor antagonists have become popular drugs to treat migraine headaches off-label (Tronvik et al., 2003; Nandha and Singh, 2012). Migraine headache could thus arise from both the spike glycoprotein's disruption of ACE2 receptors and the destruction of the myelin sheath covering critical facial nerves through a microglial inflammatory response and loss of sulfatide. The source of that spike glycoprotein could be either exogenous or endogenous.

13. Bell's palsy

Bell's palsy is a common cranial neuropathy causing unilateral facial paralysis. Even in the Phase III clinical trials, Bell's palsy stood out, with seven cases appearing in the treatment arm as compared to only one in the placebo group (FDA, 2021a; FDA, 2021b). A case study reported in the literature involved a 36-year-old man who developed weakness in the left arm one day after vaccination, progressing to numbness and tingling in the arm and subsequent symptoms of Bell's palsy over the next few days. A common cause of Bell's palsy is reactivation of herpes simplex virus infection centered around the geniculate ganglion (Eviston et al., 2015). This, in turn, can be caused by disruption of type I IFN signaling.

14. Myocarditis

There has been considerable media attention devoted to the fact that COVID-19 vaccines cause myocarditis and pericarditis, with an increased risk in particular for men below the age of 50 (Simone et al., 2021; Jain et al., 2021). The SARS-CoV-2 spike glycoprotein has been demonstrated to injure cardiac pericytes, which support the capillaries and the cardiomyocytes (Avolio et al., 2020). Myocarditis is associated with platelet activation, so this could be one factor at play in the response to the vaccines (Weikert. et al., 2002). However, another factor could be related to exosomes released by macrophages that have taken up the mRNA nanoparticles, and the specific microRNAs found in those exosomes.

A study involving patients suffering from severe COVID-19 disease looked specifically at the expression of circulating microRNAs compared to patients suffering from influenza and to healthy controls. One microRNA that was consistently upregulated in association with COVID-19 was miR-155, and the authors suggested that it might be a predictor of chronic myocardial damage and inflammation. By contrast, influenza infection was not associated with increased miR-155 expression. They concluded: "Our study identified significantly altered levels of cardiac-associated miRs [microRNAs] in COVID-19 patients indicating a strong association of COVID-19 with cardiovascular ailments and respective biomarkers" (Garg et al., 2021).

A study comparing 300 patients with cardiovascular disease to healthy controls showed a statistically significant increase in circulating levels of miR-155 in the patients compared to controls. Furthermore, those with more highly constricted arteries (according to a Gensini score) had higher levels than those with lesser disease (Qiu and Ma, 2018).

Importantly, exosomes play a role in inflammation in association with heart disease. During myocardial infarction, miR-155 is sharply upregulated in macrophages in the heart muscle and released into the extracellular milieu within exosomes. These exosomes are delivered to fibroblasts, and miR-155 downregulates proteins in the fibroblasts that protect from inflammation and promote fibroblast proliferation. The resulting impairment leads to cardiac rupture (Wang et al., 2017b).

We have already discussed how the S1 segment of the SARS-CoV-2 spike glycoprotein can be cleaved by furin and released into circulation. It binds to ACE2 receptors through its receptor binding domain (RBD), and this inhibits their function. Because ACE2 degrades Ang II, disabling ACE2 leads directly to overexpression of Ang II, further enhancing risk to cardiovascular disease. AngII-induced vasoconstriction is an independent mechanism to induce permanent myocardial injury even when coronary obstruction is not present. Repeated episodes of sudden constriction of a cardiac artery due to Ang II can eventually lead to heart failure or sudden death (Gavras and Gavras, 2002). Fatal cases of COVID-19 vaccination have been described (Choi et al., 2021; Verma et al., 2021).

ACE2 suppression had already been seen in studies on the original SARS-CoV virus. An autopsy study on patients succumbing to SARS-CoV revealed an important role for ACE2 inhibition in promoting heart damage. SARS-CoV viral RNA was detected in 35% of 20 autopsied human heart samples taken from patients who died. There was a marked increase in macrophage infiltration associated with myocardial damage in the patients whose hearts were infected with SARS-CoV. Importantly, the presence of SARS-CoV in the heart was associated with marked reduction in ACE2 protein expression (Oudit et al., 2009).

15. Considerations regarding the Vaccine Adverse Event Reporting System (VAERS)

The Food and Drug Administration's Vaccine Adverse Event Reporting System (VAERS) is an imperfect but valuable resource for identifying potential adverse reactions to vaccines. Established through collaboration between the CDC and FDA, VAERS is "a national early warning system to detect possible safety problems in U.S.-licensed vaccines." According to the CDC it is "especially useful for detecting unusual or unexpected patterns of adverse event reporting that might indicate a possible safety problem with a vaccine." (https://vaers.hhs.gov/about.html) Even the CDC recognizes that adverse events reported to VAERS represent "only a small fraction of actual adverse events" (Vaers Home, 2021). A widely cited report noted that fewer than 1% of all vaccine-related adverse events are reported to VAERS (Lazarus et al., 2010). That assertion, though, has no citation so the basis for the claim is unclear. Rose (2021) published a much more sophisticated analysis of VAERS data to offer an estimate of underreporting by a factor of 31 (Rose, 2021). While it is impossible to determine underreporting with precision, the available evidence is that underreporting very strongly characterizes the VAERS data. The information presented below should be understood in that light.

In mining VAERS for 'signals' that might indicate adverse reactions (AEs) to mRNA vaccinations, we acknowledge that no report to VAERS establishes a causal link with the vaccination. That said, the possibility of a causal relationship is strengthened through both the causal pathways we have described in this paper, and the strong temporal association between injections and reported AEs. Nearly 60% of all mRNA-injection-related -AEs have happened within 48 h of injection (https://medalerts.org/vaersdb/findfield.php?TABLE=ON&GROUP1=ONS&EVENTS=ON&VAX=COVID19&VAXTYPES=COVID-19&STATE=NOTFR).

Two important cautions regarding analysis of VAERS data should be noted. The first is that, in addition to health care professionals submitting reports, VAERS is open for public submissions as well. Members of the public may lack the skills necessary to evaluate a symptom appropriately to determine if it merits a VAERS entry. A second caution is that public access also allows for the possibility of anti-vaccination activists to populate VAERS with false reports to exaggerate the appearance of AE risk.

An interim analysis of deaths cited previously found that health service employees were the VAERS reporter in 67% of reports analyzed (Nandha and Singh, 2012), suggesting a large portion of VAERS reports are submitted by medical professionals and not the public. This finding also belies the notion that anti-vaccination activists are filing an excessive number of egregious reports of vaccine injury.

All of the data reported in this section were obtained by querying the online resource, http://wonder.cdc.gov/vaers.html. Over the 31-year history of VAERS, up to February 3, 2022, there were a total of 10,321 deaths reported as a "symptom" in association with any vaccine, and 8,241 (80%) of those deaths were linked to COVID-19 vaccines. Importantly, only 14% of COVID-19 VAERS-reported deaths as of June 2021 could have vaccination ruled out as a cause (McLachlan et al., 2021). This strongly suggests that these unprecedented vaccines exhibit unusual mechanisms of toxicity that go well beyond what is seen with more traditional vaccines.

We decided that a reasonable way to characterize the significance of adverse events linked to COVID-19 vaccines was to focus on events received in the year 2021, and to compare the counts in the "SYMPTOM" field for the events associated with COVID-19 vaccines to the total counts for that same symptom for all vaccines over that same year. In total, there were 737,689 events reported in VAERS for COVID-19 vaccines in 2021, representing a shocking 93% of the total cases reported for any vaccine that same year. While we recognize that some of the COVID-19 vaccines are based on DNA vector technology rather than mRNA technology, this class (i.e., the Johnson & Johnson vaccine) represents less than 9% of the COVID-19 reports, and its reaction profile is surely much more similar to that of the mRNA vaccines than to that of all the other vaccines.

The total number of adverse event reports for COVID-19 injections is far greater than the cumulative number of annual vaccine adverse event reports combined in all prior years, as shown by Rose (2021). The influenza vaccine is a good one to compare against. Given that the protocol for the mRNA vaccines requires two doses, and that many were persuaded to receive a booster shot as well, it is clear that the sheer number of COVID-19 vaccines administered is large compared to other vaccines. We can actually estimate what percent of the adverse reactions in 2021 would be expected to be associated with COVID-19 vaccines if the likelihood of an adverse reaction were similar to that of the influenza vaccine. The CDC tells us that 52% of the US population received a flu shot in 2021. The USAFacts web site provides percentages of the US population that received one, two or three doses of COVID-19 vaccines as a function of time (see: https://usafacts.org/visualizations/covid-vaccine-tracker-states/). The numbers they report for December 30, 2021 are 73% single dose, 62% fully vaccinated, and 21% boosted. This tallies up to 156% of the population as the total number of COVID-19 vaccines administered. This is exactly three times as many COVID vaccines as flu shots.

From VAERS, one can easily obtain the total number of adverse reactions associated with COVID-19 vaccines, the total number associated with flu vaccines, and the total number associated with all vaccines, for the US-restricted VAERS data from 2021. These come out as: COVID-19: 737,587, FLU: 9,124, and ALL: 792,935. First, we can observe that 93% of all the events reported were linked to COVID-19 vaccines. If we remove the counts for COVID-19 and replace them with three times the counts for flu (since COVID-19 vaccines were administered three times as often), we find that COVID-19 should have accounted for 32.6% of all the events, which can be compared with the actual result, which is 93%. We can also conclude that any event that shows up more than 93% as often for COVID-19 vaccines as for all other vaccines is especially significant as a potential toxic effect of these vaccines. Finally, we find that there are 27 times as many reports for COVID-19 vaccines as would be expected if its adverse reactions were comparable to those from the flu vaccine.

Table 1
Number of symptoms reported in VAERS, restricted to the US population, for the year 2021, for various adverse effects that could be caused by inflammation in associated major nerves, showing total counts for COVID-19 vaccines and for all vaccines.

Symptom	Inflamed Nerve(s)	Covid-19 Vaccines	All Vaccines	Percent COVID-19
Anosmia	olfactory nerve	3,657	3,677	99.5
Tinnitus	vestibulo-cochlear nerve	13,275	13,522	98.2
Deafness	cochlea	2,895	3,033	95.5
Bell's Palsy/ facial palsy	facial nerve	5,881	6,129	96.0
Vertigo	vestibular nerve	7,638	7,819	97.7
Migraine headache	trigeminal nerve	8,872	9,059	97.9
Dysphonia	glossopharyngeal nerve	1,692	1,751	96.6
Dysphagia	several lower cranial nerves	4,711	4,835	97.4
Nausea	vagus nerve	69,121	71,275	97.0
Vomiting	vagus nerve	27,885	28,955	96.3
Dyspnea	vagus nerve	39,551	40,387	97.9
Syncope	vagus nerve	14,701	15,268	96.3
Bradycardia	vagus nerve	673	699	96.3
TOTAL	–	**200,552**	**206,409**	**97.2**

15.1. VAERS data indicative of nerve damage and vagus nerve involvement

Table 1 lists a number of symptoms in VAERS that can be associated with inflammation of or damage to various major nerves of the body, particularly those in the head. Strikingly, COVID-19 vaccines represented from 96 to 98% of the reports in the year 2021 related to each of these debilitating conditions. There were nearly 100,000 cases of nausea or vomiting, which are common symptoms of vagus nerve stimulation or damage (Babic and Browning, 2014). 14,701 cases of syncope linked to COVID-19 vaccines represented 96.3% of all cases of syncope, a well-established feature of vagus nerve dysfunction (Fenton et al., 2000). There were 3,657 cases of anosmia (loss of smell), clearly demonstrating that the SARS-CoV-2 spike glycoprotein from the injection in the arm was reaching the olfactory nerve. Dyspnea (shortness of breath) is related to vagus nerve impairment in the lungs, and there were 39,551 cases of dyspnea connected to COVID-19 vaccines in 2021.

Altogether, these events add up to a total of over 200,000 events, representing 97.2% of all the entries related to any vaccine in 2021. This is also a substantial 27.2% of all the events listed for 2021 in association with COVID-19 vaccines.

15.2. VAERS data on the heart and liver

In this paper, we have identified both the heart and the liver as organs that can be expected to be affected by the mRNA vaccines. The VAERS database shows a strong signal for both organs. Table 2 shows the statistics for 2021 on major disorders of the heart, including myocarditis, arrest (cardiac, cardiorespiratory and sinus arrest), arrhythmia (including supraventricular, nodal, sinus, tachyarrhythmia and ventricular arrhythmia), myocardial infarction (including acute and silent), and cardiac failure (including acute, chronic and congestive). Altogether, there were a total of 8,090 COVID-19 events related to these heart conditions, representing nearly 98% of all the events for all the vaccines for these symptoms in 2021.

It is difficult to find all of the symptoms associated with liver damage in VAERS, but we selected a number that had high enough counts to be of interest and that clearly represent serious liver problems. Altogether there were 731 events in these categories for COVID-19 vaccines, as shown in Table 3, representing over 97% of all the cases connecting these conditions to any vaccine in 2021.

15.3. VAERS data related to thrombosis

There were 78 unique symptoms in VAERS involving thrombosis, specifying different arteries and veins. Table 4 shows nine symptoms with the highest counts, totaling 7,356 events. We investigated the time interval for the three dominant ones (thrombosis, deep vein thrombosis and pulmonary thrombosis), and found that these all have a sharp peak in the 15-30-day range for onset interval (time after vaccination). This coincides with a sharp peak in pulmonary embolism, a life-threatening condition, also in the 15-30-day time interval. Overall, for these nine thrombotic symptoms, a random sampling from the year 2021 would yield a COVID vaccine as opposed to any other vaccine 98.7% of the time. Pulmonary embolism, a life-threatening condition that can be caused by a blood clot that travels to the lungs, has a slightly higher probability of 98.8%, with 3,100 cases listed for COVID-19.

Table 2
Number of symptoms reported in VAERS, restricted to the US population, for the year 2021, for various disorders of the heart, showing total counts for COVID-19 vaccines and for all vaccines.

Symptom	Covid-19 Vaccines	All Vaccines	Percent COVID-19
Myocarditis	2,322	2,361	98.3
Arrest	1,319	1,371	96.2
Arrhythmia	1,069	1,087	98.3
Myocardial infarction	2,224	2,272	97.9
Cardiac failure	1,156	1,190	97.1
TOTAL	8,090	8,281	97.7

Table 3
Number of symptoms reported in VAERS, restricted to the US population, for the year 2021, for various indicators of liver disease, showing total counts for COVID-19 vaccines and for all vaccines.

Symptom	Covid-19 Vaccines	All Vaccines	Percent COVID-19
Liver disorder	83	87	95.4
[Drug-induced] liver injury	65	65	100
[Acute] hepatic failure	86	88	97.7
Hepatic cancer [metastatic]	12	12	100
Hepatic cirrhosis	67	69	97.1
Hepatic cyst	33	34	97.0
Liver function test increased	238	245	97.1
Liver function test abnormal	90	94	95.7
Hepatic function abnormal	34	34	100
Haemangioma of liver	10	10	100
Liver abscess	7	7	100
Liver transplant	6	6	100
TOTAL	**731**	**751**	**97.3**

Table 4
Number of symptoms reported in VAERS, restricted to the US population, for the year 2021, for various specific types of thrombosis, showing total counts for COVID-19 vaccines and for all vaccines. Pulmonary embolism, a highly related symptom, is also shown.

Symptom	Covid-19 Vaccines	All Vaccines	Percent COVID-19
Thrombosis	3,899	3,951	98.7
Deep vein thrombosis	2,275	2,297	99.0
Pulmonary thrombosis	631	646	97.7
Cerebral thrombosis	211	215	98.1
Portal vein thrombosis	89	90	98.9
Superficial vein thrombosis	81	81	100
Peripheral artery thrombosis	74	74	100
Mesenteric vein thrombosis	55	56	98.2
Venous thrombosis	41	41	100
TOTAL	**7,356**	**7,451**	**98.7**
Pulmonary embolism	**3,100**	**3,137**	**98.8**

15.4. VAERS data related to neurodegenerative disease

Table 5 lists results for several conditions that are linked to neurodegenerative disease. Decreased mobility can be caused by Parkinson's disease, and there were a striking 8,975 cases listed for 2021 and COVID-19 vaccines. Alzheimer's and Parkinson's are diseases that normally

Table 5
Number of symptoms reported in VAERS, restricted to the US population, for the year 2021, for various disorders linked to neurodegenerative disease, showing total counts for COVID-19 vaccines and for all vaccines.

Symptom	Covid-19 Vaccines	All Vaccines	Percent COVID-19
Alzheimer's dementia	37	39	94.9
Parkinsonian symptoms	83	89	93.3
Memory impairment	1,681	1,720	97.7
Anosmia	3,657	3,677	99.5
Mobility decreased	8,975	9,743	92.1
Cognitive disorder	779	815	92.1
TOTAL	**15,212**	**16,083**	**94.6**

take decades to develop, and ordinarily one would assume that a vaccine has nothing to do with it. While the numbers are small, most of the cases in VAERS were linked to COVID-19 vaccines. Anosmia, also included in the table on the vagus nerve, is especially interesting, because it is a well-known early sign of Parkinson's disease, and it is also a well-identified feature of SARS-CoV-2 infection. 99.5% of the cases with anosmia as a symptom were linked to COVID-19 vaccines. Overall, the symptoms in this table were linked to COVID-19 vaccines nearly 95% of the time.

15.5. VAERS signal for cancer

Cancer is a disease generally understood to take months or, more commonly, years to progress from an initial malignant transformation in a cell to development of a clinically recognized condition. Since VAERS reports of adverse events are happening primarily within the first month or even the first few days after vaccination (Rose, 2021), it seems likely that the acceleration of cancer progression following vaccines would be a difficult signal to recognize. Furthermore, most people do not expect cancer to be an adverse event that could be caused by a vaccine, and hence they fail to enter a report when cancer develops shortly after vaccination. However, as we have outlined in our paper, if the mRNA vaccinations are leading to widespread dysregulation of oncogene controls, cell cycle regulation, and apoptosis, then VAERS reports should reflect an increase in reports of cancer, relative to the other vaccines, even if the numbers are small. The experiment demonstrating impairment of DNA repair mechanisms by SARS-CoV-2 spike protein in an *in vitro* study provides compelling evidence that the vaccines could accelerate the rate of DNA mutations, increasing cancer risk (Jiang and Mei, 2021).

For our analysis of evidence of increased cancer risk in VAERS, we focused on two somewhat distinct approaches. One, represented by the results in Table 6, was to gather the counts for any terms that contained keywords clearly linked to cancer, namely, "cancer," "lymphoma," "leukaemia," "metastasis," "carcinoma," and "neoplasm." Overall, we found 1,474 entries linking these terms to COVID-19 vaccines, representing 96% of all the entries for any of these terms for any vaccine in that year.

The complementary approach was to find terms involving cancer in specific organs, namely, breasts, prostate, bladder, colon, brain, lungs, pancreas and ovaries, as shown in Table 7. Although all the numbers are small, the highest by far was for breast cancer (246 cases), with nearly four times as many hits as for lung cancer, the second most common type. All of the cases for pancreatic, ovarian and bladder cancer were linked to COVID-19 vaccines, with zero cases for any other vaccine. Altogether, we tabulated 534 cases of cancer of specific organs linked to COVID-19 vaccines, representing 97.3% of all the cases for any vaccine in 2021.

Table 6
Number of symptoms reported in VAERS, restricted to the US population, for the year 2021, for various cancer-related terms, showing total counts for COVID-19 vaccines and for all vaccines.

Symptom	Counts COVID-19 vaccines	Counts All Vaccines	Percent COVID-19
Cancer	396	403	98.3
Lymphoma	144	153	94.1
Leukaemia	155	161	96.3
Metastatic/ metastasis	175	179	97.8
Carcinoma	176	187	94.1
Neoplasm	428	452	94.7
TOTAL	**1,474**	**1,535**	**96.0**

Table 7
Number of symptoms reported in VAERS, restricted to the US population, for the year 2021, for cancer of specific organs, showing total counts for COVID-19 vaccines and for all vaccines.

Symptom	Counts COVID-19 vaccines	Counts All Vaccines	Percent COVID-19
Breast cancer	246	254	96.8
Prostate cancer	50	52	96.2
Bladder cancer	30	30	100
Colon cancer	40	41	97.6
Brain neoplasm	53	55	96.4
Lung cancer	64	66	97.0
Pancreatic cancer	24	24	100
Ovarian cancer	27	27	100
Total	**534**	**549**	**97.3**

16. Conclusions

There has been an unwavering message about the safety and efficacy of mRNA vaccinations against SARS-CoV-2 from the public health apparatus in the US and around the globe. The efficacy is increasingly in doubt, as shown in a recent letter to the Lancet Regional Health by Günter Kampf (2021b). Kampf provided data showing that the vaccinated are now as likely as the unvaccinated to spread disease. He concluded: "It appears to be grossly negligent to ignore the vaccinated population as a possible and relevant source of transmission when deciding about public health control measures." Moreover, the inadequacy of phase I, II, and III trials to evaluate mid-term and long-term side effects from mRNA genetic vaccines may have been misleading on their suppressive impact on the innate immunity of the vaccinees.

In this paper, we call attention to three very important aspects of the safety profile of these vaccinations. First is the extensively documented subversion of innate immunity, primarily via suppression of IFN-α and its associated signaling cascade. This suppression will have a wide range of consequences, not the least of which include the reactivation of latent viral infections and the reduced ability to effectively combat future infections. Second is the dysregulation of the system for both preventing and detecting genetically driven malignant transformation within cells and the consequent potential for vaccination to promote those transformations. Third, mRNA vaccination potentially disrupts intracellular communication carried out by exosomes, and induces cells taking up spike glycoprotein mRNA to produce high levels of spike-glycoprotein-carrying exosomes, with potentially serious inflammatory consequences. Should any of these potentials be fully realized, the impact on billions of people around the world could be enormous and could contribute to both the short-term and long-term disease burden our health care system faces.

Given the current rapidly expanding awareness of the multiple roles of G4s in regulation of mRNA translation and clearance through stress granules, the increase in pG4s due to enrichment of GC content as a consequence of codon optimization has unknown but likely far-reaching consequences. Specific analytical evaluation of the safety of these constructs in vaccines is urgently needed, including mass spectrometry for identification of cryptic expression and immunoprecipitation studies to evaluate the potential for disturbance of or interference with the essential activities of RNA and DNA binding proteins.

It is essential that further studies be conducted to determine the extent of the potential pathological consequences outlined in this paper. It is not practical for these vaccinations to be considered part of a public health campaign without a detailed analysis of the human impact of the potential collateral damage. VAERS and other monitoring systems should be optimized to detect signals related to the health consequences of mRNA vaccination we have outlined. We believe the upgraded VAERS monitoring system described in the Harvard Pilgrim Health Care, Inc. study, but unfortunately not supported by the CDC, would be a valuable start in this regard (Lazarus et al., 2010).

In the end, billions of lives are potentially at risk, given the large number of individuals injected with the SARS-CoV-2 mRNA vaccines and the broad range of adverse outcomes we have described. We call on the public health institutions to demonstrate, with evidence, why the issues discussed in this paper are not relevant to public health, or to acknowledge that they are and to act accordingly. Furthermore, we encourage all individuals to make their own health care decisions with this information as a contributing factor in those decisions.

Author contributions

S.S., G.N and A.K. all contributed substantially to the writing of the original draft. P.M. participated in the process of editorial revisions.

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Declaration of competing interest

The authors 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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EXHIBIT C

The extent and impact of vaccine status miscategorisation on covid-19 vaccine efficacy studies

Martin Neil (m.neil@qmul.ac.uk)
School of Electronic Engineering and Computer Science
Queen Mary, University of London

Norman Fenton (n.fenton@qmul.ac.uk)
School of Electronic Engineering and Computer Science
Queen Mary, University of London

Scott McLachlan (scott.mclachlan@kcl.ac.uk)
School of Nursing, Midwifery and Palliative Care
Kings College London

Abstract

It is recognised that many studies reporting high efficacy for Covid-19 vaccines suffer from various selection biases. Systematic review identified thirty-nine studies that suffered from one particular and serious form of bias called miscategorisation bias, whereby study participants who have been vaccinated are categorised as unvaccinated up to and until some arbitrarily defined time after vaccination occurred. Simulation demonstrates that this miscategorisation bias artificially boosts vaccine efficacy and infection rates even when a vaccine has zero or negative efficacy. Furthermore, simulation demonstrates that repeated boosters, given every few months, are needed to maintain this misleading impression of efficacy. Given this, any claims of Covid-19 vaccine efficacy based on these studies are likely to be a statistical illusion.

Keywords: simulation; covid-19; evidence-based medicine; mis-categorisation; selection bias; observational studies; public health; vaccine effectiveness.

1. Introduction

Considerable attention has been given to the reported high efficacy for the Covid-19 vaccines and how many of these studies have exhibited signs of selection bias (Reeder, 2021, Fung, Jones & Doshi, 2023; Heying & Weinstein, 2023; Ioannidis, 2022; Fenton & Neil, 2023). One major kind of selection bias takes the form of miscategorisation, whereby study participants who have been vaccinated are miscategorised as unvaccinated up to and until some arbitrarily defined time after vaccination occurred (typically up to 14 or 21 days). This selection bias, which has been seen to take several different types, all of which help exaggerate vaccine efficacy, has recently become known colloquially as the ‘cheap trick’ (Fenton & Neil, 2023).

To identify the different types of miscategorisation bias and evaluate how widespread it is, we conducted a review of Covid-19 vaccine studies to identify those studies that have employed miscategorisation selection bias and we have simulated the effects of this selection bias on measures of vaccine efficacy.

This review reveals that, up to February 2024, 39 research studies on Covid-19 vaccines have employed different types of this bias, with variants including straightforward miscategorisation from one category to another, miscategorising the vaccinated as having unverified vaccination status,

uncontrolled reporting of vaccination status and excluding those vaccinated from the study. Many of the studies have applied one or more of these biases within time periods from one week to three.

Our simulation model demonstrated that this selection bias artificially boosts vaccine efficacy in all cases, and with the application of repeated 'booster' vaccinations, the efficacy of repeated Covid-19 vaccines could be maintained at artificially high levels in perpetuity. Furthermore, in tandem with this the infection rate would likewise be artificially elevated and would be lower for the unvaccinated cohort compared to the vaccinated cohort, further compounding misleading claims that a Covid-19 vaccine reduces infection rates when it does not.

The paper is structured as follows: In Section 2 we review the work on biases in Covid-19 vaccine studies. In Section 3 we describe the search method by which relevant studies were selected. In Section 4 we classify each of the relevant studies according to novel types of miscategorisation selection biases exhibited. In Section 5 we simulate the vaccine efficacy results that would be observed during peak rollout of both a placebo and negative efficacy vaccine under the various selection biases. Section 6 offers our conclusions.

2. Background

Several studies have investigated bias in Covid-19 vaccine studies, including: (i) *outcome reporting bias* affecting interpretation of vaccine efficacy where studies report relative risk reduction (RRR) rather than actual risk reduction (ARR) (Brown, 2021); *confounding bias* in test-negative studies where other acute respiratory infections (ARI) are assumed to occur or be independent to Covid-19 (Doll et al, 2022), where authors promote the use of recently vaccinated individuals as a negative control (Hitchings et al, 2022), due to imperfect sensitivity and/or specificity of the test used to diagnose the disease (Eusebi et al, 2023; Williams et al, 2022); *state bias* wherein limited uptake, or vaccine hesitancy, is said to occur because the general public prefer domestically produced vaccines over foreign-made (Kobayashi et al, 2021) and alternatively, *confirmation bias* that causes people to disregard public information and results in the same hesitancy (Malthouse, 2023); *self-selection bias* where participants who have been vaccinated are more likely to also willingly present for swab collection and testing (Glasziou et al, 2022); and *collider stratification bias* where rather than the usual approach of reporting the *relative risk of the disease*, Covid-19, test-negative studies use the recently created alternative approach of reporting the *relative risk of infection* given a second variable, vaccination (Ortiz-Brizuela et al, 2023). The studies discussed here are approximately evenly divided between those that report biases that have exaggerated factors of vaccine safety and efficacy, and those reporting biases have negatively impacted assessment of these factors and resulting public perception.

We focus explicitly on miscategorisation selection biases, which inevitably exaggerate vaccine efficacy. We identify five types of such bias (defined in detail in Section 4), namely: (i) *Miscategorisation* (the type most closely associated with the miscategorisation selection bias); (ii) *Unverified*; (iii) *Uncontrolled*; (iv) *Excluded*; and (v) *Undefined.* Previous work (Ioannidis, 2021; Fung, Jones & Doshi, 2023, Lataster 2024) has largely focused only on miscategorisation, so our review is novel as well as more extensive than previous work. Ioannidis (2021) considers miscategorisation in terms of vaccination self-reporting by participants, the need for investigators to provide definitions for what it means to be vaccinated and whether categorisation as vaccinated occurs immediately after vaccination or after some period, and they discuss the possibility for these definitions to themselves cause miscategorisation of vaccination status. Fung et al (2023) examine this issue in terms of a case-counting window bias, in which investigators do not begin counting cases in the *fully vaccinated* until the arbitrary period after vaccination had passed. They also found that investigators could apply this period to both the vaccine and placebo arms of their study, or to the vaccine group alone.

3. Method

A search was conducted of PubMed and Scopus seeking literature presenting either a retrospective health records or prospective clinical trial of one or more Covid-19 vaccines with efficacy or safety as an endpoint. The search term used was:

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[covid] and [vaccine] and [efficacy] and [safety]
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The initial search returned 2,209 results. 476 Duplicates were removed, as well as 1,562 that while discussing or mentioning vaccines for Covid-19 did not present a study of vaccine efficacy or safety and 134 single-page works that were a mix of protocol disclosures and abstracts of results. Of the 37 remaining, 35 provided sufficient detail of the inclusion and exclusion criteria for inclusion in this study. A further 4 papers were identified through citation mining of included papers. Each paper was evaluated for a range of aspects that included the manufacturer and type of vaccine, the control cohort comparator (placebo or unvaccinated), the primary outcomes (prevention of infection, hospitalisation, ICU admission or death), the author's potential conflicts of interest (declared and undeclared) and whether they included one or more types of miscategorisation selection bias. This work reports on the last of these factors.

4.Types of miscategorisation selection bias

Our review identified the following five types of the miscategorisation selection bias:

(a) *Miscategorisation:* During the arbitrarily defined period the vaccinated are categorised as unvaccinated, twice vaccinated categorised as single vaccinated, or boosted categorised as twice vaccinated (e.g.: Buchan et al, 2022; Stock et al, 2022).
(b) *Unverified:* Participants whose vaccination status is unknown or unverified are categorised as unvaccinated (e.g.: Rosenberg et al, 2021; Lyngse et al, 2022b).
(c) *Uncontrolled:* Participants are allowed to self-administer or self-report their vaccination or infection status, became unblinded or sought vaccination outside the study (e.g.: Angel et al, 2021; Wu et al, 2023).
(d) *Excluded:* Participants who are vaccinated but who become infected or died during the arbitrarily defined period are neither categorised as unvaccinated or vaccinated but are instead simply removed from analysis (e.g.: Tabarsi et al, 2023; Heath et al, 2023);
(e) *Undefined:* The authors of the study fail to provide definitions for either or both vaccinated and unvaccinated cohorts (e.g.: Bermingham et al, 2023b; Nordstrom et al, 2022).

Table 1 lists the incidence and frequency of use for each type of miscategorisation selection bias in Covid-19 vaccine effectiveness research studies. Use of the arbitrary miscategorisation type was ubiquitous, identified in 100% of the reviewed studies. Further, nearly one-third (31%) also used one or more of the other types of bias.

Table 1 Research studies containing miscategorisation selection bias (see appendix for full citation list)

Citation	(a)	(b)	(c)	(d)	(e)	Defined Period
Dagan et al (2021)	X					14 days
Haas et al (2021)	X					7 days
Rosenberg et al (2021)	X	X				14 days
Thomas et al (2021)	X					7 days
Angel et al (2021)	X		X			7 days
NSW Health (2021)	X	X				14 days
Ali et al (2021)	X					14 days
Pilishvili et al (2021)	X		X			14 days / 7 days
Andrews et al (2022)	X					28 days
Buam et al (2022)	X					21 days / 14 days
Buchan et al (2022)	X					7 days
Carazo et al (2022)	X					14 days
Chung et al (2022)	X					7 days
Palinkas et al (2022)	X					7 days
Ferdinands et al (2022)	X	X		X		14 days
Lyngse et al (2022)	X					7-15 days

Lyngse et al (2022b)	X	X				7-15 days
Nordstrom et al (2022)	X			X	X	14 days
Petras et al (2022)	X					14 days
Robles-Fontan et al (2022)	X					14 days
Arbel et al (2022)	X					7 days
Paternina et al (2022)	X					14 days
Stock et al (2022)	X					21 days / 14 days
Bermingham et al (2023)	X					21 days
Yau et al (2023)	X					Until fully vaccinated
Mitchell et al (2023)	X					14 days
Tan et al (2023)	X					7 days
Al Kaabi et al (2023)	X					14 days
Tabarsi et al (2023)	X		X	X		14 days
Heath et al (2023)	X		X			7 days
Nadeem et al (2023)	X					14 days
Anez et al (2023)	X					7 days
Munoz et al (2023)	X					7 days
Wu et al (2023)	X		X			28 days
Bermingham et al (2023b)	X				X	21 days
Liu et al (2023)	X					7 days
Kitano et al (2023)	X					7 days / 14 days
Polack et al (2020)	X			X		7 days
Khairullin et al (2022)	X					14 days
	39	**4**	**5**	**4**	**2**	

5. Simulation of vaccine effectiveness

We used a deterministic temporal simulation to illustrate the effects of the miscategorisation selection bias on vaccine effectiveness and the reported infection rates for different cohorts, vaccinated and unvaccinated. We simulated a hypothetical vaccination campaign starting at week 1 and completing on week 6 with 85% of the observed population vaccinated by that time.

Here we examine several scenarios showing the effect of a one-week, two-week and three-week selection biases for miscategorisation (a) and exclusion (c) and the effects of repeated vaccination, by boosting, on vaccine efficacy and infection reported rates. Two scenarios present a placebo (zero-efficacy) vaccine, which does not affect infection rates, and compare this with a negative-efficacy vaccine, whereby those vaccinated suffer slightly elevated infection rates compared to the unvaccinated.

Note that observational studies might suffer from many sources of additional confounding biases so this model is a simplification and should not be taken as representative of population level data.

The scenarios simulated cover an eleven-week period with an assumed constant weekly infection rate of 1% in the placebo scenario, and a slightly elevated infection rate, 1.25%, for the vaccinated cohort in the negative-efficacy scenario. This is used in both the miscategorisation, (a), and excluded, (c), simulations. To simulate the effects of boosters we assume a population that is repeatedly vaccinated every twelve weeks, with those who are vaccinated miscategorised (a) within one week of each vaccination.

The results of the five scenarios are presented in Figure 1.

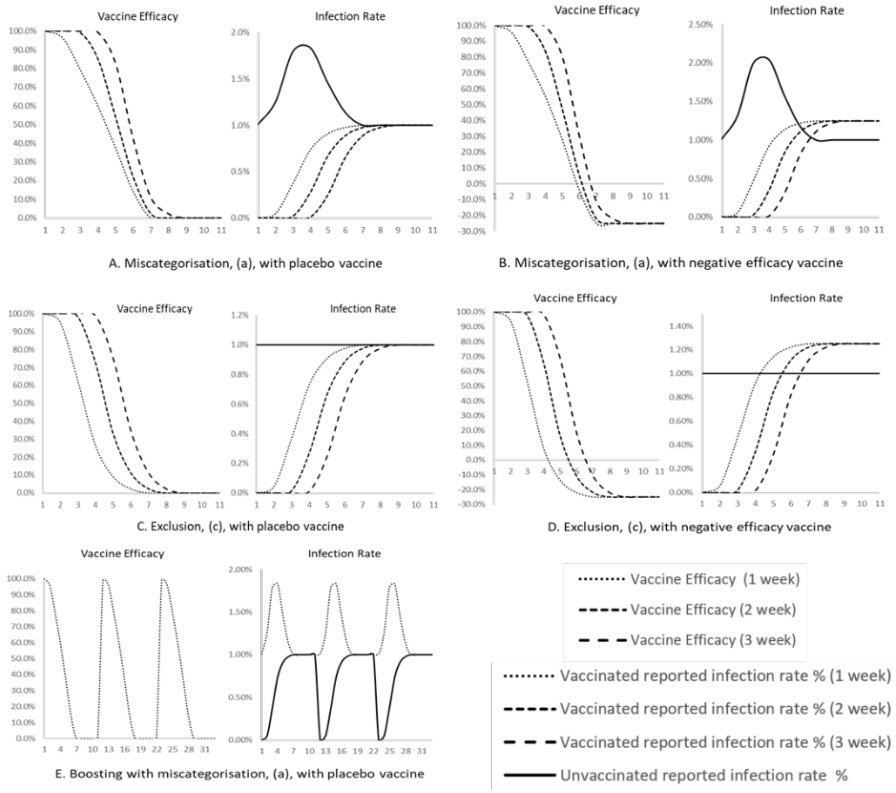

Figure 1 Five scenarios A-E. A: Miscategorisation, (a) with placebo vaccine; B: Miscategorisation, (a), with negative efficacy vaccine; C: Exclusion, (c) with placebo vaccine; D: Exclusion, (c), with negative efficacy vaccine; E: Boosting with miscategorisation, (a), with placebo vaccine

In practice, most studies do not report vaccine efficacy in the initial week(s) (when no cases are categorised as vaccinated) as this would show up as 100% efficacy. However, note that in all scenarios in the first weeks where efficacy would be reported the starting point for efficacy is over 90%.

In scenario A, miscategorisation, (a), with a placebo, high vaccine effectiveness falls towards zero after one, two or three-week periods, accompanied by an increase in the reported infection rate for the unvaccinated cohort from the start of the vaccination campaign. After seven weeks the reported infection rates for the vaccinated and unvaccinated cohorts converge on the true infection rate. In scenario B, miscategorisation, (a), with a negative effectiveness vaccine, the reported vaccine effectiveness is negative from week six onwards, and again the reported infection rate for the unvaccinated is overestimated from the start of the vaccination campaign. However, by the end of the campaign the reported infection rates for the vaccinated would be greater than that for the unvaccinated.

Scenarios C and D are simply the same as scenarios A and B, except for the fact that they are for the excluded type, (c), of selection bias. Note that here the reported infection rate for the vaccinated remains unbiased whilst that for the vaccinated rises to match the true rate for the placebo and negative efficacy scenarios.

In Scenario E, boosting with miscategorisation, (a), we can see that repeated application of the vaccine at twelve-week intervals restores vaccine efficacy to high levels after each booster and, assuming a constant infection rate, elevates the reported infection rate in the unvaccinated cohort between each booster campaign, giving rise to bias and gross overestimation.

Our simulation model has demonstrated that the effects of this selection bias are to artificially boost vaccine efficacy in all cases, and with the application of repeated ‘booster’ vaccinations, the efficacy of repeated Covid-19 vaccines could be maintained at these artificial levels in perpetuity should boosting be continued indefinitely. Furthermore, in tandem with this the infection rate is likewise artificially

elevated for the unvaccinated cohort compared to the vaccinated cohort, further compounding false claims that a Covid-19 vaccine reduces infection rates. Note that other metrics of vaccine effectiveness, such as mortality or morbidity improvements, are capable of being mis-reported in a similar way because of the same bias.

6. Conclusions

Our reviews reveals that a serious form of selection bias, miscategorisation, is pervasive throughout the many research studies that aim to measure Covid-19 vaccine efficacy. The effect of this bias is to artificially inflate vaccine efficacy and present the misleading impression that these vaccines are effective and that the non-vaccinated suffer from higher Covid-19 infection rates compared to the vaccinated.

We presented a simulation model to demonstrate the effects of this selection bias and show it artificially boosts vaccine efficacy in all cases, and with the application of repeated 'booster' vaccinations, the efficacy of repeated Covid-19 vaccines could be maintained at artificial levels in perpetuity should boosting be continued indefinitely. This effect occurs with a both a zero-efficacy (placebo) vaccine and a negative-efficacy vaccine that increases, rather than reduces, infection rates in those vaccinated.

This miscategorisation is guaranteed to lead to initially very high efficacy claims (usually above 90%) during peak vaccine rollout even if the vaccine were a placebo or worse. Efficacy then falls toward zero a few weeks later. This pattern of high initial efficacy, tapering off after 3 months is also consistently observed in real-world studies, and is often used as justification for additional, booster vaccinations to maintain efficacy. The corresponding Covid-19 infection rate is also likewise artificially elevated in the unvaccinated cohort compared to the vaccinated cohort. These issues apply to other measures of vaccination effectiveness related to mortality and morbidity.

Thus, we conclude that any claims of Covid-19 vaccine efficacy based on these studies are likely to be a statistical illusion.

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Appendix: Research studies containing miscategorisation as a selection bias

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