Review

Expanded Spectrum and Increased Incidence of Adverse Events Linked to COVID-19 Genetic Vaccines: New Concepts on Prophylactic Immuno-Gene Therapy and Iatrogenic Orphan Disease

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Expanded Spectrum and Increased Incidence of Adverse Events Linked to COVID-19 Genetic Vaccines: New Concepts on Prophylactic Immuno-Gene Therapy and Iatrogenic Orphan Disease

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Abstract: The mRNA- and DNA-based "genetic" COVID-19 vaccines can induce a broad range of adverse events (AEs), with statistics showing significant variation depending on timing and data analysis methods. Focusing only on lipid nanoparticle-enclosed mRNA (mRNA-LNP) vaccines, this review traces the evolution of statistical conclusions on AE prevalence and incidence associated with these vaccines, from initial underestimation of atypical, severe toxicities to recent claims suggesting the possible contribution of Covid-19 vaccinations to the excess deaths observed in many countries over the past few years. Among hundreds of different AEs listed in Pfizer's pharmacovigilance survey, the present analysis categorizes the main symptoms according to organ systems, nearly all being affected. Using data from the US Vaccine Adverse Event Reporting System and a global vaccination dataset, a comparison of the prevalence and incidence rates of AEs induced by genetic versus flu vaccines revealed an average 26-fold increase in AEs with genetic vaccines. The difference is especially pronounced in the case of severe 'Brighton-listed' AEs, which are also observed in COVID-19 and post-COVID conditions. Among these, the increases of incidence rates (AE^+/ AE^++AE^-) relative to flu vaccines, given as x-fold rises, were 1,152x, 455x, 226x, 218x, 162x, 152x; and 131x, for myocarditis, thrombosis, death, myocardial infarction, tachycardia, dyspnea, and hypertension, respectively. The review delineates the concepts that genetic vaccines can be regarded as prophylactic immuno-gene therapies, and that the chronic disabling AEs might be categorized as iatrogenic orphan diseases. A better understanding of the mechanisms of these AEs and diseases is urgently needed to come to consensus regarding the current risk/benefit ratio of genetic COVID-19 vaccines and to ensure the safety of future products based on gene-delivery-based technologies.

Keywords: LNP; lipid nanoparticle; mRNA; comirnaty; Spikevax; vaccinations; side effects; gene therapy; immunotherapy; COVID-19 pandemics; Brighton list

1. Introduction

Due to successive mutations of the SARS-CoV-2 virus, widespread global immunization, and effective therapies, the World Health Organization officially declared in May 2023 that COVID-19 was no longer a global public health emergency. This may warrant a reassessment of the risk-benefit ratio of continued vaccination with certain COVID-19 vaccines, referred to as "genetic", because unlike traditional vaccines delivering disease-associated peptide or protein antigens, these vaccines deliver the genetic code of antigens and rely on the body's cellular transcription and translation to induce specific immune response.

Consistent with the safety risks of gene therapy due to unintended immune responses, off-target effects and unforeseen toxicities [1], concerns have grown regarding the adverse events (AEs) caused

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by the COVID-19 genetic vaccines, which are now collectively recognized as a new disease entity, termed post-vaccination syndrome [2–5]. The most severe symptoms, which overlap with those seen in COVID-19 and post-COVID cases, are referred to as "symptoms of special interest" or "Brighton case" symptoms, a compilation of AEs by the "Brighton Collaboration", an international network of experts in drug and vaccine safety [6–10].

The post-vaccination syndrome linked to genetic vaccines, particularly Pfizer-BioNTech's BNT162b2 (Comirnaty) and Moderna's mRNA-1273 (Spikevax), has recently attracted considerable scientific and public attention as potential contributors to the excess deaths observed in several countries in the Western World over the past few years [11,12], despite the implementation of COVID-19 vaccines and advances in patient care. Analysis of the literature in MEDLINE (PubMed)[22] using the combination of search terms "Covid-19," "mRNA vaccines," and "adverse events" gave approximately 1,400 articles (November, 2024), focusing on AEs and challenging the universal claim that these vaccines are "safe". The latter statement is based on the low incidence rate of AEs [13,14], defined as the number of AE events or reactors related to the overall number of vaccine shots given in a certain time-window. Indeed, the estimated AE reactor incidence rate in the 0.03%-0.5 % range (see later) is low by pharmacotherapy standards, where higher AE rates are generally accepted. However, vaccines differ in this regard, as AEs in a large population of healthy individuals are less acceptable than in patients receiving pharmacotherapy for existing illnesses. Additionally, the global scale of vaccinations has led to very high prevalence of AEs, i.e., total number of inflicted people in a certain time, imposing a significant burden on society. For these reasons, accurate quantification of vaccine-induced AEs is critical to assessing their risk-benefit ratio. Unfortunately, in the case of COVID-19 vaccines, the AE statistics vary significantly based on time, data collection, and analysis methods.

This review therefore aims to analyze the spectrum, incidence, and prevalence of AEs associated with mRNA vaccines to support a reevaluation of their risk-benefit profile. Although the AE profile of DNA-based genetic vaccines, such as AstraZeneca's Vaxzevria and Johnson & Johnson/Janssen's Jcovden, may in some regards be even worse than that of the mRNA vaccines, these vaccines have been withdrawn from the market and are therefore not included in this analysis.

2. The Essence of mRNA Vaccines and Uniqueness of Their AEs

The mRNA in Comirnaty and Spikevax codes for de novo, in loco antigen synthesis in immune cells, which is a revolutionary innovation in vaccine technology. Its advantages include the simplification, acceleration, and cost-reduction of vaccine production [14]. The efficiency facilitates a quick response to viral mutations and allows for the possibility of delivering multiple antigens at once, enabling combined vaccines against multiple viral strains. However, the new technology has brought along new challenges, one being the rise of severe AEs.

Table 1 classifies the typical Brighton-listed AEs of post-vax syndrome according to the organ systems inflicted. The spectrum of symptoms is uniquely wide, atypical for any other types of vaccines, drugs or even toxic agents, except for infection with SARS-CoV-2. This points to one or more very fundamental interference with multiple biological processes that are also seen in Covid-19 and post-Covid syndrome. Obviously, the occasional manifestation of AEs must depend on individual genetic and epigenetic factors, just as the rise and spectrum of symptoms in acute and chronic (long) Covid.

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Table 1. Brighton case symptoms and illnesses reported as typical adverse events in post-vax syndrome.

	Cardiovascular	Coagulation	Enteral	Immune	Neural	Respiratory	Skin
Symptoms	ST elevation/AMI	cerebral venous sinus thrombosis	hepatitis	anaphylaxis	encephalitis/ myelitis/ encephalomyelitis	ARDS	acute urticaria
	tachy- or bradycardia, arrhythmias	disseminated intravascular coagulation	cholecystitis	hypersensitivity reactions	Bell's palsy	pulmonary embolism	chronic urticaria
	vascular inflammation (Kawasaki disease)	immune thrombocytopenia	colitis	lymphadenopathy (Kawasaki disease)	Guillain–Barré syndrome	stridor, hoarseness	skin graphia, dermatographia
	myocarditis/ pericarditis	pulmonary embolisms	enteritis	autoimmune glomeru-lonephritis	narcolepsy/ catalepsy	dyspnea	dermatographic urticaria
	hypo/ hypertension	stroke (hemorrhagic/ ischemic)	diarrhea	autoimmune rheumatic disease	seizures/ convulsions/ epilepsy	coughing	rash
	stroke (hemorrhagic/ ischemic)	thrombosis with thrombocytopenia (VITT)	appendicitis	autoimmune hepatitis	transverse myelitis		ocular/orbital inflammation
	arteriosclerosis	venous thrombo-embolism		CARPA	delirium		
	chest/back pain	amenorrhea/ dysmenorrhea/ oligomenorrhea			akathisa (psychomotor restlessness)		
	other forms of cardiac injury	thrombocytopenic purpura			multiple sclerosis		
	lip, tongue, face edema	intracerebral hemorrhage					

3. Epidemiology of Genetic Vaccine Side Effects: Inconsistent Statistics

Mandated AE statistics. Regarding the prevalence and incidence of Comirnaty's AEs, large-scale comprehensive statistics and those focusing on individual manifestations led to substantially different conclusions. In the initial, phase II/III randomized clinical trial studying the safety, tolerability, immunogenicity, and efficacy of RNA vaccine candidates against COVID-19 in healthy individuals (ClinicalTrials.gov ID: NCT04368728) 21,720 and 21,728 subjects were vaccinated with Comirnaty or placebo, the authors reported no significant difference between the vaccine and placebo groups in the incidence of mild, common side effects of vaccinations, while the severe AEs were claimed to have "low incidence" in both groups that were similar to that caused by other viral vaccines [15]. This was the pivotal study leading to the emergency use authorization of Comirnaty. However, a secondary analysis of the same data by Fraiman et al counting only the Brighton-listed AEs [7] found 36 % higher risk of severe events in the vaccine group compared to placebo. As it turns out from a closer look of included AEs, their selection for statistical analysis was limited only to the mild symptoms in the original [15], and to the severe symptoms, in the re-analysis [7]. The statistics in the latter study showed 18 (1.2-34.9 95% CI) serious AEs over placebo in 10,000 participants, corresponding to 1 person displaying severe vaccine-induced AE out of about 556 participants (0.18%) [7]. The ratio of "special interest" AEs among all serious AEs was ~56% [7].

Three months after the global rollout of Comirnaty, Pfizer-BioNTech's originally confidential, now publicly accessible post-authorization safety report through 28 February, 2021 [16] gave account of 42,086 AE case reports containing 158,893 events out of 126,212,580 vaccine doses in 56 countries. This means 3-4 AEs per report, ~0.03% vaccine reactors and 0.13% AE incidence rate, or 1 reactor among ~3,000, or 1 AE in 794 vaccinations. Reactions were observed mainly in the 31-50-age range, 3-times more in women than man, and full recovery ensued in 47%. The rest recovered with sequalae or did not recover within 3 months. The report listed 2.9% fatality among the reactors, (1,223 deaths) implying ~0.001% fatality of overall vaccinations, or 1 death in about 103,000 vaccinations. However, the relationship between vaccination and reported death is uncertain. Taken together these figures undoubtedly justified the conclusion on favorable risk/benefit ratio of the vaccine versus COVID-19 at that time, and the 0.13% AE incidence rate is close to the 0.18% estimated rate by Fraiman et al [7]. What is astonishing in this report is the approximately 1,590 different words or terms for AEs used in the appended nine-page cumulative list of AEs. Among many unique, surprise AEs, it contained ~40 different types of autoimmune conditions, which is

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about 1/4th of the cumulative number of registered autoimmune conditions (~160) in medical literature since the start of recording [17]. "Accordingly," the report's final summary, beyond strengthening the conclusion of the Phase II-III study on the favorable benefit risk profile of the BNT162b2 vaccine [15], stated that "the data do not reveal any novel safety concerns or risks requiring label changes".

The statement on safety was reinforced in the 6 months follow-up safety surveillance by stating that "No new safety signals relative to the previous report were observed during the longer survey involving 43,847 study participants" [18], although the 0.13% overall AE incidence in the 3 month's report rose to 0.50% (over placebo) solely for the severe reactions, which was about 4% of all AEs [18].

Comprehensive statistical analyses. The Centers for Disease Control and Prevention (CDC) and the Food and Drug Administration (FDA) have been continuously monitoring the safety of all vaccines applied in the US, through various reporting systems, including the Vaccine Adverse Event Reporting System (VAERS) [19,20]. This random list relies on passive voluntary reporting by patients, healthcare providers and manufacturers, the symptoms are not consistently defined and therefore not suitable for rigorous statistical analysis regarding the prevalence or incidence of different symptoms. Regarding exactness, a study by the US Department of Health and Human Services in 2010 estimated that fewer than 1% of vaccine AEs, and only 1-13% of serious events are reported by the VAERS. Apparently, the reporting process is very involved, and not all AEs are reported, especially if they are mild or if the person doesn't link them to vaccination [21]. It should also be noted that an AE chronologically linked to vaccination does not necessarily mean causality, since the mechanism of different symptoms are intertwined, and a symptom can be secondary or a consequence further down in the reaction chain. For example, if the vaccine causes complement activation, the anaphylactic shock and associated cardiovascular symptoms may be due to the complement C3a/C5a-induced hemodynamic changes, and not directly to the vaccine. Nevertheless, despite all these limitations, for the purpose of comparing the AEs of COVID-19 vaccines with other vaccine AEs, namely flu vaccines, the VAERS seemed to be the best data source.

Comparison with flu vaccines. Besides the prevalence of AEs, which reflects the clinical impact of side effects, another key aspect of vaccine safety is understanding how the risk of AEs compares to other vaccines, especially those that are also offered or with which people are already familiar. In the case of COVID-19 genetic vaccines, seasonal flu vaccines may serve as the best comparators since they are also administered to millions of people and target a viral respiratory illness. Accordingly, the VAERS data in Table 2 compare the prevalence of all AEs, vaccine doses, and incidence rates of AEs associated with the three genetic vaccines used during the pandemic to the corresponding statistics for flu vaccines at the same time. The latter data were compiled by aggregating the AE prevalence from 12 flu vaccines for which AEs are listed in VAERS (see legend to Table 2).

It is seen in the Table 2 that the incidence rate of AEs by the analyzed Covid-19 vaccines over 2.5 years was 25-26 times higher than that of flu vaccines during the same time. Considering only the DNA-based vaccine, Jcovden, the AE relative risk compared to flu is 54-fold higher. This also means that the DNA vaccine caused ~2-fold more AEs than the mRNA vaccines. A comparison of Comirnaty and Spikevax suggested 57% more reactions in case of Spikevax. The substantial difference between the flu and the 2 mRNA vaccines and the relative similarity between Comirnaty and Spikevax in causing AEs provide clear indication that it is the mRNA-LNP technology, rather than any other special features of the 2 mRNA vaccines that accounts for the increased risk for AEs. On the other hand, the 20 and 32-fold increase of relative risk calculated for Comirnaty vs. Spikevax shows comparably increased toxicity, somewhat higher with Spikevax than Comirnaty.

Table 2. VAERS-reported adverse events associated with genetic (mRNA and DNA) COVID-19 vaccines and 12 flu vaccines combined, from December 2020 to May 2023.

	AEs*	Jabs given	AE/M**	%	AE-/AE+***	Covid/Flu‡
Comirnaty	434,821	401,685,954	1,082	0.11	924	20
Spikevax	426,714	251,852,502	1,694	0.17	590	32

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Combined mRNA	**861,535**	**653,538,456**	**1,318**	**0.13**	**759**	**25**
Jcovden	54,728	18,991,177	2,882	0.29	347	54
All genetic	**934,959**	**672,529,633**	**1,390**	**0.14**	**719**	**26**
Flu	**18,696**	**352,670,000**	**53**	**0.01**	**18,863**	**1**

AEs*, total number of individuals displaying one or more AEs. AE/M**, AEs per million vaccine doses; AE-/AE+***, ratio of nonreactive to vaccine reactor people; Covid/Flu‡, genetic vaccine/flu vaccine AE/M ratio. The administered vaccine doses were from the Word in Data [68,69] data pool. Each AE means the number of reports by doctors or vaccinees of one or more AEs within 1 day after vaccination, regardless of severity. Thus, vaccinees with multiple symptoms were counted as one. The flu vaccines included in the statistics comprised various tri- or quadrivalent products with the brand names: AFLURIA (CSL-Limited and Seqirus Inc.), FLUAD (Novartis, Seqirus Inc.), FLUARIX (GlaxoSmithKline, GSK), FLUBLOK (Protein Sciences Corp.), FLUCELVAX (Novartis, Seqirus Inc), FLUENZ TETRA (Medimmune Vaccines), FLULAVAL (GSK), FLUMIST (Medimmune Vaccines), and FLUZONE (Sanofi Pasteur). The 3 other flu vaccines considered had no brand names.

Statistics on individual AEs. Using the flu vaccines as comparator, Table 3 shows the incidence rates of 12 Brighton-case AEs caused by the mRNA and flu vaccines in the order of decreasing prevalence.

Table 3. VAERS data on the prevalence and incidence of "special interest" AEs caused by genetic and flu vaccines in selected organ systems in the US from December 2020 to May 2023.

	Flu vaccines		mRNA vaccines		Fold increase	
	AE	AE/M	AE	*AE/M*	AE	AE/M
fever	4294	7.9	132,447	*201.70*	31	26
rash	1118	2.06	82,113	*125.05*	73	61
dyspnea	622	1.14	67355	*102.57*	204	152
hypertension	160	0.29	25,292	*38.52*	158	131
death	74	0.14	20,227	*30.8*	273	226
thrombosis	19	0.03	10,439	*15.9*	549	455
tachycardia	52	0.1	10,205	*15.54*	196	162
anaphylaxis	117	0.22	9,094	*13.85*	78	64
stroke	280	0.52	8,939	*13.61*	32	26
hypersensitivity	122	0.22	8,153	*12.42*	67	55
myocardial infarction	23	0.04	6,067	*9.24*	264	218
myocarditis	3	0.01	4,176	*6.36*	1392	1,152

Similar data collection and abbreviations as in Table 2, except that the analysis was done in SQL (Structured Query Language) using keyword search on multiple synonyms for each symptom, making sure that if multiple keywords were listed for a patient, we counted them as one. The exact cause of death is not specified in VAERS. The AEs are listed in order of increasing prevalence rate (italicized column). Other conditions are the same as in Table 2.

Like in the case of all AEs combined (Table 2), the mRNA-LNP vaccine-induced incidence rates of all 12 AEs were massively higher than those after flu vaccination, heart disease and thrombosis having the highest, roughly ~1,200 and ~500-fold increased risk, respectively. These data also imply that the incidence rates of individual AEs caused by mRNA vaccines substantially vary within the 6-200 AEs/M range. The percentage of severe AEs related to all AEs also varies in different reports between ~4 and ~18% [70].

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The 20,227 vaccine-related fatal outcomes reported to VAERS for all mRNA and DNA genetic COVID-19 vaccines (Table 3) after the administration of 672,529,633 vaccine doses (Table 2) suggest approximately 1 death per 33,000 vaccine recipients, or an incidence of ~0.003%. While this incidence is fortunately very rare, it represents a small (3-fold) increase compared to the Comirnaty-focused 3-month postmarket surveillance data (~0.001%) [16]. This difference may reflect the consistently higher aggregated adverse event (AE) incidence associated with genetic vaccines compared to Comirnaty (Tables 2 and 3).

The incidence rates of various adverse events (AEs) associated with mRNA vaccines (italicized as *AE/M* in column 5 of Table 3), when multiplied by the total number of vaccine doses administered over 2.5 years since the start of the vaccination campaign, provide a rough estimate of the absolute number of individuals affected by these AEs in the U.S. through May 2023, when the WHO declared the end of the global pandemic. The bar graph in Figure 1 illustrates these approximations, offering new insights into the mechanisms and classification of these AEs, as discussed in detail below.

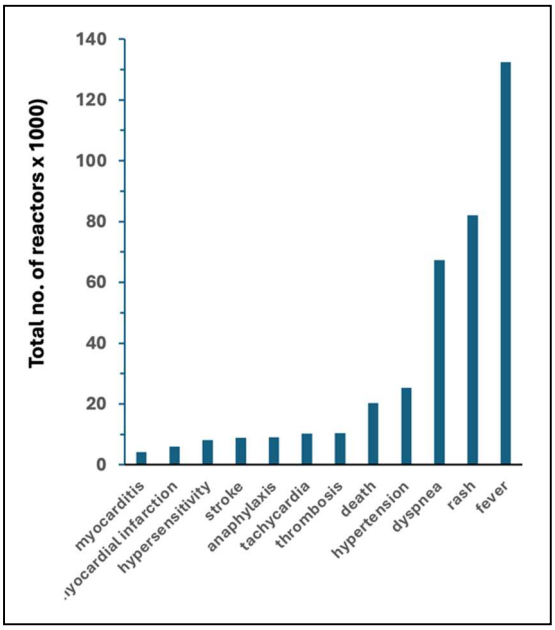

Figure 1. Rough estimates of the prevalence of mRNA vaccine-induced AEs in the USA during the COVID-19 pandemic, between December 2020 and May 2023. The calculations of the total number of AE reactors were based on the incidence rate (*AE/M* numbers) for mRNA vaccines in Table 3, obtained from the VAERS, as described in Table 1. The number of Comirnaty + Spikevax mRNA doses administered during this period was obtained from the *Our World in Data* public database [69].

Complement activation as a possible contributor to acute AEs. Most studies on vaccine AEs point to the heart, nerve, coagulations and autoimmunity problems as being the most important complications, overlooking the fact seen in Figure 1, that the front-runners of AE prevalence are fever, rash and dyspnea. Indeed, these are transient phenomena that most people tolerate without concern, not thinking into what they mean. Fever is a common sign of an innate immune response against infective agents, such as bacteria or viruses, or other types of external or internal harms, and in the case of mRNA-LNPs it may result from the proinflammatory actions of LNPs and the SP. Beyond fever, however, the association of skin symptoms (e.g., rash) with cardiopulmonary distress, manifested in dyspnea, suggests the involvement of a pseudoallergic response, specifically, complement activation-related pseudoallergy (CARPA) [62–65]. This symptom triad is characteristic of anaphylatoxin toxicity [71–75], which has been described following complement activation upon exposure of liposomes or other nanoparticulate drugs and agents to blood [76,77]. The evidence that CARPA symptoms predominate among recipients experiencing AEs to mRNA vaccines, combined with three facts, described below, raises the possibility that complement activation is a fundamental yet underrecognized cause of acute and subacute inflammatory AEs induced by mRNA vaccines.

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First, the vaccine nanoparticles, like certain liposomes, are potent complement activators [62,63,65,78]. Second, severe "AEs of special interest" associated with mRNA vaccines share similarities with the inflammatory symptoms of COVID-19, which involves intense complement activation [79–85]. Third, C3, the central molecule in the complement activation cascade, is one of the most abundant blood proteins (after albumin, globulin, and fibrinogen) and a ubiquitous innate mediator of inflammatory responses.

The Orphan Disease proposition for categorizing persistent and/or disabling chronic AEs. Despite the higher incidence of vaccine-related AEs compared to flu vaccines (Tables 2 and 3), Figure 1 shows that the cumulative number of various AEs in the U.S. (as of May 2023) ranges from approximately 4,000 to 130,000 cases. These figures remain well below the threshold of 200,000 patients used to define the upper limit for orphan disease categorization in the U.S. [86–89]. Consistent with the classification of vaccine-induced AEs as "rare," persistent and/or disabling chronic AEs, affecting any vulnerable organ system (Table 1), individually exhibit even lower prevalence than 200,000 (Table 3).

These vaccine injuries leading to persistent and/or disabling chronic conditions could be considered as rare, iatrogenic orphan disease entities. Considering many countries' special handling of orphan diseases [86–89], categorizing them as such may carry significant healthcare implications, including the potential to justify enhanced research funding and the development of specialized treatments for these conditions. The U.S. Orphan Drug Act of 1983 provides a relevant example of initiatives aimed at addressing the needs of patients with rare diseases [90].

The European experience: Paul-Ehrlich-Institute statistics. The COVID-19 vaccine-induced AEs are closely monitored in Europe as well. In Germany, the Paul Ehrlich Institute (PEI), a participant in the WHO-led Vaccine Safety Net project, serves as a primary source of statistics on genetic vaccine-induced AEs [70,91]. According to PEI, the incidence rate of severe AEs (of special interest) associated with mRNA vaccines was approximately 0.2 per 1,000 doses, or 0.02% [70]. For comparison, corresponding values from various U.S. statistics mentioned earlier in this review were 0.03% [16], 0.13% (VAERS, Table 2), 0.18% [7], and 0.5% [18].

Table 4 presents the incidence rates of different AEs as reported by PEI. While the list of symptoms differs somewhat between regions, cardiopulmonary distress (e.g., dyspnea, arrhythmia) ranks on top of AE incidence in both U.S. and German data. Since these symptoms can be linked to activation of the innate immune system, particularly through the complement system, these data are in keeping with a key role of complement activation in the acute and subacute reactions, as detailed earlier in this review. Table 4 also reveals that the rates of dyspnea and stroke are similar across the two continents; however, cardiac involvement (e.g., arrhythmia, myocarditis) is reported to be 5–6 times more frequent in the PEI statistics compared to VAERS. This discrepancy between the two partially aligned datasets warrants further investigation to determine whether it is consistent, and if yes, to explore its potential explanations.

Table 4 and Figure 2 provide detailed information on DNA vaccine-induced AEs compared to mRNA ones. Similar to mRNA vaccines in both statistics, dyspnea and cardiac abnormalities lead the incidence rankings for DNA vaccines. However, as observed in the U.S., most symptoms have higher AE incidence rates with DNA vaccines compared to mRNA vaccines, with the exception of myocarditis, which remain more prevalent with mRNA vaccines. These findings are unexpected since DNA vaccines require additional steps for spike protein expression and immunogenicity; the DNA must first be transcribed into mRNA, which is then translated into protein. In fact, a large longitudinal study found that specific antibody and T-cell immune responses develop faster and more robustly with the mRNA vaccine BNT162b2 compared to the DNA-based ChAdOx1-S [92]. The significant increase in acute AEs, particularly dyspnea, with DNA vaccines is therefore unlikely to be explained by increased immunogenicity. Instead, it may be related to exceptional complement activation by the adenoviral vectors used in these vaccines [93]. Consistent with this, adenovirus-based COVID-19 vaccines have been shown to induce higher interferon and pro-inflammatory responses than mRNA vaccines in human PBMCs [94], and in a preliminary experiment, we also observed significantly stronger induction of the terminal complement complex in human serum by DNS vaccines compared to mRNS ones (manuscript in preparation). Augmented complement

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activation underlying the increased reactogenicity of DNA vaccines aligns with their early withdrawal from the vaccination campaigns.

Table 4. The incidence rates of "special interest" AEs caused by mRNA and DNA-containing genetic vaccines in Germany. Data collected by the Paul Erlich Institute*[70]* between Dec 2, 2020 to March 2022.

AE of special interest	AEs/Million					
	Comirnaty	Spikevax	*all mRNA*	Vaxzevria	Jcovden	*all DNA*
Dyspnea	55	64	***119***	110	108	*218*
Arrhythmia	46	50	*96*	57	66	*123*
Myocarditis	14	16	*30*	6	12	*18*
Pulmonary embolism	8	7	*15*	33	20	*53*
Stroke	6	4	*10*	15	9	*24*
Facial paralysis	5	4	*9*	7	9	*16*
Syncope	5	4	*9*	25	12	*37*
Thrombosis	4	4	*8*	19	8	*27*
Deep vein thrombosis	4	4	*8*	27	8	*35*
Respiratory disorder	3	3	*6*	33	4	*37*
Anaphylactic reaction	3	2	*5*	4	3	*7*
Myocardial infarction	3	2	*5*	6	6	*12*
Thrombocytopenia	3	1	*4*	32	7	*39*
Seizure	2	1	*3*	7	4	*11*
Pericarditis	2	2	*4*	1	3	*4*
Heart failure	2	1	*3*	2	3	*5*
Cerebral hemorrhage	2	1	*3*	8	4	*12*
Cerebral thrombosis	1	1	*2*	20	6	*26*
Acute hearing loss	1	1	*2*	5	1	*6*
Multiple Sclerosis	1	1	*2*	1	1	*2*
Anaphylactic shock	1	0	*1*	3	2	*5*

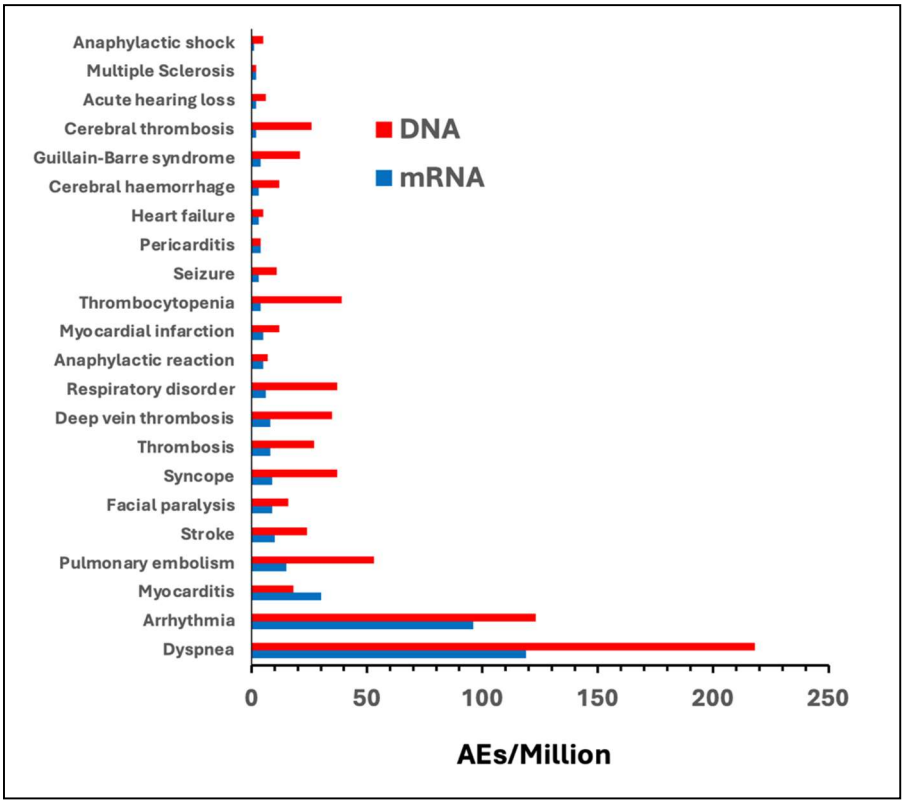

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Figure 2. Paul Erlich Institute statistics [70] on the incidence rates of different AEs in Germany following vaccinations with mRNA and DNA genetic vaccines until March 2022.

4. Discussion

The mRNA-based genetic vaccines became the most widely used preventive measure against the SARS-CoV-2 virus during the COVID-19 pandemic. By blending nanotechnology with genetic engineering, this innovative approach introduced a novel class of medicine with promising applications beyond vaccination. However, like any groundbreaking technology, it also brought new challenges. In the case of genetic COVID-19 vaccines, one such challenge has been the emergence of a significant number of rare adverse events (AEs). This is not unprecedented in the history of vaccines. For instance, during the 1976 swine flu pandemic in the U.S., an increase in the incidence of Guillain-Barré syndrome and other AEs was observed. Following reports of approximately 30 deaths among 43 million vaccine doses administered, the vaccination campaign was suspended [95]. This example underscores that the term "safe" is inherently relative, with vaccine safety evaluated according to varying criteria across different times and contexts.

Beyond safety concerns, the classification of mRNA-LNPs as vaccines has also been questioned. Some argue that genetic vaccines should be considered a form of gene therapy, as both involve the transfection of genetic material (nucleic acid) to deliver genetic information. However, those against this view point to key differences, such as the fact that the therapeutic goal of vaccination is not genetic correction, and that the administration methods for the two approaches—intramuscular for vaccines versus intravenous for gene therapies, are quite distinct. Nevertheless, animal studies have demonstrated that mRNA-LNPs can quickly enter the bloodstream and distribute to various organs following intramuscular immunization [96–98], thereby reducing the difference between the two administration methods.

Nonetheless, even if genetic vaccines cannot be considered gene therapy, they could be classified as *immuno-gene therapies*, since they utilize genetic information-carrying nucleic acid transfection to modify immune functions and prevent disease. The term "immuno-gene therapy" has previously been applied to cancer immunotherapy through tumor mRNA transfection [99]. In fact, there may be more fundamental differences between genetic vaccines and traditional vaccines than between genetic vaccines and immunotherapy. Key differences between genetic and traditional vaccines include: (i) the replacement of the protein antigen in traditional vaccines with the mRNA-coded blueprint in genetic vaccines; (ii) the substitution of external adjuvants with proinflammatory lipid nanoparticles (LNPs); (iii) the bypassing of standard antigen processing and presentation in antigen-presenting cells by using ribosomal translation of chemically modified mRNA to produce a stabilized, toxic antigen; (iv) off-target transfection of organ cells with mRNA, resulting in the secretion, MHC-Class I presentation, and MHC-independent expression of the antigen not only on immune but also on non-immune host cell surfaces, potently all body cells with blood supply; (v) autocrine and exocrine exosomal spreading of the mRNA and/or antigen SP to neighboring cells and different organs; and, finally, (vi), the antigen dosing problem, arising from the LNP uptake and mRNA-SP coupling in genetic vaccines. In the case of normal vaccines, the antigen's dose is determined in the formulation by the amount of protein or peptide antigen. However, in the case of mRNA or DNA vaccines, the antigen production depends on the transfection capacity of nucleic acid vectors (i.e., LNPs and adenoviruses), and the translation capacity of ribosomes. These are inconstant, indeterminable variables in different people making the rise of AEs unpredictable.

Due to the deviations from traditional textbook vaccine mechanisms, mRNA vaccines, as representatives of the genetic vaccine category, exhibit several atypical properties, some of which are also characteristic of certain immunotherapies. These include strong activation of both the innate and adaptive immune systems, as evidenced by the high incidence of fever (38–40°C): 19.4% after the first dose and 39.3% after the booster vaccination [100]. Additionally, mRNA-LNPs have a robust proinflammatory effect, driven by complement activation and cytokine release [65,101–108]. Complement activation is associated with acute and subacute inflammatory and hypersensitivity reactions, with anaphylaxis being the most severe outcome [63,65,78,103,105]. Meanwhile, cytokine

induction can explain subacute and chronic inflammatory diseases in different organs. Due to the LNPs' strong immune stimulating effects, acting as "superadjuvants", the mRNA-LNPs induce massive proliferation of lymph node T helper cells, follicular B cells, memory B cells, and plasma cells [101,102,104], an effect credited for the high efficacy of mRNA-LNP vaccines against SARS-Cov-2 infection. However, immune overstimulation can also be harmful, playing a role, among others, in the autoimmune AEs.

Strengthening the immunotherapy parallel, the release of proinflammatory cytokines is a hallmark side effect of immunotherapies such as CAR-T cell therapy [109–111]. Moreover, occasional cases of vaccine-induced multiorgan failure (Table 1) bear resemblance to the catastrophic TeGenero clinical trial with TGN1412, a monoclonal antibody developed for cancer immunotherapy, which resulted in severe immune reactions and multiple organ failures [112–115]. [116].

In sum, one or more, additive or synergistic unusual effects of mRNA vaccines may be theoretical causes or contributing factors to AEs, as detailed in a recent review [116].

5. Outlook

Following the success of COVID-19 mRNA vaccines, the mRNA-LNP-based technology platform has garnered unprecedented interest and investment. Over 300 new mRNA-LNP-based drugs are in development across dozens of companies. Novel mRNA vaccines targeting influenza, Zika virus, respiratory syncytial virus (RSV), HIV, cytomegalovirus, and cancer are undergoing clinical trials [117], while numerous preclinical studies highlight the potential utility of mRNA-LNPs as anticancer immunotherapies and multivalent vaccines. Conferences on mRNA technology are consistently fully booked, and the FDA recently approved Moderna's second mRNA vaccine, mRESVIA (mRNA-1345), for RSV [118]. Leading scientists in the field are actively working to educate the public and dispel misconceptions about vaccines. However, the immune mechanisms underlying adverse events (AEs) associated with COVID-19 mRNA vaccines remain poorly understood. This topic is often avoided, with only a handful of studies addressing it in detail [116]. For these reasons, reaching a consensus on the safety of these vaccines and elucidating the mechanisms of their AEs is urgently needed as the field continues to expand.

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