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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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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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 relative/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.

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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 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. This challenges the assertion by vaccine manufacturers and health authorities that these vaccines are "safe", which is based on the low reported incidence rate of AEs [13], where incidence rate of AEs, in the case of vaccinations, refers to the number of AE reactors related to the overall number of vaccine shots given in a certain time-window. Indeed, the estimated AE incidence rate of approximately 0.01-0.1% 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 Comirnaty Side Effects: Inconsistent Statistics

Mandated AE statistics. Regarding the prevalence and incidence of these AEs, large-scale comprehensive statistics and those focusing on individual manifestations led to substantially different conclusions. In the initial, phase 2/3 randomized clinical trial involving 21,720 and 21,728 subjects vaccinated with Comirnaty or placebo, respectively (NCT04368728), 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 counting only the Brighton-listed severe AEs (Table 1) found 36 % higher risk of severe AEs 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 first, and the severe symptoms, in the second analysis. The statistics in the latter study projected 1350 severe AEs/million, or 1 severe AE out of ~800 (0.13%) vaccinations[7].

Three months after the global rollout of Comirnaty, Pfizer-BioNTech's regulatory (FDA, CIBER)-mandated pharmacovigilance study [16] gave account of 42,086 AEs out of 126,212,580 vaccine doses in 56 countries. This means ~0.03% AE incidence rate, or 1 AE among ~3,000 vaccinations. Astonishingly, ~1,590 different words or terms were used in the appended, 27-page list of AEs, observed mainly in the 31-50-age range, 3-times more in women than man. Full recovery ensued in 47% and the rest recovered with sequalae or did not recover within 3 months. The report listed 2.9% fatal outcome (1,220 deaths), and ~40 different types of autoimmune conditions which is 1/4th of the cumulative number of registered autoimmune conditions (~160) in medical literature since the start of recording [17]. Yet, the final summary strengthened the conclusion of the Phase II-III study entitled "Study to Describe the Safety, Tolerability, Immunogenicity, and Efficacy of RNA Vaccine Candidates Against COVID-19 in Healthy Individuals" (ClinicalTrials.gov ID: NCT04368728) [15] by stating that "the data do not reveal any novel safety concerns or risks requiring label changes and support a favorable benefit risk profile of the BNT162b2 vaccine".

The latter statement was reinforced in the 6 months follow-up report by stating that "No new safety signals relative to the previous report[15] were observed during the longer survey involving 43,847 study participants [18]. The total AE incidence, which included reactogenicity, was 30% vs.

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14% in the placebo group, and that of severe reactions, 1.2% vs. 0.7%. Thus, the inclusion of 1656 new subjects into the 6 month survey in addition to the previous (3 months) reactor group of 8183 vaccinees, raised the incidence of all AEs by ~1000-fold (from 0.03% to 30%), ~4% of which was severe.

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, like the Vaccine Adverse Event Reporting System (VAERS) [19,20] and the Vaccine Safety Datalink. This random list relies on passive voluntary reporting by patients, healthcare providers and manufacturers, the symptoms are not consistently defined, not suitable for rigorous statistical analysis regarding the prevalence or incidence of different symptoms. It should also be noted that 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. Because no payment is made for reporting vaccine side-effects and the reporting process is very involved, not all AEs are reported, especially if they are mild or if the person doesn't link them to vaccination [21]. In the case of Covid vaccines, a fear of societal consequences may also be a factor, given the division of views on the subject.

There are, however, prospective epidemiological studies on vaccine AEs which avoid the above subjective factors in reporting. One of the largest such study was dedicated to assess the AE incidence of 13 selected neurological, hematological, and cardiac AEs occurring within 42 days after vaccination with Comirnaty, Spikevax and Jcovden[8]. The risk of AEs was quantitated by the ratio of observed AE relative to the expected AE, 1.5 being the lower threshold of significance. The data from approximately 99 million vaccine recipients across eight countries indicated a significantly increased risk for Guillain-Barré syndrome, cerebral venous sinus thrombosis, acute disseminated encephalomyelitis, myocarditis, and pericarditis. However, even if the populations and analysis times were matched in this study[8], questions arise regarding the validity of comparing historic data, i.e., all-cause AEs in the pre-COVID-19 era, with solely vaccine-caused AEs under pandemic conditions, as well as the definition of significant risk at 1.5 observed to expected AE ratio, and the arbitrary choice of AEs for analysis. It should be noted in this regard that in November, 2024 the MEDLINE (PubMed)[22] lists approximately 1,400 articles in response to search using a combination of "Covid-19," "mRNA vaccines," and "adverse events." of studies focusing on the different AEs of these vaccines, which likely would not exist without some indication of increased incidence of the discussed AEs relative to a comparator. The references [23–67] represent a selection of pivotal studies on different vaccine-induced AEs which are based on increased, or unusual rises of the addressed AEs.

Comparison with flu vaccines. For the above reasons, perhaps a more real-life conclusion on the safety of genetic vaccines can be obtained by comparing the prevalence and incidence rates of AEs with those of other vaccines used against the same infection agent. For the genetic Covid-19 vaccines, the flu vaccines seem to be the best comparators, since they are also used for millions of people against a coronavirus. Accordingly, the VAERS data in Table 2 compare the prevalence of all AEs, vaccine doses and incidence rates of AEs caused by the 3 genetic vaccines during the pandemic, with the corresponding statistics of flu vaccines over the past 10 years, data from 12 flu vaccines combined.

Table 2. VAERS-posted adverse events caused by genetic (mRNA and DNA) Covid-19 vaccines* and 12 flu vaccines**.

	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
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**

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Time windows: *Dec 2019 to May 2023; and **past 10 years. AE[♯], all people displaying one or more AEs; AE/M[§], AEs per million vaccine doses; AE-/AE+ [†], ratio of nonreactive to vaccine reactive 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.

It is seen in the Table 2 that the incidence rate of AEs by the analyzed Covid-19 vaccines over 3 years was 25-26 times higher than that of flu vaccines over 10 years. Considering only the DNA-based vaccine, Jcovden (Janssen), 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.

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 Dec 2019 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). .

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], earlier.

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It should be reminded in this regard that the AEs being chronologically linked to vaccination does not necessarily mean causality, since the mechanism of different symptoms are intertwined. For example, if the vaccine causes anaphylactic shock, the associated cardiovascular symptoms may be due to the anaphylatoxin-induced hemodynamic changes, and not directly to the vaccine. The 227 vaccine-related death in Table 3 after 401,685,954 Comirnaty doses (Table 2) implies 1 death in about 20,000 Comirnaty recipient, or 0.005% incidence, but again, direct linking death to vaccination is not straightforward in all reported cases.

The incidence rates of different AEs after mRNA vaccinations (*AE/M*, column 4 in Table 3) multiplied by the number of vaccine doses applied during this period allows for a rough estimation of the prevalence, i.e. absolute number of people inflicted with these AEs in the USA. The bar graph in Figure 1 shows these figures, which are likely underestimating the true numbers, as discussed above. Nevertheless, the data suggest new concepts on the mechanism and classification of these AEs, as follows.

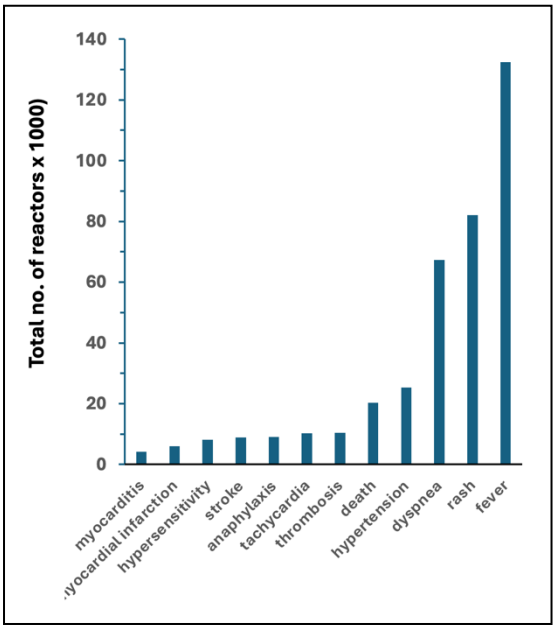

Figure 1. Rough estimates of the prevalence number of AEs in the USA during the Covid-19 pandemic, Dec 2019 to May 2023. The calculations of the total number of AE reactors was based on the incidence rate (AE/M numbers) for mRNA vaccines in Table 3, obtained from the VAERS, as described in Table 1. The number of Comirnaty + Spikevax mRNA doses administered during the same time was obtained from the Word in Data public data pool[69].

Complement activation as a possible cause of acute AEs. Most studies on vaccine AEs point to heart, nerve and coagulations problems as being the most important complications, distracting attention from 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 realizing 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. In the case of mRNA-LNPs, it may result both from the immune stimulatory actions of the LNPs and the in situ formed spike protein. However, the association of fever with skin symptoms (rash) and hemodynamic/cardiopulmonary distress can also point to the involvement of an allergic response, in particular, complement activation-related pseudoallergy (CARPA). A combination of fever with rash and dyspnea is a typical anaphylatoxin effect[71–75], also described upon liposome-induced infusion reactions that are triggered by complement activation[76,77]. The above triad of symptoms is typical of CARPA, which, combined with the facts that (i) the liposome-like COVID-19 vaccines are strong complement activators[62,63,65,78], (ii) severe COVID-19 involves intense complement activation[79–85] and (iii) C3 is one of the most abundant blood proteins (after albumin, globulin, and fibrinogen), raises the

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possibility that complement activation is a primordial, yet overlooked cause of mRNA-vaccine-induced acute inflammatory AEs

Persistent or disabling chronic AEs: the orphan disease proposition. Despite a higher incidence of vaccine-related injuries compared to flu vaccines (Tables 2 and 3), Figure 1 demonstrates that the cumulative numbers of various AEs in the USA (until May, 2023), ranges from 4,000 to 130,000 cases. This is well below the threshold of 200,000 patients used to define the upper limit of orphan disease categorization in the USA[86–89]. In line with the argument that the vaccine-induced AEs are "rare", the persistent or disabling chronic AEs, involving any vulnerable organ system (Table 1), individually exhibit even lower prevalence (Table 3). These vaccine injuries could be regarded as new, iatrogenic orphan disease entities. Such categorization would have critical health-care implications, as it could justify enhanced research funding and the development of specialized treatments for these conditions. The U.S. Orphan Drug Act of 1983 serves as a key example of initiatives aimed at addressing the needs of patients with rare diseases[90].

Paul-Ehrlich-Institute statistics. The vaccine-induced AEs are closely monitored in Europe as well. In Germany, as member of the WHO-led project Vaccine Safety Net, the Paul-Ehrlich-Institute (PEI) is the primary source or statistics on Covid vaccine AEs[70,91]. According to PEI, the incidence rate of mRNA vaccine-induced severe AEs (of special interest) was approximately 0.2 per 1,000 doses, or 0.02% incidence*[70].* The corresponding percentage values from different U.S. statistics -mentioned earlier in this review- were 0.13%[7], 0.03%[16], 1.20%[18] and 0.13% (VAERS, Table 2).

Table 4 presents the incidence rates of various adverse events (AEs) as reported by PEI. These data not only confirm the unique and special-interest AEs associated with COVID-19 vaccines but also highlight significant findings that are often overlooked in the mainstream literature.

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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One notable finding is that acute dyspnea, along with cardiopulmonary or hemodynamic changes (including arrhythmia, hypertension, and tachycardia), rank on top of the AE incidence list (AE/M) of mRNA vaccines, following fever and rash (Table 4). As highlighted in U.S. incidence data (Figure 1), these symptoms are predominantly linked to activation of the innate immune system, particularly through the complement system, a key component of the humoral innate immune response.

Another noteworthy observation in the PEI statistics[70] is the consistently higher incidence of AEs associated with DNA vaccines (Figure 1). This pattern, also evident in U.S. comparisons between mRNA and DNA-based vaccines like Jcovden (Table 2), shows an increased risk of up to 4-5 times for most AEs, excluding myocarditis. This is unexpected given that 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 outstanding 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 Jcovden compared to Comirnaty and Spikevax (manuscript in preparation).

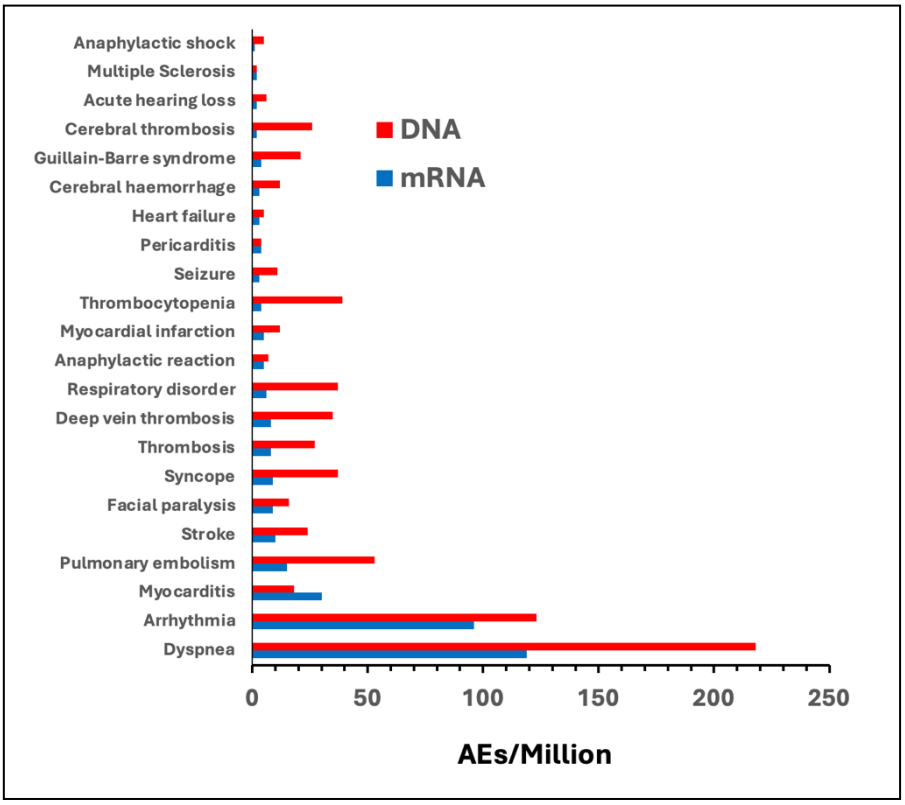

Figure 2. Paul Erlich Institute statistics [70] on the incidence rates of different AEs in Germany following vaccinations with mRNA and DNA genetic vaccines between Dec 2019 to March 2022. .

These findings, combined with the association of AEs with inflammatory and cardiopulmonary symptoms characteristic of CARPA, suggest that enhanced complement activation may be a contributing factor to the increased risk of AEs observed with DNA vaccines. This aligns with their early withdrawal from COVID-19 vaccination campaigns.

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4. Discussion

The mRNA-containing genetic vaccines became the most widely applied preventive measures against the SARS-CoV-2 virus during the Covid-19 pandemic. A blending of nanotechnology with genetic engineering gave rise to a novel type of medicine with a number of promising future applications beyond vaccinations. However, as with any new technology platform, the innovation brought along new challenges, which, in the case of genetic Covid-19 vaccines, include the rise of large number of rare adverse events. This is not unprecedented in the history of vaccines, as in 1976, during the swine flu pandemic in the US, an increase in the incidence of Guillain-Barré syndrome and other AEs were observed. After about 30 deaths out of 43 million doses, the vaccine campaign was suspended[95]. In comparison, the VAERS listed 20,227 vaccine-related death (Table 3) after 401,685,954 Comirnaty doses (Table 2), which implies 1 death in about 20,000 Comirnaty recipient (0.005%) versus 1 death in 1.43 million swine flu vaccine recipient (0.00007%), a 72-fold increase in Comirnaty-associated mortality. This example highlights that "safe" is a relative qualifier of the performance of vaccines, judged by varying criteria in different times and locations.

Beyond the safety, the classification of mRNA-LNPs as vaccines can also be questioned. There are views that the genetic vaccines represent gene therapy because both these vaccines and gene therapies act via genetic information carrying nucleic acid transfection. The arguments against this view emphasize fundamental differences between the two processes, such as the therapeutic goal of vaccination is not genetic correction, and that the administration method of the two interventions, i.m vs. i.v., is very different. However, animal studies have shown that mRNA-LNPs quickly enter the bloodstream and distribute to various organs after i.m. immunization[96–98], which lessens the the difference in administration mode.

Nonetheless, even if treatment with genetic vaccines cannot be considered as gene therapy, they may be classified as immuno-gene therapies, since they employ genetic information-carrying nucleic acid transfection for modifying immune functions to prevent a disease. The term "immuno-gene therapy" has previously been used for cancer immunotherapy via tumor mRNA transfection[99]. In fact, there may be more fundamental differences between the genetic and traditional vaccines than between the genetic vaccines and immunotherapy. The differences between the genetic and traditional vaccines include (i) the replacement in the former the protein antigen with its mRNA-coded blueprint, (ii) the substitution of external adjuvant with the proinflammatory LNP, (iii) the shortcutting of the standard processing and presentation of antigens in antigen-presenting cells by ribosomal translation of chemically boosted mRNA to a stabilized toxic antigen, (iv) the transfection of organ cells with the mRNA resulting in the secretion, MHC-Class I-presentation and MHC-independent expression of the antigen on immune and organ cell surfaces, and (v), the exosomal spreading of the mRNA and/or antigen.

Due to the above deviations from text-book vaccines, the mRNA vaccines, representing the genetic vaccine category, have numerous abnormal properties that are also characteristic of some immune therapies. These include the strong activators of both the innate and the adaptive immune system, as reflected in the high incidence of 38-40°C fever: 19.4 % after the first, and 39.3% after the booster vaccination[100]. Furthermore, the mRNA-LNPs have robust proinflammatory impact via complement activation and cytokine release [65,101–108]. The former mechanism can explain the vaccine-induced acute hypersensitivity reactions, with anaphylaxis being the worst outcome[63,65,78,103,105], while cytokine induction explains the subacute and chronic inflammatory AEs. Importantly, release of proinflammatory cytokines is a characteristic side effect of immune therapies, such as CAR-T cell therapy[109–111], representing another hallmark of vaccinal immunotherapy. Yet a further parallel, the occasional vaccine-induced multiorgan failure reminds of the TeGenero catastrophic clinical trial with TGN1412, a CD28 monoclonal antibody, which caused multiple organ failures[112–115]. Due to the LNPs acting as "superadjuvants", 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 vaccine against SARS-Cov-2 infections, but unfortunately it may also play a role in the autoimmune AEs. Finally, the antigen dosing problem can be mentioned, arising from the LNP uptake and mRNA-spike protein coupling

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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. In sum, these and other unusual features of mRNA vaccines are all 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 enjoys unprecedented interest and investment. More than 300 new mRNA-LNP-based drugs are in the pipeline of dozens of companies, novel mRNA vaccines (against flu, zika virus, respiratory syncytial virus, HIV, cytomegaloviruscurrent and cancer) are in clinical trials[117], a number of preclinical studies show the potential utility of mRNA-LNPs as anticancer immunotherapies and multivalent vaccines. Conferences on mRNA are fully booked in advance, the FDA has recently approved the second Moderna mRNA vaccine against RSV (mRESVIA, mRNA-1345)[118] and prominent scientist in the field pledge to "teach" the public why the "anti-vax" standing has no basis. Yet, the immune mechanism of Covid-19 vaccine AEs is relatively ill understood, the theme is avoided, only a few articles make an attempt to address them in detail{Szebeni}. For the above reasons, for the future, coming to consensus on the subject seems timely.

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