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Vaccines Associated Cardiac Adverse Events, including SARS-CoV-2 myocarditis, Elevated Histamine Etiology Hypothesis

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Keywords

COVID-19; adverse events; histamine intolerance; myocarditis; pericarditis; tachycardia

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Abstract

Rare cardiac adverse events are reported post vaccinations. For the SARS-CoV-2 vaccines, higher numbers of these cardiac adverse events are being reported with myocarditis disproportionately occurring in younger males. The etiology of these cardiac adverse events associated with vaccines including SARS-CoV-2 is unknown. The etiology of the higher frequency of these cardiac adverse events temporally associated with SARS-CoV-2 vaccines is also unknown. This article proposes that innate immune responses to vaccines cause elevated histamine levels post vaccination; the histamine level reached may exceed the vaccinees' histamine tolerance level for several days. This article proposes that the elevated histamine level is causative for the reported cardiac adverse events. For myocarditis reported adverse events, this article proposes that elevated histamine levels induce cardiac capillary pericyte induced vasoconstrictions followed by localized ischemia and anoxia; this is followed by the release of troponin from myocyte cells affected by anoxia. This hypothesis is supported by the temporal onset timing of adverse events reported following SARS-CoV-2 vaccinations in the United States Department of Health and Human Services Vaccine Adverse Event Reporting System (VAERS). This model applies to multiple vaccines with innate immune response histamine levels generated varying by each vaccine and incidence frequencies correlate with vaccine reactogenicity.

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Introduction

Vaccinations protect vaccinees against multiple viral and bacterial infectious diseases. Some vaccinees experience mild adverse events (AE), multiple AE, or serious AE. Immediate short-term reactions are referred to as vaccine reactogenicity. The amount of reactogenicity varies by each specific vaccine. Very rare instances of myocarditis have been reported associated with vaccinations including tetanus [1], triple immunizations [2], etc. High numbers of COVID-19 cardiac adverse events, including myocarditis [3–7], pericarditis [8–13], and tachycardia [14–20] are being reported by COVID-19 vaccinees. Myocarditis has been associated with both mRNA vaccines (mRNA-1273 Moderna and BNT162b2 Pfizer/BioNTech) [21]. Cardiac adverse events reported in the United States Department of Health and Human Services Vaccine Adverse Event Reporting System (VAERS) from 1990 until Nov. 19, 2021 are summarized in Table 1. The etiology of vaccine associated cardiac events is unknown. In COVID-19 patients with myocarditis, vasoconstrictions associated with clamped pericyte cells has been proposed as the initial step in myocarditis [22]. Pericyte cell clamping was proposed to be caused possibly by either direct SARS-CoV-2 infection or by elevated histamine levels [22].

Cardiac responses to the β-imanazolylethylamine derivative of histamine was described by Dale & Laidlaw [23]. These cardiac responses include altered blood-pressure, constriction of coronary arterioles, constriction of pulmonary arterioles, vasodilation in limbs, altered heart rate, and heart failure varying by dose and animal species [23]. In pythons, histamine induces postprandial tachycardia through a direct effect on cardiac histamine H_2-receptors [24]. See

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Wolff & Levi [25] for review histamine and cardiac arrhythmias. These cardiac symptoms are also observed in some individuals with histamine intolerance [26].

The Hypothesis

This article summarizes vaccine associated cardiac events reported following vaccinations in the United States Department of Health and Human Services Vaccine Adverse Event Reporting System (VAERS). From patterns of cardiac adverse events shared by unrelated vaccines, this article proposes that the etiology of vaccine associated cardiac events are consistent with elevated histamine levels from innate immune responses exceeding the tolerance level for some vaccinees. This article proposes that one subclass of cardiac adverse events is associated with histamine altered heart rate, including chest pain, palpitations, tachycardia, etc. This article proposes the second subclass includes vaccine associated myocarditis adverse events associated with histamine induced contraction of cardiac capillary pericyte cells resulting in vasoconstrictions followed by localized myocyte anoxia. This can be followed by elevated troponin levels released from the dead myocytes. This model of elevated histamine induced vaccine cardiac adverse events generalizes to all vaccines with cardiac associated adverse events. The model of cardiac adverse events induced by elevated histamine level directly suggest multiple candidate prophylactic and therapeutic treatment options for evaluation that have the potential to eliminate or reduce the incidence rate and severity of cardiac adverse events associated with vaccines. Therapeutically, these treatments may reduce cardiac tissue damage caused by vasoconstrictions and localized myocyte anoxia.

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Methods

The Vaccine Adverse Event Reporting System (VAERS) database [27] was utilized for cardiac adverse events from 1990 to Nov. 19, 2021. Reports of cardiac adverse events were identified by vaccine name or type, age, gender, onset day post vaccination, and vaccine dose.

Results

Cardiac associated adverse events reported in the VAERS database from 1990 to Nov. 19, 2021 are summarized in Table 1. The co-occurrence of these cardiac adverse events is shown in Table 2. The days of onset for COVID-19 vaccine cardiac adverse events are illustrated in Table 3. Differences between adverse event reports by gender are shown in Table 4.

Discussion

The vaccines with the highest numbers of reported adverse events in VAERS are shown in Table 1. With chest pain typically being the most frequently reported adverse event, the other cardiac adverse events generally fit a pattern across multiple vaccines characterized by the average percentage relative to chest pain (Table 1). This pattern suggests a generalized cause that is not vaccine specific. This article proposes that the adverse events scale approximately with the reactogenicity of each vaccine. More than one cardiac adverse event can be reported for an individual, these are illustrated in Table 2. Chest pain occurs with chest discomfort, palpitations, myocarditis, etc. “Troponin increased” is frequently observed with both myocarditis and also chest pain, indicating likely overlapping underlying loss of myocytes. The two fundamental patterns or models (subclasses) are consistent with altered heart rate and/or predicted cardiac vasoconstrictions. This article proposes that both of these patterns directly result from elevated

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histamine levels released by innate immune responses to the vaccines. The incidence of reported cardiac adverse events is highest within 24 hours and decreases rapidly within days (Table 3). For some cardiac adverse events, the proportion of reported events is lower for the second dose relative to the first dose suggesting possible attenuation from first exposure with the exception of myocarditis with the opposite trend for males (Figure 1). For lower second dose incidence frequency, it is possible for histamine metabolism gene(s) from the initial vaccination to be still upregulated for some individuals at the time of administration of the second dose.

For males, the incidence of reported myocarditis events by age can be modeled by exponential decay patterns (Figure 2) for both Moderna mRNA-1273 and Pfizer BNT162b2 COVID-19 vaccines. While the number of myocarditis reports for both anthrax and smallpox are much lower, a similar pattern decreasing by age might be envisioned. Myocarditis in males may be a function of vaccine reactogenicity coupled to male gender response that decreases with age (Figure 2). A surprising pattern for possible additional myocarditis-like cases may be seen for male teenagers receiving BNT162b2 with the “chest pain” adverse event symptom (Figure 3).

The reported incidence of cardiac adverse events varies by gender for some adverse events (Table 4, Figure 3 & 4). Immune response differences between genders is known [28–36]. This imbalance is consistent for multiple vaccines except for the anthrax and smallpox vaccines (Table 4); this may be due to imbalanced gender difference in distribution (e.g., military) or other artifact(s).

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Candidate Treatments Suggested by Elevated Histamine Model

The model that most vaccine associated cardiac adverse events are caused by elevated histamine levels exceeding an individual's tolerance level (histamine intolerance) suggests possible prophylactic and therapeutic treatments for evaluation in vaccinees. Antihistamine treatments exhibiting efficacy in treating COVID-19 patients are predicted to also target granulocytes and mast cells associated with vaccine responses [37]. These candidate treatments for further evaluation include high dose famotidine [37–40], cetirizine [41,42], and dexchlorpheniramine [41]. Oral treatment with diamine oxidase (DAO) may also minimize, reduce severity, or eliminate vaccine reactogenicity cardiac adverse event symptoms. These treatments may be effective as both prophylactic and therapeutic treatments for reducing these symptoms. Based on the cardiac symptoms onset patterns observed in Table 3, prophylactic administration prior to vaccination continuing for several days post vaccination would be worth evaluation. Treatment of vaccinees with associated cardiac events may potentially provide symptoms relief while potentially reducing anoxia of cells. Evaluation of these treatments and treatment combinations on vaccinees in case reports, case series, etc. can inform subsequent randomized controlled clinical trials for reducing vaccine reactogenicity cardiac adverse events. This model and candidate treatments is applicable to all vaccines with greater potential benefits for vaccines with higher reactogenicity.

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Summary

Herein, this article proposes that etiology of vaccine associated cardiac adverse events is caused by innate immune responses elevating histamine levels related to the reactogenicity of the vaccine(s) administered. This article proposes that cardiac associated adverse events occur when the level of histamine exceeds the vaccinees tolerance level in some individuals. Gender, age, and histamine tolerance levels are expected to vary between individuals. This model proposes that antihistamines at the proper dosage possibly combined with diamine oxidase may be effective as prophylactic and therapeutic treatments in vaccinees with the potential to eliminate or reduce the incidence rate and severity of cardiac adverse events. These treatments may reduce cardiac tissue damage caused by vasoconstrictions and localized myocyte anoxia in some vaccinees (e.g., untreated vaccinees with elevated troponin levels).

Consent statement/Ethical approval

Not required

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Authorship

The author attest they meet the ICMJE criteria for authorship.

Declaration of interests

The author 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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Table 1. Vaccine associated cardiac adverse events. Frequency numbers higher than the average percentage relative to chest pain (bottom row) are shown in bold.

Vaccine Name	Chest pain	Palpitations	Chest discomfort	Heart rate increased	Tachycardia	Myocarditis	Pericarditis
COVID19 (PFIZER-BIONTECH)	20,439	13,357	12,036	9,401	7,821	**5,468**	**3,872**
COVID19 (MODERNA)	8,711	6,270	6,080	5,530	2,915	**1,968**	1,069
COVID19 (JANSSEN)	2,131	1,159	1,305	1,357	481	125	125
HEP B (ENGERIX-B)	480	179	156	137	283	48	28
HPV (GARDASIL)	784	558	283	327	204	61	16
INFLUENZA (SEASONAL) (FLUZONE)	647	238	**641**	373	262	31	17
INFLUENZA (SEASONAL)	441	227	275	**356**	190	41	51
MEASLES + MUMPS + RUBELLA (MMR II)	272	63	110	155	**276**	29	1
PNEUMO (PNEUMOVAX)	488	148	304	237	200	38	9
VACCINE NOT SPECIFIED	344	178	210	222	115	37	53
ZOSTER (SHINGRIX)	324	251	210	**469**	95	37	18
Average percentage relative to chest pain		51.9%	59.0%	63.3%	42.6%	11.6%	7.5%

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Table 2. Co-occurrences of vaccine associated cardiac adverse events; adverse event symptom pairs with higher co-occurrences are shown in bold.

Adverse event	Cardiac arrest	Cardiac failure	Chest discomfort	Chest pain	Heart rate increased	Myocardial infarction	Myocarditis	Palpitations	Pericarditis	Tachycardia	Troponin increased
Arrhythmia	68	45	289	444	298	52	190	682	70	498	30
Atrial fibrillation	50	167	167	315	364	62	62	415	106	295	89
Cardiac arrest		60	35	124	20	107	70	17	8	47	34
Cardiac failure			44	93	32	55	132	39	27	56	41
Chest discomfort				**4,502**	**1,697**	179	562	**2,492**	443	948	310
Chest pain					**2,065**	552	**2,617**	**3,501**	**2,051**	**1,582**	**1,526**
Heart rate increased						65	142	**2,448**	103	797	48
Myocardial infarction							118	94	54	46	109
Myocarditis								469	800	265	**1,087**
Palpitations									308	**1,772**	114
Pericarditis										184	243
Tachycardia											116

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Table 3. COVID-19 vaccine cardiac adverse events onset post vaccination onset post vaccination

Onset	Chest pain	Palpitations	Chest discomfort	Heart rate increased	Tachycarditis	Myocarditis	Pericarditis	Arrhythmia
0	12,610	11,343	10,656	9,680	6,681	2,339	1,532	1,961
1	5,482	2,936	3,065	2,734	1,676	890	488	623
2	2,353	1,131	1,037	721	488	809	373	274
3	1,728	775	767	509	316	758	291	190
4	1,051	579	521	303	217	366	179	138
5	721	432	384	254	161	185	152	135
6	585	266	281	178	137	166	126	79
7	717	419	280	220	168	178	156	95
8	432	244	236	129	105	108	102	51
9	366	190	200	111	72	97	81	46
10	322	209	148	97	73	85	86	39
11	203	119	117	57	53	68	70	34
12	258	179	117	95	92	57	61	34
13	185	88	86	61	37	58	72	24
14	222	135	96	71	63	77	86	40

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Table 4. Vaccine associated cardiac adverse events gender bias; reported adverse events with imbalanced gender are shown with shaded light blue background for the higher amount.

Vaccine Type	Chest discomfort males	Chest discomfort females	Chest pain males	Chest pain females	Heart rate increased males	Heart rate increased females	Palpitations males	Palpitations female	Tachycardia male	Tachycardia male	Myoc male
COVID19	5,117	14,048	12,294	18,523	3,856	12,154	4,573	15,893	2,528	8,551	5,
FLU(H1N1)	62	145	41	111	37	120	20	77	15	46	
FLU3	243	1,063	376	1,032	217	728	108	505	134	391	
FLU4	65	294	82	241	78	202	43	180	41	93	
FLUX	61	228	162	297	109	253	43	193	85	126	
HEP	56	186	241	600	85	180	58	235	165	355	
HPV4	22	255	53	643	21	303	22	530	16	178	
PPV	84	245	190	408	84	219	47	131	87	163	
TDAP	77	244	162	242	71	188	36	173	34	99	
UNK	64	150	157	200	72	171	44	147	42	74	
VARZOS	85	240	191	335	176	380	69	265	40	72	
ANTH	132	34	361	72	46	21	69	39	51	10	
SMALL	157	55	580	162	21	20	62	43	26	18	

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Figure 1. Myocarditis by dose following SARS-CoV-2 Spike mRNA vaccination reported in the VAERS system by Nov. 19, 2021 (Pfizer BNT162b2 & Moderna mRNA-1273).

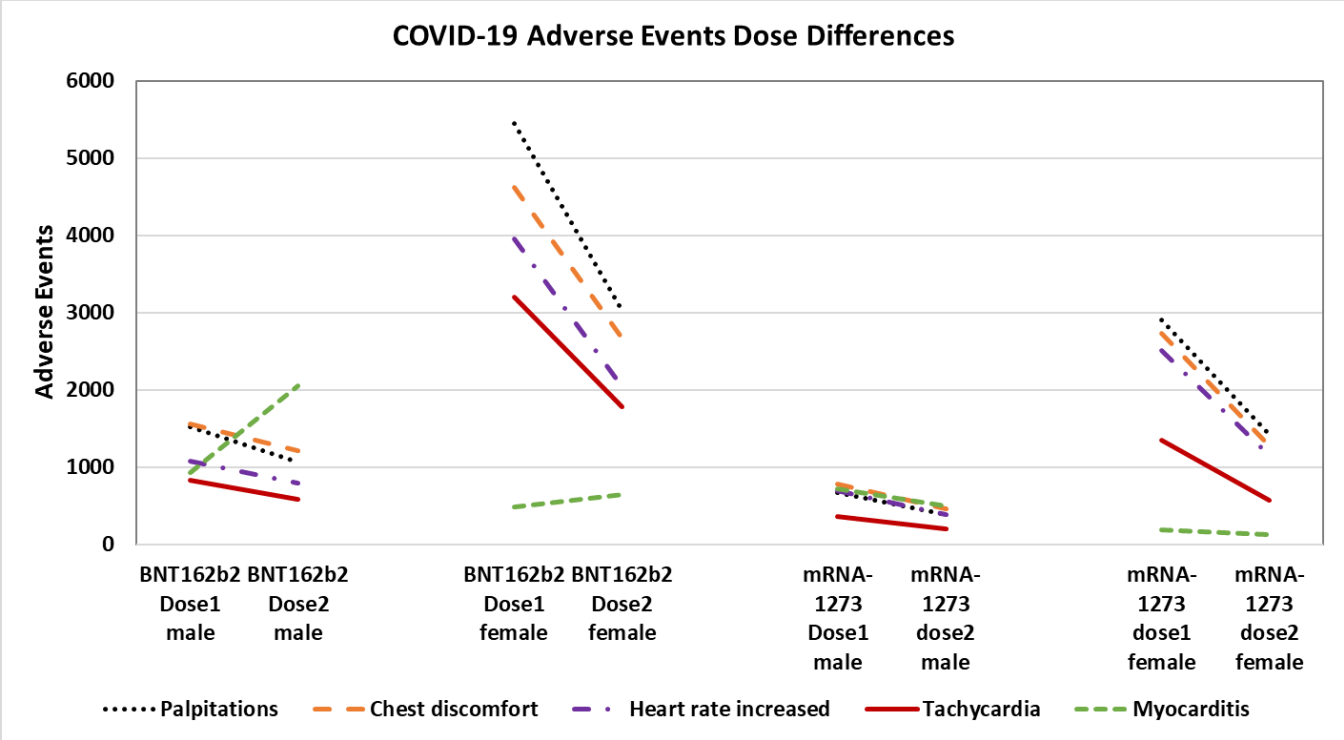

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Figure 2. Vaccine associated myocarditis cardiac adverse events in males (COVID-19 Moderna mRNA-1273, COVID-19 Pfizer BNT162b2, COVID-19 Janssen, Anthrax, and Smallpox vaccines)

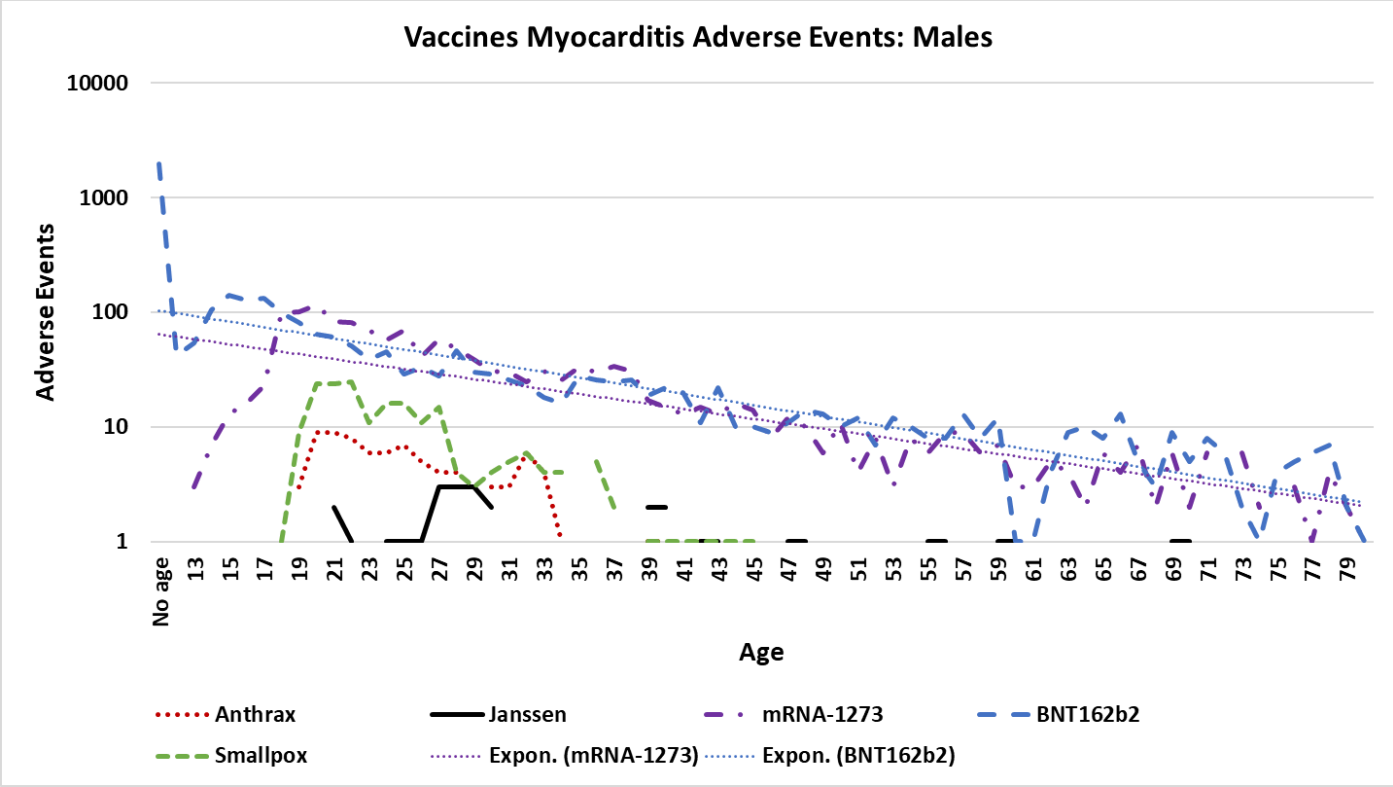

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Figure 3. COVID-19 chest pain adverse events by gender and age following SARS-CoV-2 Spike mRNA vaccination reported in the VAERS system by Nov. 19, 2021 (Pfizer BNT162b2 and Moderna mRNA-1273).

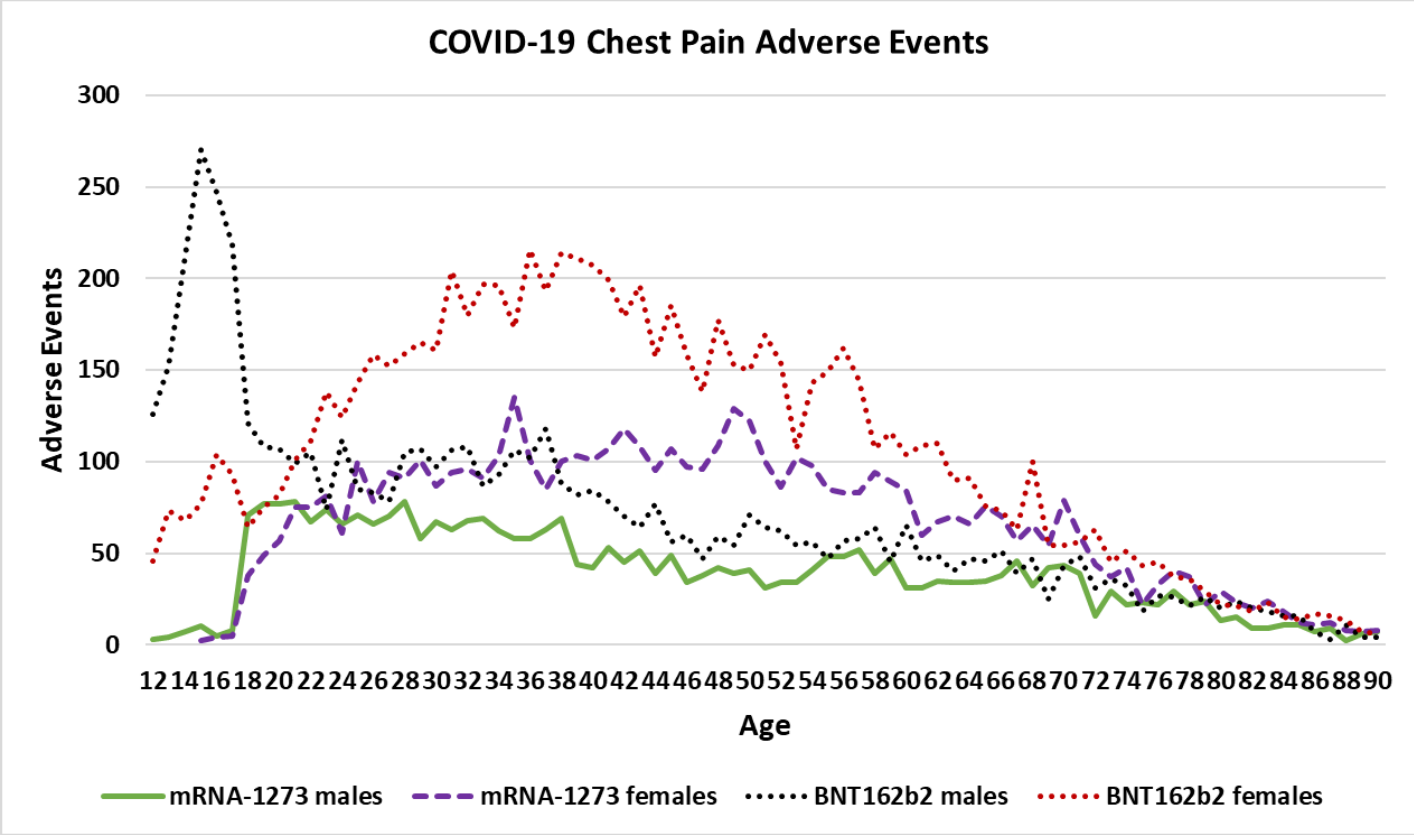

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Figure 4. COVID-19 palpitations adverse events by gender and age following SARS-CoV-2 Spike mRNA vaccination reported in the VAERS system by Nov. 19, 2021 (Pfizer BNT162b2 and Moderna mRNA-1273).