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Vaccines Associated Cardiac Adverse Events, Including SARS-Cov-2 Myocarditis, Elevated Histamine Etiology Hypothesis

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Abstract

Background: Rare cardiac adverse events are reported post vaccinations. For the SARS-CoV-2 mRNA Spike 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 mRNA Spike vaccines is also unknown.

Aim: Data mine vaccine associated cardiac adverse events to gain insights into COVID-19 mRNA associated myocarditis and pericarditis adverse events.

Methods: All adverse events, with a focus on cardiac adverse events, were summarized from the Vaccine Adverse Event Reporting System (VAERS) for all vaccines from 1990 to April 1, 2022.

Results: Analogous patterns of cardiac adverse events were observed for multiple unrelated vaccines with occurrences proportional to vaccine reactogenicity level defined all adverse events. This article proposes the hypothesis 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, with the histamine level likely correlating with the vaccine reactogenicity level. Further, it is proposed that the elevated histamine level is causative for the reported cardiac adverse events. For myocarditis and pericarditis reported adverse events, the elevated histamine levels may induce cardiac capillary pericyte 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 mRNA Spike vaccinations in VAERS.

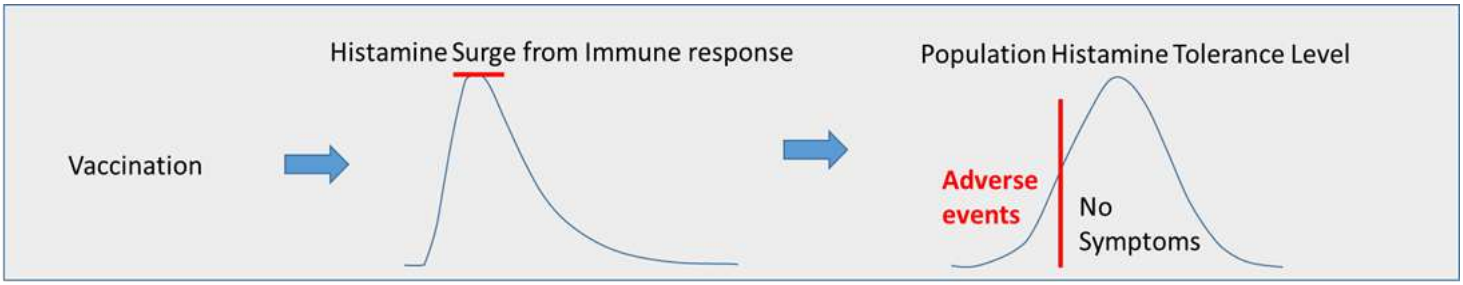
Conclusion: Onset of cardiac adverse events immediately following vaccinations for multiple unrelated vaccines may implicate elevated histamine levels from immune responses as causative for these adverse events.

Relevance for patients. An etiology model for cardiac adverse events temporally associated with vaccination is proposed. If validated, this model identifies possible candidate treatments for evaluation with the potential to reduce the severity and frequencies of these cardiac adverse events for vaccinees.

Keywords: COVID-19, adverse events, histamine intolerance, myocarditis, pericarditis, tachycardia

Abbreviations: VAERS: Vaccine Adverse Event Reporting System, AE: Adverse Events, HIT: Histamine Intolerance, DAO: Diamine Oxidase

Graphical abstract



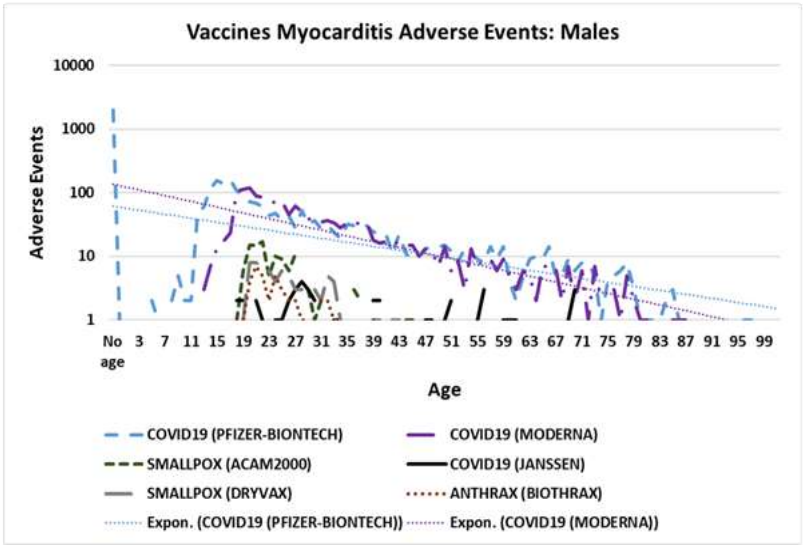
Etiology of Reactogenicity Adverse Events

1. Vaccination
2. Immune response
3. Histamine surge
4. Histamine tolerance exceeded?

- No – no adverse events
- Yes – adverse event(s)

Histamine cardiac adverse events:

- Altered heart rate
- Vasoconstriction induced myocarditis/pericarditis
- Number of adverse events correlate with vaccine reactogenicity level



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 significantly associated with both SARS-CoV-2 mRNA Spike vaccines (mRNA-1273 Moderna and BNT162b2 Pfizer/BioNTech) **[21]**. A retrospective case series including 21 COVID-19 vaccine associated myocarditis patients found elevated troponin levels in 100% of the 14 hospitalized patients **[22]**. Elevated troponin levels are a signature of some level of cardiac myocyte cell death. A Danish study of 4,931,775 individuals found absolute rates for myocarditis or myopericarditis at 1.4 per 100,000 for the BNT162b2 vaccine and 4.2 per 100,000 for mRNA-1273 vaccine **[23]**. A Nordic residents study of 23,122,522 individuals detected 5.55 (95% CI, 3.70-7.39) events per 100,000 vaccinees after the second dose of BNT162b2 and 18.39 (9.05-27.72) events per 100,000 vaccinees after the second dose of mRNA-1273 with similar estimates for pericarditis **[24]**. A survey of hospitalized Israeli Defense Forces military personnel reported an incidence rate of 5.07 per 100,000 **[25]**. A study of 404,407 Israeli adolescents reported 8.09 myocarditis cases per 100,00 for males and 0.69 cases per 100,000 for females **[26]**. A Hong Kong study of 224,560 adolescents reported incidence rates of 3.12 (1.25-6.42) and 22.15 (15.51-30.67) per 100,000 for the first and second dose of BNT162b2 vaccine **[27]**. 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 **[28]**. Pericyte cell clamping was proposed to be caused possibly by either direct SARS-CoV-2 infection or by elevated histamine levels **[28]**.

Cardiac responses to the β-imanazolylethylamine derivative of histamine was described by Dale & Laidlaw **[29]**. 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 **[29]**. In pythons, histamine induces postprandial tachycardia through a direct effect on cardiac histamine H_2-receptors **[30]**. See Wolff & Levi **[31]** for review histamine and cardiac arrhythmias. These cardiac adverse symptoms are also observed in some individuals with histamine intolerance (HIT) **[32]**.

The Hypothesis

Innate immune responses to vaccination are implicated by consistent immediate onset patterns of cardiac adverse events shared by unrelated vaccines reported in Vaccine Adverse Event Reporting System (VAERS). Elevated histamine levels from innate immune responses are hypothesized herein as causative for these reported cardiac adverse events. For affected vaccinees, these cardiac adverse events are proposed to occur when the amount of histamine released from innate immune response exceeds their histamine tolerance level causing temporary histamine intolerance. The reported cardiac adverse events can be grouped into two subclasses. In the first subclass, elevated histamine level is associated with altered heart rate, including chest pain, palpitations, tachycardia, etc. Myocarditis and pericarditis represent a second subclass hypothesized to be initiated by histamine induced contraction of cardiac capillary pericyte cells; extended contraction of pericyte cells can result in vasoconstrictions followed by localized myocyte anoxia (cell death due to lack of oxygen). Localized myocyte anoxia is consistent with observed increases in troponin levels associated with myocarditis and pericarditis.

This model of elevated histamine induced vaccine cardiac adverse events generalizes to all vaccines with reported cardiac associated adverse events. The model of cardiac adverse events induced by elevated histamine level directly suggests multiple candidate prophylactic combined with therapeutic treatment options for evaluation that have the potential to reduce the incidence rate and severity of cardiac adverse events associated with vaccines. Therapeutically, these treatments may reduce the cardiac tissue damage caused by proposed vasoconstrictions and localized myocyte anoxia.

Materials and Methods

The Vaccine Adverse Event Reporting System (VAERS) database **[33]** was utilized for cardiac adverse events from 1990 to April 1, 2022. Reports of cardiac adverse events were identified by vaccine name or type, age, gender, onset day post vaccination, and vaccine dose. The following cardiac related adverse events were extracted: Acute myocardial infarction, Arrhythmia, Atrial fibrillation, Atrial flutter, Bradycardia, Cardiac arrest, Cardiac disorder, Cardiac failure, Cardiac flutter, Cardio-respiratory arrest, Chest discomfort, Chest pain, Electrocardiogram abnormal, Electrocardiogram ST segment elevation, Heart rate abnormal, Heart rate decreased, Heart rate increased, Heart rate irregular, Ischaemic stroke, Musculoskeletal chest pain, Myocarditis, Myocardial infarction, Myocardial necrosis marker, Palpitations, Pericarditis, Pericardial effusion, Pulmonary embolism, Sinus tachycardia, Tachycardia, Troponin increased, Troponin I increased. The downloaded data include all adverse events reported from 1990 to April 1, 2022. The Ruby program, named vaers_slice.rb **[34]**, was used to tally selected reported vaccine adverse events by vaccine, age, and day of onset. The vaers_slice.rb program takes as input a list of one or more adverse events to characterize; these adverse events are summarized from the yearly VAERS Symptoms, Vax, and Data files from 1990 to 2022. The output from vaers_slice.rb consists of five reports: summaries by vaccine, summaries by age of onset of symptoms, summaries by day of onset of symptoms, and two summaries of additional symptoms reported (selected symptoms and all other symptoms). A similar program, named vaers_tally.rb, was developed to summarize all adverse events across all vaccines. Microsoft Excel was used create figures.

Results

All of the VAERS adverse events from 1990 to April 1, 2022, are summarized in the supplemental data tables named V_matrix (by vaccine name) and Vaccine_matrix (by vaccine type). Individual and combined symptoms report for selected cardiac related adverse events summarized by vaers_slice.rb are included in the supplemental data as individual Excel worksheets. Cardiac associated adverse events reported in VAERS are summarized in **Table 1** for multiple vaccines. The co-occurrence of these cardiac adverse events is shown in **Table 2.** The day of onset for COVID-19 vaccine cardiac adverse events is illustrated in **Table 3**. The frequency of COVID-19 mRNA vaccine associated myocarditis adverse event differences by dose are shown in **Table 4. Figure 1** illustrates myocarditis adverse event for multiple vaccines for males. Differences between adverse event reports by gender are shown in **Table 5** for multiple vaccines. **Figure 2** illustrates chest pain frequency differences by gender and age.

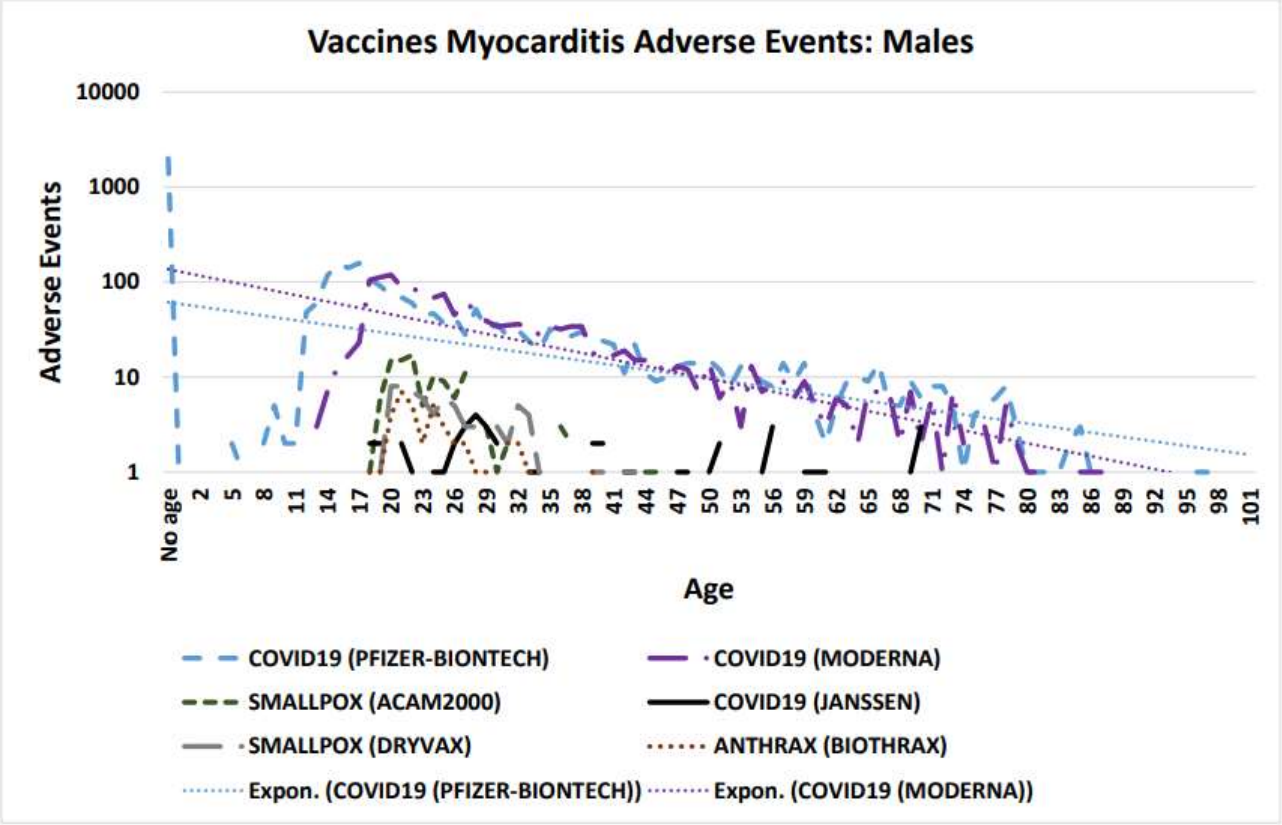


Figure 1. Vaccine associated myocarditis cardiac adverse events in males (COVID-19 Moderna mRNA-1273, COVID-19 Pfizer BNT162b2, COVID-19 Janssen, Anthrax, and Smallpox vaccines)

Discussion

Cardiac adverse events following vaccination can be categorized into the following groups: non-specific (e.g., chest pain and chest discomfort), altered heart rate (arrhythmia, heart rate increased, palpitations, and tachycardia), and cardiac (e.g., myocarditis, pericarditis, and troponin increased). Chest pain is the most frequently reported adverse event **(Table 1)**. The vaccines with the highest numbers of reported cardiac adverse events in VAERS are summarized in **Table 1**. Consistent patterns across multiple unrelated vaccines suggest a generalized cause that is not vaccine specific **(Figure 1 & Table 1)**. This article proposes that vaccine associated cardiac adverse events scale approximately with the overall reactogenicity level of each vaccine. Co-occurrences of cardiac adverse events are summarized 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 possible overlapping underlying loss of cardiac myocytes.

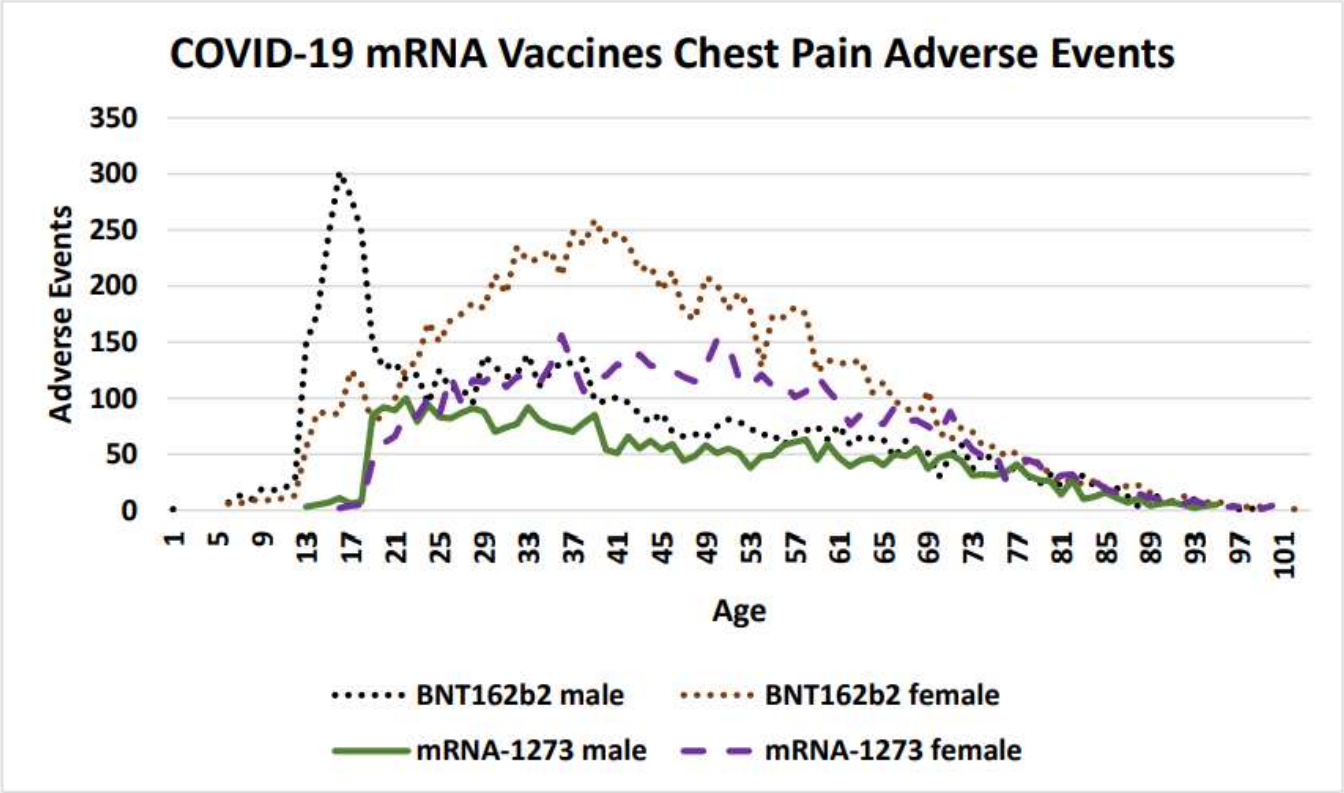


Figure 2. COVID-19 chest pain adverse events by gender and age following SARS-CoV-2 Spike mRNA vaccination reported in the VAERS system by April 1, 2022 (Pfizer BNT162b2 and Moderna mRNA-1273).

Table 1. Vaccine associated cardiac adverse events from VAERS (1990 to April 1, 2022).

Vaccine Name	Chest pain	Palpitations	Chest discomfort	Heart rate increased	Tachycardia	Myocarditis	Pericarditis
COVID19 (PFIZER-BIONTECH)	23,501	14,984	13,472	10,669	8,497	5,888	4,120
COVID19 (MODERNA)	10,624	7,383	7,058	6,376	3,403	2,206	1,247
COVID19 (JANSSEN)	2,509	1,330	1,464	1,509	565	154	147
HPV (GARDASIL)	795	569	288	331	214	10	16
INFLUENZA (SEASONAL) (FLUZONE)	647	238	642	373	263	14	17
INFLUENZA (SEASONAL) (NO BRAND NAME)	448	233	278	364	191	46	52
ZOSTER (SHINGRIX)	343	269	222	489	99	5	20
PNEUMO (PNEUMOVAX)	494	148	307	239	201	15	11
VACCINE NOT SPECIFIED (NO BRAND NAME)	405	204	245	243	135	74	60
HEP B (ENGERIX-B)	483	182	158	137	283	23	28
Average percentage relative to chest pain		54.3%	60.0%	62.5%	36.2%	9.3%	8.0%

Cardiac adverse events are consistent with altered heart rate and/or predicted cardiac vasoconstrictions. This article proposes that both of these patterns directly result from elevated histamine levels released by innate immune responses to vaccination. 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 **(Table 4)**. 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.

Table 2. Co-occurrences of vaccine associated cardiac adverse events from VAERS (1990 to April 1, 2022).

Adverse event	**Chest discomfort**	**Chest pain**	**Heart rate increased**	**Myocarditis**	**Palpitations**	**Pericarditis**	**Tachycardia**
Acute myocardial infarction	84	403	7	105	22	37	31
Arrhythmia	306	495	333	201	734	75	529
Atrial fibrillation	187	379	445	69	489	119	363
Bradycardia	96	157	34	30	115	19	168
Cardiac arrest	38	147	22	78	21	8	57
Cardiac disorder	153	274	150	63	199	33	68
Cardiac failure	52	113	36	143	40	29	61
Cardiac flutter	312	420	316	38	687	20	62
Chest discomfort		5,230	1,908	623	2,830	497	1,051
Chest pain	5,230		2,484	2,916	4,086	2,276	1,793
Electrocardiogram abnormal	461	1,423	406	507	575	416	407
Heart rate decreased	99	170	128	21	154	11	53
Heart rate increased	1,908	2,484		185	2,853	129	935
Heart rate irregular	333	483	510	67	654	40	161
Musculoskeletal chest pain	178	489	75	13	124	20	43
Myocardial infarction	204	619	74	128	112	62	55
Myocarditis	623	2,916	185		522	870	284
Palpitations	2,830	4,086	2,853	522		338	1,934
Pericardial effusion	142	547	40	240	84	540	89
Pericarditis	497	2,276	129	870	338		196
Sinus tachycardia	109	230	184	59	253	40	160
Tachycardia	1,051	1,793	935	284	1,934	196	
Troponin I increased	95	374	23	275	36	96	38
Troponin increased	385	1,843	65	1,264	150	271	165

Vaccinee gender is an important factor for reported cardiac adverse events **(Table 5, Figure 2)** Immune response differences between genders is known **[35–43]**. This imbalance is consistent for multiple vaccines except for the anthrax and smallpox vaccines **(Table 5)**; this may be due to imbalanced gender difference in distribution (e.g., military) or other artifact(s). For males, the incidence of reported myocarditis events by age can be modeled by exponential decay patterns **(Figure 1)** 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 1)**. 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 2)**. During diagnosis, it is important to consider that these cardiac adverse events are being reported for all genders.

Myocarditis has been reported associated with triple vaccination **[2]**; co-administration of multiple vaccines may increase the amount of histamine release with predicted correspondingly higher frequencies of cardiac adverse events in vaccinees.

Table 3. COVID-19 vaccine cardiac adverse events onset post vaccination from VAERS up to April 1, 2022.

Onset	Arrhythmia	Chest pain	Chest discomfort	Heart rate increased	Myocarditis	Palpitations	Pericarditis	Tachycardia	Troponin increased
0	2,037	14,255	11,659	10,632	2,505	12,504	1,642	7,049	489
1	651	6,421	3,460	3,197	1,004	3,428	539	1,823	492
2	293	2,717	1,161	829	869	1,287	403	548	457
3	199	1,989	866	577	833	892	316	346	447
4	146	1,184	590	355	407	653	194	244	180
5	140	818	423	290	193	465	159	172	65
6	82	656	310	210	173	305	136	145	62
7	100	818	327	252	187	475	165	186	76
8	55	484	254	145	114	262	110	112	50
9	51	429	234	132	103	229	89	77	52
10	44	382	175	119	91	245	94	82	38
11	37	254	164	79	82	151	76	65	37
12	39	337	163	122	66	218	68	104	39
13	24	210	101	74	66	109	75	45	30
14	41	267	124	88	86	174	90	76	17

Table 4. Myocarditis by dose following SARS-CoV-2 Spike mRNA vaccination reported in the VAERS system by April 1, 2022 (Pfizer BNT162b2 & Moderna mRNA-1273).

Adverse Event	BNT162b2 Dose1 male	BNT162b2 Dose2 male	BNT162b2 Dose1 female	BNT162b2 Dose2 female	mRNA-1273 Dose1 male	mRNA-1273 dose2 male	mRNA-1273 dose1 female	mRNA-1273 dose2 female
Palpitations	3,496	1,222	11,231	5,829	765	471	3,165	1,614
Chest discomfort	1,711	1,370	5,196	2,910	848	547	2,910	1,444
Heart rate increased	1,205	912	4,212	2,312	758	451	2,659	1,291
Tachycardia	892	662	3,313	1,937	397	269	1,445	683
Myocarditis	977	2,159	513	679	736	546	218	152
Arrhythmia	500	489	852	697	185	97	274	144
Troponin increased	380	887	190	301	185	332	117	181

Table 5. Vaccine associated cardiac adverse events gender bias from VAERS from 1990 to April 1, 2022.

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	Myocarditis male	Myocarditis female
COVID19	6,007	15,697	14,576	21,536	4,556	13,675	5,386	17,944	2,972	9,341	5,852	2,139
FLU3	243	1,064	376	1,032	217	728	108	505	134	392	23	7
HEP	58	187	242	602	86	180	58	238	165	355	27	26
HPV4	23	259	55	652	21	307	23	540	17	187	5	5
VARZOS	89	248	195	349	180	396	72	280	41	75	2	5
PPV	85	248	194	410	85	221	47	131	88	163	11	7
FLUX	61	231	164	302	111	258	45	196	86	126	31	12
FLU4	71	312	97	258	86	216	50	197	44	100	11	5
UNK	76	179	197	239	82	187	58	167	51	86	59	17
TDAP	78	246	164	247	73	189	37	174	34	101	20	7
MMR	42	84	139	169	98	116	19	66	146	182	15	10
HEPA	51	98	120	126	60	96	34	80	30	68	15	6
TD	19	60	119	161	33	47	15	55	36	94	11	2
FLU(H1N1)	62	145	41	111	37	120	20	77	15	10	1	1
VARCEL	38	65	89	94	67	79	13	41	46	52	9	7
MNQ	55	79	118	107	56	78	20	51	28	45	14	3
TYP	61	46	163	60	17	39	37	41	46	36	32	2
SMALL	157	55	580	162	21	20	62	43	26	18	212	7
ANTH	132	34	361	72	46	21	69	39	51	46	63	0

Candidate Treatments Suggested by Elevated Histamine Model

The model that most vaccine associated cardiac adverse events are caused by elevated histamine level exceeding an individual's tolerance level suggests possible combination of prophylactic followed by several days of 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 **[44]**. These candidate treatments for further evaluation include high dose famotidine **[44–47]**, cetirizine **[48,49]**, and dexchlorpheniramine **[48]**. Oral treatment with diamine oxidase (DAO) may also minimize or reduce severity vaccine reactogenicity cardiac adverse event symptoms. These treatments may be effective as combined 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 evaluating. Treatment of vaccinees with associated cardiac events may potentially provide symptoms relief while potentially reducing anoxia of cardiac myocyte cells. Evaluation of these treatments and treatment combinations on vaccinees in case reports, case series, etc. clinical studies could drive the design of subsequent randomized controlled clinical trials for reducing vaccine cardiac adverse events. This model and candidate treatments are applicable to multiple vaccines with greater potential benefits for vaccines with higher reactogenicity.

Summary

Elevated histamine levels from innate immune response to vaccination is proposed as causative for associated cardiac adverse events for affected vaccinees; these cardiac adverse events are proposed to occur when the vaccinee's histamine tolerance level was exceeded. This model predicts that the frequency of cardiac adverse events is related to the reactogenicity level of the vaccine. Specific antihistamines at the proper dosage possibly combined with diamine oxidase may be effective as combined prophylactic and therapeutic treatments in vaccinees with the potential to reduce the incidence rate and severity of cardiac adverse events. Reducing the severity of myocarditis and pericarditis may reduce associated cardiac tissue damage as reflected by troponin levels.

Acknowledgements

None

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