Allergy and Immunology

AIMS Allergy and Immunology, 6(4): 200–215.
DOI: 10.3934/Allergy.2022015
Received: 26 May 2022
Revised: 16 September 2022
Accepted: 29 September 2022
Published: 12 October 2022

http://www.aimspress.com/journal/Allergy

Research article

Etiology model for many vaccination adverse reactions, including SARS-CoV-2 spike vaccines

Darrell O. Ricke*

Molecular BioInsights, Winchester, MA 01890, USA

*** Correspondence:** Email: doricke@molecularbioinsights.com; Tel: +17818667625.

Abstract: *Objective*: Vaccinated individuals (vaccinees) experience no adverse events, mild adverse events, multiple adverse events, or serious adverse events post vaccination. Many of these vaccine adverse events occur with different vaccines with different occurrence frequencies. Many of these adverse events are generally considered as associated with immune responses to the active vaccine components (antigens) and/or to possibly one or more of the vaccine excipients. Most of these vaccine adverse events are self-limiting and resolve within days. The number of vaccine adverse reactions is higher for SARS-CoV-2 spike vaccines than all other vaccines. Can data analysis of vaccine adverse reactions responses provide etiology insights for high reactogenicity vaccines? *Methods*: The Vaccine Adverse Event Reporting System (VAERS) database was data mined for all vaccine adverse events data by vaccine, age, gender, dose, and day of onset post vaccination. Results for vaccines with the highest number of adverse events were compared. *Results*: For vaccines and adverse events with the highest numbers of reports, the day of onset approximates a power of two decay pattern for the first three days. The consistency of this pattern for multiple unrelated vaccines narrows possible etiology mechanisms. Many of these adverse event symptoms overlap symptoms associated with elevated histamine levels. Herein, innate immune responses and specifically elevated histamine levels are proposed to be causative for the majority of these adverse events. This hypothesis is based on a model of innate immune responses releasing a surge of inflammatory molecules, including histamine; this surge is hypothesized to exceed the normal histamine tolerance level for vaccinees causing reactogenicity adverse events. Further, these symptoms resolve as histamine levels fall below the vaccinee's tolerance threshold. This model can be evaluated by the detection of elevated histamine levels in vaccinees corresponding to timing of symptoms onset. If confirmed, a direct consequence of this model predicts that specific antihistamine treatments, mast cell stabilizers, and possibly diamine oxidase enzyme may reduce the incidence or severity of

adverse events experienced by vaccinees post vaccinations for most or all high reactogenicity vaccines including coronavirus disease 2019 (COVID-19) spike vaccines. *Conclusions*: The reported onset occurrences of the majority of reported adverse events are consistent with the likely etiology of innate immune responses to vaccinations for vaccines with higher reactogenicity levels. Herein, the hypothesis is proposed that the majority of these adverse events result from a histamine surge that temporarily exceeds the vaccinee's tolerance level.

Keywords: COVID-19; reactogenicity; adverse events; serious adverse events; histamine intolerance

Abbreviations: COVID-19: coronavirus disease 2019; DTAP: diphtheria, tetanus, and pertussis vaccine; FLU3: influenza vaccine; HEP: hepatitis vaccine; HIT: histamine intolerance; MMR: measles, mumps, and rubella vaccine; PPV: pneumococcal polysaccharide vaccine; SARS-CoV-2: severe acute respiratory syndrome coronavirus 2; VAERS: Vaccine Adverse Event Reporting System; VARCEL: chickenpox varicella vaccine; VARZOS: shingles varicella-zoster virus vaccine

1. Introduction

Vaccinations protect vaccinees against multiple viral and bacterial infectious diseases. Post-vaccination, vaccinees experience no, mild adverse events, multiple adverse events, or serious adverse events. Adverse events associated with vaccinations are typically rare [1]. Some of these adverse events have been associated with allergic reactions to vaccine excipients including adjuvants [2] (e.g., polyethylene glycol [3]), or manufacturing contaminants (e.g., egg proteins [4]). Adverse events can occur immediately (e.g., anaphylaxis) or within hours or days post vaccination. Vaccine reactogenicity refers to the subset of adverse events that occur soon after vaccination and are physical manifestations of the inflammatory response to vaccination [1]. The intensity of these adverse event symptoms ranges from mild to severe. Many of these vaccinees are negatively impacted by these adverse event symptoms until they resolve. Adverse events temporally associated with vaccines are generally associated with immune responses, including humoral antibody responses, to one or more of the vaccine components.

To protect against SARS-CoV-2, multiple vaccines have been developed. These vaccines include traditional inactivated virus vaccines (CoronaVac, BBIBP-CorV, Covaxin), protein subunit vaccine (Novavax, ZF2001), replication-defective viral vector vaccines (AD5-nCoV, AZD1222, Sputnik V, Ad26.Cov2.S), and mRNA vaccines (mRNA-1273 and BNT162b2/Comirnaty) [5]. The SARS-CoV-2 spike vaccines (mRNA-1273, BNT162b2/Comirnaty, and Ad26.Cov2.S) are distributed in the United States. With broad distribution of these vaccines within the United States, associated adverse events are reported to the Vaccine Adverse Event Reporting System (VAERS) database [6]. The number of vaccine adverse reactions is higher for these SARS-CoV-2 spike vaccines than all other vaccines. Can data analysis of the VAERS vaccine adverse reactions responses provide etiology insights for these SARS-CoV-2 spike vaccines and other high reactogenicity vaccines?

Herein, the VAERS databases is examined for the most frequent adverse events across all vaccines. Overlaps were observed for the most frequently reported adverse events with symptoms associated with histamine intolerance. Herein, the hypothesis is advanced that the majority of

vaccination reactogenicity adverse events are caused by elevated histamine levels from innate immune responses to vaccination temporarily exceeding the vaccinee's tolerance level; this includes the majority of the coronavirus disease 2019 (COVID-19) spike vaccine associated reactogenicity adverse events.

2. Methods

The VAERS database [6] was data mined for vaccine adverse events data by vaccine type and onset post vaccination. The downloaded data includes all VAERS reports from 1990 until May 13, 2022. A Ruby program named vaers_tally.rb was developed to tally reported vaccine adverse events by vaccine [7]. The output from vaers_tally.rb consists of summaries by vaccine by dose, adverse event, and onset. A Ruby program named vaers_slice.rb was developed to tally selected reported vaccine adverse events by vaccine [7]. The vaers_slice.rb program takes as input a list of one or more symptoms to summarize and 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). The adverse events pyrexia (fever), headache, fatigue, chills, nausea, dizziness, pain, and pain in extremity were extracted. Microsoft Excel was used to create figures and to rank order vaccine symptoms for vaccines with the most reported adverse events.

3. Results

The overlap between symptoms associated with histamine intolerance, anaphylaxis, and adverse events reported in VAERS are correlated in Table 1. The top 75 most commonly reported vaccine reactogenicity adverse events are shown for the seven highest reactogenicity vaccines in Tables 2 and 3. Figure 1 illustrates the day of onset for the most frequently reported adverse events for these seven vaccines. Extended reports by day of onset are illustrated for the pyrexia adverse event for these seven vaccines (Figure 2). Adverse events temporally associated with COVID-19 spike vaccines have more reports than adverse events associated with non-COVID-19 vaccines (Table 2).

Table 1. Symptoms overlaps between histamine intolerance, anaphylaxis, and vaccine adverse events.

Organ system	Symptoms	Associated with histamine intolerance [8,9]	Associated with anaphylaxis [10]	Found in vaccine adverse events (VAERS)
Respiratory	Rhinorrhea (clear nasal discharge)	Yes	Yes	Yes
	Rhinitis (swelling of the mucous membrane of the nose)	Yes	No	Yes
	Nasal congestion	Yes	Yes	Yes
	Sneezing	Yes	Yes	Yes
	Dyspnea (labored breathing), respiratory distress, asthmatic symptoms	Yes	Yes	Yes
	Swelling of lips, tongue, eustachian tube, glottis, watery discharge, swelling of the lining of the nose, phlegm	Yes	Yes	Yes
	Cough	Yes	Yes	Yes
Gastrointestional	Bloating	Yes	Yes	No
	Flatulence	Yes	Yes	Yes
	Postprandial fullness	Yes	Yes	No
	Diarrhoea	Yes	Yes	Yes
	Abdominal pain	Yes	Yes	Yes
	Constipation	Yes	Yes	Yes
	Nausea	Yes	Yes	Yes
	Emesis/vomiting	Yes	Yes	Yes
Neurological	Headache/migraine	Yes	Yes [11]	Yes
	Faintness, light-headed, vertigo	Yes	Yes	Yes
	Malaise, feeling abnormal, anxiety and a feeling of impending doom	Yes	Yes	Yes
	Dizziness	Yes	Yes	Yes
	Syncope, Loss of consciousness	Yes	Yes	Yes
	Blurred vision	No	Yes	Yes
	Itchy, red, watery eyes, eye pruritus	Yes	Yes	Yes
	Restlessness	Yes	Yes	Yes
	Seizure	No	Yes (seldom)	Yes
	Nervousness	Yes	No	Yes
	Sleep disturbances (insomnia)	Yes	No	Yes
	Anxiety	Yes	Yes	Yes
	Panic disorder	Yes	Yes	Yes
	Depression	Yes	No	Yes

Continued on next page

Organ system	Symptoms	Associated with histamine intolerance [8,9]	Associated with anaphylaxis [10]	Found in vaccine adverse events (VAERS)
Circulatory/cardiovascular	Tachycardia	Yes	Yes	Yes
	Hypotonia (decreased muscle tone)	Yes	Yes	Yes
	Chronic inappropriate fatigue	Yes	No	Yes
	Collapse (weakness due to decreased circulation), changes in blood pressure, palpitations, heart rhythm disorders	Yes [9]	Yes	Yes
	Chest pain	Yes	Yes	Yes
Integumentary (skin)	Pruritus (itchy skin)	Yes [12]	Yes	Yes
	Flushing/redness/erythema	Yes	Yes	Yes
	Urticaria/hives	Yes	Yes	Yes
	Dermatitis	Yes	Yes	Yes
	Swelling	Yes	Yes	Yes
	Feeling hot, body temperature increased	Yes	Yes	Yes [13]
Reproductive	Dysmenorrhoea (painful menstruation)	Yes	Yes	Yes
	Menstrual disorder, menstruation irregular, menstruation delayed, heavy menstrual bleeding, intermenstrual bleeding	No	No	Yes

Table 2. Tallies of adverse events temporally associated with vaccination reported from 1990 until May 13, 2022. Adverse events are sorted by ascending rank mean for the top seven vaccines with the highest number of reported adverse events—COVID-19, influenza (FLU3), shingles-attenuated live varicella-zoster virus (VARZOS), measles, mumps, and rubella (MMR), pneumococcal polysaccharide (PPV), hepatitis (HEP), and chickenpox varicella (VARCEL).

Symptom	Histamine intolerance	COVID-19	VARZOS	FLU3	MMR	VARCEL	HEP	PPV
Headache	Yes	182521	12418	7118	2336	1562	4351	3543
Fatigue	Yes	154437	9752	3576	1185	779	1805	2215
Pyrexia	Yes	153429	14461	12757	21749	11961	11117	14372
Chills	Yes	117962	11811	6223	846	375	1460	4885
Pain		117160	15708	11349	3276	1856	3964	9409
Nausea	Yes	102858	6603	5642	1478	1007	4096	3304
Dizziness	Yes	99763	3563	5631	1341	1106	3592	1934
Pain in extremity		96033	10210	8157	753	816	907	8319
Myalgia		69043	6524	4591	1145	354	3365	2956

Continued on next page

Symptom	Histamine intolerance	COVID-19	VARZOS	FLU3	MMR	VARCEL	HEP	PPV
Dyspnoea	Yes	69019	1152	4562	1542	788	2152	1778
Arthralgia		65501	3959	2710	1928	370	3070	1779
Rash	Yes	49046	9219	5335	11958	8709	5428	2999
Asthenia		47509	3148	4044	1221	581	3478	1721
Pruritus	Yes	45153	5753	6296	4364	4289	3906	2425
Injection site pain		44498	12795	11051	3974	3536	3353	13188
Vomiting	Yes	42942	1765	4183	3927	2048	4226	2206
Malaise	Yes	42303	3700	3209	1491	740	2157	2388
Chest pain	Yes	37375	569	1431	312	183	861	614
Diarrhoea	Yes	36144	1779	2273	2010	897	2410	1011
Cough	Yes	35952	651	4148	1993	1181	993	1087
Paraesthesia		35763	1793	3357	649	277	2367	770
Lymphadenopathy		33156	682	1012	1993	479	876	672
Hypoaesthesia		32585	1174	2752	320	228	969	679
Feeling abnormal	Yes	31485	1929	1003	228	151	245	553
Erythema	Yes	30154	7827	8131	6063	5955	1707	11633
Urticaria	Yes	29776	2490	5302	4826	3289	4001	1871
Hyperhidrosis		29631	1377	2074	715	361	1342	981
Injection site erythema		29576	14578	11384	10993	10723	2432	14793
Vaccination site pain		28312	276	223	60	62	41	347
Syncope	Yes	26054	523	1409	1403	945	1406	484
Injection site swelling	Yes	24667	9704	7781	5868	6780	1494	11723
Peripheral swelling	Yes	24487	2718	1428	266	260	204	4347
Palpitations	Yes	24101	368	619	89	54	308	179
Chest discomfort	Yes	22339	353	1324	128	105	248	337
Condition aggravated		21010	1575	946	540	284	971	599
Back pain		20440	1466	1401	289	154	850	743
Injection site pruritus		20090	4113	1909	783	1685	306	1058
Tinnitus		19982	447	327	94	39	218	95
Tremor		19157	1340	2027	1071	508	1176	735
Heart rate increased	Yes	18882	617	954	215	148	273	313
Oropharyngeal pain		18345	508	1314	321	183	193	257
Decreased appetite		17559	1132	645	1095	564	488	676
Loss of consciousness	Yes	17087	544	962	656	557	664	334
Influenza like illness		16291	4156	1244	196	109	417	883
Swelling	Yes	16149	2907	2768	2091	1684	557	4093
Feeling hot	Yes	16033	1023	1812	2215	686	646	1602
Heart rate	Yes	15899	5	13	10	20	19	10

Continued on next page

Symptom	Histamine intolerance	COVID-19	VARZOS	FLU3	MMR	VARCEL	HEP	PPV
Neck pain		15615	1247	1589	422	167	797	787
Death		15168	277	406	196	95	472	356
Injection site warmth		15028	5527	5002	4197	4164	888	5953
Migraine	Yes	14246	354	268	98	54	282	83
Insomnia	Yes	13395	1389	953	583	247	719	769
Hypertension	Yes	12896	182	536	165	49	505	217
Abdominal pain	Yes	12806	430	600	637	296	1471	319
Vertigo	Yes	12732	422	460	80	43	406	95
Tachycardia	Yes	12659	126	532	337	100	536	255
Muscle spasms		12406	536	671	186	81	393	300
Mobility decreased		12304	1472	1561	138	61	171	1835
Rash erythematous	Yes	12186	2485	1405	1986	1854	562	816
Abdominal pain upper	Yes	12141	1013	453	286	233	339	167
Muscular weakness	Yes	11975	841	1657	195	150	520	582
Gait disturbance		11672	629	892	829	389	608	317
Blood pressure increased	Yes	11523	328	506	62	25	132	203
Fall		11503	414	646	384	395	287	191
Injection site rash		11370	3074	1458	1073	1440	313	1220
Herpes zoster		11273	18449	466	555	2097	211	153
Anxiety	Yes	11251	218	403	231	97	490	133
Rash pruritic	Yes	10940	1798	768	649	832	275	179
Heavy menstrual bleeding	Yes	10694	2					
Vision blurred	Yes	10532	374	579	118	74	284	105
Flushing	Yes	10393	308	920	291	185	316	341
Sleep disorder	Yes	10345	543	429	368	112	270	351
Somnolence	Yes	10245	595	592	1389	438	1492	381
Lethargy	Yes	10238	921	616	928	562	540	484
Rhinorrhoea	Yes	10053	225	827	765	567	264	217

Table 3. Rank ordered adverse events temporally associated with vaccination for adverse events from 1990 until May 13, 2022. Adverse events are sorted by ascending rank mean for the top seven vaccines with the highest number of reported adverse events—COVID-19, influenza (FLU3), shingles-attenuated live varicella-zoster virus (VARZOS), measles, mumps, and rubella (MMR), pneumococcal polysaccharide (PPV), hepatitis (HEP), and chickenpox varicella (VARCEL).

Symptom	COVID-19	VARZOS	FLU3	MMR	VARCEL	HEP	PPV
Headache	1	6	8	18	28	3	16
Fatigue	2	9	21	47	56	27	24
Pyrexia	3	4	1	1	1	1	2
Chills	4	7	10	71	87	33	9
Pain	5	2	3	12	20	7	6
Nausea	6	13	11	41	42	5	17
Dizziness	7	22	12	44	40	9	27
Pain in extremity	8	8	5	76	50	50	7
Myalgia	9	14	16	49	90	11	19
Dyspnoea	10	50	17	38	55	21	33
Arthralgia	11	20	28	27	88	13	32
Rash	12	11	13	2	3	2	18
Asthenia	13	24	20	46	63	10	34
Pruritus	14	15	9	7	8	8	20
Injection site pain	15	5	4	10	10	12	3
Vomiting	16	37	18	11	16	4	25
Malaise	17	21	23	40	57	20	21
Chest pain	18	87	47	143	141	55	68
Diarrhoea	19	36	31	21	47	16	46
Cough	20	77	19	22	35	43	42
Paraesthesia	21	35	22	84	104	18	58
Lymphadenopathy	22	73	66	23	73	54	67
Hypoaesthesia	23	49	27	140	122	47	65
Feeling abnormal	24	33	67	174	158	177	73
Erythema	25	12	6	4	6	28	5
Urticaria	26	29	14	6	11	6	29
Hyperhidrosis	27	44	32	81	89	36	47
Injection site erythema	28	3	2	3	2	15	1
Vaccination site pain	29	139	203	411	273	555	93
Syncope	30	95	49	42	44	34	76
Injection site swelling	31	10	7	5	5	30	4
Peripheral swelling	32	28	48	158	108	210	10
Palpitations	33	117	102	323	305	138	138
Chest discomfort	34	123	55	263	197	175	96
Condition aggravated	35	39	76	97	103	46	69
Back pain	36	41	51	146	155	56	61

Continued on next page

Symptom	COVID-19	VARZOS	FLU3	MMR	VARCEL	HEP	PPV
Injection site pruritus	37	18	36	73	26	139	45
Tinnitus	38	103	168	311	384	195	230
Tremor	39	45	33	55	71	39	63
Heart rate increased	40	82	72	182	162	156	100
Oropharyngeal pain	41	99	56	139	140	217	116
Decreased appetite	42	52	99	52	66	92	66
Loss of consciousness	43	91	69	83	68	69	97
Influenza like illness	44	17	58	194	193	98	51
Swelling	45	26	26	20	27	80	12
Feeling hot	46	54	37	19	60	70	35
Heart rate	47	928	871	811	534	739	822
Neck pain	48	47	42	111	147	59	55
Death	49	138	141	195	207	93	91
Injection site warmth	50	16	15	9	9	53	8
Migraine	51	122	183	303	303	152	263
Insomnia	52	43	73	90	114	63	59
Hypertension	53	176	116	217	331	89	124
Abdominal pain	54	105	105	86	99	32	98
Vertigo	55	106	133	348	368	104	229
Tachycardia	56	229	118	130	201	84	117
Muscle spasms	57	93	96	200	227	109	103
Mobility decreased	58	40	43	253	275	247	31
Rash erythematous	59	30	50	24	22	79	54
Abdominal pain upper	60	55	134	147	120	126	144
Muscular weakness	61	63	41	197	159	87	71
Gait disturbance	62	80	78	72	85	71	99
Blood pressure increased	63	131	119	405	468	303	130
Fall	64	107	98	121	84	147	137
Injection site rash	65	25	46	53	29	135	41
Herpes zoster	66	1	129	93	15	197	158
Anxiety	67	162	142	169	206	91	180
Rash pruritic	68	34	85	85	49	154	139
Heavy menstrual bleeding	69	1020	1111	1119	1119	1122	1125
Vision blurred	70	116	109	273	239	151	213
Flushing	71	135	77	145	138	134	95
Sleep disorder	72	92	136	123	187	158	92
Somnolence	73	84	106	43	75	31	88
Lethargy	74	59	103	63	67	82	77
Rhinorrhoea	75	159	81	74	65	164	125

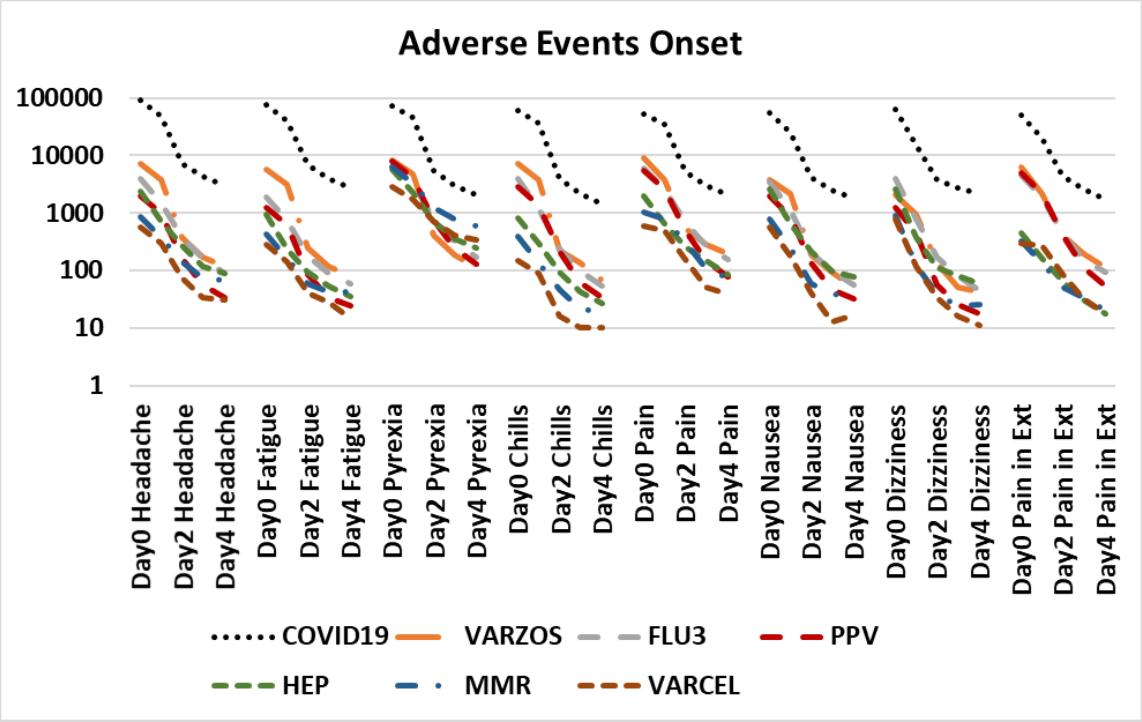

Figure 1. Most frequent vaccine adverse events (headache, fatigue, pyrexia, chills, pain, nausea, dizziness, and pain in extremities (pain in ext)) days to onset (days 0, 1, 2, 3, & 4 plotted with X-axis legends for days 0, 2, & 4) reported in VAERS from 1990 until May 13, 2022 for vaccines with most reported adverse events—COVID-19, influenza (FLU3), shingles-attenuated live varicella-zoster virus (VARZOS), measles, mumps, and rubella (MMR), pneumococcal polysaccharide (PPV), hepatitis (HEP), and chickenpox varicella (VARCEL).

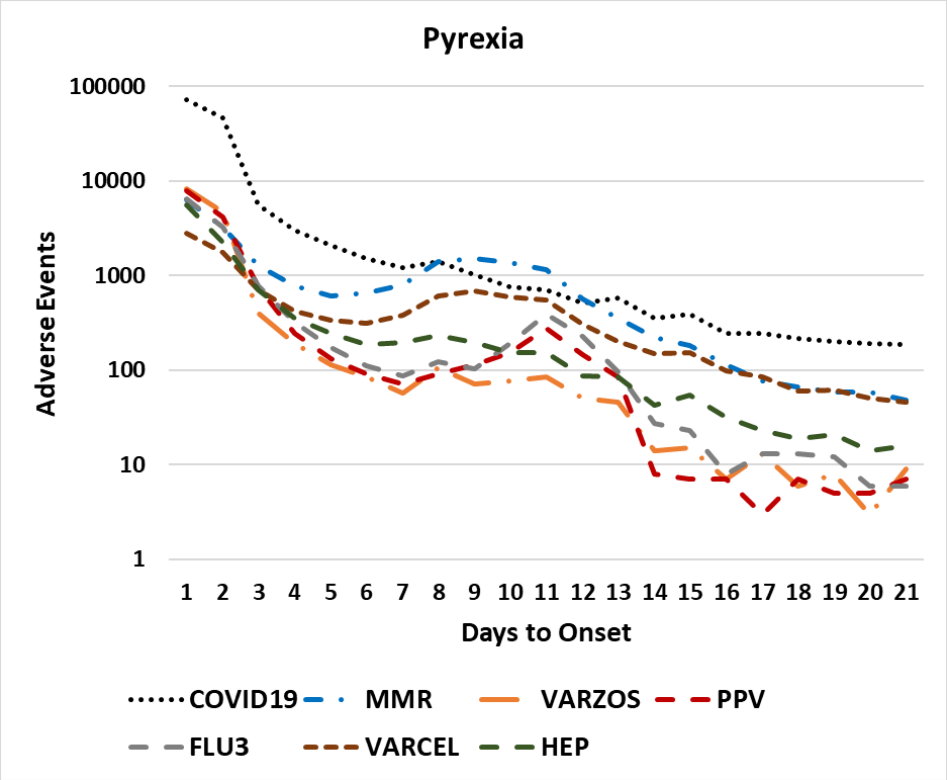

Figure 2. Pyrexia adverse events by days to onset reported in VAERS from 1990 until May 13, 2022 for vaccines with most reported adverse events—COVID-19, influenza (FLU3), shingles-attenuated live varicella-zoster virus (VARZOS), measles, mumps, and rubella (MMR), pneumococcal polysaccharide (PPV), hepatitis (HEP), and chickenpox varicella (VARCEL).

4. Discussion

A variety of adverse events are commonly associated with vaccination adverse events. Examples of common COVID-19 spike vaccine temporally associated adverse events include flushing or erythema (28%), dizziness or lightheadedness (26%), tingling (24%), throat tightness (22%), hives (21%), and wheezing or shortness of breath (21%) [14]; they note that 32 (20%) reported immediate and potentially allergic symptoms that were associated with the second COVID-19 vaccine dose were self-limited, mild, and/or resolved with antihistamines alone [14]. Many of the most commonly reported vaccine reactogenicity adverse events overlap with those of histamine intolerance syndrome (HIT) and anaphylaxis, see Table 1.

The top ranked ordered adverse events temporally associated with vaccinations are illustrated in Tables 2 and 3. Some adverse events are anticipated to be specific to injection sites without overlaps with oral vaccines. Two dominant patterns emerge in Figures 1 and 2 with respect to onset of adverse events in vaccinees. The first pattern is characterized by the highest frequency of reported adverse events post vaccinations having the highest numbers of reports immediately following vaccinations with rapid declines for subsequent days. Reporting bias likely contributes to lower frequencies of reports as the number of days post vaccination increases. For some vaccinees, a second pattern is noted for some symptoms consistent with the timing of humoral response to the vaccination days 7 to

10 days post vaccination, see Figure 2. The majority of reported vaccination associated adverse events are associated with immediate onsets for the first several days; this is illustrated for pyrexia with an average of 72% for days 0 & 1 and 84% for days 0 to 5 (Figure 2). For COVID-19 spike vaccines, 85% of the pyrexia adverse events are reported for days 0 & 1 and 94% for days 0 to 5 (Figure 2).

Herein, the observed overlap of vaccine associated adverse events across different vaccines suggests sharing of common cellular responses to vaccines; this enables exclusion of specific vaccine components as candidate causative entities. For initial vaccine exposures, the onset timing for the majority of the reported adverse events is insufficient for engagement of humoral immune responses. This immediate onset of symptoms is consistent with innate immune system response to vaccination. Granulocytes including mast cells are predicted to release inflammatory molecules, including histamine, as part of innate immune responses to vaccination. The majority of the top 75 ordered most frequently reported adverse events (Table 2) have significant overlaps with symptoms associated with histamine intolerance syndrome and anaphylaxis (64% for the top 25, 54% for the top 50, and 61% for the top 75 adverse events—Tables 1 and 2). Note that excluding adverse events associated with injection will increase these observed percentages. Histamine intolerance, also referred to as enteral histaminosis or sensitivity to dietary histamine, results from a disequilibrium of accumulated histamine and the capacity for histamine degradation [8,15,16].

5. Hypothesis

Innate immune responses to vaccines include activation of mast cells to release histamine [17,18]. Based on symptoms associated with elevated histamine levels, see Table 2, this article proposes the hypothesis that innate immune response to vaccination release histamine to elevated levels that are causative for the majority of vaccine reactogenicity adverse events. Multiple vaccine reactogenicity adverse events parallel those of histamine intolerance syndrome, see Table 1. A rapid increase in histamine from innate immune responses to vaccination may exceed the histamine tolerance level for many vaccinees with low to normal histamine tolerance. The number of vaccinees with adverse reactions is proposed to increase corresponding to the reactogenicity level of the vaccine. Coadministration of two or more vaccines may increase the likelihood of exceeding the vaccinees' normal histamine tolerance level. When the normal histamine tolerance level is not exceeded for some vaccinees, no adverse events are expected. Resolution of adverse event symptoms is predicted as histamine levels fall below the tolerance level. For most vaccinees, their vaccine adverse events resolve within a few days post vaccination. Elevated histamine levels are consistent with many of the adverse events temporally associated with vaccinations (Table 2). Histamine is involved in the contraction of smooth muscles, secretion of gastric acid in the stomach, vasodilation, modulation of heart rate and contractility [19], and body temperature [13]. Histamine can also sensitize nociceptive nerves associated with pain sensation [20]. Many histamine intolerance symptoms occur in combinations [11]. Some conditions can predispose individuals to vaccine associated adverse events. Histamine is metabolized by the diamine oxidase (DAO) enzyme. Genetic variants and medications can affect the histamine tolerance threshold for vaccinees. Patients with migraines have been identified with low serum DAO activity levels [21]; perhaps exhibiting histamine intolerance. Patients with allergies have higher frequencies of vaccine adverse events [22]. Other patients have experienced increased histamine sensitivity post vaccination [23].

6. Testing the hypothesis

The model predicts elevated histamine levels peaking immediately prior to onset of vaccine adverse events; for most vaccinees, the start of symptoms onset is within one to two days following vaccination. This model can be evaluated by correlating histamine levels with onset and resolution of adverse event symptoms. It may be possible to confirm elevated histamine by elevated levels in urine or blood with the standard histamine laboratory test, its metabolite methylimidazole acetic acid in urine, plasma histamine, or serum tryptase (acute serum tryptase measurements >20 ng/mL) [24] in vaccinees with adverse response symptoms. An institutional review board (IRB) approved study could evaluate and compare histamine levels in volunteers (unvaccinated controls, vaccinees who experience no adverse reactions, and vaccinees with adverse reactions). Histamine baseline levels for volunteers could be measured prior to vaccination. Including the standard laboratory serum DAO test may provide additional supportive evidence.

Histamine levels are predicted by the model to peak prior to the onset of symptoms. Histamine levels are predicted to be returning towards baseline levels consistent with resolution of symptoms. One approach to evaluating this model would be to sample histamine levels prior to vaccination, at onset of symptoms, and at the resolution of symptoms. The model predicts that the histamine levels should be observed to be highest at the onset of symptoms; if observed, this would establish correlation. An alternative sampling approach collect samples at prior to vaccination and at defined time intervals (e.g., every 12 or 24 hours) for several days post vaccination. This second sampling strategy would include data from unvaccinated control volunteers and also vaccinated volunteers who develop no adverse event symptoms. The model predicts that histamine levels will be observed to increase in all vaccinees (with and without adverse event symptoms) but not in unvaccinated controls. Either of these sampling approaches should be able to establish or reject correlation of increased histamine levels corresponding with vaccine adverse event symptoms.

The model predicts that increased histamine levels is causative for the majority of vaccine reactogenicity adverse events. Hence, combination of prophylactic and therapeutic treatments may enable reductions in incidence rates and symptoms duration for some vaccinees. Treatments targeting granulocytes/mast cells, antihistamines, and supplemental DAO enzyme for histamine metabolism may provide some efficacy to vaccinees. IRB approved case-control studies could compare incidence rates, severity, and duration lengths of symptoms between control volunteers and volunteers treated prophylactically and therapeutically with these candidate treatments (overviewed in the next section). Positive efficacy results from these studies would further support the proposed model.

7. Treatments

Treatments for reactogenicity adverse events include pain mitigation, antipyretics (prevent or reduce fever), etc. include local application of ice, paracetamol (acetaminophen), aspirin, or anti-inflammatories (e.g., ibuprofen) [1]. The model that most reactogenicity adverse events represent histamine intolerance symptoms suggests possible prophylactic and/or 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. These candidate treatments for further evaluation include high dose famotidine [25–28], cetirizine [29,30], and dexchlorpheniramine [29]. Oral treatment with diamine oxidase may also

minimize, reduce severity, or eliminate vaccine reactogenicity adverse event symptoms in some vaccinees. 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 adverse events. This model and candidate treatments should be applicable to all vaccines.

8. Conclusions

The hypothesis that most vaccine reactogenicity adverse events are caused by temporal excess of histamine level is presented. The pattern of reactogenicity adverse events share overlaps between most or all vaccines including reports for COVID-19 spike vaccines. Evaluating histamine, histamine metabolite, and DAO serum levels in affected vaccinees can support or refute this model. The proposed etiology suggests possible prophylactic and therapeutic treatments for reducing vaccine reactogenicity symptoms, including antihistamines, mast cell stabilizers, and DAO enzyme supplements. Antihistamines are already occasionally used as therapeutic treatments for selected vaccine reactogenicity symptoms like rashes.

Conflict of interest

The author declares that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

References

1. Hervé C, Laupèze B, Del Giudice G, et al. (2019) The how's and what's of vaccine reactogenicity. *NPJ Vaccines* 4: 39. https://doi.org/10.1038/s41541-019-0132-6
2. Forsyth JR (1967) An assessment of oil adjuvant and aqueous influenza vaccines. I. Reactions to the vaccines. *J Hyg (Lond)* 65: 485–495. https://doi.org/10.1017/S0022172400046027
3. Bruusgaard-Mouritsen MA, Johansen JD, Garvey LH (2021) Clinical manifestations and impact on daily life of allergy to polyethylene glycol (PEG) in ten patients. *Clin Exp Allergy* 51: 463–470. https://doi.org/10.1111/cea.13822
4. Rubing SS (1946) An allergic reaction following typhus-fever vaccine and yellow-fever vaccine due to egg yolk sensitivity. *J Allergy* 17: 21–23. https://doi.org/10.1016/0021-8707(46)90017-2
5. Kyriakidis NC, López-Cortés A, González EV, et al. (2021) SARS-CoV-2 vaccines strategies: a comprehensive review of phase 3 candidates. *NPJ Vaccines* 6: 28. https://doi.org/10.1038/s41541-021-00292-w
6. VAERS (2021) Vaccine Adverse Event Reporting System, U.S. Department of Health & Human Services. Available from: https:/vaers.hhs.gov/data/datasets.html.
7. Ricke DO (2022) VAERS-Tools. Available from: https://github.com/doricke/VAERS-Tools/.
8. Comas-Basté O, Sánchez-Pérez S, Veciana-Nogués MT, et al. (2020) Histamine intolerance: The current state of the art. *Biomolecules* 10: 1181. https://doi.org/10.3390/biom10081181
9. Kovacova-Hanuskova E, Buday T, Gavliakova S, et al. (2015) Histamine, histamine intoxication and intolerance. *Allergol Immunopathol* 43: 498–506. https://doi.org/10.1016/j.aller.2015.05.001

10. Mali S, Jambure R (2012) Anaphyllaxis management: Current concepts. *Anesth Essays Res* 6: 115–123. https://doi.org/10.4103/0259-1162.108284
11. Schnedl WJ, Lackner S, Enko D, et al. (2019) Evaluation of symptoms and symptom combinations in histamine intolerance. *Intest Res* 17: 427–433. https://doi.org/10.5217/ir.2018.00152
12. Shim WS, Oh U (2008) Histamine-induced itch and its relationship with pain. *Mol Pain* 4: 1–6. https://doi.org/10.1186/1744-8069-4-29
13. Lundius EG, Sanchez-Alavez M, Ghochani Y, et al. (2010) Histamine influences body temperature by acting at H1 and H3 receptors on distinct populations of preoptic neurons. *J Neurosci* 30: 4369. https://doi.org/10.1523/JNEUROSCI.0378-10.2010
14. Krantz MS, Kwah JH, Stone CA Jr, et al. (2021) Safety evaluation of the second dose of messenger RNA COVID-19 vaccines in patients with immediate reactions to the first dose. *JAMA Intern Med* 181: 1530–1533. https://doi.org/10.1001/jamainternmed.2021.3779
15. Maintz L, Novak N (2007) Histamine and histamine intolerance. *Am J Clin Nutr* 85: 1185–1196. https://doi.org/10.1093/ajcn/85.5.1185
16. Hrubisko M, Danis R, Huorka M, et al. (2021) Histamine intolerance—The more we know the less we know. A review. *Nutrients* 13: 2228. https://doi.org/10.3390/nu13072228
17. Riley JF (1963) Functional significance of histamine and heparin in tissue mast cells. *Ann N Y Acad Sci* 103: 151–163. https://doi.org/10.1111/j.1749-6632.1963.tb53695.x
18. Graham HT, Lowry OH, Wahl N, et al. (1955) Mast cells as sources of tissue histamine. *J Exp Med* 102: 307–318. https://doi.org/10.1084/jem.102.3.307
19. Parsons ME, Ganellin CR (2006) Histamine and its receptors. *Br J Pharmacol* 147: S127–S135. https://doi.org/10.1038/sj.bjp.0706440
20. Rosa AC, Fantozzi R (2013) The role of histamine in neurogenic inflammation. *Br J Pharmacol* 170: 38–45. https://doi.org/10.1111/bph.12266
21. Izquierdo-Casas J, Comas-Bast é O, Latorre-Moratalla ML, et al. (2018) Low serum diamine oxidase (DAO) activity levels in patients with migraine. *J Physiol Biochem* 74: 93–99. https://doi.org/10.1007/s13105-017-0571-3
22. Shavit R, Maoz-Segal R, Iancovici-Kidon M, et al. (2021) Prevalence of allergic reactions after Pfizer-BioNTech COVID-19 vaccination among adults with high allergy risk. *JAMA Netw Open* 4: e2122255–e2122255. https://doi.org/10.1001/jamanetworkopen.2021.22255
23. Sen DK, Arora S, Gupta S, et al. (1974) Studies of adrenergic mechanisms inrelation to histamine sensitivity in children immunized with Bordetella pertussis vaccine. *J Allergy Clin Immunol* 54: 25–31. https://doi.org/10.1016/S0091-6749(74)80005-9
24. Bil ò MB, Martini M, Tontini C, et al. (2019) Idiopathic anaphylaxis. *Clin Exp Allergy* 49: 942–952. https://doi.org/10.1111/cea.13402
25. Malone RW, Tisdall P, Fremont-Smith P, et al. (2021) COVID-19: famotidine, histamine, mast cells, and mechanisms. *Front Pharmacol* 12: 216. https://doi.org/10.3389/fphar.2021.633680
26. Tomera KM, Malone, Robert W., Kittah JK (2020) Brief report: Rapid clinical recovery from severe COVID-19 with high dose famotidine and high dose celecoxib adjuvant therapy. *Enliven: Pharmacovigil Drug Saf* 6: 1–5. https://doi.org/10.20944/preprints202008.0519.v1
27. Mather JF, Seip RL, McKay RG (2020) Impact of famotidine use on clinical outcomes of hospitalized patients with COVID-19. *Am J Gastroenterol* 115: 1617–1623. https://doi.org/10.14309/ajg.0000000000000832

28. Sethia R, Prasad M, Mahapatra SJ, et al. (2020) Efficacy of famotidine for COVID-19: A systematic review and meta-analysis. *medRxiv*. https://doi.org/10.1101/2020.09.28.20203463
29. Blanco JIM, Bonilla JAA, Homma S, et al. (2021) Antihistamines and azithromycin as a treatment for COVID-19 on primary health care—A retrospective observational study in elderly patients. *Pulm Pharmacol Ther* 67: 101989–101989. https://doi.org/10.1016/j.pupt.2021.101989
30. Hogan II RB, Hogan III RB, Cannon T, et al. (2020) Dual-histamine receptor blockade with cetirizine-famotidine reduces pulmonary symptoms in COVID-19 patients. *Pulm Pharmacol Ther* 63: 101942. https://doi.org/10.1016/j.pupt.2020.101942

AIMS Press