Elevated Histamine Etiology Model for Most Major Vaccine Associated Adverse Events including SARS-CoV-2 Spike Vaccines

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Research Article

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Abstract

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. Many of these adverse events symptoms overlap symptoms associated with elevated histamine levels. Based on these observations, the hypothesis that the majority of vaccine associated reactogenicity adverse events are caused by temporal histamine intolerance in vaccinees is proposed. 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 with 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 some 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.

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. Some of these adverse events have been associated with allergic reactions to vaccine excipients including adjuvants [1] (e.g., polyethylene glycol [2]), or manufacturing contaminants (e.g., egg proteins [3]). 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 [4]. 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. Reducing the incidence rates and duration of symptoms will positively impact vaccinees. Table S1 summarizes the most common adverse events for vaccines with the highest reactogenicity levels. Adverse events associated with vaccinations are typically rare [4]. Adverse events temporally associated with vaccines that consist primarily of the COVID-19 spike vaccine overlap with adverse events temporally associated with non-COVID-19 vaccines, see Figure 1. Adverse events temporally associated with vaccines are generally associated with immune responses, including antibody responses, to one or more of the vaccine components.

The overlap of vaccine associated adverse events across different vaccines suggests sharing of common cellular responses to vaccines. These symptoms also have considerable overlap with symptoms associated with histamine intolerance (HIT), see Table S2. 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 [5–7].

The Hypothesis

Innate immune responses to vaccines include activation of mast cells to release histamine [8,9]. Based on symptoms associated with elevated histamine levels, the hypothesis is proposed that innate immune response to vaccination release elevated histamine 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 S2. A rapid spike in histamine release from innate immune responses to vaccination may exceed the histamine tolerance level for many vaccinees with normal histamine tolerance. The number of vaccinees with adverse reactions is anticipated to increase corresponding to the reactogenicity level of the vaccine. Coadministration of two or more vaccines may increase the likelihood of exceeding the vaccinee's 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.

Methods

The Vaccine Adverse Event Reporting System (VAERS) database [10] was utilized for vaccine adverse events data by vaccine manufacturers and onset post vaccination. The downloaded data includes all VAERS reports from 1990 until Nov. 12, 2021. A Ruby program named vaers_slice.rb was developed to tally reported vaccine adverse events by vaccine. Microsoft Excel was used to rank order vaccine symptoms for vaccines with the most reported adverse events, see Table S3. All vaccine adverse events by vaccine are summarized in Table S4.

Results

The most commonly reported vaccine reactogenicity adverse events are shown ranked by number of reported adverse events for the eight vaccines with the most reported adverse in Table S3; the number of reported adverse events associated with Table S3 are shown in Table S1. The most common adverse event, pyrexia, is illustrated in Fig. 2 for the top eight vaccines with the most reported adverse events. Graphs of the most frequently reported adverse events for the top eight vaccines with reported adverse events are shown in Fig. 1. Adverse events temporally associated with COVID-19 spike vaccines occur at higher frequency levels than adverse events associated with non-COVID-19 vaccines (Table S1).

Discussion

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%) [11]; 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 [11].

The top ranked ordered adverse events temporally associated with vaccinations illustrated in Tables 2 and 3 illustrate overlap between unrelated diverse vaccines including COVID-19, influenza (FLU3), Shingles - attenuated live varicella-zoster virus (VARZOS), Measles, Mumps, and Rubella (MMR), Pneumococcal polysaccharide (PPV), Hepatitis (HEP), Chickenpox varicella (VARCEL), and Tetanus, Diphtheria, and Pertussis (TDAP). Some adverse events are anticipated to be specific to injection sites without overlaps with oral vaccines. Two dominant patterns emerge in Fig. 2 with respect to onset of adverse events in vaccinees. The highest frequency of reported adverse events post vaccinations have immediate temporal onsets within the first day with rapidly declining frequencies for subsequent days. This immediate onset of symptoms is consistent with immediate innate immune system response to all vaccines. Granulocytes including mast cells release molecules including histamine as part of normal innate immune responses. The hypothesis proposes that for a subset of vaccinees, the level of released histamine exceeds their individual tolerance threshold inducing temporary histamine intolerance associated symptoms. For most vaccinees, these histamine intolerance symptoms abate within a few days, predicted to decline as histamine levels decrease. The majority of the top 100 + ordered most frequently reported adverse events (Table S2) have significant overlaps with symptoms associated with histamine intolerance syndrome. 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 post vaccination, see Fig. 2 Pyrexia for MMR, VARCEL, and HPV4 vaccines.

Elevated histamine levels are consistent with many of the adverse events temporally associated with vaccinations (Table S1 and S2). Histamine involved in contraction of smooth muscles, secretion of gastric acid in the stomach, vasodilation, modulation of heart rate and contractility [12], body temperature [13]. Many histamine intolerance symptoms occur in combinations [14]. 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 [15]; perhaps exhibiting histamine intolerance. Patients with allergies have higher frequencies of vaccine adverse events [16]. Other patients have experienced increased histamine sensitivity post vaccination [17].

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) [18] 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.

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) [4]. 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 [19–22], cetirizine [23,24], and dexchlorpheniramine [23]. 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.

Summary

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 high incidence 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.

Declarations

Declaration of Competing 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.

Consent statement/Ethical approval

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Figures

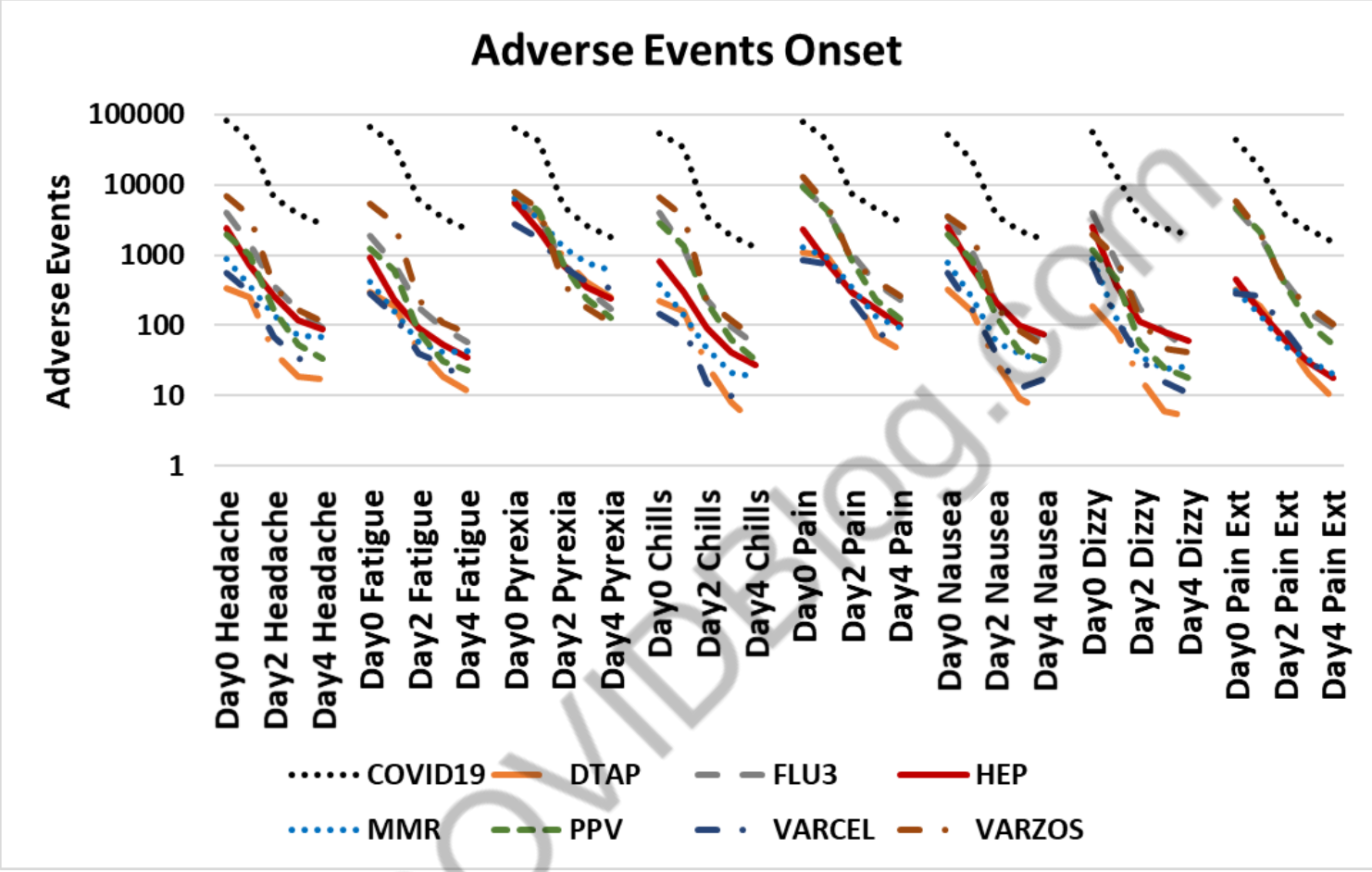

Figure 1

Most frequent vaccine adverse events (headache, pain, pyrexia, nausea, pruritus, vomiting, rash, erythema, and urticaria) days to onset (0, 1, 2, 3, & 4) reported in VAERS from 1990 until Nov. 12, 2021 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), Chickenpox varicella (VARCEL), and Tetanus, Diphtheria, and Pertussis (DTAP).

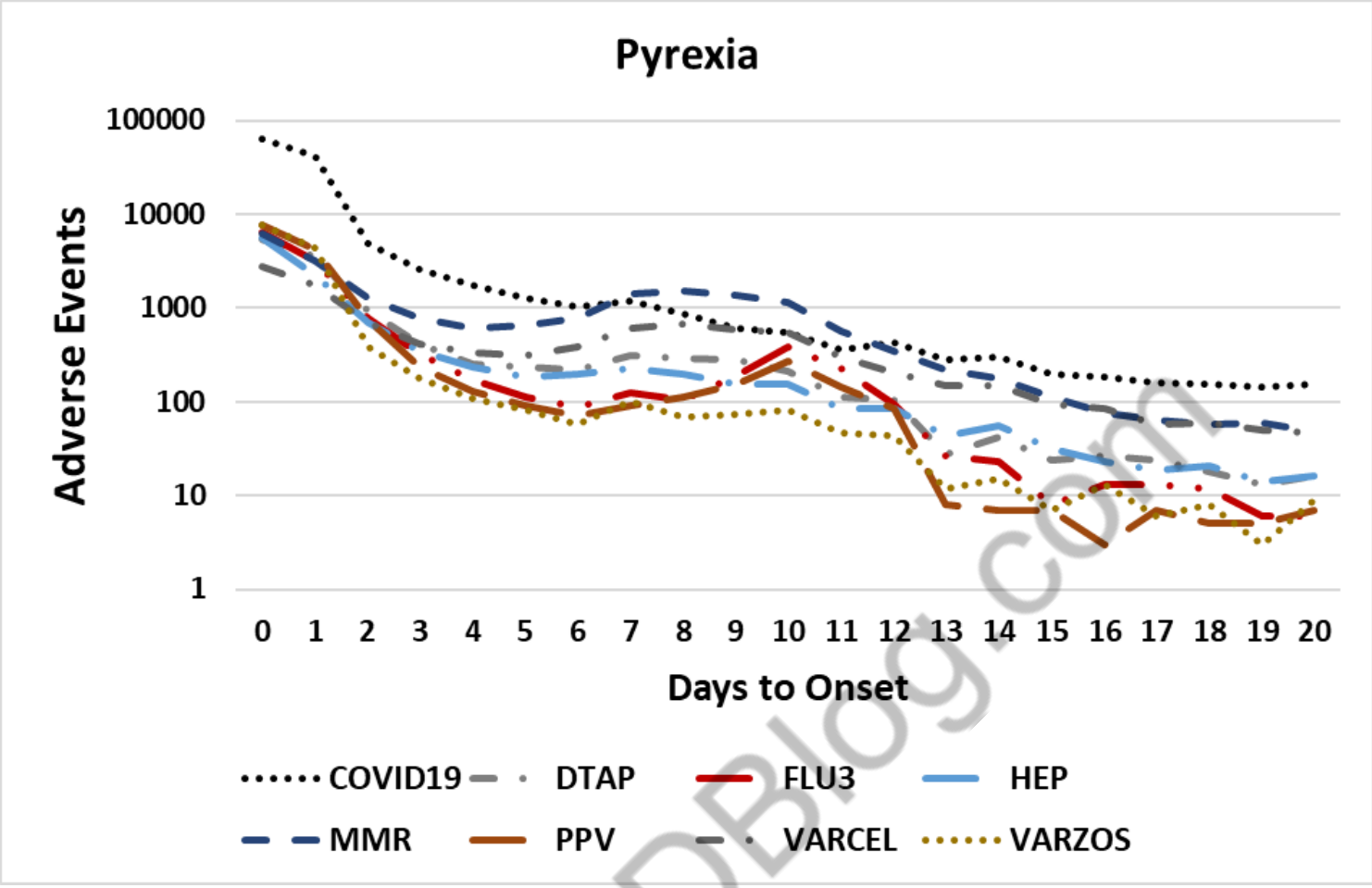

Figure 2

Pyrexia adverse events by days to onset reported in VAERS from 1990 until Nov. 12, 2021 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), Chickenpox varicella (VARCEL), Tetanus, and Diphtheria, and Pertussis (DTAP).

Supplementary Files

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- SupplementalData.docx
- TableS4.xlsx