https://doi.org/10.53964/jmbdd.2022003

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Journal of
Modern Biology and Drug Discovery

ISSN 2788-8088 (Online)

Open Access

Research Article

Pain Adverse Events, Bell's Palsy, and Guillain-Barré Syndrome Following Vaccination

Darrell O Ricke[1*]

[1]Molecular BioInsights Inc, Winchester, Massachusetts, USA

[*]**Correspondence to: Darrell O Ricke**, PhD, Computational Biologist, Molecular BioInsights Inc, 37 Pilgrim Drive, Winchester, Massachusetts 01890, USA; Email: doricke@molecularbioinsights.com

Received: June 15, 2022 **Accepted:** September 6, 2022 **Published:** October 26, 2022

Abstract

Objective: Some individuals (vaccinees) experience pain related adverse events following vaccinations. The majority of these pain related vaccination reactogenicity adverse events resolve within days. Rare adverse events like Bell's palsy and Guillain-Barré syndrome (GBS) have been associated with some vaccines. Herein, multiple working hypotheses are examined in the context of available characteristics of vaccinees and onset of these pain related adverse events post vaccination.

Methods: The Vaccine Adverse Event Reporting System database was data mined for pain associated vaccine adverse events data by vaccine, age, gender, dose, and onset post vaccination. Results for vaccines with the highest number of pain related adverse events were compared.

Results: For the pain related adverse events examined, the highest number of adverse events are reported within 1 day, roughly half this number the second day, and roughly a quarter this number by the third day. The day of onset for these pain related adverse events approximates a power of two decay pattern for the first three days. This same pattern is observed for all of the vaccines with the highest number of pain related adverse events. The consistency of these day of onset frequency patterns of examined adverse events following vaccinations for multiple unrelated vaccines enables the exclusion of specific vaccine components and excipients as specifically causative entities.

Conclusion: The observed onset occurrences of examined pain associated adverse events are consistent with likely etiology relationship with innate immune responses to vaccinations for multiple vaccines including severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) coronavirus disease 2019, influenza, and additional vaccines. Innate immune responses may be contributing to the initial etiology of Bell's palsy and GBS post SARS-CoV-2 mRNA and adenoviral vaccinations.

Keywords: vaccines, adverse events, innate immune response, histamine

Citation: Ricke DO. Pain Adverse Events, Bell's Palsy, and Guillain-Barré Syndrome Following Vaccination. *J Mod Biol Drug Discov*, 2022; 1: 3. DOI: 10.53964/jmbdd.2022003.

https://doi.org/10.53964/jmbdd.2022003

1 INTRODUCTION

Vaccines are designed to protect vaccinees (vaccinated individuals) against viral and bacterial infectious disease. Some vaccinees experience one or more adverse events 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]. Most reactogenicity adverse events resolve within days. Other adverse events have persistent symptoms that may last weeks, months, or longer. The etiology of these adverse events remains unknown.

Pain is a common element in a subset of the adverse events reported post vaccination. Some adverse events like "injection site pain" have obvious causal relationship with injection vaccinations. Other rare adverse events like Bell's palsy and Guillain-Barré syndrome (GBS) can occur with causality difficult to assess with frequencies close to background occurrence frequencies[2,3]. GBS is a rapid-onset muscle weakness caused by the immune system damaging the peripheral nervous system. GBS has been associated with influenza[4] and coronavirus disease 2019 (COVID-19) vaccinations[5]. GBS has been reported following Moderna[6-10], Pfizer BioNTech BNT162b2[11-19], Oxford AstraZeneca ChAdOx1 day[15,20-34], Johnson & Johnson/Janssen Ad26.CoV2.S[10,35-39], Sinopharm[33,34], and Sputnik V[34,40] COVID-19 vaccines. Many GBS patients are expected as sporadic cases and should not be considered causal[41]. For Pfizer BioNTech BNT162b2 mRNA vaccine, no increased incidence of GBS in a cohort of 3.9 million recipients was detected[42]. A review of GBS incidence in Vaccine Safety Datalink found an increased incidence following Ad.26.COV.2 but not BNT172b2 or mRNA-1273 vaccines[43]. An excess of GBS cases following AstraZeneca-Oxford ChAdOx1-S vaccination has also been identified[44]. An increased risk for GBS after first dose but not second dose of ChAdOx1 nCov-19 vaccination has been reported[45]. Warnings that rare GBS cases may link to J&J and AstraZeneca vaccines have been issued[46]. One etiology model for GBS following COVID-19 vaccination is autoimmune autoantibodies[5]; but, no serum anti-ganglioside antibodies were found in 15 of 17 patients tested[47]. Nearly all GBS patients after COVID-19 vaccinations also had facial weakness or paralysis[43].

Bell's palsy is a disease characterized by a rapid and unilateral onset of peripheral paresis (paralysis) of the seventh cranial nerve. Bell's palsy has been reported as an adverse event following immunization for influenza[48] and COVID-19 CoronaVac (Sinovac Biotech, Hong Kong)[49]. Bell's palsy cases have also been reported following Moderna mRNA-1273[50-54], Pfizer/BioNTech BNT162b2[55-59], Johnson & Johnson/Janssen Ad26.CoV2.S[60,61] COVID-19 vaccinations. Burrows et al.[55] report a patient with sequential contralateral facial nerve palsies following the first and second doses of Pfizer-BioNTech BNT162b2 COVID-19 vaccine. Other studies do not detect an enrichment signal for Bell's palsy or facial paralysis with COVID-19 vaccines[2,62]. Some cases of facial paralysis may be caused by reactivation of latent herpes simplex virus (HSV)[63] or varicella zoster virus (VSV) in a mechanism similar to Ramsey Hunt syndrome. An increased risk for Bell's palsy has been observed for concomitant administration of meningococcal conjugate vaccine with another vaccine[64]. A population based study reported 132 cases in 2.6 million vaccinees and 152 cases in 2.4 million vaccinees after first and second doses for BNT162b2 mRNA COVID-19 vaccine[65]. An excess of 1.112 Bell's palsy reports per 100,000 people who received 2 doses of BNT162b2 has been estimated[66]. Significantly fewer adverse neurological events were reported following BNT162b2 or mRNA-1273 vaccination compared to Ad26.CoV2.S[67].

The Vaccine Adverse Event Reporting System (VAERS) database tracks reported adverse events following vaccinations for the United States. Herein, VAERS is data mined for reports of pain associated adverse events. Multiple working hypotheses[68] are evaluated for pain related adverse events following vaccination leveraging these VAERS data mining results.

2 MATERIALS AND METHODS

The VAERS database (https://vaers.hhs.gov)[69] was data mined for pain associated vaccine adverse events data by vaccine name or vaccine type, age, gender, dose, and onset post vaccination. The downloaded data includes all VAERS reports from 1990 until May 13, 2022. A Ruby program named vaers_slice.rb[70] was used to tally selected reported vaccine adverse events by vaccine. The vaers_slice.rb program takes as input a list of one or more symptoms and outputs a summary of 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 VAERS adverse events by vaccine name were extracted for Abdominal pain, Abdominal pain lower, Abdominal pain upper, Arthralgia (pain in joint), Asthenia (abnormal physical weakness or lack of energy), Axillary pain, Back pain, Bell's palsy, Bone pain, Breast pain, Chest pain, Dysphagia (difficulty or discomfort in swallowing), Ear pain, Eye pain, Facial pain, Facial paralysis, Facial paresis, Guillain-Barre syndrome, Hemiparesis, Hypoaesthesia (partial or total loss of sensation), Injection site pain, Lymph node pain, Lymphadenopathy (enlarged lymph nodes), Musculoskeletal chest pain, Musculoskeletal pain, Musculoskeletal stiffness, Myalgia (muscle pain), Neck pain, Neuralgia, Oropharyngeal pain (mouth and pharynx pain), Pain, Pain in extremity, Pain in jaw, Pain of skin, Paraesthesia (an abnormal sensation, typically tingling or pricking), Renal pain, Spinal pain, and Swelling face were extracted. The

VAERS adverse events by vaccine type were extracted for Bell's palsy, Fatigue, Guillain-Barre syndrome, Headache, Miller Fisher syndrome, and Pyrexia. Microsoft Excel was used create figures.

3 RESULTS

The results include all reports of selected adverse events from 1990 until May 13, 2022. These adverse events share a non-random pattern of onset; Figures 1 and 2 illustrate this onset pattern for 16 pain associated adverse events in VAERS. This onset pattern is also present for GBS and Bell's palsy (Figures 3 and 4). These adverse events also exhibit excess reports of pain associated adverse events post vaccination for females compared to males for twenty vaccines (Figure 5). Some vaccinees experience more than one adverse event; correlations of reports of multiple pain associated adverse events are summarized in Table 1 for the most frequently reported adverse events for selected pain associated adverse events with all adverse events.

Both GBS and Bell's palsy are rare adverse events reported post vaccination. The three most commonly reported adverse events for many vaccines are headache, fatigue, and pyrexia (fever). The proportion of GBS and Bell's palsy reports are compared to these commonly reported adverse events as a comparison metric for unrelated vaccines. Proportional enrichment by vaccine for GBS and Bell's palsy are calculated for three reactogenicity adverse events (headache, fatigue, and pyrexia/fever) in Tables 2 and 3.

4 DISCUSSION

For all of the pain associated adverse events examined, the highest reports are within 24h of vaccination (day 0). For each pain associated adverse event, the number of reports for day 1 are roughly half that of day 0; likewise, the number of adverse events reported for day 2 are roughly half that of day 1 (Figures 1 and 2). Females report pain associated adverse events between two and three fold more frequently than males (Figure 5). Vaccinees sometimes report more than one pain associated adverse event (Table 1). For adverse events like injection site pain, this is consistent with expectations. Other adverse events reported by vaccinees are nausea, headache, pyrexia, fatigue, chills, and other. The consistency of the frequency patterns of these adverse events following vaccinations for multiple unrelated vaccines enables the exclusion of specific vaccine components and excipients as specifically causative entities; however, these components and excipients are likely the key determinants of the reactogenicity level associated with each vaccine. Possible working hypotheses of the causes of pain, paresis, or paralysis related adverse events following vaccination include innate immune responses, inflammation, latent virus reactivation, and autoimmune antibodies.

Vaccinations are designed to stimulate immune humoral (e.g., antibody) immune responses. Vaccines elicit immediate innate immune responses from vaccinees. These innate immune responses include the release of inflammatory molecules including chemokines, cytokines, interleukins, lymphokines, and monokines from immune cells[71-74]. The blood-nerve barrier is not as tight as the blood-brain barrier; it is possible for T cells and macrophages to leak in at inflamed tissue[75]. Vaccination-induced autoimmune antibody responses would require either primary humoral immune response or memory humoral immune responses; these humoral immune responses would peak roughly 7 to 10 days post vaccination. Hence, autoimmune antibody responses are unlikely associated with the majority of observed immediate onset reactogenicity adverse responses observed (Figures 1 and 2). Miller Fisher syndrome has some presentation overlaps with GBS[76]; like other examined adverse events, immediate onset signals also occur for Miller Fisher syndrome adverse events in VAERS associated with COVID-19 and influenza vaccines. Reactivation of latent viruses has been observed post Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) vaccinations[77,78]; clinical and molecular evidence of reactivation of latent viruses associated with the majority of the reported pain associated adverse events is currently lacking. While reactivation of latent viruses has occurred post vaccinations, the onset timing of 7 to 21 days[77,78] is inconsistent with observed immediate onset of pain associated adverse events. Consistent with the observed immediate onset of reported pain associated adverse events, innate immune response molecules are known to be associated with pain. These innate immune responses include the release of inflammatory molecules, including histamine, interleukin 1β (IL-1β), interleukin 6 (IL-6), monocyte chemoattractant protein, prostaglandin E_2 (PGE_2), tumor necrosis factor (TNF; formerly TNFα), etc.; these innate immune cells include macrophages, granulocytes including mast cells, T helper cells, and other immune cells[71,72,79,80]. PGE_2 is a well-known lipid mediator that contributes to inflammatory, neuropathic, and visceral pain, see[80]. IL-1β, IL-6, and TNF are involved in the process of pathological pain[72]. Histamine is known to be algesic (cause pain) to peripheral nervous system[74]. Type I interferons have been proposed as a potential mechanism linking COVID-19 mRNA vaccines to Bell's palsy[81].

4.1 GBS

VAERS reports for GBS illustrate a pattern of immediate onset timing associated with seven vaccines (Figure 3). The onset for the majority of the GBS reports are within 24h (day 0), roughly ½ this the next day (day 1), and roughly ¼ this the second day (Figure 3). This onset pattern is too rapid for molecular mimicry, epitope sharing, and autoimmune antibodies to be causative prior to day 7. Similar patterns shared by COVID-19, Influenza, Shingles Zoster, human papillomavirus, and Pneumococcal vaccines support innate immune responses as a major component of disease early etiology. Three of the highest frequencies reactogenicity adverse events shared across the examined pain related

https://doi.org/10.53964/jmbdd.2022003

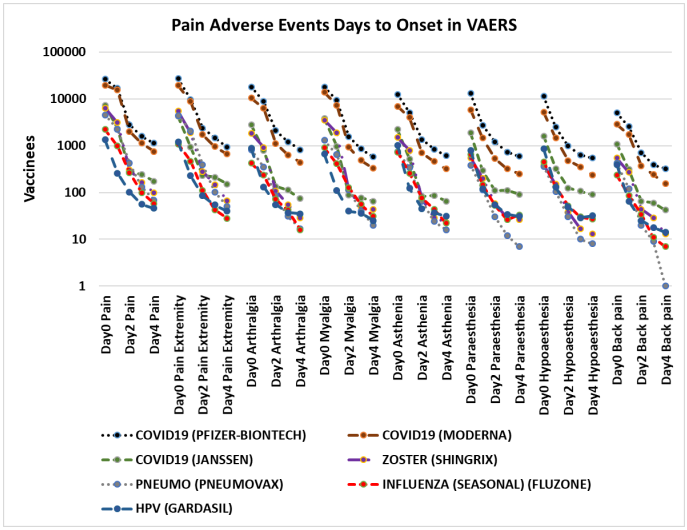

Figure 1. Pain adverse events days to onset in VAERS[69]. Vaccines plotted include COVID-19 (Pfizer-BioNTech, Moderna, and Janssen), Influenza (FLUZONE), Shingles Zoster (SHINGRIX), Human papillomavirus HPV (GARDASIL), and Pneumococcal PNEUMO (PREVNAR13) for adverse events pain, pain in extremity, arthralgia (joint pain), myalgia (muscle pain), asthenia (weakness), paraesthesia (tingling sensation), and back pain.

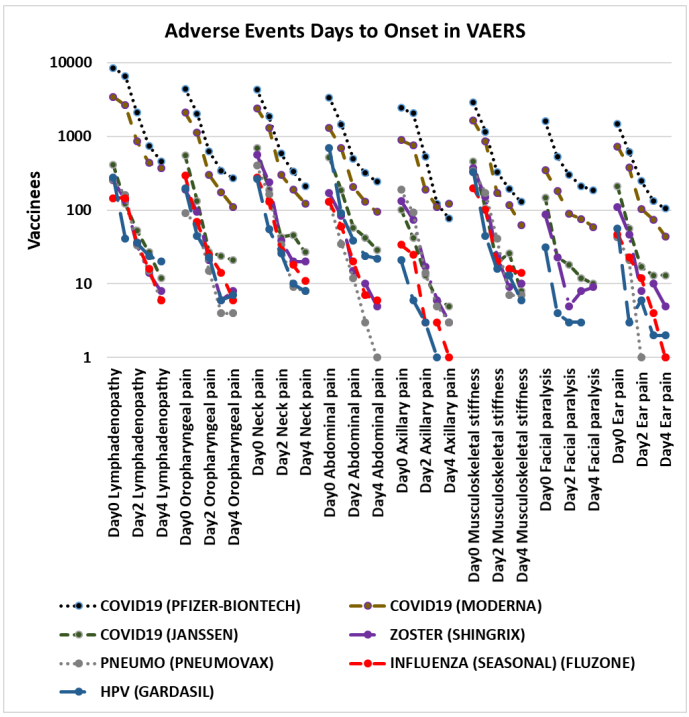

Figure 2. Additional pain adverse events days to onset in VAERS[69]. Vaccines plotted include COVID-19 (Pfizer-BioNTech, Moderna, and Janssen), Influenza (seasonal) (FLUZONE), Shingles Zoster (SHINGRIX), Human papillomavirus HPV (GARDASIL), and Pneumococcal PNEUMO (PNEUMOVAX) for adverse events abdominal pain, axillary pain, ear pain, facial paralysis, lymphadenopathy, musculoskeletal stiffness, neck pain, and oropharyngeal pain (mouth and pharynx pain).

adverse events are headache, fatigue, and pyrexia (fever). Examining the frequencies of GBS in proportion to these reactogenicity adverse events illustrates that the frequency of GBS is highest for Influenza vaccines with a lower frequency for COVID-19 vaccines (Table 2). The general consistency of occurrence frequencies across all of the examined unrelated vaccines in Table 2 further supports the hypothesis that reactogenicity responses to vaccination in general are coupled to the frequency of GBS following vaccinations.

Clinically, most GBS patients following COVID-19 vaccination showed typical demyelination neuropathy with albumin-cytological dissociation[82]; the timing suggests that demyelination neuropathy and albumin-cytological dissociation might be subsequent events in the disease etiology for patients with immediate onset adverse events. The immediate onset pattern of GBS following vaccination is different from the observed pattern for Zoster vaccines[83]; their reported Zoster vaccine onset pattern is consistent with

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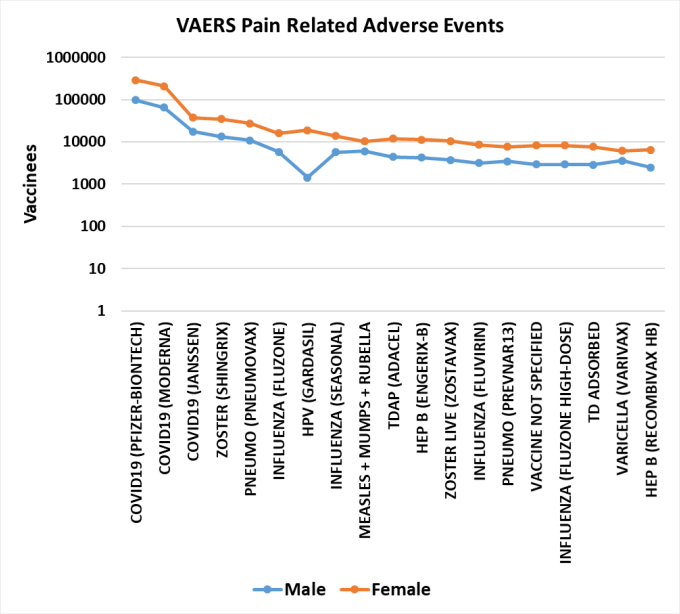

Figure 3. GBS days to onset in VAERS[69]. Vaccines plotted include COVID-19 (Pfizer-BioNTech, Moderna, and Janssen), Influenza, Shingles Zoster (SHINGRIX), Human papillomavirus HPV (GARDASIL), and Pneumococcal PNEUMO (PREVNAR13).

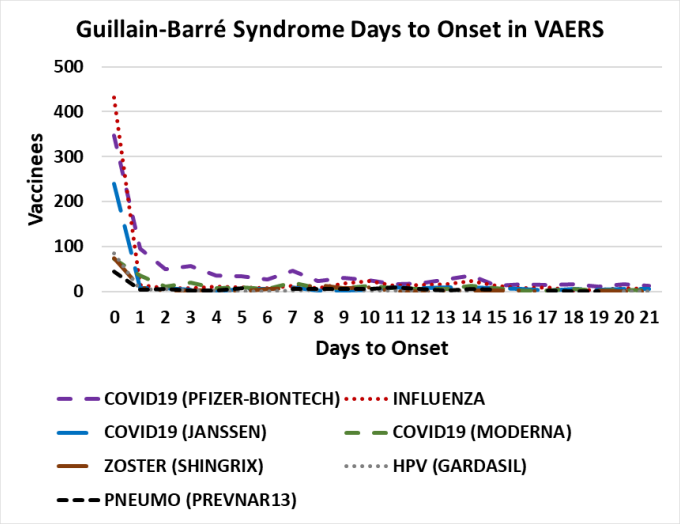

Figure 4. Bell's palsy days to onset in VAERS[69]. Vaccines plotted include COVID-19 (Pfizer-BioNTech, Moderna, and Janssen) and Shingles Zoster (SHINGRIX, ZOSTAVAX, and no brand name).

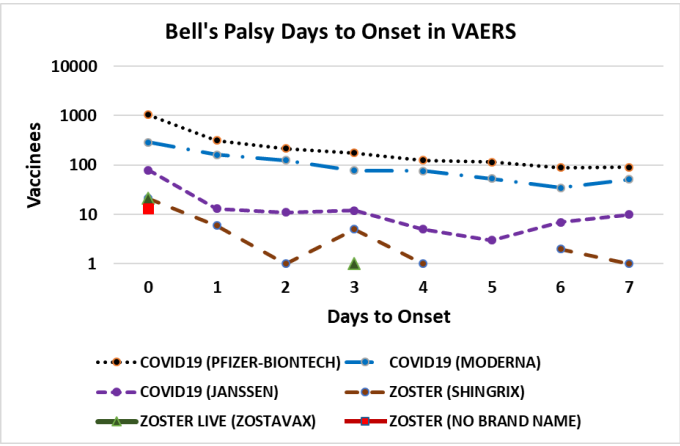

Figure 5. Pain adverse events by gender in VAERS[69] from 1990 to May 13, 2022.

Table 1. Co-occurrences of Highest Frequency Vaccine Associated Pain Adverse Events from VAERS[69] (1990 to May 13, 2022)

Adverse Event	Arthralgia	Asthenia	Hypoaesthesia	Myalgia	Pain	Pain in Extremity	Paraesthesia
Arthralgia		8,315	4,195	26,645	19,818	18,744	4,982
Asthenia	8,315		3,895	10,336	13,827	7,990	4,674
Hypoaesthesia	4,195	3,895		2,731	6,556	8,138	16,237
Myalgia	26,645	10,336	2,731		14,898	12,787	3,975
Pain	19,818	13,827	6,556	14,898		28,608	7,683
Pain in extremity	18,744	7,990	8,138	12,787	28,608		8,002
Paraesthesia	4,982	4,674	16,237	3,975	7,683	8,002	

Table 2. Proportional GBS Compared to Reactogenicity Adverse Events Headache, Fatigue, and Pyrexia (Fever); the Proportions were Normalized to Highest Observed Proportion (e.g., FLUX).

Vaccine	Headache	Guillain-Barré Syndrome	Normalized Proportion	Fatigue	Normalized proportion	Pyrexia	Normalized Proportion
FLUX	2,970	779	92.1%	1,797	100.0%	5,249	100.0%
FLU3	7,118	1,386	68.4%	3,576	89.4%	12,757	73.2%
FLU (H1N1)	966	139	50.5%	458	70.0%	1,065	87.9%
FLUX (H1N1)	421	65	54.2%	228	65.8%	581	75.4%
HEPAB	537	84	54.9%	424	45.7%	636	89.0%
FLUC4	343	48	49.1%	271	40.9%	359	90.1%
HPV2	899	61	23.8%	394	35.7%	513	80.1%
HIBV	165	47	100.0%	342	31.7%	18,576	1.7%
FLUN3	570	58	35.7%	245	54.6%	993	39.4%
FLU4	2,716	297	38.4%	1,794	38.2%	3,956	50.6%
YF	640	50	27.4%	284	40.6%	871	38.7%
PNC13	872	137	55.2%	1,079	29.3%	7,916	11.7%
IPV	679	81	41.9%	474	39.4%	8,900	6.1%
TYP	1,266	77	21.4%	551	32.2%	1,592	32.6%
TDAP	4,194	267	22.3%	2,178	28.3%	5,935	30.3%
TD	1,595	94	20.7%	518	41.9%	3,596	17.6%
MNQ	2,802	132	16.5%	1,007	30.2%	2,957	30.1%
HEPA	1,764	131	26.1%	1,092	27.7%	5,691	15.5%
HPV4	5,049	154	10.7%	3,024	11.7%	2,681	38.7%
HEP	4,351	219	17.7%	1,805	28.0%	11,117	13.3%
MMR	2,336	133	20.0%	1,185	25.9%	21,749	4.1%
PPV	3,543	199	19.7%	2,215	20.7%	14,372	9.3%
DTAP	776	52	23.5%	687	17.5%	12,832	2.7%
UNK	2,750	78	10.0%	2,356	7.6%	3,450	15.2%
VARCEL	1,562	55	12.4%	779	16.3%	11,961	3.1%
VARZOS	12,418	270	7.6%	9,752	6.4%	14,461	12.6%
COVID-19	182,521	2,001	3.8%	154,437	3.0%	153,429	8.8%

Notes: The following vaccines with at least 40 reports of GBS in VAERS[69] were included: COVID-19, DTAP (diphtheria, pertussis, & tetanus), Influenza: FLU(H1N1), FLU3 (trivalent), FLU4 (quadivalent), FLUC4 (Flucelvax quadrivalent), FLUN3 (Flumist), FLUX (Influenza (seasonal) unknown manufacturer), FLUX(H1N1), HEP (hepatitis B), HEPA (hepatitis A), HEPAB (hepatitis B), HIBV (haemophilus), HPV2 (human papillomavirus), HPV4 (human papillomavirus type 4), IPV (inactivated poliovirus), MMR (measles, mumps, & rubella), MNQ (Menigococcal), PNC13 (Pneumococcal conjugate), PPV (Pneumococcal polysaccharide), TD (tetanus & diphtheria), TDAP (diphtheria, pertussis, & tetanus), TYP (typhoid), UNK (unknown), VARCEL (chickenpox Varicella), VARZOS (Herpes Zoster), and YF (yellow fever). Enrichment was normalized to the vaccine (FLUX) with the highest ratio of adverse events: GBS/reactogenicity adverse event for headache, fatigue, and pyrexia.

Table 3. Proportional Bell's Palsy Compared to Reactogenicity Adverse Events Headache, Fatigue, and Pyrexia (Fever); the Proportions were Normalized to the Highest Observed Proportion (e.g., COVID-19).

Vaccine	Headache	Bell's Palsy	Enrichment	Fatigue	Enrichment	Pyrexia	Enrichment
COVID-19	182,521	5,711	100.0%	154,437	100.0%	153,429	100.0%
UNK	2,750	49	56.9%	2,356	56.2%	3,450	38.2%
FLU4	2,716	40	47.1%	1,794	60.3%	3,956	27.2%
VARZOS	12,418	94	24.2%	9,752	26.1%	14,461	17.5%

Notes: The following vaccines with at least 40 reports of Bell's palsy were included: COVID-19, FLU4 (influenza quadivalent), UNK (unknown), and VARZOS (Herpes Zoster). Enrichment was normalized to the vaccine (COVID-19) with the highest ratio of adverse events: Bell's palsy/reactogenicity adverse event for headache, fatigue, and pyrexia.

the development of autoimmune antibodies in contrast to the immediate onset Zoster vaccine records in VAERS (Figure 3). Note that autoantibodies are detected for some GBS patients post COVID-19 vaccination[14,84]; onset of GBS for multiple patients is consistent with the development of autoantibodies[9,13-15,19,22-31].

In one report, nearly all GBS patients after COVID-19 vaccinations also had facial weakness or paralysis[43]. Another report included nine GBS patients with rare subtype known as Bilateral Facial Palsy with paresthesias (BFP) with five vaccinated with Sputnick V and four with ChAdOx1[40]. Of these nine patients, four tested positive with with ganglioside antibody panel (2: anti-GM1, antig-GD1a, and anti-sulfatide) [40].

4.2 Bell's Palsy

The frequency of Bell's palsy is highest for COVID-19 and lower for Zoster and Influenza vaccines (Table 3 and Figure 4). The frequencies for non-COVID-19 vaccines is low for vaccines but with enrichment for day 0 onsets for a few vaccines. Onset of Bell's palsy within 5h of BNT162b2 vaccination[55] and 12h after mRNA-1273 vaccination[51] together with VAERS day 0 onset reports can be leveraged to limit candidate etiology possibilities. The association pattern for immediate onset is consistent with innate immune responses for very high reactogenicity vaccines (COVID-19 mRNA and adenovirus) or concomitant administration of vaccines. The working hypothesis for live Zoster vaccines reactivating latent Herpes family viruses is also consistent with current models for Bell's palsy[72].

4.3 Persistent Pain Models

Candidate models for persistent pain include autoimmune antibodies, nerve damage and/or demyelination, reactivated latent viruses, immune cells infiltration at blood-never barrier during inflammation (albumin-cytological dissociation seen in GBS), innate immune cells with feedback loops with nerve cells, mast cell and eosinophil paired couplets, and ongoing expression of vaccine protein[85] by innate immune cells. Immediate onset adverse event lymphadenopathy (Figure 2) is consistent with ongoing expression of vaccine protein by innate immune cells. Mast cells and eosinophils are known to form bidirectional interactions resulting in a hyperactivated state, reviewed[86]. Additional research is needed to resolve the pathogenesis model(s) of persistent pain adverse events following vaccinations. Immediate onset of pain related adverse events might suggest that early interventions might lessen the severity of symptoms and possibly even decrease the frequencies of occurrences. Cellular feedback loops are possible between nerve cells and mast cells driving neurogenic inflammation and nociceptive pain[87].

4.4 Histamine

Pain related inflammatory molecules released by innate immune responses include histamine. Histamine is known to be associated with peripheral nerve pain[74,88]. Elevated histamine levels are predicted as drivers of cardiac adverse events including myocarditis and pericarditis[70] and menstrual adverse events[89]. Ongoing vaccine expression in innate immune cells, lasting months[85], may drive localized release of inflammatory molecules including histamine.

4.5 Exploratory Treatment Candidates

Dampening histamine responses from innate immune mast cells may reduce the population frequency and severity of some pain adverse events following vaccinations. Antihistamine treatments exhibiting efficacy in treating COVID-19 patients may target possible granulocytes and mast cells associated with vaccine responses. Candidate treatments for evaluation include high dose famotidine[90-92], cetirizine[93,94], and dexchlorpheniramine[93]. Oral treatment with diamine oxidase may also be beneficial. Alternatively, if mast cell and eosinophil couplets are involved, targeting them with anti-IL-5 (mepolizumab)[95] may be beneficial. 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 pain adverse events.

5 CONCLUSION

Data mining VAERS for pain associated adverse events illustrates likely etiology of innate immune responses driving pain related adverse events post vaccination including rare reports of GBS and Bell's palsy. The consistency of the frequency patterns of examined adverse

events following vaccinations for multiple unrelated vaccines enables the exclusion of specific vaccine components and excipients as specifically causative entities. Identification of likely role of innate immune responses in the etiology of pain related adverse events post vaccination suggest possible candidate treatments for evaluation in clinical studies. Innate immune responses may be contributing to the initial etiology of rare cases of GBS and Bell's palsy post SARS-CoV-2 mRNA and adenoviral vaccinations.

Acknowledgements
The authors thank Nora Smith for useful discussions.

Conflicts of Interest
The author declared no conflict of interest.

Author Contribution
The author contributed to the manuscript and approved the final version.

Supplementary Data and Availability of Data
Data files summarizing the pain related adverse events summarized from VAERS are available from the Corresponding Author (Dr. Darrell O. Ricke) upon a reasonable request whenever possible.

Abbreviation List
COVID-19, Coronavirus disease 2019
GBS, Guillain-Barré syndrome
IL-1β, Interleukin 1β
IL-6, Interleukin 6
PGE_2, Prostaglandin E_2
SARS-CoV-2, Severe acute respiratory syndrome coronavirus 2
TNF, Tumor necrosis factor
VAERS, Vaccine Adverse Event Reporting System

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