Pain adverse events, Bell's palsy, and Guillain-Barré syndrome Following Vaccination

Darrell O. Ricke (doricke@gmail.com)
https://orcid.org/0000-0002-2842-2809

Research Article

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Abstract

Some individuals (vaccinees) experience pain related adverse events following vaccinations. The majority of 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 datamining results of the Vaccine Adverse Event System (VAERS) database. 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 SARS-CoV-2 COVID-19, 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.

Introduction

Vaccines are designed to protect vaccinees 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. Recently, it was proposed that the majority of the reactogenicity adverse events are caused by innate immune response to vaccination releasing inflammatory molecules including histamine [2].

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 [3, 4]. GBS has been associated with influenza [5] and COVID-19 vaccinations [6]. One etiology model for GBS following COVID-19 vaccination is autoimmune autoantibodies [6]; but, no serum anti-ganglioside antibodies were found in 15 of 17 patients tested [7]. Nearly all GBS patients after COVID-19 vaccinations also had facial weakness or paralysis [8].

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 [9] and COVID-19 CoronaVac (Sinovac Biotech, Hong Kong) [10]. Burrows et al. [11] 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 [3, 12]. Some cases of facial paralysis may be caused by reactivation of latent herpes simplex virus (HSV) [13] 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 [14].

The Vaccine Adverse Event 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[15] are evaluated for pain related adverse events following vaccination leveraging these VAERS data mining results.

Methods

The Vaccine Adverse Event Reporting System (VAERS) database [16] was datamined 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 [17] 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 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 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.

Results

Figures 1 and 2 illustrate day of onset for 16 pain associated adverse events in VAERS. Figure 3 illustrates excess reports of pain associated adverse events post vaccination for females compared to males for twenty vaccines. Immediate onset of GBS and Bell’s palsy are illustrated in Figs. 4 and 5. Summarized data for each VAERS pain associated adverse event are included in the supplemental data tables for days 0 to 120 for each vaccine with associated adverse event. Correlations of multiple pain associated adverse events are summarized in Table 1 for the most frequently reported adverse events and Table S1 for selected pain associated adverse events with all adverse events. Each vaers_slice.rb report in the Supplemental data includes correlations with all other reported adverse events; the top 20 for selected pain adverse events are illustrated in Supplemental Table S2. 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.

Table 1
Co-occurrences of highest frequency vaccine associated pain adverse events from VAERS (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 Guillain-Barré syndrome enrichment compared to reactogenicity adverse events headache, fatigue, and pyrexia (fever). The following vaccines with at least 50 reports of Guillain-Barré syndrome were included: COVID19, DTAP (diphtheria, pertussis, & tetanus), Influenza: FLU(H1N1), FLU3, FLU4 (quadivalent), FLUN3, FLUX, FLUX(H1N1), HEP (hepatitis B), HEPA (hepatitis A), HEPAB (hepatitis B), 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: Guillain-Barré syndrome /reactogenicity adverse event for headache, fatigue, and pyrexia.

Vaccine	Headache	Guillain-Barré syndrome	Enrichment	Fatigue	Enrichment	Pyrexia	Enrichment
FLUX	29,755	779	100.0%	1,797	100.0%	5,249	100.0%
FLUX(H1N1)	2,681	65	92.6%	228	65.8%	581	75.4%
FLU3	97,513	1,386	54.3%	3,576	89.4%	12,757	73.2%
FLU(H1N1)	9,179	139	57.8%	458	70.0%	1,065	87.9%
HEPAB	5,707	84	56.2%	424	45.7%	636	89.0%
HPV2	4,798	61	48.6%	394	35.7%	513	80.1%
FLUN3	6,443	58	34.4%	245	54.6%	993	39.4%
YF	4,239	50	45.1%	284	40.6%	871	38.7%
FLU4	37,252	297	30.5%	1,794	38.2%	3,956	50.6%
TYP	9,923	77	29.6%	551	32.2%	1,592	32.6%
TDAP	42,404	267	24.1%	2,178	28.3%	5,935	30.3%
MNQ	26,174	132	19.3%	1,007	30.2%	2,957	30.1%
TD	18,558	94	19.3%	518	41.9%	3,596	17.6%
HPV4	46,341	154	12.7%	3,024	11.7%	2,681	38.7%
HEPA	41,067	131	12.2%	1,092	27.7%	5,691	15.5%
PNC13	38,876	137	13.5%	1,079	29.3%	7,916	11.7%
HEP	71,720	219	11.7%	1,805	28.0%	11,117	13.3%
IPV	43,249	81	7.2%	474	39.4%	8,900	6.1%
PPV	68,903	199	11.0%	2,215	20.7%	14,372	9.3%
MMR	86,556	133	5.9%	1,185	25.9%	21,749	4.1%
UNK	23,789	78	12.5%	2,356	7.6%	3,450	15.2%
VARZOS	105,019	270	9.8%	9,752	6.4%	14,461	12.6%
DTAP	62,560	52	3.2%	687	17.5%	12,832	2.7%

Vaccine	Headache	Guillain-Barré syndrome	Enrichment	Fatigue	Enrichment	Pyrexia	Enrichment
VARCEL	82,205	55	2.6%	779	16.3%	11,961	3.1%
COVID19	1,116,854	2,001	6.8%	154,437	3.0%	153,429	8.8%

Table 3

Bell's palsy enrichment compared to reactogenicity adverse events headache, fatigue, and pyrexia (fever). The following vaccines with at least 50 reports of Guillain-Barré syndrome were included: COVID19, FLU4 (influenza quadivalent), UNK (unknown), and VARZOS (Herpes Zoster). Enrichment was normalized to the vaccine (COVID19) with the highest ratio of adverse events: Bell's palsy/reactogenicity adverse event for headache, fatigue, and pyrexia.

Vaccine	Headache	Bell's palsy	Enrichment	Fatigue	Enrichment	Pyrexia	Enrichment
COVID19	1,116,854	5,711	100.0%	154,437	100.0%	153,429	100.0%
UNK	23,789	49	40.3%	2,356	56.2%	3,450	38.2%
FLU4	37,252	40	21.0%	1,794	60.3%	3,956	27.2%
VARZOS	105,019	94	17.5%	9,752	26.1%	14,461	17.5%

Discussion

For all of the pain associated adverse events examined, the highest reports are within 24 hours 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 (Figs. 1 and 2). Females report pain associated adverse events between two and three fold more frequently than males (Fig. 3). 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 onset of pain associated adverse events coincides with the same onset as these reactogenicity adverse events [2]. 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 determinates 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 [18–21]. 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 tissues [22]. 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 (Figs. 1, 2, and supplemental data). Miller Fisher syndrome has some presentation overlaps with GBS

[23]; 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 (supplemental data table V_Miller_Fisher). Reactivation of latent viruses has been observed post SARS-CoV-2 vaccinations [24, 25]; clinical and molecular evidence of reactivation of latent viruses associated with the majority of the reported pain associated adverse events is current lacking. While reactivation of latent viruses has occurred post vaccinations, the onset timing of 7 to 21 days [24, 25] 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 (MCP-1), prostaglandin E_2 (PGE_2), tumor necrosis factor (TNF; formerly TNFα), etc. from macrophages, granulocytes including mast cells, T helper cells, and other immune cells [18, 19, 26, 27]. PGE_2 is a well-known lipid mediator that contributes to inflammatory, neuropathic, and visceral pain, see [27]. IL-1β, IL-6, and TNF are involved in the process of pathological pain [19]. Elevated histamine levels has been proposed to be causative for the majority of reactogenicity adverse events [2]. Histamine is known to be algesic (cause pain) to peripheral nervous system [21]. Type I interferons have been proposed as a potential mechanism linking COVID-19 mRNA vaccines to Bell's palsy [28].

Guillain-Barré Syndrome (GBS)

VAERS reports for GBS illustrate a pattern of immediate onset timing associated with seven vaccines (Figure 4). The onset for the majority of the GBS reports are within 24 hours (day 0), roughly ½ this the next day (day 1), and roughly ¼ this the second day (Figure 4 and supplemental data table: V_Guillain_Barre). 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 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 [29]; 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 [30]; their reported Zoster vaccine onset pattern is consistent with the development of autoimmune antibodies in contrast to the immediate onset Zoster vaccine records in VAERS (Figure 4).

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 5). The frequencies for non-COVID-19 vaccines is low for vaccines but with enrichment for day 0 onsets for a few vaccines (supplemental data V_Bells_palsy). 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 [19].

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[31] by innate immune cells. Immediate onset adverse event lymphadenopathy (Figure 3) 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 [32]. 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 lesson 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 [33].

Histamine

Pain related inflammatory molecules released by innate immune responses include histamine. Histamine is known to be associated with peripheral nerve pain [21,34]. Elevated histamine levels are predicted as drivers of most post vaccination adverse events including reactogenicity adverse events [2], cardiac adverse events including myocarditis and pericarditis [17], and menstrual adverse events [2]. Ongoing vaccine expression in innate immune cells, lasting months, [31] may drive localized releases of inflammatory molecules including histamine.

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 are may target possible granulocytes and mast cells associated with vaccine responses. Candidate treatments for evaluation include high dose famotidine [35–38], cetirizine [39,40], and dexchlorpheniramine [39]. 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) [41] 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.

Summary

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 Guillain-Barré syndrome and Bell's palsy. 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.

Abbreviations

COVID-19	Coronavirus Disease 2019
GBS	Guillain-Barré syndrome
IL-1β	Interleukin 1β
IL-6	Interleukin 6
MCP-1	Monocyte Chemoattractant Protein
PGE_2	Prostaglandin E_2
SARS-CoV-2	Severe Acute Respiratory Syndrome Coronavirus 2
TNF	Tumor Necrosis Factor
VAERS	Vaccine Adverse Event System

Declarations

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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.

Consent statement/ethical approval

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Figures

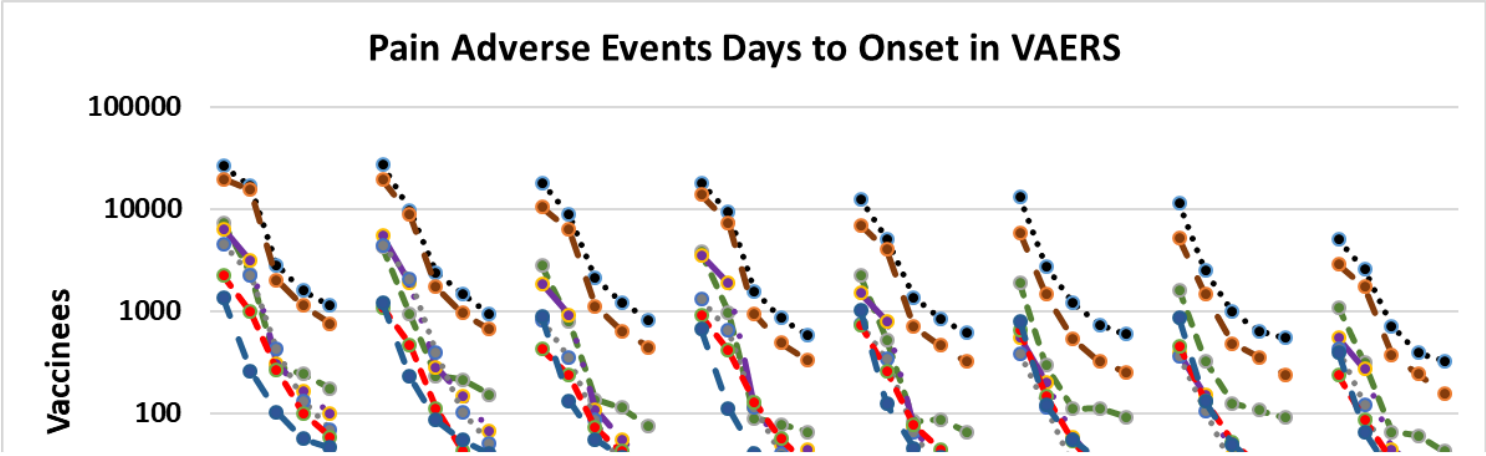

Figure 1

Pain adverse events days to onset in VAERS. 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.

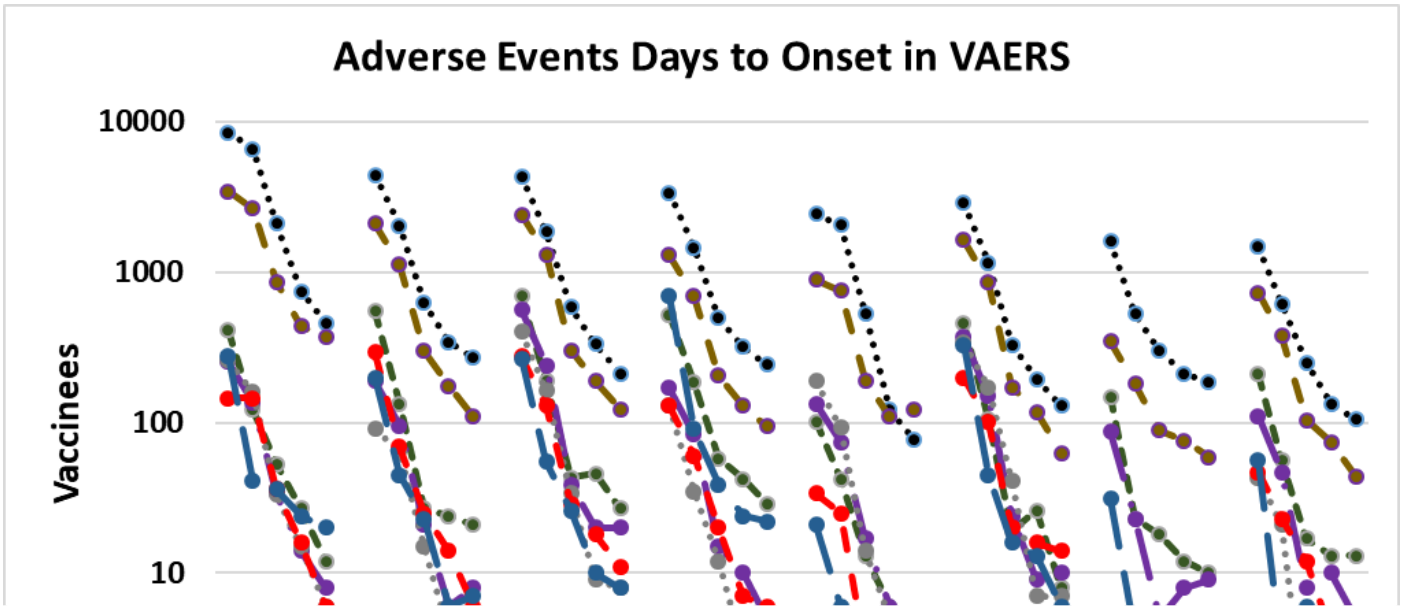

Figure 2

Additional pain adverse events days to onset in VAERS. 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).

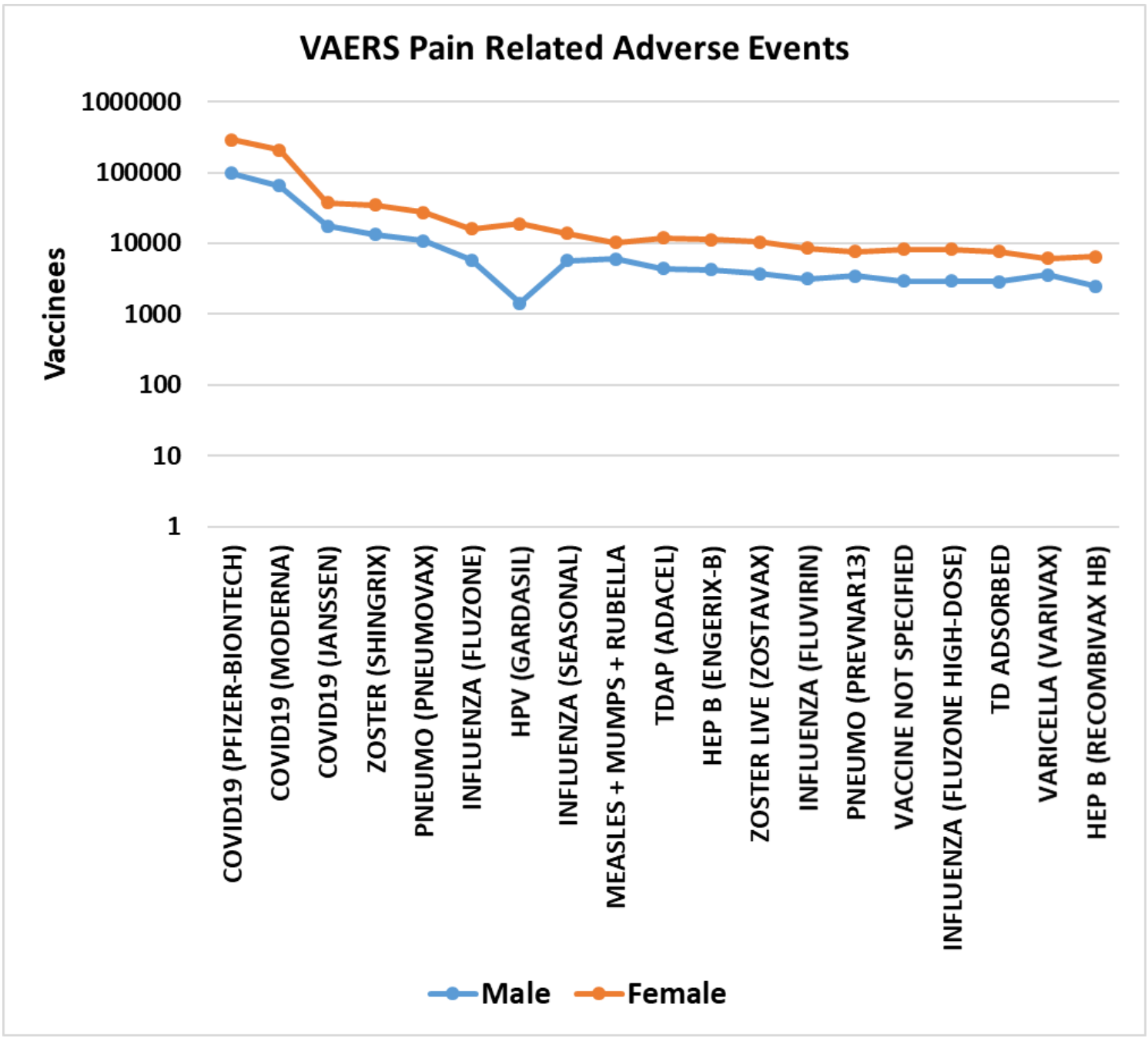

Figure 3

Pain adverse events by gender in VAERS from1990 to May 13, 2022.

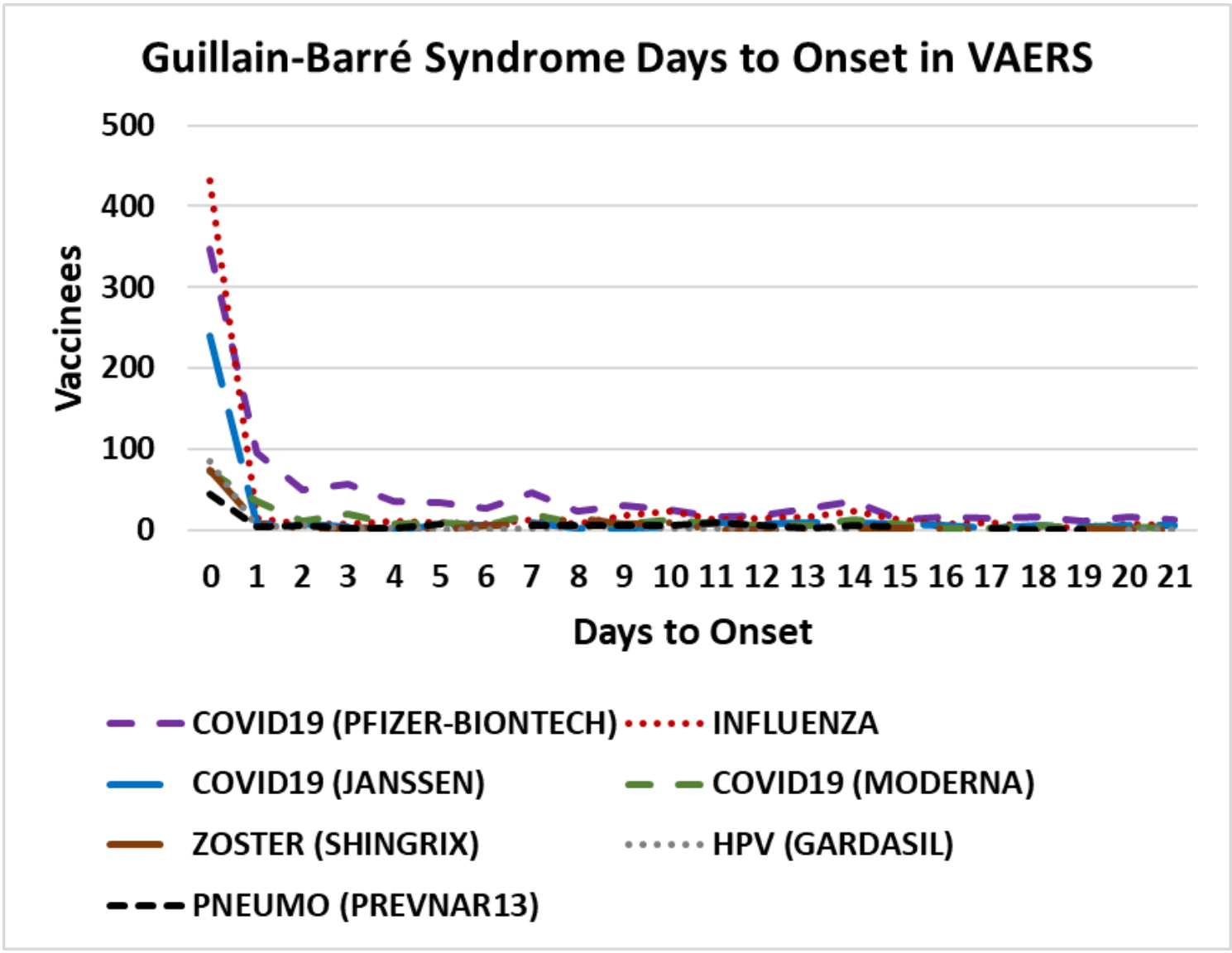

Figure 4

Guillain-Barré syndrome days to onset in VAERS. Vaccines plotted include COVID-19 (Pfizer-BioNTech, Moderna, and Janssen), Influenza, Shingles Zoster (SHINGRIX), Human papillomavirus HPV (GARDASIL), and Pneumococcal PNEUMO (PREVNAR13).

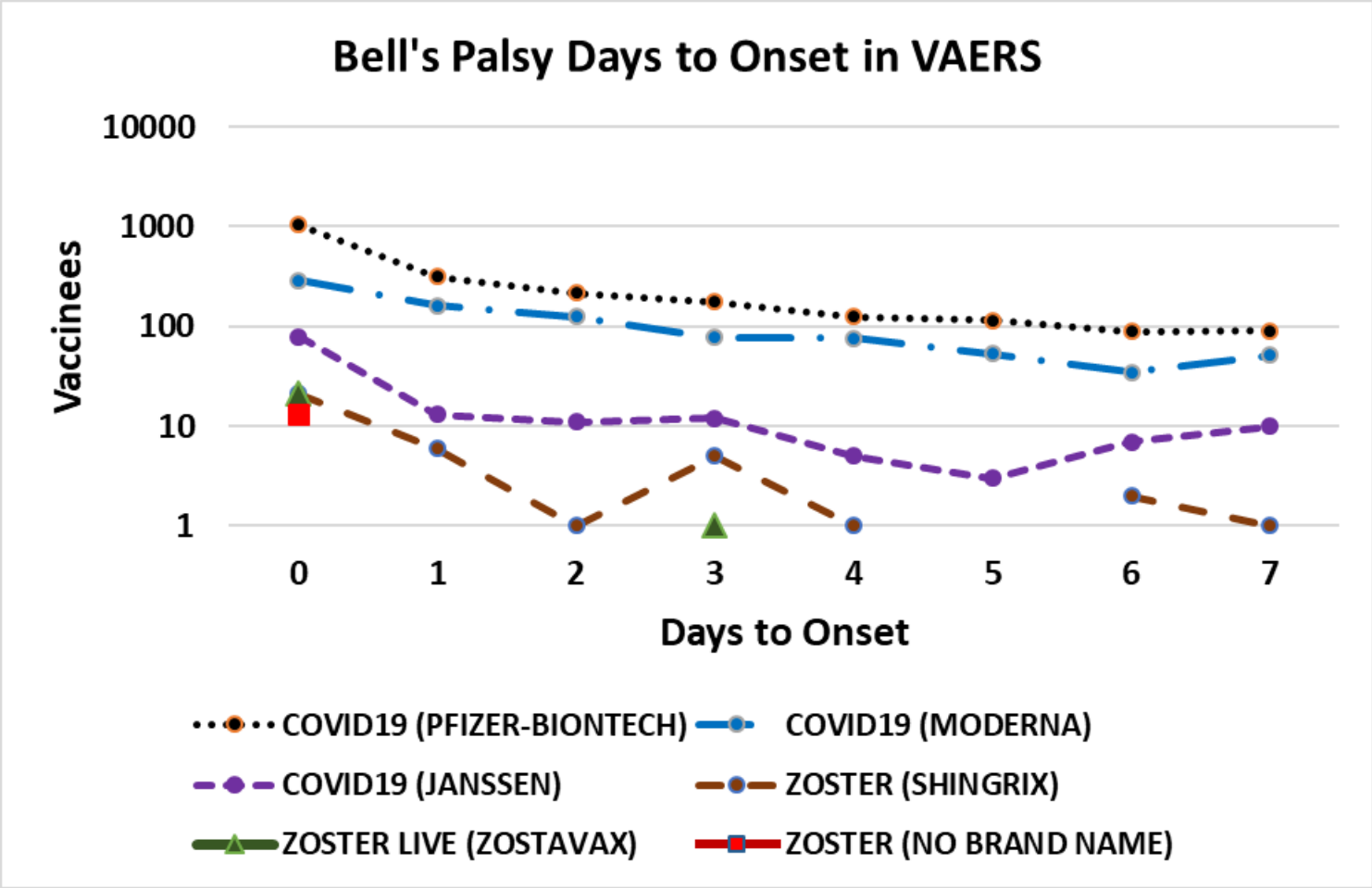

Figure 5

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

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- Pain1.xlsx
- Pain2.xlsx
- VaccineSummaries.xlsx