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Immediate onset signatures of autoimmune diseases after vaccination

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Abstract

Severe adverse events, including autoimmune diseases, have been noted in some individuals following vaccination. It is still unknown whether a subset of these autoimmune disease adverse events (ADAE) is triggered by the immunization and is not background chance occurrences. Only a small fraction of adverse events experienced by vaccinees has been reported to the Vaccine Adverse Event Reporting System (VAERS) database. In this study, ADAEs within VAERS are examined. The frequency of autoimmune disease adverse reactions reported immediately following vaccination was compared to the background population adverse event frequency. The frequency of immediate-onset autoimmune diseases, extracted from VAERS, arisen after vaccination was found to exceed the expected background occurrences. Vaccinees who receive a second COVID-19 mRNA vaccination dose 3 weeks after the first dose appear to experience an increased number of ADAE. Furthermore, human papillomavirus (HPV), hepatitis A, and hepatitis B vaccines exhibit distinctive patterns of associations with autoimmune diseases. The potential role of vaccine aluminum adjuvant, included in these vaccines, cannot be ruled out as contributing to ADAE. VAERS data illustrate immediate onset correlations for multiple autoimmune diseases across various vaccines. Autoimmune diseases immediate temporal onset associations that occur following COVID-19 mRNA and adenoviral vaccinations are predicted to occur with similar frequencies for all mRNA and adenoviral vaccines and therapeutics. Taken together, removal of aluminum adjuvants from HPV, hepatitis A, and hepatitis B vaccines, among others, should be considered in the effort to reduce the occurrence of immediate-onset autoimmune diseases.

Keywords: Autoimmune diseases; Vaccines; COVID-19 vaccines; Human papillomavirus vaccines; Hepatitis vaccines; Aluminum adjuvant

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1. Introduction

Adverse events following immunization (AEFI) occur with many vaccines. These events encompass adverse events caused by immunization as well as unrelated background occurrences. The likelihood of reporting them as AEFI decreases as the time between immunization and the onset of autoimmune disease increases, creating a time bias in reporting, with a decreasing pattern over time. Following immunization, autoimmune diseases occur at background population frequencies unrelated to the immunization itself. The number of background AEFIs should ideally be proportional to autoimmune disease population frequencies for each vaccine dose administered to vaccinees. This

can be calculated as the background rate multiplied by the number of days examined, with adjustments for reporting bias. The United States Vaccine Adverse Event Reporting System (VAERS) database collects AEFI reports[1], which represent a sample (i.e., subset) of the actual number of adverse events estimated by the underreporting factor (URF). Deviations from background population patterns in the VAERS data serve as indicators of relationships between immunization and the adverse event(s).

Possible associations between autoimmune diseases and immunization have been reported in several studies[2-4]. For example, Guillain-Barré syndrome (GBS) has been linked to influenza vaccination[5-7], narcolepsy to the 2009 H1N1 influenza vaccine[8], and immune thrombocytopenia (ITP) to various vaccinations[9-11]. In addition, multiple autoimmune diseases have been reported following COVID-19 vaccination[12-21]. Some researchers have explored the concept of autoimmune (auto-inflammatory) syndrome induced by adjuvants (ASIA), implicating adjuvants such as aluminum[22] and mercury. Watad *et al.*[23] have provided an overview of thyroid autoimmunity within the ASIA framework. However, it is important to note that other studies have found no significant associations between autoimmune diseases and vaccinations[24-26]. Detecting potential adverse events related to immunization amid a backdrop of background adverse events can lead to observations of both correlation and no correlations. Distinguishing possible adverse events triggered by immunization requires the identification of distinctive signals that set them apart from background adverse events. Possible signals may be overlooked as the number of days considered increases, potentially overshadowing association signals by extending the considered time frame and consequently elevating the expected number of background events.

In this study, VAERS data were examined to assess the relationships between autoimmune disease adverse events (ADAE) and vaccines. Varying frequencies of multiple immediate-onset autoimmune diseases were observed in response to different vaccines. These observed correlation patterns of immediate onset are inconsistent with the notion that these autoimmune diseases are solely background occurrences. Furthermore, an increase in reports of ADAE was observed in association with the second dose of the Pfizer-BioNTech COVID-19 mRNA vaccine (tozinameran, also known as BNT162b2/Comirnaty), occurring 3 weeks after the initial dose. Associations of vaccine platforms with numerous autoimmune diseases are apparent for both mRNA and adenoviral COVID-19 vaccines. When comparing unrelated vaccines, it is predicted that the likelihood of immediate autoimmune disease onset exceeds a certain threshold, particularly in individuals at risk, in proportion to the strength of immune system stimulation (e.g., vaccine reactogenicity[27]). Based on similar ADAE patterns observed for tozinameran (mRNA vaccine), Moderna mRNA-1273 elasomeran (mRNA vaccine), and Janssen Ad26.Cov2.S (adenoviral vaccine), it is predicted that the frequencies of ADAE observed for COVID-19 vaccines will be comparable across all mRNA and adenoviral vaccines and therapeutics in proportion to the level of stimulated immune system response. Understanding the etiology and relationships between ADAE and vaccines can inform strategies for minimizing the risk of ADAE occurrences. These strategies may include: (i) Extending the interval between immunizations within a dose series to at least 4 weeks (or longer), (ii) eliminating aluminum adjuvants and mercury excipients from vaccines, (iii) considering lower-reactogenicity alternatives to mRNA and adenoviral platforms, and so forth.

2. Materials and methods

2.1. VAERS data mining

The VAERS database underwent data mining to identify autoimmune adverse events, including: Acute disseminated encephalomyelitis, alopecia, ankylosing spondylitis, antiphospholipid syndrome, arthritis, autoimmune disorder, autoimmune hemolytic anemia, autoimmune hepatitis, autoimmune thyroiditis, Behcet's syndrome, Bell's palsy, chronic fatigue syndrome, chronic inflammatory demyelinating polyradiculoneuropathy, chronic lymphocytic leukemia, complex regional pain syndrome, Crohn's disease, dermatomyositis, diabetes mellitus, eczema, encephalitis autoimmune, endometriosis, erythema nodosum, giant cell arteritis, glomerulonephritis, granulomatosis with polyangiitis, GBS, Henoch-Schonlein purpura, hidradenitis, hypogammaglobulinaemia, idiopathic pulmonary fibrosis, IgA nephropathy, ITP, juvenile idiopathic fibrosis, Kawasaki's disease, Lichen planus, Lichen sclerosus, Lyme disease, Meniere's disease, Miller Fisher syndrome, mixed connective tissue disease, multiple sclerosis, multiple sclerosis relapse, myasthenia gravis, myositis, narcolepsy, neuromyelitis optica spectrum disorder, neutropenia, optic neuritis, pemphigus, polymyalgia rheumatica, polymyositis, postural orthostatic tachycardia syndrome, psoriasis, psoriatic arthropathy, Raynaud's phenomenon, restless legs syndrome, rheumatoid arthritis, sarcoidosis, scleritis, scleroderma, Sjogren's syndrome, Still's disease, systemic lupus erythematosus, Type 1 diabetes mellitus, Type 2 diabetes mellitus, uveitis, vasculitis, and vitiligo. The downloaded VAERS data include all adverse events reported from 1990 to May 19, 2023. The Ruby program, named vaers_slice2.rb[27,28], was used to tally selected reported vaccine adverse events based on vaccine type and the day of onset. The vaers_slice2.rb program takes a list of one or more adverse events for characterization,

summarizing them from the yearly VAERS Symptoms, Vax, Data files spanning from 1990 to 2023, and NonDomestic. The output generated by vaers_slice2.rb consists of six reports: Summaries categorized by vaccine, annual summaries, summaries based on the age of vaccinees, summaries categorized by day of symptom onset, which is further divided by (i) dose and gender and (ii) vaccine name/type, and two summaries covering additional reported symptoms (selected symptoms and all other symptoms). For tables and figures, adverse events associated with diphtheria, tetanus, and pertussis vaccines are combined under "DTAP/TDAP," influenza vaccines are consolidated as "FLU," hepatitis A and B vaccines are represented as "HEP," human papillomavirus (HPV) vaccines are grouped as "HPV," and pneumococcal vaccines are consolidated as "PNC." Microsoft Excel was used for creating figures.

2.2. AEFI

AEFI can be represented as the sum of two components: Immunization-associated adverse events (if any) and background occurrences of adverse events. These adverse events diminish due to reporting bias as the time since immunization increases. This relationship can be represented mathematically for a group of vaccinated people (P) by considering reporting bias (r_i) for the ith day post-immunization, the vaccine-associated adverse events reported on the ith day post-immunization (v_i), and the background rate of adverse events (b^X) for a single day (Equations I–III).

$$\text{Adverse events}(X) = AE^X = V^X + B^X \quad \text{(I)}$$

$$V^X = \sum_{i=0}^{n\,days} r_i\, v_i^X P \quad \text{(II)}$$

$$B^X = \sum_{i=0}^{n\,days} r_i\, b_i^X P \quad \text{(III)}$$

If immunization does not lead to any autoimmune adverse events (X), this simplifies to Equation IV:

$$\text{Adverse events}(X) = B^X = \sum_{i=0}^{n\,days} r_i b^X P \quad \text{(IV)}$$

The first 24 h following vaccination can be examined to derive the term v_0^X (Equations V and VI):

$$\text{Adverse events}(\text{X within 24 h}) = AE_0^X = r_0(v_0^X + b^X)P \quad \text{(V)}$$

Immunization-associated adverse events (X) become detectable when $v_0^X > 0$ (when the number of adverse events exceeds the background rate within the first 24 h of immunization). By comparing the frequency of reports of common adverse events in the clinical trial(s) to the frequency of VAERS reports, valuable insights into the values of reporting bias (r_i) can be gained.

2.3. VAERS URF estimate

By June 1, 2023, COVID-19 vaccine doses administered included 366,979,906 tozinameran, 232,147,784 elasomeran, and 19,007,537 Ad26.Cov2.S. Considering 898,860 common adverse events reported in VAERS, with an average of 35% (combining averages of 47.4% and 22.8% for fatigue after doses 1 and 2) of vaccinees experiencing headache, fatigue, pyrexia, chills, and/or pain, the estimation of VAERS underreporting is represented in Equation VII and subsequently applied in Equation VIII:

$$UDF_{common\ AEs\%} = \frac{\text{Vaccine doses} * (\text{faction common adverse events})}{\text{VAERS common adverse events}} \quad \text{(VII)}$$

$$UDF_{35\%} = \frac{617{,}135{,}227\ \text{doses} * 0.35}{898{,}860} = 241 \quad \text{(VIII)}$$

3. Results

3.1. VAERS data mining results

Reports from Vaers_slice2.rb were generated for selected autoimmune diseases in VAERS, and Figures 1 and 2 illustrate ADAEs for vaccines with the highest reported cases by day of onset.

The vaccine types associated with the highest number of multiple ADAE reported are summarized in Table S1. Comparisons of the frequency of vaccine-associated ADAE to background rate estimates are found in Table S2. Regarding COVID-19 ADAEs, VAERS includes reports of ADAE for two different types of vaccines: mRNA (elasomeran and tozinameran) and adenoviral (Ad26.Cov2.S). The contributions of ADAE by individual COVID-19 vaccines are illustrated in Table 1. For GBS, Ad26.Cov2.S represents 3.1% of the vaccine doses administered but accounts for 16.2% of the GBS-related adverse events reported — 91 expected based on elasomeran and tozinameran ([657 + 2,200]/0.97 = 91) but 554 GBS ADAEs were reported (Table 1). The initial immunization of COVID-19 mRNA vaccines involved a two-dose series, with 3 weeks (tozinameran) and 4 weeks (elasomeran) between doses. The ratio of autoimmune adverse events when comparing dose 2 to dose 1 for these COVID-19 vaccines is presented in Figure 3.

4. Discussion

Numerous articles have suggested potential associations between immunization and autoimmune diseases[2-21],

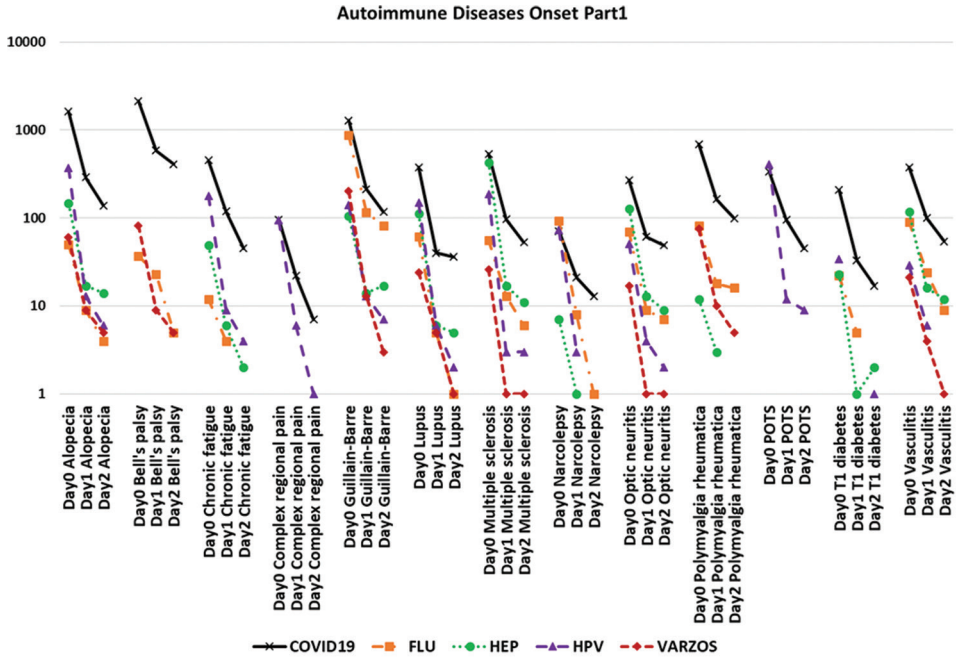

Figure 1. Day of onset of autoimmune diseases after administration of selected vaccines (1 of 2). Vaccine labels: COVID-19: COVID-19 vaccines; FLU: Influenza vaccines; HEP: Hepatitis A and hepatitis B vaccines; HPV: Human papillomavirus; VARZOS: Varicella-zoster vaccines. Autoimmune disease labels: Lupus: Systemic lupus erythematosus; POTS: Postural orthostatic tachycardia syndrome.

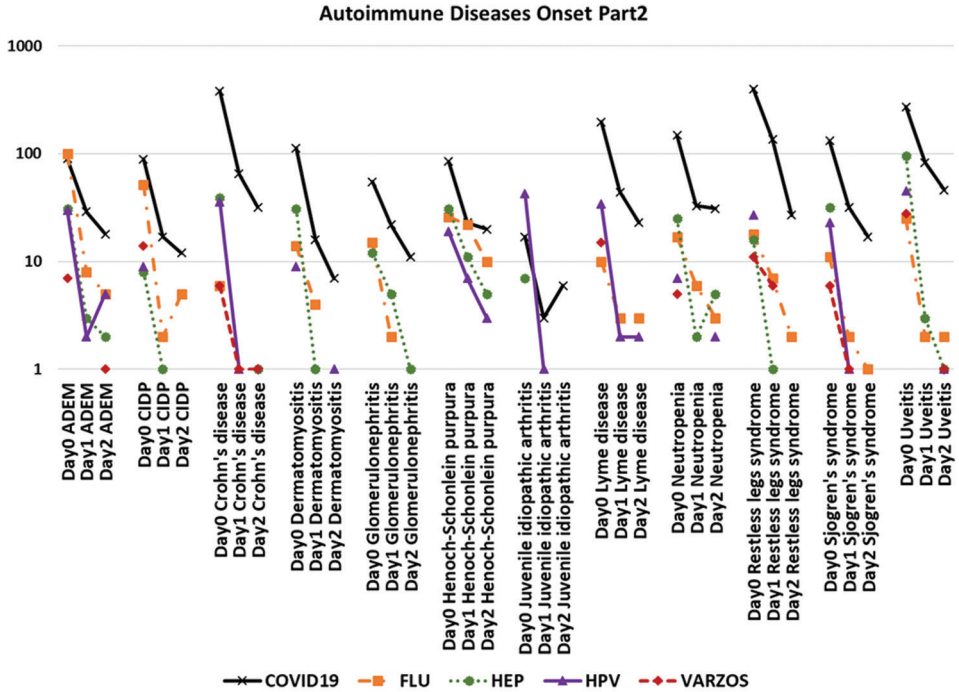

Figure 2. Day of onset of autoimmune diseases after administration of selected vaccines (2 of 2). Vaccine labels: COVID-19: COVID-19 vaccines; FLU: Influenza vaccines; HEP: Hepatitis A and hepatitis B vaccines; HPV: Human papillomavirus; VARZOS: Varicella-zoster vaccines. Autoimmune disease labels: ADEM: Acute disseminated encephalomyelitis; CIDP: Chronic inflammatory demyelinating polyneuropathy.

while other opposing articles contend that no such associations can be detected[24-26]. When considering any immunization, the number of adverse events (AE^X), if there are any vaccine-caused adverse events (V^X) in a

Table 1. Autoimmune adverse events and doses by COVID-19 vaccine. VAERS data include adverse event reports from 1990 to May 19, 2023

Adverse event	COVID-19 Ad26.Cov2.S	COVID-19 elasomeran	COVID-19 tozinameran
Administered doses	19,007,537 (3.1%)	232,147,784 (37.6%)	366,979,906 (59.4%)
Alopecia	220 (5.5%)	1,174 (29.6%)	2,570 (64.8%)
Arthritis	204 (4.9%)	1,277 (30.6%)	2,692 (64.5%)
Bell's palsy	343 (4.7%)	1,981 (27.1%)	4,980 (68.2%)
Guillain-Barré syndrome	554 (16.2%)	657 (19.3%)	2,200 (64.5%)
Immune thrombocytopenia	108 (6.6%)	383 (23.3%)	1,155 (70.2%)
Rheumatoid arthritis	109 (3.2%)	824 (24.4%)	2,443 (72.4%)

Note: The percentages in parentheses represent the proportion of this adverse event by vaccine.

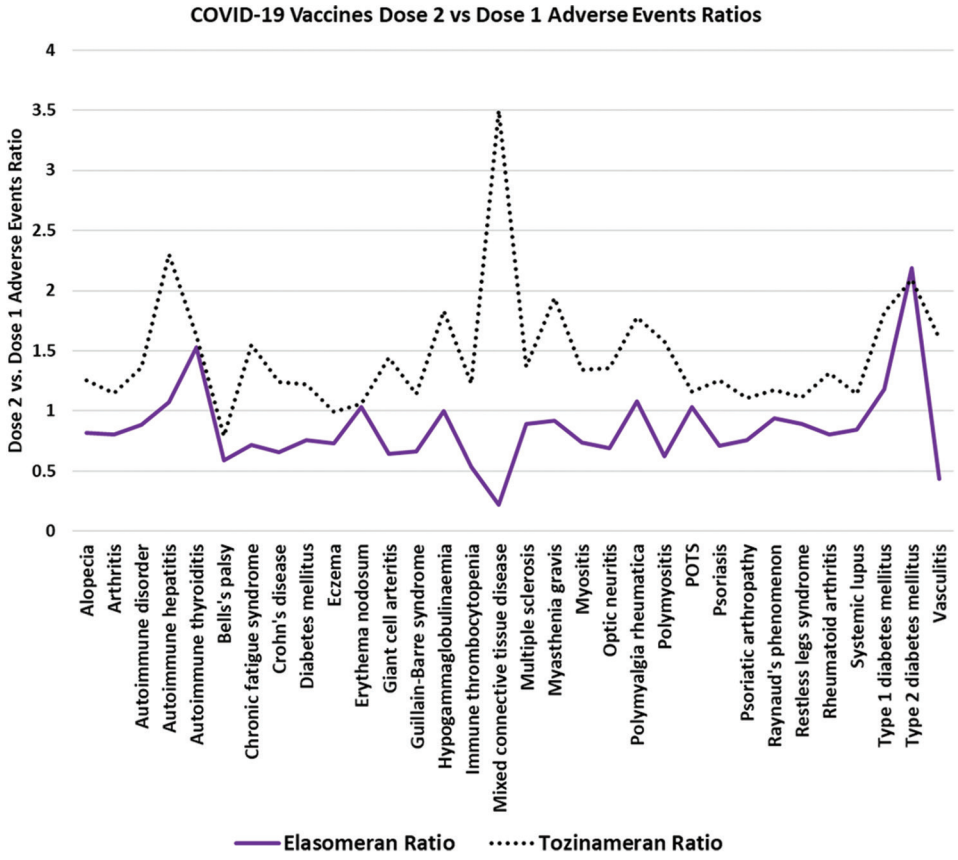

Figure 3. The autoimmune disease adverse event ratios after COVID-19 vaccines dose 2 versus dose 1 administration. Labels of autoimmune diseases: POTS: Postural orthostatic tachycardia syndrome.

population sample, remains constant. However, the sum of background adverse events (B^X) is proportional to the number of days considered. Hence, it is always possible to find no associations by increasing the number of days examined (e.g., by selecting a timespan where $B^X > V^X$ since V^X remains constant while B^X increases with time).

Following immunizations, the occurrence of autoimmune diseases is expected to align with population background rates unrelated to immunization. Any autoimmune diseases resulting from immunization are in addition to these background events. Vaccines with the highest ADAEs in VAERS are summarized in Table S1 and Figures 1 and 2. Following immunization, ADAE reports are anticipated to decrease over time, a phenomenon referred to as reporting bias. Most ADAE reports in VAERS indicate symptom onset within 24 h of immunization (Figures 1 and 2, Table S2).

Table S2 illustrates reporting bias values (r_0) of 1/20 and 1/40; however, based on the frequency of VAERS reports related to common adverse events of COVID-19 vaccines, the r_0 (URF) for these vaccines (Equation VIII) could be closer to 1/241. If r_0 is indeed close to 1/241, then many of the detected COVID-19 ADAEs (Table S1) hold significant.

Primary and secondary humoral immune responses, with the amplification of B-cell antibodies, increase over a period of multiple days (peaking around 7- – 11-day post-immunization). Observed ADAEs (Table S1) that occur within 24 h after immunization cannot be attributed to either primary or secondary humoral immune responses (the immediate timespan is inconsistent with humoral immune responses). Immediate ADAEs are more consistent with the hypothesis of autoimmune disease threshold being exceeded due to immune dysregulation on a rapid timescale post-immunization.

4.1. COVID-19 mRNA and adenoviral vaccines

Most COVID-19 vaccines available on the market are the novel mRNA and adenoviral vaccines, and both of these vaccine platforms have been associated with multiple ADAE (Table 1). For both Ad26.Cov2.S and tozinameran vaccines, the percentage of associated ADAE is higher than the elasomeran vaccine. For instance, for the Ad26.Cov2.S vaccine, GBS accounts for 16.2% of the adverse events but represents only 3.1% of the COVID-19 vaccine doses (Table 1). All three of these COVID-19 vaccines contribute to the combined COVID-19 results reported in Table S1. Of particular note is the high percentage of Bell's palsy occurrence when compared to other vaccines (Table S1). In comparison to widely provided vaccines like influenza and others, COVID-19 immunizations show a broad association with many autoimmune diseases (Table S1). Furthermore, high percentages of these ADAEs are reported within 24 h of immunization (Table S1).

The timing of mRNA vaccine doses appears to be important for ADAE onset (Figure 3). Specifically, the tozinameran mRNA COVID-19 vaccine exhibits a higher number of ADAE reports for 30 out of 32 autoimmune adverse events for dose 2 compared to dose 1, with a ratio >1.0. In 29 of these cases, the ratio >1.1, with Bell's palsy being the only exception (ratio = 0.79) (Figure 3). On the other hand, the elasomeran mRNA COVID-19 vaccine shows seven vaccines with ratios >1.0 and three vaccines >1.1. Notably, the elasomeran vaccine contained 100 micrograms of mRNA, with 4 weeks between the first and second vaccine doses, whereas the tozinameran vaccine contained 30 μg of mRNA, with only 3 weeks between the first and second vaccine doses. The higher ADAE ratios observed for the tozinameran vaccine compared to elasomeran vaccines (Figure 3) suggest that increasing the time between first and second doses for this vaccine to at least 4 weeks or longer would likely decrease the dose 2 to dose 1 ratio, as observed in Figure 3. This extended interval is predicted to help mitigate higher non-specific amplification observed for the tozinameran COVID-19 vaccine when the second dose is administered just 3 weeks after the first dose (Figure 3).

These COVID-19 vaccines appear to induce immediate-onset ADAEs, which are consistent with subsets of at-risk vaccinees exceeding the disease onset thresholds for a broad spectrum of autoimmune diseases (Table S1). Based on the onset data reported in VAERS, the highest risks appear to be immediately post-immunization, especially for at-risk vaccinees. By design, both mRNA and adenoviral vaccine platforms elicit high levels of expression of the SARS-CoV-2 spike protein, which is foreign to the immune systems, effectively stimulating strong immune responses. COVID-19 ADAEs associated with 33 autoimmune diseases/groups are summarized in Table S1. The observed patterns of immediate-onset frequencies, common to all ADAEs (Figures 1 and 2, Table S1), suggest the possibility of unintended immune responses triggering these ADAEs. These frequency patterns are consistent with the hypothesis of bystander or polyclonal activation but not epitope molecular mimicry[2] (as there is insufficient time for adaptive immune responses to vaccine epitopes). Note that Guo *et al.*[15] have considered molecular mimicry, adjuvants, and bystander activation. In examining the etiology of COVID-19 vaccine ADAEs, Table S1 presents data on 33 different autoimmune diseases with immediate onset, indicating an immediate effect rather than a direct result of the expressed spike protein or possible shared epitopes. Differences in age distributions among vaccinees for selected autoimmune diseases are illustrated in Figure 4. The demographic characteristics of individuals experiencing these ADAEs are consistent with the amplification of pre-existing mechanisms, especially for individuals at higher risk of developing these autoimmune diseases. For instance, polymyalgia rheumatica, one of the COVID-19 ADAEs, is predominantly reported in older adults[29] (Figure 4).

4.2. HPV vaccines

The HPV vaccines contain aluminum as an adjuvant[3]. While aluminum has a long history of use in vaccines, it is also associated with neurotoxicity[3,22]. In mice, macrophages have been shown to transport aluminum to lymph nodes, spleen, liver, and brain[30]. Regarding the correlation of HPV vaccines with adverse events, it is noteworthy that temporal onset correlations exist with multiple ADAEs (Table S1). Among these, the ADAEs with

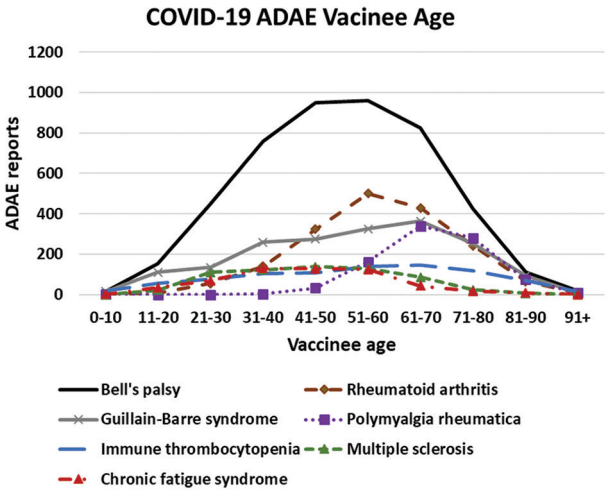

Figure 4. The age of COVID-19 vaccinees experiencing various autoimmune disease adverse events.

the highest descending order of correlations, expressed as a percentage of common adverse events, include postural orthostatic tachycardia syndrome (POTS) (1.91%), alopecia (1.72%), multiple sclerosis (0.87%), chronic fatigue syndrome (0.83%), systemic lupus erythematosus (0.70%), GBS (0.59%), narcolepsy (0.34%), complex regional pain syndrome (0.30%), arthritis (0.30%), optic neuritis (0.24%), rheumatoid arthritis (0.22%), uveitis (0.21%), eczema (0.21%), juvenile idiopathic arthritis (0.20%), Raynaud's phenomenon (0.20%), restless legs syndrome (0.20%), Crohn's disease (0.17%), Type 1 diabetes mellitus (0.16%), autoimmune thyroiditis (0.15%), acute disseminated encephalomyelitis (0.14%), vasculitis (0.14%), Lyme disease (0.13%), and Sjogren's syndrome (0.11%) (Table S1). Furthermore, it is important to highlight that multiple ADAEs manifest with neurological implications. Multiple autoimmune diseases have been reported in case reports following HPV immunization, including POTS[31], systemic lupus erythematous[32], myasthenia gravis[33], complex regional pain syndrome (CRPS)[34], arthritis and rheumatoid arthritis[32], uveitis[35], vasculitis[36], and pseudoneurological syndrome[37]. In addition, antinuclear antibodies were found to be enriched in patients with autoimmune-like symptoms following HPV vaccination[38]. The ADAEs associated with HPV vaccination present as non-random signals higher than the expected background ADAEs (Table S2). Several of these ADAEs, such as POTS, multiple sclerosis, chronic fatigue syndrome, systemic lupus erythematous, GBS, narcolepsy, CRPS, optic neuritis, restless legs syndrome, acute disseminated encephalomyelitis, and myasthenia gravis, are neurological in nature. This raises concerns given that HPV vaccines include the aluminum adjuvant, which is known to be neurotoxic[3,22]. To date, other possible components within HPV vaccine contributing to the etiology of these neurological adverse events have not been identified. It is a clinically testable hypothesis that reducing or eliminating the aluminum adjuvant from HPV vaccines might mitigate or eliminate these ADAEs. The observed ADAEs associated with HPV vaccine exhibit a unique pattern, which does share some similarities with those linked to hepatitis A and B (HEP) vaccines.

4.3. Hepatitis A and B vaccines

Similar to HPV vaccines, HEP vaccines also contain aluminum as an adjuvant[39]. The highest frequencies of ADAEs associated with HEP vaccines, expressed as a percentage of common adverse events, include multiple sclerosis (1.18%), arthritis (0.73%), rheumatoid arthritis (0.43%), alopecia (0.40%), optic neuritis (0.35%), vasculitis (0.32%), systemic lupus erythematosus (0.31%), GBS (0.29%), eczema (0.27%), uveitis (0.27%), chronic fatigue syndrome (0.14%), and more (Table S1). Furthermore, there have been case reports of multiple autoimmune diseases following HPV immunization[40], encompassing conditions such as arthritis and rheumatoid arthritis[41,42], alopecia[43], optic neuritis[44,45], vasculitis[46,47], systemic lupus erythematosus[48], and GBS[49]. In addition, there was a previous report suggesting a potential association between the hepatitis B vaccine and multiple sclerosis[50], although it was subsequently found to have a strong family history of multiple sclerosis, with an overrepresentation of the HLA-DR2 antigen (as reviewed in Pordeus *et al.*[51]). The frequency pattern of ADAEs for HEP vaccines appears different from that of ADAEs for HPV vaccines (Table S1), possibly implicating aluminum[22] in combination with additional factors contributing to the etiologies of ADAEs associated with these vaccines. Similar to HPV vaccines, the presence of multiple sclerosis, optic neuritis, systemic lupus erythematosus, GBS, and chronic fatigue syndrome as ADAEs establishes a set of neurological ADAEs associated with HEP vaccines. Moreover, like HPV vaccines, HEP vaccines also incorporate aluminum as an adjuvant. Therefore, it is plausible that to consider the reduction or elimination of aluminum from HEP vaccines as clinically testable approach to potentially reduce the occurrence of neurological and other ADAEs associated with HEP vaccines.

4.4. Influenza, pneumococcal, and varicella-zoster vaccines

Influenza displays the strongest association with GBS[5-7]. Moreover, GBS appears to be associated with multiple vaccines, including HPV, varicella-zoster, HEP, and others (Tables S1 and S3). The pneumococcal (PNC) vaccine demonstrates significant associations with eczema,

Kawasaki disease, neutropenia, and GBS (Table S1). In the case of influenza, there is a possibility of slight epitope molecular mimicry, which may be more pronounced for specific influenza strain protein(s) included within yearly vaccines. However, for other vaccines, the associations with GBS might align more with the hypothesis of bystander or polyclonal activation, and the likelihood of epitope molecular mimicry appears lower. In addition to the PNC vaccine (0.43%), 6VAX-F (diphtheria and tetanus toxoids and acellular pertussis absorbed + inactivated poliovirus + hepatitis B + Haemophilus B conjugate vaccine) (1.78%), RV (rotavirus vaccine) (0.83%), MENB (meningococcal group B, rDNA absorbed vaccine) (0.69%), and HIBV (*Haemophilus influenzae* Type B vaccine) (0.23%) vaccines exhibit significant temporal onset associations with adverse events related to Kawasaki disease (Table S3). Despite the unknown etiology of Kawasaki disease, the observed associations with multiple vaccines represent unexpected observations. One proposed hypothesis suggests that high-titer antibodies capable of activating mast cells may play a key role in the etiology of Kawasaki disease[52,53]. It is plausible that immunizations for these vaccines may activate mast cells due to the high titers of immunization-stimulated antibodies binding to vaccine antigens. Consequently, therapeutic approaches targeting activated mast cells may hold promise for patients experiencing vaccine-associated Kawasaki disease[52,53].

4.5. Patients with pre-existing autoimmune diseases

Immunosuppressed individuals and those with autoimmune diseases are advised to consult with licensed medical professional regarding suitable vaccine candidates. It is important to note that live-attenuated vaccines are not recommended for patients with autoimmune inflammatory rheumatic diseases, especially those who are immunosuppressed[54]. In the work of Frasca *et al.*[55], there is a debate concerning the necessity of COVID-19 vaccines for individuals with autoimmune diseases as well as for the general population. It is worth highlighting that impaired immunogenicity to COVID-19 vaccines has been reported in individuals with autoimmune systemic diseases[56], although there have been reports of vaccine efficacy in patients with autoimmune hepatitis[57]. In the consideration of candidate treatments, relevant information needs to be provided to ensure that informed consent requirements have been met while carefully weighing the risks against the benefits.

4.6. Study limitations

This study is based on adverse events reported to the VAERS database, which are considered a subset of all adverse events experienced by vaccinees. Any reporting biases or exclusion of reported adverse events would perturb the accuracy of VAERS in representing the immunized populations. By comparing the relative proportions of adverse events with large clinical trial datasets, we can detect possible perturbations in the VAERS dataset.

4.7. Study recommendations

The risks associated with developing autoimmune diseases following vaccinations may be mitigated through the following measures: (i) Evaluating alternative vaccine and therapeutic platforms to either avoid or minimize the use of mRNA and adenoviral platforms, and (ii) increasing the time between mRNA vaccine doses to 4 weeks or longer, and perhaps (iii) removing aluminum adjuvants and mercury excipients from vaccines.

5. Conclusion

Autoimmune diseases appear to be triggered by specific vaccines in some vaccinees (COVID-19 vaccine: alopecia, Bell's palsy, chronic fatigue syndrome, CRPS, GBS, Henoch-Schonlein purpura, ITP, myositis, multiple sclerosis, narcolepsy, optic neuritis, POTS, rheumatoid arthritis, systemic lupus erythematosus, and Type 1 diabetes mellitus. Influenza vaccine: GBS [already known]. HEP vaccine: Alopecia, chronic fatigue syndrome, GBS, multiple sclerosis, optic neuritis, systemic lupus erythematosus, and vasculitis. HPV vaccine: alopecia, chronic fatigue syndrome, CRPS, GBS, multiple sclerosis, narcolepsy, optic neuritis, POTS, and systemic lupus erythematosus. PNC vaccine: GBS, Kawasaki disease, and neutropenia. Vericella-zoster vaccine: Bell's palsy, GBS, and rheumatoid arthritis. Refer to Table S2. The study reveals specific temporal onset correlations of ADAEs for multiple vaccines (Figures 1 and 2, Table S1). Both mRNA and adenoviral COVID-19 vaccine platforms appear to non-specifically increase the occurrence of ADAEs associated with multiple autoimmune diseases (Table S1). Increasing the time between initial COVID-19 mRNA shots to at least 4 weeks is likely to mitigate the observed increase in ADAEs for tozinameran (Figure 3). It is important to note that increased non-specific ADAEs are not observed for all other vaccines. These well-established platforms may offer safer alternatives for COVID-19 vaccination with respect to ADAEs. HEP and HPV vaccines, on the other hand, appear to induce specific patterns of ADAEs, with aluminum being a common adjuvant to both vaccines. The removal of aluminum adjuvants from HPV vaccines, HEP vaccines, and potentially other vaccines may reduce the frequency of ADAEs. Adhering to the principle of informed consent and the disclosure of information, it is advisable to provide ADAE risk notifications for COVID-19, HPV, HEP, and other vaccines.

ADAEs associated with Kawasaki disease have been observed in relation to multiple vaccines (PNC, 6VAX-F, RV, MENB, and HIBV). These observations suggest a potential link between immunization-stimulated antibodies and the activation of mast cells. It concludes by proposing a further investigation into therapeutics targeting mast cell activation for Kawasaki disease patients.

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Conflict of interest

The author declares that he/she has no competing interests.

Author contributions

This is a single-authored article.

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Availability of data

The vaers_slice2.rb reports are available here: Ricke D, 2023, "ADAE Post Vaccination", Harvard Dataverse, V1, https://doi.org/10.7910/DVN/EROCQQ.

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