

ORIGINAL RESEARCH ARTICLE

Signature patterns of vaccine adverse events

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Abstract

Some vaccine recipients can develop serious adverse events (SAEs) following coronavirus disease 2019 (COVID-19) immunization. In a retrospective study of the Vaccine Adverse Event Reporting System (VAERS) menstrual AEs following immunization, statistically significant differences were observed for multiple manufacturing lots of the COVID-19 Pfizer–BioNTech and the COVID-19 Moderna vaccines. Other candidate manufacturing contaminants associated with AEs may be detectable by comparing normalized frequency rates between predicted higher-contamination lots or vaccines and lower-contamination lots or vaccines. This retrospective study identified candidate pattern signatures for the most frequently reported AEs in VAERS for identified COVID-19 vaccine lots associated with these menstrual AEs, as well as differences in AE frequencies between three human papillomavirus (HPV) vaccines. Six candidate AE patterns (AEPs) were identified: hemorrhage (female), gynecologic including hemorrhage pattern, myopericarditis (male-biased), HPV vaccine-associated, neuropathy, and fetus patterns. The hemorrhage pattern was identified in six vaccines, including four influenza vaccines. The gynecologic pattern was identified in seven vaccines, including three COVID-19 and three HPV vaccines. The myopericarditis pattern was identified in 14 vaccines, including five COVID-19 vaccines, with two bivalent COVID-19 vaccines and three smallpox vaccines. The myopericarditis pattern appears to be associated with possible contaminant microbial protein activation of immune responses and live attenuated virus vaccines. The four AEP_{HPV} AEs were elevated primarily among HPV vaccines. One or more of the five AEP_{neuropathy} AEs were elevated in 11 vaccines, while one or more of the AEP_{fetus} AEs were elevated in 11 vaccines.

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1. Introduction

Adverse events (AEs) following immunization include random background events unrelated to immunization and possible vaccine-associated AEs. Vaccine-associated AEs are often related to normal immune responses to the vaccine. Other AEs and serious AEs (SAEs) are caused by specific vaccine components, adjuvants, excipients, manufacturing contaminants, or combinations of more than one of these constituents. The Vaccine Adverse Event Reporting System (VAERS) and similar databases collect population samples of AEs to detect associated safety signals. Safety signals can be detected from patterns of AEs associated with specific vaccines and vaccine lots that occur more

frequently than in other vaccines and vaccine lots. Closer examination of AEs, such as menstrual disturbances, is warranted for AEs with higher frequencies for specific vaccines and vaccine lots.

Menstrual disturbances, including heavy menstrual bleeding, were reported following coronavirus disease 2019 (COVID-19) vaccination.¹⁻⁷ Menstrual abnormalities include amenorrhea (absence of menstruation)/oligomenorrhea (infrequent or irregular menstrual periods) (33.3%), dysmenorrhea (severe, cyclical menstrual pain) (12.7%), heavy menstrual blood loss (29.4%), intermenstrual blood loss (18.7%), irregular blood loss (22.7%), and less menstrual blood loss (3.5%).⁸ In an online questionnaire study, 60%–70% of reproductive-age women reported menstrual irregularities after the second COVID-19 vaccine dose, with approximately half of the cases resolving within two months.⁹ A study of 14,153 women reported that 78% experienced menstrual cycle changes following COVID-19 vaccination.² Furthermore, in a study of 2,269 women, 66.3% reported menstrual symptoms post-vaccination.¹⁰ Another online questionnaire study with 338 responses found 63.9% reporting changes to their menstrual cycle.¹¹ A similar survey of 383 women found increased reporting for women with polycystic ovarian syndrome (23.88% vs. 37.78%, $p=0.045$), hormonal contraceptive use (odds ratio [OR]: 2.09, 95% confidence interval [CI]: 1.23–3.57, $p=0.006$), and COVID-19 vaccine skepticism (OR: 2.96, 95% CI: 1.79–4.90, $p<0.001$).¹² In a study of 24,090 menstrual AE case reports, increased risks were observed for the Johnson & Johnson vaccine (OR: 1.83, 95% CI: 1.33–2.49), the Moderna vaccine (OR: 2.44, 95% CI: 1.86–3.20), and the Pfizer–BioNTech vaccine (OR: 3.04, 95% CI: 2.36–3.93) compared to the AstraZeneca COVID-19 vaccine.⁸ A comparative retrospective study of reproductive-age women with COVID-19 found that 28% had menstrual cycle changes.¹³ Unexpected vaginal bleeding also developed in some non-menstruating women following COVID-19 vaccination.¹⁴ Moreover, batch-dependent variability of AEs has been reported for the BNT162b2 mRNA COVID-19 vaccine.^{15,16} Menstrual AEs were observed to vary significantly by lot for the COVID-19 Pfizer–BioNTech, COVID-19 Moderna, human papillomavirus (HPV) Cervarix, and HPV Gardasil vaccines.¹⁷ HPV vaccination is associated with elevated risks of autonomic dysfunction and menstrual irregularities, which vary by age.¹⁸ Cases of premature ovarian insufficiency (POI) have been reported post-HPV vaccination¹⁹; a VAERS retrospective study found a safety signal for premature ovarian insufficiency with HPV4 vaccination.²⁰ The frequencies of multiple AEs vary by

vaccine and sometimes between lots of the same vaccine.

Discordant differences between vaccines and specific vaccine lots with higher and lower normalized AE frequencies can be leveraged to detect other AEs correlated with these differences. Here, the VAERS database was retrospectively examined for AEs that vary between selected discordant COVID-19 Pfizer–BioNTech lots, discordant COVID-19 Moderna lots, HPV vaccines with higher menstrual AEs, and COVID-19 lots and HPV vaccines with lower menstrual AEs to identify candidate AE patterns (AEPs) for future studies. In total, six AEPs were identified: AEP_{hemorrhage}, AEP_{gynecologic}, AEP_{myopericarditis}, AEP_{HPV}, AEP_{neuropathy}, and AEP_{fetus} signatures.

2. Materials and methods

2.1. Vaccine Adverse Event Reporting System retrospective analysis

The VAERS database²¹ was retrospectively examined for the AEs associated with the COVID-19 Pfizer–BioNTech and the COVID-19 Moderna vaccines for lots with a minimum of 100 AE reports with the Ruby program `vaers_tally_lots.rb`.²² The downloaded VAERS data included all AEs reported from 1990 to May 30, 2025. The VAERS database was retrospectively examined for the AEs for all vaccines with the Ruby programs `vaers_tally.rb` and `vaers_tally_gender.rb`²² for males and females. Age group analyses were performed using the Ruby program `vaers_slice5.rb`.²² These tools were used to calculate the frequencies of reported AEs normalized to 100,000 VAERS reports²³ (**Equation 1**):

$$\text{AE normalized frequency} = (\text{observed AEs} / \text{all individuals with any vaccine AEs}) \times 100,000 \quad (1)$$

These normalized frequencies do not represent true incidence rates but estimated rates of reported AEs, excluding asymptomatic individuals. To avoid duplicate data, data were tabulated by the unique “`vaers_id`” identifier. Normalized frequencies were filtered for a minimum of 200 per 100,000 VAERS reports and a minimum of five AEs for a vaccine or vaccine combination. Vaccines and vaccine combinations, including the text “no brand name,” “foreign,” “unknown,” and “vaccine not specified,” were excluded to avoid possible reporting biases due to the possibility of underrepresentation of less severe AEs resulting in increased normalized frequency estimates. For reproducibility of results, AE names represent decapitalized VAERS names; AEs such as “abortion spontaneous” were not altered to common names such as “spontaneous abortion.” The figures use VAERS vaccine names with the brand name in parentheses.

2.2. Adverse events following immunization

Adverse events (X) following immunization can be represented as the sum of immunization-associated AEs and background (B) AE occurrences. A background AE is considered an event that develops independently of immunization in the population being examined during the time period examined; background AEs are not considered correlated with immunizations. Reported AEs diminish due to reporting bias as time since immunization increases. Vaccine-associated AEs can be modeled for vaccine (V) and AEs (X) by the risks linked to specific vaccine components (C : $0..r$), excipients (E : $0..s$), manufacturing contaminants (M : $0..t$), and population background (B^X) events in **Equation 2**:

$$\text{Adverse events}(V|X) = \sum_{i=0}^r C_i^V + \sum_{j=0}^s E_j^V + \sum_{k=0}^t M_k^V + B^X \quad (2)$$

If $AE(V|X) = 0$ for multiple vaccines for X , then each of the components C_i , E_j , and M_k is approximately zero for these vaccines, and B is approximately zero for all vaccines. If $AE(V|X) = 0$ for multiple vaccines and $AE(V|X) >> 0$ for other vaccines, then there are vaccine-associated AEs for the second set of vaccines. If two different lots for the same vaccine exhibit significant differences, these differences are likely due to intentional changes by the manufacturer to one or more of C_i and/or E_j or most likely M_k .

2.3. Adverse event pattern signature identification

The VAERS AE reports from 1990 to May 30, 2025, were examined to identify candidate patterns for manufacturing contamination signatures. The approach focused on previously published COVID-19 Moderna and Pfizer-BioNTech lots with higher and lower normalized frequencies for menstrual AE frequencies.¹⁷ For example, for heavy menstrual bleeding, the COVID-19 Pfizer-BioNTech manufacturing lots with higher normalized frequencies FG2975=14,285 (11 AEs, $P_{\text{female}}=77$), FE3064=14,388 (20 AEs, $P_{\text{female}}=139$), and FG7372=15,189 (12 AEs, $P_{\text{female}}=79$) were compared with manufacturing lots with lower normalized frequencies EJ6136=0 (0 AEs, $P_{\text{female}}=970$), EJ6788=0 (0 AEs, $P_{\text{female}}=846$), and EJ6795=0 (0 AEs, $P_{\text{female}}=796$).

The second approach leveraged differences in normalized frequencies between the three HPV vaccines. The HPV Cervarix bivalent vaccine had the most menstrual AEs, followed by HPV Gardasil (a quadrivalent vaccine) and HPV Gardasil 9 (a nonavalent vaccine). Candidate AEs were identified for patterns from comparisons between HPV Cervarix vs. Gardasil, HPV Cervarix vs. HPV Gardasil 9, and HPV Gardasil vs. HPV Gardasil 9 (**Table 1**). Identified AEs were characterized across all vaccines,

with inclusion of vaccines with normalized frequency at or above 200 per 100,000 VAERS reports.

The COVID-19 Pfizer-BioNTech vaccine lots FG2975, FE3064, and FG7372 were identified as lots with predicted higher levels of manufacturing contamination, and lots EJ6136, EJ6788, and EJ695 were identified as lots with predicted lower levels.¹⁷ The COVID-19 Moderna vaccine lot 3002332 was identified as the lot with the highest level of predicted manufacturing contamination, and lots 004M20A, 012L20A, and 013L20A were identified as lots with predicted lower levels.¹⁷ For each VAERS AE, the average of the lower lots was subtracted from the higher lots. Within the top 100 AEs with the highest differences between the higher and lower averages, multiple gynecologic AEs were identified. To improve assessments of normalized frequencies, VAERS AEs were also examined by sex.

Previously, menstrual AEs were identified using candidate manufacturing contamination signatures for three HPV vaccines¹⁷, followed by differences in normalized frequencies between pairs of HPV vaccines based on their different patterns of menstrual AEs.¹⁷ In this study, additional candidate AEs for manufacturing contamination were selected by subtracting normalized frequencies for HPV Gardasil 9 from HPV Gardasil for females; the AEs identified included “abortion induced,” “caesarean section,” “cognitive disorder,” “fetal disorder,” “menorrhagia,” “orthostatic intolerance,” “postural orthostatic tachycardia syndrome (POTS),” and “smear cervix abnormal.” Subsequently, additional candidate AEs for manufacturing contamination were selected from the sorted HPV Cervarix normalized frequencies: “autonomic nervous system imbalance,” “chronic fatigue syndrome,” “complex regional pain syndrome (CRPS),” “mental impairment,” “post-vaccination syndrome,” and “POTS.” Given the current female bias in HPV vaccine administration, only the female AE-normalized frequencies were examined.

2.4. Statistical analysis

Microsoft Excel was used to prepare figures and calculate Pearson correlation coefficients. An online calculator was used for the Chi-square test for a 2×2 contingency table.²⁴

3. Results

3.1. COVID-19 vaccine adverse event patterns

For both the COVID-19 Pfizer-BioNTech and the Moderna vaccines, selected AEs ranked in the top 100 for females (**Figure 1A**), males (**Figure 1B**), and both genders (**Figure 1C**) are illustrated, contrasting manufacturing lots with higher and lower normalized frequencies for both vaccines.

Table 1. Selected candidate adverse events with discordant normalized frequencies between human papillomavirus vaccines

Adverse event	Cervarix	Gardasil	Delta
Cervarix and Gardasil			
Altered state of consciousness	1,449	134	1,315
Autonomic nervous system imbalance	1,905	582	1,323
Chronic fatigue syndrome	1,657	422	1,235
Cognitive disorder	2,920	743	2,177
Complex regional pain syndrome	1,284	181	1,103
Mental impairment	1,822	108	1,714
Orthostatic intolerance	2,154	466	1,688
Post-vaccination syndrome	2,982	15	2,967
Cervarix and Gardasil 9			
Abortion induced	683	37	646
Abortion spontaneous	1,180	193	987
Dysmenorrhea	2,009	252	1,757
Menstrual disorder	1,367	267	1,100
Menstruation irregular	2,464	453	2,011
Vaginal hemorrhage	621	148	473
Gardasil and Gardasil 9			
Caesarean section	613	59	554
Fetal disorder	504	7	497
Smear cervix abnormal	1,830	401	1,429

For example, for heavy menstrual bleeding (Figure 1A), the difference between the COVID-19 Pfizer-BioNTech and the COVID-19 Moderna higher and lower manufacturing lots was significant ($p=0.00000$). Likewise, for myocarditis (Figure 1B), the difference between the COVID-19 Pfizer-BioNTech and the COVID-19 Moderna manufacturing lots with higher and lower normalized frequencies was also significant ($p=0.00000$). Additionally, for hemorrhage (Figure 1C), the difference between the COVID-19 Pfizer-BioNTech and the COVID-19 Moderna manufacturing lots with higher and lower normalized frequencies was significant ($p=0.00000$). Candidate vaccine AEP signatures were identified for females (AEP_{hemorrhage} signature [Figure 2A] and AEP_{gynecologic} signature [Figure 2B], including the hemorrhage pattern) and males (AEP_{myopericarditis} signature) (Figure 2C). Comparing myocarditis for the smallpox (ACAM2000) vaccine (Figure 2C) to the measles + mumps + rubella (MMR II) vaccine (normalized frequency of 31) yielded $p=0.00000$. The candidate hemorrhage pattern was detected for the six vaccines (Figure 2A), excluding elevated menstrual AEs (Figure 2B). The pulmonary embolism AE safety signals were detected for seven of 14 candidate myopericarditis pattern vaccines (anthrax Biothrex, five COVID-19, and smallpox Dryvax).

Examining normalized frequencies by lot identified candidate safety signals. For the COVID-19 Janssen vaccine, six lots detected hemorrhage safety signals, including lot 1822809 (5 AEs, 0.7%) (Table S1). For the COVID-19 Moderna vaccine, 16 lots detected hemorrhage safety signals, including lots 3002621 (14 AEs, 1.6%), 3002332 (18 AEs, 1.6%), and 3001659 (7 AEs, 0.9%) (Table S2). For the COVID-19 Pfizer-BioNTech vaccine, 124 lots had detectable hemorrhage safety signals, including lots EP6775 (13 AEs, 6.4%), FA9090 (4 AEs, 4.3%), EY5456 (13 AEs, 3.6%), and FE3380 (36 AEs, 3.1%) (Table S3). For myocarditis, the COVID-19 Janssen vaccine lots ABZ5320 (6 AEs, 2.1%), XD395 (5 AEs, 2.1%), ABZ8354 (4 AEs, 3.4%), and 1821286 (4 AEs, 0.8%), and 2 additional lots had detectable safety signals (Table S4); the COVID-19 Moderna vaccine lots 052C2A1 (4 AEs, 80.0%), 045D21A (30 AEs, 63.8%), 044D21A (37 AEs, 63.7%), 092D21A (30 AEs, 60.0%), 042D21A (34 AEs, 50.7%), 016E21A (19 AEs, 50.0%), 043D21A (24 AEs, 49.0%), 093D21A (18 AEs, 43.9%), 3002182 (8 AEs, 40.0%), and 179 additional lots had detectable safety signals (Table S5); and the COVID-19 Pfizer-BioNTech lots 1E027A (20 AEs, 40.0%), 1E023-1A (12 AEs, 37.5%), FG9984 (13 AEs, 36.1%), FA9099 (56 AEs, 30.9%), ER0866 (15 AEs, 30.6%), FD7206 (44 AEs, 24.4%),

and 462 additional lots had detectable safety signals (Table S6). For pericarditis, the COVID-19 Janssen vaccine lots XD974 (6 AEs, 0.5%), 042A21A (6 AEs, 0.2%), 201A21A (6 AEs, 0.3%), 1805029 (4 AEs, 0.2%), and 205A21A (4 AEs, 0.2%) had detectable safety signals (Table S7); the COVID-19 Moderna vaccine lots 019J21A (4 AEs, 30.8%), 042D21A (14 AEs, 20.9%), 3002182 (4 AEs, 20.0%), 3002187 (4 AEs, 19.0%), 044D21A (11 AEs, 19.0%), and 101 additional lots had detectable safety signals (Table S8); and the COVID-19 Pfizer–BioNTech vaccine lots FL3210 (7 AEs, 23.3%), FA9091 (38 AEs, 22.9%), FA9094 (19 AEs, 21.6%), FA9099 (38 AEs, 21.0%), FD7206 (37 AEs, 20.6%), EY0578 (28 AEs, 20.4%), and 373 additional lots had detectable safety signals (Table S9).

3.2. Human papillomavirus vaccine adverse event patterns

For HPV vaccines, three groups of candidate AEP signatures: HPV, neuropathy, and fetus were identified (Figure 3). For AE CRPS, the HPV vaccine (Cervarix) had a value of 1,101 (50 AEs; $P_{\text{female}} = 4,539$). For AE orthostatic intolerance, the HPV vaccines Cervarix and Gardasil had values of 2,137 (97 AEs; $P_{\text{female}} = 4,539$) and 557 (159 AEs; $P_{\text{female}} = 28,530$), respectively. For AE post-vaccination syndrome, HPV (Cervarix) had a value of 2,952 (134 AEs; $P_{\text{female}} = 4,539$), while DTP (Tri-Immunol) + *Hemophilus influenzae* type B (Hib) (HibTITER) had a value of 465 (5 AEs; $P_{\text{female}} = 1,073$). The AEP_{fetus} signature was identified for abortion induced, caesarean section, and fetal disorder occurring for HPV Gardasil at 421, 554, and 497 per 100,000 VAERS reports, respectively, while 92%, 90%, and 99% lower, respectively, for HPV Gardasil 9. Four candidate AEP_{HPV} signatures were identified in the HPV Cervarix vaccine, two in HPV Gardasil, one in HPV Gardasil 9, and one in the DTP Tri-Immunol vaccine. (Figure 3A). The candidate AEP_{neuropathy} signatures are illustrated in Figure 3B; the normalized frequency for cognitive disorder for Hib (Tetracoq) of 53,333 per 100,000 (based on 8 AEs of 15 VAERS reports) is not shown due to a high value. Normalized frequencies greater than 1,000 included HPV (Cervarix) (population: 4,539) for altered state of consciousness (1,498; 68 AEs), autonomic nervous system imbalance (1,916; 87 AEs), chronic fatigue syndrome (1,520; 69 AEs), cognitive disorder (3,018; 137 AEs), mental impairment (1,806; 82 AEs), and POTS (1,211; 55 AEs); HPV (Gardasil 9) + HPV (Gardasil) (population = 286) for cognitive disorder (2,797; 8 AEs) and POTS (4,895; 14 AEs); HPV (Gardasil) (population = 28,530) for POTS (1,493; 426 AEs); and Lyme (Lymerix) (population = 4,845) for cognitive disorder (4,845; 47 AEs). The COVID-19 (Pfizer–BioNTech bivalent) vaccine had a contusion normalized frequency of 365 (56 AEs;

population = 15,330), a heavy menstrual bleeding value of 241 (37 AEs; population = 15,330), and the dengue tetravalent (Dengvaxia) had a hemorrhage value of 6,299 (16 AEs; population = 254) and a heavy menstrual bleeding value of 2,755 (7 AEs; population = 254). In addition to the AEP_{hemorrhage} and AEP_{gynecologic} signatures that include “abortion spontaneous,” the AEP_{fetus} signature included abortion induced, caesarean section, and fetal disorder (Figure 3C). Normalized frequencies larger than 1,000 included RSV (Abrysvo) caesarean section with a value of 2,190 (32 AEs; population = 1,461) and Rubella (Meruvax II) fetal disorder with a value of 1,408 (9 AEs; population = 639). The AEP_{fetus} signature was not identified in any COVID-19 vaccines. Most Cervarix HPV lots had fewer than 50 total AEs reported; examples include lots AHPVA161BA and AHPVA16AA, with multiple reports of multiple AEs identified in Figure 3.

Safety signals can be detected for individual lots for multiple AEs for HPV signatures. For smear cervix abnormal, the HPV Gardasil lots 1448U (5 AEs, 4.95% in females), 1967U (5 AEs, 4.5%), 1448U (5 AEs, 5.0%), 1060U (4 AEs, 2.9%), 1061U (4 AEs, 3.4%), and 1757U (4 AEs, 3.8%) had detectable safety signals. For orthostatic intolerance, the HPV Cervarix lots AHPVA149BA (5 AEs, 16.1% in females), AHPVA161BA (5 AEs, 10.6%), AHPVA164BB (4 AEs, 12.5%), and AHPVA143BA (4 AEs, 8.2%) had detectable safety signals. For AE post-vaccination syndrome, the HPV Cervarix lots AHPVA162AA (9 AEs, 22.5%), AHPVA149BA (8 AEs, 25.8%), AHPVA161BA (7 AEs, 14.9%), AHPVA164BB (7 AEs, 21.9%), AHPVA149AA (6 AEs, 26.1%), AHPVA156AB (6 AEs, 33.3%), AHPVA123BA (5 AEs, 38.5%), AHPVA138BA (4 AEs, 8.7%), AHPVA162DA (4 AEs, 13.3%), AHPVA148BA (4 AEs, 17.4%), and AHPVA143BA (4 AEs, 8.2%) had detectable safety signals. For autonomic nervous system imbalance, the HPV Cervarix lots AHPVA164AA (4 AEs, 11.1%) and AHPVA161BA (4 AEs, 8.5%) had detectable safety signals. For chronic fatigue syndrome, the HPV Cervarix lot AHPVA161BA (4 AEs, 8.5%) had a detectable safety signal. The HPV Cervarix lot AHPVA161BA was detected for two AEP_{HPV}, two AEP_{neuropathy}, and mental impairment (4 AEs, 8.5%) signatures for safety signals.

For abortion induced, HPV Gardasil lot 0243U (4 AEs, 9.1%) had a detected safety signal. When stratified by age, abortion induced safety signals were detected for HPV Cervarix for ages 11 to 20 (17 AEs, 0.6%) and ages 21 to 30 (5 AEs, 2.3%); and HPV Gardasil for ages 11 to 20 (101 AEs, 0.4%), ages 21 to 30 (49 AEs, 0.9%), and ages 31 to 40 (4 AEs, 0.7%). For caesarean section, RSV Abrysvo lot HR4961 (5 AEs, 25.0%), HPV Gardasil lot 0523U (5 AEs, 4.6%), and the influenza seasonal Flucelvax quadrivalent

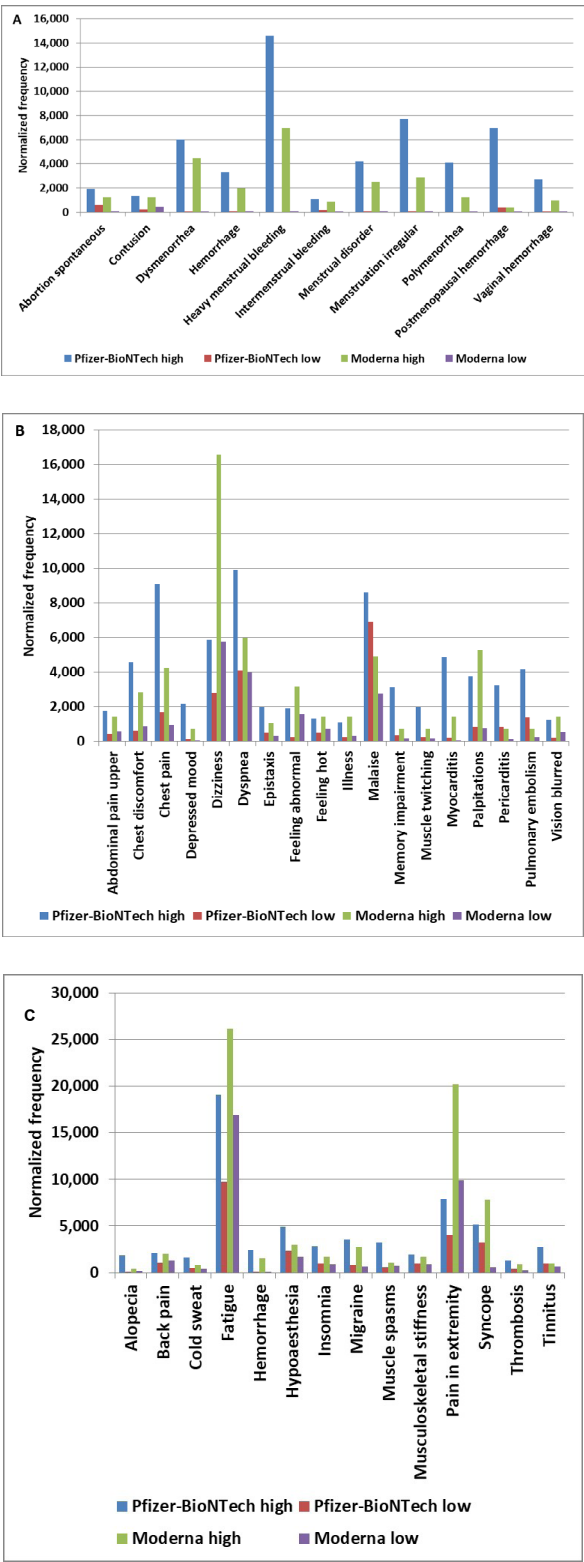


Figure 1. Common top adverse events for COVID-19 Pfizer-BioNTech and Moderna vaccines comparing selected lots with higher menstrual adverse events normalized frequencies to lots with lower normalized frequencies¹⁷ for (A) common female adverse events, (B) common male adverse events, and (C) common adverse events for both genders

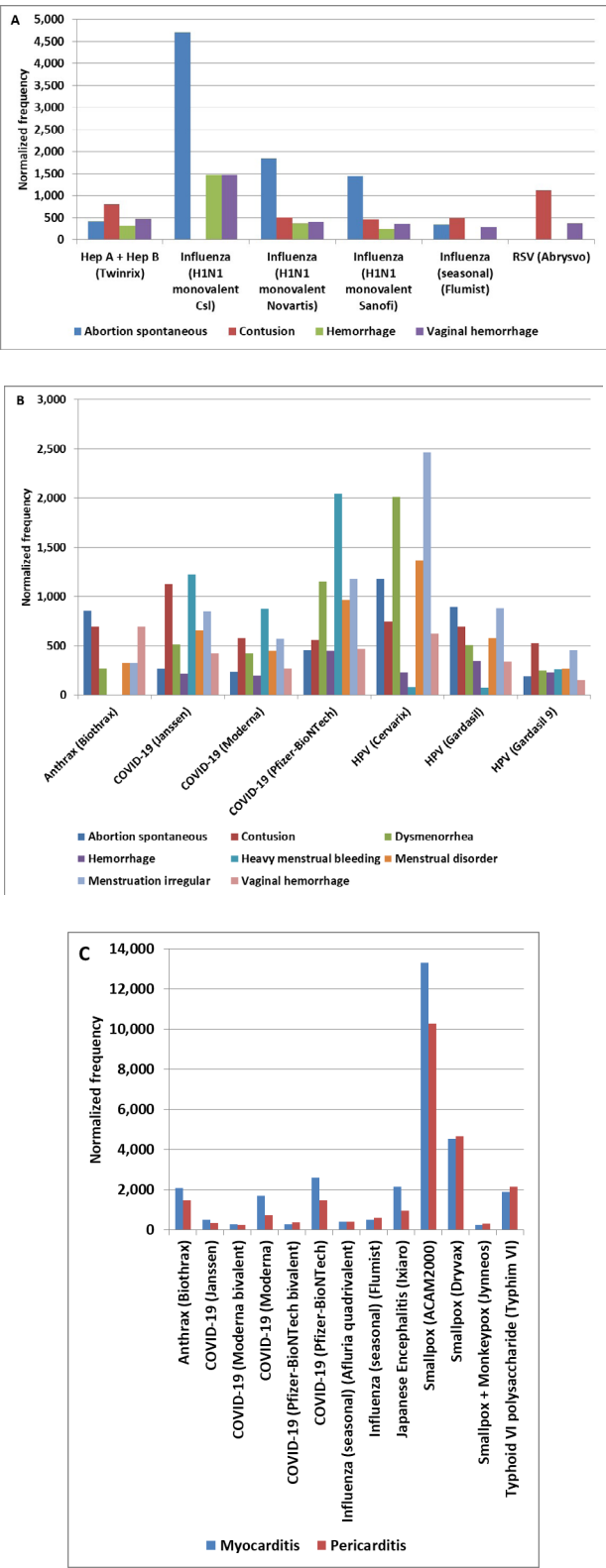
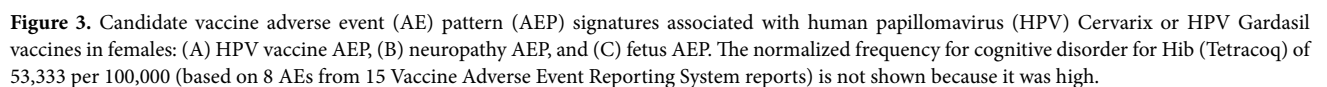


Figure 2. Candidate adverse event pattern signatures associated with (A) hemorrhage (female) adverse event pattern (AEP), (B) gynecologic (including hemorrhage pattern) AEP, and (C) myopericarditis (male-biased) AEP



lots 252664 (13 AEs, 13.0%), 252232 (9 AEs, 30.0%), and 261218 (5 AEs, 31.3%) had detectable safety signals.

3.3. Identified fetal adverse events

The four adverse events (abortion induced, abortion spontaneous, caesarean section, and fetal disorder) are relevant primarily to females of reproductive age; therefore, including females outside the reproductive-age range in the denominator when calculating normalized frequencies is expected to underestimate these frequencies. For comparison purposes, AEs were stratified by three age groups (11 to 20, 21 to 30, and 31 to 40) for abortion induced (Figure 4A), abortion spontaneous (Table S10), caesarean section (Figure 4B), and fetal disorder (Figure 4C). For caesarean section, the normalized frequencies for women aged 20–29 and women aged 30–39 have a Pearson correlation coefficient $r=0.99$ for the seven vaccines (Figure 4B). The manufacturing lot details for the COVID-19 manufacturing lots with 3 or more pregnancy adverse events are shown in Table S11.

4. Discussion

4.1. Candidate adverse event pattern signatures

The candidate manufacturing contamination of specific COVID-19 BioNTech and COVID-19 Moderna lots was identified from statistically significant differences in normalized frequencies for COVID-19 and HPV vaccines for menstrual AEs.¹⁷ Batch-dependent variability of AEs has been reported for the BNT162b2 mRNA COVID-19 vaccine.^{15,16} Rank ordering AEs for both COVID-19 vaccines and focusing upon AEs shared for females, males, and both genders (Figure 1) identified additional candidate AEs potentially linked to putative manufacturing contaminants in these COVID-19 vaccines. Gender-specific normalized frequencies were calculated for these AEs for all vaccines in VAERS. AE-normalized frequency results across all vaccines were consistent with two female-specific and one male-enriched candidate vaccine AEP signatures (Figure 2). Endotoxins are one possible manufacturing contaminant. Endotoxin content varying by vaccine batches has been reported for the Hib vaccine.²⁵ Three additional candidate AEP signatures were identified from HPV Cervarix, HPV Gardasil, and HPV Gardasil 9 vaccine data (Figure 3).

The AEs identified in the AEP_{hemorrhage}, AEP_{gynecologic}, AEP_{myopericarditis}, AEP_{HPV}, AEP_{neuropathy}, and AEP_{fetus} signatures may be linked to specific vaccine components (C) or excipients (E) and not manufacturing contaminants. None of the identified AEs are candidates for population background (B) events, as elevated normalized frequencies were not observed for any other vaccines.

4.2. Adverse event pattern hemorrhage signature

The candidate hemorrhage AEP_{hemorrhage} signature matched six vaccines (Figure 2A), and additional vaccines were included in the overlapping AEP_{gynecologic} signature (Figure 2B); it includes abortion spontaneous, contusion, hemorrhage, and vaginal hemorrhage. Notably, RSV Abrysvo only had elevated AEs for contusion and vaginal hemorrhage (and caesarean section in Figure 3C). In the context of COVID-19 vaccine AEs (Figure 2B), rare cases of vaccine-induced immune thrombotic thrombocytopenia have been reported associated with the Oxford–AstraZeneca adenovirus COVID-19 vaccine^{26,27}, linked to anti-platelet factor 4 antibodies.^{28,29} Cases have been reported of hemorrhage associated with the Moderna^{30–33} and the Pfizer–BioNTech^{33–36} vaccines. These mRNA COVID-19 hemorrhage cases are consistent with the reported hemorrhage data in Figure 1A. A case of suspected pulmonary hemorrhage associated with the monovalent H1N1 influenza vaccine has been reported³⁷; this case report aligns with the AEP_{hemorrhage} signature in Figure 2A. Aside from COVID-19 adenovirus-associated thrombocytopenia, hemorrhage safety signals were detectable for other COVID-19 vaccines in the VAERS database. Three influenza H1N1 monovalent CSL, Novartis, and Sanofi vaccines matched the AEP_{hemorrhage} signature; for these vaccines, the candidate causative component may be one of the H1N1 influenza proteins rather than shared manufacturing contaminants.

4.3. Adverse event pattern gynecologic signature

The candidate gynecologic AEP_{gynecologic} signature matched eight AEs for seven vaccines (Figure 2B); this study builds upon these previously identified candidate safety signals.¹⁷ For abortion spontaneous, the pregnancy status of women was not available, and the denominator for the normalized frequency calculation included both pregnant and nonpregnant women; hence, the calculated normalized frequencies may be substantial underestimates. The spontaneous abortion signal has also been detected for HPV bivalent and non-valent vaccines.³⁸ A study of 638 women receiving HPV quadrivalent during pregnancy found no adverse pregnancy or birth outcomes.³⁹ A retrospective study of 2,800 women receiving HPV quadrivalent during pregnancy was not significantly correlated with an increased risk for spontaneous abortion.⁴⁰ No association with spontaneous abortion and adverse birth outcomes was identified for the 9-valent HPV vaccine.⁴¹ While these studies did not detect safety signals associated with HPV vaccines in these population samples, this study detected safety signals in VAERS database data associated with the AEP_{gynecologic} signature. The candidate signature results have not been adjusted for female pregnancy status or

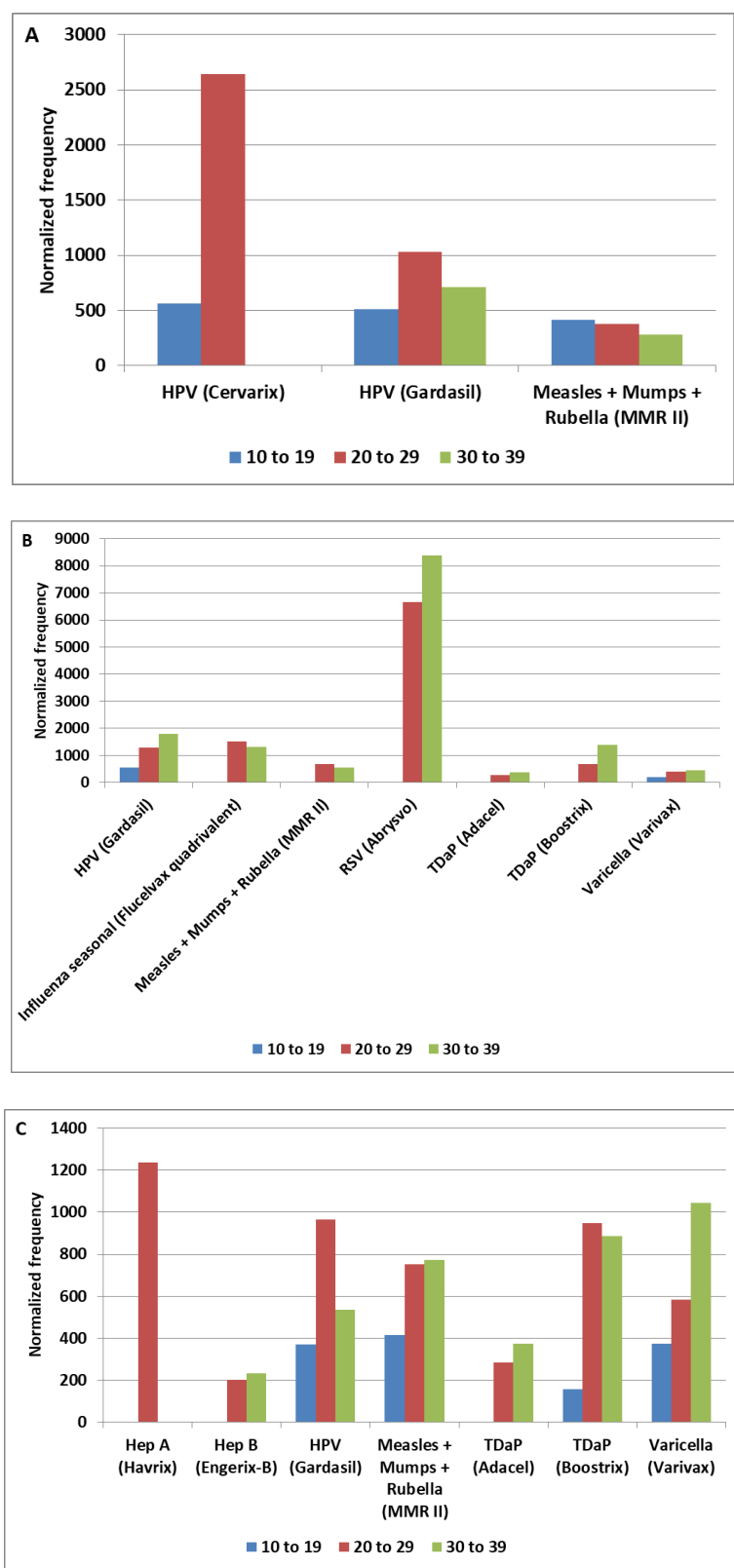


Figure 4. Adverse events normalized frequencies by age group for (A) abortion induced, (B) caesarean section, and (C) fetal disorder

comorbidities, which are not tracked by VAERS data fields outside of text descriptions.

4.4. Adverse event pattern myopericarditis signature

Myocarditis and pericarditis are well-known COVID-19 mRNA vaccine-associated AEs.⁴²⁻⁵³ The candidate male-enriched myopericarditis, AEP_{myopericarditis} signature, matched 13 vaccines (Figure 2C). The smallpox vaccines ACAM2000 and Dryvax are both live, attenuated vaccinia virus vaccines. The smallpox + monkeypox (Jynneos) vaccine is based on live attenuated modified vaccinia Ankara virus that cannot replicate in human cells. For the smallpox vaccines, the normalized frequencies were calculated using the total number of all AEs reported to VAERS for males (ACAM2000 $n=2,260$, Dryvax $n=2,280$, and Jynneos $n=1,722$), with observed differences consistent with replication in human cells due to likely differences among the attenuated vaccinia viruses (Figure 2C). For smallpox ACAM2000 AE reports in VAERS for males, the myocarditis normalized frequency was 13,318 per 100,000 VAERS reports (1 in 7.5), and the pericarditis normalized frequency was 10,265 per 100,000 VAERS reports (1 in 9.7) (Figure 2C). Activation of mast cells by smallpox ACAM2000, smallpox Dryvax, and other vaccines may be associated with AEP_{myopericarditis} AEs.⁴² Differences between the COVID-19 Pfizer–BioNTech with subsequent bivalent version and the COVID-19 Moderna with subsequent bivalent version for both males and females by age groups are illustrated in Figure 5. Lower myocarditis adverse event normalized frequencies for both COVID-19 bivalent vaccines indicate likely reductions in causative component(s).

4.5. Adverse event pattern human papillomavirus signature

The AEP_{HPV} candidate signature included CRPS, orthostatic intolerance, post-vaccination syndrome, and smear cervix abnormal AEs (Figure 3A). Orthostatic intolerance is an AE in which a vaccinee experiences symptoms such as dizziness, lightheadedness, or fatigue when standing up, relieved by sitting or lying down. A case of post-vaccination syndrome has been reported following HPV Cervarix vaccination.⁵⁴ Three overlapping reports describe multiple Japanese patients with orthostatic intolerance, CRPS, and/or cognitive dysfunction following HPV Cervarix or HPV Gardasil vaccination.⁵⁵⁻⁵⁷ These four AEs occurred at higher frequencies for one or more HPV vaccines, all four AEs for HPV Cervarix, and only post-vaccination syndrome had a detectable signal for DTP Tri-Immunol.

4.6. Adverse event pattern neuropathy signature

The AEP_{neuropathy} candidate signature included altered state of consciousness, autonomic nervous system imbalance, chronic fatigue syndrome, cognitive disorder, mental impairment, and POTS (Figure 3B). Similar to the Lyme (Lymerix) vaccine (population_{female} = 970) cognitive disorder safety signal (4,845; 47 AEs) shown in Figure 3B, safety signals for amnesia (6,161; 65 AEs) and nervous system disorder (5,154; 50 AEs) were also identified in the VAERS data for the Lyme (Lymerix) vaccine. For the altered state of consciousness safety signal detected for the *Meningococcal B* (Bexsero), *Meningococcal B* (Trumenba), and *Meningococcal conjugate* (Menactra) vaccines, this AE may involve a vaccine component rather than a less likely shared manufacturing contaminant. POTS AEs were only evident in the HPV Cervarix, HPV Gardasil, HPV Gardasil 9, and COVID-19 Novavax vaccines. For cognitive disorder, the normalized frequency for HPV Gardasil was 795 (795 AEs, population_{female} = 28,530) and HPV Gardasil 9 was 200 (16 AEs, population_{female} = 7,984), and when concurrently coadministered, it was 2,797 for HPV Gardasil 9+HPV Gardasil (8 AEs, population_{female} = 286) (Figure 3B), which is higher than the sum of the normalized frequencies for each HPV vaccine administered individually. Likewise, the AE POTS normalized frequency for HPV Gardasil was 1,493 (426 AEs, population_{female} = 28,530), 901 for HPV Gardasil 9 (72 AEs, population_{female} = 7,984), and 4,895 when concurrently coadministered (HPV Gardasil 9+HPV Gardasil; 14 AEs, population_{female} = 286) (Figure 3B), which is again higher than the sum of the normalized frequencies for each HPV vaccine administered individually.

4.7. Abortion spontaneous adverse events and adverse event pattern fetus signature

In 2021, the United States Centers for Disease Control and Prevention stated that, “COVID-19 vaccination before and during pregnancy is safe, effective, and beneficial to both the pregnant woman and the baby.”⁵⁸ The observed normalized frequencies for abortion spontaneous were 455 per 100,000 VAERS reports for COVID-19 Pfizer–BioNTech, 263 per 100,000 for COVID-19 Janssen, and 234 per 100,000 for COVID-19 Moderna vaccines. Lower abortion spontaneous normalized frequencies were observed for the COVID-19 Pfizer–BioNTech bivalent (45 per 100,000 VAERS reports) and the COVID-19 Moderna bivalent (97 per 100,000 VAERS reports) vaccines. For the abortion induced, caesarean section, and fetal disorder, the pregnancy status of women was not available, and the denominator for the normalized frequency calculations included both pregnant and non-pregnant women; hence,

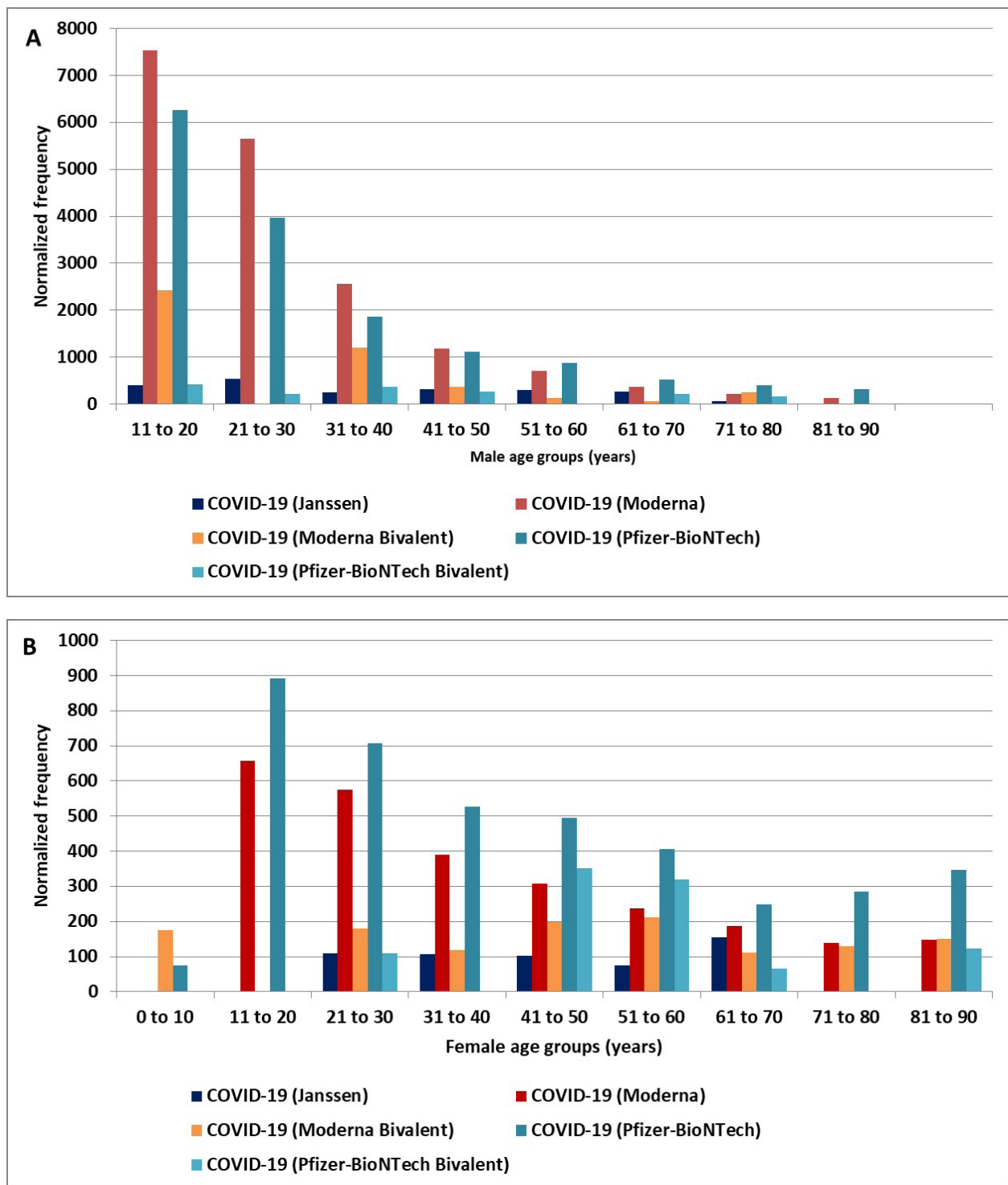


Figure 5. Myocarditis adverse events normalized frequencies by age group for (A) males and (B) females

the calculated normalized frequencies may be substantial underestimates. Activation of innate immune responses, including mast cells and elevated histamine levels, may contribute to the age group safety signals detected for spontaneous abortion (**Table S10**). The AEP_{fetus} candidate signature included abortion induced, caesarean section, and fetal disorder AEs (**Figures 3C A and 4**). The normalized frequencies for these three AEs were calculated based on the total of all AEs reported by females immunized with these vaccines—not pregnant females. The normalized frequencies would be higher if the pregnancy status of females were known for these VAERS AE reports and used as the denominator in these normalized frequency calculations; this also applies to the abortion spontaneous AEs included in the AEP_{hemorrhage} and AEP_{gynecologic} signatures (**Figure 2**). **Figure 4** shows AEs by age group; identifying AE safety signals in two or three age categories provides independent validation of the safety signal detections. While the above Centers for Disease Control and Prevention claim may be true for COVID-19 vaccines in general, it may be incorrect for lots with predicted higher levels of manufacturing contaminants. Endotoxins are one candidate group of manufacturing contaminants that are worthy of characterization in the identified COVID-19 lots.¹⁷ The candidate signature results have not been adjusted for female pregnancy status or comorbidities, which are not tracked by VAERS data fields outside of text descriptions.

Varicella (Varivax) is a live attenuated varicella vaccine; it is contraindicated during pregnancy due to the theoretical risk of causing congenital varicella syndrome. Safety signals were observed for Varicella (Varivax) for caesarean section (**Figure 4B**) and fetal disorder (**Figure 4C**). The measles + mumps + rubella vaccine also contains live attenuated measles, mumps, and rubella viruses; abortion induced, caesarean section, and fetal disorder were detected for this vaccine (**Figure 4A-C**). Similar safety signals were observed for the Tdap Adacel and Boostrix vaccines (**Figure 4B and C**); these vaccines contain inactivated tetanus toxoid, inactivated diphtheria toxoid, inactivated pertussis toxoid, and pertussis component pertactin, along with aluminum adjuvant and trace amounts of formaldehyde; one or more of these components may be associated with the detected safety signals.

4.8. Endotoxins–lipopolysaccharides–pyrogens

Lipopolysaccharides, also known as endotoxins or pyrogens, are constituents of the outer membrane of Gram-negative bacteria. Endotoxins are a common manufacturing contaminant of vaccines. Detected levels of endotoxins can vary widely by vaccine.^{59,60} Endotoxins can disrupt female reproductive function.⁶¹ Reiterating Geier

et al., “selection of vaccine lots with the least endotoxin might reduce some of the adverse effects of vaccinations”.⁵⁹ Nanoparticles should be manufactured under endotoxin-free conditions.⁶² For COVID-19 vaccines, endotoxins represent potential manufacturing contaminants that should be evaluated in future studies to confirm or exclude their presence in the identified lots. Associations between potential manufacturing contaminants, including endotoxins, and the identified candidate safety signals remain hypothetical and cannot be established from the present study.

4.9. Safety signals and signatures

This study aimed to examine patterns of safety signals identified by differences between HPV vaccines and by differences between COVID-19 mRNA vaccine manufacturing lots. Differences can occur between vaccine distribution patterns by patient age and gender, resulting in different patterns of AEs (e.g., HPV vaccines have a biased distribution with more females than males, with age skewing toward teenagers). Yet, the myocarditis and pericarditis safety signals were not associated with any of the three HPV vaccines. This may be an indicator that the causative agent(s) in the HPV vaccines are distinct from the causative agent(s) in the COVID-19 vaccines; a key distinction is the AEP_{myopericarditis} signature. For the HPV Cervarix, HPV Gardasil, and HPV Gardasil 9 vaccines, 19, 15, and 11 safety signals were identified, respectively. Nine safety signals were identified as part of the AEP_{gynecologic} and the AEP_{myopericarditis} signatures for the COVID-19 Janssen, COVID-19 Moderna, and COVID-19 Pfizer-BioNTech vaccines; for the COVID-19 Moderna vaccine, the AE hemorrhage safety signal was not detected, but in Moderna manufacturing lot 3002332, the overall normalized frequency was 1,567 (18 AEs, population=1,148) and in males 1,703 (3,111 AEs, population_{male}=182,573). While the AEP_{myopericarditis} signature was detected in both the COVID-19 Moderna bivalent and COVID-19 Pfizer-BioNTech bivalent vaccines, the AEP_{gynecologic} signature was not detected; this suggests the causative agent of the AEP_{gynecologic} signature was either reduced in concentration or possibly eliminated. The absence of AEP_{gynecologic} AE safety signals from both COVID-19 mRNA bivalent vaccines is consistent with the causative agent being manufacturing contaminants rather than the Spike protein, lipid nanoparticles, or other vaccine excipients shared between the original and the more recently developed bivalent vaccines.

Multiple AEP signatures might be linked with elevated histamine levels associated with possible manufacturing contaminants, vaccine components, and live attenuated virus vaccines activating innate immune responses,

including activation of mast and platelet cells. First, the Anthrax (Biothrax) vaccine matches the AEP_{gynecologic} and AEP_{myopericarditis} signatures, cognitive disorder in AEP_{neuropathy} and fetal disorder in the AEP_{fetus} signature. Possible *Bacillus* protein manufacturing contaminants could exacerbate innate immune responses. Second, in parallel to the AE caesarean section safety signal for RSV (Abrysvo)=1,967 (37 AEs, population_{female}=1,881) (Figure 3C), other AEs including premature delivery (5,794; 109 AEs), premature baby (1,063; 20 AEs), and premature labor (2,817; 53 AEs) were also in the VAERS data. The RSV (Abrysvo) vaccine is recommended for pregnant individuals at 32 to 36 weeks of gestation to protect infants. Third, the AEs myocarditis and pericarditis safety signals detected for the smallpox vaccines Dryvax and ACAM2000 were also detected with the AE chest pain, with normalized frequencies of 13,777 (1 in 7.3) and 20,266 (1 in 4.9) for Dryvax and ACAM2000, respectively; for males, AE chest pains normalized frequencies for Dryvax (15,219; 347 AEs) and ACAM2000 (23,495; 531 AEs) were observed. The normalized frequencies for these three safety signals were lower for the smallpox + monkeypox (Jynneos) vaccine (Figure 2C), suggesting possible differences in causative component concentrations consistent with the replication ability of live, attenuated vaccinia viruses. Follow-up studies are suggested to investigate the identified safety signals.

4.10. Study limitations

The VAERS is a passive, voluntary surveillance system. Results based on VAERS data are hypothesis-generating rather than causal. VAERS data lacks clinical verification of reported AEs. Identified candidate safety signals cannot prove that a vaccine caused an AE; all AEs include population background AEs. The VAERS system receives only a small fraction of actual AEs, particularly for minor or well-known AEs; likewise, the total number of people vaccinated cannot be determined (referred to as “Lack of Denominator Data”). Here, all normalized frequencies were based on the total number of AEs reported to VAERS by vaccine as an alternative to the lack-of-denominator issue. The calculated normalized frequencies are higher than population frequencies because the sampled population data lack asymptomatic individuals. The results presented herein lack an unvaccinated comparison group to determine background event frequencies; therefore, AE-normalized data were used for comparisons with other vaccines. For all vaccines, serious AEs are more likely to be reported than minor AEs; candidate safety signals can be identified by comparing serious AE-normalized frequencies between vaccines with matched populations (age and sex). VAERS data is subject to reporting bias

in response to media attention, public awareness, and legal action; this can create false or inflated safety signals. Adverse events in VAERS can be overreported or underreported. Confounding factors can include differences in age, gender, demographic differences, healthcare-seeking behavior, vaccine uptake, and temporal changes in reporting. This exploratory study examines the safety signatures of candidate manufacturing contaminants following immunization; hence, it could not control for unknown confounders. AEs following immunization can represent background AEs, possible vaccine-associated AEs, and possible manufacturing contaminant AEs. The evidence herein identifies candidate safety signals and does not establish causality for associated AEs. Based on the observed patterns of safety signals, candidate vaccines have been identified for future investigation of potential COVID-19 vaccine manufacturing contaminants. However, the specific manufacturing contaminants responsible for these signals have not yet been identified. This exploratory study aimed to identify candidate AEP signatures and presented only four *p*-values of 0.00000. False positives in the candidate safety signatures identified within the AEP patterns likely reflect the multiple AEs and vaccines examined.

5. Conclusion

This study identified six candidate AEP signatures: AEP_{hemorrhage}, AEP_{gynecologic}, AEP_{myopericarditis}, AEP_{HPV}, AEP_{neuropathy}, and AEP_{fetus} signatures. Future studies could identify the causative agents correlated with these patterns to reduce or replace them in vaccines, thereby reducing associated AEs and SAEs. Live attenuated virus vaccines were associated with safety signals for hemorrhage (1 vaccine), myopericarditis (4 vaccines), neuropathy (2 vaccines), and fetal disorder (2 vaccines).

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Conflict of interest

The authors declare they have no competing interests.

Author contributions

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Not applicable.

Consent for publication

Not applicable.

Availability of data

The data analyzed in this study is available at <https://doi.org/10.7910/DVN/3BT4JR>, Harvard Dataverse, V1.

Further disclosure

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