Simultaneous vaccine administration and co-administration with COVID-19 vaccine in the Vaccine Safety Datalink

Investigators:
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Other investigators from sites: TBD

Role of CDC and collaborating sites: CDC will be leading the analysis and taking primary responsibility for protocol development, data analysis, and interpretation of results. CDC will have access to coded, private information. All VSD sites participating in COVID-19 Rapid Cycle Analysis (RCA) surveillance (VSD #1342) are invited and encouraged to participate. Sites will provide feedback on the design and assist with the preparation of reports for publication.

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Summary

This project will describe: 1) the occurrence of simultaneous vaccine administration (i.e., vaccine administered on same day as COVID-19 vaccine) with any dose of COVID-19 vaccine among individuals of any age, 2) vaccine co-administration (i.e., vaccine administered 1-14 days before or after COVID-19 vaccine administration) with any dose of COVID-19 vaccine among individuals of any age, and 3) any pre-specified outcomes that occur post COVID-19 vaccination among individuals of any age who received simultaneous vaccine and/or co-administered vaccine with any dose of COVID-19 vaccine in the Vaccine Safety Datalink (VSD).

Background

Vaccines are a vital component to ending the coronavirus disease 2019 (COVID-19) pandemic. On December 11, 2020, the U.S. Food and Drug Administration (FDA) issued the first Emergency Use Authorization (EUA) for the use of the two-dose Pfizer-BioNTech COVID-19 vaccine (Pfizer) for persons 16 years of age and older.[1] On December 18, 2020 the FDA issued a second EUA for the use of the two-dose Moderna COVID-19 vaccine in persons 18 years of age and older, and on February 27, 2021 the FDA issued a third EUA for the use of the one-dose Janssen COVID-19 vaccine for persons 18 years of age and older.[2,3] On May 10, 2021, the FDA expanded the Pfizer COVID-19 vaccine EUA to authorize use in persons 12-15 years of age.[4]

Experimental evidence and clinical experience support the practice of simultaneous vaccine administration.[5] At the beginning of the U.S. COVID-19 vaccination program it was recommended by the Advisory Committee on Immunization Practices (ACIP) out of caution that COVID-19 vaccines be administered alone with a minimum interval of 14 days before or after any other vaccine administration.[6] Due to the availability of sufficient safety data on COVID-19 vaccine administration, and the "extensive experience with non-COVID-19 vaccines that have demonstrated that immunogenicity and adverse event profiles are generally similar when vaccines are administered simultaneously as when they are administered alone", the recommendation was updated.[7] As of May 12, 2021, the current co-administration recommendation is as follows: "COVID-19 vaccines and other vaccines may now be administered without regard to timing. This includes simultaneous administration of COVID-19 vaccine and other vaccines on the same day, as well as co-administration within 14 days."[7,8]

Since 2010, the ACIP has recommended routine influenza vaccination for all persons aged ≥6 months.[9] In the VSD, the total number of influenza vaccines administered has steadily increased from over 3.6M doses in 2010 to over 6M doses in 2019. In 2020, throughout the COVID-19 pandemic, the number of administered influenza doses dropped to 5.6M doses; however, based on historical trends we expect to see a rise in influenza vaccination among the VSD population in 2021 and 2022. The COVID-19 pandemic also had an impact on routine pediatric vaccine ordering and administration in the United States. After the COVID-19 emergency declaration in March 2020, there were substantial reductions in Vaccines for Children (VFC) funded pediatric (≤18 years of age) vaccine orders. There was also a corresponding decline observed in measles-containing pediatric vaccine administration in the VSD.[10] Subsequent analyses of immunization information systems data from 10 U.S. jurisdictions during the period of March-September 2020 also observed that fewer administered doses of routine childhood and adolescent vaccines were recorded compared with the same period in 2018 and 2019 in all 10 jurisdictions. The number of vaccine doses administered did increase during June-September 2020 to near pre-pandemic baseline levels, but this increase was not sufficient to achieve catch-up coverage.[11] Adolescents are more likely than adults to have simultaneous vaccine administration and co-administration with COVID-19 vaccine as they return to in-person school and complete well-child visits

during the summer. Most states require incoming sixth or seventh graders to receive the Tetanus-diphtheria-pertussis booster (Tdap) and varicella (chickenpox) vaccines, and the ACIP recommends 11-12-year-old adolescents also receive the human papillomavirus (HPV) and the meningococcal vaccines.[12,13]

Due to the novelty of COVID-19 vaccines, safety data are not yet available for simultaneous vaccine administration and co-administration with COVID-19 vaccine under EUA in the United States. Pfizer initiated a study to explore co-administration of its 20-valent pneumococcal conjugate vaccine candidate with a third dose of the Pfizer COVID-19 vaccine among adults 65 years of age or older in May 2021, but results of this study are not yet available.[14] Novavax, Inc. conducted a sub-study as part of their phase 3 randomized trial of the safety and efficacy of dose 1 of NVX-CoV2373 (Novavax, Inc. COVID-19 vaccine candidate) and an age-appropriate, licensed influenza vaccine among individuals 18 to <65 years old. They found that rates of unsolicited adverse events, medically attended events, and serious adverse events were low and balanced between the two groups (i.e., those who received dose 1 of NVX-CoV2373, and those who received an age-appropriate, licensed, influenza vaccine with dose 1 of NVX-CoV2373).[15]

It is important to monitor simultaneous vaccine administration and/or co-administration with COVID-19 vaccines under EUA in the United States to identify and investigate potential safety signals. This is especially important as adolescents complete well-child visits before returning to in-person school. We propose to do this project in two-phases. Our objective in Phase 1 is to describe the occurrence of simultaneous vaccine administration and co-administration within 14 days of any dose of COVID-19 vaccine among individuals of any age, to look at descriptive statistics presented by age to describe any differences observed in simultaneous and/or co-administered vaccination with COVID-19 vaccine among adolescents compared to adults, and to describe any pre-specified outcomes that occur following simultaneous and/or co-administered vaccine administration with any dose of COVID-19 vaccine among individuals of any age in the VSD. If outcomes among individuals who received simultaneous and/or co-administered vaccines with any dose of COVID-19 vaccine are more common than in people who received COVID-19 vaccine without simultaneous and/or co-administered vaccine in Phase 1, we will develop an analytical plan for assessing the safety of simultaneous and/or co-administered vaccination as Phase 2. However, Phase 2 will be conducted only for those outcomes of which the number of cases observed among individuals who received simultaneous and/or co-administered vaccines is large enough that sufficiently powered safety analyses can be conducted. This activity will primarily utilize data from the ongoing COVID-19 Rapid Cycle Analysis (RCA) surveillance for COVID-19 vaccines (VSD #1342). The remainder of this protocol focuses on describing Phase 1.

Phase 1

Phase 1 Aims

Aim 1: To describe simultaneous vaccine administration with any dose of COVID-19 vaccine among individuals of any age in the VSD, describe differences in the frequency of simultaneous vaccine administration before and after the May 12, 2021 ACIP guidance, and describe any differences between adolescent and adult vaccinees.

Aim 2: To describe vaccine co-administration within 14 days before and after any dose of COVID-19 vaccine among individuals of any age in the VSD, describe differences in vaccine co-administration

before and after the May 12, 2021 ACIP guidance, and describe any differences between adolescent and adult vaccinees.

- **Aim 3:** To monitor pre-specified outcomes post COVID-19 vaccination among individuals of any age who received simultaneous and/or co-administered vaccine with any dose of COVID-19 vaccine, describe the frequency of such outcomes, and assess whether such outcomes occur more frequently among individuals who received simultaneous and/or co-administered vaccine compared with COVID-19 vaccinees not receiving simultaneous and/or co-administered vaccines.

Phase 1 Methods and Analysis Plan

Design: Retrospective cohort analysis utilizing automated data

Time Period: November 27, 2020 through TBD

Population: Individuals enrolled in participating VSD sites, including adolescents ≤17 years old and adults ≥18 years old

Data Source: VSD COVID-19 RCA surveillance data (VSD #1342) and VSD dynamic data files (DDF)

Aim 1: To describe simultaneous vaccine administration with any dose of COVID-19 vaccine among individuals of any age in the VSD.

Inclusion Criteria: Individuals of any age enrolled in participating VSD sites on the date of COVID-19 vaccination who received at least one dose of any COVID-19 vaccine.

Exposure Definition: Individuals who received at least one simultaneous vaccine during the study period with any dose of COVID-19 vaccine. Centers for Disease Control and Prevention (CDC) CVX codes will be used to identify COVID-19 vaccine types and simultaneous vaccine types administered.[16] COVID-19 vaccine types not under EUA or licensed in the U.S. will be excluded. Unspecified/unknown COVID-19 vaccine types and simultaneous vaccine CVX codes that do not match to any CDC CVX codes will be excluded. Individuals with a simultaneous CDC CVX vaccine code of 998 ("No vaccine administered") will be excluded from analyses. Simultaneous vaccine types that contain non-vaccine CVX codes (e.g., immune globulin) will be included in the analyses to explore non-vaccine administration with COVID-19 vaccines. Capture of non-vaccine CVX codes is not complete in VSD files. Simultaneous vaccines will be grouped into vaccine families (see Supplementary Table 1 for a crosswalk of vaccines grouped by vaccine family).

Outcomes: The primary outcomes are the frequency and pattern of simultaneous vaccine administration with any dose of COVID-19 vaccine within the study population.

Analysis Plan:

- Describe the number and proportion of individuals who received at least one simultaneous vaccine type with any dose of COVID-19 vaccine compared to the number and proportion of individuals who did not receive any simultaneous vaccines with any dose of COVID-19 vaccine,

by COVID-19 vaccine type and dose number before 5/12/2021 and on or after 5/12/2021 (Table 1).

- Describe the number and proportion of individuals who received simultaneous vaccines, grouped by vaccine family, with any dose of COVID-19 vaccine, by COVID-19 vaccine type and dose number before 5/12/2021 and on or after 5/12/2021 (Table 2).
  Describe the characteristics of individuals who received simultaneous vaccines, including demographics, VSD site, high-risk status for COVID-19 disease, and pregnancy status at time of vaccination, before 5/12/2021 and on or after 5/12/2021 (Table 3 and 4).
- Describe any differences observed in simultaneous vaccination trends among adolescents compared to adults.

Table 1. Number and proportion of individuals who received at least one simultaneous vaccine type, by COVID-19 vaccine type and dose number

Received at least one simultaneous vaccine	Pfizer Dose 1	Pfizer Dose 2	Moderna Dose 1	Moderna Dose 2	Janssen	Total
Before 5/12/2021						
Yes	N (% of column sub-total)					
No						
Sub-Total						
On or after 5/12/2021						
Yes	N (% of column sub-total)					
No						
Sub-Total						
Grand Total						

Table 2. Number and proportion of simultaneous vaccine doses administered with COVID-19 vaccine, by vaccine family, and COVID-19 vaccine type and dose number*

	Before 5/12/2021						On or after 5/12/2021					
Vaccine Family	Pfizer Dose 1	Pfizer Dose 2	Moderna Dose 1	Moderna Dose 2	Janssen	Total	Pfizer Dose 1	Pfizer Dose 2	Moderna Dose 1	Moderna Dose 2	Janssen	Total
Vaccine family	N (% of column total)											
Vaccine family												
…												
…												
Total												

***** Note: Table is an example and vaccine families will be filled in when available.

Table 3. Characteristics of individuals who received at least one simultaneous vaccine with any dose of COVID-19 vaccine before 5/12/2021*

Characteristic	Vaccine Family	Vaccine Family	Vaccine Family	Vaccine Family	Vaccine Family	Vaccine Family	Vaccine Family	Vaccine Family
Age category at COVID-19 vaccination, median (SD), years								

Adolescents 12-17 years								
Adults ≥18 years								
Female sex, No (%)								
Race, No (%) Hispanic/Latino, No (%) American Indian/Alaska Native Asian Black Native Hawaiian/other Pacific Islander White Multiple/Other Unknown								
VSD site, No (%)** Kaiser Permanente Northern California Kaiser Permanente Colorado Marshfield Clinic Kaiser Permanente Northwest Kaiser Permanente Southern California Kaiser Permanente Washington Health Partners Denver Health								
High-risk for COVID-19 disease, Yes (%)								
History of COVID-19 disease, Yes (%)								
Pregnancy Status, Pregnant (%)								

***** Note: Table is an example and vaccine families will be filled in when available. Individuals who received more than one simultaneous vaccine will be counted in the table more than once.

** Note: Site-specific totals will be for internal use only.

Table 4. Characteristics of individuals who received at least one simultaneous vaccine with any dose of COVID-19 vaccine on or after 5/12/2021*

Characteristic	Vaccine Family	Vaccine Family	Vaccine Family	Vaccine Family	Vaccine Family	Vaccine Family	Vaccine Family	Vaccine Family
Age category at COVID-19 vaccination, median (SD), years								
Adolescents 12-17 years								
Adults ≥18 years								
Female sex, No (%)								
Race, No (%) Hispanic/Latino, No (%) American Indian/Alaska Native Asian Black Native Hawaiian/other Pacific Islander White								

Multiple/Other Unknown								
VSD site, No (%)** Kaiser Permanente Northern California Kaiser Permanente Colorado Marshfield Clinic Kaiser Permanente Northwest Kaiser Permanente Southern California Kaiser Permanente Washington Health Partners Denver Health								
High-risk for COVID-19 disease, Yes (%)								
History of COVID-19 disease, Yes (%)								
Pregnancy Status, Pregnant (%)								

***** Note: Table is an example and vaccine families will be filled in when available. Individuals who received more than one simultaneous vaccine will be counted in the table more than once.

** Note: Site-specific totals will be for internal use only.

Aim 2: To describe vaccine co-administration within 14 days before and after any dose of COVID-19 vaccine among individuals of any age in the VSD.

Inclusion Criteria: Individuals of any age enrolled in participating VSD sites on the date of COVID-19 vaccination who received at least one dose of any COVID-19 vaccine.

Exposure Definition: Individuals who received at least one co-administered vaccine during the study period within 14 days of any dose of COVID-19 vaccine. CDC CVX codes will be used to identify COVID-19 vaccine types and co-administered vaccine types. COVID-19 vaccine types not under EUA or licensed in the U.S. will be excluded. Unspecified/unknown COVID-19 vaccine types and co-administered vaccine CVX codes that do not match to any CDC CVX codes will be excluded. Individuals with a co-administered CDC CVX vaccine code of 998 ("No vaccine administered") will be excluded from analyses. Co-administered vaccine types that contain non-vaccine CVX codes (e.g., immune globulin) will be included in the analyses to explore non-vaccine administration with COVID-19 vaccines. Capture of non-vaccine CVX codes is not complete in VSD files. Co-administered vaccine types will be grouped into vaccine families (see Supplementary Table 1 for a crosswalk of vaccines grouped by vaccine family).

Outcomes: The primary outcomes are the frequency and pattern of co-administered vaccines within 14 days of any dose of COVID-19 vaccine within the study population.

Analysis Plan:

- Describe the number and proportion of individuals who received at least one co-administered vaccine, by COVID-19 vaccine type and dose number before 5/12/2021 and on or after 5/12/2021 (Table 5).

- Describe the number and proportion of co-administered vaccine families received with any dose of COVID-19 vaccine, by timing from first and second dose of COVID-19 vaccine, respectively, before 5/12/2021 and on or after 5/12/2021 (Table 6 and 7).
- Describe the number and proportion of co-administered vaccine families received with any dose of COVID-19 vaccine, by COVID-19 vaccine type and dose number before 5/12/2021 and on or after 5/12/2021 (Table 8).
- Describe the characteristics of individuals who received co-administered vaccines, including demographics, VSD site, high-risk status for COVID-19 disease, and pregnancy status at time of vaccination, before 5/12/2021 and on or after 5/12/2021 (Table 9 and 10).
- Explore the timing of co-administered vaccination for those who had multiple instances of co-administered and/or simultaneous vaccines following one or more doses of COVID-19 vaccine. Describe individuals who received multiple co-administered/simultaneous vaccines with one or more doses of COVID-19 vaccine.
- Describe any differences observed in simultaneous vaccination trends among adolescents compared to adults

Table 5. Number and proportion of individuals who received at least one co-administered vaccine, by COVID-19 vaccine type and dose number

Received at least one co-administered vaccine	Pfizer Dose 1	Pfizer Dose 2	Moderna Dose 1	Moderna Dose 2	Janssen	Total
Before 5/12/2021						
Yes	N (% of column total within sub-categories)					
No						
Sub-Total						
On or after 5/12/2021						
Yes	N (% of column total within sub-categories)					
No						
Sub-Total						
Grand Total						
Days since COVID-19 vaccine	N (% of column total within sub-categories)					
10-14 before						
5-9 before						
1-4 before						
1-4 after						
5-9 after						
10-14 after						

Table 6. Number and proportion of co-administered doses with first dose of COVID-19 vaccine, by vaccine family and time since COVID-19 vaccine*

	Before 5/12/2021						On or after 5/12/2021					
Vaccine Family	10-14 days before	5-9 days before	1-4 days before	1-4 days after	5-9 days after	10-14 days after	10-14 days before	5-9 days before	1-4 days before	1-4 days after	5-9 days after	10-14 days after
…	N (%)											

Total												

***** Note: Table is an example and vaccine families will be filled in when available. Individuals who received more than one co-administered vaccine will be counted in the table more than once.

Table 7. Number and proportion of co-administered doses with second dose of COVID-19 vaccine, by vaccine family and time since COVID-19 vaccine*

	Before 5/12/2021						On or after 5/12/2021					
Vaccine Family	**10-14 days before**	**5-9 days before**	**1-4 days before**	**1-4 days after**	**5-9 days after**	**10-14 days after**	**10-14 days before**	**5-9 days before**	**1-4 days before**	**1-4 days after**	**5-9 days after**	**10-14 days after**
…	N (%)											
Total												

***** Note: Table is an example and vaccine families will be filled in when available. Individuals who received more than one co-administered vaccine will be counted in the table more than once.

Table 8. Number and proportion of co-administered vaccine doses, by co-administered vaccine type, COVID-19 vaccine type, and dose number*

	Before 5/12/2021					On or after 5/12/2021				
Vaccine Family	**Pfizer Dose 1**	**Pfizer Dose 2**	**Moderna Dose 1**	**Moderna Dose 2**	**Janssen**	**Pfizer Dose 1**	**Pfizer Dose 2**	**Moderna Dose 1**	**Moderna Dose 2**	**Janssen**
…	N (% of colum n total)									
Total										

***** Note: Table is an example and vaccine families will be filled in when available. Individuals who received more than one co-administered vaccine will be counted in the table more than once.

Table 9. Characteristics of individuals who received at least one co-administered vaccine with any dose of COVID-19 vaccine before 5/12/2021*

Characteristic	**Vaccine Family**	**Vaccine Family**	**Vaccine Family**	**Vaccine Family**	**Vaccine Family**	**Vaccine Family**	**Vaccine Family**	**Vaccine Family**
Days since COVID-19 vaccine								
10-14 before								
5-9 before								
1-4 before								
1-4 after								
5-9 after								
10-14 after								
Age category at COVID-19 vaccination, median (SD), years								
Adolescents 12-17 years								
Adults ≥18 years								
Female sex, No (%)								
Race, No (%) Hispanic/Latino, No (%) American Indian/Alaska Native								

Asian Black Native Hawaiian/other Pacific Islander White Multiple/Other Unknown								
VSD site, No (%)** Kaiser Permanente Northern California Kaiser Permanente Colorado Marshfield Clinic Kaiser Permanente Northwest Kaiser Permanente Southern California Kaiser Permanente Washington Health Partners Denver Health								
High-risk for COVID-19 disease, Yes (%)								
History of COVID-19 disease, Yes (%)								
Pregnancy Status, Pregnant (%)								

***** Note: Table is an example and vaccine families will be filled in when available. Individuals who received more than one co-administered vaccine will be counted in the table more than once.

** Note: Site-specific totals will be for internal use only.

Table 10. Characteristics of individuals who received at least one co-administered vaccine with any dose of COVID-19 vaccine on or after 5/12/2021*

Characteristic	Vaccine Family	Vaccine Family	Vaccine Family	Vaccine Family	Vaccine Family	Vaccine Family	Vaccine Family	Vaccine Family
Days since COVID-19 vaccine								
10-14 before								
5-9 before								
1-4 before								
1-4 after								
5-9 after								
10-14 after								
Age category at COVID-19 vaccination, median (SD), years								
Adolescents 12-17 years								
Adults ≥18 years								
Female sex, No (%)								
Race, No (%) Hispanic/Latino, No (%) American Indian/Alaska Native Asian Black Native Hawaiian/other Pacific Islander White Multiple/Other Unknown								
VSD site, No (%)** Kaiser Permanente Northern California Kaiser Permanente Colorado Marshfield Clinic Kaiser Permanente Northwest Kaiser Permanente Southern California Kaiser Permanente Washington Health Partners Denver Health								
High-risk for COVID-19 disease, Yes (%)								

History of COVID-19 disease, Yes (%)								
Pregnancy Status, Pregnant (%)								

***** Note: Table is an example and vaccine families will be filled in when available. Individuals who received more than one co-administered vaccine will be counted in the table more than once.

** Note: Site-specific totals will be for internal use only.

Aim 3: To describe pre-specified outcomes post COVID-19 vaccination among individuals of any age who received simultaneous and/or co-administered vaccine with any dose of COVID-19 vaccine.

Inclusion Criteria: Individuals of any age enrolled in participating VSD sites on the date of COVID-19 vaccination who received at least one dose of any COVID-19 vaccine.

Exposure Definition: Individuals who received at least one simultaneous vaccine with any dose of COVID-19 vaccine and/or received a co-administered vaccine during the study period within 14 days of any dose of COVID-19 vaccine, and experienced a pre-specified outcome (see Table 8 for list of pre-specified outcomes). CDC CVX codes will be used to identify COVID-19 vaccine types, simultaneous vaccine types, and co-administered vaccine types. COVID-19 vaccine types not under EUA or licensed in the U.S. will be excluded. Unspecified/unknown COVID-19 vaccine types and simultaneous and co-administered vaccine CVX codes that do not match to any CDC CVX codes will be excluded. Individuals with a simultaneous and/or co-administered CDC CVX vaccine code of 998 ("No vaccine administered") will be excluded from analyses. Simultaneously administered and co-administered vaccine types that contain non-vaccine CVX codes (e.g., immune globulin) will be included in the analyses to explore non-vaccine administration with COVID-19 vaccines. Capture of non-vaccine CVX codes is not complete in VSD files. Simultaneous and co-administered vaccine types will be grouped into vaccine families (see Supplementary Table 1 for a crosswalk of vaccines grouped by vaccine family).

Outcomes: The primary outcomes are the frequency and pattern of pre-specified outcomes that occur following any dose of COVID-19 vaccine among individuals who received a simultaneous vaccine, and/or a co-administered vaccine within 14 days of receiving any dose of COVID-19 vaccine. COVID-19 RCA outcomes criteria will be applied, including outcome incidence criteria, settings, risk windows, and exclusion if COVID-19 disease occurred in X prior days (see Supplementary Table 2). Information from chart reviews already completed under the RCA protocol for pre-specified outcomes that occurred will be used to validate any observed outcomes among individuals who had a simultaneous and/or co-administered vaccine with any dose of COVID-19 vaccine. A determination will be made whether to review charts for any observed outcomes not already chart reviewed under the RCA protocol, if such an occasion arises.

Analysis plan:

- Calculate the proportion of individuals who received simultaneous vaccine(s) and/or co-administered vaccines with any dose of COVID-19 vaccine and had pre-specified outcomes compared to the proportion of individuals who did not receive simultaneous and/or co-administered vaccine(s) with any dose of COVID-19 vaccine and had pre-specified outcomes (Table 11). Rate ratios and 95% confidence intervals will be calculated to compare the two groups.
- Describe the proportion of individuals who experienced a pre-specified outcome and received at least one simultaneous and/or co-administered vaccine, by number of simultaneous and/or co-administered vaccines received with any dose of COVID-19 vaccine (Table 12).

- Describe the number and proportion of observed outcomes by type of simultaneous and co-administered vaccine type received (Table 13).
- Describe the characteristics of individuals who experienced any pre-specified outcomes and received at least one simultaneous vaccine, including demographics, VSD site, high-risk status for COVID-19 disease, history of COVID-19 disease, and pregnancy status at time of vaccination, before 5/12/2021 and on or after 5/12/2021 (Table 14).
- Describe the characteristics of individuals who experienced any pre-specified outcomes and received at least one co-administered vaccine, including demographics, VSD site, high-risk status for COVID-19 disease, history of COVID-19 disease, and pregnancy status before 5/12/2021 and on or after 5/12/2021 (Table 15).

Table 11. Number and proportion of individuals who experienced any pre-specified outcomes in the 1-21 days following any COVID-19 vaccine, by COVID-19 vaccine type and dose number

Vaccine Receipt Status	Pfizer Dose 1	Pfizer Dose 2	Moderna Dose 1	Moderna Dose 2	Janssen	Total
No simultaneous vaccines and no co-administered vaccines	N (%)					
1+ simultaneous vaccines and no co-administered vaccines						
1+ co-administered vaccines and no simultaneous vaccines						
1+ simultaneous vaccines and 1+ co-administered vaccines						

Table 12. Number and proportion of individuals who experienced pre-specified outcomes in the 1-21 days following any COVID-19 vaccine, by number of simultaneous and/or co-administered vaccine doses received*

	# Simultaneous Vaccines Received					# Co-administered Vaccines Received				
Pre-specified outcome	**0**	**1**	**2**	**3**	**4+**	**0**	**1**	**2**	**3**	**4+**
ADEM	N (%)									
AMI										
ARDS										
ANAPH										
APPND										
BP										
CVST										
SZ										
DIC										
ENCEPH										
GBS										
ITP										
KD										
MISC, MISA										
MYOC										
NARC										
PE										
HSTK										
ISTK										
TTS										
TTP										
TM										
VTE										

***** Note: Individuals who experienced more than one adverse event will be counted in the table more than once. Anaphylaxis (ANAPH) risk window is 0-1 days; all other outcomes are 1-21 days.

Table 13. Number and proportion of individuals who experienced any pre-specified outcomes in the 1-21 days following any COVID-19 vaccine, by simultaneous and/or co-administered vaccine type*

Outcome	Vaccine Family	Vaccine Family	Vaccine Family	Vaccine Family	Vaccine Family	Vaccine Family	Vaccine Family	Vaccine Family	Vaccine Family	Vaccine Family
Received 1+ Simultaneous Vaccines										
ADEM	N (%)									
AMI										
ARDS										
ANAPH										
APPND										
BP										
CVST										
SZ										
DIC										
ENCEPH										
GBS										
ITP										
KD										
MISC, MISA										
MYOC										
NARC										
PE										
HSTK										
ISTK										
TTS										
TTP										
TM										
VTE										
Received 1+ Co-administered Vaccines										
ADEM										
AMI										
ARDS										
ANAPH										
APPND										
BP										
CVST										
SZ										
DIC										
ENCEPH										
GBS										
ITP										
KD										
MISC, MISA										
MYOC										
NARC										
PE										
HSTK										
ISTK										
TTS										
TTP										
TM										
VTE										

***** Note: Table is an example and vaccine families will be filled in when available. Individuals who received more than one simultaneous and/or co-administered vaccine or experienced more than one adverse event will be counted in the table more than once. Anaphylaxis (ANAPH) risk window is 0-1 days; all other outcomes are 1-21 days.

Table 14. Characteristics of individuals who experienced any pre-specified outcomes on days 1-21 following receipt of at least one simultaneous vaccine with any dose of COVID-19 vaccine, by vaccine family type*

Characteristic	Vaccine Family	Vaccine Family	Vaccine Family	Vaccine Family	Vaccine Family	Vaccine Family	Vaccine Family	Vaccine Family	Totals
Age category at COVID-19 vaccination, median (SD), years									
Adolescents 12-17 years									
Adults ≥18 years									
Female sex, No (%)									
Race, No (%) Hispanic/Latino, No (%) American Indian/Alaska Native Asian Black Native Hawaiian/other Pacific Islander White Multiple/Other Unknown									
VSD site, No (%) Kaiser Permanente Northern California Kaiser Permanente Colorado Marshfield Clinic Kaiser Permanente Northwest Kaiser Permanente Southern California Kaiser Permanente Washington Health Partners Denver Health									

***** Note: Table is an example and vaccine families will be filled in when available. Individuals who received more than one simultaneous vaccine will be counted in the table more than once.

** Note: Site-specific totals will be for internal use only.

Table 15. Characteristics of individuals who experienced any pre-specified outcomes on days 1-21 after receipt of at least one co-administered vaccine with any dose of COVID-19 vaccine, by vaccine family type*

Characteristic	Vaccine Family	Vaccine Family	Vaccine Family	Vaccine Family	Vaccine Family	Vaccine Family	Vaccine Family	Vaccine Family	Total
Days since COVID-19 vaccine									
1-4 before									
5-9 before									
10-14 before									

1-4 after									
5-9 after									
10-14 after									
Age category at COVID-19 vaccination, median (SD), years									
Adolescents 12-17 years									
Adults ≥18 years									
Female sex, No (%)									
Race, No (%) Hispanic/Latino, No (%) American Indian/Alaska Native Asian Black Native Hawaiian/other Pacific Islander White Multiple/Other Unknown									
VSD site, No (%) Kaiser Permanente Northern California Kaiser Permanente Colorado Marshfield Clinic Kaiser Permanente Northwest Kaiser Permanente Southern California Kaiser Permanente Washington Health Partners Denver Health									

***** Note: Table is an example and vaccine families will be filled in when available. Individuals who received more than one co-administered vaccine will be counted in the table more than once.

** Note: Site-specific totals will be for internal use only.

Phase 2

If outcomes among individuals who received simultaneous and/or co-administered vaccines with any dose of COVID-19 vaccine are more common than in people who received any dose of COVID-19 vaccine without simultaneous and/or co-administered vaccines in Phase 1, we will develop an analytical plan for assessing the safety of simultaneous and/or co-administered vaccination as Phase 2 of this project. However, Phase 2 will be conducted only for those outcomes of which the number of cases observed among individuals who received simultaneous and/or co-administered vaccines is large enough that sufficiently powered safety analyses can be conducted. If Phase 2 is warranted, this protocol will be updated to include a description of Phase 2.

Limitations

Data are limited to data available in the VSD and may not capture all vaccinations administered to an individual that were received at pharmacies and the workplace. Results may not be generalizable to the entire U.S. population. There is a possibility that vaccination status (both COVID-19 vaccine and other

vaccines received) may be inaccurate due to data entry errors. Furthermore, we are only capturing pre-specified medically attended events and will therefore miss capturing other events that may occur that are not included in the pre-specified list.

Impact

This goal of this project is to describe the occurrence of simultaneous vaccine administration and vaccine co-administration within 14 days of receipt of any dose of COVID-19 vaccine among individuals of any age, and describe any differences observed in simultaneous vaccine administration and/or co-administration by age. We will also describe any pre-specified outcomes that occurred among individuals who received simultaneous vaccines and/or co-administered vaccines with any dose of COVID-19 vaccine. Coverage and safety data are not yet widely available for simultaneous vaccine administration and co-administration with the COVID-19 vaccine. It will be important to monitor the safety of simultaneous vaccine administration and co-administration with COVID-19 vaccine, especially as COVID-19 vaccination expands into younger age groups who already receive simultaneous and/or co-administered childhood vaccines.

Data Management Plan

Data Files: The project will use CONSTANT, ENROLL, and VACCINE files (see Supplementary Table 3 for file purpose). The project will also use COVID-19 Rapid Cycle Analysis (RCA) surveillance (VSD #1342) data, which also include inpatient and outpatient files, and the following ancillary files: platelet, dxidhist, dxid, covltest, covlrslt; and weekly generated datasets covid19vachr and pregpsd_ddf. Additional standard data files including procdre and mort and mdcdYYYY may be accessed if necessary.

Data Sources: COVID-19 Rapid Cycle Analysis (RCA) surveillance (VSD #1342) files and the DDF will be used to extract data for this project. All data will be extracted using the distributed data model (DDM). Currently, RCA programs leave vaccine data sets at each site with the COVID-19 vaccination cohort identified. CDC will write a new SAS program that builds on RCA's vaccinated cohort to identify any vaccines co-administered within 14 days of any dose of COVID-19 vaccine.

Data Management: The VSD team at CDC will be primarily responsible for data management activities, including data extraction, documentation and archival. All electronic documents, data sets, and files relevant to the project will be stored on network folders with restricted access on CDC computers. Data will be exchanged using methods that will assure security, primarily through the VSD DDM. The DDM allows all individual level standardized data files to reside at the health plan, and ownership is retained by the VSD site. The DDM maintains confidentiality of the health plan's data by utilizing encrypted and secure methods. SAS programs will be sent to participating sites for approval prior to data extraction.

Site Responsibilities: We hope that all sites with appropriate data will participate. VSD sites and CDC will be encouraged to provide feedback on the protocol and manuscripts.

Human Subjects: The privacy and confidentiality of patients will be strictly protected according to VSD standard procedures. The VSD project is covered by an Assurance of Confidentiality. CDC has obtained an Assurance of Confidentiality under Section 308(d) of the Public Health Service Act (42 U.S.C. 242 m(d)), which provides that this data can only be used for the purpose for which is obtained, unless such institution or individual has consented to that disclosure. Pursuant to this, all CDC and VSD site project personnel have signed a nondisclosure statement. There will be minimal risks to patient privacy and confidentiality. Only VSD Study IDs will be used as identification (linkage to personal information is

stored at VSD sites and not the CDC), and all coded information will be stored on secure CDC computers in network folders with restricted access. There are minimal risks to privacy based on the lack of identifiable information that will be available to CDC investigators, which are reasonable in relation to the importance of the knowledge to be gained.

Equitable selection of subjects: Subject selection is based on clinical parameters and the availability of data to assess the surveillance objectives. No segment of the population is unfairly excluded from the benefits of this program, and no segment of the population bears an undue burden of risk or burden. HIPAA: Because the information being provided to CDC is a limited dataset, and because data use agreements are in place for all VSD sites, formal HIPAA authorization is not required. However, each participating VSD site will confirm compliance with their privacy boards and/or IRBs prior to disclosing information to CDC.

Request for non-research determination:

1. The purpose of this activity is to obtain information to describe the frequency of simultaneous vaccine administration and/or vaccine co-administration with the COVID-19 vaccine and monitor for adverse events to inform both the need for further investigation of safety signals and possibly revision of current recommendations.
2. This activity is within the scope of CDC's mandate to monitor vaccine safety.
3. This activity is limited to activities necessary to monitor the safety of simultaneous vaccine administration and/or co-administration with the COVID-19 vaccine, investigate potential signals, and update recommendations, as warranted.

Project Timeline

Date	**Description**
June 2021	Review concept on VSD project call
July/August 2021	Review proposal on VSD project call
August 2021	Finalize protocol and send to sites
September 2021	Obtain IRB approvals and DUAs, if necessary
October 2021	SAS code development/testing
October 2021	Data analysis
November 2021 - January 2022	Manuscript preparation

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Supplementary Tables

Supplementary Table 1. Vaccines grouped by vaccine type*

Vaccine Family	CVX Code	Vaccine Name
Tdap/Dt**	09	Td (adult), 2 Lf tetanus toxoid, preservative free, adsorbed
Tdap/Dt	113	Td (adult), 5 Lf tetanus toxoid, preservative free, adsorbed
Tdap/Dt	115	Tdap
Tdap/Dt	139	Td(adult) unspecified formulation
Tdap/Dt	196	Td, adsorbed, preservative free, adult use, Lf unspecified
Influenza	111	influenza virus vaccine, live, attenuated, for intranasal use
Influenza	15	influenza virus vaccine, split virus (incl. purified surface antigen)-retired CODE
Influenza	16	influenza virus vaccine, whole virus
Influenza	88	influenza virus vaccine, unspecified formulation
Influenza	123	influenza virus vaccine, H5N1, A/Vietnam/1203/2004 (national stockpile)
Influenza	69	parainfluenza-3 virus vaccine
Influenza	135	influenza, high dose seasonal, preservative-free
Influenza	128	Novel influenza-H1N1-09, all formulations
Influenza	125	Novel Influenza-H1N1-09, live virus for nasal administration
Influenza	126	Novel influenza-H1N1-09, preservative-free, injectable
Influenza	127	Novel influenza-H1N1-09, injectable
Influenza	140	Influenza, seasonal, injectable, preservative free
Influenza	141	Influenza, seasonal, injectable
Influenza	144	seasonal influenza, intradermal, preservative free
Influenza	149	influenza, live, intranasal, quadrivalent
Influenza	150	Influenza, injectable, quadrivalent, preservative free
Influenza	151	influenza nasal, unspecified formulation
Influenza	153	Influenza, injectable, Madin Darby Canine Kidney, preservative free
Influenza	155	Seasonal, trivalent, recombinant, injectable influenza vaccine, preservative free
Influenza	158	influenza, injectable, quadrivalent, contains preservative
Influenza	160	Influenza A monovalent (H5N1), adjuvanted, National stockpile 2013
Influenza	161	Influenza, injectable,quadrivalent, preservative free, pediatric
Influenza	166	influenza, intradermal, quadrivalent, preservative free, injectable
Influenza	168	Seasonal trivalent influenza vaccine, adjuvanted, preservative free
Influenza	171	Influenza, injectable, Madin Darby Canine Kidney, preservative free, quadrivalent
Influenza	185	Seasonal, quadrivalent, recombinant, injectable influenza vaccine, preservative free
Influenza	186	Influenza, injectable, Madin Darby Canine Kidney, quadrivalent with preservative
Influenza	194	influenza, Southern Hemisphere, unspecified formulation
Influenza	197	influenza, high-dose seasonal, quadrivalent, .7mL dose, preservative free
Influenza	200	influenza, seasonal, Southern Hemisphere, quadrivalent, pediatric 0.25mL dose, preservative free

Influenza	201	influenza, seasonal, Southern Hemisphere, quadrivalent, 0.5mL dose, no preservative
Influenza	202	influenza, seasonal, Southern Hemisphere, quadrivalent, 0.5mL dose, with preservative
Influenza	205	influenza, seasonal vaccine, quadrivalent, adjuvanted, .5mL dose, preservative free

* Note: Table is fille in with an example using the influenza vaccine; all simultaneous and co-administered vaccines will be grouped based on vaccine family, where appropriate.

** In the RCA COVID-19 data to date, no one has received CVX code 138 (Td(adult)), so CVX code 138 is excluded from the list of vaccines in the Tdap/DT vaccine family. If CVX code 138 shows up in later data pulls, the CVX code will be included in the vaccine family table.

Supplementary Table 2. COVID-19 RCA Surveillance Study: List of pre-specified VSD outcomes and criteria

#	VSD Outcomes	Abbreviation	Settings	Risk Window (Days)	Exclude if COVID 19 in X prior days	Monitoring Only	Chart Review
1	Acute disseminated encephalomyelitis	ADEM	E, I	1-21, 1-42			Yes
2	Acute myocardial infarction	AMI	E, I	1-21, 1-42	30 days		
3	Acute respiratory distress syndrome	ARDS	E, I	1-21, 1-42	42 days	Yes	
4	Anaphylaxis	ANAPH	E, I	0-1		Yes	Yes
5	Appendicitis	APPND	E, I	1-21, 1-42			
6	Bell's palsy	BP	E, I, O	1-21, 1-42	30 days		
7	Cerebral venous sinus thrombosis	CVST	E, I	1-21, 1-42	30 days		Yes
8	Convulsions / seizures	SZ	E, I	1-21, 1-42 (day 0 included for children)	30 days		
9	Disseminated intravascular coagulation	DIC	E, I	1-21, 1-42	42 days		
10	Encephalitis / myelitis / encephalomyelitis / encephalopathy	ENCEPH	E, I	1-21, 1-42	30 days		
11	Guillain-Barré syndrome	GBS	E, I	1-21, 1-42			Yes
12	Immune thrombocytopenia	ITP	E, I, O	1-21, 1-42	30 days		
13	Kawasaki disease	KD	E, I	1-21, 1-42			
14	Multisystem Inflammatory Syndrome in Children & Adults	MISC, MISA	E, I			Yes	
15	Myocarditis / pericarditis	MYOC	E, I	1-21, 1-42	30 days		
16	Narcolepsy and cataplexy	NARC	E, I, O			Yes	
17	Pulmonary embolism	PE	E, I	1-21, 1-42	30 days		
18	Stroke, hemorrhagic	HSTK	E, I	1-21, 1-42	30 days		
19	Stroke, ischemic	ISTK	E, I	1-21, 1-42	30 days		

20	Thrombosis with Thrombocytopenia Syndrome	TTS	E, I	1-21, 1-42			Yes
21	Thrombotic thrombocytopenic purpura	TTP	E, I	1-21, 1-42	30 days		
22	Transverse myelitis	TM	E, I	1-21, 1-42			Yes
23	Venous thromboembolism	VTE	E, I, O	1-21, 1-42	30 days		

Supplementary Table 3. VSD files to be utilized in this study and their purpose

VSD File	**Purpose**
CONSTANT	Basic demographics of population, VSD site
ENROLL	MCO membership start and stop dates to identify continuous enrollment periods
VACCINE	Identify COVID-19, simultaneous, and co-administered vaccines received