Safety of Simultaneous versus Sequential Administration of mRNA COVID-19 and Quadrivalent Inactivated Influenza (IIV4) Vaccines: A Randomized Placebo Controlled Trial

(ClinicalTrials.gov ID: NCT05028361)

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Disclaimer

- The findings and conclusions in this presentation are those of the presenter and do not necessarily represent the official position of the Centers for Disease Control and Prevention

- Mention of a product or company name is for identification purposes only and does not constitute endorsement by CDC

- This study was supported by the CDC Clinical Immunization Safety Assessment (CISA) Project

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Study Rationale

- Influenza and COVID-19 vaccines are recommended for persons 6 months of age and older to prevent illness and complications resulting from these infections.*
- Available data support the simultaneous administration of these vaccines as currently ACIP recommended.
- However, there are limited data from placebo-controlled studies (none from the US) evaluating the safety of simultaneous administration of influenza and mRNA COVID-19 vaccines.

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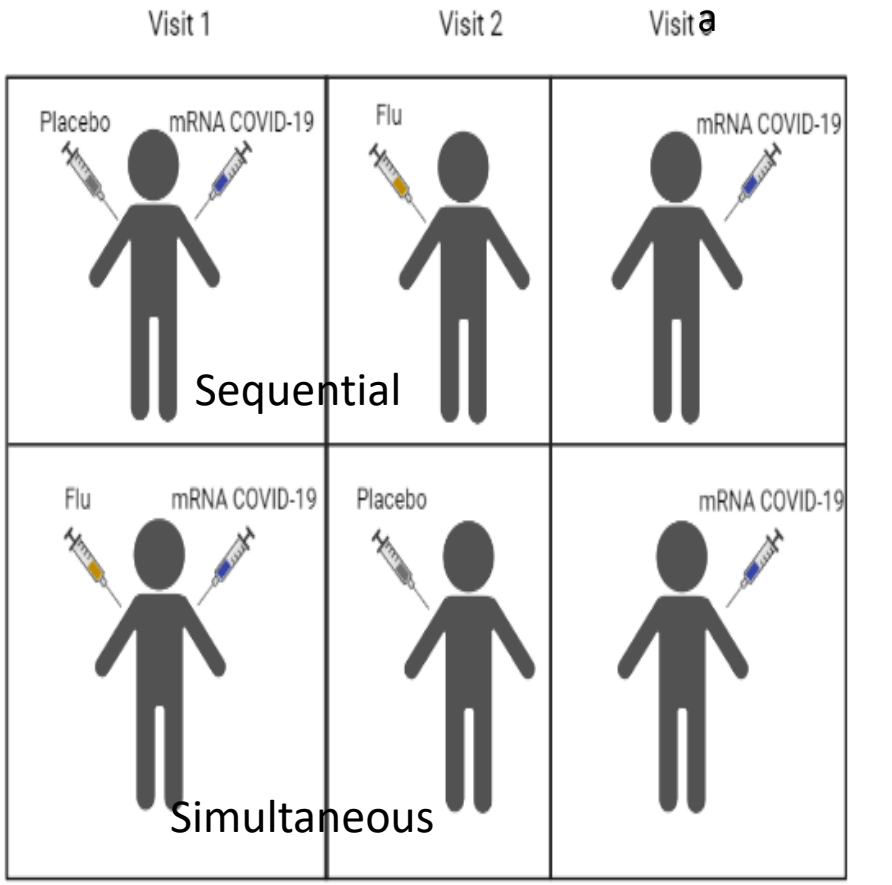
*Clinical Guidance for COVID-19 Vaccination | CDC and Prevention and Control of Seasonal Influenza with Vaccines: Recommendations of the Advisory Committee on Immunization Practices — United States, 2023–24 Influenza Season | MMWR (cdc.gov)

Design, Population, Recruitment

- Design: prospective, randomized, placebo-controlled, observer-blind study
- Population: non-pregnant persons aged ≥5 years if receiving primary two-dose mRNA COVID-19 vaccine series or persons aged ≥12 years if receiving a booster mRNA COVID-19 vaccine dose and intending to receive a quadrivalent inactivated influenza vaccine (IIV4)*
- Recruitment: 3 CISA sites – Duke University, Cincinnati Children's Hospital Medical Center (CCHMC), and John Hopkins University (JHU) during the 2021-2022 and 2022-2023 influenza seasons



*Persons ≥65 years received High-Dose IIV4 (Fluzone High-Dose Quadrivalent); those <65 years received standard dose IIV4 (FluLaval or Fluzone Quadrivalent)

Study Aims and Objectives:

Primary objective: To compare the proportion of participants with moderate or more severe fever, chills, myalgia, or arthralgia (RE)* in the group receiving IIV4 simultaneously with mRNA COVID-19 vaccine at Vaccination Visit 1 (Simultaneous group) with the group receiving IIV4 alone one to two weeks later at Vaccination Visit 2 (Sequential group) following **both Vaccination Visit 1 and 2**

- Primary outcome: considered present if participant has at least one of the RE symptoms on at least one day during days 1 to 7 following Visit 1 and/or Visit 2

Hypothesis: The proportion of participants with moderate or more severe fever, chills, myalgia or arthralgia will be non-inferior (not higher) in the Simultaneous group versus the Sequential group

*RE: reactogenicity event

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Secondary Objectives

- To compare the proportion of participants with RE in the Simultaneous group versus the Sequential group following **Vaccination Visit 1 and 2 separately**

- To describe the proportions of participants in each group with solicited local and systemic reactogenicity events according to severity grade after vaccination visits

- To describe the proportions of participants in each group experiencing at least one serious adverse event and a description of these events

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Study Aims and Objectives: Exploratory Objectives

- To further characterize and describe the proportion of participants in each group with local or systemic reactogenicity events of greater severity

- To describe the proportion of participants each group experiencing at least one unsolicited adverse event and one adverse event of special interest and to characterize these events

- To compare the change of health-related quality of life (HRQOL) from baseline in both groups following the Vaccination Visit 1

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Study Procedures Summary

- After randomization (1:1) to either the simultaneous or sequential group and a baseline blood draw, participants received study influenza vaccine or placebo according to assignment
- Solicited Reactogenicity: Days 1-7* after V1, V2, V3a
- Unsolicited Adverse Events: Days 1-7 after V1, V2, V3a
- Health-Related Quality of Life (HRQOL): Days 1-7 after V1 only
- Adverse Events of Special Interest (AESIs): Days 1-121
- Serious Adverse Events (SAEs): Days 1-121
- Blood draws for immunogenicity: baseline and post-vaccination (data not yet available)

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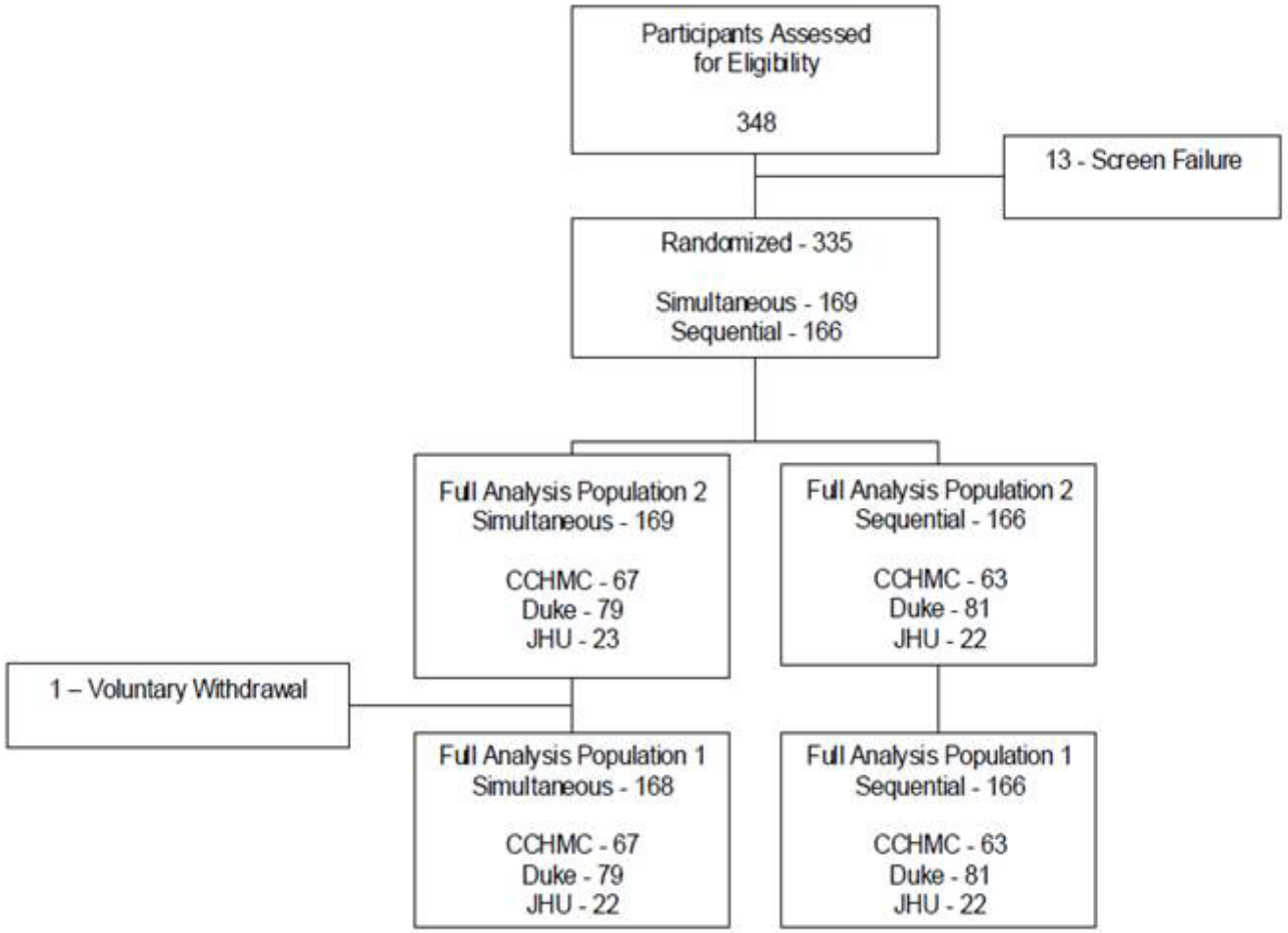
*Day 1 is the vaccination day

Statistical Methods

- **Full Analysis Population 2**
  - All randomized and vaccinated participants
  - Participant characteristics and adverse event outcomes
- **Full Analysis Population 1**
  - All participants who are randomized, vaccinated, and provide at least one day of complete data on the symptom diary
  - Reactogenicity outcomes
- **Statistical Testing**
  - Primary outcome was conducted at the one-sided alpha 0.025 level using the upper bound of a stratified by site Newcombe binomial confidence interval with Cochran-Mantel-Haenszel (CMH) weighting of the difference with a noninferiority margin of 10%.
  - Comparisons of proportions between the simultaneous and sequential groups used an exact Mantel-Haenszel statistic in a stratified analysis by site to control for the randomization blocks at the two-sided alpha 0.05 level. Study site adjusted odds ratios and corresponding 95% confidence intervals for proportions were also calculated.
  - The changes in HRQOL after Visit 1 were evaluated using Mann-Whitney U tests. For the HRQOL comparisons we used a two-sided alpha at the 0.05 level.
  - Summary statistics were used to describe REs, AEs, SAEs and AESIs. 95% confidence intervals of the difference between vaccination groups were calculated.

Study Consort Diagram



Demographics / Enrollment Site

Characteristic		Simultaneous (n=169)	Sequential (n=166)	Total (N=335)
Sex:	Female	96 (56.8%)	115 (69.3%)	211 (63.0%)
	Male	73 (43.2%)	51 (30.7%)	124 (37.0%)
Race:	White Only	123 (72.8%)	113 (68.1%)	236 (70.4%)
	Black Only	31 (18.3%)	33 (19.9%)	64 (19.1%)
	Other	15 (8.9%)	20 (12.0%)	35 (10.4%)
Ethnicity:	Hispanic	12 (7.1%)	9 (5.4%)	21 (6.3%)
Age (yrs):	5 to <12	4 (2.4%)	2 (1.2%)	6 (1.8%)
	12 to <18	11 (6.5%)	13 (7.8%)	24 (7.2%)
	18 to <65	146 (86.4%)	143 (86.1%)	289 (86.3%)
	>=65	8 (4.7%)	8 (4.8%)	16 (4.8%)
Site:	CCHMC	67 (39.6%)	63 (38.0%)	130 (38.8%)
	Duke	79 (46.7%)	81 (48.8%)	160 (47.8%)
	JHU	23 (13.6%)	22 (13.3%)	45 (13.4%)

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Season, COVID-19 Vaccine Received, Vaccination and COVID-19 History

Characteristic	Simultaneous (n=169)	Sequential (n=166)	Total (N=335)
Season: 2021-2022	37 (21.9%)	36 (21.7%)	73 (21.8%)
2022-2023	132 (78.1%)	130 (78.3%)	262 (78.2%)
COVID-19 Vaccine Brand: Pfizer-BioNTech Monovalent	34 (20.1%)	35(21.1%)	69 (20.6%)
Pfizer-BioNTech Bivalent	130 (76.9%)	125 (75.3%)	255 (76.1%)
Moderna Monovalent	4 (2.4%)	4 (2.4%)	8 (2.4%)
Moderna Bivalent	1 (0.6%)	2 (1.2%)	3 (0.9%)
Prior COVID-19 Vaccine Yes	165 (97.6%)	166 (100.0%)	331 (98.8%)
Prior COVID-19 and/or + nucleocapsid ab Yes	96 (56.8%)	95 (57.2%)	191 (57.0%)

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Primary Outcome

Proportions with moderate or more severe fever, chills, myalgia, or arthralgia (RE) in participants in sequential versus simultaneous group

Moderate or more severe fever, chills, myalgia, or arthralgia following Visit 1 and/or Visit 2								
	No		Yes		Non-inferiority Test 10% Margin*			
Group	**N**	**%**	**N**	**%**	**Diff**	**Lower 95% CI**	**Upper 95% CI**	**p-value**
Simultaneous	125	74.40	43	**25.60**				
Sequential	114	68.67	52	**31.33**	-0.0563	-0.1517	0.0404	**0.0007**

*Site-stratified Newcombe binomial confidence interval with Cochran-Mantel-Haenszel (CMH) weighting of the difference

Ho: Sim-Seq ≥ 0.10 (10%)

Conclusion: The rate of moderate or more server fever, chills, myalgia, or arthralgia in simultaneous group is considered **not worse/not higher** than the rate in sequential group and the noninferiority criteria was met. The upper limit of the 95% confidence interval (CI) of the difference for Sim minus Seq was 4.0% and the noninferiority margin was 10%; therefore, the null hypothesis of inferiority was rejected.

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Secondary Objective

Objective: To compare the proportion of participants with moderate or more severe fever, chills, myalgia, or arthralgia in the Simultaneous versus the Sequential Group following the **first vaccination visit**

Moderate or more severe fever, chills, myalgia, or arthralgia following Visit 1						
	No		Yes			
Group	**N**	**%**	**N**	**%**	**Odds Ratio (95%CI)**	**p-value***
Simultaneous	128	76.19	40	**23.81**		
Sequential	119	71.69	47	**28.31**	0.80 (0.49, 1.30)	**0.3851**

*Exact Mantel-Haenszel statistic in a stratified analysis by site

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Secondary Objective

Objective: To compare the proportion of participants with moderate or more severe fever, chills, myalgia, or arthralgia in the Simultaneous versus the Sequential Group following the **second vaccination visit**

Moderate or more severe fever, chills, myalgia, or arthralgia following Visit 2						
	No		Yes			
Group	N	%	N	%	Odds Ratio (95%CI)	p-value*
Simultaneous	163	97.02	5	**2.98**		
Sequential	157	94.58	9	**5.42**	0.54 (0.18, 1.63)	**0.2886**

*Exact Mantel-Haenszel statistic in a stratified analysis by site

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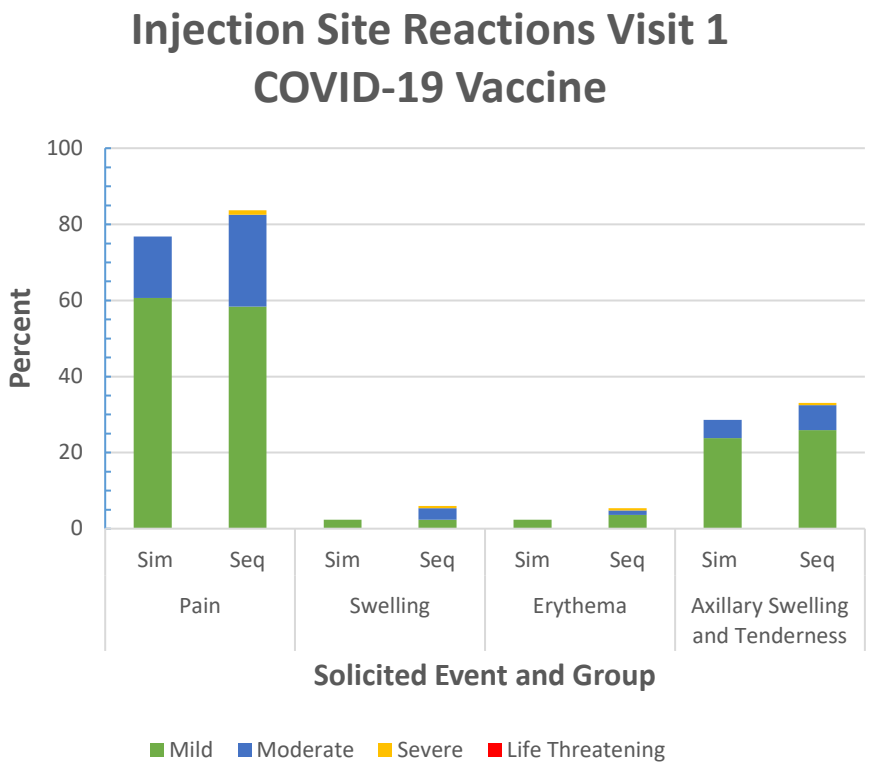
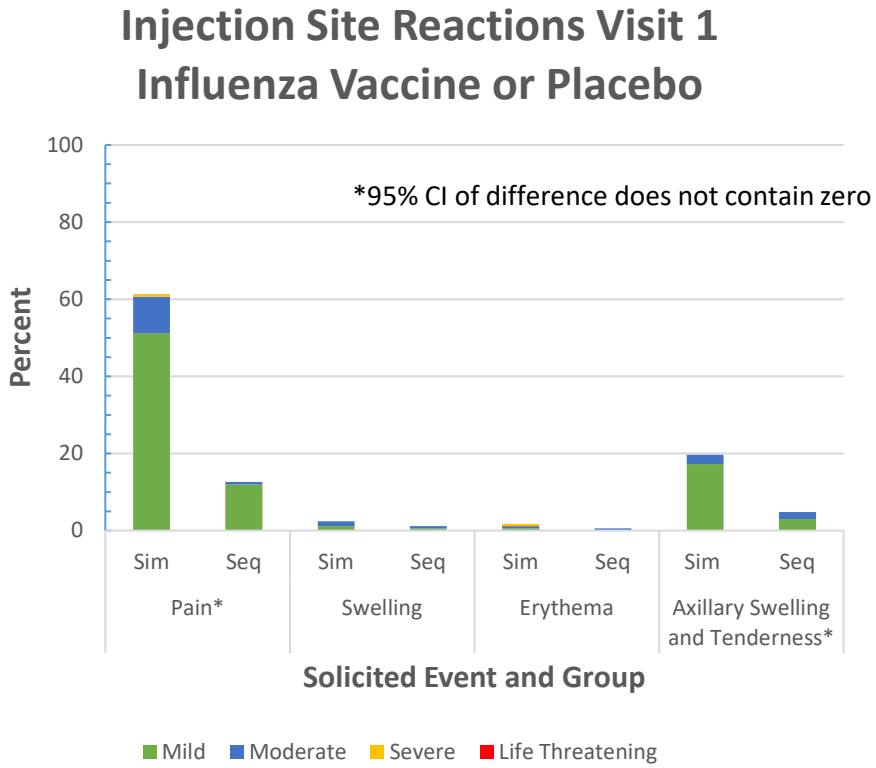
Percent With Injection Site Reaction Visit 1



More ≥ moderate pain and swelling in sequential group*

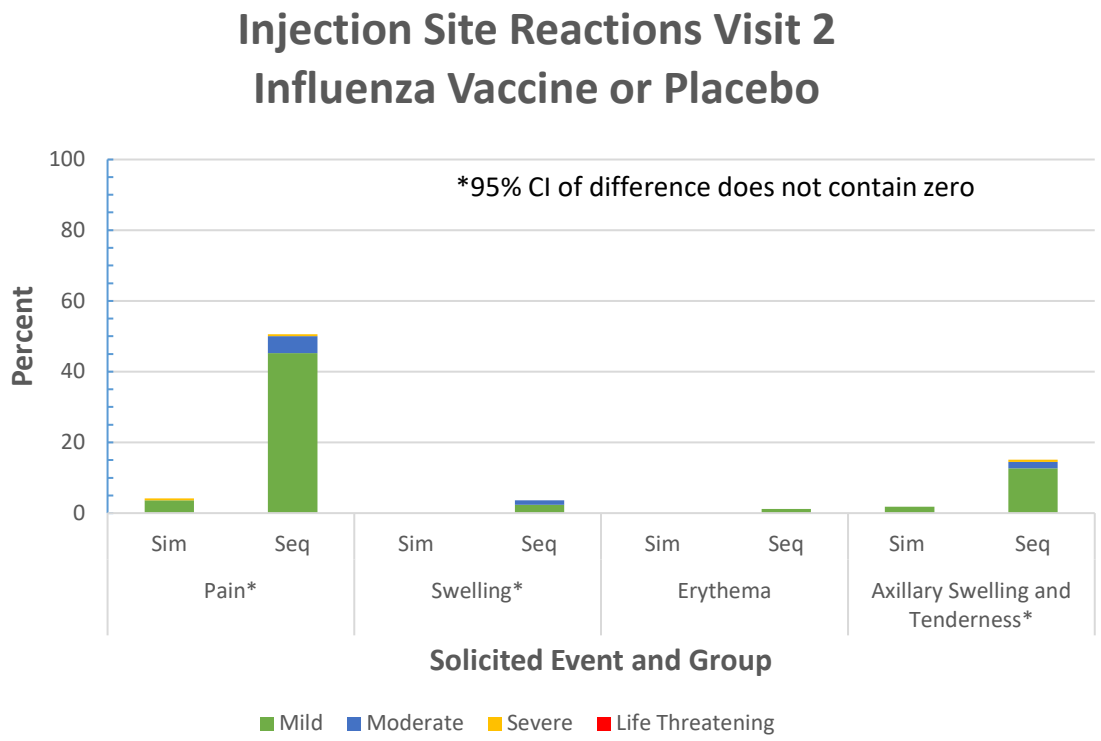
*95% CI of difference in proportions between does not contain zero



More ≥ moderate pain in simultaneous group*

*95% CI of difference in proportions between does not contain zero

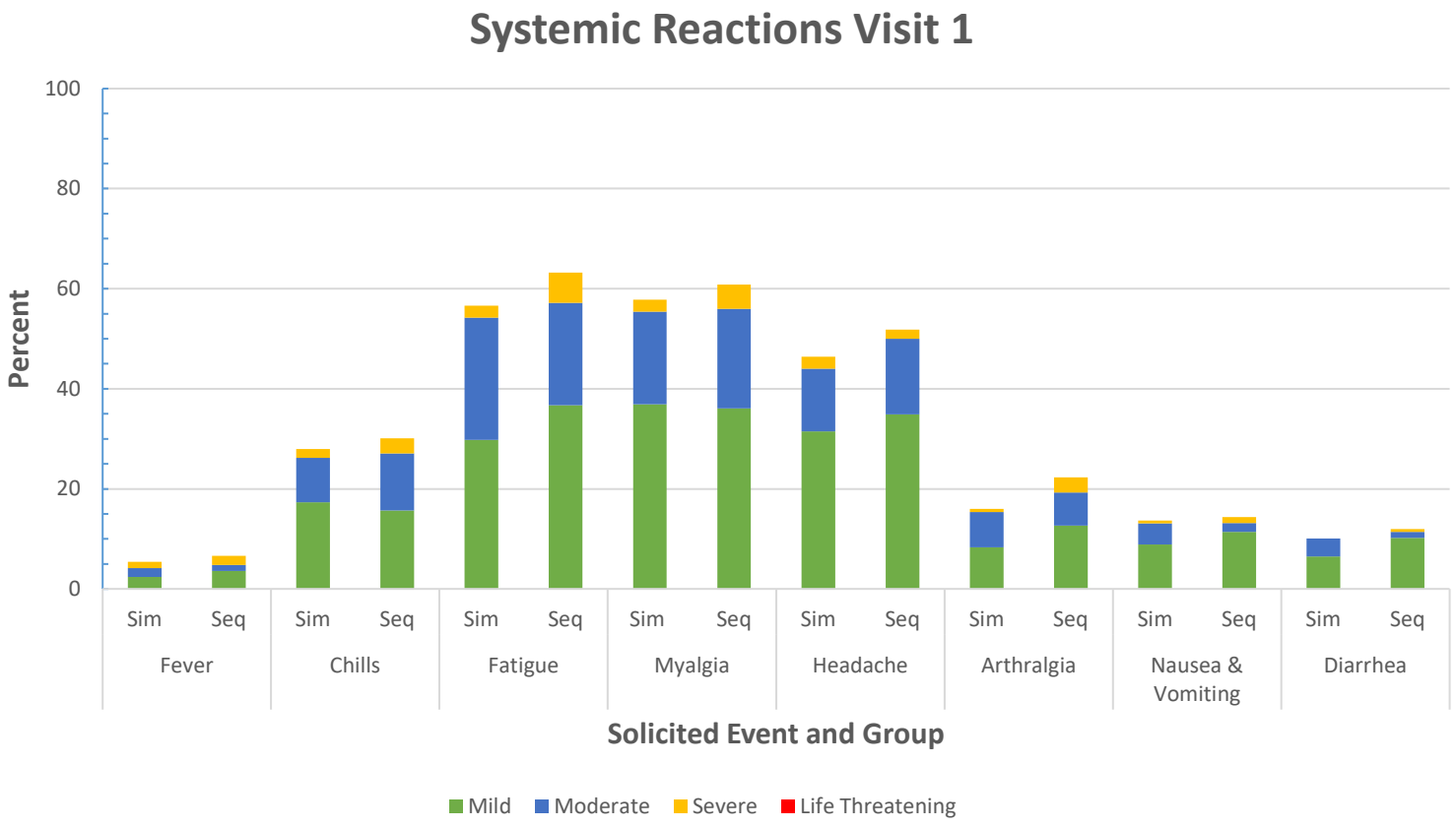
Percent With Injection Site Reaction Visit 2



More ≥ moderate pain and axillary swelling/ tenderness in sequential group*

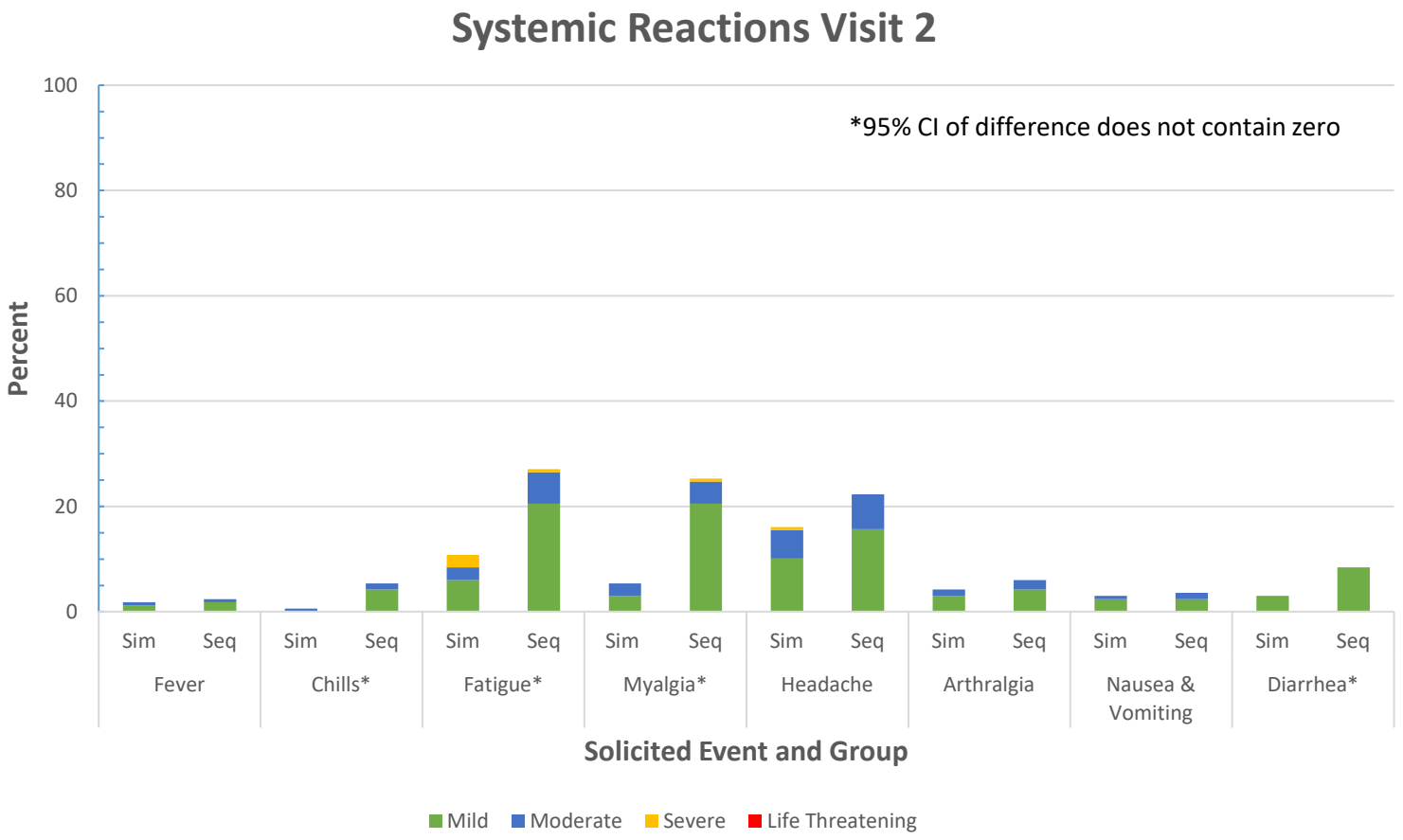
*95% CI of difference in proportions between does not contain zero

Percent With Systemic Reaction Visit 1



No differences in ≥ moderate systemic symptoms

Percent With Systemic Reaction Visit 2



No differences in ≥ moderate systemic symptoms

Secondary Objective

Objective: To describe the proportions of participants in the Simultaneous and Sequential vaccination groups experiencing at least one **serious adverse event** and a description of these events

At Least One Serious Adverse Event					
	No		**Yes**		
Group	**N**	**%**	**N**	**%**	**Difference (Sim-Seq) (95%CI)**
Simultaneous	168	99.41	1	**0.59**	
Sequential	165	99.40	1	**0.60**	**-0.01 (-1.66, 1.64)**

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SAE Descriptions

Group	Vaccine	Onset since Visit 1	Sex	Age group	Category	Relatedness	Description
Sequential	Pfizer-BioNTech Bivalent	14 days	Female	50-64	Hospitalization/ prolongation of existing hospitalization	Unlikely related	**Small bowl obstruction with incarcerated ventral hernia** Past medical history (PMH): abdominal surgeries and cancer
Simultaneous	Pfizer-BioNTech Monovalent	19 Weeks	Female	18-49 years	Other important medical event	Not related	**Spontaneous abortion** occurring at 16 weeks gestation PMH: COVID-19 illness (mild) 9 weeks after visit 1; (Note: Participant did not report being pregnant or intention of becoming pregnant at enrollment)

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Exploratory Objective

- Objective: To describe the proportion of participants in Simultaneous and Sequential groups experiencing at least one **unsolicited adverse event** and one adverse event of special interest and to characterize these events

At Least One Unsolicited Adverse Event within 7 Days of a Vaccination Visit (Preliminary)						
	No		Yes		Percent Yes	
Group	**N**	**%**	**N**	**%**	**95% CI**	**Difference (Sim-Seq) (95%CI)**
Simultaneous	148	87.57	21	**12.43**	(7.86, 18.37)	
Sequential	150	90.36	16	**9.64**	(5.61, 15.18)	**2.79 (-3.91, 9.49)**

- AEs within 7 days of vaccine (n=45)
  - 29 simultaneous group in 21 participants (3 possibly related)
  - 16 sequential group in 16 participants (1 related, 2 possibly related)

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Exploratory Objective

- Objective: To describe the proportion of participants in Simultaneous and Sequential groups experiencing at least one unsolicited adverse event and one **adverse event of special interest** and to characterize these events

At Least One Adverse Event of Special Interest						
	No		Yes		Percent Yes	
Group	**N**	**%**	**N**	**%**	**95% CI**	**Difference (Sim-Seq) (95%CI)**
Simultaneous	150	88.76	19	**11.24**	(6.91, 17.00)	
Sequential	157	94.58	9	**5.42**	(2.51, 10.04)	**5.82 (-0.06, 11.70)**

- AESIs (n=28)
  - 29 COVID-19 illnesses (unrelated): Sim Group* (n=18) Seq Group* (n=9)
  - 1 allergic type reaction (possibly related): Sim Group (n=1)

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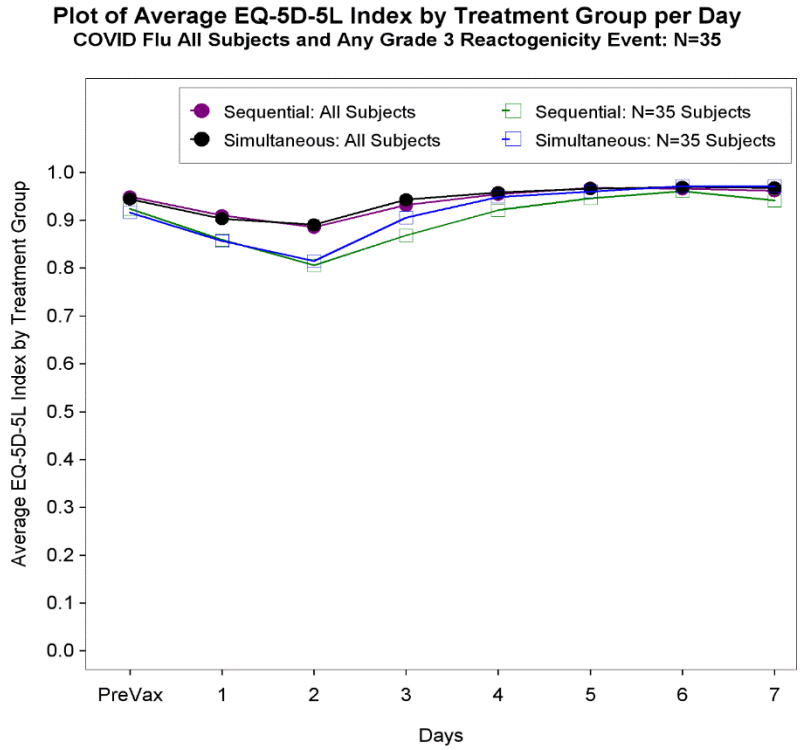
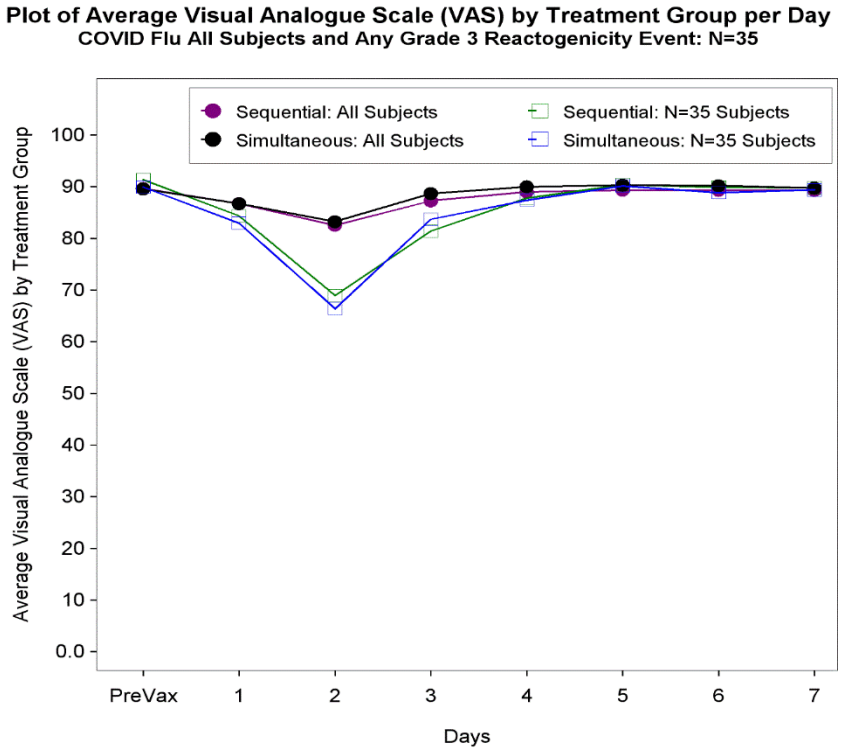
*One person in each group reported 2 COVID-19 illness events

Exploratory Objective

- Objective: To compare the change of health-related quality of life **(HRQOL)** from baseline in the Simultaneous versus Sequential groups following the Vaccination Visit 1





Limitations

- Most data come from use of bivalent Pfizer-BioNTech mRNA COVID-19 vaccine during one season
  - Very little use of Moderna mRNA vaccine
- Very few children ages 5-11 years and older adults ≥65 years enrolled
- Enrollment limited by COVID-19 pandemic; enrolled ~70% of target
- Study too small to detect rare adverse events
- People known to be pregnant not included; a future CISA study assessing safety of simultaneous influenza and COVID-19 vaccines during pregnancy is planned

Summary

- Simultaneous administration of influenza and mRNA COVID-19 vaccines is well tolerated when compared to sequential administration
  - Occurrence of moderate or more severe fever, chills, myalgia, or arthralgia was not higher in the simultaneous (25.6%) vs. sequential (31.3%) group
  - No significant differences in occurrence of adverse events within 7 days, adverse events of special interest, serious adverse events, and HRQOL
- As previously observed in other studies injection site and systemic reactions were associated with mRNA COVID-19 vaccine and influenza vaccine; most reactions were mild or moderate
  - Most frequent injection site reactions after either vaccine were pain and axillary swelling/tenderness
  - Most frequent systemic reactions after COVID-19 vaccine, with or without influenza vaccine, were fatigue, myalgia, headache, chills and arthralgia
  - Receipt of influenza vaccine alone was associated chills, fatigue, myalgia and diarrhea

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  - Principal Investigator: Kawsar Talaat, MD
- **Cincinnati Children's Hospital Medical Center (CCHMC)**
  - Principal Investigator: Elizabeth Schlaudecker, MD, MPH
  - Investigator: Mary Staat, MD, MPH
- **CDC**
  - Principal Investigator: Karen Broder, MD
  - Investigators: Jonathan Duffy, MD, MPH, Oidda Museru MSN, MPH, Lisa A. Grohskopf MD, MPH, Anju Goel MD, MPH (contractor)

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Extra Slides

Serious Adverse Event (SAE) Definition

- An SAE is defined as an AE that meets one of the following conditions:
  - Results in death during the period of protocol-defined surveillance
  - Is life-threatening (defined as immediate risk of death at the time of the event)
  - Requires inpatient hospitalization or prolonged hospitalization during the period of protocol-defined surveillance
  - Results in congenital anomaly or birth defect
  - Results in a persistent or significant disability/incapacity
  - Any other important medical event that may not result in death, be life threatening, or require hospitalization, may be considered an SAE when, based upon appropriate medical judgment, the event may jeopardize the participant and may require medical or surgical intervention to prevent one of the outcomes listed above. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

Adverse Event of Special Interest (AESI) Definition

- An AESI includes the following:
  - COVID-19 illness
  - Multisystem inflammatory syndrome
  - Guillain-Barre syndrome
  - Allergic type reactions (including anaphylaxis, hives, or facial and limb swelling occurring within 7 days of a vaccination visit)
  - Myocarditis or pericarditis

Injection Site Reactions Grading

Table 8. Injection-site Reactogenicity Grading				
Local Reaction to Injectable Product	**Mild (Grade 1)**	**Moderate (Grade 2)**	**Severe (Grade 3)**	**Potentially Life Threatening (Grade 4)**
Pain	Noticeable but does not interfere with activity	Interferes with activity but did not need a medical visit or absenteeism [i.e. missing work or school]	Significant; prevents daily activity and/or resulted in medical visit and/or absenteeism [i.e. missing work or school]	Requires an emergency room (ER) visit or hospitalization
Induration/Swelling (≥ 12 years of age)	2.5 – 5 cm	5.1 – 10 cm	> 10 cm	Requires an emergency room (ER) visit or hospitalization
Induration/Swelling (< 12 years of age)	0.5 – 2 cm	2.0 -7.0 cm	> 7 cm	Requires an emergency room (ER) visit or hospitalization
Erythema/Redness (≥ 12 years of age)	2.5 – 5 cm	5.1 – 10 cm	> 10 cm	Requires an emergency room (ER) visit or hospitalization
Erythema/Redness (< 12 years of age)	0.5 – 2 cm	2.0 -7.0 cm	> 7 cm	Requires an emergency room (ER) visit or hospitalization
Axillary (underarm) swelling or tenderness ipsilateral to side of injection	Noticeable but does not interfere with activity	Interferes with activity but did not need a medical visit or absenteeism [i.e. missing work or school]	Significant; prevents daily activity and/or resulted in medical visit and/or absenteeism [i.e. missing work or school]	Requires an emergency room (ER) visit or hospitalization

Systemic Reactions Grading

Table 9. Systemic Reactogenicity Grading (FDA modified)				
Systemic	**Mild (Grade 1)**	**Moderate (Grade 2)**	**Severe (Grade 3)**	**Potentially Life Threatening (Grade 4)**
Fever (° C) **(° F)**	38.0 - 38.4 100.4 - 101.1	38.5 - 38.9 101.2 - 102.0	39.0 – 40.0 102.1-104.0	> 40.0 >104.0
Nausea/vomiting	Noticeable but does not interfere with activity or 1 – 2 episodes/24 hours	Some interference with activity or > 2 episodes/24 hours	Significant; prevents daily activity and/or resulted in medical visit and/or absenteeism [i.e. missing work or school]	Requires an ER visit or hospitalization
Diarrhea	Noticeable but does not interfere with activity or 2 – 3 loose stools/24 hours	Some interference with activity or 4-5 loose stools/24 hours	Significant; prevents daily activity and/or resulted in medical visit and/or absenteeism [i.e. missing work or school] or 6 or more watery stools or > 24 hours	Requires an ER visit or hospitalization
Headache	Noticeable but does not interfere with activity	Some interference with activity but did not need a medical visit or absenteeism [i.e. missing work or school]	Significant; prevents daily routine activity and/or resulted in medical visit and/or absenteeism [i.e. missing work or school]	Requires an ER visit or hospitalization
Fatigue	Noticeable but does not interfere with activity	Some interference with activity but did not need a medical visit or absenteeism [i.e. missing work or school]	Significant; prevents daily routine activity and/or resulted in medical visit and/or absenteeism [i.e. missing work or school]	Requires an ER visit or hospitalization
Myalgia	Noticeable but does not interfere with activity	Some interference with activity but did not need a medical visit or absenteeism [i.e. missing work or school]	Significant; prevents daily routine activity and/or resulted in medical visit and/or absenteeism [i.e. missing work or school]	Requires an ER visit or hospitalization
Arthralgia	Noticeable but does not interfere with activity	Some interference with activity but did not need a medical visit or absenteeism [i.e. missing work or school]	Significant; prevents daily routine activity and/or resulted in medical visit and/or absenteeism [i.e. missing work or school]	Requires an ER visit or hospitalization
Chills	Noticeable but does not interfere with activity	Some interference with activity but did not need a medical visit or absenteeism [i.e. missing work or school]	Significant; prevents daily routine activity and/or resulted in medical visit and/or absenteeism [i.e. missing work or school]	Requires an ER visit or hospitalization

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EQ-5D-5L and VAS

Under each heading, please check the ONE box that best describes your health TODAY.

MOBILITY
- I have no problems walking ❑
- I have slight problems walking ❑
- I have moderate problems walking ❑
- I have severe problems walking ❑
- I am unable to walk ❑

SELF-CARE
- I have no problems washing or dressing myself ❑
- I have slight problems washing or dressing myself ❑
- I have moderate problems washing or dressing myself ❑
- I have severe problems washing or dressing myself ❑
- I am unable to wash or dress myself ❑

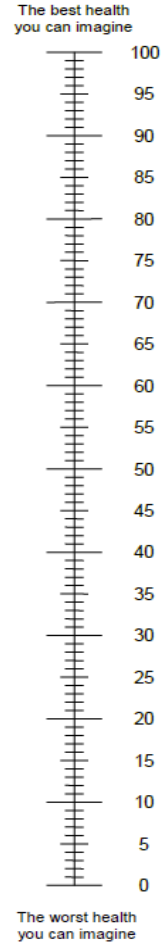
USUAL ACTIVITIES *(e.g. work, study, housework, family or leisure activities)*
- I have no problems doing my usual activities ❑
- I have slight problems doing my usual activities ❑
- I have moderate problems doing my usual activities ❑
- I have severe problems doing my usual activities ❑
- I am unable to do my usual activities ❑

PAIN / DISCOMFORT
- I have no pain or discomfort ❑
- I have slight pain or discomfort ❑
- I have moderate pain or discomfort ❑
- I have severe pain or discomfort ❑
- I have extreme pain or discomfort ❑

ANXIETY / DEPRESSION
- I am not anxious or depressed ❑
- I am slightly anxious or depressed ❑
- I am moderately anxious or depressed ❑
- I am severely anxious or depressed ❑
- I am extremely anxious or depressed ❑

- We would like to know how good or bad your health is TODAY.
- This scale is numbered from 0 to 100.
- 100 means the best health you can imagine.
  0 means the worst health you can imagine.
- Mark an X on the scale to indicate how your health is TODAY.
- Now, please write the number you marked on the scale in the box below.

YOUR HEALTH TODAY = ☐



Subject Inclusion Criteria

- Persons aged ≥5 years if receiving primary two-dose mRNA COVID-19 vaccine series or persons aged ≥12 years if receiving a booster mRNA COVID-19 vaccine dose according to FDA authorization or approval and ACIP recommendation. Note: receipt of an mRNA COVID-19 vaccine within 8 hours of enrollment is permitted

  ** Individuals age 5-11 receiving a booster may be enrolled in the event a booster for individuals age 5-11 is authorized or approved and recommended by the ACIP.*
- English or Spanish literate
- Intention of receiving influenza vaccine and mRNA COVID-19 vaccine based on ACIP-CDC guidelines
- Willing to provide written informed consent
- Intention of being available for entire study period and complete all relevant study procedures, including follow-up phone calls and clinic visits

Subject Exclusion Criteria

- Currently pregnant, planning to become pregnant within the first three months of the study per participant self-report or likely to be pregnant per screening criteria as defined in protocol at Visit 1
- Prior receipt of IIV4 during the respective influenza season in which they are being enrolled
- < 9 years of age and recommended to receive two doses of IIV4 during the respective influenza season in which they are being enrolled
- Prior receipt of non-mRNA COVID-19 vaccine
- Documented COVID-19 infection within 6 weeks prior to enrollment confirmed by either medical history or lab testing
- History of severe allergic reaction after a previous dose of any influenza vaccine; or to an influenza vaccine component, including egg protein
- History of severe adverse reaction associated with a vaccine and/or severe allergic reaction (e.g. anaphylaxis) to any component of an mRNA vaccine
- Receipt of any licensed inactivated vaccine within 2 weeks prior to enrollment in this study, receipt of any licensed live vaccine within 4 weeks prior to enrollment in this study, or receipt of Shingrix (Zoster Vaccine Recombinant, Adjuvanted) or HEPLISAV-B (Hepatitis B Vaccine (Recombinant), Adjuvanted) vaccine within 6 weeks prior to enrollment in this study or planning receipt of any vaccines following enrollment until 6 weeks after receipt of the second dose of mRNA COVID-19 vaccine

Subject Exclusion Criteria

- Has an active neoplastic disease (excluding non-melanoma skin cancer or prostate cancer that is stable in the absence of therapy) or a history of any hematologic malignancy*

  **Participants with a history of malignancy may be included if, after previous treatment by surgical excision, chemotherapy or radiation therapy, the participant has been observed for a period that in the investigator's estimation provides a reasonable assurance of sustained cure*
- Thrombocytopenia, bleeding disorder, or anticoagulant use contraindicating intramuscular injection (a daily aspirin may be acceptable).
- Has immunosuppression as a result of an underlying illness or medications, such as antirejection/transplant regimens or immunomodulatory agents. Stable HIV disease is permitted per the following parameters:
  - Confirmed stable HIV disease defined as document viral load <50 copies/mL and CD4 count >200 within 6 months before enrollment, and on stable antiretroviral therapy for at least 6 months
- Has known hepatitis B (HBV) or hepatitis C (HBC). Stable HBV or HBC are permitted per the following parameters:
  - If known HBV: confirmed inactive chronic HBV infection: HBsAg present for ≥6 months and HBeAg negative, anti-HBe positive; serum HBV DNA <2000 IU/mL; persistently normal ALT or AST levels; in those who had liver biopsy, findings that confirm absence of significant necroinflammation
  - If known HCV: evidence of sustained virological response for ≥12 weeks after treatment or without evidence of HCV RNA viremia (undetectable HCV RNA)

Subject Exclusion Criteria

- Use of oral, parenteral, or high-dose inhaled glucocorticoids*
  **For definition of high-dose inhaled glucocorticoids, reference Appendix B.*
- History of Guillain-Barré syndrome
- Prior enrollment in this study during the 2021-22 flu season
- Anyone who is already enrolled or plans to enroll in another clinical trial with an investigational product during the study period.*
  **Per protocol, co-enrollment in observational or behavioral intervention studies are permitted at any time. An investigational product may be permitted for therapy of an illness condition that occurs during the study period e.g. COVID-19 illness.*
- Hearing loss determined by the investigators to prevent successful communication over the phone
- History of myocarditis or pericarditis
- History of multisystem inflammatory syndrome in children (MIS-C) or adults (MIS-A).
- Has injury or other reason why deltoid site on both arms cannot be used for vaccinations.
- Any condition which, in the opinion of the investigators, may pose a health risk to the subject or interfere with the evaluation of the study objectives.
- Anyone who is a relative of any research study personnel.
- Anyone who is an employee of any research study personnel.