Assessing safety of COVID-19 mRNA vaccine administration in the setting of a previous adverse reaction

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1. Objective

This study will evaluate the safety of administering an additional dose of a currently FDA approved mRNA COVID-19 vaccine to individuals who have had adverse reactions to a previous dose of a COVID-19 vaccination. In addition, this study will evaluate the safety of administering an additional dose of the currently FDA approved mRNA COVID-19 vaccine to individuals experiencing an adverse reaction to a natural COVID-19 infection ("long COVID").

We hypothesize that individuals who have had adverse reactions to a previous dose of an mRNA COVID-19 vaccine will tolerate an additional dose of the current FDA recommended vaccine, as indicated, and those with a personal history of allergic reaction will tolerate an initial dose of this vaccine as well. We also hypothesize that those individuals experiencing an adverse reaction to a natural COVID-19 infection will tolerate an additional dose of the current FDA recommended vaccine, as indicated.

2. Endpoints

Primary Endpoint 1: Determine the safety of administering an additional dose of an mRNA COVID-19 vaccine to individuals who have had adverse reactions to a previous dose of an mRNA vaccine and the safety of administering an additional dose of an mRNA COVID-19 vaccine to individuals experiencing an adverse reaction to a natural COVID-19 infection ("long COVID").
Primary Endpoint 2: Determine the reaction rate in this population.
Secondary Endpoint: Define clinical reaction type when they occur.

3. Background

The RNA based COVID-19 vaccines have been remarkably effective in preventing infection, severe disease, and death even with the advent of more contagious variants (1). The side effects have been relatively minimal; however, one concern has been adverse reactions that are potentially immune mediated, hypersensitivity or allergic in nature. (2) There are many of these reactions after the first dose of the vaccine, and most have not been fully evaluated. (3) As a result, individuals have been told simply to avoid the second dose of the vaccine. This approach has been reinforced by CDC recommendations issued at the beginning of the vaccine campaign. (4)

In addition, many individuals with a personal history of allergic reaction were advised early in the vaccination campaign to avoid mRNA COVID-19 vaccination due to widely

publicized anecdotal reports of individuals with a personal history of allergic reaction experiencing adverse reactions to the mRNA vaccines.
Initially, avoiding a second shot of RNA based COVID-19 vaccine appeared to be the safer alternative to receiving a second dose as a single dose seemed to provide significant protection from infection. Recent events, unfortunately, have changed the risks and benefits of incomplete vaccination. It appears that two full doses of vaccine are necessary to protect against infection with the delta variant. (5) In addition, the immunity provided by these vaccines appears to wane to some degree over time. (1) This diminution is greater in individuals who receive only a single dose of vaccine. (6) More recently, the Omicron variant demonstrated that additional booster doses of the mRNA COVID-19 vaccines significantly enhanced the protection provided by these vaccines against infection, hospitalization, and death from COVID-19. (13) Together, these emerging problems have raised concerns of COVID-19 morbidity, mortality, and transmissibility for those individuals who do not get a second dose of vaccine or who were advised against receiving a booster dose following an adverse reaction to the second dose in the primary vaccine series.(14) Though the initial suggestion that these individuals should avoid mRNA COVID-19 vaccination was revised (15), many individuals avoided vaccination because of the initial concerns raised during the early vaccination campaign. What literature is available on first dose reactions to COVID vaccines have suggested that most individuals with reactions do not have events that preclude receiving a second dose. A study out of Harvard examined their health care providers reactions to the RNA vaccines and found out that 1,365 individuals (2.1% of those vaccinated) felt that they had an adverse allergic reaction to the first dose of vaccine. (2) Despite this, when reviewing the clinical records of these reactions it appeared that only 14 had symptoms resembling a hypersensitivity reaction that would preclude a second dose. Unfortunately, this hypothesis was not tested as these individuals did not receive a second dose of vaccine.

A recent study from Denmark also suggested that most individuals with first dose vaccine reactions could safely receive a second dose. (7) But again, this was not prospectively tested in a controlled manner and all allergic individuals were excluded from vaccine re-challenge.

Previously, the CDC added recommendations that increasing the time between first and second doses of the mRNA COVID-19 vaccines may be optimal and should be considered. (9) This follows several recent studies reporting enhanced immune response following a delayed dosing interval between the first and second doses of mRNA COVID-19 vaccines. (10)(11)(12)

Recently, on September 3rd, 2024, the FDA announced the release of an updated COVID-19 vaccine. The updated mRNA vaccines (manufactured by ModernaTX Inc. and Pfizer Inc.) formulas work to target the circulating variant strains of COVID-19 more accurately. This 2024-2025 formula includes a monovalent (single) component that corresponds to the Omicron variant KP.2 strain of SARS-CoV-S. The timeline for administering an additional dose to individuals that receive a previous dose is at least two months after the last dose. (18)

In addition, the Omicron variant raised additional concerns about the waning of vaccine efficacy over time requiring the need for booster doses of the mRNA COVID-19 vaccines for optimal protection. This followed evidence of waning vaccine effectiveness and

increased breakthrough infections observed during the Delta variant surge. (13) Those individuals who have experienced an adverse reaction to a second dose of an mRNA vaccine have faced uncertainty regarding the safety of booster doses, with many vaccine providers advising against additional doses of mRNA vaccine. Determining the safety of administering additional doses to individuals following an adverse reaction to either dose of mRNA COVID-19 vaccine is essential as public health officials anticipate the need for additional doses in the future as variants continue to emerge and annual mRNA-based vaccinations for COVID-19 and influenza are developed for future use.

Finally, as the COVID-19 pandemic has continued, a growing population of individuals who have experienced adverse reaction to natural COVID-19 infection ("long COVID") has flooded the healthcare system. Many of these individuals have avoided initiating or completing vaccination. Available research suggests that not only is it safe to vaccinate these individuals (16), but that many long COVID patients report improved symptoms after administration of a COVID-19 vaccine (17). As the potential for re-infection with newer variants continues to be a concern for those previously infected, fully vaccinating this population provides significant personal and societal benefit.

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4. Study Team Expertise

Dr. Baker is the Ruth Dow Doan Professor of Internal Medicine in Allergy/Clinical Immunology, has a history of NIH and other funded laboratory work, has served as CEO of FARE (the national food allergy nonprofit), and SVP of vaccine development for Merck. He is currently a protocol co-chair on the NIAID national clinical trial 'Systemic Allergic Reactions to SARS-CoV-2 Vaccination' Dr. Schuler is a Clinical Assistant Professor in Allergy/Clinical Immunology, has an expertise in respiratory virus immunopathology and clinical allergy/immunology, and has served as PI on clinical data and sample collection studies. Dr. Slack is a Clinical Assistant Professor in Allergy/Clinical Immunology, has an expertise in food allergy desensitization and clinical allergy/immunology, and has served as a sub-investigator on several clinical trials. Dr. O'Shea is a Clinical Assistant Professor in Allergy/Clinical Immunology, has an expertise in mast cell biology and has served as a co-investigator on clinical data and sample collection studies. Together, the study team has the expertise in study design, sample collection, subject recruitment, sample analysis, data management, analysis, and interpretation to successfully execute this proposed study.

5. Methodology

a. Inclusion/Exclusion Criteria

Inclusion Criteria

1. Age over 18.
2. Participant must be able to understand and provide informed consent
3. No evidence of infectious illness (defined as fever >38ºC, vomiting, diarrhea, new cough, new shortness of breath, new

congestion, new runny nose, new headache or sore throat) within 14 days of vaccine administration.
4. Subjects must have a history of adverse reaction to either the Pfizer-BioNTech mRNA COVID vaccination or the Moderna mRNA COVID vaccination, a personal history of allergic reaction without prior mRNA COVID vaccination, or a history of adverse reaction to natural COVID infection.
5. Females of childbearing potential must have a negative pregnancy test prior to vaccination.

Exclusion Criteria

1. Under age 18
2. Inability or unwillingness of a participant to give written informed consent
3. Evidence of COVID-19 infection within 21 days of vaccination visit
4. History of antibody agent or convalescent plasma for treatment or prevention of COVID-19 within 90 days
5. Individuals with known history of a severe allergic reaction (e.g., anaphylaxis) to any component of the Pfizer-BioNTech mRNA COVID-19 vaccination or the Moderna mRNA COVID-19 vaccination.
6. History of underlying immune disorder.
    - Pregnancy
    - Immunocompromised
        - Persons with primary or acquired immunodeficiency
        - Persons on anti-rejection therapy following solid organ transplant or bone marrow transplant
        - Persons on biologic therapeutic agents
        - Persons with malignancy and ongoing or recent chemotherapy
        - Persons receiving systemic immunosuppressive therapy, including corticosteroids equivalent to 20 mg/day of prednisone for 2 weeks
    - Persons with chronic kidney disease stage 3 or higher
    - Persons with history of significant pulmonary compromise

b. Recruitment Plan and Study Design

i. Number of Subjects

N=200 individuals

ii. Method of Contact

We will screen and recruit individuals that have been identified either as having a personal history of allergic reaction without prior mRNA COVID-19 vaccination, having a history of adverse reaction to natural COVID-19 infection, or as having possibly had an adverse reaction to either the Pfizer mRNA COVID vaccine or the Moderna mRNA COVID vaccine by medical chart review following healthcare provider referral or Data Direct database identification or from a response to a study advertisement. Individuals will be contacted initially by a member of the study team in person or over the phone

following identification as a possible subject by healthcare provider referral, Data Direct database identification and chart review, or self-referral from study advertisement.

iii. Method of Consent

Individuals will be contacted as above. Individuals approached for the study will be provided the consent document for review, offered background on the study, and asked to provide verbal permission for pre-screening questions. If a participant provides verbal permission for pre-screening, a set of pre-defined questions will be used to confirm eligibility. This process may take place in person during a clinical visit or over the phone by a member of the study team. Eligible participants will be provided the informed consent document and a thorough review of the document will take place. Participants will have as much time as needed to ask questions and decide if they'd like to participate in the study. In most cases, consent will be provided to the participant electronically and they will be asked to sign using the University of Michigan's FDA 21 CFR Part 11 compliant e-signature service ("SignNow"). This service automatically provides a copy of the fully signed document to all parties and a copy will be placed in the participant's medical record. There may be circumstances where a participant is able to complete the consent process in person during a clinical visit; sufficient time for review and questions will be provided for in person consenting as well. Rarely, consents may send via postal mail for ink signatures. In this case no study procedures will take place until the consent has been signed by all parties and a copy of the fully signed document is provided to the participant. The method, location, and individuals involved in the consent process will be fully documented in the study records.

iv. Method of Interaction/Procedure/Intervention

Pre-Vaccination Visit

1. Obtain written informed consent
2. Collect demographics from the electronic medical record
3. Review medical history and prior physical exam within the electronic medical record by a study physician or other qualified medical professional
4. Assessment of concomitant medications
5. Blood and urine sample collections for assessments to be obtained within 2 weeks of vaccination visit
    - Blood sample collections
        - CBC with differential
        - Serum tryptase
        - ESR
        - Comprehensive metabolic panel
        - COVID-19 spike antibody level
        - COVID-19 nucleocapsid antibody level
    - Urine sample collections
        - Urinalysis
        - Urine pregnancy test in all female participants

The timeframe of scheduled vaccination visits:

1. Participant will then be scheduled for a vaccination visit.

2. Subjects with a history of receipt of one previous dose of monovalent Moderna COVID-19 Vaccine (SpikeVax),one previous dose of monovalent Pfizer-BioNTech COVID-19 Vaccine (Comirnaty), or history of a previous bivalent booster will be given an additional dose of the current FDA recommended COVID-19 vaccine. The timeline for administering an additional dose to individuals that have received a previous dose is at least 2 months after the last dose.
3. Subjects who have received both of their primary doses of an approved, monovalent mRNA vaccine and want a booster dose of the current FDA recommended COVID-19 mRNA vaccine), will receive this additional dose at least 2 months after their last dose.
4. Enrolled subjects who have received a primary dose in the study can receive a booster dose as well (i.e. at least three doses of mRNA COVID-19 vaccine) but must wait at least 2 months after last dose before receiving an additional FDA recommended COVID-19 booster dose.
5. Subjects will have booster vaccination with the current FDA recommended vaccine (i.e. Moderna COVID-19 Vaccine or Pfizer-BioNTech COVID-19 Vaccine). Regardless of whether the last dose was a monovalent primary or monovalent booster dose, subjects will be required to wait at least 2 months before the receiving the current FDA recommended booster dose in this study.
6. It is possible that subjects might receive multiple COVID-19 vaccine doses) within this study if they meet relevant enrollment criteria and desire to receive multiple doses within the context of this study.

Vaccination Visit

1. The participant will undergo an abbreviated medical history and targeted physical exam by a study physician.
2. Assessment of concomitant medications.
3. Vital signs (temperature, pulse rate, respiratory rate, O2 saturation, blood pressure) will be obtained.
4. Participants will then receive a Pfizer-BioNTech COVID mRNA vaccination, or Moderna COVID-19 Vaccine as indicated by the FDA and CDC guidelines. They will receive the same vaccination as their initial reaction, if applicable.
5. Following vaccination, the study participant will be observed for adverse events (AEs) for 30 minutes, including examination of the vaccination site, and have vital sign measurements 30 minutes post-vaccination and/or after the onset of an adverse reaction.
6. During the 30-minute observation period, all AEs will be recorded, and AEs judged by an investigator to constitute an allergic reaction, even if not severe, will be documented.

7. In the event of a systemic allergic reaction, participants will be treated with rescue medications as appropriate. The site investigators for this trial are allergists, trained to recognize, and familiar with the treatment of anaphylaxis, and will be available within 60 seconds in the event of a reaction. Emergency medications, oxygen, and equipment will be available to treat any allergic reactions. Vital signs will be monitored during a systemic allergic reaction.
    - The following medications may be used to treat an allergic reaction:
        i. Epinephrine 1 mg/mL; 0.3 – 0.5mg IM
        ii. β-adrenergic agonist inhaler or nebulizer (e.g. albuterol)
        iii. Antihistamines
        iv. Steroids
        v. IV fluids
        vi. Oxygen
8. To assist study participants in the identification of and steps to take in the event of an allergic reaction after they leave the study site, each participant that has evidence of a systemic allergic reaction within 30 minutes of vaccination will be provided with epinephrine auto-injectors (2-pack) as well as an Anaphylaxis Emergency Care Plan. The PI or designee shall review the symptoms and steps to take in the event of an allergic reaction, including training on how to use the epinephrine auto-injector, with the participant prior to discharge.

Post-Vaccination

1. Participants without evidence of an adverse reaction within 30 minutes of vaccination will receive a follow-up phone call after 7 days to assess for development or lack of symptoms post-vaccination.
2. Participants that had a suspected reaction within 30 minutes of vaccination will be scheduled for a follow-up in-person visit within 7 days to assess for additional symptoms or resolution of symptoms.

c. Subject Withdrawal

i. Under what conditions will a subject be withdrawn prior to completion
ii. If a subject withdraws prior to completion, what is the plan for the use of their data

Any subject may withdraw at any time for any reason. These reasons may include but are not limited to:

- Subject's request, no reason needed
- Adverse event – at Investigator's request
- Other

The data for any subject who withdraws prior to completion will be flagged as incomplete data in our data set. We will delete data if the subject requests this.

d. Data Retention and/or Data Destruction Plan

i. How long will you keep subject data?

ii. If you plan to destroy the data, how will you destroy it?

Data collected will be retained for study record keeping purposes and for future research use for up to 5 years. No data will be destroyed.

Risks & Benefits

a. What are the risks and what will be done to monitor the risks?

b. What is the likelihood of each risk (common, likely, infrequent, or rare)?

Potential Risks

- Adverse reactions following the Pfizer-BioNTech COVID-19 Vaccine that have been reported in clinical trials include injection site pain, fatigue, headache, muscle pain, chills, joint pain, fever, injection site swelling, injection site redness, nausea, malaise, and lymphadenopathy. LIKELY
- Severe allergic reactions, including anaphylaxis, other hypersensitivity reactions (e.g., rash, pruritus, urticaria, angioedema), myocarditis, pericarditis, diarrhea, vomiting, and pain in extremity (arm) have been reported following the Pfizer-BioNTech COVID-19 Vaccine during mass vaccination outside of clinical trials. RARE
- Adverse reactions reported in a clinical trial following administration of the Moderna COVID-19 Vaccine include pain at the injection site, fatigue, headache, myalgia, arthralgia, chills, nausea/vomiting, axillary swelling/tenderness, fever, swelling at the injection site, and erythema at the injection site. LIKELY
- Severe allergic reactions, including anaphylaxis, myocarditis, and pericarditis have been reported following the Moderna COVID-19 Vaccine during mass vaccination outside of clinical trials. RARE
- Allergic reactions have been reported to occur after vaccination with the Pfizer-BioNTechCOVID-19 Vaccine and Moderna COVID-19 Vaccine. Allergic reactions range from mild to severe and include life threatening anaphylactic reactions, although no deaths have been reported with either vaccine. If a participant experiences a systemic allergic reaction within 30 minutes of vaccination, the site will provide the participant with an epinephrine auto-injector 2-pack. In addition, participants who experience a systemic allergic reaction will receive an Anaphylaxis Emergency Care Plan at the vaccination visit. The PI or designee will review the plan including symptoms of an allergic reaction and steps to take in the event of an allergic reaction, including training on how to use the epinephrine auto-injector, with the participant prior to discharge. If a participant has an allergic reaction, he/she may need oral, IM, or IV medications. The site investigators for this trial are allergists, trained to recognize, and familiar with the treatment of anaphylaxis, and will be available within 60 seconds in the event of a

reaction. Emergency medications, oxygen, and equipment will be available to treat any allergic reactions. RARE

- Treatment of individual acute allergic reactions during the conduct of the study should be with epinephrine, IV fluids, β-adrenergic agonists (e.g., albuterol), oxygen, antihistamines, and steroids, as indicated for the severity of the reaction. RARE
    - Risks of these common medications are summarized below:
        - Antihistamines: drowsiness, dizziness, constipation, stomach upset, blurred vision, or dry mouth/nose/throat
        - Epinephrine: tachycardia, palpitations, nervousness, sweating, nausea, vomiting, trouble breathing, headache, dizziness, anxiety, tremors, or pale skin
        - β-adrenergic agonists: nervousness, shaking (tremor), headache, or dizziness
        - Steroids: nausea, vomiting, loss of appetite, heartburn, trouble sleeping, increased sweating, or acne
- Participation in this study poses a risk for breach of confidentiality. RARE
- Subjects may experience discomfort during the blood draw, as well as bleeding, bruising and/or infection at the puncture site. However, this should be no greater than that experienced at the time of a routine blood draw. LIKELY
- Taking part in more than one research study may be harmful to the subject. If subjects are already taking part in another study, we ask that they let us know. Subjects should not take part in more than one study at the same time, unless the subject and the investigators agree that the subject is not likely to be harmed, and the outcome of the study will not be disturbed. RARE
- As with any research study, though, there may be additional risks of participating that are unforeseeable or hard to predict. RARE

What will be done to reduce or monitor these risks?

- To minimize the breach of confidentiality risk, information shared outside of the University of Michigan will not use the subject's name or hospital number, but rather a unique study number.
- The site investigators for this trial are allergists, trained to recognize, and familiar with the treatment of anaphylaxis, and will be available within 60 seconds in the event of a reaction. Emergency medications, oxygen, and equipment will be available to treat any allergic reactions.
- The clinical team will provide prescriptions for epinephrine auto-injectors for participants that experience systemic allergic reactions within 30 minutes of vaccination. In addition, participants will receive an Anaphylaxis Emergency Care Plan at the vaccination visit. The PI or designee will review the plan including symptoms of an allergic reaction and steps to take in the event of an allergic reaction, including training on how to use the epinephrine auto-injector, with the participant prior to discharge.

c. <u>What are the benefits?</u>

iii. <u>To the individual</u>

- Participants receive an additional dose of a highly protective COVID-19 mRNA vaccine for the SARS-CoV-2 virus in an environment where the investigators and staff are experienced

in the care of patients with allergic reactions. Two full doses of a COVID-19 mRNA vaccine are necessary to protect against infection with the delta variant. In addition, the immunity provided by these vaccines appears to wane to some degree over time, with additional booster doses recommended after completion of the primary vaccination series for optimal protection against emerging variants. This diminution is greater in individuals who receive only a single dose of vaccine.

- Participants will be compensated for their loss of time with a $75 VISA giftcard that they will receive at the completion of their vaccination visit.

iv. To society

This data is valuable for childhood and booster immunizations with mRNA vaccines to COVID-19 which are in planning stages. These findings will also be important for other vaccines based on RNA technology. Vaccines for influenza, respiratory syncytial virus and cancer are all being theorized using this technology.

Data & Safety Monitoring

a. *Will there be a board your study will report adverse events and other problems to?*

Yes

b. *Adverse Events*

Adverse Events (AEs): Any untoward medical occurrence associated with the use of an intervention in humans, whether or not considered intervention-related. AEs include expected and unexpected harmful effects, and unexpected risks of an interaction or an intervention.

Serious Adverse Event (SAE): An adverse event or suspected adverse reaction is considered “serious” if, in the view of the investigator:

1. Death.
2. A life-threatening event: An AE is considered “life-threatening” if, in the view of the investigator, its occurrence places the subject at immediate risk of death. It does not include an AE that, had it occurred in a more severe form, might have caused death.
3. Inpatient hospitalization.
4. Persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions.
5. Congenital anomaly or birth defect.
6. Important medical events that may not result in death, be life threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed above.

The investigator must report adverse events regardless of relationship to study therapy regimen or study mandated procedures.

i. Method of Identifying, Recording, Monitoring and Reporting Adverse Events

Identifying:
For this study, an adverse event will include the following associated with the vaccination administration:

- All AEs occurring within 7 days after vaccination administration
- All local reactions, except for injection site reactions of erythema/redness and induration/swelling measuring <2.5 cm, will be reported as AEs

Collecting Adverse Events: Adverse events may be discovered through any of these methods:

- Observing the participant
- Receiving an unsolicited complaint from the participant

Grading of Adverse Events Other than Systemic Allergic Reactions: The study sites will grade the severity of non-allergic adverse events experienced by the study participants according to the criteria set forth in the FDA Guidance for Industry Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials (September 2007); hereafter, referred to as the FDA Toxicity Grading Scale. Adverse events will be graded on a scale from 1 to 5 according to the following standards in the FDA Toxicity Grading Scale:

Grade 1 = Mild
Grade 2 = Moderate
Grade 3 = Severe
Grade 4 = Life-threatening
Grade 5 = Death

Grading of Systemic Allergic Reactions:

The investigator will grade severity of systemic allergic reactions on a scale of 1 to 5 according to criteria set forth in the CoFAR Grading Scale modified for use in adults only.

CoFAR Grading Scale for Systemic Allergic Reactions Version 3.0:

Grade 1: Reaction involving one of the following organ systems in which the symptoms are mild:

- Cutaneous: Generalized pruritus, generalized urticaria, flushing, angioedema
- Upper respiratory: Rhinitis, cough unrelated to laryngeal edema or bronchospasm
- Conjunctival: Injection/redness, itching, tearing
- GI: Nausea, abdominal pain (no change in activity level), single episode of vomiting and/or single episode of diarrhea

Grade 2: Reaction involving two or more of the following organ systems in which the symptoms are mild:

- Cutaneous: Generalized pruritus, generalized urticaria, flushing, angioedema
- Upper respiratory: Rhinitis, cough unrelated to laryngeal edema or bronchospasm
- Conjunctival: Injection/redness, itching, tearing GI Nausea, abdominal pain (no change in activity level), single episode of vomiting, and/or single episode of diarrhea

OR

Reaction involving at least one of the following organ systems in which the symptoms are moderate:

- Cutaneous: Generalized pruritus, generalized urticaria, flushing, angioedema
- Upper respiratory: Rhinitis, cough unrelated to laryngeal edema or bronchospasm
- Conjunctival: Injection/redness, itching, tearing
- GI: Nausea, abdominal pain (with change in activity level), two episodes of vomiting and/or diarrhea

Grade 3: Reaction involving one or more of the following organ systems:

- Lower respiratory: Throat tightness, wheezing, chest tightness, dyspnea, cough that respond to short acting bronchodilator treatment (including IM epinephrine) with or without supplemental oxygen
- GI: Severe abdominal pain, more than two episodes of vomiting and/or diarrhea
- Cardiovascular: Reduced BP with lightheadedness, presyncope or tachycardia

Grade 4: Life-threatening reaction involving one or more of the following organ systems with or without other symptoms listed in Grades 1 to 3:

- Lower respiratory: Throat tightness with stridor, wheezing, chest tightness, dyspnea, or cough associated with a requirement for supplemental oxygen and refractoriness to short-acting bronchodilator treatment (including IM epinephrine)[1]
  OR
- Respiratory compromise requiring mechanical support
- Cardiovascular: Reduced BP with associated symptoms of end-organ dysfunction (e.g., hypotonia [collapse], syncope) defined as: systolic BP of less than 90 mmHg or >30% decrease from baseline

Grade 5: Death

1. Examples of refractoriness could include continuous albuterol nebulizer or epinephrine IV infusion or more than three IM epinephrine injections

The investigator will also grade the diagnostic certainty of anaphylaxis according to criteria set forth by the Brighton Collaboration case definition and guidelines for anaphylaxis. Please see attached supporting documents in Section 44.

Recording/Monitoring:
Throughout the study, the investigator will record adverse events and serious adverse events on the appropriate AE/SAE electronic Case Report Form (eCRF) regardless of the relationship to study vaccine or study procedure. Once recorded, an AE/SAE will be followed until it resolves with or without sequelae, or the AE/SAE stabilizes, or until 7 days after the participant's vaccine dose, whichever occurs first.

Attribution of Adverse Events Code Descriptor Relationship
RELATED CATEGORIES
1. Definitely Related
2. Probably Related
3. Possibly Related

NOT RELATED CATEGORY
4. Unlikely to be Related
5. Definitely not Related

Reporting:
We will report any adverse events and other reportable incidences and occurrences (ORIO) to the IRB. Any adverse event or ORIO will be documented of that event including a description, subject number, date, outcome, and follow-up. Reporting of adverse events and ORIOs will follow IRBMED's reporting timetable and will occur at least yearly.

Statistical Design

Descriptive characteristics of the samples will be described using means and standard deviations for normal-distributed continuous variables (medians and interquartile ranges for non-normal) and frequencies and percentages for categorical variables.

To achieve 90% power with two-sided alpha=0.05 to detect a 2% allergic reaction rate and a 2% febrile reaction rate in the study population each vs a 0% null hypothesis rate using a t-test, 172 minimum total subjects would be needed for this study. To account for potential drop-out or follow-up failure of 20%, we will seek to enroll 200 total subjects.