Title: An Assessment of Immunogenicity of Respiratory Syncytial Virus (RSV) vaccines in residents of Long-Term Care Facilities (LTCF) and community-dwelling older adults receiving RSV vaccine as part of standard medical care

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An Assessment of Immunogenicity of licensed RSV vaccines in residents of Long-Term Care Facilities (LTCF) and community-dwelling older adults planning Respiratory Syncytial Virus (RSV) vaccination as part of medical care

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STATEMENT OF COMPLIANCE

This study will be carried out in accordance with Good Clinical Practice (GCP) as required by the U.S. Code of Federal Regulations applicable to clinical studies (45 CFR 46), and the International Commission on Harmonization (ICH) guidelines for Good Clinical Practice (GCP) E6. Investigators will complete and remain current with appropriate Human Subjects Protection Training. The study will be conducted in accordance with HHS-regulatory compliance for the Federal Wide Assurance and Institutional Review Boards (IRB).

SIGNATURE PAGE

The signature below constitutes the approval of this protocol and the attachments and provides the necessary assurances that this trial will be conducted according to all stipulations of the protocol, including all statements regarding confidentiality, and according to local legal and regulatory requirements and applicable US federal regulations and ICH guidelines.

The University of Rochester Institutional Review Board will be guided by the ethical principles described in the Belmont Report and by the regulations of the U.S. Food and Drug Administration (21 CFR 50 and 56) and the U.S. Department of Health and Human Services (45 CFR 46). The University of Rochester maintains an Assurance of Compliance with the Office for Human Research Protection (OHRP).

Primary Investigator: Ann R. Falsey, M.D.

Signed: Date:

Ann R. Falsey, MD
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Protocol Summary

Title: An Assessment of immunogenicity of licensed Respiratory Syncytial Virus (RSV) vaccines in residents of Long-Term Care Facilities (LTCF) and community-dwelling older adults planning to receive RSV vaccination as part of medical care.

Population: Adults ≥ 60 years of age: 76 residents of LTCF and 76 participants from community-dwelling adults. Adults living in the community will serve as the control group to reflect the study population enrolled in the Phase 3 Trials of the Pfizer and GSK RSV vaccines.

Number of Sites: The study will be conducted at 3 sites (URMC and 2 local LTCF).

Study Duration: 6 months

Participant Duration: The protocol requires a participant to remain in the study for 1 month.

Objectives: The primary objective of this study is to compare the neutralizing antibody response at one-month post-vaccination with a licensed RSV vaccine in adults ≥ 60 years of age living in skilled nursing facilities with adults living in the community. A secondary objective will be to evaluate the binding antibody responses to RSV preF proteins at 1 month.

Study Design

The study will be conducted at URMC and 2 local LTCFs. Approximately 76 persons ≥ 60 years of age who live in LTCF and an equal number of older adults living independently in the community who are planning to receive one of the licensed RSV vaccines as part of standard of care (SOC) will be recruited for participation in the study.

Study procedures: Visits will occur at the LTCF for residents of LTCF or in the research clinic for community-dwelling older adults. After informed consent by the participant or legally authorized representative (LAR), demographic and medical history will be collected and a symptom-targeted physical exam will be performed. A 10 cc blood sample will be collected prior to vaccination. Following vaccine administration, individuals will be monitored for 15 minutes for immediate adverse events. One additional visit will occur at 1 month post vaccination at which time 10 cc of blood will be collected, the participant will be interviewed and medical records reviewed. Subjects will be queried about any intervening respiratory illnesses and persons testing positive for RSV infection as part of the standard of care (SOC) after vaccination or by a non-vaccine RSV protein by ELISA and before the 1-month blood draw will not be included in the immunogenicity analysis. Serum samples will be tested for binding (RSV A and RSV B PreFusion F, Attachment (G) protein) and neutralizing antibodies to RSV A and RSV B in the URMC research laboratory.

BACKGROUND and RATIONALE

RSV is a major cause of respiratory infection in all ages, which can result in severe illness in both infants and older adults.[1-4] Like influenza, RSV infection follows a seasonal pattern, causing yearly wintertime epidemics in temperate climates. Although most well recognized as a pediatric pathogen, RSV was first acknowledged as a serious threat to adults when outbreaks of acute respiratory infection (ARI) with high pneumonia and mortality rates were reported in nursing homes settings in the 1980s.[5,6] Since the initial reports, prospective studies demonstrate infection rates in LTCF ranging from 1-12%.[7-10] RSV infection is particularly problematic for very elderly adults and those with underlying medical conditions, particularly heart and lung disease.[1,11-13] RSV not only causes respiratory tract infection but can also trigger exacerbations of underlying comorbid conditions such as COPD and CHF.[14] RSV infection has been associated with up to 22% of acute COPD exacerbations in prospective cohort studies and 11% of wintertime hospitalizations for COPD exacerbations.[1,15]

Current epidemiology shows that RSV is responsible for approximately 100,000-177,000 hospitalizations and 9,000-14,000 deaths annually in US adults 65 years of age and older.[4,16,17] Morbidity is significant among adults hospitalized with RSV disease, with 18% requiring intensive care, 31% needing home health services at discharge, and 26% dying within 1 year of hospitalization. In some studies, the risk of poor outcomes and death is higher among patients hospitalized for RSV compared to influenza.[13,18] In addition to the acute morbidity, longer term functional loss has been demonstrated following RSV hospitalization and the group most severely affected are residents of LTCFs.[19] The overall burden of adult RSV disease is likely underestimated since testing for RSV is less common in older adults than in children and RSV is more difficult to detect due to low levels of virus in the upper airways.[20,21]

Presently there is no specific antiviral treatment for RSV disease and management in adults is limited to supportive therapies such as hydration and oxygenation. Thus, a major unmet public health need has been to prevent RSV infection in at risk adults through vaccination. Two adult RSV vaccines (produced by GSK and Pfizer) are now licensed by the FDA, and are available in the fall of 2023 for use in adult populations age 60 years or older. The current vaccines are both based on the RSV prefusion F protein. The RSV F glycoprotein facilitates fusion of the virion and host cell membranes through a transition from an unstable but highly immunogenic prefusion conformation to a more stable post-fusion state.[22] Preclinical studies show that prefusion F elicits much higher neutralizing antibody titers than post-fusion F and that the most potent neutralizing antibodies from post-infection human sera target the prefusion form. [23,24] The vaccine manufactured by Pfizer is a bivalent RSV prefusion F subunit vaccine (RSVpreF) and is marketed under the brand name ABRYSVO. The vaccine manufactured by GSK is a monovalent RSV prefusion F with the adjuvant $AS01_E$ and is marketed under the brand name AREXVY.

Although the placebo-controlled randomized phase 3 studies of the Pfizer and GSK RSV vaccines each demonstrated >80% efficacy to prevent lower respiratory tract disease (LRTD), the trials have been criticized because the populations were relatively healthy older adults and not representative of individuals who are at highest risk for poor outcomes, including residents of LTCF.[26,27] Conducting large efficacy vaccine studies in LTCF residents is particularly challenging, and therefore this population was not well assessed in the clinical trials. For example, only 1.2 % resided in LTCF in the GSK RSV vaccine trial and LTCF residence was not reported in the Pfizer trial. Although a valid criticism, given the high efficacy demonstrated in the clinical trials, randomized clinical trials with a placebo is no longer ethical in high-risk populations. Concern about the lack of representation has resulted in the AMDA (American Medical Directions Association for Post-Acute and Long-Term Care Medicine) and the American Geriatric Society's reluctance to make strong recommendations for RSV vaccine use in this very high-risk population. RSV vaccines are to be prescribed in LTCFs using shared clinical decision making per ACIP recommendations, despite clear evidence that the general medical community is not familiar with the risks of RSV disease and the risks and benefits of RSV vaccine. Although there is no precise correlate of immunity to RSV, the high efficacy of the current pre-F vaccines that stimulate

robust neutralizing antibodies against RSV suggests that a significant vaccine-induced antibody response in residents of LTCF would likely be protective. This study will assess the antibody response to the current RSV vaccines in the vulnerable population of LTCF residents and compare the immune response to a concurrently enrolled group of community-dwelling adults ≥60 years that reflect the phase 3 trial population. These data will be important to help support the likely benefit of RSV vaccination in LTCF populations.

STUDY DESIGN and OBJECTIVES

This is an open label non-inferiority study where all participants will receive either the licensed Pfizer RSV Vaccine (ABRYSVO) or the GSK RSV Vaccine (AREXVY) as part of Standard of Care (SOC) and immune responses will be compared between adults living in the community and adults living in LTCF. The vaccines available at the participating LTCF as part of SOC will direct what product is administered at the individual LTCF and the community cohort will be matched for similar proportions of ABRYSVO and AREXVY.

Primary Objectives:

Demonstrate that the peak immune response at 1 month post vaccination of adults 60 years and older residing in LTCF is non-inferior to community-dwelling adults 60 years and older as measured by:

- Serum neutralizing antibody against RSV A & B

Secondary Objectives:

Demonstrate that the peak immune response at 1-month post vaccination of adults 60 years and older residing in LTCF is non-inferior to community-dwelling adults 60 years and older as measured by:

- Serum binding antibody to RSV prefusion F protein against RSV A & B

Study Period and Sites:

The study will be conducted at the University of Rochester Medical Center (URMC) in collaboration with 2 local LTCFs and include the Highlands at Brighton and St. Ann's Home. These LTCFs are located geographically close to URMC and have expressed a high interest in participating in this study. The study period will be from November 2023 to April 2024. There will be 1 month of direct participant involvement and 6 months for completion of the immune assays and data analysis.

Participant Recruitment:

For the cohort of LTCF residents, participant recruitment will be coordinated with the staff of the participating LTCF. At Highlands of Brighton the LTCF will identify individuals who express interest in the study. The LTCF staff contact individuals and legally authorized representatives to obtain consent for influenza, RSV, and COVID vaccination during the annual vaccination campaigns. During the conversation regarding SOC RSV vaccination with an FDA-approved RSV vaccine, LTCF staff will also assess potential interest in participating in the clinical study related to RSV vaccination for residents accepting the RSV vaccine as part of SOC. Those individuals who express interest in both receiving a licensed RSV vaccine as SOC and also participating in a research study will be directed to a member of the study team who will provide more detailed information about the study and if appropriate provide an IRB-approved consent form for review and consideration. St Ann's Home uses an opt-out approach when communicating with residents and LAR about vaccines. If residents or LAR's do not opt-out they will be scheduled for RSV vaccination. St Ann's will include in the opt-out letter a statement that a member of the research team will contact them about the study if they do not opt-out of RSV vaccination. Included in the communication will be the ability to-opt out of contact with the research team.

The major source for recruitment for the community cohort at URMC will be our RedCap Database Registry (STUDY00000413) of participants who have previously agreed to be contacted for future research

opportunities. We will send them an email to ascertain interest in the proposed study if RSV vaccination is planned as part of routine medical care. Potential participants will be provided the clinic phone number and the web-based registry to express interest (https://www.urmc.rochester.edu/idrc-research-studies.aspx). We will include all genders, races, and ethnicities in the study. We will use our IRB-approved screening protocol (STUDY00000484) to perform an initial pre-screening for basic inclusion and exclusion criteria after which, for those interested and meeting study criteria, we will set up a screening/enrollment appointment in the clinic. We will e-mail information on their scheduled appointment and a copy of the IRB-approved consent for the participant to review. Questions about the study will be answered prior to or during the enrollment visit.

Inclusion and Exclusion:

Inclusion criteria are intended to be broad with relatively few exclusions to reflect a real-life population in LTCF.

Inclusion:

- ≥60 years of age who live in skilled nursing facilities or reside independently in the community
- Life expectancy of >6 months, as assessed by the investigator
- Able to sign informed consent or to provide consent via a legally authorized representative (LAR)
- Planning to receive an RSV vaccine as part of standard medical care

Exclusion criteria:

- History of a current immunosuppressive condition or receipt of chemotherapy or other immunosuppressive or cytotoxic therapy, including chronic prednisone use of ≥ 20 mg/day for more than 14 days within 3 months of study vaccination
- History of hypersensitivity or reaction to any vaccine component
- Simultaneous administration of another vaccine (influenza, SARS-CoV-2) or within a 14-day window before or after intervention
- Previous receipt or intended receipt of an RSV vaccine outside the study
- Receipt of blood/plasma products or immunoglobulin within 60 days before study intervention administration.
- Documented RSV infection within 2 months prior to study intervention (enrollment).

Criteria for Temporarily Delaying Enrollment/Administration of Study Intervention:

The following conditions may allow a participant to be enrolled once the conditions have been resolved and the participant is otherwise eligible. Participants meeting these criteria at Visit 1 will be considered screen failures if enrollment has closed once the condition(s) has/have resolved.

- Current febrile illness (temperature ≥38.0°C [≥100.4°F]) or other acute illness within 48 hours before study intervention administration
- Receipt of any vaccine (including COVID-19 vaccines authorized for temporary or emergency use) within 14 days before study intervention administration
- Anticipated receipt of any non-study vaccine within 14 days after study intervention administration
- Receipt of short-term (<14 days) systemic corticosteroids (the equivalent of ≥20 mg/day of prednisone)
- Study intervention administration should be delayed until systemic corticosteroid use has been discontinued for at least 28 days.

Note: Systemic corticosteroids administered at a dose of <20 mg/day of prednisone or equivalent are permitted. Inhaled/nebulized, intra-articular, intrabursal, or topical (skin or eyes) corticosteroids are permitted.

Study Procedures:

For residents of LTCF all procedures will be conducted on-site at the LTCF and for the community cohort, all procedures will be conducted in the research clinic. No study procedures will be performed prior to consent.

It is anticipated that most LTCF residents will have a screening/enrollment visit and that vaccination will occur separately as per the LTCF vaccination plans. In most cases, the community cohort will have screening and vaccination on the same visit.

Schedules of Activities are listed below.

Schedule of Activities

Category of Activity	Research	Standard of Care	Research
Visit Number	V0[a]	V1[a]	V2
Visit Type	Screening and Enrollment	Vaccination	1-month (D28)
Visit Window	up to -21 days before vaccination		D21-42 after vaccination/infection
Visit Location	LTCF/clinic	LTCF/clinic	LTCF/clinic
Informed Consent	up to -21 days before vaccination		
I/E	X		
Medical History	X		X
Vaccine History	X		X
Prohibited Medication Review	X		X
Vital Signs	X	X[c]	
Targeted PE[b]	X	X[c]	
Collect 10cc serum	X		X
Vaccinate		X	
15-minute Observation (post vaccination)		X[c]	
Review ARI history and test results			X
SAE review			X

[a] Informed consent and screening activities can be separate or combined with Visit 1.

[b] Targeted physical exam will be performed on screening and before vaccination only as clinically indicated based on the presence of signs or symptoms warranting further investigation.

[c] Vaccination related procedures will be guided by SOC at each location

CONSENT PROCESS

Research Clinic: Consent and HIPAA Authorization will be documented by signing of an approved Informed Consent Form. Consent will be obtained utilizing the procedures outlined in the IDRC Research Group (SOP 1.1, version 6) by either the study investigator, research nurse, or a study coordinator. In brief, an IRB-approved consent describing the study will be provided to participants to review in the clinic. After adequate time to review the form, an informed consent discussion will take place in a room in the Infectious Diseases Research Clinic. During the visit, the document will be reviewed with the participant and all questions will be answered. Brief questioning of the participant will be completed after reading the forms to ensure understanding. At all times, we will ensure that all concerns are fully addressed and no procedures will be performed prior to obtaining informed consent. After signing the consent, the participant will be provided with a copy of the form, with the original copy filed with source documentation. A Consent Checklist is employed at the end of the visit to ensure that all essential tasks have been completed.

LTCF: Since it is anticipated that many residents of the LTCF will have some degree of cognitive impairment and be unable to sign the Informed Consent Form we will use one of two methods for consent. If the potential subject has mental capacity and autonomy, we will utilize the same consent process described above in the Research Clinic. If, however, the subject does not have the mental capacity to sign their own consent we will obtain consent from their Legally Authorized Representative (LAR). When feasible this will also use the same process described in the Research Clinic. Alternatively, this will be performed by obtaining a **verbal consent** by phone from the LAR that documents consent for subjects to participate in the study and addresses Privacy Protection described in HIPAA Authorization statements (see under Privacy and Confidentiality section). We request a **waiver of documentation of consent** and **alteration of elements of consent** for the verbal consent process. This is considered reasonable as it is not practical to carry out this minimal risk study without a waiver. For many LARs it may be inconvenient and a hardship to appear in-person due to work or family commitments, living out of town, or health reasons. Consent will be obtained utilizing the procedures outlined in the IDRC standard operating procedures (SOP 1.1, version 6.0) by either the study investigators, research nurse, or a study coordinator. SOP 1.6, version 1.0 specifically outlines the procedures to be used for remote consent by LAR. By phone or tele-visit, the consent will be reviewed with the LAR by research personnel and the LAR will be provided time for questions. The consent form will indicate that results of the study, and additional information if appropriate, will be provided to the LAR once the study has been completed. The LAR will indicate their consent and the consent will then be signed by study personnel. A signed copy of the informed consent will be mailed back to the LAR.

If after LAR consent is obtained, it is clear that the participant does not wish to participate, the participant will be withdrawn.

PRIVACY AND CONFIDENTIALITY OF PARTICIPANTS AND RESEARCH DATA

We have requested an **alteration of HIPAA Authorization** in the verbal consenting process (described above). Elements of the authorization will not be altered. The disclosure of Protected Health Information (HPI) is necessary in order to accurately enroll eligible subjects and for verification of medical conditions that would make a subject ineligible for this minimal risk study. PHI will not be reused or shared except as required by law, such as with the IRB for oversight of the study, and potentially the FDA who may evaluate results of the study, or for other research for which the use or disclosure of PHI would be permitted by the HIPAA Privacy Rule. This information sharing is included in the standard and verbal ICFs. All source data will be maintained in a locked office in a locked file cabinet, with all electronic data maintained on a password-protected University computer. All transmitted data inputted into the eCRF (Redcap) will be identified by only a study ID. All samples will be identified with only a sample ID. Future analyses of these samples may be performed in-house or in collaboration with other research groups

Standard of Care Vaccines Offered

Name	**RSVpreF (ABRYSVO)**
Type	Vaccine
Formulation	The active ingredients in RSVpreF are 2 stabilized RSV prefusion F antigens, in equal amounts from virus subgroups A and B, in a lyophilized dosage form for reconstitution.
Dose	120ug of the RSV prefusion F antigen
Route of Administration	IM in non-dominant deltoid muscle
Source	Pfizer

Name	**RSVpreF (AREXVY)**
Type	Vaccine
Formulation	The active ingredient is RSVpreF stored in single use lyophilized form requiring reconstitution. The adjuvant $AS01_E$ is composed of MPL and QS-21 combined in a phosphate buffered solution and water for reconstituting RSVpreF.
Dose	120ug of the RSV prefusion F antigen
Route of Administration	IM in non-dominant deltoid muscle
Source	GSK

Study Procedures

No study-specific procedure will be conducted before informed consent is obtained. Visits 0 and 1 may be performed on the same day, where feasible.

Visit 0 (Research Procedures)

- Obtain informed consent from the participant or LAR before performing any study-specific procedures
- Assign a single participant identifier
- Ensure and document that all of the inclusion criteria and none of the exclusion are met
- Obtain and record the participant's demography (including complete date of birth, sex, race, racial designation, and ethnicity)
- Obtain and record medical history
- Obtain and record details of any non-study vaccinations, and prohibited concomitant medications and treatments
- Perform a clinical assessment including vital signs (Blood pressure, heart rate and oxygen saturation) and symptom-targeted physical exam
  **Note: Height and weight will be recorded as by participant report or medical record in LTCF.*
- Collect 10 cc of serum
- Confirm contact and alternate contact information with participant and LTCF staff
- Schedule visit 2.

Visit 1 (Standard of Care) [Vaccination: For LTCF this will be performed by LTCF staff per their facility protocol and for Community Cohort this will be performed in the clinic]

- Perform a clinical assessment including vital signs (Blood pressure, heart rate and temperature) and symptom-targeted physical exam as dictated by location of vaccination standard procedures.
- Vaccinate with ABRYSVO or AREXVY and in non-dominant arm and document product, time and location.
- 15 minutes of observation in the clinic, in LTCF standard practice will be followed

If a person has an intercurrent RSV infection and is not vaccinated as part of SOC, visit 2 will be scheduled 28 -42 days after infection was documented.

Visit 2 (Research Procedures) [1-month]

- Verbally confirm the participant wishes to continue in the study
- Obtain and record any new medical history
- Inquire about any respiratory illnesses and record results any viral testing performed.
- Collect information on AEs, SAEs related to study procedures
- Obtain and record details of any non-study vaccinations, and prohibited concomitant medications and treatments
- Perform a symptom-targeted clinical assessment and physical exam
- Collect 10 cc of serum.

Individuals who do not meet the criteria for participation in the study (screen failure) can be rescreened if the exclusionary condition is considered to be temporary in nature by the investigator.

Only the following information will be collected on screen failures: demographics (age, screen number, sex, ethnicity, and race) and reason for ineligibility. Participants who are found to be ineligible will be told the reason for ineligibility.

LABORATORY METHODS:

RSV PCR will be performed as standard of care in the LTCF.

Enzyme Immunoassay (EIA): Serum IgG titers to RSV F (prefusion) protein of group A and B RSV will be determined by enzyme immunoassay using established methods.[28] Briefly, purified RSV proteins are coated to 96-well EIA plates to which serum 2-fold dilutions are added in duplicate. Bound antibody is detected with alkaline phosphatase-conjugated goat anti-human IgG antibody and substrate.

Microneutralization Assay (MNA): Serum neutralizing titers will be performed using an established microneutralization method for RSV A and B strains.[28] Briefly, 2-fold serum dilutions are incubated with 75 plaque forming units of RSV for 30 min at room temperature followed by the addition of 10^4 HEp-2cells in 96-well culture plates. After 3 days, the quantity of RSV antigen is determined by enzyme immunoassay using a monoclonal antibody to the RSV F protein. The neutralization titer is defined as the serum dilution that results in a 50% reduction in color development.

ANALYTICAL AND STATISTICAL METHODS

The primary immunogenicity analysis will include persons vaccinated but without documented RSV infection (PCR or G ELISA. The immune response to infection alone or combined infection and vaccination will be analyzed descriptively and separate from the primary analysis. This study is designed to demonstrate non-inferiority to within a 1.5-fold difference in the 1-month titer level, adjusting for baseline titer level. Since the distribution of titer levels is strongly positively skewed, and we are interested in relative changes, all titer levels

will be log transformed to help symmetrize the distribution while simultaneously stabilizing the variance. Exponentiating arithmetic mean log(titer), and their differences, thus results in geometric mean titer levels, and relative changes therein, which are the desired metrics. A linear model will be used to model log (1-month titer) as a function of an indicator for population, adjusted for continuous log (baseline titer). This model is equivalent to modeling log (relative change in titer), 1-month vs baseline, as a function of an indicator for population, adjusted for continuous log (baseline titer). The adjustment for log (baseline titer) improves statistical efficiency compared with using a 2-sample t-test to compare either (a) log (relative change in titer) or (b) log (1-month titer) by population, while obviating the choice between them. The focal parameter is the regression coefficient on population, whose antilog represents the ratio (test population vs reference population) of the adjusted geometric mean titer level (and, equivalently, the ratio of the adjusted relative geometric mean 1-month change in titer level). If the 1-sided 95% lower bound for this ratio exceeds 2/3, indicating with 95% confidence that the geometric mean titer level for the test population is at least 2/3 as high as that of the reference population (i.e. that the geometric mean titer level for the reference population is at most 1.5 times that of the test population), then we will conclude non-inferiority of the test population relative to the reference population.

Power and Sample Size Considerations:
Based on data from 52 participants in a prior study of the Pfizer RSV vaccine, the geometric mean titer level was estimated to be 2218 (95% CI: 1822-2699) at baseline, and 22,510 (17,003-29,799) at 1-month, corresponding with a relative change of 10.15-fold (95% CI: 7.39-13.95). From this data we estimate the Standard Deviation (SD) of log(titer) to be 0.71 at baseline and 1.01 at 1-month, while the SD of the 1-month change in log(titer) is 1.14 –larger than SD (log (1-month titer), indicating that a 2-sample t-test of the change in log(titer) would be less efficient than a t-test of the 1-month log(titer). Since we plan to adjust for baseline log(titer), our residual SD < min (SD (log (1-month titer), SD (log (relative change in titer) = min (1.01, 1.14) = 1.01. But not much less, since the prior data suggests the correlation between baseline and 1-month log(titer) is very weak (r=0.14), with log (baseline titer) explaining only 2% of the variability in log (1-month titer). In particular, we estimate residual SD = 1, suggesting that a 2-sample t-test of log (1-month titer) would be nearly as efficient as our linear model-based test adjusting for log (baseline titer). Given this estimate of variability (SD=1), a sample size of 76, 89, or 105 per group provides 80%, 85%, or 90% power to demonstrate non-inferiority to within a relative non-inferiority margin of 1.5-fold using a 1-sided 0.05 level linear model-based t-test comparing log (1-month titer) by population, adjusted for log (baseline titer). We have chosen a sample size of 76 in each group which will provide 80% power to demonstrate non-inferiority.

POTENTIAL RISKS AND BENEFITS

This study may be associated with risk due to sample collection or loss of privacy.

Sample Collection:

- **Blood draws:** A blood draw may cause faintness, inflammation of the vein, pain, bruising, or bleeding at the site of the puncture. There is also a slight chance of infection.

Loss of Confidentiality: Basic demographic and health information will be collected on participants in this study; therefore, there is a possibility of breach of confidentiality. Participant confidentiality will be maintained using study numbers on all data collection forms and keeping personal health information (PHI) separate. These documents are available to study personnel only and are kept under double-locked secure areas at URMC. Only study numbers are written on the data collection forms. All data are entered into Redcap and stored on the University of Rochester's Server. This server requires two authentications and specific training and documentation for access by investigators and staff.

Potential Benefits

There are no benefits to subjects for participating in the study

Costs/Payments

- The participant or their insurance company will not incur any additional costs for being in the study; any additional research testing will be paid for by the study
- Subjects will receive a $100 check for visit 1 (this may be split into two $50 payments if screening and vaccination occur on separate days) and $50 for visit 2.

Participant Status

- Participants will be free to withdraw at any time without providing a reason
- A participant may be withdrawn from the study if the investigator feels it is unsafe for them to continue
- New findings that might influence a participant's decision to participate will be made known to potential participants.

Safety

SAEs will be monitored from the time of consent to the final visit. Any SAE related to a study procedure will be reported to the IRB within 24 hours.

Definitions:
A **serious adverse event (SAE**) is any AE that:

- Results in death
- Is life-threatening (i.e., causes an immediate risk of death)
- Requires inpatient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability or incapacity (i.e., substantial disruption of the ability to conduct normal life functions)
- Results in a congenital anomaly or birth defect
- Considered to be an important medical event.

Reporting Responsibilities:

A medically qualified investigator will provide a causality assessment for each SAE. The Principal Investigator should provide a rationale and medical justification for this determination. This assessment is to be recorded on the CRF and the SAE Report Form (for SAEs) along with a description of the SAE that is sufficiently detailed to allow for a complete medical assessment of the case and determination of possible causality. All SAEs will be followed until resolution, until the event is considered stable, or until a non-study causality is assigned.

FUTURE USE OF SAMPLES

The purpose of allowing future testing of samples obtained as part of the current protocol is to maximize value for biomedical research. Specimens to be used for future use will be blood. Samples will be stored in the University of Rochester Infectious Diseases Unit laboratories at URMC (Biorepository IRB 00008473). The samples will be maintained in locked freezers in secure locations in the medical center. All freezers have temperature monitors and are alarmed if temperatures deviate from the control range. Only the investigators listed on the protocol will maintain this repository and will have access to these samples. Samples will not be stored with any personal identifiers and will be labeled only with a coded study number. Data linked to the samples will be kept in a separate secure location on password protected computers. Investigators outside the investigative team or at other institutions may request permission to use the samples only with the permission of the primary investigators. Samples will be de-identified and coded anonymously if tested outside the University. Analyses of these future use of samples may be performed in-house or in collaboration with other research groups.

Genetic testing that might result in health consequences for an individual will not be permitted as part of this protocol. No samples will be sold for commercial development.

Samples will be kept indefinitely in the repository. Participants may withdraw from future use at any time by

contacting the investigators. Samples will be located and destroyed at that time.

No future contact with participants will be sought regarding health conditions or related to the stored samples.

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