ARIC Manuscript Proposal #3980

PC Reviewed: 12/14/21 **Status: _____** **Priority: 2**

SC Reviewed: _____ **Status: _____** **Priority:**

C4R Common Proposal Form

Concise proposals are greatly appreciated! Proposals must be 4 pages or less excluding references

Project title: Factors associated with post-vaccination antibody response

Lead investigator(s):
John Kim (University of Virginia)
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Elizabeth C. Oelsner (Columbia University)
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Writing Group Chair
Senior C4 author (Elizabeth C. Oelsner)

Potential overlap

- Among approved C4R proposals (see website), which ones are the most similar to this proposal?
- Is there any potential overlap? Please explain and describe
    - If there is potential overlap, please summarize how this proposal is different

C4R cohort inclusion table:

Cohorts	Include: Yes / No	Co-author*	Comments**
ARIC	Yes	Ryan Demmer	
CARDIA	Yes	Nori Allen	
COPDGene	Yes	Russell Bowler	
Familial Interstitial Pneumonia	Yes	David Schwartz, Joyce Lee	
Framingham	Yes	Vasan Ramachandran	
Jackson Heart Study	Yes	Russ Tracy Margaret Doyle	
HCHS/SOL	Yes	Lisa Lavange	
MASALA	Yes	Alka Kanaya	
MESA	Yes	R. Graham Barr Mary Cushman	

NOMAS	Yes	Mitchell Elkind	
REGARDS	Yes	Mary Cushman, Virginia Howard	
SARP	Yes	Victor Ortega	
SPIROMICS	Yes	Prescott Woodruff	
Strong Heart Study	Yes	Shelley Cole	
Other***			

*If you do not have a co-author identified to represent a cohort, we will be happy to assist you in identifying one.
**Please justify exclusion of any C4R cohort from your proposal.
***If you anticipate including data from another cohort, please indicate which one(s).

Co-authors not already listed above:
Michaela Anderson (University of Pennsylvania)
Taison Bell (University of Virginia)

Specific aims and hypotheses:

Specific Aim	Hypothesis
Determine factors that are associated with post SARS-CoV2 vaccine antibody response.	We hypothesize that clinical factors, specifically older age, male sex, higher body mass index, and socioeconomic factors, will be associated with a lower post SARS-CoV2 vaccine antibody response as detected by dried blood spot testing. We also hypothesize that prior infection will be associated with higher post SARS-CoV2 vaccine antibody response.
Determine the association between body surface area-adjusted vaccine dosage with post-vaccine SARS-CoV-2 antibody levels.	We hypothesize that a higher vaccine dosage-to-body surface area ratio will be associated with increased antibody response.

Rationale (300 words maximum):

Significance	The development and administration of vaccines for SARS-CoV2 have significantly impacted the trajectory of this disease on an individual and population level.[1,2] While the vaccine has demonstrated excellent efficacy in reducing the risk of infection and severe outcomes (i.e., hospitalizations), recent evidence suggests differential antibody responses and waning immunity, particularly by vaccine type and vaccine recipient characteristics.[3,4] Older age, male sex, and immunocompromised status have been identified as potential factors linked to lower and more rapidly waning antibody responses 6 months after vaccination.[5,6] Body habitus may also play a role in post-vaccination antibody responses, particularly among men with a higher body mass index.[7] However, these studies have largely been limited to cohorts from clinical trials or few clinical sites comprised of healthcare workers.[5,8] Whether similar findings are

	seen or new factors identified among more general/population-based cohorts is a major gap that C4R can potentially fill.
Relevant prior literature	Refer to references below proposal.
Summary of proposed study	We propose to identify factors associated with a lower antibody response after receiving the SARS-CoV2 vaccine and whether vaccine dosage adjusted for body surface area is associated with post-vaccine antibody levels.
Justification for use of C4R	C4R has antibody levels measured from dried blood spot tests and vaccine status/type captured.

Data:

	Variables needed	Questions and comments*
Exposure(s)	Primary: Age, smoking status, height, weight, body mass index, sex, prior SARS-CoV-2 infection history, nucleocapsid protein levels, time since vaccination	
Outcome(s)	Primary: SARS-CoV-2 anti-spike protein antibodies	
Covariates	Age, sex, self-reported race/ethnicity, educational attainment, vaccine type, history of prior SARS-CoV2 infection, history of prior SARS-CoV2 hospitalization, time since vaccination	

*For meritorious proposals, we will work with you to assess the status of data harmonization of variables of interest.

Analysis plan:

- Primary analyst(s): Pallavi Balte, John Kim
- Brief statistical plan, organized by specific aim

SA1: Determine factors that are associated with post SARS-CoV2 vaccine antibody response. We will initially examine the means, medians, and ranges of antibody levels and visualize their distribution using histograms. We will initially use generalized linear regression models regressing LN transformed continuous titers against spike and nucleocapsid protein on age, smoking status, height, weight, body mass index, sex, race/ethnicity, educational attainment, vaccine type, history of prior SARS-CoV2 infection, history of prior SARS-CoV2 hospitalization, and time since vaccination.

SA2: The same approach will be used to determine the association between body surface area-adjusted vaccine dosage with post-vaccine SARS-CoV-2 antibody levels. Important predictors identified in SA 1 will be incorporated into the SA 2 models as appropriate as we will use directed acyclic graphs to identify potential confounders and collider variables to account for in our regression models.

Additional considerations of primary importance to C4R approval -- please comment:

- Inclusion of women and minorities: We will include all participants

    - Treatment of sex as a biological variable: We plan to examine this as a potential predictor variable and co-variate for adjustment in our models.
    - Appropriate analysis and interpretation of differences by race and ethnicity: We will examine this as a potential predictor variable.
- Consideration of social determinants of health: We will examine educational attainment as a predictor variable in our models.
- Use (or non-use) of genetic data: Do not plan to use genetic data.
- Respect for data sharing restrictions on Strong Heart Study data: We will adhere to data sharing guidelines from the Strong Heart Study.

References:

1. Polack FP, Thomas SJ, Kitchin N, et al. Safety and Efficacy of the BNT162b2 mRNA Covid-19 Vaccine. *N Engl J Med.* 2020;383(27):2603-2615.
2. Baden LR, El Sahly HM, Essink B, et al. Efficacy and Safety of the mRNA-1273 SARS-CoV-2 Vaccine. *N Engl J Med.* 2021;384(5):403-416.
3. Steensels D, Pierlet N, Penders J, Mesotten D, Heylen L. Comparison of SARS-CoV-2 Antibody Response Following Vaccination With BNT162b2 and mRNA-1273. *JAMA.* 2021.
4. Collier AY, Yu J, McMahan K, et al. Differential Kinetics of Immune Responses Elicited by Covid-19 Vaccines. *N Engl J Med.* 2021.
5. Levin EG, Lustig Y, Cohen C, et al. Waning Immune Humoral Response to BNT162b2 Covid-19 Vaccine over 6 Months. *N Engl J Med.* 2021.
6. Boyarsky BJ, Werbel WA, Avery RK, et al. Antibody Response to 2-Dose SARS-CoV-2 mRNA Vaccine Series in Solid Organ Transplant Recipients. *JAMA.* 2021;325(21):2204-2206.
7. Yamamoto S, Mizoue T, Tanaka A, et al. Sex–associated differences between body mass index and SARS-CoV-2 antibody titers following the BNT162b2 vaccine among 2,435 healthcare workers in Japan. *medRxiv.* 2021:2021.2008.2030.21262862.
8. Pellini R, Venuti A, Pimpinelli F, et al. Initial observations on age, gender, BMI and hypertension in antibody responses to SARS-CoV-2 BNT162b2 vaccine. *EClinicalMedicine.* 2021;36:100928.