

**Determining RSV Burden and Outcomes in Pregnant Women and Older Adults  
Requiring Hospitalization  
Short Title: RSV in Older Adults and Pregnant Women Study  
(ROAPS)**

**VERSION 8.0; 23MAR2021**

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**ABBREVIATIONS**

<b>Abbreviation</b>	<b>Stands for</b>
ACIP	Advisory Committee on Immunization Practices
ADL	activities of daily life
AE	Adverse Event
AIDS	acquired immunodeficiency syndrome
ARI	acute respiratory illness
BAL	bronchoalveolar lavage
BMI	body mass index
CCI	Charlson comorbidity index
cCCI	classic Charlson comorbidity index
CHF	congestive heart failure
CHOA	Children's Healthcare of Atlanta
CI	confidence interval
COPD	chronic obstructive pulmonary disease
COVID-19	coronavirus disease 2019
DSU	Drug Safety Unit
ED	emergency department
EDB	Exposure during breastfeeding
EDP	Exposure during pregnancy
EUA	emergency use authorization
EUH	Emory University Hospital
EUHM	Emory University Hospital Midtown
HIV	human immunodeficiency virus
ICD9	International Classification of Diseases
LAR	legally-authorized representative
LOE	Lack of efficacy
MOP	Manual of procedures
mRNA	messenger RNA
NAAT	Nucleic acid amplification test
NP	nasopharyngeal
OP	oropharyngeal
OR	odds ratio
PCR	polymerase chain reaction
PBMC	peripheral blood mononuclear cells
PPE	personal protective equipment
QOL	quality of life
RRI	Research Reportable Injury
RSV	respiratory syncytial virus
RVP	respiratory viral panel
SAE	Serious Adverse Event
SARS-CoV-2	severe acute respiratory syndrome coronavirus – 2
SAP	statistical analysis plan
SOC	standard of care
TND	test-negative design
uCCI	updated Charlson comorbidity index

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VE	vaccine effectiveness
wGA	weeks gestational age
WHO	World Health Organization

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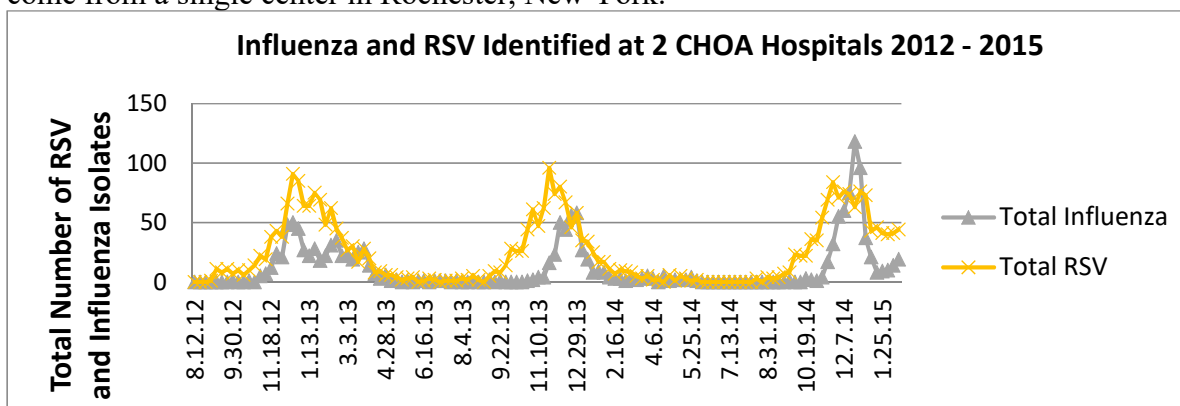
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**1. BACKGROUND**

**1.1. RSV IN OLDER ADULTS AND PREGNANT WOMEN (ROAPS)**

Respiratory syncytial virus (RSV) is the single most important cause of serious lower respiratory tract infections in U.S. children. RSV is estimated to cause 50,000 – 125,000 hospitalizations/year in U.S. children <5 years of age.<sup>1,2</sup> After an initial infection, subsequent infections tend to be less severe and often manifest as mild upper respiratory tract infections. RSV is also an important pathogen later in life with severe disease also occurring among those with compromised cardiac, pulmonary or immune systems and in the elderly.<sup>3-5</sup> It is uncertain the extent to which severe disease in the elderly is due to lack of immunological control due to complications from age-associated co-morbidities. Estimates of the RSV disease burden requiring hospitalization in adults are limited but suggest that up to 10% of adults presenting with acute respiratory illness (ARI) during the winter have RSV.<sup>3,5-8</sup> Data regarding RSV in pregnant women, a candidate population for vaccine implementation, are particularly limited.

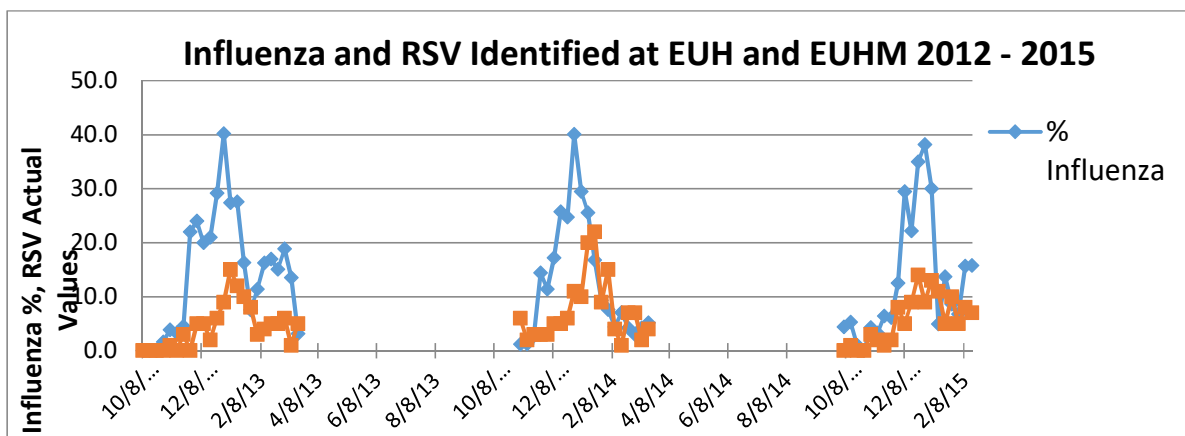
The RSV season frequently overlaps with the influenza season which confounds the ability to define RSV’s clinical and epidemiological features. The limited available data show that age, chronic medical conditions (e.g., COPD, cardiac disease, immunodeficiency) are significant risk factors and that fever is less commonly observed with RSV than with influenza infection, while cough, dyspnea, and wheezing may be more common.<sup>9-11</sup> These limited data primarily come from a single center in Rochester, New York.<sup>5,10-24</sup>



The exact timing of the adult RSV season relative to the pediatric season is not known. We know that the RSV season in children extends beyond the influenza season (See **Figure above Influenza and RSV Identified at 2 Children’s Healthcare of Atlanta (CHOA) Hospitals 2012-2015**). In Atlanta, RSV in children extends from the beginning of October through early-mid March. Available data suggests that most cases of RSV in adults occur during the winter season, similar to cases in children.<sup>3,5,12,14,15,24,25</sup> Cases detected by standard of care (SOC) testing from several large adult hospitals in Atlanta are outlined in the Figure below (**Influenza and RSV Identified at EUH and EUHM 2012 – 2015**).

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Despite nearly 50 years of effort, neither a vaccine nor highly effective antiviral therapy has been licensed; however, promising RSV vaccines are in development. Phase 2 and 3 clinical trials in pregnant women have begun (NCT04032093 and NCT04424316).<sup>26,27</sup> Establishing the current population-based RSV burden of disease, clinical and epidemiological features in hospitalized adults is crucial for understanding the potential for an RSV vaccine impact. By expanding our understanding of RSV in pregnant women and older adults, we will be better positioned to assess potential impact and cost benefit of a vaccination program in pregnant women and older adults.

Substantial RSV-related disease and hospitalizations occurs in infants with highest risk in those <2 months of age (1970/100,000) followed by those 3 – 5 months of age (897/100,000).<sup>28</sup> Risk among those that are preterm is even higher due to underlying chronic lung disease, smaller airways, and decreases in maternal antibody transfer across the placenta to preterm infants.<sup>29-31</sup> The current leading approaches towards prevention of disease among infants are maternal RSV vaccination and potentially monoclonal antibodies and clinical trials are ongoing. Maternal vaccination is likely to be utilized for prevention of RSV in neonates and infants. In addition to directly protecting the mother, maternal antibodies are likely to be transferred across the placenta beginning at 32 weeks gestational age (wGA) to the unborn fetus. Data about the timing (wGA) and quantity of antibodies transferred across the placenta are fairly limited for RSV.<sup>32-35</sup> Additional data about antibody transfer across the placenta of RSV antibodies could be determined by collecting maternal serology and cord blood specimens at the time of delivery.

SARS-CoV-2, the cause of COVID-19, emerged as a pathogen in humans in December 2019 and spread worldwide to become a pandemic over the next several months.<sup>36,37</sup> The rapid emergence of COVID-19 in Atlanta resulted in the need to halt enrollment into ROAPS in mid-March 2020 (end of season 2 of surveillance). Early data from the Southern Hemisphere indicates that COVID-19 and the social interventions that have been implemented (e.g., face masks, social distancing) and potential changes in the willingness to seek healthcare have had substantial impact upon the burden of influenza and the influenza season.<sup>38</sup> It is unknown whether such interventions might impact the influenza and RSV seasons in the US. Such data are critical for understanding the lower bound of influenza and RSV disease that occur in the

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setting of substantial social interventions and changes in healthcare seeking behavior. After discussion with the study funder (Pfizer), we will continue to perform prospective RSV and viral surveillance (e.g., SARS-CoV-2) among pregnant women, adults with CHF or COPD, and older adults requiring hospitalization during the pre-planned Season 3 (2020 – 2021). The approach to respiratory virus surveillance during ROAPS needed to change due to the unique impact that COVID-19 has had upon healthcare. This includes, but is not limited to, risk of transmission to healthcare providers, potential shortages of personal protective equipment (PPE), and shortages of respiratory swabs.

Beginning the summer of 2020, all admitted patients to EUH and EUHM are receiving standard of care (SOC) testing for SARS-CoV-2 upon hospital admission. Note that beginning in Season 3 (2020 – 21), we will modify the approach to salvage SOC specimens sent from admitted patients meeting enrollment criteria. These salvaged SOC specimens will then be tested with study-specific BioFire RVP testing retrospectively and potentially with future Pfizer assays (e.g., dedicated PCR). Substudies #1, 2, and 4 will continue during Season 3 with modifications as detailed below. Additionally, patient interviews and onsite follow-ups will be limited to those enrolled in certain substudies, cough specimens will not be obtained, and a control population of healthy outpatients will not be enrolled. This will simplify Season 3 and the efforts involved, while minimizing risks for study staff and patients.

To clarify where procedures will differ beginning in Season 3, we have offset changes throughout the protocol with ***Modifications Beginning in Season 3: with the modification in italics.***

In addition to modifications to Season 3 due to SARS-CoV-2, Pfizer and Emory identified an opportunity for ROAPS to further evaluate both RSV and SARS-CoV-2 illness and antibody transfer among pregnant women. SARS-CoV-2 can cause severe disease in pregnant women (including fetal loss) and in infants and young children.<sup>39,40</sup> Vaccines for COVID-19 are rapidly being developed with a number of candidates already in Phase 3 clinical trials.<sup>41-46</sup> Although expansion of vaccine clinical trials into children has occurred down to age 12,<sup>47,48</sup> it is unlikely that vaccines will be available for children <6 months of age in the near future. Maternal vaccination, in addition to providing benefit to the mother, could provide benefit to the infant through decreasing maternal disease and through the passive transfer of maternal antibody to the infant. In addition to directly protecting the mother, maternal antibodies are likely to be transferred across the placenta beginning at 32 weeks gestational age (wGA) to the unborn fetus. Data about the timing (wGA) and quantity of antibodies transferred across the placenta are limited for COVID-19. Additional data about antibody transfer across the placenta of COVID-19 antibodies could be determined by collecting maternal serology and cord blood specimens at delivery. The Advisory Committee on Immunization Practices (ACIP) noted that “potential risks of mRNA vaccines to the pregnant person and the fetus are unknown because these vaccines have not been studied in pregnant people.” They advised that “If pregnant people are part of a group that is recommended to receive a COVID-19 vaccine (e.g., healthcare personnel), they may choose to be vaccinated.” In addition, “When making a decision, pregnant people and their healthcare providers should consider the level of COVID-19

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community transmission, the patient’s personal risk of contracting COVID-19, the risks of COVID-19 to the patient and potential risks to the fetus, the efficacy of the vaccine, the side effects of the vaccine, and the lack of data about the vaccine during pregnancy.”<sup>49</sup> In an effort to better define transplacental antibody transfer of both RSV and SARS-CoV-2 antibodies across gestational ages, Substudy 5 has been incorporated as part of this ROAPS amendment. It is expected that enrollment for Substudy 5 as defined in Methods Section may begin around or after the start of enrollment for the COVID VE Substudy 6 and aims to enroll healthy women who present at EUH or EUHM for delivery, regardless of RSV or COVID status.

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**1.2. COVID-19 Amendment for COVID VE / Sub-study 6**

In December 2019 the Wuhan Municipal Health Committee identified an outbreak of pneumonia that was ultimately identified as a novel pathogen named SARS-CoV-2. The disease caused by SARS-CoV-2 is called Coronavirus disease 2019 (COVID-19). On March 11, 2020 the WHO declared COVID-19 a pandemic. As of March 8, 2021, >29 million cases and 530,000 deaths had occurred in the US.<sup>50</sup> Morbidity and mortality have disproportionately affected older adults and racial and ethnic minorities.<sup>51</sup> Since the emergence of SARS-CoV-2, additional mutations in the virus have been observed including D614G, B.1.1.7 (which emerged in the UK), P1 (which emerged in South America), and B.1.351 (which emerged in South Africa).

Currently, there are over 170 vaccines in preclinical development and 60 vaccines that have entered into clinical trials.<sup>52</sup> In the US, 6 candidate vaccines have had vaccine doses purchased by Operation Warp Speed to advance promising candidate vaccines rapidly toward licensure,<sup>53</sup> and 2 mRNA vaccines [Moderna (mRNA-1273), Pfizer (BNT162b2)] received FDA EUA in December 2020. BNT162b2 is a mRNA vaccine recommended as 2 doses 21 days apart that encodes the full-length, membrane-anchored S glycoprotein of SARS-CoV-2 with two introduced proline mutations to lock it in the prefusion conformation.<sup>54-56</sup> It was co-developed by BioNTech SE and Pfizer, Inc. The vaccine showed an acceptable safety profile in a Phase 1/2 study.<sup>57</sup> Data supporting the FDA EUA came from a pivotal Phase 3 clinical trial.<sup>47</sup> The BNT162b2 study vaccinated over 43,000 participants, and vaccine was 95% effective in prevention of COVID-19 in comparison to placebo.<sup>58</sup> It also was highly effective against severe cases (9 in placebo: 1 in vaccine). Millions of BNT162b2 doses have now been administered under EUA to individuals at high risk including healthcare workers, nursing home residents, and other high-risk groups (e.g., ≥65 years of age).

Although clinical trials provide initial vaccine efficacy in a highly controlled setting, real world estimates of COVID-19 vaccine effectiveness (VE) are needed since this can vary substantially.<sup>58</sup>

The optimal methodology for VE studies uses the “test-negative design” (TND) in which vaccination rates among test-positive individuals (“cases”) are compared with vaccination rates among test-negative individuals (“controls”). VE is calculated as: (1-odds ratio for vaccination) x 100.<sup>59</sup> A test-negative case-control study design using a molecular assay is important in estimating VE accurately and rapidly,<sup>60</sup> and can control for differences that might exist due to access to care.<sup>60-63</sup> Test-negative controls have been demonstrated to accurately estimate VE theoretically and through retrospective reanalysis of prospectively collected data of vaccine efficacy from randomized controlled trials.<sup>60-63</sup>

Such studies have been used extensively for influenza.<sup>64-71</sup> The ROAPS study was modified during the Spring of 2020 to retrospectively characterize the emergence of novel respiratory pathogens (e.g., SARS-CoV-2) in these adults (Version 4.0). Beginning the summer of 2020, all admitted patients to EUH and EUHM are receiving standard of care (SOC) testing for SARS-CoV-2 using a molecular test upon hospital admission to EUH and EUHM. Reasons

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for this include identification of SARS-CoV-2 infection prior to hospital admission (community-onset) that is presenting presymptomatically, asymptotically, or atypically. This provides a unique opportunity to evaluate the VE of COVID-19 vaccination with BNT162b2 against hospital admission due to ARI in adults (**Sub-Study #6**).

Critical to VE studies is correctly determining the vaccination status for all cases and controls enrolled in this study. To determine vaccination status, review of government-issued COVID-19 vaccination cards, medical records from relevant healthcare providers (e.g., primary care, public health department), health-insurance providers, pharmacies, and any local, state, or national adult immunization registries will need to occur for each enrolled patient. For each potential source of vaccination, a record of whether BNT162b2 (or other COVID-19 vaccine) was received, including the date(s) of administration and the number of doses received, will be obtained.

It is also critical to control for potential bias and confounding that may exist in the absence of randomized assignment of vaccine and blinded follow-up. Thus, in addition to constructing crude OR and VE estimates, logistic regression modeling to assess BNT162b2 VE after adjustment for time of enrollment, recruitment site, and other potentially confounding sociodemographic, clinical factors (e.g., comorbidities, history of SARS-CoV-2 infection), and behavioral and lifestyle factors will be performed. It is particularly critical as potential for receipt of vaccine will be rapidly changing over time. As such, it will be necessary to control tightly the ‘vaccine priority group’ of enrolled subjects along with the window for enrollment to limit the risk of findings being due to vaccine access. In addition, the risk of SARS-CoV-2 exposure is anticipated to rapidly change over time, so it will be critical to identify and control for timing of illness. The approach to this will be by multivariable analysis.

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## **2. STUDY OBJECTIVES**

For clarity Sub-Studies 1-5 are presented first followed by Sub-Study 6

- 2.1 Sub-Studies 1-5 reflect ROAPS RSV and only non-COVID VE Objectives
- 2.2 Sub-Study 6 reflects only [COVID VE Objectives](#)

### **2.1. ROAPS RSV AND SUB-STUDIES 1 – 5 OBJECTIVES**

#### **2.1.1. Primary Objective**

- To determine the population-based incidence of RSV-related hospitalizations in pregnant women and adults  $\geq 50$  years of age.

#### **2.1.2. Secondary Objectives**

- 1) To describe the epidemiology and clinical presentation of RSV-related hospitalizations in pregnant women and adults  $\geq 50$  years of age.
- 2) To describe the outcomes of RSV-related hospitalizations in pregnant women and adults  $\geq 50$  years of age.
- 3) To compare the population-based incidence of hospitalization, epidemiology, clinical presentation, and outcomes observed in RSV-positive pregnant women and adults  $\geq 50$  years of age versus those with influenza.
- 4) To compare RSV antibodies in cord blood and maternal serum at various wGA.
- 5) To compare SARS-CoV-2 antibodies in cord blood and maternal serum at various wGA.

#### **2.1.3. Exploratory Objectives**

- 1) To determine the rates of seroresponse to RSV between acute and convalescent serology and the concordance with molecular test results in hospitalized pregnant women and adults  $\geq 50$  years of age.
- 2) To determine the prevalence of RSV and other viral pathogens (including SARS-CoV-2) in healthy control populations of pregnant women and adults  $\geq 50$  years of age.
- 3) To compare the rate of RSV and other viral pathogen detections among enrolled control populations with the rate of RSV and other viral pathogen detections among hospitalized pregnant women and adults  $\geq 50$  years of age.
- 4) To describe the clinical and epidemiologic characteristics of patients hospitalized with ARI in whom specific pathogens are identified, including those who are co-infected.
- 5) To determine the rates, risk factors for, and outcomes of RSV-related pneumonias.
- 6) To correlate RSV viral load with clinical symptomatology and outcomes in a subset of enrolled patients (Sub-Study #1).
- 7) To collect clinical specimens for future analyses.

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- 8) To assess the risk of RSV infection/re-infection through 1 year after enrollment in a subset of patients enrolled in the primary study (Sub-Study #2).
- 9) To describe the durability of the serological response to RSV through 1 year after enrollment in a subset of patients enrolled in the primary study (Sub-Study #2).
- 10) To determine rates of influenza vaccination and influenza vaccine effectiveness against influenza-related hospitalizations in pregnant women and adults  $\geq 50$  years of age hospitalized with ARI.
- 11) To determine rates of RSV and other viral pathogens among adults 18 – 49 years of age admitted with congestive heart failure (CHF) or chronic obstructive pulmonary disease (COPD) exacerbations (Sub-Study #3).
- 12) To assess the performance characteristics of cough specimens submitted for the detection of RSV and other viral pathogens.
- 13) To assess the cellular immune response to RSV at baseline and in follow-up in a subset of RSV positive patients and controls (Sub-Studies #1, 2, and 4).
- 14) To assess the risk of RSV infection/re-infection through almost 3 years after enrollment in a subset of patients enrolled in the primary study (Sub-Study #4).
- 15) To describe the durability of the serological response to RSV through almost 3 years after enrollment in a subset of patients enrolled in the primary study (Sub-Study #4).
- 16) To determine the population-based incidence of SARS-CoV-2-related hospitalizations in pregnant women and adults  $\geq 50$  years of age.
- 17) To describe the epidemiology and clinical presentation of SARS-CoV-2-related hospitalizations in pregnant women and adults  $\geq 50$  years of age.
- 18) To describe the outcomes of SARS-CoV-2-related hospitalizations in pregnant women and adults  $\geq 50$  years of age.
- 19) To compare the population-based incidence of hospitalization, epidemiology, clinical presentation, and outcomes observed in SARS-CoV-2-positive pregnant women and adults  $\geq 50$  years of age versus those with influenza, RSV, or other respiratory viral pathogens.
- 20) To describe the seroprevalence of antibodies to SARS-CoV-2 among subjects infected with SARS-CoV-2, other circulating coronaviruses, and other respiratory viruses.

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**2.2. COVID VE / SUB-STUDY 6 OBJECTIVES**

Objectives	Endpoints
<b>Primary</b>	<b>Primary</b>
<ul style="list-style-type: none"> <li>Objective 1: To estimate the effectiveness of 2 doses of BNT162b2 (i.e., fully vaccinated) against hospitalization for ARI* due to SARS-CoV-2 infection.</li> </ul>	<ul style="list-style-type: none"> <li>VE calculated as 1 minus the OR comparing the odds of being fully vaccinated (2 doses) with BNT162b2 for hospitalized cases and controls, multiplied by 100%.*</li> </ul>
<b>Secondary</b>	<b>Secondary</b>
<ul style="list-style-type: none"> <li>Objective 2: To describe the effectiveness of only 1 dose of BNT162b2 (i.e., partially vaccinated) against hospitalization for due to SARS-CoV-2 infection.</li> </ul>	<ul style="list-style-type: none"> <li>VE calculated as 1 minus the OR comparing the odds of being partially vaccinated with BNT162b2 (only 1 dose) for hospitalized cases and controls, multiplied by 100%.*</li> </ul>
<ul style="list-style-type: none"> <li>Objective 3: To describe the effectiveness of <math>\geq 1</math> dose of BNT162b2 (i.e., ever vaccinated) against hospitalization for ARI due to SARS-CoV-2 infection.</li> </ul>	<ul style="list-style-type: none"> <li>VE calculated as 1 minus the OR comparing the odds of ever being vaccinated (<math>\geq 1</math> dose) with BNT162b2 for hospitalized cases and controls, multiplied by 100%.*</li> </ul>
<ul style="list-style-type: none"> <li>To evaluate the effectiveness of BNT162b2 against ARI hospitalization stratified by prevalent or important viral strains.</li> </ul>	<ul style="list-style-type: none"> <li>BNT162b2 VE estimates by prevalent or important virus variants.</li> </ul>
<ul style="list-style-type: none"> <li>To evaluate the effectiveness of BNT162b2 against severe hospitalization-related outcomes (e.g., ICU admission, mechanical ventilation, and death).</li> </ul>	<ul style="list-style-type: none"> <li>BNT162b2 VE estimates against severe outcomes including ICU admission, mechanical ventilation, and death.</li> </ul>
<b>Tertiary/Exploratory</b>	<b>Tertiary/Exploratory</b>
<ul style="list-style-type: none"> <li>To further describe the effectiveness of BNT162b2 stratified by various patient characteristics (e.g., age, sex, race/ethnicity, chronic medical conditions, history of SARS-CoV-2 infection, long-term care facility residence, pregnancy status, and receipt of influenza vaccine).</li> </ul>	<ul style="list-style-type: none"> <li>BNT162b2 VE estimates by age group.</li> <li>BNT162b2 VE estimates by sex.</li> <li>BNT162b2 VE estimates by race/ethnicity.</li> </ul>

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Objectives	Endpoints
	<ul style="list-style-type: none"> <li>• BNT162b2 VE estimates by presence of chronic medical conditions, history of SARS-CoV-2 infection, pregnancy status.</li> <li>• BNT162b2 VE estimates by receipt of influenza vaccine in the last year.</li> <li>• BNT162b2 VE estimates among long-term care facility residents.</li> <li>• BNT162b2 VE estimates by time since vaccination (durability).</li> <li>• BNT162b2 VE estimates by time between first and second dose among those who received 2 doses.</li> </ul>
<ul style="list-style-type: none"> <li>• To describe the proportion of patients with ARI where SARS-CoV-2 was identified.</li> </ul>	<ul style="list-style-type: none"> <li>• Proportion of ARI hospitalizations where SARS-CoV-2 is identified.</li> </ul>
<ul style="list-style-type: none"> <li>• To summarize the proportion of patients who receive 0, 1, or 2 doses of BNT162b2.</li> <li>• To summarize the time between administration of the first and second dose of BNT162b2 among patients who received 2 doses.</li> <li>• To summarize the time since vaccination with BNT162b2 (most-recent dose) from study enrollment.</li> </ul>	<ul style="list-style-type: none"> <li>• Proportion of patients who receive 0, 1, and 2 doses of BNT162b2</li> <li>• Average and median time between receipt of the first and second dose BNT162b2 among patients who received two doses.</li> <li>• Average and median time between study enrollment and receipt of last dose among patients receiving BNT162b2.</li> </ul>
<ul style="list-style-type: none"> <li>• To describe demographic, clinical, and laboratory (i.e., viral strain) characteristics and disease severity of any BNT162b2 vaccine failures.</li> </ul>	<ul style="list-style-type: none"> <li>• Describe age, gender, race/ethnicity, clinical characteristics, and severity (ICU admission, ventilator, death) of any patients who received BNT162b2 and test positive for SARS-CoV-2.</li> <li>• Sequence isolates of available SARS-CoV-2 viral variants and identify whether these are due to major viral variants (e.g., B.1.351).</li> </ul>
<ul style="list-style-type: none"> <li>• To describe COVID-19 disease severity for vaccinated and unvaccinated cases.</li> </ul>	<ul style="list-style-type: none"> <li>• Describe disease severity for vaccinated and unvaccinated cases (e.g., average hospital LOS, 30-day readmission, the proportion requiring ICU admission or mechanical ventilation, death).</li> </ul>

*\* ARI as defined by WHO as an acute respiratory infection that occurred within the last 10 days and required hospitalization with history of fever or measured fever of  $\geq 38\text{ C}^\circ$  AND cough. Because many COVID-19 patients do not necessarily have fever (~15%) or cough (~15%), we will vary this definition in sensitivity analyses.<sup>51</sup>*

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### 3. METHODS

For clarity, Sub-Studies 1 – 5 (ROAPS RSV and all non-COVID VE methods) are presented first followed by Sub-Study 6 (COVID VE only).

Schedule of Events for Sub-Studies 1-6 can be found in the following Appendices:

- [Appendix A](#): Schedule of Events – ROAPS Acutely Ill Cases
- [Appendix B](#): Schedule of Events – Sub-Study #4
- [Appendix C](#): Schedule of Events – Healthy Controls
- [Appendix D](#): Schedule of Events – Sub-Study #5
- [Appendix E](#): Schedule of Events - COVID VE Sub-Study #6

#### 3.1. ROAPS RSV Sub-Studies #1 – 5 and All Non-COVID VE Methods

- **To accomplish Primary, Secondary #1 – 3, and Exploratory Objectives #1, 4 – 7:** We will prospectively identify and enroll pregnant women and adults  $\geq 50$  years of age who meet the case definition of acute respiratory tract infection (ARI) and are admitted for inpatient care. This will include those who are admitted for observation or remain in the ED for  $\geq 24$  hours. Nasopharyngeal/oropharyngeal (NP/OP) swabs as well as cough specimens, will be obtained from all enrolled patients as soon as possible after admission (see specimen collection section for specific guidelines) and blood will be obtained. A study questionnaire detailing clinical and epidemiology information will be completed via patient and/or healthcare power of attorney interview and medical chart review. This will include an assessment of Activities of Daily Living (ADL), Quality of Life (QOL), frailty, and data to determine the other disease-specific scores (for older adults) and a pregnancy-related questionnaire for pregnant women. In order to ensure that specimens are collected in a timely manner, we will aim for 7 days a week enrollment using study nurses and other qualified personnel. Enrolled patients also will have standard of care (SOC) results and specimens scavenged and will be asked to return for convalescent serology 21 – 60 days (goal 21 – 45 days) after initial presentation. Home visits may be used if needed, but follow-up at Emory will be highly encouraged. If ARI symptoms develop after hospital discharge but before the follow-up appointment for convalescent serology, an additional follow-up visit will occur prior to the convalescent visit. If symptoms are present at the convalescent visit, NP and OP swabs as well as cough specimens will be obtained at the convalescent visit. Data will be analyzed separately for pregnant women and adults  $\geq 50$  years of age.

**Modifications Beginning in Season 3:** *Beginning the summer of 2020, all admitted patients to EUH and EUHM are receiving standard of care (SOC) testing for SARS-CoV-2 upon hospital admission. Reasons for this include identification of SARS-CoV-2 infection prior to hospital admission (community-onset) that is presenting presymptomatically, asymptotically, or atypically. Beginning in Season 3 (2020 – 21), we will salvage SOC specimens sent from admitted patients meeting enrollment criteria (we will not obtain additional NP/OP swabs or cough specimens beyond those*

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*collected as SOC except as detailed below for those enrolled in Substudies 1, 2 and 4). We are requesting a waiver of all element of informed consent for review of medical records and collection of SOC specimens from patients meeting eligibility criteria. A small subset will be prospectively consented and enrolled into Substudies 1, 2, and/or 4 (e.g., those that have SOC testing that are RSV positive, influenza positive, or PCR-negative controls). This is important as the COVID-19 pandemic has impacted resources available (e.g., PPE) to approach all admitted patients making it impractical to conduct the study as had occurred in Seasons 1+2. These salvaged SOC specimens will then be tested with study-specific BioFire RVP testing retrospectively 3 weeks or more after hospital discharge and potentially with future Pfizer assays (e.g., dedicated PCR). These results will not be available to the patient or patient care teams (the result will no longer be clinically relevant from these specimens). Patient interviews will not be conducted except on those subjects enrolled in Substudies 1, 2, or 4. Patients will not have follow-up or direct contact with the research staff unless enrolled in Substudies 1, 2, or 4.*

- **To accomplish the Secondary Objectives #4 – 5 (Sub-Study #5):** We will identify and enroll pregnant women admitted to EUHM for a one-time inpatient visit at the time of delivery. A subset of these will have been enrolled in the Emory Cord Blood research study (EmPOWR), the Cleveland Core Bank, or other research entities obtaining cord blood. These women will be approach to co-enroll into ROAPS. Cord blood will be collected and saved at the time of birth and SOC maternal serum will be salvaged from the laboratory. Cord blood and maternal serum antibody levels will be compared at the time of delivery between various wGA for both RSV and also SARS-CoV-2. If insufficient cord blood is available, residual infant SOC sera may be salvaged from the laboratory (if available).
- **To accomplish the Exploratory Objectives #2-3:** We will prospectively identify and enroll pregnant women and adults  $\geq 50$  years of age without recent illness or hospitalizations. These adults will also have NP/OP swabs, cough specimens and blood obtained on enrollment. They will also be asked to return for follow-up serology 21 – 60 days (goal 21 – 45 days) after initial enrollment. If ARI symptoms develop after enrollment, but before the follow-up appointment for follow-up serology, an additional follow-up visit will occur prior to the convalescent visit. If symptoms are present at the convalescent visit, NP and OP swabs will be obtained at the follow-up visit. To the extent feasible, efforts will be made to match the age, gender, and co-morbidities to the cohort of hospitalized and enrolled older adults. Pregnant women controls will be matched to cases roughly on age, race/ethnicity, time, and weeks gestational age (wGA). Data will be analyzed separately for pregnant women and adults  $\geq 50$  years of age.  
*Modifications Beginning in Season 3: Beginning in Season 3, a control population of healthy outpatients will NOT be enrolled due to the COVID-19 pandemic.*

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- **To accomplish Exploratory Objectives #6 and 13 (Sub-Study #1):** We will serially sample a subset of adults every other day who have RSV identified on standard of care testing and controls (e.g., those with influenza, those that are SOC PCR-negative) with NP/OP swabs along with obtaining information about the resolution of symptoms from the patient interview. This will only occur until hospital discharge, follow-up will occur according to the main study except that those enrolled in this optional substudy will also have NP/OP swabs obtained at the convalescent visit. If these Sub-Study adults agree, they will also have PBMCs collected at enrollment, approximately day 7 of symptoms (if this occurs after the enrollment visit), and at the convalescent visit.

*Modifications Beginning in Season 3: None.*

- **To accomplish Exploratory Objectives #8-9 (Sub-Study #2):** We will enroll in follow-up a subset of patients beyond the follow-up visit at Days 21 – 60. This will include RSV positive (either through RSV SOC testing or through study-specific BioFire testing) and roughly matched RSV negative patients enrolled into this study that will be identified and asked to complete follow-up by the study team. They will be asked to return for a NP/OP swab, cough specimen and blood draw for any symptoms consistent with ARI (see Inclusion Criteria #5c) and for follow-up blood draw just prior to the onset of the next RSV season. The study team will make contact with them every 2 weeks between enrollment into Sub-Study #2 and the final visit to ascertain for interval ARI. If these Sub-Study adults agree, they will also have PBMCs collected at their final Sub-Study #2 visit.

*Modifications Beginning in Season 3: Those identified with study-specific BioFire testing will not be approached for enrollment into Sub-Studies 2 and/or 4. These subjects will not have follow-up NP/OP swab testing cough specimen collection performed. Similar to the overall study, a small subset (e.g., individuals that have SOC testing that are RSV positive, influenza positive, and are PCR-negative controls) will be prospectively consented and enrolled into Substudies 1, 2, and/or 4.*

- **To accomplish Exploratory Objective #10:** We will obtain vaccination histories from patients that meet enrollment criteria for the **Primary, Secondary, and Exploratory Objectives #1, 4 – 7**. We will use a test negative design to determine influenza vaccine effectiveness (VE). Sensitivity analyses will be used to determine VE by varying the definition of ARI and subgroup analyses will be performed (e.g., different age groups, co-morbidities, multiple seasons of influenza vaccination).

*Modifications Beginning in Season 3: This exploratory objective will now be limited to obtaining vaccination history only from the medical record and central electronic registries (patients and medical providers will not be contacted for records).*

- **To accomplish Exploratory Objective #11 (Sub-Study #3):** We will enroll 18 – 49 year old adults who otherwise meet all of the Inclusion and Exclusion Criteria (**Except for Inclusion Criterion #1**) who are admitted with COPD or CHF exacerbations (**Inclusion Criteria #5a OR 5b**). These will be followed similarly to the Primary, Secondary, and Exploratory Objectives #4 – 7 above.

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*Modifications Beginning in Season 3: The same modification will occur as for Primary, Secondary, and Exploratory Objectives #1, 4 – 7 (see above) in that a waiver of informed consent will be requested to test SOC specimens and review medical records.*

- **To accomplish Exploratory Objective #12:** We will collect cough specimens from adults that can provide cough specimens for viral testing. We will test these specimens for evidence of RSV and other viral pathogens. The results of the viral testing of these cough specimens will be compared with other RVP SOC testing, Biofire RVP testing, and serology to determine the performance characteristics of this sample type.

*Modifications Beginning in Season 3: Beginning in Season 3, cough specimens will NOT be obtained in the study.*

- **To accomplish Exploratory Objectives #13 and 14 (Sub-Study #4):** Similar to Sub-Study #2, we will enroll and follow-up a subset of patients beyond the follow-up visit that occurs just prior to the RSV season in Sub-Study #2. This will include RSV positive and RSV negative patients enrolled into this study. They will be asked to return for a NP/OP swab, cough specimen and blood draw for any symptoms consistent with ARI (see Inclusion Criteria #5c) and for follow-up blood draw just prior to the onset of the subsequent 2 RSV seasons (last visit occurring almost 3 years after initial enrollment). The study team will make contact with them every 2 weeks between enrollment into Sub-Study #4 and the final visit to ascertain for interval ARI. PBMCs will be collected from them on a yearly basis.

*Modifications Beginning in Season 3: Substudy #4 will continue in Season 3, but will not include cough specimens. All other study procedures will occur as detailed above.*

- **To accomplish Exploratory Objectives #16-20:** We will identify SARS-CoV-2 positive patients among those who meet enrollment criteria for the primary study. Similar to the primary and secondary objectives, we will test collected nasopharyngeal/oropharyngeal (NP/OP) swabs as well as cough specimens and blood specimens by PCR and antibody assays. We will also assess clinical and epidemiology information including assessment of Activities of Daily Living (ADL), Quality of Life (QOL), frailty, and data to determine the other disease-specific scores (for older adults) and a pregnancy-related questionnaire for pregnant women.

*Modifications Beginning in Season 3: The same modification will occur as for Primary, Secondary, and Exploratory Objectives #1, 4 – 7 (see above) in that a waiver of informed consent will be requested to test SOC specimens and review medical records. SOC specimens will have already been tested by SOC SARS-CoV-2 PCR testing. We will not obtain questionnaires on these COVID-19 positive patients.*



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**3.2. COVID VE Sub-Study #6 Methods**

To accomplish the Objectives for Sub-Study #6: COVID VE, the following approach and definitions will be utilized. An NP or nasal swab to test for the presence of SARS-CoV-2 by NAAT will be required for all study participants as a study-related procedure (if not performed as standard of care). NAAT will be performed in an approved local laboratory. Whole-genome sequencing will be performed on SARS-CoV2-positive swabs from enrolled patients when possible from study specimens and/or SOC specimens when available.

**Cases will be defined as patients who meet selection criteria and:**

1. Test positive for SARS-CoV-2 via NAAT performed upon sample(s) collected as a study-related procedure upon admission/enrollment, OR
2. Tested positive by NAAT\* from samples collected  $\leq 14$  days prior to admission/enrollment.

*\* All efforts will be made to confirm test results from specimens prior to admission as a NAAT test. If a positive test cannot be confirmed as a NAAT, it will still be included. We will examine the proportion of cases identified in the 14 days prior to admission/enrollment (Criteria #2 above). If this is a substantial component of the total number of cases, we will consider a sensitivity analysis using only samples collected upon admission/enrollment (Criteria #1 above only).*

Patients who have positive results for SARS-CoV-2 from samples taken  $\geq 72$  hours after hospital admission/enrollment will be considered to have nosocomial COVID-19 and will be excluded from the primary analysis. The impact of excluding these patients on VE estimates will be examined in sensitivity analyses. Laboratory confirmation is defined by NAAT, however, results from viral culture, direct or indirect fluorescent antibody staining, or rapid antigen testing will be collected and analyzed in sensitivity analyses.

**3.2.1. Definition of Test-Negative Controls**

All other patients who met study inclusion criteria (e.g., at least one NP or nasal swab that was tested for SARS-CoV-2 using NAAT) but for whom SARS-CoV-2 is not identified from NAAT will serve as test-negative controls.

**3.2.2. Vaccination**

A natural (“real-life”) history of vaccination with BNT162b2 will be obtained for both cases and controls from government-issued COVID-19 vaccination cards, medical and billing records collected from relevant healthcare providers (e.g., primary care, public health department), health-insurance providers, pharmacies, and any local, state, or national immunization registries for each enrolled patient. For each potential source of vaccination, a record of whether BNT162b2 was received, including the date(s) of administration and number of doses received, will be obtained. Self-reported COVID-19 vaccination status will be also captured as part of the patient interview and will be analyzed in sensitivity analyses.

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The primary exposure of interest is history of vaccination with BNT162b2. For the primary objective, patients will be considered vaccinated if they have documented evidence of receiving the second dose of BNT162b2  $\geq 7$  days before ARI symptom onset. When evaluating the effectiveness of one dose of BNT162b2, patients will be considered vaccinated if they have documented evidence of receiving the first dose of BNT162b2  $\geq 14$  days before ARI symptom onset. Four levels of the primary exposure variable will be assessed:

1. **Fully vaccinated** defined as 2 doses of BNT162b2 received with  $\geq 7$  days between receipt of the 2nd dose and ARI symptom onset. This group will serve as the ‘exposed’ group evaluated in the primary objective. Patients who received only 1 dose or 2 doses of BNT162b2 with  $< 7$  days between receipt of the 2nd dose and ARI symptom onset and will be excluded from this analysis. In sensitivity analyses, VE will also be calculated for 2 doses of BNT162b2 received with  $\geq 14$  days between receipt of the 2nd dose and ARI symptom onset.
2. **Partially vaccinated** defined as 1 dose (only) of BNT162b2 received with  $\geq 14$  days between receipt of the 1st dose and ARI symptom onset. This group will serve as the ‘exposed’ group as a secondary endpoint. Patients who received 2 doses or 1 dose of BNT162b2 with  $< 14$  days between receipt of the 1st dose and ARI symptom onset will be excluded from this analysis.
3. **Ever vaccinated** defined as  $\geq 1$  dose of BNT162b2 received with  $\geq 14$  days between receipt of the 1st dose and ARI symptom onset. Patients who received 1 dose of BNT162b2 received with  $< 14$  days between receipt of the 1st dose and ARI symptom onset will be excluded from this analysis. This group will serve as the ‘exposed’ group as a secondary endpoint.
4. **Never vaccinated** defined as never received BNT162b2. This group will serve as the reference exposure group (i.e., ‘unexposed’ group) in all VE analyses.

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**Table: Definitions of study population, exposure, cases, and test-negative controls for  
primary and secondary study objectives**

Objective	Study Population	Exposure*	Case	Test-negative Control
<b>Primary Objective</b>				
1	patients ≥18 years of age hospitalized for ARI	<b>Fully vaccinated</b> defined as 2 doses of BNT162b2 received with ≥7 days between receipt of the 2nd dose and ARI symptom onset.	SARS-CoV-2 identified by NAAT	SARS-CoV-2 NOT identified by NAAT
<b>Secondary Objectives</b>				
1	patients ≥18 years of age hospitalized for ARI	<b>Partially vaccinated</b> defined as 1 dose (only) of BNT162b2 received with ≥14 days between receipt of the 1st dose and ARI symptom onset.	SARS-CoV-2 identified by NAAT	SARS-CoV-2 NOT identified by NAAT
2	patients ≥18 years of age hospitalized for ARI	<b>Ever vaccinated</b> defined as 1 or 2 doses of BNT162b2 received with ≥14 days between receipt of the 1st dose and ARI symptom onset.		

*ARI= acute respiratory illness; NAAT= nucleic acid amplification test; SARS-CoV-2= severe acute respiratory syndrome coronavirus 2.*

*\* Patients who never received BNT162b2 or another SARS-CoV-2 vaccine will serve as the reference exposure group (i.e., ‘unexposed’ group) in all VE analyses. For the primary objective, patients will be considered vaccinated if they have documented evidence of receiving the second dose of BNT162b2 ≥7 days before ARI symptom onset. When evaluating the effectiveness of one dose of BNT162b2, patients will be considered vaccinated if they have documented evidence of receiving the first dose of BNT162b2 ≥14 days before ARI symptom onset.*

Patients who receive any other licensed or investigational SARS-CoV-2 vaccine or COVID-19 prophylactic agent other than Pfizer’s BNT162b2 prior to enrollment will be excluded from the analysis.

Odds of being fully vaccinated with BNT162b2 for cases and test-negative controls will be constructed and compared using odds ratios (OR) and 95% confidence intervals (CI). VE will be calculated as 1–OR multiplied by 100%. Like all observational designs, the TND still requires assessment for bias and confounding that may exist in the absence of randomized assignment of vaccine and blinded follow-up. Thus, in addition to constructing crude OR and VE estimates, logistic regression modeling to assess BNT162b2 VE after adjustment for time of enrollment, recruitment site, and other potentially confounding sociodemographic, clinical factors, and behavioral and lifestyle factors will be performed.

Informed consent will be obtained prior to enrollment for all participants. Patients will be consented and have an interview performed that will occur as close to enrollment as possible and will participate in 1 visit. Data from the hospitalization and outcomes (e.g., vital status,

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discharge disposition) will be collected through 30 days post enrollment (V2) via medical record review. No additional direct patient contact will necessarily occur at this visit.

**3.2.3. Patient Sociodemographic Characteristics, Clinical History, and Health Behaviors and Lifestyle**

Sociodemographic and clinical characteristics for each participant will be collected and described. Importantly, these characteristics will be used to assess and control for potential confounding in adjusted VE models. Factors assessed for confounding will include individual-level variables related to participant sociodemographic characteristics (i.e., time and site of enrollment, age, sex, race, ethnicity, and socioeconomic status), clinical history and disease severity (i.e., presence of chronic medical or immunocompromising conditions, history of SARS-CoV-2 infection body mass index [BMI], nursing home residency or other healthcare facility exposure in the past 3 months, and antibiotic use in previous 14 days), health and lifestyle behaviors (e.g., smoking status, weekly exposure to children <5 years of age, current drug abuse, workplace exposure to COVID-19, and adherence to social distancing measures), and vaccination history (e.g., influenza vaccine in last year, pneumococcal vaccine[s] in last 5 years, any prior SARS-CoV-2 vaccine). These are factors that we have either found to be important covariates in previous work, have been identified in other risk factor literature, or are variables that may be associated with the exposure as well as outcome (i.e. prior positive SARS-CoV-2 PCR test, etc.).<sup>72-77</sup>

Prior infection with SARS-CoV-2 will be assessed for all patients. Clinical characteristics describing the presence or absence of underlying immunocompromising and chronic medical conditions will also be collected. History of immunocompromising conditions will include a history of human immunodeficiency virus/acquired immune deficiency syndrome (HIV/AIDS), leukemia, lymphoma, Hodgkin's Disease, generalized malignancy (excluding skin cancer), diseases requiring treatment with immunosuppressive drugs including long term corticosteroids or radiation therapy, nephrotic syndrome, chronic renal failure (including end-stage renal disease), organ transplantation, multiple myeloma, sickle cell disease, functional or anatomic asplenia, and immune deficiency or other conditions consistent with an immunocompromised state. Other chronic medical conditions and health behaviors to be evaluated will include: hypertension, obesity, chronic heart disease (including heart failure, coronary artery disease, cardiomyopathy, and pulmonary hypertension), diabetes (including type 1, type 2, or gestational), stroke, asthma (moderate or severe persistent), chronic lung disease (such as chronic obstructive pulmonary disease [COPD, including emphysema and chronic bronchitis], idiopathic pulmonary fibrosis, and cystic fibrosis), chronic kidney disease (with dialysis), chronic liver disease (including cirrhosis), alcoholism, or cigarette smoking. A classical and updated Charlson comorbidity index (cCCI<sup>78</sup> and uCCI<sup>79</sup>) will be calculated for each patient based on history of chronic medical and immunocompromising conditions. These are factors that we have either found to be important covariates in previous work, have been identified in other risk factor literature, or are variables that may be associated with the exposure as well as outcome. Outcome data including duration of hospitalization, ICU admission and duration, and mechanical ventilation and duration, will be collected through last

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hospital contact or day 30 after enrollment (e.g., discharged home, discharged to rehabilitation, death, still hospitalized at day 30).

### 3.2.4. Sensitivity Analyses

The following sensitivity analyses will be performed:

- 1) Including self-reported vaccination without documentation.
- 2) Peak COVID-19 circulation when  $\geq 5\%$  of COVID-19 PCRs are positive
- 3) Hospitalization  $< 7$  days of symptom onset
- 4) Hospitalization  $< 14$  days of symptom onset
- 5) Controls positive for other viruses
- 6) Controls negative for other viruses
- 7) Cases with a control virus (e.g., rhinovirus) to evaluate for confounding in the model.<sup>65,80,81</sup>
- 8) Excluding those with prior SARS-CoV-2 infection
- 9) SARS-CoV-2 positivity excluding test results obtained prior to hospitalization
- 10) Varying the definition of ARI (e.g., fever, cough).
- 11) VE calculated for 2 doses of BNT162b2 received with  $\geq 14$  days (rather than  $\geq 7$  days) between receipt of the 2<sup>nd</sup> dose and ARI symptom onset.

Additional sensitivity analyses may also be performed including altering the approach from a multivariable to a propensity-based analysis.

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**4. STUDY POPULATION**

**4.1. ROAPS RSV and COVID VE ARI**

The study sites are Emory University Hospital (EUH) and Emory University Hospital Midtown (EUHM). EUH is located on the Emory University campus in northeast Atlanta. EUHM is located in Midtown Atlanta, separated by about 5 miles from EUH. The Georgia Department of Public Health District 3 (HD3) is an 8 county region that comprises Atlanta proper and the inner ring of surrounding counties [Fulton, DeKalb, Gwinnett, Cobb, Douglas, Clayton, Rockdale, and Newton Counties (see Figure **Atlanta Regional Map**)]. We will establish population-based active surveillance of pregnant women and adults  $\geq 50$  years of age for RSV among HD3 residents. We previously have used ICD9-based coded data to establish the population base served by hospitals in both adult and pediatric EPIC study enrollments of community-acquired pneumonia.<sup>8,82</sup> ICD9 data from Oct – December 2013 showed that EUH and EUHM totaled 9.58% of HD3 hospital admissions (ARI ICD9 codes available for this analysis were 466, 480-88, 518.5, and 518.81). This will be our preferred method for determining the population-based incidence since it was used in EPIC.<sup>8,82</sup> Using data from the EIP Active Bacterial Core Surveillance network from 2012 – 2014, EUH/EUHM comprised 11.1% of admissions in the HD3 region for invasive *H. influenzae*, Group B Streptococcus, and *S. pneumoniae*. Thus, data from multiple sources confirm that EUH and EUHM comprise about 9.5 – 11.1% of HD3 region admission.

We will use these two geographically separate hospitals to minimize potential biases that might exist with a single location (e.g., patient population, referral biases, and admission biases) that could impact RSV estimates.

<b>Data on Emory University Hospital and Emory University Hospital Midtown</b>				
Hospital	ED Beds	Annual ED Visits	Inpatient Beds	Annual Inpatient Admissions
Emory University Hospital (EUHM)	35	57,000	511	23,205
Emory University Hospital (EUH)	21	36,000	579	23,710

**For ROAPS RSV and Sub-Studies 1-5:** We will conduct population-based surveillance among pregnant women and adults  $\geq 50$  years of age requiring hospitalization with ARI by performing active surveillance at EUH and EUHM.

**For COVID VE (Sub-Study #6):** We will conduct population-based surveillance among adults  $\geq 18$  years of age requiring hospitalization with ARI to determine COVID VE by performing active surveillance at EUH and EUHM.

We will review the two hospitals’ emergency departments for potential admissions of adult patients with ARI daily during the influenza season using a combination of clinical research associates (CRAs) and nurse coordinators. Screening in the emergency departments will begin immediately upon starting the day shift to capture some of the ARI patients waiting for a bed from the overnight shift. All admissions from the preceding 24 hours will be screened for ARI admissions. The Cerner Powerchart system, which is the electronic medical record (EMR) that

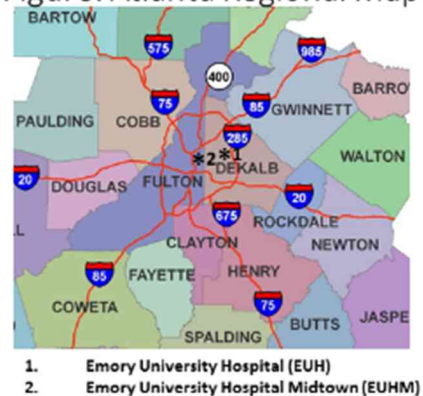
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is used at EUH and EUHM, will allow screening by hospital location and by time from hospital admission. This will facilitate identification of potentially eligible patients. Additionally, SOC specimens that are sent to the microbiology laboratory will be reviewed to determine whether they are associated with a hospitalized patient who meets study enrollment criteria. We also will work with the Emory Data Warehouse to screen electronically for patients who are not identified by either of these two standard methodologies.

It will be crucial to demonstrate that there is minimal enrollment bias and that any biases that occur are adjusted for. We know from prior experience in the EPIC adult study that elderly and sicker patients with ultimately worse outcomes (mechanical ventilation and death) were less likely to consent and enroll.<sup>8</sup> Basic epidemiological and outcome information will be obtained on all screened patients to help identify biases and to adjust the analysis if biases are identified (See [Appendix F](#) and [Appendix G](#)).

Figure: Atlanta Regional Map



2013 Total HD3 Population						
AGE GROUP	White-NH	Black-NH	Hispanic	Asian/P. Is	Unknown/Other	TOTAL
40-64 YEARS	594,162	491,681	103,356	84,195	3,197	1,276,591
65+ YEARS	228,600	109,517	13,183	18,305	744	370,349
Adults (≥40 Years)	822,762	601,198	116,539	102,500	3,941	1,646,940

**4.1.1. ROAPS SUB-STUDY 5 Study Population**

**For the Exploratory Objectives #2-3:** We will enroll healthy pregnant women and adults ≥50 years of age who are residents of HD3 as control populations. These adults will be recruited from outpatient clinics and/or from advertisements to this population. Modifications Beginning in Season 3: Beginning in Season 3, a control population of healthy outpatients will NOT be enrolled due to the COVID-19 pandemic.

**4.1.2. ROAPS RSV Sample Size**

As this study is a descriptive study, sample size is based on feasibility instead of power for hypothesis testing. We identified 1055 admissions/year and 936 admissions/year to EUH and EUHM, respectively (1991 combined admissions/year) in all adults using classic ARI codes that were used in adult EPIC incidence calculations (480-486, 487.0, and 510).<sup>8</sup> Three prior influenza seasons (2012 – 2015) have had 1300 – 1700 adults tested for influenza as SOC at EUH/EUHM combined, but we know that many adults with ARIs are not tested for influenza. To accomplish Sub-Study #3, we also will enroll adult patients of any age (≥18 years of age) with ‘chronic obstructive pulmonary disease (COPD) exacerbations’ and ‘congestive heart failure (CHF) exacerbations’ who are not included in these codes. Based upon an overall eligible number of 2,500, given an anticipated enrollment rate of 70% and approximately 75% of these being ≥50 years of age or admitted with COPD or CHF exacerbations, we anticipate

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enrolling around 1,300 HD3 adults/year with ARI-related admissions, COPD, or CHF which should result in 60-140 enrolled RSV-positive adults/year.

We know that there are 52,291 live births in HD3 in 2012. EUHM had 3,716 live births in 2014 (7.1% of the HD3 catchment). We roughly anticipate that 5 – 10% of these will have had an acute ARI in the 2 weeks prior to hospital admission (anticipate enrolling 186 – 372 pregnant women). Controls for the pregnant women will be enrolled that are similar to the cases with an anticipated ratio of 1:1 resulting in 186 – 372 enrolled pregnant women controls/season (see MOP for additional details about matching strategy).

We will ideally enroll about 10 healthy controls/week in the older adults for 30 weeks. This would result in about 300 enrolled healthy controls/season. ***Modifications Beginning in Season 3: Beginning in Season 3, a control population of healthy outpatients will NOT be enrolled due to the COVID-19 pandemic.***

At present, our best estimates of total enrollments would be between 1,500 and 1700 sick adults/year with an additional 485 – 670 healthy controls.

#### **4.2. ROAPS Inclusion / Exclusion Criteria**

Participant eligibility should be reviewed and documented by an appropriately qualified member of the investigator's study team before participants are included in the study.

##### **4.2.1. ROAPS RSV Inclusion / Exclusion Criteria for the Acutely Ill Cases**

- **Inclusion Criteria for the Primary, Secondary #1 – 3, and Exploratory Objectives #1, 4 – 7 (Acutely Ill Cases)**
  1.  $\geq 50$  years of age OR pregnant at admission or post-partum  $\leq 14$  days
  2. Hospitalized (or admitted to an observation unit for  $\geq 24$  hours, or remaining in the ED for  $\geq 24$  hours) at either EUH or EUHM,
  3. Enrollment between mid-September and mid-April (if ongoing laboratory-confirmed cases of influenza or RSV are continuing outside these boundaries then the enrollment window may be extended),
  4. Resident of HD3,
  5. Admitted with
    - a. CHF exacerbation **OR**
    - b. COPD exacerbation **OR**
    - c. ARI symptoms (nasal congestion, rhinorrhea, sore throat, hoarseness, new or increased-from-baseline cough, sputum production, dyspnea, wheezing) **OR**
    - d. Admitting diagnosis suggestive of ARI (Pneumonia, Upper respiratory infection, Bronchitis, Influenza, Cough, Asthma, Viral respiratory illness, Respiratory distress, **AND/OR** Respiratory failure.

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- **Exclusion Criteria for the Primary, Secondary #1 – 3, and Exploratory Objectives #1, 4 – 7 (Acutely Ill Cases)**
  - 1) Onset of symptoms >14 days prior to admission,
  - 2) Prior enrollment in this study within the last 28 days,
  - 3) Total duration of acute care hospitalization >3 days (also applies if transferred into EUH or EUHM from another acute care hospital. Transfer from nursing home or short term care facility are NOT considered acute care hospitals here).

**4.2.2. Sub-Study #5 Inclusion and Exclusion Criteria for the Secondary Objectives #4 (pregnant women)**

- **Inclusion criteria for Secondary Objectives #4 – 5 Sub-Study #5 (pregnant women)**
  - 1) ≥18 years of age and pregnant,
  - 2) Anticipated delivery or delivery of infant.
- **Exclusion criteria for Secondary Objectives #4 – 5 Sub-Study #5 (pregnant women)**
  - 1) Non-enrollment into the cord blood research study,

**4.2.2.1. Inclusion and Exclusion Criteria for the Healthy Controls (Exploratory Objective #2-3)**

***Season 3 Modifications: In Season 3, a control population of healthy outpatients will NOT be enrolled due to the COVID-19 pandemic.***

- **Inclusion Criteria for Exploratory Objectives #2-3 (Healthy Controls):**
  - 1) ≥50 years of age OR pregnant,
  - 2) At a routine outpatient appointment or a healthy volunteer without acute illness,
  - 3) Enrollment between mid-September and mid-April (if ongoing laboratory-confirmed cases of influenza or RSV are continuing outside these boundaries then the enrollment window may be extended),
  - 4) HD3 resident.
- **Exclusion Criteria for Exploratory Objectives #2-3 (Healthy Controls):**
  - 1) ARI symptoms, CHF symptoms, or COPD symptoms within the preceding 14 days or the 7 days after the enrollment visit,\*  
*\*Since the presence of these symptoms in the 7 days after the visit will not be known prospectively, subjects will be retrospectively excluded if they develop symptoms in the 7 days after enrollment.*
  - 2) Acute care hospitalization <28 days prior to enrollment,
  - 3) Prior enrollment in this study during the same season.

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**4.2.3. ROAPS RSV Inclusion and Exclusion Criteria for the 18-49 year olds with COPD or CHF Exacerbations (Exploratory Objective #11)**

- Inclusion Criteria for Exploratory Objective #11
  - 1) Age 18 – 49 years,
  - 2) Hospitalized (or admitted to an observation unit for  $\geq 24$  hours, or remaining in the ED for  $\geq 24$  hours) at either EUH or EUHM,
  - 3) Enrollment between mid-September and mid-April (if ongoing laboratory-confirmed cases of influenza or RSV are continuing outside these boundaries then the enrollment window may be extended),
  - 4) Resident of HD3,
  - 5) Admitted with
    - CHF exacerbation OR
    - COPD exacerbation
  
- **Exclusion Criteria for Exploratory Objective #11**
  - 1) Onset of symptoms  $>14$  days prior to admission,
  - 2) Prior enrollment in this study within the last 28 days,
  - 3) Total duration of acute care hospitalization  $>3$  days (also applies if transferred into EUH or EUHM from another acute care hospital. Transfer from nursing home or short term care facility are NOT considered acute care hospitals here).

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**4.3. COVID VE Inclusion / Exclusion Criteria**

- **Inclusion Criteria**

- 1) Age 18 years or older.
- 2) Admitted to hospital for ARI\* at a participating site.
- 3) Previously provided a standard of care specimen (NP or nasal swab) on this hospital admission or willing and able to provide specimen (NP or nasal swab) and comply with all data collection requested.
- 4) Capable of providing informed consent (or LAR capable and willing to give informed consent), which includes compliance with the requirements and restrictions listed in the protocols.

- **Exclusion criteria**

- 1) Any participant who received SARS-CoV-2-directed antiviral treatment within the past 30 days, or COVID-19 monoclonal antibody therapy or COVID-19 convalescent serum therapy within the past 90 days prior to collection of required study-related procedures for the detection of SARS-CoV-2 (i.e., NP or nasal swab).
- 2) Previous enrollment in this study within the past 30 days.\*\*
- 3) Any contraindication to have a NP or nasal swab (if specimen was not collected as SOC).

*\*ARI for study enrollment will be defined as:*

- a. *ARI symptoms (nasal congestion, rhinorrhea, sore throat, hoarseness, new or increased-from-baseline cough, sputum production, dyspnea, wheezing) **OR***
- b. *Admitting diagnosis suggestive of ARI (Pneumonia, Upper respiratory infection, Bronchitis, Influenza, Cough, Asthma, Viral respiratory illness, Respiratory distress, **AND/OR** Respiratory failure.*

*The ARI definition for analysis will include the WHO definition (e.g., acute symptoms of fever and cough) and variations since about 15% of patients admitted with COVID-19 do not have fever or cough.<sup>51</sup>*

*\*\* Thus, patients can contribute >1 ARI event to the study if a subsequent ARI event for the same patient occurred >30 days after the previous event.*

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**5. ROAPS RSV CASE FINDING, ENROLLMENT, AND PROCEDURES  
INCLUDING SPECIMEN COLLECTION**

Case ascertainment will occur at EUH or EUHM through emergency departments, outpatient clinics, hospital admitting departments, and labor and delivery at EUHM. At each site, dedicated study staff will review electronic emergency department records and hospital admission patient logs to screen for patients meeting the clinical case definition that would be appropriate to approach for potential enrollment. If a patient meets the enrollment criteria, informed consent will be obtained before enrollment into the study. ***Modifications beginning in Season 3: Beginning in Season 3, a control population of healthy outpatients will NOT be enrolled due to the COVID-19 pandemic.***

In order to optimize the quality of specimens, patients will be identified and enrolled in the study as early as is possible. Patients who are enrolled in the study also will be interviewed and their medical charts will be reviewed to complete the study CRF that focuses on clinical and epidemiologic information. This will include an assessment of frailty, and data collection to determine the Charleston Comorbidity Index, AHA CHF score (in those with underlying CHF), and the MMRC score (in those with underlying COPD). Ideally, patients will be interviewed at the time of enrollment but if the patient is too ill at that time, study staff will follow-up with the patient during their hospitalization to complete the study CRF. At the time of enrollment, a NP and OP swab will be obtained from all patients. Patients who refuse the collection of an NP swab will have the option to have a midturbinate obtained or if they also refuse the midturbinate swab then a nasal swab obtained. Subjects that refuse both a NP swab and a midturbinate swab may still be enrolled if they have had a SOC NP swab obtained. Residual standard of care specimens will be collected from the laboratory (e.g., blood, NP SOC swab, urine). Phlebotomy will be performed to obtain 10mL of blood. Subjects may still be enrolled if they refuse the study phlebotomy.

***Season 3 Modifications:*** Modifications will occur for Primary, Secondary, and Exploratory Objectives #1, 4 – 7 (see above) furthermore, as needed a waiver for all elements of informed consent will allow research staff to review medical records and test SOC specimens for those patients meeting eligibility criteria. When at all possible, the participant/LAR will be approached for written or oral consent. SOC specimens will have already been tested by SOC SARS-CoV-2 PCR testing. Additional specimens and salvage of SOC specimens will only be performed for those enrolled Substudies 1, 2, and 4.

**5.1. Convalescent Serology**

In order to collect convalescent sera on patients at the appropriate time, arrangements will be made for a follow-up visit 21 to 60 days (ideally 21 – 45 days) after the day of enrollment. Phlebotomy will be performed to obtain 10mL of blood. For patients who are still hospitalized, this visit could occur while hospitalized. For patients who will return, incentives and reminders will be used to help ensure patients return for the convalescent sera sample.

***Modifications Beginning in Season 3: Convalescent serology and salvage of SOC specimens will only be performed for those enrolled Substudies 1, 2, and 4.***

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**5.2. ROAPS RSV Laboratory Procedures**

NP and OP swabs, midturbinate, nasal, and cough specimens will have laboratory testing performed for a variety of viruses (SARS-CoV-2, adenovirus, coronaviruses, human metapneumovirus, influenza viruses, parainfluenza viruses 1-3, respiratory syncytial virus, and rhinovirus) and bacteria (*Chlamydia*, *Mycoplasma*). For patients who require thoracentesis or collection of lower respiratory tract samples (e.g., bronchoalveolar lavage (BAL), mini-BAL, or endotracheal aspiration) for clinical care, residual samples will be salvaged and may be tested for the same pathogens. Specimens will be tested  $\geq 21$  days after initial enrollment using BioFire FilmArray Respiratory Viral Panel (RVP). Additional testing as part of the future use exploratory endpoint may be performed on specimens collected as part of this study. Pathogens not specifically tested for during the study but that are discovered during routine clinical care (e.g., *Streptococcus pneumoniae*, *Staphylococcus aureus*) will be noted in the case report form and may be collected by the study team. Respiratory and serum specimens may be tested by both Emory and Pfizer laboratories. Specimen handling and labeling details will be included in a study-specific Manual of Operating Procedures (MOP). Please see the MOP for more specific specimen collection guidelines and laboratory algorithms.

PBMCs collected from Sub-study #1, 2, and 4 participants if subjects agree to this. These PBMCs will be collected in CPT tubes and will be processed according to existing SOPs. Cells may be used immediately or may be saved (moving to liquid nitrogen storage within 2 weeks of processing) for future cellular analyses.

**Modifications Beginning in Season 3:** Beginning in season 3 specimens that are known to be from SARS-CoV-2 negative patients will be processed at usual BSL2 enhanced levels. Beginning in season 3 specimens from patients positive for SARS-CoV-2 or unknown will be processed at a higher level of Biosafety according to existing preapproved Biosafety protocols in Evan Anderson's laboratory.

**5.3. ROAPS RSV Ethical Considerations and Sub-Studies #1 – 5**

A waiver of documentation/signature will be used to obtain basic information for the purpose of recruitment on potentially eligible adults. Following recruitment, informed consent will be obtained and a signature will be obtained. For patients who are unable to consent due to medical reasons, either a written or verbal consent will be obtained by the study staff from the legal representative of the patient. Cases or their proxies will be contacted and interviewed by study staff (see [Appendix I: Screening Log](#)). ).

***Season 3 Modifications: We are requesting a waiver of all elements of informed consent for the review of medical records and for the collection of residual SOC specimens from patients meeting eligibility criteria. When at all possible, a written or oral consent will be provided to the participant/LAR with or without signature. A small subset will be prospectively consented and enrolled into Substudies 1, 2, and/or 4. This is important as the COVID-19***

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*pandemic has impacted resources available (e.g., PPE) to approach all admitted patients making it impractical to conduct the study as had occurred in Seasons 1+2.*

Patient privacy and confidentiality will be maintained throughout this study. Project paperwork (e.g., signed consent, some CRF data) will remain in a locked, secure location, available only to a minimum number of local project staff, and will not be reused or disclosed to any other person or entity except as required by law, or for authorized oversight of the research project. Reports will only present data in aggregate form. Identifiers will be destroyed at the earliest opportunity, unless there is a public health or research justification for retaining the identifiers or they are required to by law. No personal identifiers will leave Emory.

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**6. COVID VE / SUB-STUDY #6 DATA ANALYSIS AND REPORTING OF RESULTS**

**6.1. COVID VE Analysis Populations**

**6.1.1. Per-Protocol Population**

The Per-Protocol Population will include all participants who:

1. Meet all inclusion and exclusion criteria,
2. Have a final diagnosis consistent with ARI\*,
3. Meet the definition of either case or test-negative control from the text of COVID VE Sub-Study #6 Methods (section [3.2](#));
4. Have a record of SARS-Cov-2 vaccination history available from government-issued COVID-19 vaccination cards, medical and billing records collected from relevant healthcare providers (e.g., primary care, public health department), health-insurance providers, pharmacies, and any local, state, or national immunization registries
5. Did not receive any other newly-licensed or investigational SARS-CoV-2 vaccine or COVID-19 prophylactic agent other than Pfizer's BNT162b2.

*\*For the purposes of the primary COVID VE analysis, the WHO definition of ARI will be used: an acute respiratory infection that occurred within the last 10 days and required hospitalization with history of fever or measured fever of  $\geq 38\text{ }^{\circ}\text{C}$  AND cough. Because many COVID-19 patients do not necessarily have fever (~15%) or cough (~15%), we will vary this definition in sensitivity analyses.<sup>51</sup>*

**6.2. Statistical Analysis**

**6.2.1. Estimated Crude (Unadjusted) VE**

Odds of having received BNT162b2 (fully, ever, and partially vaccinated) for cases and test-negative controls will be constructed and compared using ORs and 95% CIs. VE will be calculated as  $1 - \text{OR}$  multiplied by 100%. Corresponding 95% CIs will be calculated using the Wald method.

**6.2.2. Estimating Adjusted VE**

In addition to constructing crude OR and VE estimates, logistic regression modeling to assess BNT162b2 VE after adjustment for potentially confounding factors will be performed. Variables described in the text of COVID VE Sub-Study #6 Methods (section [3.2](#)); will be entered in the logistic regression model in backward stepwise manner. Only variable(s) that change the estimated OR for BNT162b2 by  $\geq 10\%$  (i.e., confounder)<sup>83</sup> will remain in the final VE model. A 2-sided alpha of .05 will be used for logistic regression modelling. Corresponding

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95% CIs will be calculated using the Wald method. In addition to results from the final model, univariate VE results will be presented for each independent variable that is assessed for potential confounding, as the results from a fully-adjusted model. When assessing the impact of underlying chronic medical conditions, the uCCI (Quan et al.)<sup>79</sup> will serve as the primary approach. Sensitivity analyses using the cCCI<sup>78</sup> and individual comorbidities in adjusted models will be performed.

### **6.2.3. Handling Missing Data**

Crude estimates of VE will be based on the observed, determinate SARS-CoV-2 test results and BNT162b2 vaccination status. For adjusted VE evaluations, patients with all available covariates will be included in the logistic regression model. If there is a substantial amount of missing data (>10%) for any variables deemed necessary to include in our final analyses, sensitivity analysis will be performed using multiple imputation for missing covariates (under the assumption of missing at random) to understand the impact of excluding patients with missing information in adjusted models.

### **6.2.4. Analysis Timings**

The COVID-19 pandemic continues to cause substantial morbidity and mortality with new data becoming rapidly available. As such, flexibility and a rapid response to the changing dynamics of disease is needed. We plan to conduct informal interim analyses to inform decision making which may be presented or published. Any interim analyses will be described in a SAP. Analyses for the primary, secondary, and exploratory outcomes will be analyzed when available following LPLV of the study.

### **6.2.5. Hypothesis Testing**

The overall study type-I error is 5%. For the primary objective, hypothesis testing will be used to assess if 2 doses of BNT162b2 are effective in preventing ARI requiring admission to hospital where SARS-CoV-2 is identified. The primary null hypothesis ( $H_0$ ) vs the alternative hypothesis ( $H_1$ ) is  $H_0: VE \leq 20\%$  vs  $H_1: VE > 20\%$ , where VE is  $1 - OR$  multiplied by 100%, and the OR is equal to the odds of being fully vaccinated (i.e., 2 doses with  $\geq 7$  days since the second dose since time of admission/enrollment) with BNT162b2 for ARI cases requiring hospitalization where SARS-CoV-2 is identified relative to the odds of being fully vaccinated (i.e., 2 doses) with BNT162b2 for ARI cases requiring hospitalization where SARS-CoV-2 is not identified. For the primary objective, BNT162b2 will be considered effective for preventing ARI requiring hospitalization where SARS-CoV-2 is identified if the lower bound of the 95% confidence interval for the estimated VE is  $>20\%$ .

No hypothesis testing will be applied to secondary or exploratory objectives.



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**6.2.6. Sample Size Determination**

This will be an event-driven study based on the number of cases identified. Study sample size is based on the primary endpoint (BNT162b2 VE against ARI requiring hospitalization where SARS-CoV-2 is identified). The required sample size will depend primarily on i) the proportion of all-cause ARI requiring hospitalization caused by SARS-CoV-2 (which determines the number of cases identified and the ratio of cases to controls in the primary analysis), ii) the average uptake of BNT162b2 in the study population over the duration of the study, and iii) the assumed VE of BNT162b2 against ARI requiring hospitalization where SARS-CoV-2 is identified. Sample size calculations were based on the following fixed assumptions:

- Two-sided, type-I error of 5%
- 90% power
- Log (OR) following approximated normal distribution
- Assumed true BNT162b2 (2 doses) VE varying from 70–90% to prevent ARI requiring hospitalization was modeled
- 5% of all-cause ARI episodes requiring hospitalization will test positive for SARS-CoV-2. A range of 5–30% was also modeled given the attack rate of COVID-19 may vary based on social distancing and shelter-in-place measures, underlying levels of population immunity, and other factors.

Average BNT162b2 uptake in controls over the study period was allowed to vary in sample size calculations (range: 10–90%) and will depend on potential future vaccination uptake scenarios and timing of the conduct of the study. Final study enrollment size will also depend on the proportion of enrolled patients excluded from the Per Protocol Population because i) vaccination records could not be obtained, ii) they received a newly-licensed or investigational SARS-CoV-2 vaccine other than BNT162b2, or iii) they received BNT162b2, but did not receive the full 2-dose schedule. [Appendix J](#) presents sample size calculations for various scenarios of BNT162b2 uptake and the proportion of all-cause ARI where SARS-CoV-2 is identified. Depending on the uptake of BNT162b2 and the proportion of ARI hospitalizations where SARS-CoV-2 is identified at the time of the study, approximately 3,000 to 12,000 persons  $\geq 18$  years of age will be enrolled. Emory expects to enroll approximately 3,000 patients/year at the 2 participating hospitals. A Statistics Center will monitor BNT162b2 uptake among controls and the proportion of all-cause ARI where SARS-CoV-2 is identified to inform decisions on the sample size required to reach an effectiveness endpoint.

Sample size requirements for the final analysis population to detect COVID-19 vaccine VE  $>20\%$  assuming true VE=70–90% with 90% power and type-I error of 5% (2-sided) under various BNT162b2 uptake scenarios (1 to 15% of ARI events requiring hospitalization due to SARS-CoV-2) – please see [Appendix J](#).

Methodology for summary and statistical analyses of the data collected in this study is outlined here and will be further detailed in statistical analysis plan (SAP). The SAP may modify what is outlined in the protocol where appropriate, however, any major modifications of the primary endpoint definitions or their analyses will also be reflected in a protocol amendment.

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**7. ROAPS AND SUB-STUDIES 1-5 DATA ANALYSIS AND REPORTING OF RESULTS**

As this is a descriptive study, data may be summarized on an ongoing basis. Analyses include estimations of incidence, frequency of pathogen-specific etiologies, and descriptive clinical epidemiology of hospitalized patients and their associated precision (e.g. 95% CIs). All of the analyses will be descriptive.

For incidence rates, hospital market share data (of EUH and EUHM), percentage of eligible subjects enrolled from the screening log, and the percentage of SOC RSV positive cases enrolled/percentage of RSV positive SOC RSV positive cases on the screening log will be used to determine the multiplier for calculating the total estimated cases of RSV in HD3. Together with the corresponding total population denominator in HD3 (i.e. total population of pregnancy, total population of adults  $\geq 50$  years of age) the estimated number of hospitalized RSV cases per 1,000 people will be determined in HD3. For the primary and secondary endpoints, a case of RSV will be considered any patient with a positive molecular test for RSV from any specimen type (either study PCR or molecular PCR) or RSV seroconversion (4 fold rise in titer between acute and convalescent sera).

All of the epidemiological, clinical, and outcome related data will be descriptively summarized by proportion and counts, or by means, median, and range as appropriate, along with 95% CI wherever is needed. We will estimate the association of RSV detection with symptoms using the odds of detecting RSV in case versus control specimens (Exploratory Objectives 2 and 3) and estimate attributable risk in  $\geq 50$  age group and pregnant women. Interim and final results will be presented at scientific meetings and published in peer-reviewed literature.

**Results of research laboratory testing conducted only for this study may be shared with patients only at/after the Day 21-60 visit as by that time results will not be clinically relevant (RSV, COVID-19 are a self-limited viral illness for which medications have not been proven to be useful). This will be done to help facilitate determination of whom should be followed in the Sub-study #2 that will continue until the subsequent RSV season. Enrollment into this primary study will not affect the treating physician's ability to obtain Standard of Care (SOC) respiratory viral testing.**

*Modifications Beginning in Season 3: No research laboratory testing will be shared with subjects.*

**7.1. Justification**

This study will not directly benefit those persons enrolled in this study. However, the overall results will potentially benefit the US population as a whole by increasing our understanding of RSV, influenza, and COVID-19 in pregnant women and older adults which could guide public health policy for RSV vaccine development and implementation.

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**7.2. Data Entry and Management**

Staff at each site will enter clinical, epidemiological, and laboratory data based on the study CRF into a REDCap database that correlates with a case report form. This database will meet all regulatory standards and requirements. It is anticipated that initially documentation will occur on paper CRFs (source). Once the REDCap database is fully built and tested, direct data entry may occur to REDCap (source). Timing of this transition will be clarified in the MOP. The REDCap database for the COVID VE Sub-Study 6 will be revised from the original ROAPS REDCap database to collect the required variables.

**8. COMPLIANCE WITH GOOD CLINICAL PRACTICE**

**8.1. Ethical Conduct of the Study**

This study will be conducted in accordance with the Declaration of Helsinki on Ethical Principles for Medical Research Involving Human Participants, adopted by the General Assembly of the World Medical Association (1996 & 2008). In addition, the study will be conducted in accordance with the protocol, the principles of the International Conference on Harmonization (ICH) guideline on Good Clinical Practice and applicable local regulatory requirements and laws.

**8.2. Institutional Review Board (IRB)/Independent Ethics Committee (IEC)**

The Investigator will have prospective approval of the study protocol, protocol amendments, informed consent forms, and other relevant documents (e.g., advertisements, if applicable, from the IRB/IEC). All correspondence with the IRB/IEC should be retained in the Investigator File. Copies of IRB/IEC approvals should be forwarded to Pfizer. The only circumstance in which an amendment may be initiated prior to IRB/IEC approval is where the change is necessary to eliminate apparent immediate hazards to the participants. In that event, the Investigator must notify the IRB/IEC and Pfizer in writing within 5 working days after the implementation.

**8.3. Participant Information and Consent**

All parties will ensure protection of participant personal data and will not include participant names or initials on any Sponsor forms, reports, publications, or in any other disclosures. Participant names, address, birth date and other identifiable data will be replaced by a numerical code consisting of a numbering system provided by Pfizer to de-identify the trial participant. In case of data transfer, Pfizer will maintain high standards of confidentiality and protection of participant personal data.

The Investigator must ensure that each study participant, or his or her legal representative, is fully informed about the nature and objectives of the study and possible risks associated with participation. For eligible participants included in vulnerable populations (e.g., illiterate, elderly, cognitive or physical impairments) that may require a third party to complete the

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informed consent process, sites must defer to their institution's requirement for obtaining informed consent. The institution's policy must be provided to the Sponsor for approval prior to first patient first visit.

The Investigator, or a person designated by the Investigator, will obtain informed consent from each participant or the participant's legal representative before any study specific activity is performed. The informed consent document(s) used during the informed consent process must be reviewed by the Sponsor, approved by the IRB/IEC before use, and available for inspection. The Investigator will retain the original of each participant's signed consent form.

#### **8.4. Participant Recruitment**

Due to the epidemiological nature of the study, participant recruitment will include, at the minimum, a daily review of admissions databases for potential participants, as well as healthcare-provider-to-healthcare-provider communication regarding the study.

Participants may be identified from multiple sources, for example: inpatient departments, general medical wards, pulmonary or respiratory disease wards, infectious disease wards, or intensive care units.

To maximize enrollment, the site should establish a ARI surveillance system to capture all eligible persons with suspected ARI who meet the selection criteria and are willing to give consent. The surveillance system must account for participants presenting to the healthcare facility 24 hours a day, 7 days a week for 365 days per year.

### **9. SAFETY**

#### **Adverse Events and Serious Adverse Events**

In this study, the "product under study" refers to the Pfizer-BioNTech COVID-19 vaccine and is referred to as such when appropriate in the text below.

The investigator (or designee) is responsible for detecting, documenting, and recording events that meet the definition of an AE or SAE and remains responsible to pursue and obtain adequate information both to determine the outcome and to assess whether the event meets the criteria for classification as an SAE or caused the participant to discontinue the study.

The awareness date is the date that the sponsor/investigator becomes aware of the presence of all 4 minimum reporting criteria (i.e. an identifiable subject, an identifiable reporter, an event meeting SAE or special exposure definition, and a suspect Pfizer product)

The time period for actively eliciting and collecting AEs and SAEs (active collection period) will begin when the first protocol-required procedure (swab sample) is performed at Visit 1 and will conclude 15 minutes after the procedure is performed.

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If the participant withdraws from the study and also withdraws consent for the collection of future information, the active collection period ends when consent is withdrawn.

During the active collection period, each participant will be proactively questioned about the occurrence of AEs in a nonleading manner. AEs identified during the active collection period may be based on symptoms or other complaints reported to the Investigator (or designee) by the participant or may be based on clinical findings made by the Investigator (or designee).

SAEs that are explicitly related to the product under study (BNT162b2) must be reported to the Pfizer Drug Safety Unit (DSU) within 24 hours of awareness throughout the entire study period, if the investigator should become aware. In addition, the investigator may be requested by Pfizer Safety to obtain specific follow-up information in an expedited fashion.

The sponsor/investigator may incidentally become aware of reportable events, as described above, through **unsolicited** patient report (e.g., the study participant contacts the investigator or study staff **outside** of the active collection period or the Investigator becomes aware of events explicitly related to the Pfizer product under study, BNT162b2). Special exposure scenarios, including Exposure During Breastfeeding [EDB], Occupational/Environmental exposure, medication errors and overdose related to Pfizer product under study (BNT162b2), will be reported to the DSU within 24 hours of awareness. Definitions and reporting instructions are included in the Safety Reporting Reference Manual.

Exposure during pregnancy (EDP) to the product under study (BNT162b2) is not reportable as an individual safety report since these will be summarized as endpoints of the study.

Lack of Effectiveness (LOE) for BNT162b2 is a study endpoint. It will not be reported as individual SAE reports. Effectiveness will be summarized in the CSR. Potential COVID-19/MIS-C/Acute Respiratory Illnesses and their sequelae that are consistent with the clinical endpoint definition should not be recorded as AEs.

The definitions of an AE, SAE, Research Related Injury (RRI), LOE and special exposure scenarios can be found in the Safety Reporting Reference Manual. The investigator is required to assess whether any AE occurring during the active collection period may be related to participation in the study. All AEs that occur during the active collection period (i.e., serious and non-serious, including those attributed to a protocol-required procedure identified as RRI) are collected in the clinical study database.

Should a participant, in the investigator's opinion, suffer a medically important research related injury caused by participation in the study, the Pfizer clinical study team must be notified immediately by telephone or email.

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**11. APPENDICES**

**11.1. Appendix A: Schedule of Events – ROAPS Acutely Ill Cases**

Study Visit	Enrollment	All: Daily	Optional Substudy 1: Every other day while hospitalized	ARI Illness before Convalescent Visit*	Convalescent	Optional Substudy 2: Telephone call q2 weeks	Optional Substudy 2: ARI illness	Optional Substudy 2: Final Visit <sup>8</sup>
<b>Study Day Windows<sup>1</sup></b>	1	Daily	Every other day +/- 1 day		22 - 60		Day 23 – 61 <sup>5</sup> through to final visit	Day <365 (just prior to next RSV season)
<b>STUDY PROCEDURES</b>								
Obtain Informed Consent	X							
Review Eligibility Criteria	X							
Patient Interview <sup>9</sup>	X		X <sup>1</sup>	X	X	X	X	X
Review of Medical Record	X	X		X	X <sup>3</sup>		X <sup>3</sup>	X <sup>3</sup>
Record Concomitant Medications	X	X		X	X <sup>3</sup>		X <sup>3</sup>	X <sup>3</sup>
<b>SPECIMEN COLLECTION</b>								
Obtain nasopharyngeal (NP) swab <sup>6,9</sup>	X		X	X	X <sup>2</sup>		X	X <sup>2</sup>
Obtain oropharyngeal (OP) swab <sup>9</sup>	X		X	X	X <sup>2</sup>		X	X <sup>2</sup>
Obtain cough specimen (if possible) <sup>9</sup>	X			X	X <sup>2</sup>		X	X <sup>2</sup>
Obtain acute serum <sup>7,9</sup>	X						X	
Obtain follow-up serum <sup>9</sup>				X	X			X
Collect residual SOC blood <sup>9</sup>	X	{X}		{X}	{X}		{X}	{X}
Collect residual NP or OP SOC swabs	X	{X}						
Collect residual SOC urine <sup>9</sup>	X	{X}	X	{X}	{X}		{X}	{X}
Collect other residual SOC specimens <sup>4,9</sup>	X	{X}	X	{X}	{X}		{X}	{X}
PBMC collection: Optional Sub-Study #1, if agreeable to this	48 mL		Day 7 symptoms: 32 mL (if different than enrollment)		40 mL			48 mL

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SOC: Standard of care; NP: Nasopharyngeal; OP: Oropharyngeal; { } If available; \*Visit will occur only if patient develops new ARI illness prior to the Convalescent Visit (D 22 – 60)

<sup>1</sup>Record resolution date of signs and symptoms from patient interview

<sup>2</sup>A NP and OP swab/cough sample will be obtained at the follow-up visit only if the patient develops active ARI symptoms prior to the Convalescent Visit.

<sup>3</sup>The follow-up visit could occur while still hospitalized. Final outcomes and medications (e.g., duration of hospitalization) will be collected from the medical record until hospital discharge even if this occurs after the follow-up visit.

<sup>4</sup>Including SOC testing from other specimen types (e.g., BAL, Endotracheal tube aspirate, thoracentesis).

<sup>5</sup>The Optional Substudy 2 visit for ARI illness may occur repeatedly before the subsequent RSV season (the Final Visit at Day<365).

<sup>6</sup> Patients who refuse the collection of an NP swab will have the option to have a midturbinate or nasal swab obtained.

<sup>7</sup> Patients who refuse the collection of acute serum, will have additional residual SOC specimen collected.

<sup>8</sup> The Optional Substudy 2 Final Visit may occur at the same time as the Option Substudy 4 Enrollment Visit. If this occurs, the serum and the PBMCs will only be collected once. If these occur on different dates, then serum and PBMCs will be collected at both visits.

<sup>9</sup> **Modifications Beginning in Season 3:** *Beginning the summer of 2020, all admitted patients to EUH and EUHM are receiving standard of care (SOC) testing for SARS-CoV-2 upon hospital admission. Reasons for this include identification of SARS-CoV-2 infection prior to hospital admission (community-onset) that is presenting presymptomatically, asymptotically, or atypically. Beginning in Season 3, we will salvage SOC specimens sent from admitted patients meeting enrollment criteria (we will not obtain additional NP/OP swabs or cough specimens beyond those collected as SOC except as detailed below for those enrolled in Substudies 1, 2 and 4). We are requesting a waiver of informed consent for collection of SOC specimens and review of medical records from patients meeting eligibility criteria. A small subset will be prospectively consented and enrolled into Substudies 1, 2, and/or 4. This is important as the COVID-19 pandemic has impacted resources available (e.g., PPE) to approach all admitted patients making it impractical to conduct the study as had occurred in Seasons 1+2. These salvaged SOC specimens will then be tested with study-specific BioFire RVP testing retrospectively 3 weeks or more after hospital discharge. These results will not be available to the patient or patient care teams (the result will no longer be clinically relevant from these specimens). Patient interviews will not be conducted except on those subjects enrolled in Substudies 1, 2, or 4. Patients will not have follow-up or direct contact with the research staff unless enrolled in Substudies 1, 2, or 4.*

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**11.2. Appendix B: Schedule of Events – Sub-Study #4**

Study Visit	Substudy 2 Final Visit/ Enrollment Substudy 4*	Telephone call q2 weeks	ARI illness	Year #2 Visit	Year #3 Final Visit
Study Day Windows <sup>1</sup>	<365 from initial enrollment			<730 from initial enrollment	<1095 from initial enrollment
<b>STUDY PROCEDURES</b>					
Obtain Informed Consent	X				
Review Eligibility Criteria	X				
Patient Interview	X	X	X	X	X
Review of Medical Record	X		X <sup>3</sup>	X <sup>3</sup>	X <sup>3</sup>
Record Concomitant Medications	X		X <sup>3</sup>	X <sup>3</sup>	X <sup>3</sup>
<b>SPECIMEN COLLECTION</b>					
Obtain nasopharyngeal (NP) swab <sup>4</sup>	X <sup>2</sup>		X	X <sup>2</sup>	X <sup>2</sup>
Obtain oropharyngeal (OP) swab	X <sup>2</sup>		X	X <sup>2</sup>	X <sup>2</sup>
Obtain cough specimen (if possible)	X <sup>2</sup>		X	X <sup>2</sup>	X <sup>2</sup>
Obtain serum	X		X	X	X
Collect residual SOC blood	X		{X}	/{X}	{X}
Collect residual SOC urine	X		{X}	{X}	{X}
Collect other residual SOC specimens	X		{X}	{X}	{X}
PBMC collection: if agreeable to this	48 mL			48 mL	48 mL

<sup>1</sup>Record resolution date of signs and symptoms from patient interview

<sup>2</sup>A NP and OP swab/cough sample will be obtained only if the patient develops active ARI symptoms prior to the Visit.

<sup>3</sup>Final outcomes and medications will also be collected from the medical record.

<sup>4</sup>Patients who refuse the collection of an NP swab will have the option to have a midturbinate (preferred) or nasal swab obtained.

\*The Optional Substudy 2 Final Visit may occur at the same time as the Option Substudy 4 Enrollment Visit. If this occurs, the serum and the PBMCs will only be collected once. If these occur on different dates, then serum and PBMCs will be collected at both visits.

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**11.3. Appendix C: Schedule of Events – Healthy Controls\***

<b>Study Visit</b>	<b>Enrollment</b>	<b>Final</b>
<b>Study Day Windows<sup>1</sup></b>	1	22 - 60
<b>STUDY PROCEDURES</b>		
Obtain Informed Consent	X	
Review Eligibility Criteria	X	
Patient Interview	X	X
Review of Medical Record	X	X <sup>1</sup>
Record Concomitant Medications	X	X <sup>1</sup>
<b>SPECIMEN COLLECTION</b>		
Obtain nasopharyngeal (NP) swab	X	X <sup>2</sup>
Obtain oropharyngeal (OP) swab	X	X <sup>2</sup>
Obtain cough specimen (if possible)	X	X <sup>2</sup>
Obtain acute serum	X	
Obtain follow-up serum		X

SOC: Standard of care; NP: Nasopharyngeal; OP: Oropharyngeal; { } If available

<sup>1</sup>To determine whether an ARI may have occurred between enrollment and convalescent visits.

<sup>2</sup>A NP and OP swab will be obtained at the follow-up visit only if the patient develops interim ARI symptoms.

\* *Note that beginning in Season 3 healthy controls will not be enrolled.*

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**11.4. Appendix D: Schedule of Events – Sub-Study #5**

<b>Study Visit</b>	<b>1</b>
<b>Study Day Windows</b>	Enrollment
<b>STUDY PROCEDURES</b>	
Obtain Informed Consent	X
Review Eligibility Criteria	X
Patient Interview	X
Review of Medical Record	X
Record Concomitant Medications	X
<b>SPECIMEN COLLECTION<sup>1</sup></b>	
Collect residual SOC blood	X
Collect cord blood from time of delivery	X
Collect other residual SOC specimens (mother and infant)	X

<sup>1</sup>Cord blood, SOC blood or other SOC specimens may be collected from time of admission to the hospital and throughout the hospital stay.

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**11.5. Appendix E: Schedule of Events – COVID VE Sub-Study #6**

<b>Visit Identifier</b>	<b>V1 Screening Enrollment</b>	<b>V2 Vital Status Assessment / Data Collection Only</b>
<b>Visit Window</b>	<b>Day 1-3 post admission</b>	<b>Up to 30 days post admission</b>
Informed consent	X	
Patient interview for demographic characteristics, risk factors, and life-event data collection <sup>^</sup>	X	
Specimen collection (NP or nasal swab)*	X	
SARS-CoV-2 NAAT testing*	X	
Data from SOC NAAT testing for SARS-CoV-2	X	
Data from SOC sample culture –(blood, urine, or respiratory culture (if applicable))	X	
Vital status assessment <sup>a</sup>		X
Collection of data describing all potential sources of vaccination history to be investigated <sup>b</sup>	X	X
Medical Record review and collection of medical history / hospitalization data <sup>c</sup>	X	
Adverse event reporting <sup>d</sup>	X	X

<sup>^</sup> Patient interview may occur on the day of enrollment or shortly thereafter depending upon patient/LAR capacity to undergo interview at that time.

\* If not performed as standard of care (SOC)

<sup>a</sup> Vital status will be assessed using medical record data and does not involve patient participation.

<sup>b</sup> This process may continue beyond 30 days to identify all potential sources of vaccine history information. Alternatively, if all data are available, verified and recorded at V1 then this will not be requested at later visits (V2).

<sup>c</sup> Medical record review will include, but not be limited to, all medical records related to the current hospitalization to assess underlying patient data, comorbidities, and outcomes of the hospitalization (e.g., duration of hospitalization, ICU admission, mechanical ventilation, survival, disposition).

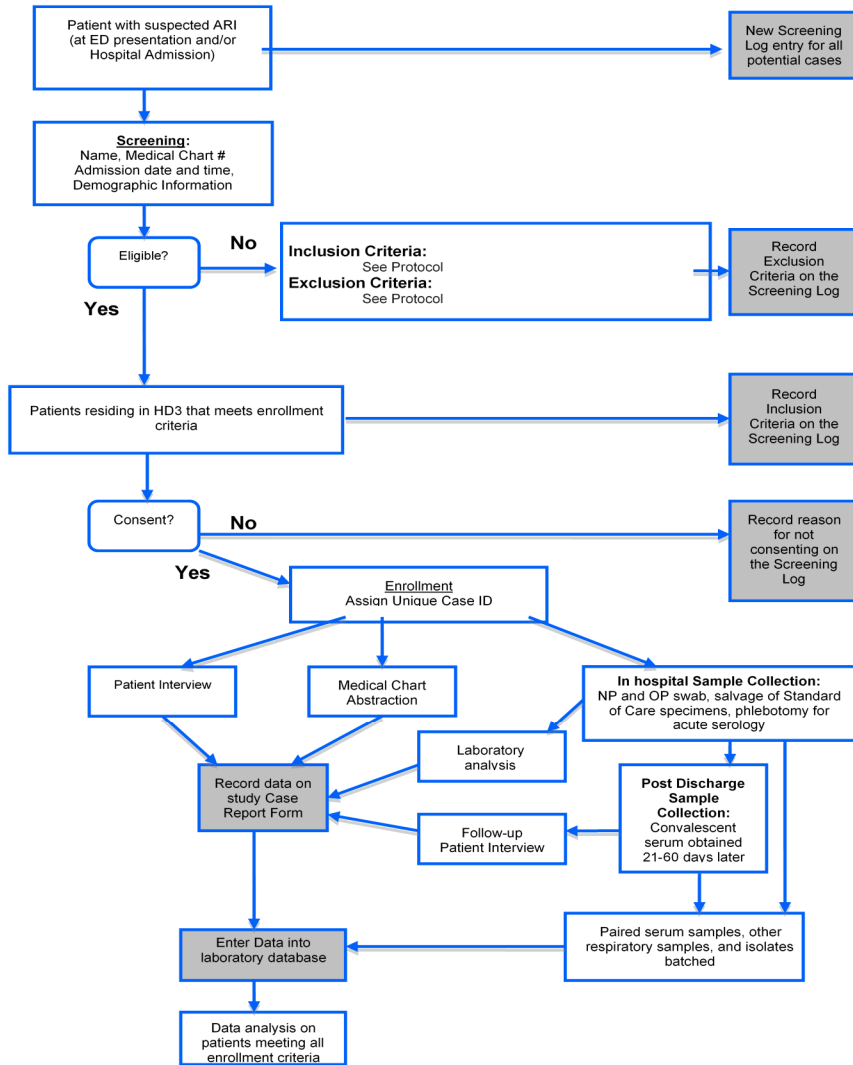
<sup>d</sup> Adverse event reporting is required as specified in Section 9.

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**11.6. Appendix F: Study Patient Flow – Acutely Ill Cases ROAPS RSV and COVID VE\***

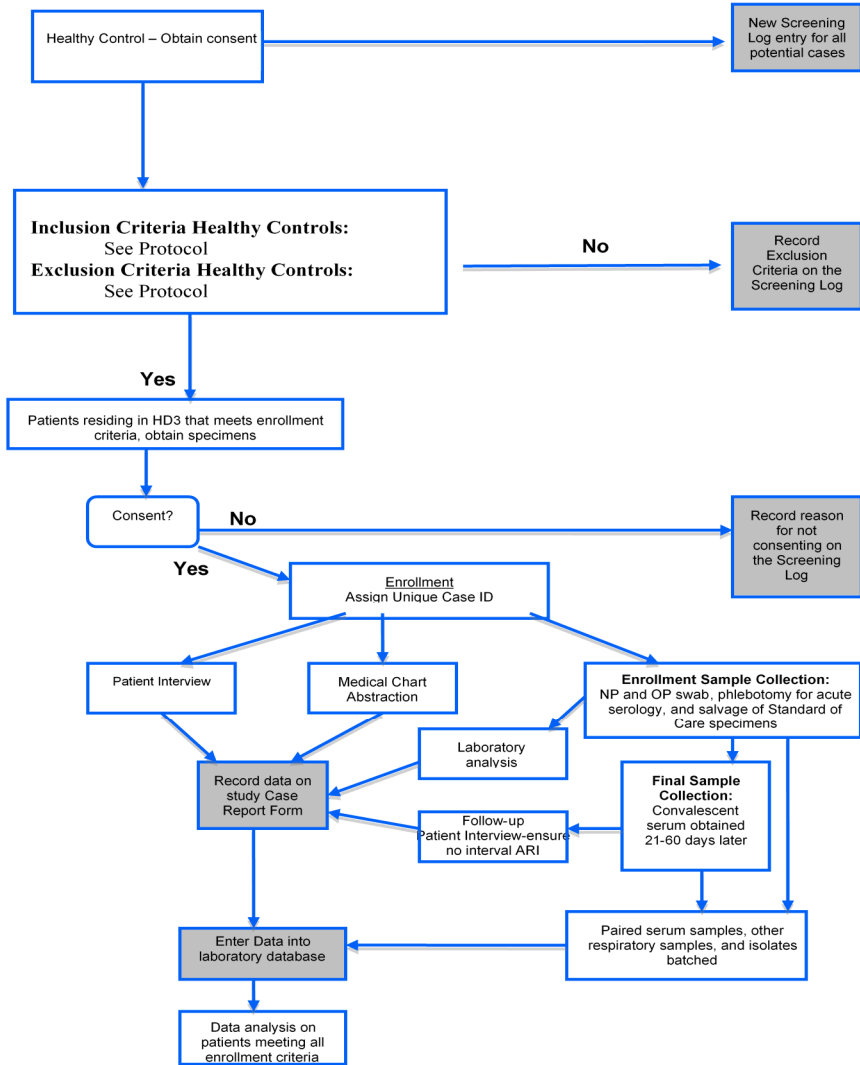


*\* Note changes throughout the protocol for alterations in Season 3.*

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**11.7. Appendix G: Patient Flow – Healthy Controls\***



*\* Note that healthy controls will not be enrolled in Season 3.*

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**11.8. Appendix H: Proposed Definitions for Chest Radiography Confirmed Pneumonia**

To accomplish **Exploratory Aim #5**, we will use the following definitions of pneumonia in interpreting SOC chest radiographs. To be diagnosed with pneumonia, subjects must meet the clinical case definition and have an abnormal chest radiograph (within 72 hours of admission), defined as: presence of consolidation, other infiltrate, and/or pleural effusion. Based on WHO criteria, these are defined as:

Consolidation: A dense or fluffy opacity that occupies a portion or whole of a lobe or the entire lung that may or may not contain air bronchograms. Atelectasis of an entire lobe that produces a dense opacity and a positive silhouette sign with the mediastinal border is considered consolidation.

Other Infiltrate: Linear and patchy densities (interstitial infiltrate) in a lacy pattern involving both lungs, featuring peribronchial thickening and multiple areas of atelectasis which may be difficult to distinguish from consolidation.

Pleural effusion: Presence of fluid in the lateral pleural space between the lungs and chest wall; in most cases, this will be seen at the costophrenic angle or as a layer of fluid adjacent to the lateral chest wall; this does not include fluid seen in the horizontal or oblique fissures.

**Additional definitions for descriptive terminology:**

- Air Bronchogram – The air containing bronchus which becomes visible when the surrounding lung parenchyma is opacified due to air space consolidation or volume loss. Generally, the bronchial tree is in contiguity with water density pulmonary parenchymal structures, generally believed to be a reflection of air space disease (alveolar, acinar).
- Bronchial Wall Thickening – Peribronchial thickening: peribronchial inflammatory edema or peribronchial inflammation which causes peribronchial “cuffing” that is usually a manifestation of bronchitis, asthma, reactive airway disease, or viral lower respiratory tract infection, and is a non-specific finding.
- Bronchiolitis, uncomplicated – moderate to marked hyperaeration (generalized air trapping), bronchial wall thickening, with or without minimal parahilar linear opacities, in the appropriate clinical setting. This condition does not meet the criteria for enrollment.
- Bronchiolitis, complicated – moderate to marked hyperaeration, bronchial wall thickening, perihilar linear opacities, and patchy areas of peribronchial parenchymal opacity or atelectasis of an entire segment or lobe. Some observers may refer to these findings as viral pneumonia or viral bronchopneumonia. This condition does meet criteria for “Other Infiltrate”.
- Bronchopneumonia – A descriptive term which refers to shaggy bronchial inflammatory changes which involve the adjacent air spaces; a subjective of term which means different things to different observers, and should be avoided if possible.
- Alveolar (air space) Disease – a disorder in which the air spaces of the lung become filled with water density material such as

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edema, pus or blood, all of which produce identical radiographic appearances. Alveolar disease is generally ill-defined and fluffy, tends to coalesce and may involve large areas of lobe or lung.

- Interstitial Disease – an increase in diffuse linear markings in the lung parenchyma which does not cause air bronchograms, but may be reflected in a *reticulonodular pattern, a “ground-glass” or cloudy appearance, a honeycomb lung, and may be either nodular or linear in appearance. The findings of interstitial disease when seen on high resolution computed tomography include bronchial wall thickening, thickened interlobular septa, ground-glass opacity, nodules and reticular densities of varying sizes.*
- Pulmonary Edema – Leakage of fluid from the pulmonary microvasculature into the interstitium, from any cause, results in interstitial pulmonary edema. Edema is a typical interstitial pattern and may be manifested by Kerley A and B lines which are due to fluid in the interlobular septa. Alveolar edema is usually preceded by interstitial edema, and fills acinae and air spaces, producing more ill-defined homogenous shadows of water density.
- Atelectasis – collapse of lung parenchyma either due to airway obstruction or pleural fluid or mass effect. Atelectasis reflects volume loss of varying amounts of lung parenchyma and may be linear, subsegmental, segmental, lobar, or entire lung. Significant lung collapse is generally associated with nearby lung compensatory over inflation.

### 11.9. Appendix I: Screening Log

Example here, actual screening log is likely to be in REDCap

# Determining RSV Burden and Outcomes in Pregnant Women and Older Adults Requiring Hospitalization

## Short Title: RSV in Older Adults and Pregnant Women Study (ROAPS)

RSV in Older Adults and Pregnant women Study (ROAPS); Screening Log														
Insurance		Race		Inclusion Criteria				Consent Codes:			RSV and Influenza SOC Testing			
1-Med/CAFE	1-White	1. ≥50 years of age OR pregnant				1-Yes			1 - Positive molecular					
2-Med/CAID	2-Asian	2. Hospitalized (or admitted to an observation unit for ≥24 hours, or remaining in the ED for ≥24 hours) at either EUH or EUHM.				2-Refused			2 - Negative molecular					
3-Private	3-Black/African American	3. Enrollment between mid-September and mid-April (if ongoing laboratory-confirmed cases of influenza or RSV are continuing outside these boundaries then the enrollment window may be extended).				3-Discharged			3 - No testing performed					
4-Multiple	4-Native Hawaiian or Pacific Is	4. Resident of HD3.				4-MD Refused			4 - Other RSV or influenza test performed (write in)					
5-None	5-American Indian, Alaskan nat	5. Admitted with				5-Missed								
6-Other	99-Unknown/ refused	a. CHF exacerbation OR				6-No interpreter								
		b. COPD exacerbation OR				7-Enrolled in different study								
99-Unknown/ refused		c. ARI symptoms (nasal congestion, rhinorrhea, sore throat, hoarseness, new or increased from-baseline cough, sputum production, dyspnea, wheezing) OR				8-No LAR								
		d. Admitting diagnosis suggestive of ARI (Pneumonia, Upper respiratory infection, Bronchitis, Influenza, Cough, Asthma, Viral respiratory illness, Respiratory distress, AND/OR Respiratory failure.												
		Exploratory Objective #11 (Substudy #3):												
		Denote as #6: 18-49 year olds that meet all of the above Inclusion and Exclusion Criteria (Except for Inclusion Criteria #1) that are admitted with COPD or CHF exacerbations (Inclusion Criteria #5a OR 5b)												
		Exclusion Criteria:												
Sex	Ethnicity	1) Onset of symptoms >14 days prior to admission							Death					
1-Male	1-Hispanic	2) Prior enrollment in this study within the last 28 days							1-Yes					
		3) Total duration of acute care hospitalization >3 days (also applies if transferred into EUH or EUHM from another acute care hospital. Transfer from nursing home or short term care facility are NOT considered acute care hospitals here).				ICU Admission and Mechanical Ventilation			2-No					
2-Female	2-non-Hispanic					1 - Yes			3-Hospice					
99-Unknown/ refused	99-Unknown/ refused					2 - No								
Name	Screen Date	Admit Date	Birth Date	Sex/ Ethnicity	Chief Complaint	Inclusion	Eligible	Consent Code	Case ID	RSV SOC Testing	Discharge Date	ICU Admission	Mechanical Ventilation	Death
MRR#	Screening Initials	Admit Time	Insurance	Race	Admission Diagnosis	Exclusion	Enrolled	Zip		Influenza SOC Testing	Discharge Time	ICU Date(s)	Mechanical Vent. Dates	
				1299/1299		1 2 3 4 5 6	N Y	12345678		1 2 3		1 2	1 2	1 2 3
				1299/1299		1 2 3 4 5 6 99	N Y			1 2 3				
				1299/1299		1 2 3 4 5 6	N Y	12345678		1 2 3		1 2	1 2	1 2 3
				1299/1299		1 2 3 4 5 6 99	N Y			1 2 3				
				1299/1299		1 2 3 4 5 6	N Y	12345678		1 2 3		1 2	1 2	1 2 3
				1299/1299		1 2 3 4 5 6 99	N Y			1 2 3				
				1299/1299		1 2 3 4 5 6	N Y	12345678		1 2 3		1 2	1 2	1 2 3
				1299/1299		1 2 3 4 5 6 99	N Y			1 2 3				
				1299/1299		1 2 3 4 5 6	N Y	12345678		1 2 3		1 2	1 2	1 2 3
				1299/1299		1 2 3 4 5 6 99	N Y			1 2 3				
				1299/1299		1 2 3 4 5 6	N Y	12345678		1 2 3		1 2	1 2	1 2 3
				1299/1299		1 2 3 4 5 6 99	N Y			1 2 3				
				1299/1299		1 2 3 4 5 6	N Y	12345678		1 2 3		1 2	1 2	1 2 3
				1299/1299		1 2 3 4 5 6 99	N Y			1 2 3				
				1299/1299		1 2 3 4 5 6	N Y	12345678		1 2 3		1 2	1 2	1 2 3
				1299/1299		1 2 3 4 5 6 99	N Y			1 2 3				
				1299/1299		1 2 3 4 5 6	N Y	12345678		1 2 3		1 2	1 2	1 2 3
				1299/1299		1 2 3 4 5 6 99	N Y			1 2 3				
				1299/1299		1 2 3 4 5 6	N Y	12345678		1 2 3		1 2	1 2	1 2 3
				1299/1299		1 2 3 4 5 6 99	N Y			1 2 3				
				1299/1299		1 2 3 4 5 6	N Y	12345678		1 2 3		1 2	1 2	1 2 3
				1299/1299		1 2 3 4 5 6 99	N Y			1 2 3				
				1299/1299		1 2 3 4 5 6	N Y	12345678		1 2 3		1 2	1 2	1 2 3
				1299/1299		1 2 3 4 5 6 99	N Y			1 2 3				
				1299/1299		1 2 3 4 5 6	N Y	12345678		1 2 3		1 2	1 2	1 2 3
				1299/1299		1 2 3 4 5 6 99	N Y			1 2 3				

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**11.10. Appendix J: COVID VE Sample Size**

Requirements for the final analysis population to detect BNT162b2 VE >20% assuming true VE=70–90% with 90% power and type-I error of 5% (2-sided) under various BNT162b2 uptake scenarios (5 to 30% of ARI hospitalizations due to SARS-CoV-2)

Assume true VE=70%																
BNT162 Uptake	5% of ARI is SARS-CoV-2 positive				15% of ARI is SARS-CoV-2 positive				25% of ARI is SARS-CoV-2 positive				30% of ARI is SARS-CoV-2 positive			
	Controls	Cases	Tot Eval	Tot Enroll*	Controls	Cases	Tot Eval	Tot Enroll*	Controls	Cases	Tot Eval	Tot Enroll*	Controls	Cases	Tot Eval	Tot Enroll*
10	6769	356	7125	11875	2104	371	2475	4125	1171	390	1561	2602	938	402	1340	2233
20	3266	172	3438	5730	1022	180	1202	2003	573	191	764	1273	461	198	659	1098
30	2108	111	2219	3698	665	117	782	1303	377	126	503	838	304	130	434	723
40	1540	81	1621	2702	491	87	578	963	281	94	375	625	229	98	327	545
50	1213	64	1277	2128	392	69	461	768	228	76	304	507	187	80	267	445
60	1015	53	1068	1780	335	59	394	657	199	66	265	442	165	71	236	393
70	909	48	957	1595	308	54	362	603	187	62	249	415	157	67	224	373
80	905	48	953	1588	318	56	374	623	200	67	267	445	171	73	244	407
90	1174	62	1236	2060	435	77	512	853	287	96	383	638	251	108	359	598
Assume true VE=80%																
BNT162 Uptake	5% of ARI is SARS-CoV-2 positive				15% of ARI is SARS-CoV-2 positive				25% of ARI is SARS-CoV-2 positive				30% of ARI is SARS-CoV-2 positive			
	Controls	Cases	Tot Eval	Tot Enroll*	Controls	Cases	Tot Eval	Tot Enroll*	Controls	Cases	Tot Eval	Tot Enroll*	Controls	Cases	Tot Eval	Tot Enroll*
10	4945	260	5205	8675	1518	268	1786	2977	832	277	1109	1848	661	283	944	1573
20	2325	122	2447	4078	717	127	844	1407	396	132	528	880	315	135	450	750
30	1455	77	1532	2553	452	80	532	887	252	84	336	560	201	86	287	478
40	1024	54	1078	1797	321	57	378	630	181	60	241	402	146	63	209	348
50	770	41	811	1352	245	43	288	480	140	47	187	312	114	49	163	272
60	608	32	640	1067	197	35	232	387	115	38	153	255	95	41	136	227
70	505	27	532	887	169	30	199	332	102	34	136	227	85	36	121	202
80	455	24	479	798	160	28	188	313	101	34	135	225	86	37	123	205

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90	513	27	540	900	196	35	231	385	132	44	176	293	116	50	166	277
<b>Assume true VE=90%</b>																
	5% of ARI is SARS-CoV-2 positive				15% of ARI is SARS-CoV-2 positive				25% of ARI is SARS-CoV-2 positive				30% of ARI is SARS-CoV-2 positive			
BNT162 Uptake	Controls	Cases	Tot Eval	Tot Enroll*	Controls	Cases	Tot Eval	Tot Enroll*	Controls	Cases	Tot Eval	Tot Enroll*	Controls	Cases	Tot Eval	Tot Enroll*
10	4275	225	4500	7500	1294	228	1522	2537	698	233	931	1552	549	235	784	1307
20	1955	103	2058	3430	594	105	699	1165	322	107	429	715	253	108	361	602
30	1183	62	1245	2075	361	64	425	708	197	66	263	438	155	66	221	368
40	798	42	840	1400	245	43	288	480	135	45	180	300	107	46	153	255
50	568	30	598	997	176	31	207	345	98	33	131	218	78	33	111	185
60	417	22	439	732	132	23	155	258	74	25	99	165	60	26	86	143
70	313	16	329	548	101	18	119	198	59	20	79	132	49	21	70	117
80	241	13	254	423	83	15	98	163	51	17	68	113	43	18	61	102
90	212	11	223	372	82	14	96	160	56	19	75	125	50	21	71	118

\*Assumes 40% of enrolled participants will be unevaluable (i.e., excluded from the Per Protocol Population because i) vaccination records could not be obtained, ii) they received a newly-licensed or investigational SARS-CoV-2 vaccine other than COVID-19 vaccine, or iii) they received COVID-19 vaccine, but did not receive the full 2-dose schedule.

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