# Long COVID in the Active Component US Military: Risk Factors, Effect of Vaccination, and Predicting Incident Long COVID Diagnoses

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## Dedication

I would like to dedicate this dissertation to my wife, Rebecca, for your endless support, patience, and unwavering optimism throughout this whole process. I couldn't have finished this without you. To my daughter, Ella, you are my inspiration. I want you to remember that you are capable of anything you want to achieve and to never give up on your dreams. Lastly, to my family, thank you for instilling in me a sense of purpose and determination, and to never quit until the job is finished.

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**Abstract of Dissertation**

Long COVID in the Active Component US Military: Risk factors, effect of vaccination, and predicting incident long COVID diagnoses

Analysis 1

**Background:** Long COVID risk factors have been established in civilian populations, including female sex, older age, smoking, and certain comorbidities. However, little research has been conducted on risk in the U.S. military.

**Objective:** To identify the rate of and risk factors for long COVID in the U.S. military.

**Design:** Retrospective cohort study

**Setting:** Military Health System

**Patients:** 464,356 active component U.S. servicemembers with confirmed COVID-19 between January 1, 2020, and December 31, 2022.

**Measurement:** Incidence of long COVID was measured and demographic, COVID-19 infection, and comorbidity characteristics were assessed as risk factors using Poisson regression.

**Results:** 104,024 servicemembers developed long COVID (70.4 cases per 100,000 person-days of follow-up). Male sex (CIR, 0.72; 95% CI, 0.71 to 0.73), age ≥45 (CIR, 1.45; 95% CI, 1.39 to 1.52), non-Hispanic Black race (CIR, 1.11; 95% CI, 1.08 to 1.15), symptomatic COVID-19 infection (CIR, 1.04; 95% CI, 1.03 to 1.06), COVID-19 hospitalization (CIR, 1.25; 95% CI, 1.18 to 1.31), COVID-19 re-infection (CIR, 1.11; 95% CI, 1.08 to 1.13), vaccination against COVID-19 (CIR, 0.95; 95% CI, 0.93 to 0.98),

antiviral treatment for COVID-19 (CIR, 0.82; 95% CI, 0.72 to 0.93), and any comorbidity (CIR, 1.22; 95% CI, 1.19 to 1.25) were significantly associated with incidence of long COVID.

**Limitation:** Risk factors were assessed only through 2022, precluding investigation into more recent treatments, vaccines, and variants.

**Conclusions:** Despite being a younger and healthier population, incidence of long COVID was high in U.S. servicemembers. Similar risk factors were observed compared to the general population, including female sex, increased age, comorbidities, and being unvaccinated against COVID-19. Additionally, characteristics of the infection, such as reinfection, symptoms, and hospitalization were associated with long COVID.

Analysis 2

**Objective:** To identify whether COVID-19 vaccination and time since last dose impact the risk of long COVID in the U.S. military

**Methods:** Incidence of long COVID was measured in a cohort of active component U.S. servicemembers with confirmed COVID-19 between January 1, 2020, and December 31, 2022. COVID-19 vaccination and length of time since last vaccine dose were assessed as risk factors for long COVID using Cox proportional hazards regression with a step function for follow-up periods.

**Results:** Of 464,356 servicemembers with a confirmed COVID-19 event, 104,024 (22.4%) servicemembers developed long COVID within one year of follow-up. Being partially or fully vaccinated (aHR, 0.96; 95% CI, 0.94 to 0.98) and receipt of one or more booster doses (aHR, 0.91; 95% CI, 0.88 to 0.94) prior to the COVID-19 event were

associated with lower rates of long COVID compared to those who were unvaccinated. The protective effect was strongest for those whose most recent dose was within 3 months of the COVID-19 event (aHR, 0.94; 95% CI, 0.91 to 0.97). However, significant reductions in long COVID risk were only seen for the first 3 months of follow-up, with nonsignificant differences between vaccinated and unvaccinated groups for the remainder of the follow-up period. Neurological (4 months of follow-up) and respiratory (7 months of follow-up) symptoms showed significant decreases in diagnoses for vaccinated servicemembers vs unvaccinated for a longer duration compared to the overall long COVID outcome.

**Conclusions:** Vaccination against COVID-19 appears to provide modest reductions in risk of long COVID, and benefits for those vaccinated closer to their COVID-19 event may be even greater. However, the effect of vaccination on long COVID risk may wane over time, with the greatest reduction in risk in the first 3 months after infection. Protection against individual diagnostic groups, like neurological and respiratory diagnoses, may be longer.

Analysis 3

Long COVID represents a potentially serious threat to military readiness. Forecasts of future long COVID diagnoses could help prepare senior leaders for disruptions. However, few studies predicting long COVID have been published to date. Using existing COVID-19 and long COVID diagnoses, as well as demographic and outpatient encounter data, 1- to 6-month ahead and full 6-month forecasts were generated using time series and machine learning models trained on various covariate data. Forecasting models generated accurate predictions of long COVID diagnoses up to 6

months ahead of the forecasted date. Several model and covariate combinations were within 5% of the observed number of diagnoses over the full 6 month testing period, and monthly forecasts of long COVID diagnoses had MAPE ranging from 3-10% for the best performing model combinations. Simple forecasting models and distribution-based forecasts that utilize existing clinical databases can provide accurate predictions of long COVID up to 6 months in advance and can be used to prepare for the burden of new long COVID diagnoses.

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## Glossary of Terms

| Term | Definition |
|---|---|
| ADSM | Active Duty Service Member |
| AFHSD | Armed Forces Health Surveillance Division |
| CDC | Centers for Disease Control and Prevention |
| CLI | COVID-Like Illness |
| COVID-19 | Coronavirus Disease 2019 |
| DCPH-P | Defense Centers for Public Health – Portsmouth |
| DHA | Defense Health Agency |
| DMSS | Defense Medical Surveillance System |
| DoD | Department of Defense |
| DRSi | Disease Reporting System internet |
| ESSENCE | Electronic Surveillance System for the Early Notification of Community-based Epidemics |
| ICD-10 | International Classification of Diseases, 10th Revision |
| MHS | Military Health System |
| MTF | Military Treatment Facility |
| PASC | Post-Acute Sequelae of COVID-19 |
| SARS-CoV-2 | Severe Acute Respiratory Syndrome coronavirus 2 |
| WHO | World Health Organization |
| WIS | Weighted Interval Score |

## CHAPTER 1: Introduction and Significance

Beginning in December 2019 an outbreak of pneumonia of unknown origin emerged in Wuhan City in the Hubei Province of China, quickly spreading to nearby countries before being declared a Public Health Emergency of International Concern by the World Health Organization in March 2020[1–3]. The causative agent was quickly identified as a novel bat coronavirus from the genus Betacoronavirus and was named SARS-CoV-2 by the International Committee on Taxonomy of Viruses, while the resulting disease was named COVID-19[4–6]. COVID-19 spread globally, resulting in more than 775 million cases and over 7 million deaths as of June 2025[7]. The virus has been able to mutate frequently leading to new variants and surges in cases over time.

Early studies detailed the symptoms of COVID-19 to include fever, cough, shortness of breath, and fatigue with fatality rates as high as 15%[8–10]. As testing became more widespread and cases were identified in other countries, less severe outcomes were noted. Symptoms in non-hospitalized patients included fever, cough, and fatigue, with the case-fatality rate estimated around 2% and as many as 40% of cases being asymptomatic[11–15]. More recent variants of SARS-CoV-2, such as Omicron and it's subvariants, have shown lower rates of asymptomatic infections but higher rates of mild, seasonal respiratory symptoms like fever, runny nose, and sore throat[16]. Since the beginning of the pandemic, increased age has been identified as a significant risk factor for the development of severe COVID-19 and death, as have male sex, obesity, and comorbid conditions such as hypertension, diabetes, and cardiovascular disease[17,18].

Several treatments have been developed to combat COVID-19 and are currently approved by the U.S. Food and Drug Administration, including the antiviral drugs

Remdesivir (Veklury), Nirmatrelvir/Ritonavir (Paxlovid), and Molnupiravir (Lagevrio)[19–21]. In addition to treatments, a worldwide push was made to quickly develop and distribute a vaccine against SARS-CoV-2. Operation Warp Speed was launched in mid-2020 to identify and develop promising vaccine candidates[22]. Five vaccines were approved for use in the U.S. and Europe between December 2020 and July 2022, including the two-dose mRNA vaccines from Pfizer-BioNTech and Moderna, two adenovirus vector vaccines from AstraZeneca and Janssen, and an adjuvanted vaccine from Novavax[23,24]. Vaccines were shown to be effective at reducing the risk of symptomatic disease, hospitalization, and death in real-world studies, though effectiveness was reduced after 6 months and with the emergence of new variants, particularly the Omicron variant[25–27]. New booster doses and schedules were approved for use that include protection from more recent Omicron subvariants[26–28].

Soon after COVID-19 was declared a pandemic it was discovered that, in some, symptoms persisted long after the initial infection. This syndrome was dubbed "long COVID", and incidence was estimated at between 10% and 60% in people with a previous SARS-CoV-2 infection up to one year after the initial infection[29–34]. Symptoms of long COVID included milder symptoms like fatigue, exertional dyspnea, brain fog, joint pain, and weakness as well as more severe symptoms like depression, stroke, and dementia[29–34]. Challenges with long COVID surveillance and description include heterogeneous case definitions, lack of an agreed-upon diagnostic approach, and highly varied symptoms[35,36].

The high prevalence of long COVID symptoms led to formal attempts to define the condition. The CDC began defining long COVID, or "Post-COVID conditions", as a

broad set of symptoms including fatigue, respiratory, heart-related, neurological, and digestive symptoms beginning at least 4 weeks after a COVID-19 infection[36]. The WHO initially defined "Post COVID-19 conditions" as symptoms beginning at least 3 months after a SARS-CoV-2 infection and lasting for at least 3 months[35]. Risk factors for long COVID are similar to those of COVID-19, including older age, smoking, obesity, and having at least one comorbidity, though notably female sex has been linked to incidence of long COVID which differs from COVID-19[37–39]. The risk of long COVID has shown to be lower during the most recent variant waves, most notably during the Omicron wave[40].

No treatments are currently approved to treat long COVID, though clinicians can treat individual symptoms of long COVID. Preliminary studies have found contradictory results regarding treatment with the antiviral Nirmatrelvir/Ritonavir during the initial SARS-CoV-2 infection, though other treatment options may also be available[41–43]. There has been some research showing that the currently approved COVID-19 vaccines do reduce the risk of long COVID, especially after receiving at least 2 doses in people who were vaccinated prior to their initial SARS-CoV-2 infection[44–47]. Another study showed that vaccination after an initial SARS-CoV-2 infection but before development of long COVID may provide a modest protection against the development of long COVID[48].

Despite the breadth of research available on COVID-19, significant gaps still exist for long COVID. Estimates of the incidence of long COVID differ widely, especially in terms of symptoms measured and availability of longitudinal health records. No standard set of risk factors have been tested, and most studies lack data on many possible risk factors. In addition, more research is needed on the role of treatments, vaccinations (in

particular the role of waning immunity), and new and ever-changing variants on the incidence of long COVID. Lastly, very little research to date has been conducted to estimate long COVID or its risk factors in the U.S. military.

This dissertation research proposal aims to fill gaps in long COVID research. The first aim of this dissertation will identify the incidence of long COVID and risk factors in a cohort of COVID-19 cases in the active component U.S. military. This cohort is large, representing over 450,000 COVID-19 cases, with access to linked medical records, vaccination records, and demographic data. The incidence of long COVID will be measured throughout the duration of the pandemic, including during major variant waves, using a validated definition of long COVID developed by the Navy. The second aim will study the effect of vaccination, and in particular the role of waning immunity from vaccinations, on the incidence of long COVID as well as the effect of circulating variant on this relationship. The third aim of this proposal is to develop a long COVID definition for use in real-time syndromic surveillance and to develop a predictive model of long COVID incidence in the U.S. military. It is expected that this dissertation project will further knowledge of the incidence of long COVID over time and significant risk factors, especially in the U.S. military, as well as highlight how well current vaccines are protecting against long COVID and provide guidance as new variants of SARS-CoV-2 emerge.

# CHAPTER 2: Background and Specific Aims

## 2.1 SARS-CoV-2 and COVID-19 Disease

### 2.1.1 Overview of COVID-19 Pandemic

On December 31, 2019, the World Health Organization (WHO) was alerted to several cases of pneumonia of unknown etiology in Wuhan City in the Hubei Province of China[1]. By January 3, 2020, China had reported 44 cases of pneumonia of unknown etiology to WHO. No causal agent had been identified, but Chinese authorities linked the outbreak to a seafood market in Wuhan City[1]. By February 2020 the causative agent of the outbreak was identified as a new coronavirus, named 2019-nCoV (2019 novel coronavirus)[4]. The genome of 2019-nCoV was found to be 96% identical to a bat coronavirus, and 79.6% identical to SARS-CoV. Further, 2019-nCoV was determined to be in the genus Betacoronavirus, subgenus Sarbecovirus[5]. In February 2020 the virus 2019-nCoV was renamed SARS-CoV-2 (severe acute respiratory syndrome coronavirus 2) by the International Committee on Taxonomy of Viruses (ICTV), while the resulting disease caused by the virus was named COVID-19 (coronavirus disease 2019)[6].

The outbreak quickly spread around the world, first to countries in the region (including Thailand, Japan, and the Republic of Korea) before spreading to other regions[1]. By the end of February 2020, COVID-19 cases were reported in every region of the world, including nearly 80,000 confirmed cases in China and over 6,000 confirmed cases outside of China, and COVID-19 was declared a Public Health Emergency of International Concern (PHEIC) by WHO on March 11, 2020[2,3].

The Centers for Disease Control and Prevention (CDC) reported the first case of COVID-19 in the United States on January 20, 2020, in a patient with recent travel to Wuhan

City[49,50]. In March of 2020 the United States declared a nationwide emergency due to COVID-19, and shortly after states began issuing stay-at-home orders to reduce transmission of COVID-19[51]. From early 2020 through 2022, COVID-19 inflicted serious damage in the United States and around the world. On May 5, 2023, the COVID-19 PHEIC was declared over by WHO, while on May 11, 2023, the U.S. ended the public health emergency for COVID-19[52,53]. As of June 1, 2025, there have been over 103 million confirmed cases of COVID-19 and 1.2 million deaths in the United States[7]. Globally there have been more than 778 million confirmed cases and nearly 7.1 million deaths[7]. The virus continues to mutate, and several variants of concern (VOC) have been identified over time and have caused large outbreaks, including Alpha (B.1.1.7), Beta (B.1.351), Delta (B.1.617.2) and most recently Omicron (B.1.1.529), which includes the BA.1, BA.2, BA.3, BA.4, BA.5, XBB, and JN.1 subvariants that emerged as the dominant lineages worldwide[54–56].

### 2.1.2 COVID-19 Symptoms and Risk Factors

Initial reports of SARS-CoV-2 infections focused on pneumonia, and initial studies were limited to this group. In early studies of hospitalized COVID-19 patients with pneumonia in China, the most reported symptoms were fever, cough, shortness of breath, and fatigue, and less common symptoms like myalgia, muscle aches, confusion, and headaches were also reported. Severe outcomes like acute respiratory distress syndrome (ARDS) were reported in over 15% of patients and between 4 and 15% of patients died[8–10]. As COVID-19 spread to other countries and testing became more widespread, less severe cases were detected. In a study of the first 18 cases of COVID-19 detected in Singapore, fever, cough, and sore throat were frequently reported, though no cases suffered ARDS, and

none died[11]. A subsequent systematic review of common symptoms in COVID-19 patients also found the most frequently reported symptoms to be fever, cough, fatigue, dyspnea, and sputum production[12]. Additionally, early studies suggested that a large proportion, up to 40%, of people infected with SARS-CoV-2 were asymptomatic, and that asymptomatic or presymptomatic transmission of COVID-19 was possible[13,14]. A review of a large case series of more than 72,000 cases published by the Chinese CDC found 81% of cases to be mild, 19% to be severe or critical, and a case-fatality rate of 2.3%[15].

Over time as new variants of SARS-CoV-2 have emerged and new treatments and vaccines have become available the reported symptoms and severity of COVID-19 have evolved. A study of over 1.5 million adults in England, including more than 17,000 cases of COVID-19, found the highest proportion of symptomatic cases in people infected with the Omicron BA.1 (70%) and BA.2 (74%) subvariants compared to Delta (64%), Alpha (55%), and the wild-type (45%) variants[16]. In addition, the study found the odds of a positive SARS-CoV-2 test to be increased across all variants among people with a range of symptoms including cough, fever, chills, muscle aches, and loss of taste or smell, however odds ratios for seasonal respiratory symptoms like fever, runny nose, and sore throat were highest in people infected with Omicron BA.1 or BA.2 subvariants while loss of taste or smell was highest in people infected with wild type, Alpha, and Delta variants[16]. This shift during the Omicron variant wave to increased symptoms consistent with more mild, seasonal respiratory infections has also been found to coincide with a shift to less severe outcomes during this wave compared to previous waves. In an analysis of severity markers of COVID-19 in the U.S., the CDC found that although the

overall number of cases, ED visits, and hospital admissions due to COVID-19 were higher during the Omicron wave than the Delta wave and winter 2020-2021 wave, the ratio of ED visits, hospital admissions, and deaths compared to cases was lowest during the Omicron wave[57]. In addition, ICU admission rates among hospitalized COVID-19 patients was lowest during the Omicron wave, as were the percentage of patients receiving invasive mechanical ventilation and the percentage of patients who died[57].

Additionally, risk factors associated with increased severity of COVID-19 have been identified. A meta-analysis of over 100,000 patients in 58 studies found age greater than 65, male sex, obesity, hypertension, diabetes, cardiovascular disease, and cancer to be significantly associated with mortality due to COVID-19[17]. An additional meta-analysis of more than 36,000 patients also found both male sex and age greater than 70 to be associated with higher risk of COVID-19 infection, severe disease, and death[18]. Additionally, another meta-analysis showed the risk of death among hospitalized COVID-19 patients to be higher for males, people who smoke, and people with certain medical conditions like chronic obstructive pulmonary disease (COPD), cardiovascular disease, diabetes, hypertension, obesity, and cancer[58]. Currently, the CDC considers the following people to be at increased risk for COVID-19 hospitalization, severe disease, and death: people older than 65, in racial and ethnic minority groups, with disabilities, and with certain medical conditions such as cancer, chronic lung disease, dementia, diabetes, heart disease, HIV, obesity, and pregnancy[59].

### 2.1.3 COVID-19 Treatments

Over the course of the pandemic, several treatments have been approved for use in the treatment of COVID-19. An antiviral drug Remdesivir, which acts as a viral RNA

synthesis inhibitor, was shown to reduce the recovery time of patients with severe COVID-19 in clinical trials as well as improved clinical status in patients with moderate COVID-19[60,61]. Remdesivir was approved by the U.S. Food & Drug Administration (FDA) for use in hospitalized adults and children ages 28 days or older on October 22, 2020, becoming the first FDA-approved treatment for COVID-19, after previously receiving an emergency use authorization (EUA) in May of 2020[19].

In addition to Remdesivir, several anti-SARS-CoV-2 monoclonal antibody drugs have been developed for the treatment of COVID-19. Bamlanivimab was shown to reduce viral load, rates of hospitalization, and symptom severity in a phase II clinical trial of adults with COVID-19 who were not hospitalized and was given EUA by the FDA in November 2020 for use in mild-to-moderate cases of COVID-19[62,63]. However, the FDA revoked the EUA in April 2021 due to concerns about resistance to Bamlanivimab alone in newer variants[64]. Additional solo or combinations of monoclonal antibodies, including casirivimab + imdevimab (REGEN-COV), bamlaniviimab + etesevimab, and sotrovimab were shown to reduce COVID-19 viral loads, hospitalizations, or disease progression and were granted EUAs by the FDA, however all three have since had their EUAs revoked in light of reduced effectiveness against Omicron subvariants, in particular BA.2[65–69].

Additional treatment options have been developed and are currently approved for use against COVID-19, including two oral antiviral treatments. Nirmatrelvir/ritonavir (Paxlovid) showed 88% decreased risk of progression to severe disease in non-hospitalized adults at high risk of severe COVID-19, while Molnupiravir (Lagevrio) was shown to reduce the risk of hospitalization and death in adults with COVID-19 by about 30%[37,70]. Both drugs were given EUA by the FDA in December 2021, with

Nirmatrelvir/Ritonavir becoming the first oral antiviral treatment for COVID-19[20,21]. As of July 2024, Remdesivir, Nirmatrelvir/Ritonavir, and Molnupiravir are the only antivirals approved for treating COVID-19[71].

### 2.1.4 COVID-19 Vaccines

At the onset of the COVID-19 pandemic, a global push was made to develop a vaccine to reduce the burden of COVID-19. The U.S. launched Operation Warp Speed in mid-2020, a program aimed at identifying promising vaccine candidates and manufacturing them at industrial scales while clinical trials were ongoing, potentially speeding up the pace of vaccines reaching the market[22]. The FDA issued EUAs for the first two COVID-19 vaccines in adults in December 2020, Pfizer-BioNTech's BNT162b2 monovalent mRNA vaccine and Moderna's mRNA-1273 monovalent mRNA vaccine[23]. In phase III clinical trials, a two-dose series of Pfizer-BioNTech's BNT162b2 COVID-19 vaccine given 21 days apart resulted in 95% efficacy against SARS-CoV-2 infection, with a safety profile similar to that of other vaccines[72]. In a phase III trial of two doses Moderna's mRNA-1273 vaccine given 28 days apart, the vaccine was found to be 94% effective against symptomatic infection and 100% effective against severe COVID-19[73]. Both the Pfizer-BioNTech BNT162b2 (Comirnaty) and Moderna mRNA-1273 (Spikevax) vaccines were given full approval in adults and children aged 16 and older by the FDA in August 2021 and January 2022, respectively[23].

Additional COVID-19 vaccines were approved later. Astra-Zeneca's ChAdOx1 nCoV-19 adenovirus vector vaccine was approved in the European Union in January 2021 after a pooled analysis of four clinical trials in the UK, Brazil, and South Africa found two doses of the vaccine to be over 70% effective at preventing symptomatic SARS-CoV-2

infection and 100% effective at preventing severe disease[24,74]. Efficacy increased to over 90% if participants were given a half dose followed by a full dose 21 days later[74]. Similarly, the Janssen adenovirus vector vaccine was granted EUA by the US FDA in February 2021 after clinical trials showed a single dose of the vaccine was 67% effective against moderate to severe COVID-19[23,75]. However, the FDA briefly paused administration of the Janssen COVID-19 vaccine in April 2021 after 6 cases of a rare blood clot were linked to the vaccine, before restricting its use in May of 2022[76]. Additionally, Novavax's adjuvanted COVID-19 vaccine was given EUA by the US FDA in July 2022[23]. Vaccines have since been approved for use in children as young as 6 months and additional booster doses of each vaccine have also been approved over time to combat waning immunity[23]. The vaccine schedule was simplified to one annual dose for non-ummunocompromised adults under age 65, similar to influenza[23].

While clinical trials on the efficacy of COVID-19 vaccines focused mainly on markers of severe disease such as hospitalization and death, real-world studies placed additional emphasis on markers of transmission such as symptomatic infections. Real world studies of COVID-19 vaccines have shown reduced efficacy compared to phase III trials, especially against SARS-CoV-2 infection as new variants have emerged. In a real-world, test negative case-control study of more than 170,000 adults aged 70 or older in the UK, the Pfizer-BioNTech BNT162b2 vaccine was found to be 60-70% effective against symptomatic disease after one dose and 85-90% effective after two doses, as well as reduce the risk of hospitalization by 44% and the risk of death by 51%[25]. In the same study, the single dose Oxford-Astra-Zeneca ChAdOx1-S vaccine was 65-70% effective against symptomatic disease[25]. A test negative case-control study in Ontario, Canada

found vaccine effectiveness against symptomatic COVID-19 infection after two doses of COVID-19 vaccine to be 89% for the Delta variant and only 36% for Omicron variant, with effectiveness decreasing 6 months after the most recent vaccine dose and increasing after receiving a booster dose[26]. The same study found vaccine effectiveness to be 95% or higher against severe disease for both Delta and Omicron variants[26]. An additional study showed two doses of a COVID-19 vaccine to be more than 80% effective at preventing symptomatic COVID-19 for Delta variant, with effectiveness dropping against Omicron variant[27]. Booster doses were shown to increase effectiveness of the vaccines against both Delta and Omicron variants, with both primary series and booster doses showing reduced effectiveness over time[27]. Longer follow-up after vaccination showed decreased efficacy against clinical disease after several weeks to months, though efficacy against severe disease remained high[25–27]. New vaccine formulations targeting the spike protein of SARS-CoV-2 XBB variants have shown to be effective in increasing neutralizing antibodies to newer subvariants, including JN.1[28].

### 2.1.5 Gaps in Knowledge

Much research has been conducted since 2020 to describe the basic epidemiology of SARS-CoV-2 infection, identify key risk factors for COVID-19, evaluate the effect of COVID-19 treatments and vaccines, and monitor changing conditions due to the emergence of new variants. One still relatively understudied aspect of COVID-19 is the noted persistence of symptoms after the acute phase of infection has passed. This phenomenon, sometimes called long COVID, is poorly understood. This project aims to further the body of knowledge around long COVID by furthering its research in a relatively young, active population with complete medical records.

## 2.2 Long COVID and Post-Acute Sequelae of COVID-19

### 2.2.1 Long COVID Symptoms, Presentation, and Definitions

Shortly after the emergence of COVID-19 and its spread around the world, clinicians and researchers noticed symptoms of COVID-19 persisting after the acute phase of infection had ended. An Italian study was conducted in April and May of 2020 of nearly 150 patients previously hospitalized for COVID-19 who were no longer infected with SARS-CoV-2 and were not in the acute phase of the infection. The study found only 18% of patients were symptom-free, with the most reported symptoms being fatigue, dyspnea, joint pain, and chest pain[29]. These persisting symptoms were eventually known as "long COVID", "post COVID disease", and "post-acute sequalae of COVID-19". While the cause of long COVID has not been established, long COVID has been associated with increased complement activation and dysregulation during the acute phase of COVID-19[77].

More recently, in a study of 137 people previously hospitalized for COVID-19, nearly 70% reported long COVID symptoms, with the most common physical symptoms being fatigue, exertional dyspnea, musculoskeletal pain, and brain fog, and the most common psychological symptoms being anxiety and depression[30]. In another study of a cohort of 968 patients in France with post COVID disease, 85% still reported symptoms of long COVID one year after COVID-19 symptom onset[31]. In that same study some symptoms decreased over time, including loss of taste or smell, coughing, and diarrhea, while others increased over time (hair loss)[31]. A large retrospective cohort study of more than 200,000 cases of COVID-19 using electronic health records found an increased risk of neurological and psychiatric conditions among people who had COVID-19 compared to

people who had recovered from influenza and unspecified upper respiratory infections, as well as among COVID-19 patients who had required hospitalization or treatment in an intensive care unit compared to COVID-19 patients who did not[32]. Most notably, incidence of ischemic stroke and first diagnosis of dementia were increased after COVID-19 infection[32].

A meta-analysis of 32 long COVID studies found the most frequently reported symptoms in long COVID to be weakness (41%), general malaise (33%), fatigue (31%), concentration impairment (26%), and breathlessness (25%)[33]. Other symptoms with frequently reported were sweat or night sweats (24%), loss of appetite (17%), other stomach/abdominal discomfort (18%), weight loss (21%), muscle pain/myalgia (11%), impaired mobility (14%), taste (14%) or smell (15%) disturbances, decreased sensation or sensibility (11%), abnormal reflex status (23%), anxiety (19%), sleep disorder (18%), memory impairment (18%), frontal release signs (15%), and hair loss (14%), and 37% of people reported a reduced quality of life[33]. Certain symptoms were more prevalent in hospitalized patients compared to non-hospitalized patients including fatigue, breathlessness/exertional dyspnea, other respiratory symptoms, weight loss, tremors, memory impairment, and hair loss while smell disturbances were more likely in non-hospitalized patients[33]. And in a cohort of nearly 4,000 participants, 92% of patients still had at least one symptom after 35 weeks, with the most common symptoms reported after six months being fatigue, post-exertional malaise, brain fog, headaches, and memory issues[34]. Additionally, a longitudinal cohort study of post-acute sequelae of COVID-19 (PASC) found 55% of the initial cohort to be exhibiting symptoms consistent with PASC

at baseline enrollment compared to only 13% of controls who had no history of COVID-19[78].

With such a broad range of reported long COVID symptoms, attempts to create a formal definition have differed. The CDC initially defined long COVID or Post-COVID conditions as symptoms beginning 4 weeks or later after a COVID-19 infection from several broad categories including general symptoms like fatigue and post-exertional malaise, as well as respiratory, heart-related, neurological, and digestive symptoms[36]. The WHO defines Post COVID-19 condition as symptoms continuing or developing 3 months or later after an initial SARS-CoV-2 infection and lasting for at least 2 months[35].

A study of over 400,000 non-hospitalized individuals found that those infected with SARS-CoV-2 were more likely to report at least one symptom of long COVID in the WHO definition at least 12 weeks after the initial COVID-19 infection compared to those with no recorded SARS-CoV-2 infection[38]. The same study found 62 symptoms to be significantly associated with SARS-CoV-2 infection, including shortness of breath, fatigue, chest pain, brain fog, loss of smell, and hair loss, with hazard ratios decreasing over time[38].

### 2.2.2 Long COVID Risk Factors

Risk factors for long COVID are similar to those for COVID-19, though there are some notable differences. In a cohort of patients hospitalized for COVID-19, female sex, increased age, and smoking were associated with increased risk of long COVID[8]. Another study of non-hospitalized individuals found female sex, being part of an ethnic minority, smoking, obesity, and certain comorbidities including COPD, fibromyalgia, anxiety, depression, migraine, multiple sclerosis, and celiac disease to be associated with

an increased risk of long COVID[38]. A study of adults and children previously hospitalized for COVID-19 also found female sex to be associated with higher rates of long COVID, as well as hypertension[39].

The risk of long COVID has also changed over time as new variants have emerged. A study of non-hospitalized people in the UK found the association between some reported symptoms of long COVID and SARS-CoV-2 infection to be higher during the second wave of infection in the fall of 2020 and winter of 2021 compared to the initial wave in the spring and summer of 2020, including cough, sneezing, rash, and fever[38]. One study of over 50,000 cases of COVID-19 in the UK between June 2021 and March 2022 found the prevalence of long COVID to be lower during the Omicron wave (4.5%) compared to the Delta wave (10.8%)[79].

### 2.2.3 Long COVID Treatments

Currently, no treatments are approved for the explicit purpose of treating long COVID, however individual symptoms of long COVID can be treated by a health provider. An article detailing a retrospective cohort study from the U.S. Department of Veterans Affairs found that the risk of post-acute sequelae of COVID-19 was significantly reduced in patients who took the oral antiviral drug Molnupiravir within 5 days of their initial positive SARS-CoV-2 test[41]. However, in an observational cohort study, treatment with nirmatrelvir during the acute phase of COVID-19 was not associated with long COVID symptoms, nor was rebound symptoms after treatment[43]. In a phase 3 RCT in overweight and obese US adults with COVID-19, outpatient treatment with metformin within 3 days of symptom onset was associated with a 41% reduction in long COVID incidence compared to placebo[42]. Additional research is required to determine whether treatment of

COVID-19 in the acute phase of infection reduces the risk of developing long COVID symptoms.

### 2.2.4 Long COVID and Vaccination

Vaccination appears to have some effect on incidence of long COVID, though more research is needed. One systematic review of 17 peer-reviewed articles and pre-prints found that vaccination was associated with lower odds of long COVID, especially after two doses[44]. Another study found the odds of any long COVID symptoms and activity-limiting long COVID symptoms to both be reduced by 41% in persons who received two doses of a COVID-19 vaccine compared to those were unvaccinated[45]. A staggered cohort study in the UK, Spain, and Estonia found that vaccination with one dose of a COVID-19 vaccine prior to COVID-19 infection reduced the incidence of long COVID by between 29 and 52%[46]. And a retrospective cohort study in children aged 5-17 found vaccine effectiveness against long COVID within 12 months of acute COVID-19 between 35-42%, with higher VE in adolescents and within 6 months compared to children and between 6-12 months, respectively[47].

Additional studies have looked at the effect of vaccination after an initial infection with SARS-CoV-2. One study found the odds of experiencing long COVID symptoms decreased by 13% after a first COVID-19 vaccine dose, and by a further 9% after a second dose, with improvements sustaining at least a median of 67 days in people vaccinated after being infected with SARS-CoV-2[48]. The authors found no difference between adenovirus and mRNA-based vaccines.

### 2.2.5 Gaps in Long COVID Knowledge

While significant research on long COVID has been performed, additional research is needed. Additional research is needed to determine the incidence of long COVID, particularly in younger, healthier populations that were not hospitalized for COVID-19. The incidence of severe long COVID symptoms or those resulting in significant disability need to be assessed separately from general definitions of long COVID.

Questions also remain about the effect of new variants on long COVID incidence, as well as the role and timing of COVID-19 vaccination. Waning immunity against SARS-CoV-2, especially with less frequent recommended doses, may play a role in increasing risk of long COVID symptoms. Additionally, research on the role of treatments on COVID-19 are still needed.

## 2.3 Predictive Modeling of Infectious Diseases

Infectious disease forecasting models have been around for decades and have been used to forecast a variety of diseases, most notably influenza. CDC began hosting an influenza challenge during the 2013-2014 influenza season where participating teams were asked to submit bi-weekly forecasts of influenza activity[80]. Forecasting models used in the challenge included mechanistic models like SIR (susceptible-infected-recovered) and SEIR (susceptible-exposed-infected-recovered), statistical models like Poisson, time series models, and combinations of models called ENSEMBLE models, though forecasts were not considered useful for public health decision making[80]. CDC has continued hosting yearly influenza challenges, finding that ENSEMBLE models averaging together individual models perform well at forecasting short-term targets of influenza activity[81]. Predictive modeling has since been performed for COVID-19 as well. Evaluations of

COVID-19 death forecasts submitted to the COVID-19 Forecast Hub found an ensemble approach was more stable and accurate across all forecasted locations and targets than any individual models[82].

## 2.4 U.S. Active Duty Military Population

### 2.4.1 Overview of the U.S. Active Duty Military Population

The U.S. military is comprised of five service branches, the Army, Navy, Marine Corps, Air Force, and Space Force, though the Space Force had minimal to no encounters at the time of this study and is included within the Air Force numbers. As of 2020 there were more than 1.3 million active duty servicemembers (ADSM) in the U.S. military, with the Army serving as the largest branch at 36% of ADSM, followed by the Navy (26%), the Air Force (25%), and the Marine Corps (14%)[83]. The demographics of ADSM differ significantly from those of the general population. Overall, ADSM are significantly younger than the general population, with 45% of the population aged 25 or younger and 92% aged 40 or younger compared to 32% and 52% of the U.S. population, respectively. Male sex is more prevalent in ADSM, comprising 83% of servicemembers compared to 49% of the general population. ADSM are more likely to identify as Black or African American, with 17% falling into that category compared to 12% of the U.S. Population. ADSM are also less likely to have a college degree, with only 23% having a bachelor's degree or higher compared to 30% of people aged 18 or older in the general population[83,84].

### 2.4.2 Overview of ADSM Health Status

ADSM are provided health insurance free of charge through TRICARE, the health care program for the U.S. military, which provides care within the Military Health System

(MHS) or through TRICARE-authorized civilian providers[85]. Due to demographic differences, notably age, and the presence of universal healthcare ADSM have lower rates of chronic illness and risk factors for COVID-19 such as obesity, however they also have high rates of substance use, behavioral health disorders, and sexually-transmitted infections[86].

### 2.4.3 COVID-19 in ADSM

As of December 8th, 2022, there have been over 450,000 cases of COVID-19 in ADSM, reserves, and national guard, including more than 2,700 hospitalizations and 96 deaths due to COVID-19[87]. Over 90% of active duty, reserve, and national guard servicemembers have been fully vaccinated for COVID-19[87]. The rate of hospitalizations and deaths due to COVID-19 in the general U.S. population is significantly higher than in the active component population, with COVID-19 admissions being nearly ten times more frequent and deaths being nearly 55 times more frequent in the general population. Less than 1% of active component cases resulted in an admission due to COVID-19 compared to 5.8% of U.S. cases, and only 0.02% of cases resulted in death compared to 1.1% of cases in the U.S. general population[87,88]. Few studies have been published exploring the incidence and effects of long COVID in the U.S. military, though one cohort study in U.S. servicemembers showed Post Acute Sequelae of COVID-19 was associated with increased risk of cardiac events, including myocarditis, pericarditis, and atrial fibrillation[89].

## 2.5 Specific Aims

### 2.5.1 Specific Aim 1

**To characterize the incidence and risk factors of long COVID in the Active Component US military.**

Aim 1 will look at the incidence of long COVID during the period of January 2020 through December 2022 in a cohort of Active Component service members with a confirmed case of COVID-19, and risk factors for developing incident long COVID will be assessed in this population. To measure this, we will use a cohort of Active Component service members with a confirmed case of COVID-19 maintained by the Armed Forces Health Surveillance Division (AFHSD) as well as demographic, medical encounter, and other risk factor information maintained by AFHSD.

### 2.5.2 Specific Aim 2

**To determine whether the incidence of long COVID in the Active Component US military differs by vaccination status prior to infection and time since last vaccine dose.**

Aim 2 will look at whether the risk of developing long COVID differs by the length of time since the most recent COVID-19 vaccine received prior to the diagnosis of long COVID, and whether the type of vaccine or the dose modifies this relationship. We hypothesize that the risk of long COVID will increase as the length of time since the most recent vaccine dose increases. We also hypothesize that this relationship will not be modified by type of vaccine, but will be modified by dose, with the relationship between time since most recent dose and risk of long COVID becoming less pronounced with

increased number of doses received. To measure this, we will use the cohort from Aim 1 as well as COVID-19 vaccination information maintained by AFHSD.

### 2.5.3 Specific Aim 3

**To develop a forecasting model of long COVID incidence in the Active Component US military.**

Aim 3 will attempt to develop a predictive time series model of incident long COVID diagnoses in Active Component service members by Military Health System (MHS) market. The model will include time series data of COVID-19 activity (confirmed cases, COVID-like-illness outpatient encounters, COVID-19 outpatient encounters), COVID-19 vaccinations, and aggregate information about long COVID risk factors to predict the number of incident long COVID diagnoses over the upcoming weeks. In addition to time series data on COVID-19 activity, time series data of ESSENCE long COVID diagnoses will also be used as an input. The model outputs will be compared to the actual number of ESSENCE long COVID diagnoses during the same time period for accuracy using established methods for other COVID-19 forecasting targets. To develop this model, we will use information learned from Aims 1 and 2 as well as time series and demographic data maintained by AFHSD.

# CHAPTER 3: Methods

## 3.1 Data Sources

### 3.1.1 Armed Forces Health Surveillance Division (AFHSD)

The Armed Forces Health Surveillance Division (AFHSD) is the "centralized epidemiologic health resource for the U.S. Military." AFHSD is a division within the Defense Health Agency's (DHA) Public Health Directorate, and their mission is to provide "timely, relevant, actionable, and comprehensive health surveillance support to the Joint Staff, Combatant Commands, and Military Services in order to promote health and enhance Force Health Protection, Readiness, and Lethality." AFHSD is divided into four branches: DMTS (Data Management and Technical Support), E&A (Epidemiology & Analysis), GEIS (Global Emerging Infections Surveillance), and IB (Integrated Biosurveillance). AFHSD is responsible for collecting health surveillance information and distributing that information as well as policy recommendations to Department of Defense (DoD) stakeholders[90].

### 3.1.2 Defense Medical Surveillance System (DMSS)

The Defense Medical Surveillance System (DMSS) is a large relational database of health information collected on all DoD service members in service since 1990. DMSS includes data from the time a service member enters military service until they are ineligible to receive care. DMSS contains many individual datasets, including but not limited to personnel data, medical data (indirect and outsourced inpatient and outpatient medical encounters, immunizations, reportable medical events, prescriptions, and periodic health assessments), laboratory data (serologic specimens, microbiology, chemistry), and deployment data. DMSS data are updated regularly and can be efficiently

queried to answer a number of research questions. A full list of DMSS datasets and associated variables is provided in Table 3-1, and a brief description of each table is provided below[91].

**PERSON Table**

This table contains personnel records that include characteristics of the service member that do not change over time. There is only one record per person in this table.

**DEMOG Table**

This table includes time varying demographic information for servicemembers. A new record is created in this table each time a servicemember updates their information.

**MEPS_DEMOG Table**

This table is similar to the DEMOG table but includes height and weight data.

**INPT and INPT_ICD10 Tables**

These tables include inpatient encounter data on care received in fixed Military Treatment Facilities (MTFs) and encounters outside the military medical system which are billed to TRICARE. The switch from using ICD-9 to ICD-10 coding occurred on October 1, 2015. The INPT table includes all records with an event date on or before September 30, 2015, while the INPT_ICD10 table includes all records after September 30, 2015.

**OUTPT and OUTPT_ICD10 Tables**

These tables include outpatient/ambulatory encounter data on care received in fixed MTFs and encounters outside the military medical system which are billed to TRICARE.

The switch from using ICD-9 to ICD-10 coding occurred on October 1, 2015. The OUTPT table includes all records with an event date on or before September 30, 2015, while the OUTPT_ICD10 table includes all records after September 30, 2015.

**REP_EVENTS Table**

This table includes CDC and military relevant reportable events.

**CHEM and MICRO Tables**

These tables include laboratory and microbiology data from MTFs.

**PHA Table**

This table includes information from the Periodic Health Assessment (PHA) form, which is a standard form used across all services and required to be filled out annually by each service member. The form includes self-reported data on health conditions, medical readiness, behavioral health, family history and lifestyle, and women's health. The form also includes a medical chart review and provider review section.

**PDTS Table**

This table includes information on filled outpatient prescriptions from MTFs, Theater Medical Data Store (TMDS), TRICARE, and Veterans Affairs (VA) provided by the Pharmacy Data Transaction Services (PDTS).

### 3.1.3 AFHSD COVID-19 Data Collection and Reporting

Since April 2020, when the global pandemic of SARS-CoV-2 was declared, AFHSD has been collecting information on COVID-19 in active component service members and DoD beneficiaries. AFHSD maintains a master list of all confirmed COVID-19 cases in

DoD beneficiaries which includes event date, beneficiary type, re-infection status, hospitalization status, and demographic information as well as COVID-19 vaccination information. A full list of AFHSD COVID-19 datasets and associated variables is provided in Table 3-2.

The COVID-19 Master Positive List includes DoD beneficiaries with a positive SARS-CoV-2 PCR or antigen test reported using Health Level 7 (HL7) laboratory data and confirmed COVID-19 reportable event data reported from the Disease Reporting System Internet (DRSi). Prior to July 2023, laboratory data was provided by the Defense Centers for Public Health – Portsmouth and DRSi data was provided by the Defense Centers for Public Health – Aberdeen. Beginning in July 2023, both laboratory and DRSi data were downloaded from the Electronic Surveillance System for the Early Notification of Community-Based Epidemics (ESSENCE). COVID-19 vaccination data for ADSM are downloaded from the IMMUNIZATIONS table in DMSS and merged with the COVID-19 Master Positive List. Information on whether a case was hospitalized due to COVID-19, including dates of hospitalization and discharge, is provided by the DHA J5 Directorate (Strategy, Plans, and Functional Integration), DRSi, and DMSS and merged with the COVID-19 Master Positive List.

### 3.1.4 Electronic Surveillance System for the Early Notification of Community-Based Epidemics (ESSENCE)

ESSENCE is a secure web-based syndromic surveillance platform developed by the Johns Hopkins Applied Physics Laboratory and used by public health authorities across the United States. ESSENCE is used by both the DoD and CDC to conduct syndromic surveillance in near real-time. CDC maintains the National Syndromic Surveillance

Program (NSSP), a collaboration between CDC and local and state health departments, which use ESSENCE as a tool for analyzing syndromic surveillance data. The DoD maintains their own instance of ESSENCE, which receives outpatient medical encounters from two electronic health record (eHR) systems, MHS GENESIS and AHLTA. Outpatient and inpatient medical encounter data are transmitted into ESSENCE in near real-time and binned into syndrome categories, allowing the ability to quickly query chief complaint and diagnostic codes within the health records. In addition to outpatient medical encounters, DoD ESSENCE also contains laboratory results and DRSi reportable medical events.

### 3.1.5 Post-Acute Sequelae of COVID-19

The Defense Centers for Public Health- Portsmouth, EpiData Center has developed a Post-Acute Sequelae of COVID-19 (PASC) definition to identify DoD service members with long COVID. The most recent version (V4) was last updated in May 2022.

The definition has three requirements:

1) A positive SARS-CoV-2 PCR or antigen test or a confirmed COVID-19 reportable medical event
2) Any of the defining diagnosis of a Mental Health, Neurological, Cardiac, or Respiratory event (Table 3) in any diagnostic position between 4 and 52 weeks after the positive SARS-CoV-2 PCR test, antigen test, or COVID-19 reportable medical event onset date
3) No previous history of the defining diagnosis of a Mental Health, Neurological, Cardiac, or Respiratory event (Table 3-3) in any diagnostic position within one year prior to the positive SARS-CoV-2 PCR test, antigen test, or COVID-19

reportable medical event onset date. **Note:** Only the prior history of the exact diagnosis description will exclude a patient. For example, prior history of seizure in the previous year will act as an exclusion factor only for seizure related codes.

## 3.2 Methods for Specific Aims

### 3.2.1 Methods for Aim 1

*Aim 1: To characterize the incidence and risk factors of long COVID in the Active Component US military.*

#### 3.2.1.1 Study Population

To evaluate risk factors for long COVID in active component service members, the study population includes all active component service members with a confirmed case of COVID-19 in the COVID-19 master positive list with event dates between January 1, 2020, and December 31, 2022. Any service members not in the active component at the time of their COVID-19 event date will be excluded from the analyses.

#### 3.2.1.2 Definition and Measurement of Key Variables

##### 3.2.1.2.1 Exposures of Interest

As Aim 1 is focusing on risk factors for long COVID, exposures of interest will include demographic data, information about each service member's qualifying COVID-19 case, and information about known COVID-19 risk factors. To standardize all demographic variables and ensure all demographic variables are included for analysis, the COVID-19 master positive list will be matched to the DEMOG table in DMSS. In the DEMOG table, the service member record that overlaps their COVID-19 case date will be used, or their most recent DEMOG record if that is unavailable. Demographic exposures assessed in

Aim 1 will include age (categorical: <20, 20-24, 25-29, 30-34, 35-39, 40-44, ≥45), sex (categorical: male, female, other), race/ethnicity (categorical: Asian, non-Hispanic Black, Hispanic, non-Hispanic White, Other/Unknown), service (categorical: Air Force, Army, Marine Corps, Navy), rank (categorical: Enlisted, Officer, Other/Unknown), and education level (categorical: Less than High School, High School only, Some college, Bachelor's degree, Advanced degree).

Information about each service member's qualifying COVID-19 case will include symptomology of the acute phase of infection (dichotomous: asymptomatic or symptomatic), hospitalization status (dichotomous: hospitalized or not hospitalized), re-infection status (dichotomous: first COVID-19 infection or re-infection), COVID-19 vaccination status at time of COVID-19 case (dichotomous: vaccinated or unvaccinated), the dominant SARS-CoV-2 variant at time of COVID-19 case (categorical: wild-type/ancestral, alpha, delta, omicron), and COVID-19 treatment received during the acute phase of the infection as defined as an event date in the PDTS table within 7 days after the initial COVID-19 case date (see list of drug names in Table 3-4). For each country/region where U.S. servicemembers are located (North America., U.K., Europe, Africa, South America, and Asia), the time period where a SARS-CoV-2 variant was dominant was estimated using months where the proportion of sequenced samples in which the variant was detected in GISAID was approximately 50% or greater[92]. The period for the wild-type/ancestral strain of SARS-CoV-2 is defined as follows: January 2020 through December 2020 for the U.K., January 2020 through February 2021 for Europe (non-U.K.), January 2020 through April 2021 for North America, January 2020 through August 2021 for South America, and January 2020 through June 2021 for Africa

and Asia. The period for the Alpha variant is from December 2020 through May 2021 for the U.K., and from February 2021 or April 2021 for Europe and North America, respectively, to June 2021. The Alpha variant was never the dominant variant in Africa, Asia, or South America. The Delta variant spans the period from May [U.K.]/June [Europe, Africa, & Asia]/July [North America]/August [South America] 2021 through December 2021. And the Omicron variant spans the period from January through December 2022 for all regions. The dominant variant for each servicemember will be determined using the event date for the acute COVID-19 infection and the country/region where the servicemember was located at the time of the infection. For months represented by more than one dominant variant, the mid-point of the month will be used as the cutoff (i.e. December 16$^{th}$, 2020, for the cutoff between wild-type and Alpha variant in the UK). COVID-19 case information will be taken from a combination of the COVID-19 master positive list (hospitalization status, re-infection status, vaccination status, dominant variant) and the PDTS table in DMSS (treatments). Symptomology of the acute phase of the COVID-19 infection will utilize two data sources. First, the REP_EVENTS table in DMSS will be assessed to determine if symptoms were reported. Second, the INPT_ICD10 and OUTPT_ICD10 tables in DMSS will be assessed to determine if the ADSM had a CLI diagnosis in the period from 10 days prior to 10 days after the date of the positive SARS-CoV-2 PCR test or antigen test or COVID-19 reportable medical event onset date. A CLI diagnosis is defined as having one or more inpatient or outpatient encounter with a CLI ICD-10 diagnosis code in any diagnostic position. The list of ICD-10 codes used in the CLI definition are included in Table 3-5. An ADSM will be

considered to have a symptomatic acute COVID-19 infection if they meet either of the two criteria listed above.

Information on known COVID-19 risk factors will include obesity (dichotomous: yes or no) and current smoking status (dichotomous: yes or no). In addition, the presence of individual comorbidities (hypertension, any cardiovascular disease including stroke, chronic lower respiratory disease, asthma, lung disease, metabolic disease, immunocompromising conditions including HIV, substance use disorders, chronic liver disease, chronic kidney disease, chronic neurologic disorders, and cancer) will be assessed as dichotomous variables (yes or no). Comorbidity and risk factor information will come from the DEMOG_MEPS table in DMSS (obesity), the PHA table in DMSS (smoking status), and the INPT and OUTPT tables in DMSS (comorbidities). The presence of any individual comorbidity will be defined as having one or more inpatient encounter or two or more outpatient encounters for that comorbidity category within one year prior to the COVID-19 case. A list of comorbidities and associated ICD-10 diagnosis codes is provided in Table 3-6. In addition to individual comorbidities, the presence of any of the comorbidity categories in Table 3-6 will also be assessed as a dichotomous (yes or no) variable.

Five-year age categories were selected to align with existing DoD categorizations, while education levels were taken from DMSS and not collapsed into larger categories. For demographic risk factors, reference groups were selected according to alphabetical order unless there is a specific order to the categories, as is the case for age and education level. For COVID-19 event-based risk factors, the reference group was chosen either as the least severe group (i.e. asymptomatic, not hospitalized), the group with no intervention

(i.e. no treatment, no vaccination), or using the earliest time group (i.e. COVID-19 variant wave). For comorbidities, the group without the specified comorbidity was chosen as the reference group.

3.2.1.2.2 Outcome of Interest

The primary outcome of interest for Study 1 is the incidence of long COVID. Incident long COVID will be defined using the PASC V4 definition outlined in section 3.1.2. Prior history of a defining diagnosis of a mental health, neurological, cardiac, or respiratory event will be assessed using the INPT and OUTPT tables in DMSS for each diagnosis description in Table 3. Incidence of each diagnostic description will be assessed individually, then aggregated to determine incidence of each diagnostic group and any long COVID symptoms. In addition to the primary outcome of incident long COVID, the incidence of each diagnostic group and diagnosis description in Table 3-3 will be evaluated as secondary outcomes.

3.2.1.3 Statistical Methods

Descriptive statistics for each exposure and outcome variable in Study 1 will be presented. Means and standard deviations will be presented for all continuous variables, and the normality of all continuous variables will be assessed using the Kolmogorov-Smirnov test for normality and by visualizing QQ plots and assessing skewness and kurtosis. Frequencies and percentages will be presented for all categorical variables.

Active component service members are only required to visit a provider once annually for a periodic health assessment that includes a dental examination, screening for cardiovascular disease risk factors, and immunizations[93]. With no requirement to visit a

provider on a regular interval, there could be differences in healthcare-seeking behaviors that impact a service member's likelihood of being diagnosed with long COVID during the study period. To account for differences in healthcare-seeking behaviors, the number of medical encounters during the study period will be included as a potential confounding variable in all analyses.

Aim 1 will utilize Poisson regression to assess whether the crude risk of incident long COVID (any diagnostic group) is increased within each of the exposure variables listed in 3.2.1.2.1, as well as the number of medical encounters during the study period. An offset of the log of the follow-up time will be used in the model to account for differences in follow-up times for each group. The amount of person-time accrued for each ADSM will be calculated as the length of time (in days) between the date of the incidence COVID-19 case and either the date of the incident long COVID diagnosis or the end of the study period, whichever comes first. The crude relative risks (RRs), 95% confidence intervals (CIs), and p-values will be presented for each variable. Subsequent Poisson regression will be performed using all the exposure variables listed in 3.2.1.2.1 as well as the number of medical encounters during the study period (if significant) as predictors and incident long COVID as the outcome. The overall significance of the model, as well as the adjusted RRs, 95% CIs, and p-values will be presented for each variable. In addition to the overall incidence of long COVID in any diagnostic group, the incidence of each diagnostic group and diagnosis description in Table 3-3 will also be assessed using Poisson regression. All statistical analyses will be conducted using R (version 4.1, The R Foundation for Statistical Computing, Vienna, Austria), and an alpha ($\alpha$) level of 0.05 will be considered statistically significant.

### 3.2.2 Methods for Aim 2

*Aim 2: To determine whether the incidence of long COVID in the Active Component US military differs by vaccination status prior to infection and time since last vaccine dose.*

#### 3.2.2.1 Study Population

The study population for Aim 2 will remain the same as Aim 1 and will include all active component service members with a confirmed case of COVID-19 in the COVID-19 master positive list with event dates between January 1, 2020 and December 31, 2022. Any service members not in the active component at the time of their COVID-19 event date will be excluded from the analyses.

#### 3.2.2.2 Definition and Measurement of Key Variables

##### 3.2.2.2.1 Exposures of Interest

As study 2 is focusing on the risk of long COVID by vaccination status, exposures of interest will include information about each service member's COVID-19 vaccination status, including COVID-19 vaccination status at the time of the COVID-19 case (categorical: unvaccinated, partially or fully vaccinated, one or more booster doses), the type of COVID-19 vaccine received for the initial vaccine series (categorical: no vaccine, any vaccine), the type of COVID-19 vaccine received for the most recent vaccine (categorical: no vaccine, mRNA vaccine, other vaccine type), and the number of days between the last vaccine dose received and the date of the COVID-19 case (categorical: unvaccinated, <3 months, 3-6 months, >6 months). COVID-19 vaccination information will be taken from the COVID-19 Master Positive List.

For the COVID-19 vaccine exposures, the reference group was chosen as the group with no intervention (i.e. no vaccination/unvaccinated). Categories for both the COVID-19 vaccination status and the COVID-19 vaccine received were chosen based on sample size in each category. Partially and fully vaccinated were combined due to smaller numbers of partially vaccinated servicemembers and because both were related to the initial COVID-19 vaccine series. Due to small numbers of service members with more than one booster doses, all booster doses were combined into one category. Similarly, no servicemembers received a non-mRNA vaccine for the initial vaccine series, while only a small number received a non-mRNA vaccine for the most recent series. Therefore, only mRNA was considered for initial vaccine series and any other vaccine types were combined for the most recent series.

3.2.2.2.2 Outcome of Interest

The primary outcome of interest for Study 2 is the incidence of long COVID, as outlined in Aim 1, and the number of days between the date of the COVID-19 case and the onset date of long COVID. Prior history of each diagnostic group within the previous one year will be noted to determine baseline status for each group.

3.2.2.3 Statistical Methods

Descriptive statistics for each vaccination exposure will be presented, including frequencies and percentages for categorical variables and means and standard deviations for continuous variables. Aim 2 will utilize Cox proportional hazards regression to assess whether the risk of long COVID (any diagnostic group) is increased within each of the exposure variables listed in 3.2.2.2.1. The crude hazard ratios (HRs), 95% confidence

intervals (CIs), and p-values will be presented for each variable. Subsequent Cox proportional hazards regression will be performed separately for each of the exposure variables listed in 3.2.2.2.1 as predictors, as well as all significant predictors identified in Aim 1, and incident long COVID as the outcome. In addition, the length of time between the most recent vaccine dose received and the date of the COVID-19 case will be assessed as a possible effect modifier by including an interaction term between the variable and the other predictors in the model. The overall significance of the model, as well as the adjusted HRs, 95% CIs, p-values, and the presence of any effect modification will be presented for each variable. Each exposure variable will be assessed on whether it meets the proportional hazards assumption using the "cox.zph" function from the "survival" package in R. If a variable violates the proportional hazards assumption, a step function will be included to calculate different $\beta(t)$ coefficients for each specified time period using the "survSplit" function from the "survival" package. In addition to the overall incidence of long COVID in any diagnostic group, the incidence of each diagnostic group and diagnosis description in Table 3-3 will also be assessed using Cox proportional hazards regression, with adjustments made for baseline status for that specific diagnostic group. All statistical analyses will be conducted using R (version 4.1, The R Foundation for Statistical Computing, Vienna, Austria), and an alpha ($\alpha$) level of 0.05 will be considered statistically significant.

### 3.2.3 Methods for Aim 3

*Aim 3: To develop a forecasting model of long COVID incidence in the Active Component U.S. military.*

#### 3.2.3.1 Study Population

The study population for Aim 3 will include all current active component service members in the U.S. military assigned to a DoD installation within the United States.

#### 3.2.3.2 Definition and Measurement of Key Variables

##### 3.2.3.2.1 Exposures of Interest

As aim 3 is focusing on the development of a predictive time series model of long COVID incidence in the US military, input data will include time series data of confirmed COVID-19 infections, COVID-like-illness (CLI) outpatient encounters (using CLI definition from Table 3-5), and outpatient encounters with a COVID-19 ICD-10 code (Table 3-7) in active component service members. Monthly aggregated COVID-19 cases and encounters (CLI and COVID-19) will be taken from the COVID-19 Master Positive List and ESSENCE, respectively. In addition, monthly aggregated encounters coded as Post COVID-19 Condition (ICD-10 code U09.9) will be taken from ESSENCE. The number of monthly cases and encounters will be calculated. In addition, the monthly number of cases by COVID-19 vaccination status (categorical: unvaccinated, vaccinated) will be calculated. Information about key risk factors identified in Aim 1 will also be calculated by month to be used in the models. Each time series dataset (COVID-19 cases, CLI encounters, COVID-19 encounters, cases by COVID-19 vaccination status, and demographics) will be merged by month to generate a master dataset of time series information.

##### 3.2.3.2.2 Outcome of Interest

The primary outcome of interest for Aim 3 is the predicted number of monthly incident long COVID diagnoses 1- through 6-months ahead of the current month. Predictions will

be generated monthly using current data for a period of 6 months. A secondary outcome, the predicted number of incident long COVID diagnoses for the entire 6-month testing period, will be generated at the beginning of the period.

3.2.3.3 Statistical Methods

Aim 3 will utilize time series and machine learning forecasting models to predict the number of incident long COVID diagnoses. Common time series models used for the prediction of COVID-19 and influenza will be used to generate monthly 1- through 6-month ahead forecasts, including Autoregressive Integrated Moving Average (ARIMA), Vector Autoregressive (VAR), and Neueral Network (NNET) models. An ensemble model calculated as the mean forecasted value across the 3 models will also be generated. Forecasts will be generated as a point forecast for each monthly target as well as a quantile representation of a probability distribution in accordance with guidelines used by the Centers for Disease Control and Prevention (CDC) in other COVID-19 forecasting collaborations[94]. Quantile forecasts will be generated for 23 levels (0.01, 0.025, 0.05, 0.10, 0.15, 0.20, 0.25, 0.30, 0.35, 0.40, 0.45, 0.50, 0.55, 0.60, 0.65, 0.70, 0.75, 0.80, 0.85, 0.90, 0.95, 0.975, 0.99). Weighted interval score (WIS), a measure of distributional accuracy used in respiratory disease forecasting will be used in this study[95]. Lower WIS indicate more accurate forecasts. Additionally, mean absolute percent error (MAPE) will also be used. Each individual time series model listed above will be calibrated on a training dataset of time series data from January 1, 2020 through June 30, 2022 using the various inputs listed in 3.2.3.2.1, and the models producing the lowest combination of AIC, Sigma$^2$, Root Mean Squared Error (RMSE), and MAPE will be used on the prediction dataset of time series data from July 1, 2022 through December 31, 2022.

Monthly forecasts will be scored by comparing the distribution of forecasted values with the true number of long COVID diagnoses in that month. Multiple baseline models will be established. The first will be a seasonal Naïve model estimated using the approximate percent of COVID-19 cases that develop long COVID and the average length of time to diagnosis from Aim1. The second will be calculated by first estimating the number of expected long COVID diagnoses for each month by multiplying the overall proportion of COVID-19 cases being diagnosed with long COVID in Aim 1 by the number of COVID-19 cases that month, and then estimating the month of subsequent long COVID diagnosis and number of total diagnoses using the appropriate distribution around the average duration between incident COVID-19 infection and long COVID diagnosis identified in Aim 1. Each of the models listed above (ARIMA, VAR, NNET, Ensemble) will be compared to the baseline models to determine their relative accuracy. All statistical analyses will be conducted using R software (version 4.1, The R Foundation for Statistical Computing, Vienna, Austria), and an alpha (α) level of 0.05 will be considered statistically significant. The R packages “fable” and “tidymodels” will be used to generate forecasts, and the “evalcast” package will be used to calculate the WIS.

**Table 3-1. DMSS Tables and Associated Variables**

| Variable | Description | Type |
|---|---|---|
| DEMOG Table | | |
| Age | Age | Continuous |
| DOD_POC | Primary occupation code | Categorical |
| ED_Level | Education Level | Categorical |
| Grade | Pay grade | Categorical |
| Mar_stat | Marital status code | Categorical |
| Sex | Sex | Categorical |
| Race_ethnicity | Race/ethnicity category | Categorical |
| Unit_Country | Duty location country code | Categorical |
| Unit_Zip | Duty location ZIP code | Continuous |
| Service | Service | Categorical |
| MEPS_DEMOG Table | | |
| Height | Height | Continuous |
| Weight | Weight | Continuous |
| INPT/INPT_ICD10 Tables | | |
| D_event | Date of admission | Date |
| D_disp | Date of disposition | Date |
| DISPTYPE | Type of disposition | Categorical |
| DMISID | Treatment facility code | Categorical |
| DX1-DX9 | Diagnosis codes | Categorical |
| PR01-PR20 | Procedure codes | Categorical |
| OUTPT/OUTPT_ICD10 Tables | | |
| D_event | Date of admission | Date |
| DISPCODE | Type of disposition | Categorical |
| DMISID | Treatment facility code | Categorical |
| DX1-DX4 | Diagnosis codes | Categorical |
| CPT1-CPT4 | Procedure codes | Categorical |
| REP_EVENTS Table | | |
| D_event | Event date | Date |
| CHEM/MICRO Table | | |
| Test_Name | Test type | Categorical |
| Test_Results | Test result | Categorical |
| Specimen_Source | Specimen source | Categorical |
| PDTS Table | | |
| D_event | Date of encounter | Date |
| Drug_Name | Prescription drug name | Categorical |
| Drug_Strength | Drug dosage | Categorical |
| Quantity | Metric quantity of drug | Categorical |
| Days_Supply | Number of days supply of drug dispensed | Categorical |
| PHA Table | | |
| D_event | Date of encounter | Date |
| TOB_Cigs | Used once in last 30 days: Cigarettes | Dichotomous |
| TOB_Long | How long have you been using tobacco products? | Categorical |
| TOB_Past | Past use of tobacco? | Dichotomous |
| RR_Height | Height in inches | Continuous |
| RR_Weight | Weight in pounds | Continuous |

**Table 3-2. AFHSD COVID-19 Variables**

| Variable | Description | Type |
|---|---|---|
| Master Positive List | | |
| D_event_C19 | Date of COVID-19 event | Date |
| Case_status | Case status | Categorical |
| DMISID | Treatment facility code | Categorical |
| Installation_name | Name of treatment facility installation | Text |
| CCMD | Combatant command | Categorical |
| Country_name | Country name | Text |
| Facility_country_code | Treatment facility country code | Categorical |
| Facility_state_code | Treatment facility state code | Categorical |
| Service | Service | Categorical |
| Hosp_Overall | Hospitalization status | Dichotomous |
| Age | Age | Continuous |
| Sex | Sex | Categorical |
| Repeat_90 | Repeat infection over previous 90 days | Dichotomous |
| First_Case | Is this the patient's first case? | Dichotomous |
| Vaccinated_DRSi | COVID-19 vaccination category (DRSi) | Categorical |
| Vaccine_Date_DRSi | Full Vaccination Date (DRSi) | Date |
| ADMIT_DT | Date of hospital admission (DRSi) | Date |
| ADMISSION_DT | Date of hospital admission (J5) | Date |
| INPT_D_EVENT | Date of hospital admission (DMSS) | Date |
| DISCHARGE_DT | Date of hospital discharge (DRSi) | Date |
| D_DISP | Date of hospital discharge (DMSS) | Date |
| DISP_DT | Date of hospital discharge (J5) | Date |
| Full_Date | Date when fully vaccinated | Date |
| Booster_imm[1-4] | Booster dose received | Categorical |
| Booster_date[1-4] | Date when booster dose received | Date |
| Partial_imm | Partial immunization dose received | Categorical |
| Partial_date | Date when partially vaccinated | Date |
| Full_imm | Full immunization dose received | Categorical |

**Table 3-3. PASC Diagnostic Categories and ICD-10 Diagnosis**

| Diagnostic Group | Diagnosis Description | ICD10 Codes |
|---|---|---|
| Mental Health | Anxiety | F4323, F419, F411, F418, F4322 |
| | Insomnia | G4700, F51 |
| | PTSD | F4312 |
| | Major Depression | F321, F329, F331, F332, F339, R45851 |
| Neurological | Headache | R51 |
| | Taste Loss | R430, R431, R432, R438, R439 |
| | Seizure | R5600, R5601, R569, G40001, G40009, G40011, G40019, G40101, G40109, G40111, G40119, G40201, G40209, G40211, G40219, G40301, G40309, G40311, G40319, G40401, G40409, G40411, G40419, G40501, G40509, G40801, G40802, G40803, G40804, G40811, G40812, G40813, G40814, G40821, G40822, G40823, G40824, G4089, G40901, G40909, G40911, G40919, G40A01, G40A09, G40A11, G40A19, G40B01, G40B09, G40B11, G40B19 |
| | Blurred Vision | H53 |
| | Fatigue | R53 |
| | Memory Loss | R413 |
| | Cognitive Dysfunction | R410, R411, R412 |
| | Vertigo | H8110, H8111, H8112, H8113, H8141, H8142, H8143, H8149 |
| Respiratory | Cough | R05 |
| | Short of Breath | R0602, R0600, R0609 |
| | Pulmonary Embolism | I2699 |
| | Asthma | J45909, J4520, J45901, J4530, R062 |

| Diagnostic Group | Diagnosis Description | ICD10 Codes |
|---|---|---|
| Cardiac | Chest Pain | R079, R0789, R072 |
| | Palpitations | R002 |
| | Atrial Fibrillation | I4891, I480 |
| | Syncope | R55 |
| | Tachycardia | R000 |
| | Heart Failure | I509, I517 |
| | Bradycardia | R001 |
| | Myocardial Infarction | I21, I22 |
| | Cerebral infarction/Stroke | I63 |
| | Post Exertional Malaise | T733 |
| | Myocarditis | I40, I41, I514, B3322 |
| | Pericarditis | I30, I32, B3323 |

**Table 3-4. COVID-19 Treatment Names**

| Treatment | Category | Drug Name |
|---|---|---|
| Nirmatrelvir/Ritonavir | Antiviral | Paxlovid |
| Remdesivir | Antiviral | Veklury |
| Molnupiravir | Antiviral | Lagevrio |
| Tocilizumab | Immune Modulator | Actemra |
| Baricitinib | Immune Modulator | Olumiant |
| Anakinra | Immune Modulator | Kineret |
| Sotrovimab | Monoclonal Antibodies | Sotrovimab |
| Bamlanivimab/Etesevimab | Monoclonal Antibodies | Bamlanivimab and Etesevimab |
| Bebtelovimab | Monoclonal Antibodies | Bebtelovimab |

**Table 3-5. ESSENCE COVID-Like Illness (CLI) Definition**

| Diagnosis Description | ICD-10 Codes |
|---|---|
| Coronavirus, unspecified | B34.2 |
| SARS-associated coronavirus as the cause of disease classified elsewhere | B97.21 |
| Other coronavirus as the cause of disease classified elsewhere | B97.29 |
| Acute nasopharyngitis; common cold | J00 |
| Acute upper respiratory infection, unspecified | J06.9 |
| Pneumonia due to SARS-associated coronavirus | J12.81 |
| Other viral pneumonia | J12.89 |
| Viral pneumonia unspecified | J16.8 |
| Pneumonia in diseases classified elsewhere | J17 |
| Bronchopneumonia, unspecified organism | J18.0 |
| Lobar pneumonia, unspecified organism | J18.1 |
| Other pneumonia, unspecified organism | J18.8 |
| Pneumonia, unspecified organism | J18.9 |
| Acute bronchitis due to other specified organisms | J20.8 |
| Acute bronchitis, unspecified | J20.9 |
| Unspecified acute lower respiratory infection | J22 |
| Bronchitis, not specified as acute or chronic | J40 |
| Acute respiratory distress syndrome | J80 |
| Idiopathic interstitial pneumonia not otherwise specified | J84.111 |
| Cough | R05 |
| Dyspnea | R06.0 |
| Dyspnea, unspecified | R06.00 |
| Shortness of breath | R06.02 |
| Acute respiratory distress | R06.03 |
| Other forms of dyspnea | R06.09 |
| Anosmia | R43.0 |
| Ageusia | R43.2 |
| Fever, unspecified | R50.9 |
| 2019-nCoV acute respiratory disease, COVID-19, virus identified | U07.1 |

**Table 3-6. Comorbidity Categories and ICD-10 Diagnosis**

| Diagnosis Description | ICD-10 Codes |
|---|---|
| Hypertension | I10*-I16*, O10*-O16* |
| Any cardiovascular disease | I05*-I89*, Z95* |
| Chronic lower respiratory disease | J40*-J44* |
| Asthma | J45* |
| Any lung disease | J40*-J99* |
| Metabolic disease | E08*-E13*, O24*, Z794*, E00*-E07*, E50*-E64*, E88.81 |
| Immune compromising conditions | B20, D55*-D77*, D80*-D89*, Z94*, Z795*, L40*, M04*-M08*, K50*-K52* |
| Substance use disorders (including nicotine dependence) | F10*-F16*, F18*-F19*, F17* |
| Chronic liver disease | K70*-K77*, B18* |
| Chronic kidney disease | N03*-N16*, N18*-N19* |
| Chronic neurologic disorders | G10*-G40* |
| Neoplasms | C00*-D49* |
| Obesity or overweight | E66.0*, E66.1, E66.2, E66.3, E66.8, E66.9, Z68.3*, Z68.4*, Z68.25- Z68.29 |
| HIV** | B20* |
| * Indicates all underlying ICD-10 codes are included<br>**HIV is also included as part of the Immune Compromising Conditions category | |

**Table 3-7. ESSENCE COVID-19 Specific Definition**

| Diagnosis Description | ICD-10 Codes |
|---|---|
| 2019-nCoV acute respiratory disease, COVID-19, virus identified | U07.1 |
| Pneumonia due to coronavirus disease 2019 | J12.82 |

## CHAPTER 4: Manuscript 1

Risk Factors for Long COVID in the Active Component U.S. Military, 2020-2022

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***Disclaimer***

*The views expressed in this manuscript are those of the author and do not necessarily reflect the official policy or position of the Defense Health Agency, Department of Defense, nor the U.S. Government.*

### 4.1 Abstract

**Background:** Long COVID risk factors have been established in civilian populations, including female sex, older age, smoking, and certain comorbidities. However, little research has been conducted on risk in the U.S. military.

**Objective:** To identify the rate of and risk factors for long COVID in the U.S. military.

**Design:** Retrospective cohort study

**Setting:** Military Health System

**Patients:** 464,356 active component U.S. servicemembers with confirmed COVID-19 between January 1, 2020, and December 31, 2022.

**Measurement:** Incidence of long COVID was measured and demographic, COVID-19 infection, and comorbidity characteristics were assessed as risk factors using Poisson regression.

**Results:** 104,024 servicemembers developed long COVID (70.4 cases per 100,000 person-days of follow-up). Male sex (CIR, 0.72; 95% CI, 0.71 to 0.73), age ≥45 (CIR, 1.45; 95% CI, 1.39 to 1.52), non-Hispanic Black race (CIR, 1.11; 95% CI, 1.08 to 1.15), symptomatic COVID-19 infection (CIR, 1.04; 95% CI, 1.03 to 1.06), COVID-19 hospitalization (CIR, 1.25; 95% CI, 1.18 to 1.31), COVID-19 re-infection (CIR, 1.11; 95% CI, 1.08 to 1.13), vaccination against COVID-19 (CIR, 0.95; 95% CI, 0.93 to 0.98), antiviral treatment for COVID-19 (CIR, 0.82; 95% CI, 0.72 to 0.93), and any comorbidity (CIR, 1.22; 95% CI, 1.19 to 1.25) were significantly associated with incidence of long COVID.

**Limitation:** Risk factors were assessed only through 2022, precluding investigation into more recent treatments, vaccines, and variants.

**Conclusions:** Despite a younger and healthier population, incidence of long COVID was high in U.S. servicemembers. Similar risk factors were observed compared to the general population, including female sex, increased age, comorbidities, and being unvaccinated against COVID-19. Additionally, characteristics of the infection, such as reinfection, symptoms, and hospitalization were associated with long COVID.

### 4.2 Introduction

In December 2019, COVID-19 emerged in China, spreading globally by March 2020[1–3]. COVID-19 has resulted in over 775 million cases and 7 million deaths as of July 2025[7]. The virus evolution has occurred, leading to new surges and variants. Soon after COVID-19 emerged, symptoms lingering more than four weeks post infection were seen and were dubbed "long COVID." Prevalence of long COVID has been estimated to be between 10% and 60% up to 6 months after initial infection, with one study finding prevalence as high as 85% within 1 year in a population of previously hospitalized patients[29–34]. Symptoms could be mild, including fatigue, brain fog, joint pain, dyspnoea, anxiety, and weakness; or more severe like depression, stroke, and dementia[29–34]. Surveillance has been challenging due to heterogeneous case definitions, lack of an agreed-upon diagnostic approach, and highly varied symptoms[35,36].

Long COVID, also called "post-COVID conditions" and "post-acute sequelae of COVID-19", has been defined by multiple organizations, including the U.S. Centers for Disease Control and Prevention, World Health Organization, and the National Academies for Science, Engineering, and Math to include a range of symptoms beginning 4 weeks to

3 months after a COVID-19 infection and persisting for at least 2 months or up to 12 months after the COVID-19 infection[35,36,96]. Risk factors for long COVID include increased age, female sex, smoking, obesity, and at least one comorbidity[38,39]. The risk of long COVID has been shown to be lower during recent variant waves, including Omicron[39]. No treatments have been approved to treat long COVID. Recent studies have had discordant findings regarding the efficacy of the antiviral nirmatrelvir/ritonavir for preventing long COVID[41,79,97]. Research has shown that COVID-19 vaccinations are associated with a reduced risk of long COVID, especially in people vaccinated prior to infection[43–46].

To date, little research has been conducted to estimate the incidence of long COVID or its risk factors in the U.S. active component military, though one recent study reported long COVID symptoms in approximately 25% of a cohort of U.S. Marines[98]. This population differs from the general public, leaning younger, predominantly male, more likely to identify as Black or African American, and less likely to have a college degree[83,84]. Active component servicemembers are also provided health insurance free of charge through the U.S. military's TRICARE program[85]. This study aims to address that gap by identifying the incidence of long COVID and risk factors in a large cohort of COVID-19 cases in the active component U.S. military with linked medical records, vaccination records, and demographic information.

### 4.3 Methods

The study protocol was approved by both the George Washington University Committee on Human Research, Institutional Review Board and the Component Office for Human Research Protections, Defense Health Agency Office of Research Protections in

compliance with all applicable Federal regulations governing the protection of human and animal subjects.

4.3.1 Study Population:

The study population included active component service members, which includes full time active duty servicemembers but excludes members of the reserves and National Guard, with a confirmed case of COVID-19, defined as either a positive SARS-CoV-2 polymerase chain reaction (PCR) or antigen test or a confirmed COVID-19 reportable medical event (RME) in the Disease Reporting System Internet, between January 1, 2020, and December 31, 2022, using a master list of cases maintained by the Armed Forces Health Surveillance Division.

4.3.2 Risk Factors:

Risk factor information was taken from the Defense Medical Surveillance System (DMSS), a large relational database of health information collected on all DoD service members[91]. Demographic risk factors included age, sex, race/ethnicity, branch of service, military rank, and education level. Risk factors of the COVID-19 acute phase included symptomology, hospitalization, re-infection, vaccination, dominant SARS-CoV-2 variant at time and location of the COVID-19 event[92], and COVID-19 treatment (within 7 days after the initial COVID-19 event date). Symptomology was determined if the servicemember had a COVID-like illness (CLI) diagnosis in an inpatient or outpatient setting in any diagnostic position within 10 days prior to or after the date of the COVID-19 infection. The list of ICD-10 codes used in the CLI definition is included in Supplemental Table 4-2.

Information on known COVID-19 risk factors included obesity, current smoking status, and individual comorbidities. Comorbidity and risk factor information were taken from demographic, health assessment, and health encounter tables in DMSS. A list of individual comorbidities and associated ICD-10 diagnosis codes is provided in Supplemental Table 4-3.

4.3.3 Case Definition:

Long COVID was assessed using the Defense Centers for Public Health- Portsmouth (DCPH-P), EpiData Center Post-Acute Sequelae of COVID-19 (PASC) definition version 4 (updated May 2022). The definition has three requirements:

1) A positive SARS-CoV-2 PCR or antigen test or a confirmed COVID-19 RME
2) Any of the ICD-10 codes for the Mental Health, Neurological, Cardiac, or Respiratory diagnostic groups (Table S1) in any diagnostic position between 4 and 52 weeks after the event in criteria 1
3) No previous history of the diagnosis description from criteria 2 in any diagnostic position within one year prior to the event in criteria 1. **Note:** Only the prior history of the exact diagnosis description will exclude a patient. For example, prior history of seizure will act as an exclusion factor only for seizure related codes.

Incidence of and prior history of each diagnosis description were assessed using health encounter tables in DMSS. The incidence of each diagnosis description was assessed individually, then aggregated to determine incidence of each diagnostic group and any long COVID symptoms. In addition to the primary outcome of incident long COVID, the

incidence of each diagnostic group and diagnosis description in Supplemental Table 4-1 were evaluated as secondary outcomes.

4.3.4 Analyses:

Descriptive statistics for each risk factor are presented, including means and standard deviations for all continuous variables and frequencies and percentages for all categorical variables. Multivariate Poisson regression was utilized to assess whether the number of incident long COVID cases (any diagnostic group) is increased within each of the risk factors described above, as well as the number of medical encounters during the study period. An offset of the log of the follow-up time was used in the model to account for differences in follow-up times for each group. The amount of person-time accrued for each active duty servicemember (ADSM) was calculated as the length of time (in days) between the incident COVID-19 case and either the incident long COVID diagnosis or the end of the follow-up period, whichever came first. Service members are only required to visit a provider annually for a periodic health assessment, which may lead to differences in healthcare-seeking behavior[93]. To account for these differences, the number of medical encounters during the study period was included as a potential confounding variable in all analyses. The adjusted incident rate ratios [IRRs], 95% confidence intervals [CIs], and p-values are presented for each variable. In addition to the overall incidence of long COVID in any diagnostic group, the incidence of each diagnostic group and diagnosis description was also assessed using Poisson regression. All statistical analyses were conducted using R (version 4.1, The R Foundation for Statistical Computing, Vienna, Austria), and an alpha (α) level of 0.05 was considered statistically significant.

### 4.4 Results

Between 2020 and 2022, 464,356 cases of COVID-19 met the eligibility criteria for inclusion in the study, yielding 104,024 (22.4%) incident case of long COVID. Characteristics of long COVID cases and non-cases are shown in Table 1. Compared to non-cases, a higher proportion of long COVID cases were female (29.9% vs 18.3%), over 35 years of age (25.1% vs 18.2%), non-Hispanic Black (21.0% vs 16.5%), members of the Army (41.6% vs 38.6%), and have attended at least some college (34.4% vs 31.6%), and a lower proportion were non-Hispanic White (47.6% vs 51.3%), members of the Marines (9.1% vs 12.6%), and officer rank (12.2% vs 14.9%). A larger proportion of long COVID cases were also symptomatic (55.5% vs 50.8%), hospitalized due to COVID-19 (1.4% vs 0.5%), and a repeat case during the acute phase (8.5% vs 7.0%). Additionally, the presence of any comorbidity was higher in long COVID cases compared to non-cases (36.2% vs 27.0%), with obesity, hypertension, any cardiovascular disease, asthma, metabolic disease, immune compromising conditions, and substance use disorders having higher prevalence in long COVID cases than in non-cases (Table S5). No major difference between cases and non-cases was seen for COVID-19 vaccination status, COVID-19 wave, and COVID-19 treatment.

**Table 4-2** shows the incidence rate of long COVID by risk factor, as well as the crude and adjusted incidence rate ratios. The rate of long COVID in the study population was 70.4 per 100,000 person-days at risk. Service members who were male sex (aIRR, 0.72; 95% CI, 0.71 to 0.73), were members of the Coast Guard (aIRR vs Air Force, 0.85; 95% CI, 0.79 to 0.91, members of the Marines (aIRR vs Air Force, 0.77; 95% CI, 0.75 to 0.79), officer rank (aIRR, 0.78; 95% CI, 0.76 to 0.80), had increased levels of education

[some college (aIRR vs. less than high school, 0.81; 95% CI, 0.68 to 0.98), Bachelor's degree (aIRR, 0.78; 95% CI, 0.65 to 0.94), and advanced degree (aIRR, 0.77; 95% CI, 0.65 to 0.93)], were vaccinated for COVID-19 (aIRR, 0.95; 95% CI, 0.93 to 0.98), and received COVID-19 antiviral treatment (aIRR vs. no treatment, 0.82; 95% CI, 0.72 to 0.93) had significantly reduced rates of long COVID after adjusting for all other potential risk factors. Servicemembers with increased age [30-34 (aIRR vs. less than 20, 1.08; 95% CI, 1.05 to 1.12), 35-39 (aIRR, 1.28; 95% CI, 1.24 to 1.32), 40-44 (aIRR, 1.44; 95% CI, 1.38 to 1.49), and 45+ (aIRR, 1.45; 95% CI, 1.39 to 1.52)], who identified as non-Hispanic Black (aIRR vs. Asian, 1.11; 95% CI, 1.08 to 1.15) or unknown race (aIRR vs Asian, 1.10; 95% CI, 1.04 to 1.17), had a symptomatic COVID-19 infection (aIRR, 1.04; 95% CI, 1.03 to 1.06), were hospitalized due to COVID-19 (aIRR, 1.25; 95% CI, 1.18 to 1.31), had a COVID-19 re-infection (aIRR, 1.11; 95% CI, 1.08 to 1.13), were infected during the Delta (aIRR vs. wild-type, 1.06; 95% CI, 1.03 to 1.08) and Omicron (aIRR, 1.05; 95% CI, 1.02 to 1.08) waves, and had any comorbidity (aIRR, 1.22; 95% CI, 1.19 to 1.25) had significantly increased rates of long COVID in the adjusted analyses.

**Table 4-3** shows the incidence rate of each long COVID diagnostic group by risk factor. Mental health had the highest incidence rate (39.6 per 100,000 person-days), followed by cardiac (21.9), respiratory (15.4), and neurological (3.9). Results were similar to those identified in **Table 4-2**, however notable differences between the diagnostic group results and the overall long COVID results were observed. Those hospitalized for COVID-19 had lower rates of mental health diagnoses than those who were not hospitalized (aIRR, 0.90; 95% CI, 0.84 to 0.96), while modestly higher rates of the mental health diagnoses were seen among those who were vaccinated for COVID-19 (aIRR, 1.05; 95% CI, 1.01 to

1.08). Lower rates of neurological diagnoses were seen after the wild-type wave, including during the Alpha (aIRR vs. wild-type, 0.69; 95% CI, 0.58 to 0.82), Delta (aIRR, 0.69; 95% CI, 0.63 to 0.77), and Omicron (aIRR, 0.64; 95% CI, 0.57 to 0.71) waves. Lastly, rates of cardiac diagnoses were lower in the 20-24 (aIRR vs. less than 20, 0.95; 95% CI, 0.91 to 0.99) and 25-29 (aIRR, 0.93; 95% CI, 0.88 to 0.97) age groups, but higher in older age groups.

### 4.5 Discussion

Despite a younger and healthier population, active component servicemembers had a high incidence of long COVID, particularly mental health symptoms. Among >450,000 individuals diagnosed with COVID-19 from 2020-22, more than 22% developed symptoms of long COVID, well within the range of previous estimates[29–34]. The incidence of mental health symptoms was highest (39.6 per 100,000 person-days of follow-up), while incidence of neurological symptoms was lowest (3.9 per 100,000 person-days). Demographic factors, such as sex, age, and race/ethnicity were significantly associated with incidence of long COVID, as was the presence of any comorbidity and certain factors related to the initial COVID-19 infection (symptomology, hospitalization, re-infection, vaccination, treatment, and variant wave).

The most commonly reported symptoms were anxiety, chest pain, insomnia, shortness of breath, major depression, and heart palpitations. Other studies have found similar symptoms, including shortness of breath, chest pain, and loss of smell[33,38]. Previous studies identified increased age, female sex, smoking, obesity, and having at least one comorbidity as risk factors for long COVID, which were similar to the results identified in this study[38,39]. Other studies have also suggested that COVID-19 vaccination prior to a

COVID-19 infection and treatment with COVID-19 antivirals may reduce risk of long COVID, both of which were seen in the current study[41–46]. However, the risk of long COVID was higher after the Omicron wave of infections compared to the wild-type wave, despite previous studies finding lower incidence during Omicron[40].

This study has several strengths. First, it utilizes a large cohort of COVID-19 cases with linked medical records. Second, the long COVID case definition used in this study has been validated by DCPH–P and relies on ICD-10 coded medical encounters. Lastly, this study is the first large-scale effort to quantify long COVID and its risk factors in the U.S. military population. This study has limitations as well. A servicemember could meet the definition for multiple diagnoses or diagnostic groups, making conclusions about risk factors for individual diagnoses difficult. Of the diagnosed cases of long COVID, 79% met only one of the four diagnostic group definitions, while 3.3% met the definition for three or more diagnostic groups. While this makes it more difficult to interpret the results of individual diagnoses, this presents a more "real-world" scenario, in which people frequently have more than one diagnosis. Second, this study relies on previously collected medical encounter data rather than active surveillance of long COVID symptoms. While servicemembers are required to attend a yearly check-up with a provider, they are not required to visit a provider for any symptoms related to long COVID. Third, healthcare utilization may confound the results of this study, though the number of total medical encounters for each servicemember and demographic factors that may be related to healthcare utilization were both controlled for in the analyses. Fourth, the long COVID case definition requires 12 months of follow-up time for each person, so the period for assessment of risk factors is limited to 2020 through 2022. Although we

found a protective association between vaccination and long COVID, several limitations are present. Much of the window for these data occurred prior to availability of COVID-19 vaccines and antiviral treatment, so outcomes associated with vaccination, antiviral treatment, and other prevention and treatment interventions should be interpreted with caution. Given the assessment of those intervention correlates is not as complete as it could be if data from 2023 and later were included, future studies should evaluate data from expanded windows to gain a more comprehensive picture of the relationship between vaccination, antiviral treatment, and long COVID. Lastly, residual confounding may be present due to additional risk factor and outcome information not collected for this study or collapsed into grouped categories. For example, mental health diagnostic groupings contain several outcomes, making interpretation of individual relationships complex and subject to limitations.

This study is an essential first step towards characterizing long COVID in the U.S. military. Risk factors for the development of long COVID in this population were identified and can be used by providers to assess risk for individual patients. The study also highlights that vaccination and treatment may be important tools for reducing risk of long COVID in the DoD population, as is avoiding hospitalization. Future research could explore more recent time periods, which may provide additional insight into the role of new booster doses, treatments, and SARS-CoV-2 variants, as well as additional risk factors.

### 4.6 Acknowledgements

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**Table 4-1. Characteristics of long COVID cases and non-cases, active component service members, 2020-2022**

| Characteristic | Cases | Non-Cases |
|---|---|---|
| | N = 104,024[1] | N = 360,332[1] |
| Sex | | |
| Female | 31,107 (29.9%) | 66,007 (18.3%) |
| Male | 72,917 (70.1%) | 294,325 (81.7%) |
| Age (years) | 29.0 (7.9) | 27.7 (7.2) |
| Age Group | | |
| <20 | 5,879 (5.7%) | 25,347 (7.0%) |
| 20-24 | 32,683 (31.4%) | 124,972 (34.7%) |
| 25-29 | 23,816 (22.9%) | 87,534 (24.3%) |
| 30-34 | 15,548 (14.9%) | 56,962 (15.8%) |
| 35-39 | 14,230 (13.7%) | 38,734 (10.7%) |
| 40-44 | 7,608 (7.3%) | 17,504 (4.9%) |
| 45+ | 4,259 (4.1%) | 9,278 (2.6%) |
| Unknown/Missing | 1 (0.0%) | 1 (0.0%) |
| Race | | |
| Asian | 3,877 (3.7%) | 14,357 (4.0%) |
| Hispanic | 20,478 (19.7%) | 72,726 (20.2%) |
| Non-Hispanic Black | 21,888 (21.0%) | 59,613 (16.5%) |
| Non-Hispanic White | 49,549 (47.6%) | 184,803 (51.3%) |
| Other | 6,522 (6.3%) | 23,634 (6.6%) |
| Unknown | 1,710 (1.6%) | 5,199 (1.4%) |
| Service | | |
| Air Force | 29,121 (28.0%) | 98,098 (27.2%) |
| Army | 43,248 (41.6%) | 139,184 (38.6%) |
| Coast Guard | 838 (0.8%) | 3,711 (1.0%) |
| Marines | 9,511 (9.1%) | 45,376 (12.6%) |
| Navy | 21,306 (20.5%) | 73,963 (20.5%) |
| Rank | | |
| Enlisted | 91,339 (87.8%) | 306,533 (85.1%) |
| Officer | 12,685 (12.2%) | 53,799 (14.9%) |
| Education Level | | |
| Less than High School | 120 (0.1%) | 332 (0.1%) |
| High School | 66,760 (64.2%) | 239,758 (66.5%) |
| Some College | 15,214 (14.6%) | 42,701 (11.9%) |
| Bachelor's Degree | 13,226 (12.7%) | 47,923 (13.3%) |
| Advanced Degree | 7,297 (7.0%) | 23,294 (6.5%) |
| Other/Unknown | 1,407 (1.4%) | 6,324 (1.8%) |
| COVID-19 Symptomology | | |
| Asymptomatic | 46,262 (44.5%) | 177,195 (49.2%) |
| Symptomatic | 57,762 (55.5%) | 183,137 (50.8%) |
| COVID-19 Hospitalization | | |

| Characteristic | Cases | Non-Cases |
|---|---|---|
| Not Hospitalized | 102,555 (98.6%) | 358,423 (99.5%) |
| Hospitalized | 1,469 (1.4%) | 1,909 (0.5%) |
| COVID-19 Re-Infection Status | | |
| First Infection | 95,187 (91.5%) | 335,190 (93.0%) |
| Re-infection | 8,837 (8.5%) | 25,142 (7.0%) |
| COVID-19 Vaccination Status | | |
| Not Vaccinated | 37,166 (35.7%) | 127,265 (35.3%) |
| Vaccinated | 66,858 (64.3%) | 233,067 (64.7%) |
| COVID-19 Wave | | |
| Wild-type | 27,946 (26.9%) | 97,163 (27.0%) |
| Alpha | 2,326 (2.2%) | 7,989 (2.2%) |
| Delta | 17,540 (16.9%) | 59,087 (16.4%) |
| Omicron | 56,212 (54.0%) | 196,093 (54.4%) |
| COVID-19 Treatment | | |
| No Treatment/Unknown | 103,750 (99.7%) | 359,972 (99.9%) |
| Antivirals | 269 (0.3%) | 353 (0.1%) |
| Immune Modulators | 1 (0.0%) | 2 (0.0%) |
| Monoclonal Antibodies | 4 (0.0%) | 5 (0.0%) |
| Comorbidity | | |
| No Comorbidity | 66,417 (63.8%) | 263,081 (73.0%) |
| Has Comorbidity | 37,607 (36.2%) | 97,251 (27.0%) |
| Number of Health Encounters | | |
| 0 | 0 (0.0%) | 5,799 (1.6%) |
| 1 | 135 (0.1%) | 11,547 (3.2%) |
| 2 | 426 (0.4%) | 17,559 (4.9%) |
| 3 | 734 (0.7%) | 21,527 (6.0%) |
| 4 | 1,152 (1.1%) | 23,775 (6.6%) |
| ≥5 | 101,577 (97.6%) | 280,125 (77.7%) |

[1]n (%); Mean (SD)

## Table 4-2. Incidence rate of and factors associated with incident PASC, active component service members, 2020-2022

| Characteristic | Cases | Person-Days | Rate | Crude IRR (95% CI)[1] | Adj IRR (95% CI)[1,2] | p-value |
|---|---|---|---|---|---|---|
| Sex | | | | | | |
| Female | 31,107 | 28,790,234 | 108. | — | — | |
| Male | 72,917 | 119,043,462 | 61.3 | 0.567 (0.559, 0.574) | 0.724 (0.714, 0.734) | <0.001 |
| Age Group | | | | | | |
| <20 | 5,879 | 10,203,204 | 57.6 | — | — | |
| 20-24 | 32,683 | 50,763,305 | 64.4 | 1.117 (1.087, 1.149) | 1.033 (1.004, 1.062) | 0.024 |
| 25-29 | 23,816 | 35,701,641 | 66.7 | 1.158 (1.125, 1.191) | 1.079 (1.048, 1.112) | <0.001 |
| 30-34 | 15,548 | 23,252,008 | 66.9 | 1.161 (1.126, 1.196) | 1.082 (1.048, 1.117) | <0.001 |
| 35-39 | 14,230 | 16,358,295 | 87.0 | 1.510 (1.465, 1.556) | 1.278 (1.236, 1.321) | <0.001 |
| 40-44 | 7,608 | 7,533,137 | 101. | 1.753 (1.694, 1.814) | 1.437 (1.384, 1.492) | <0.001 |
| 45+ | 4,259 | 4,021,499 | 105. | 1.838 (1.767, 1.912) | 1.454 (1.391, 1.520) | <0.001 |
| Unknown/Missing | 1 | 607 | 164. | 2.859 (0.163, 12.58) | 2.605 (0.149, 11.47) | 0.338 |
| Race | | | | | | |
| Asian | 3,877 | 5,851,773 | 66.3 | — | — | |
| Hispanic | 20,478 | 29,787,072 | 68.7 | 1.038 (1.003, 1.074) | 1.028 (0.993, 1.064) | 0.125 |
| Non-Hispanic Black | 21,888 | 25,142,825 | 87.1 | 1.314 (1.270, 1.360) | 1.114 (1.076, 1.153) | <0.001 |
| Non-Hispanic White | 49,549 | 75,247,773 | 65.8 | 0.994 (0.962, 1.027) | 1.010 (0.977, 1.044) | 0.564 |
| Other | 6,522 | 9,649,213 | 67.6 | 1.020 (0.980, 1.062) | 0.995 (0.956, 1.036) | 0.799 |
| Unknown | 1,710 | 2,155,040 | 79.3 | 1.198 (1.131, 1.268) | 1.101 (1.039, 1.166) | 0.001 |
| Service | | | | | | |
| Air Force | 29,121 | 40,380,790 | 72.1 | — | — | |
| Army | 43,248 | 57,512,711 | 75.2 | 1.043 (1.027, 1.058) | 1.013 (0.998, 1.029) | 0.091 |
| Coast Guard | 838 | 1,490,265 | 56.2 | 0.780 (0.727, 0.835) | 0.848 (0.791, 0.908) | <0.001 |
| Marines | 9,511 | 18,097,001 | 52.6 | 0.729 (0.712, 0.746) | 0.767 (0.749, 0.786) | <0.001 |
| Navy | 21,306 | 30,352,929 | 70.2 | 0.973 (0.956, 0.991) | 0.972 (0.954, 0.990) | 0.002 |
| Rank | | | | | | |
| Enlisted | 91,339 | 126,159,301 | 72.4 | — | — | |
| Officer | 12,685 | 21,674,395 | 58.5 | 0.808 (0.793, 0.823) | 0.783 (0.763, 0.804) | <0.001 |
| Education Level | | | | | | |
| Less than High School | 120 | 139,543 | 86.0 | — | — | |
| High School | 66,760 | 98,006,528 | 68.1 | 0.792 (0.666, 0.953) | 0.849 (0.713, 1.021) | 0.073 |
| Some College | 15,214 | 17,938,903 | 84.8 | 0.986 (0.828, 1.187) | 0.813 (0.683, 0.979) | 0.024 |
| Bachelor's Degree | 13,226 | 19,572,123 | 67.6 | 0.786 (0.660, 0.946) | 0.778 (0.653, 0.937) | 0.006 |
| Advanced Degree | 7,297 | 9,635,021 | 75.7 | 0.881 (0.739, 1.061) | 0.772 (0.647, 0.931) | 0.005 |
| Other/Unknown | 1,407 | 2,541,578 | 55.4 | 0.644 (0.537, 0.780) | 0.781 (0.651, 0.947) | 0.010 |
| COVID-19 Symptomology | | | | | | |
| Asymptomatic | 46,262 | 72,133,293 | 64.1 | — | — | |
| Symptomatic | 57,762 | 75,700,403 | 76.3 | 1.190 (1.175, 1.204) | 1.045 (1.031, 1.058) | <0.001 |
| COVID-19 Hospitalization | | | | | | |
| Not Hospitalized | 102,55 | 146,989,330 | 69.8 | — | — | |
| Hospitalized | 1,469 | 844,366 | 174. | 2.494 (2.367, 2.624) | 1.247 (1.182, 1.314) | <0.001 |

| Characteristic | Cases | Person-Days | Rate | Crude IRR (95% CI)[1] | Adj IRR (95% CI)[1,2] | p-value |
|---|---|---|---|---|---|---|
| COVID-19 Re-Infection | | | | | | |
| First Infection | 95,187 | 137,304,248 | 69.3 | — | — | |
| Re-infection | 8,837 | 10,529,448 | 83.9 | 1.211 (1.184, 1.237) | 1.108 (1.084, 1.133) | <0.001 |
| COVID-19 Vaccination Status | | | | | | |
| Not Vaccinated | 37,166 | 52,127,314 | 71.3 | — | — | |
| Vaccinated | 66,858 | 95,706,382 | 69.9 | 0.980 (0.967, 0.992) | 0.954 (0.930, 0.978) | <0.001 |
| COVID-19 Wave | | | | | | |
| Wild-type | 27,946 | 39,836,953 | 70.2 | — | — | |
| Alpha | 2,326 | 3,262,339 | 71.3 | 1.016 (0.974, 1.060) | 1.025 (0.982, 1.070) | 0.252 |
| Delta | 17,540 | 24,238,207 | 72.4 | 1.032 (1.012, 1.051) | 1.057 (1.031, 1.084) | <0.001 |
| Omicron | 56,212 | 80,496,197 | 69.8 | 0.995 (0.981, 1.010) | 1.048 (1.019, 1.078) | <0.001 |
| COVID-19 Treatment | | | | | | |
| No Treatment/Unknown | 103,75 | 147,665,807 | 70.3 | — | — | |
| Antivirals | 269 | 164,851 | 163. | 2.322 (2.056, 2.612) | 0.820 (0.724, 0.925) | 0.002 |
| Immune Modulators | 1 | 779 | 128. | 1.827 (0.104, 8.037) | 0.719 (0.041, 3.163) | 0.741 |
| Monoclonal Antibodies | 4 | 2,259 | 177. | 2.520 (0.782, 5.854) | 0.953 (0.296, 2.216) | 0.923 |
| Comorbidity | | | | | | |
| No Comorbidity | 66,417 | 106,746,037 | 62.2 | — | — | |
| Has Comorbidity | 37,607 | 41,087,659 | 91.5 | 1.471 (1.453, 1.490) | 1.221 (1.190, 1.253) | <0.001 |

[1] IRR = Incidence Rate Ratio; [2]Adjusted for other risk factors displayed in this table

**Table 4-3. Incidence rate of and factors associated with incident PASC Diagnostic Groups, active component service members, 2020-2022**

| Variable | Mental Health | | Neurological | | Respiratory | | Cardiac | |
|---|---|---|---|---|---|---|---|---|
| | **Rate** | **Adj IRR (95% CI)**[1,2] | **Rate** | **Adj IRR (95% CI)**[1,2] | **Rate** | **Adj IRR (95% CI)**[1,2] | **Rate** | **Adj IRR (95% CI)**[1,2] |
| Sex | | | | | | | | |
| Female | 63.9 | — | 5.1 | — | 22.4 | — | 30.4 | — |
| Male | 33.5 | 0.686 (0.674, 0.699) | 3.5 | 0.838 (0.791, 0.888) | 13.5 | 0.737 (0.716, 0.759) | 19.7 | 0.823 (0.803, 0.843) |
| Age Group | | | | | | | | |
| <20 | 30.1 | — | 2.9 | — | 14.5 | — | 20.0 | — |
| 20-24 | 36.4 | 1.063 (1.024, 1.104) | 3.1 | 1.106 (0.984, 1.248) | 13.8 | 0.982 (0.931, 1.037) | 20.5 | 0.949 (0.906, 0.994) |
| 25-29 | 38.5 | 1.135 (1.091, 1.180) | 3.1 | 1.107 (0.978, 1.255) | 14.1 | 1.018 (0.961, 1.078) | 20.2 | 0.928 (0.884, 0.975) |
| 30-34 | 35.8 | 1.059 (1.015, 1.105) | 3.6 | 1.342 (1.177, 1.533) | 15.1 | 1.103 (1.037, 1.174) | 21.5 | 0.982 (0.932, 1.035) |
| 35-39 | 49.7 | 1.316 (1.260, 1.375) | 5.7 | 1.909 (1.672, 2.185) | 18.3 | 1.226 (1.149, 1.309) | 25.3 | 1.049 (0.992, 1.109) |
| 40-44 | 58.1 | 1.496 (1.425, 1.571) | 7.4 | 2.329 (2.016, 2.695) | 21.8 | 1.415 (1.315, 1.524) | 28.4 | 1.119 (1.050, 1.193) |
| 45+ | 57 | 1.421 (1.341, 1.505) | 8.9 | 2.609 (2.221, 3.067) | 24.7 | 1.553 (1.425, 1.692) | 32.2 | 1.226 (1.138, 1.320) |
| Race | | | | | | | | |
| Asian | 40.1 | — | 3.7 | — | 13.3 | — | 18.4 | — |
| Hispanic | 39.4 | 1.037 (0.993, 1.083) | 3.9 | 1.121 (0.979, 1.289) | 15.2 | 0.997 (0.927, 1.073) | 20.3 | 1.027 (0.965, 1.093) |
| Non-Hispanic Black | 50.8 | 1.134 (1.086, 1.185) | 4.2 | 0.998 (0.871, 1.148) | 18.4 | 1.017 (0.946, 1.094) | 26.2 | 1.173 (1.103, 1.249) |
| Non-Hispanic White | 36 | 0.990 (0.950, 1.033) | 3.8 | 1.107 (0.973, 1.265) | 14.6 | 0.977 (0.912, 1.049) | 21.2 | 1.093 (1.030, 1.161) |
| Other | 37.2 | 0.984 (0.935, 1.036) | 3.6 | 1.085 (0.924, 1.276) | 15 | 0.978 (0.899, 1.064) | 21.6 | 1.045 (0.973, 1.122) |
| Unknown | 45.8 | 1.122 (1.042, 1.206) | 4.4 | 1.140 (0.906, 1.426) | 17.4 | 1.085 (0.964, 1.219) | 24.0 | 1.127 (1.019, 1.245) |
| Service | | | | | | | | |
| Air Force | 34.6 | — | 3.5 | — | 19 | — | 26.1 | — |
| Army | 43.9 | 1.247 (1.222, 1.274) | 4.7 | 1.281 (1.203, 1.364) | 16.5 | 0.819 (0.795, 0.844) | 21.4 | 0.789 (0.769, 0.809) |
| Coast Guard | 32.4 | 1.024 (0.936, 1.118) | 2.8 | 0.835 (0.615, 1.104) | 9.3 | 0.537 (0.455, 0.629) | 18.2 | 0.763 (0.677, 0.856) |
| Marines | 30.1 | 0.906 (0.877, 0.935) | 2.9 | 0.849 (0.809, 0.987) | 9.7 | 0.563 (0.535, 0.592) | 16.8 | 0.696 (0.668, 0.724) |
| Navy | 44 | 1.265 (1.235, 1.295) | 3.5 | 0.989 (0.915, 1.068) | 12 | 0.616 (0.593, 0.641) | 20.2 | 0.783 (0.759, 0.808) |
| Rank | | | | | | | | |
| Enlisted | 41.2 | — | 3.9 | — | 15.6 | — | 22.3 | — |
| Officer | 29.8 | 0.707 (0.683, 0.732) | 3.9 | 0.806 (0.732, 0.887) | 13.8 | 0.847 (0.803, 0.892) | 19.5 | 0.888 (0.849, 0.928) |

| Variable | Mental Health | | Neurological | | Respiratory | | Cardiac | |
|---|---|---|---|---|---|---|---|---|
| | **Rate** | **Adj IRR (95% CI)**[1,2] | **Rate** | **Adj IRR (95% CI)**[1,2] | **Rate** | **Adj IRR (95% CI)**[1,2] | **Rate** | **Adj IRR (95% CI)**[1,2] |
| Education Level | | | | | | | | |
| Less than High School | 42 | — | 1.8 | — | 21.6 | — | 26.1 | — |
| High School | 38.8 | 1.024 (0.809, 1.323) | 3.5 | 2.564 (0.987, 10.32) | 14.6 | 0.665 (0.483, 0.950) | 21.3 | 0.852 (0.636, 1.177) |
| Some College | 47.7 | 0.982 (0.775, 1.270) | 5 | 2.514 (0.967, 10.13) | 19.2 | 0.648 (0.470, 0.927) | 25.0 | 0.789 (0.589, 1.091) |
| Bachelor's Degree | 37.2 | 0.940 (0.741, 1.215) | 4.3 | 2.510 (0.964, 10.11) | 14.8 | 0.588 (0.426, 0.841) | 21.2 | 0.769 (0.573, 1.064) |
| Advanced Degree | 39.7 | 0.930 (0.732, 1.205) | 5.2 | 2.363 (0.903, 9.542) | 18.2 | 0.634 (0.458, 0.910) | 23.9 | 0.759 (0.564, 1.053) |
| Other/Unknown | 29.3 | 0.901 (0.704, 1.175) | 3.1 | 2.380 (0.891, 9.704) | 11.6 | 0.589 (0.420, 0.856) | 18.7 | 0.786 (0.579, 1.099) |
| COVID-19 Symptomology | | | | | | | | |
| Asymptomatic | 38 | — | 3.4 | — | 12.1 | — | 19.4 | — |
| Symptomatic | 41.1 | 0.992 (0.976, 1.009) | 4.3 | 0.965 (0.916, 1.016) | 18.5 | 1.145 (1.115, 1.176) | 24.2 | 1.087 (1.063, 1.111) |
| COVID-19 Hospitalization | | | | | | | | |
| Not Hospitalized | 39.3 | — | 3.8 | — | 15.1 | — | 21.7 | — |
| Hospitalized | 82.2 | 0.898 (0.837, 0.963) | 9.7 | 0.888 (0.729, 1.070) | 54.7 | 1.672 (1.534, 1.819) | 49.6 | 1.207 (1.105, 1.315) |
| COVID-19 Re-Infection Status | | | | | | | | |
| First Infection | 38.7 | — | 3.9 | — | 15.4 | — | 21.7 | — |
| Re-infection | 50.7 | 1.104 (1.074, 1.135) | 3.8 | 1.091 (0.990, 1.200) | 15.4 | 1.148 (1.093, 1.205) | 24.6 | 1.062 (1.022, 1.104) |
| COVID-19 Vaccination Status | | | | | | | | |
| Not Vaccinated | 35 | — | 5 | — | 21.2 | — | 22.5 | — |
| Vaccinated | 42.1 | 1.048 (1.014, 1.083) | 3.3 | 0.890 (0.803, 0.987) | 12.2 | 0.818 (0.778, 0.860) | 21.5 | 0.905 (0.868, 0.943) |
| COVID-19 Wave | | | | | | | | |
| Wild-type | 33.5 | — | 5.4 | — | 22.1 | — | 21.7 | — |
| Alpha | 37.1 | 1.117 (1.054, 1.182) | 3.7 | 0.692 (0.579, 0.819) | 20.5 | 0.911 (0.844, 0.981) | 22.6 | 1.047 (0.974, 1.124) |
| Delta | 40.7 | 1.196 (1.156, 1.236) | 3.6 | 0.694 (0.628, 0.766) | 15.8 | 0.778 (0.742, 0.816) | 22.9 | 1.098 (1.053, 1.145) |
| Omicron | 42.4 | 1.245 (1.200, 1.292) | 3.2 | 0.639 (0.571, 0.715) | 11.8 | 0.627 (0.593, 0.662) | 21.6 | 1.102 (1.052, 1.155) |
| COVID-19 Treatment | | | | | | | | |
| No Treatment/Unknown | 39.5 | — | 3.9 | — | 15.3 | — | 21.8 | — |
| Antivirals | 78.5 | 0.636 (0.538, 0.746) | 9.4 | 0.674 (0.418, 1.026) | 45 | 1.093 (0.878, 1.342) | 48.2 | 1.072 (0.872, 1.303) |
| Immune Modulators | 103.6 | 0.672 (0.038, 2.962) | 104.2 | 2.875 (0.163, 12.87) | 128.4 | 2.944 (0.168, 12.98) | 0.0 | 0.000 (0.000, 0.001) |
| Monoclonal Antibodies | 119.8 | 1.244 (0.309, 3.228) | 0 | 0.000 (0.000, 0.000) | 32.8 | 0.436 (0.025, 1.922) | 71.4 | 1.512 (0.251, 4.679) |
| Comorbidity | | | | | | | | |

| Variable | Mental Health | | Neurological | | Respiratory | | Cardiac | |
|---|---|---|---|---|---|---|---|---|
| | **Rate** | **Adj IRR (95% CI)**[1,2] | **Rate** | **Adj IRR (95% CI)**[1,2] | **Rate** | **Adj IRR (95% CI)**[1,2] | **Rate** | **Adj IRR (95% CI)**[1,2] |
| No Comorbidity | 34.6 | — | 3.3 | — | 13.6 | — | 19.7 | — |
| Has Comorbidity | 52.2 | 1.246 (1.205, 1.288) | 5.2 | 1.233 (1.118, 1.360) | 19.7 | 1.146 (1.088, 1.208) | 27.1 | 1.119 (1.071, 1.170) |

[1] IRR = Incidence Rate Ratio; [2]Adjusted for other risk factors displayed in this table

## Supplemental Table 4-1. PASC Diagnostic Categories and ICD-10 Diagnosis

| Diagnostic Group | Diagnosis Description | ICD10 Codes |
|---|---|---|
| Mental Health | Anxiety | F4323, F419, F411, F418, F4322 |
| | Insomnia | G4700, F51 |
| | PTSD | F4312 |
| | Major Depression | F321, F329, F331, F332, F339, R45851 |
| Neurological | Headache | R51 |
| | Taste Loss | R430, R431, R432, R438, R439 |
| | Seizure | R5600, R5601, R569, G40001, G40009, G40011, G40019, G40101, G40109, G40111, G40119, G40201, G40209, G40211, G40219, G40301, G40309, G40311, G40319, G40401, G40409, G40411, G40419, G40501, G40509, G40801, G40802, G40803, G40804, G40811, G40812, G40813, G40814, G40821, G40822, G40823, G40824, G4089, G40901, G40909, G40911, G40919, G40A01, G40A09, G40A11, G40A19, G40B01, G40B09, G40B11, G40B19 |
| | Blurred Vision | H53 |
| | Fatigue | R53 |
| | Memory Loss | R413 |
| | Cognitive Dysfunction | R410, R411, R412 |
| | Vertigo | H8110, H8111, H8112, H8113, H8141, H8142, H8143, H8149 |
| Respiratory | Cough | R05 |
| | Short of Breath | R0602, R0600, R0609 |
| | Pulmonary Embolism | I2699 |
| | Asthma | J45909, J4520, J45901, J4530, R062 |
| Cardiac | Chest Pain | R079, R0789, R072 |
| | Palpitations | R002 |
| | Atrial Fibrillation | I4891, I480 |
| | Syncope | R55 |
| | Tachycardia | R000 |
| | Heart Failure | I509, I517 |
| | Bradycardia | R001 |
| | Myocardial Infarction | I21, I22 |
| | Cerebral infarction/Stroke | I63 |
| | Post Exertional Malaise | T733 |
| | Myocarditis | I40, I41, I514, B3322 |
| | Pericarditis | I30, I32, B3323 |
| Abbreviations: PASC, Post Acute Sequelae of COVID-19 | | |

**Supplemental Table 4-2. ESSENCE COVID-Like Illness (CLI) Definition**

| Diagnosis Description | ICD-10 Codes |
|---|---|
| Coronavirus, unspecified | B34.2 |
| SARS-associated coronavirus as the cause of disease classified elsewhere | B97.21 |
| Other coronavirus as the cause of disease classified elsewhere | B97.29 |
| Acute nasopharyngitis; common cold | J00 |
| Acute upper respiratory infection, unspecified | J06.9 |
| Pneumonia due to SARS-associated coronavirus | J12.81 |
| Other viral pneumonia | J12.89 |
| Viral pneumonia unspecified | J16.8 |
| Pneumonia in diseases classified elsewhere | J17 |
| Bronchopneumonia, unspecified organism | J18.0 |
| Lobar pneumonia, unspecified organism | J18.1 |
| Other pneumonia, unspecified organism | J18.8 |
| Pneumonia, unspecified organism | J18.9 |
| Acute bronchitis due to other specified organisms | J20.8 |
| Acute bronchitis, unspecified | J20.9 |
| Unspecified acute lower respiratory infection | J22 |
| Bronchitis, not specified as acute or chronic | J40 |
| Acute respiratory distress syndrome | J80 |
| Idiopathic interstitial pneumonia not otherwise specified | J84.111 |
| Cough | R05 |
| Dyspnea | R06.0 |
| Dyspnea, unspecified | R06.00 |
| Shortness of breath | R06.02 |
| Acute respiratory distress | R06.03 |
| Other forms of dyspnea | R06.09 |
| Anosmia | R43.0 |
| Ageusia | R43.2 |
| Fever, unspecified | R50.9 |
| 2019-nCoV acute respiratory disease, COVID-19, virus identified | U07.1 |

**Supplemental Table 4-3. Comorbidity Categories and ICD-10 Diagnosis**

| **Diagnosis Description** | **ICD-10 Codes** |
|---|---|
| Hypertension | I10*-I16*, O10*-O16* |
| Any cardiovascular disease | I05*-I89*, Z95* |
| Chronic lower respiratory disease | J40*-J44* |
| Asthma | J45* |
| Any lung disease | J40*-J99* |
| Metabolic disease | E08*-E13*, O24*, Z794*, E00*-E07*, E50*-E64*, E88.81 |
| Immune compromising conditions | B20, D55*-D77*, D80*-D89*, Z94*, Z795*, L40*, M04*-M08*, K50*-K52* |
| Substance use disorders (including nicotine dependence) | F10*-F16*, F18*-F19*, F17* |
| Chronic liver disease | K70*-K77*, B18* |
| Chronic kidney disease | N03*-N16*, N18*-N19* |
| Chronic neurologic disorders | G10*-G40* |
| Neoplasms | C00*-D49* |
| Obesity or overweight | E66.0*, E66.1, E66.2, E66.3, E66.8, E66.9, Z68.3*, Z68.4*, Z68.25- Z68.29 |
| HIV** | B20* |
| * Indicates all underlying ICD-10 codes are included | |
| **HIV is also included as part of the Immune Compromising Conditions category | |

**Supplemental Table 4-4. Characteristics, incidence rate of, and factors associated of long COVID cases, active component service members, 2020-2022**

| Variable | Cases (%) | Person-Days | Rate | Crude IRR (95% CI)[2] | Adj IRR (95% CI)[2,3] | p-value |
|---|---|---|---|---|---|---|
| Overall | N = 104,024[1] | | | | | |
| Comorbidity | | | | | | |
| No Comorbidity | 66,417 (63.8%) | 106,746,037 | 62.2 | — | — | |
| Has Comorbodity | 37,607 (36.2%) | 41,087,659 | 91.5 | 1.471 (1.453, 1.490) | 1.221 (1.190, 1.253) | <0.001 |
| Obesity | | | | | | |
| Not Obese | 84,048 (80.8%) | 125,207,933 | 67.1 | — | — | |
| Obese | 19,976 (19.2%) | 22,625,763 | 88.3 | 1.315 (1.295, 1.336) | 0.905 (0.883, 0.928) | <0.001 |
| Current Smoking Status | | | | | | |
| Not Current Smoker | 97,163 (93.4%) | 138,642,587 | 70.1 | — | — | |
| Current Smoker | 6,861 (6.6%) | 9,191,109 | 74.6 | 1.065 (1.039, 1.091) | 0.954 (0.925, 0.983) | 0.002 |
| Hypertension | | | | | | |
| No Hypertension | 99,832 (96.0%) | 144,550,314 | 69.1 | — | — | |
| Hypertension | 4,192 (4.0%) | 3,283,382 | 127.7 | 1.849 (1.792, 1.906) | 1.046 (0.998, 1.096) | 0.059 |
| Any Cardiovascular Disease | | | | | | |
| No Cardiovascular Disease | 98,507 (94.7%) | 143,454,114 | 68.7 | — | — | |
| Any Cardiovascular Disease | 5,517 (5.3%) | 4,379,582 | 126.0 | 1.834 (1.785, 1.885) | 0.983 (0.942, 1.025) | 0.424 |
| Chronic Lower Respiratory Disease | | | | | | |
| No Chronic Lower Respiratory Disease | 103,860 (99.8%) | 147,736,532 | 70.3 | — | — | |
| Chronic Lower Respiratory Disease | 164 (0.2%) | 97,164 | 168.8 | 2.401 (2.052, 2.788) | 1.639 (1.380, 1.934) | <0.001 |
| Asthma | | | | | | |
| No Asthma | 102,646 (98.7%) | 146,887,905 | 69.9 | — | — | |
| Asthma | 1,378 (1.3%) | 945,791 | 145.7 | 2.085 (1.976, 2.198) | 1.306 (1.185, 1.441) | <0.001 |
| Any Lung Disease | | | | | | |
| No Lung Disease | 101,974 (98.0%) | 146,394,680 | 69.7 | — | — | |
| Lung Disease | 2,050 (2.0%) | 1,439,016 | 142.5 | 2.045 (1.957, 2.136) | 0.799 (0.733, 0.869) | <0.001 |
| Metabolic Disease | | | | | | |
| No Metabolic Disease | 100,782 (96.9%) | 145,241,787 | 69.4 | — | — | |

| Variable | Cases (%) | Person-Days | Rate | Crude IRR (95% CI)[2] | Adj IRR (95% CI)[2,3] | p-value |
|---|---|---|---|---|---|---|
| Metabolic Disease | 3,242 (3.1%) | 2,591,909 | 125.1 | 1.803 (1.740, 1.866) | 0.847 (0.816, 0.879) | <0.001 |
| Immune Compromising Condition | | | | | | |
| No Immune Compromising Condition | 100,877 (97.0%) | 145,202,679 | 69.5 | — | — | |
| Immune Compromising Condition | 3,147 (3.0%) | 2,631,017 | 119.6 | 1.722 (1.661, 1.784) | 0.913 (0.878, 0.948) | <0.001 |
| Substance Use Disorder | | | | | | |
| No Substance Use Disorder | 100,096 (96.2%) | 144,130,684 | 69.4 | — | — | |
| Substance Use Disorder | 3,928 (3.8%) | 3,703,012 | 106.1 | 1.527 (1.479, 1.577) | 0.855 (0.826, 0.885) | <0.001 |
| Chronic Liver Disease | | | | | | |
| No Chronic Liver Disease | 103,555 (99.5%) | 147,509,663 | 70.2 | — | — | |
| Chronic Liver Disease | 469 (0.5%) | 324,033 | 144.7 | 2.062 (1.880, 2.254) | 1.070 (0.975, 1.172) | 0.145 |
| Chronic Kidney Disease | | | | | | |
| No Chronic Kidney Disease | 103,544 (99.5%) | 147,485,999 | 70.2 | — | — | |
| Chronic Kidney Disease | 480 (0.5%) | 347,697 | 138.1 | 1.966 (1.795, 2.148) | 1.096 (0.999, 1.198) | 0.048 |
| Chronic Neurological Disorder | | | | | | |
| No Chronic Neurologic Disorder | 103,441 (99.4%) | 147,378,725 | 70.2 | — | — | |
| Chronic Neurologic Disorder | 583 (0.6%) | 454,971 | 128.1 | 1.826 (1.681, 1.978) | 0.721 (0.664, 0.783) | <0.001 |
| Neoplasm | | | | | | |
| No Neoplasm | 100,607 (96.7%) | 144,681,658 | 69.5 | — | — | |
| Neoplasm | 3,417 (3.3%) | 3,152,038 | 108.4 | 1.559 (1.506, 1.613) | 0.901 (0.868, 0.935) | <0.001 |
| HIV | | | | | | |
| No HIV | 103,919 (99.9%) | 147,742,635 | 70.3 | — | — | |
| HIV | 105 (0.1%) | 91,061 | 115.3 | 1.639 (1.345, 1.973) | 1.121 (0.917, 1.355) | 0.249 |

[1]n (%); Mean (SD), [2]IRR = Incidence Rate Ratio; [3]Adjusted for other risk factors displayed in this table

**Supplemental Table 4-5. Incidence rate of and factors associated with incident PASC diagnostic groups, active component service members, 2020-2022**

| Variable | Mental Health | | Neurological | | Respiratory | | Cardiac | |
|---|---|---|---|---|---|---|---|---|
| | **Rate** | **Adj IRR (95% CI)** | **Rate** | **Adj IRR (95% CI)** | **Rat** | **Adj IRR (95% CI)** | **Rat** | **Adj IRR (95% CI)** |
| Overall | 39.6 | | 3.9 | | 15. | | 21. | |
| Comorbidity | | | | | | | | |
| No Comorbidity | 34.6 | — | 3.3 | — | 13. | — | 19. | — |
| Has Comorbodity | 52.2 | 1.246 (1.205, | 5.2 | 1.233 (1.118, | 19. | 1.146 (1.088, | 27. | 1.119 (1.071, |
| Obesity | | | | | | | | |
| Not Obese | 37.7 | — | 3.7 | — | 14. | — | 21. | — |
| Obese | 49.8 | 0.875 (0.848, | 4.8 | 0.836 (0.761, | 20. | 1.049 (0.998, | 25. | 0.932 (0.894, |
| Current Smoking Status | | | | | | | | |
| Not Current Smoker | 39.2 | — | 3.9 | — | 15. | — | 21. | — |
| Current Smoker | 45.5 | 1.015 (0.977, | 3.8 | 0.824 (0.729, | 14. | 0.869 (0.815, | 21. | 0.967 (0.917, |
| Hypertension | | | | | | | | |
| No Hypertension | 38.8 | — | 3.8 | — | 15. | — | 21. | — |
| Hypertension | 70.1 | 1.136 (1.071, | 7.1 | 0.947 (0.794, | 25. | 0.955 (0.870, | 40. | 1.017 (0.942, |
| Any Cardiovascular Disease | | | | | | | | |
| No Cardiovascular Disease | 38.7 | — | 3.7 | — | 15 | — | 21. | — |
| Any Cardiovascular Disease | 66 | 0.813 (0.770, | 7.5 | 0.958 (0.818, | 26. | 1.069 (0.983, | 42. | 1.241 (1.159, |
| Chronic Lower Respiratory Disease | | | | | | | | |
| No Chronic Lower Respiratory Di | 39.6 | — | 3.9 | — | 15. | — | 21. | — |
| Chronic Lower Respiratory Di | 70.3 | 1.292 (1.014, | 11.4 | 1.766 (0.966, | 49. | 1.848 (1.383, | 53. | 1.877 (1.416, |
| Asthma | | | | | | | | |
| No Asthma | 39.4 | — | 3.8 | — | 15. | — | 21. | — |
| Asthma | 68.1 | 1.160 (1.021, | 7.2 | 1.12 (0.787, | 43. | 1.617 (1.360, | 39. | 1.372 (1.160, |
| Any Lung Disease | | | | | | | | |
| No Lung Disease | 39.3 | — | 3.8 | — | 15. | — | 21. | — |
| Lung Disease | 69.2 | 0.719 (0.644, | 7.7 | 0.820 (0.600, | 40. | 0.974 (0.830, | 39. | 0.747 (0.642, |
| Metabolic Disease | | | | | | | | |

| **Variable** | Mental | Neurological | Respirato | Cardiac | | | | |
|---|---|---|---|---|---|---|---|---|
| | **Rate** | **Adj IRR (95%** | **Rate** | **Adj IRR (95%** | **Rat** | **Adj IRR (95%** | **Rat** | **Adj IRR (95%** |
| No Metabolic Disease | 39 | — | 3.8 | — | 15. | — | 21. | — |
| Metabolic Disease | 70.1 | 0.799 (0.762, | 8.3 | 1.008 (0.883, | 25. | 0.876 (0.813, | 37. | 0.935 (0.878, |
| Immune Compromising Condition | | | | | | | | |
| No Immune Compromising | 39 | — | 3.8 | — | 15. | — | 21. | — |
| Immune Compromising | 68.1 | 0.868 (0.826, | 7.4 | 1.042 (0.904, | 24. | 0.926 (0.856, | 35. | 0.952 (0.892, |
| Substance Use Disorder | | | | | | | | |
| No Substance Use Disorder | 38.9 | — | 3.8 | — | 15. | — | 21. | — |
| Substance Use Disorder | 63.9 | 0.829 (0.793, | 6.3 | 0.900 (0.789, | 19. | 0.835 (0.775, | 29. | 0.871 (0.820, |
| Chronic Liver Disease | | | | | | | | |
| No Chronic Liver Disease | 39.5 | — | 3.9 | — | 15. | — | 21. | — |
| Chronic Liver Disease | 80.4 | 1.062 (0.944, | 7.7 | 0.852 (0.591, | 30. | 1.043 (0.869, | 45. | 1.090 (0.936, |
| Chronic Kidney Disease | | | | | | | | |
| No Chronic Kidney Disease | 39.5 | — | 3.9 | — | 15. | — | 21. | — |
| Chronic Kidney Disease | 74.3 | 1.031 (0.916, | 7.1 | 0.987 (0.681, | 27 | 1.035 (0.856, | 46. | 1.277 (1.104, |
| Chronic Neurological Disorder | | | | | | | | |
| No Chronic Neurologic Disorder | 39.5 | — | 3.8 | — | 15. | — | 21. | — |
| Chronic Neurologic Disorder | 67.5 | 0.608 (0.545, | 11.9 | 1.069 (0.831, | 28 | 0.844 (0.717, | 34. | 0.720 (0.622, |
| Neoplasm | | | | | | | | |
| No Neoplasm | 39.1 | — | 3.8 | — | 15. | — | 21. | — |
| Neoplasm | 60.1 | 0.860 (0.819, | 6.7 | 0.905 (0.788, | 23. | 0.980 (0.910, | 33. | 0.973 (0.914, |
| HIV | | | | | | | | |
| No HIV | 39.6 | — | 3.9 | — | 15. | — | 21. | — |
| HIV | 62.7 | 1.131 (0.871, | 5.3 | 0.724 (0.285, | 24 | 1.125 (0.742, | 36. | 1.245 (0.889, |

[1] IRR = Incidence Rate Ratio; [2]Adjusted for other risk factors displayed in this table and Table 1

**Supplemental Table 4-6a. Incidence rate of and factors associated with incident Mental Health PASC Diagnostic Description, active component service members, 2020-2022**

| Variable | Anxiety | Insomnia | PTSD | Major Depression |
|---|---|---|---|---|
| | Adj IRR (95% CI)[1,2] | | | |
| Sex | | | | |
| Female | — | — | — | — |
| Male | 0.516 (0.505, 0.528) | 0.860 (0.831, 0.889) | 0.574 (0.542, 0.608) | 0.606 (0.585, 0.627) |
| Age Group | | | | |
| <20 | — | — | — | — |
| 20-24 | 1.087 (1.037, 1.139) | 1.204 (1.121, 1.296) | 1.574 (1.306, 1.915) | 0.746 (0.702, 0.791) |
| 25-29 | 1.196 (1.139, 1.256) | 1.457 (1.353, 1.570) | 2.099 (1.738, 2.560) | 0.689 (0.646, 0.735) |
| 30-34 | 1.108 (1.052, 1.169) | 1.408 (1.300, 1.525) | 2.507 (2.065, 3.072) | 0.551 (0.512, 0.593) |
| 35-39 | 1.345 (1.273, 1.421) | 1.900 (1.752, 2.063) | 5.175 (4.270, 6.329) | 0.608 (0.562, 0.657) |
| 40-44 | 1.502 (1.411, 1.599) | 2.274 (2.080, 2.488) | 7.356 (6.031, 9.048) | 0.666 (0.607, 0.731) |
| 45+ | 1.281 (1.187, 1.382) | 2.299 (2.077, 2.544) | 7.269 (5.891, 9.035) | 0.529 (0.469, 0.598) |
| Race | | | | |
| Asian | — | — | — | — |
| Hispanic | 1.079 (1.021, 1.141) | 1.067 (0.989, 1.153) | 1.190 (1.041, 1.365) | 0.956 (0.882, 1.036) |
| Non-Hispanic Black | 1.104 (1.045, 1.167) | 1.370 (1.272, 1.478) | 1.158 (1.013, 1.327) | 1.085 (1.001, 1.175) |
| Non-Hispanic White | 1.058 (1.003, 1.116) | 0.890 (0.827, 0.958) | 1.025 (0.902, 1.169) | 0.811 (0.750, 0.876) |
| Other | 0.967 (0.906, 1.033) | 1.023 (0.934, 1.121) | 0.992 (0.842, 1.170) | 0.923 (0.838, 1.016) |
| Unknown | 1.148 (1.045, 1.260) | 1.214 (1.066, 1.379) | 1.244 (1.001, 1.538) | 0.999 (0.871, 1.146) |
| Service | | | | |
| Air Force | — | — | — | — |
| Army | 1.147 (1.117, 1.177) | 1.643 (1.583, 1.704) | 1.850 (1.726, 1.985) | 1.240 (1.189, 1.293) |
| Coast Guard | 1.142 (1.025, 1.269) | 0.866 (0.722, 1.029) | 0.831 (0.587, 1.137) | 1.158 (0.962, 1.393) |
| Marines | 0.841 (0.806, 0.876) | 0.838 (0.788, 0.891) | 0.993 (0.881, 1.117) | 0.666 (0.621, 0.713) |
| Navy | 1.419 (1.378, 1.462) | 1.029 (0.983, 1.078) | 1.463 (1.349, 1.588) | 1.811 (1.731, 1.894) |
| Rank | | | | |
| Enlisted | — | — | — | — |

| Variable | Anxiety | Insomnia | PTSD | Major Depression |
|---|---|---|---|---|
| | Adj IRR (95% CI)[1,2] | | | |
| Officer | 0.672 (0.642, 0.702) | 0.715 (0.674, 0.758) | 0.672 (0.609, 0.742) | 0.650 (0.601, 0.704) |
| Education Level | | | | |
| Less than High School | — | — | — | — |
| High School | 0.994 (0.745, 1.368) | 0.927 (0.632, 1.439) | 1.248 (0.614, 3.145) | 1.427 (0.810, 2.516) |
| Some College | 0.991 (0.742, 1.365) | 0.895 (0.609, 1.390) | 1.273 (0.626, 3.210) | 1.302 (0.738, 2.299) |
| Bachelor's Degree | 0.935 (0.699, 1.288) | 0.882 (0.600, 1.371) | 1.154 (0.567, 2.914) | 1.142 (0.646, 2.017) |
| Advanced Degree | 0.885 (0.660, 1.223) | 0.811 (0.549, 1.265) | 0.983 (0.480, 2.491) | 1.111 (0.625, 1.973) |
| Other/Unknown | 0.879 (0.650, 1.224) | 0.801 (0.534, 1.265) | 0.912 (0.431, 2.353) | 0.986 (0.547, 1.776) |
| COVID-19 Symptomology | | | | |
| Asymptomatic | — | — | — | — |
| Symptomatic | 0.975 (0.955, 0.996) | 1.101 (1.069, 1.134) | 0.980 (0.929, 1.034) | 0.940 (0.910, 0.971) |
| COVID-19 Hospitalization | | | | |
| Not Hospitalized | — | — | — | — |
| Hospitalized | 0.987 (0.900, 1.079) | 0.783 (0.686, 0.888) | 0.719 (0.586, 0.873) | 1.092 (0.970, 1.228) |
| COVID-19 Re-Infection Status | | | | |
| First Infection | — | — | — | — |
| Re-infection | 1.164 (1.123, 1.205) | 1.081 (1.027, 1.136) | 1.132 (1.036, 1.235) | 1.171 (1.110, 1.236) |
| COVID-19 Vaccination Status | | | | |
| Not Vaccinated | — | — | — | — |
| Vaccinated | 1.094 (1.050, 1.141) | 1.038 (0.979, 1.100) | 1.071 (0.962, 1.195) | 1.022 (0.960, 1.089) |
| COVID-19 Wave | | | | |
| Wild-type | — | — | — | — |
| Alpha | 1.197 (1.112, 1.287) | 1.148 (1.038, 1.265) | 1.133 (0.911, 1.391) | 1.230 (1.110, 1.363) |
| Delta | 1.301 (1.246, 1.358) | 1.190 (1.121, 1.263) | 1.478 (1.317, 1.656) | 1.185 (1.112, 1.263) |
| Omicron | 1.358 (1.295, 1.425) | 1.291 (1.208, 1.379) | 1.563 (1.378, 1.770) | 1.207 (1.124, 1.297) |
| COVID-19 Treatment | | | | |
| No Treatment/Unknown | — | — | — | — |
| Antivirals | 0.533 (0.429, 0.654) | 0.486 (0.355, 0.649) | 0.309 (0.190, 0.476) | 0.506 (0.365, 0.703) |
| Immune Modulators | 0.000 (0.000, 0.000) | 1.128 (0.064, 4.994) | 0.000 (0.000, 0.000) | 0.000 (0.000, |

| Variable | Anxiety | Insomnia | PTSD | Major Depression |
|---|---|---|---|---|
| | Adj IRR (95% CI)[1,2] | | | |
| Monoclonal Antibodies | 1.013 (0.168, 3.134) | 0.000 (0.000, 0.000) | 2.358 (0.134, 10.44) | 1.622 (0.228, 11.55) |
| Comorbidity | | | | |
| No Comorbidity | — | — | — | — |
| Has Comorbody | 1.287 (1.232, 1.344) | 1.292 (1.219, 1.370) | 1.550 (1.411, 1.703) | 1.308 (1.227, 1.395) |
| [1]IRR = Incidence Rate Ratio; [2]Adjusted for other risk factors displayed in this table | | | | |
| [3]Excludes diagnoses with insufficient numbers of incident cases, including blurred vision, fatigue, cognitive dysfunction, myocardial infarction, cerebral infarction, post exertional malaise, and pericarditis | | | | |

**Supplemental Table 4-6b. Incidence rate of and factors associated with incident Neurological PASC Diagnostic Description, active component service members, 2020-2022**

| Variable | Headache | Taste Loss | Seizure | Memory Loss | Vertigo |
|---|---|---|---|---|---|
| | Adj IRR (95% CI)[1,2] | | | | |
| Sex | | | | | |
| Female | — | — | — | — | |
| Male | 0.673 (0.575, 0.788) | 0.777 (0.694, 0.870) | 0.836 (0.719, | 1.191 (1.063, | 0.615 (0.537, 0.705) |
| Age Group | | | | | |
| <20 | — | — | — | — | — |
| 20-24 | 0.799 (0.622, 1.027) | 1.404 (1.127, 1.749) | 0.814 (0.633, | 1.620 (1.194, | 1.330 (0.901, 1.963) |
| 25-29 | 0.848 (0.646, 1.113) | 1.243 (0.983, 1.572) | 0.535 (0.403, | 2.134 (1.566, | 1.520 (1.021, 2.264) |
| 30-34 | 0.724 (0.526, 0.996) | 1.472 (1.145, 1.891) | 0.650 (0.478, | 2.886 (2.103, | 2.326 (1.552, 3.488) |
| 35-39 | 1.014 (0.729, 1.410) | 1.680 (1.291, 2.186) | 0.755 (0.547, | 5.149 (3.763, | 3.261 (2.165, 4.914) |
| 40-44 | 1.008 (0.676, 1.504) | 2.208 (1.655, 2.946) | 0.670 (0.454, | 6.563 (4.739, | 4.256 (2.771, 6.538) |
| 45+ | 1.153 (0.717, 1.854) | 2.263 (1.623, 3.156) | 0.695 (0.437, | 7.177 (5.095, | 5.871 (3.733, 9.234) |
| Race | | | | | |
| Asian | — | — | — | — | — |
| Hispanic | 0.878 (0.618, 1.247) | 1.179 (0.877, 1.585) | 1.700 (1.076, | 1.459 (1.137, | 0.723 (0.542, 0.963) |
| Non-Hispanic Black | 1.161 (0.825, 1.635) | 1.045 (0.777, 1.407) | 1.717 (1.089, | 1.121 (0.870, | 0.530 (0.394, 0.712) |
| Non-Hispanic White | 0.701 (0.500, 0.982) | 1.055 (0.793, 1.405) | 2.060 (1.326, | 1.518 (1.199, | 0.669 (0.510, 0.877) |
| Other | 0.573 (0.354, 0.928) | 1.270 (0.910, 1.772) | 1.770 (1.063, | 1.394 (1.036, | 0.717 (0.511, 1.006) |
| Unknown | 1.096 (0.592, 2.029) | 0.954 (0.585, 1.556) | 0.910 (0.385, | 1.714 (1.149, | 0.975 (0.620, 1.532) |
| Service | | | | | |
| Air Force | — | — | — | — | — |
| Army | 1.557 (1.285, 1.886) | 0.901 (0.801, 1.014) | 1.366 (1.150, | 2.170 (1.923, | 0.835 (0.718, 0.972) |
| Coast Guard | 0.215 (0.030, 1.539) | 1.115 (0.694, 1.792) | 1.416 (0.723, | 0.788 (0.418, | 0.596 (0.294, 1.209) |
| Marines | 0.837 (0.614, 1.142) | 0.581 (0.474, 0.712) | 0.775 (0.592, | 1.690 (1.417, | 0.566 (0.430, 0.745) |
| Navy | 1.211 (0.966, 1.518) | 0.795 (0.687, 0.919) | 1.262 (1.032, | 1.034 (0.882, | 0.891 (0.750, 1.059) |
| Rank | | | | | |
| Enlisted | — | — | — | — | — |

| Variable | Headache | Taste Loss | Seizure | Memory Loss | Vertigo |
|---|---|---|---|---|---|
| | Adj IRR (95% CI)[1,2] | | | | |
| Officer | 0.424 (0.305, 0.587) | 0.914 (0.755, 1.107) | 0.891 (0.658, | 0.787 (0.672, | 0.952 (0.758, 1.195) |
| Education Level | | | | | |
| Less than High School | — | — | — | — | — |
| High School | 131,341 (0.000, | 39,306 (0.000, | 1.162 (0.163, | 0.913 (0.350, | 86,340 (0.000, |
| Some College | 112,886 (0.000, | 41,363 (0.000, | 0.951 (0.132, | 0.925 (0.353, | 83,649 (0.000, |
| Bachelor's Degree | 147,005 (0.000, | 43,417 (0.000, | 0.895 (0.124, | 0.920 (0.351, | 78,879 (0.000, |
| Advanced Degree | 180,841 (0.000, | 46,291 (0.000, | 0.800 (0.108, | 0.828 (0.312, | 56,259 (0.000, |
| Other/Unknown | 215,097 (0.000, | 29,181 (0.000, | 1.001 (0.129, | 1.023 (0.366, | 54,894 (0.000, |
| COVID-19 Symptomology | | | | | |
| Asymptomatic | — | — | — | — | — |
| Symptomatic | 0.912 (0.786, 1.058) | 1.095 (0.985, 1.216) | 0.960 (0.836, | 0.824 (0.752, | 1.131 (0.995, 1.285) |
| COVID-19 Hospitalization | | | | | |
| Not Hospitalized | — | — | — | — | — |
| Hospitalized | 0.759 (0.413, 1.392) | 0.601 (0.373, 0.969) | 2.216 (1.580, | 0.913 (0.646, | 0.470 (0.250, 0.885) |
| COVID-19 Re-Infection | | | | | |
| First Infection | — | — | — | — | — |
| Re-infection | 1.060 (0.768, 1.463) | 1.083 (0.845, 1.389) | 1.223 (0.979, | 1.144 (0.977, | 1.018 (0.813, 1.276) |
| COVID-19 Vaccination | | | | | |
| Not Vaccinated | — | — | — | — | — |
| Vaccinated | 1.180 (0.802, 1.738) | 0.520 (0.425, 0.636) | 0.937 (0.727, | 1.115 (0.925, | 1.150 (0.882, 1.499) |
| COVID-19 Wave | | | | | |
| Wild-type | — | — | — | — | — |
| Alpha | 0.105 (0.044, 0.255) | 0.566 (0.418, 0.766) | 1.035 (0.653, | 1.224 (0.887, | 0.969 (0.605, 1.551) |
| Delta | 0.137 (0.093, 0.203) | 0.606 (0.510, 0.720) | 1.293 (1.001, | 1.062 (0.870, | 0.952 (0.725, 1.250) |
| Omicron | 0.179 (0.120, 0.268) | 0.295 (0.235, 0.370) | 1.239 (0.928, | 1.125 (0.907, | 0.986 (0.734, 1.325) |
| COVID-19 Treatment | | | | | |
| No Treatment/Unknown | — | — | — | — | — |
| Antivirals | 0.664 (0.091, 4.826) | 0.626 (0.152, 2.585) | 0.409 (0.126, | 0.456 (0.211, | 1.246 (0.536, 2.896) |
| Immune Modulators | 0.000 (0.000, Inf) | 0.000 (0.000, Inf) | 36.72 (4.877, | 0.000 (0.000, | 0.000 (0.000, Inf) |

| Variable | Headache | Taste Loss | Seizure | Memory Loss | Vertigo |
|---|---|---|---|---|---|
| | Adj IRR (95% CI)[1,2] | | | | |
| Monoclonal Antibodies | 0.000 (0.000, Inf) | 0.000 (0.000, Inf) | 0.000 (0.000, Inf) | 0.000 (0.000, [illegible]) | 0.000 (0.000, Inf) |
| Comorbidity | | | | | |
| No Comorbidity | — | — | — | — | — |
| Has Comorbody | 1.273 (0.932, 1.739) | 1.219 (0.979, 1.517) | 1.349 (1.055, [illegible]) | 1.197 (1.015, [illegible]) | 1.318 (1.029, 1.689) |
| [1]IRR = Incidence Rate Ratio; [2]Adjusted for other risk factors displayed in this table | | | | | |
| [3]Excludes diagnoses with insufficient numbers of incident cases, including blurred vision, fatigue, cognitive dysfunction, myocardial infarction, cerebral infarction, post exertional malaise, and pericarditis | | | | | |

**Supplemental Table 4-6c. Incidence rate of and factors associated with incident Respiratory PASC Diagnostic Description, active component service members, 2020-2022**

| Variable | Cough | Shortness of Breath | Pulmonary Embolism | Asthma |
|---|---|---|---|---|
| | Adj IRR (95% CI)[1,2] | | | |
| Sex | | | | |
| Female | — | — | — | — |
| Male | 0.714 (0.666, | 0.734 (0.710, | 1.200 (0.939, | 0.691 (0.650, |
| Age Group | | | | |
| <20 | — | — | — | — |
| 20-24 | 0.983 (0.886, | 1.009 (0.945, | 1.495 (0.770, | 0.989 (0.868, |
| 25-29 | 0.901 (0.803, | 1.074 (1.003, | 2.056 (1.052, | 0.976 (0.852, |
| 30-34 | 0.989 (0.867, | 1.156 (1.074, | 2.533 (1.276, | 1.004 (0.868, |
| 35-39 | 0.996 (0.861, | 1.313 (1.215, | 4.474 (2.260, | 1.119 (0.960, |
| 40-44 | 0.966 (0.804, | 1.581 (1.450, | 3.771 (1.826, | 1.302 (1.099, |
| 45+ | 1.249 (1.003, | 1.707 (1.544, | 3.921 (1.804, | 1.427 (1.179, |
| Race | | | | |
| Asian | — | — | — | — |
| Hispanic | 1.001 (0.839, | 1.036 (0.951, | 1.012 (0.542, | 0.872 (0.752, |
| Non-Hispanic Black | 0.984 (0.824, | 1.016 (0.933, | 1.536 (0.839, | 0.992 (0.857, |
| Non-Hispanic White | 0.929 (0.784, | 1.021 (0.941, | 1.045 (0.577, | 0.800 (0.695, |
| Other | 1.077 (0.876, | 0.991 (0.898, | 0.756 (0.361, | 0.906 (0.763, |
| Unknown | 1.272 (0.958, | 1.130 (0.983, | 1.431 (0.632, | 0.829 (0.635, |
| Service | | | | |
| Air Force | — | — | — | — |
| Army | 0.740 (0.689, | 0.793 (0.766, | 0.742 (0.583, | 1.028 (0.961, |
| Coast Guard | 0.481 (0.306, | 0.472 (0.386, | 0.425 (0.105, | 0.894 (0.657, |
| Marines | 0.462 (0.408, | 0.540 (0.509, | 0.497 (0.321, | 0.622 (0.552, |
| Navy | 0.529 (0.481, | 0.572 (0.547, | 0.703 (0.524, | 0.753 (0.691, |
| Rank | | | | |
| Enlisted | — | — | — | — |
| Officer | 0.895 (0.781, | 0.814 (0.766, | 1.633 (1.144, | 0.902 (0.805, |
| Education Level | | | | |
| Less than High School | — | — | — | — |
| High School | 0.529 (0.273, | 0.691 (0.474, | 0.502 (0.070, | 0.782 (0.350, |
| Some College | 0.523 (0.269, | 0.657 (0.450, | 0.499 (0.069, | 0.823 (0.368, |
| Bachelor's Degree | 0.451 (0.230, | 0.623 (0.427, | 0.352 (0.048, | 0.664 (0.296, |
| Advanced Degree | 0.433 (0.218, | 0.649 (0.442, | 0.241 (0.032, | 0.820 (0.364, |
| Other/Unknown | 0.424 (0.206, | 0.612 (0.410, | 0.643 (0.081, | 0.654 (0.281, |
| COVID-19 | | | | |
| Asymptomatic | — | — | — | — |
| Symptomatic | 1.129 (1.056, | 1.164 (1.128, | 1.289 (1.019, | 1.150 (1.086, |

| Variable | Cough | Shortness of Breath | Pulmonary Embolism | Asthma |
|---|---|---|---|---|
| | Adj IRR (95% CI)[1,2] | | | |
| COVID-19 | | | | |
| Not Hospitalized | — | — | — | — |
| Hospitalized | 1.318 (1.055, | 1.769 (1.601, | 18.62 (14.26, | 1.283 (1.040, |
| COVID-19 Re-Infection | | | | |
| First Infection | — | — | — | — |
| Re-infection | 1.00 (0.779, | 1.171 (1.107, | 1.247 (0.860, | 1.322 (1.208, |
| COVID-19 Vaccination | | | | |
| Not Vaccinated | — | — | — | — |
| Vaccinated | 0.500 (0.414, | 0.817 (0.772, | 0.538 (0.389, | 0.982 (0.881, |
| COVID-19 Wave | | | | |
| Wild-type | — | — | — | — |
| Alpha | 0.585 (0.503, | 1.044 (0.953, | 1.779 (1.068, | 1.135 (0.933, |
| Delta | 0.154 (0.131, | 1.014 (0.960, | 2.032 (1.496, | 1.282 (1.145, |
| Omicron | 0.034 (0.027, | 0.808 (0.758, | 1.333 (0.902, | 1.199 (1.057, |
| COVID-19 Treatment | | | | |
| No Treatment/Unknown | — | — | — | — |
| Antivirals | 0.552 (0.135, | 1.003 (0.776, | 0.508 (0.227, | 1.161 (0.783, |
| Immune Modulators | 0.000 (0.000, | 3.735 (0.213, | 0.000 (0.000, | 0.000 (0.000, |
| Monoclonal Antibodies | 0.000 (0.000, | 0.001 (0.000, | 41.09 (5.532, | 0.000 (0.000, |
| Comorbidity | | | | |
| No Comorbidity | — | — | — | — |
| Has Comorbodity | 1.028 (0.894, | 1.149 (1.081, | 0.918 (0.647, | 1.263 (1.132, |

[1]IRR = Incidence Rate Ratio; [2]Adjusted for other risk factors displayed in this table

[3]Excludes diagnoses with insufficient numbers of incident cases, including blurred vision, fatigue, cognitive dysfunction, myocardial infarction, cerebral infarction, post exertional malaise, and

## Supplemental Table 4-6d. Incidence rate of and factors associated with incident Cardiac PASC Diagnostic Description, active component service members, 2020-2022

| Variable | Chest Pain | Palpitations | Atrial Fibrillation | Syncope | Tachycardia | Heart Failure | Bradycardia | Myocarditis |
|---|---|---|---|---|---|---|---|---|
| | Adj IRR (95% CI)[1,2] | | | | | | | |
| Sex | | | | | | | | |
| Female | — | — | — | — | | | | |
| Male | 0.927 (0.899, 0.957) | 0.715 (0.679, 0.753) | 3.398 (2.237, 5.163) | 0.561 (0.527, 0.597) | 0.580 (0.545, 0.617) | 2.029 (1.655, 2.487) | 1.642 (1.446, 1.863) | 1.776 (1.248, 2.526) |
| Age Group | | | | | | | | |
| <20 | — | — | — | — | — | — | — | — |
| 20-24 | 1.016 (0.959, 1.077) | 1.323 (1.167, 1.506) | 0.983 (0.437, 2.211) | 0.592 (0.538, 0.652) | 1.034 (0.908, 1.183) | 1.198 (0.778, 1.846) | 1.068 (0.848, 1.344) | 0.783 (0.480, 1.277) |
| 25-29 | 0.999 (0.940, 1.062) | 1.461 (1.284, 1.669) | 2.149 (0.971, 4.752) | 0.469 (0.421, 0.524) | 0.949 (0.827, 1.092) | 1.227 (0.787, 1.913) | 1.074 (0.844, 1.366) | 0.687 (0.402, 1.173) |
| 30-34 | 1.053 (0.987, 1.125) | 1.730 (1.512, 1.987) | 2.647 (1.176, 5.955) | 0.479 (0.423, 0.543) | 0.939 (0.810, 1.092) | 1.321 (0.832, 2.097) | 1.124 (0.871, 1.451) | 0.700 (0.388, 1.261) |
| 35-39 | 1.156 (1.079, 1.240) | 2.077 (1.808, 2.393) | 3.931 (1.747, 8.846) | 0.405 (0.352, 0.467) | 0.835 (0.712, 0.981) | 2.061 (1.302, 3.264) | 1.226 (0.940, 1.598) | 0.714 (0.381, 1.341) |
| 40-44 | 1.214 (1.121, 1.315) | 2.242 (1.928, 2.614) | 4.329 (1.859, 10.08) | 0.430 (0.361, 0.512) | 0.862 (0.718, 1.035) | 2.540 (1.572, 4.103) | 1.443 (1.082, 1.925) | 0.847 (0.417, 1.721) |
| 45+ | 1.304 (1.186, 1.432) | 2.392 (2.021, 2.835) | 10.42 (4.485, 24.21) | 0.548 (0.445, 0.671) | 0.776 (0.620, 0.967) | 3.505 (2.131, 5.766) | 1.845 (1.350, 2.522) | 0.636 (0.259, 1.563) |
| Race | | | | | | | | |
| Asian | — | — | — | — | — | — | — | — |
| Hispanic | 1.043 (0.966, 1.127) | 1.127 (0.974, 1.310) | 0.829 (0.440, 1.564) | 0.957 (0.809, 1.140) | 0.981 (0.828, 1.169) | 1.085 (0.690, 1.706) | 1.059 (0.796, 1.410) | 0.860 (0.381, 1.939) |
| **Variable** | **Chest Pain** | **Palpitations** | **Atrial Fibrillation** | **Syncope** | **Tachycardia** | **Heart Failure** | **Bradycardia** | **Myocarditis** |
| | Adj IRR (95% CI)[1,2] | | | | | | | |
| Non-Hispanic Black | 1.259 (1.168, 1.360) | 1.213 (1.050, 1.409) | 1.137 (0.614, 2.104) | 1.129 (0.957, 1.342) | 0.861 (0.726, 1.028) | 2.110 (1.369, 3.253) | 1.141 (0.858, 1.519) | 1.214 (0.547, 2.694) |
| Non-Hispanic White | 1.030 (0.957, 1.109) | 1.392 (1.212, 1.608) | 1.202 (0.675, 2.140) | 1.228 (1.047, 1.449) | 1.223 (1.041, 1.447) | 1.149 (0.749, 1.762) | 1.063 (0.808, 1.397) | 0.973 (0.449, 2.108) |
| Other | 1.016 (0.930, 1.110) | 1.209 (1.028, 1.426) | 0.993 (0.485, 2.035) | 1.203 (0.993, 1.462) | 1.003 (0.828, 1.220) | 1.017 (0.602, 1.717) | 0.819 (0.586, 1.145) | 0.860 (0.338, 2.186) |

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| Unknown | 1.155 (1.019, 1.307) | 1.237 (0.990, 1.541) | 1.045 (0.393, 2.779) | 1.229 (0.921, 1.625) | 1.018 (0.768, 1.337) | 1.375 (0.713, 2.651) | 1.074 (0.692, 1.665) | 1.975 (0.683, 5.709) |
| Service | | | | | | | | |
| Air Force | — | — | — | — | — | — | — | — |
| Army | 0.816 (0.790, 0.843) | 0.649 (0.614, 0.686) | 0.869 (0.654, 1.154) | 1.046 (0.973, 1.125) | 0.604 (0.563, 0.648) | 0.916 (0.770, 1.088) | 0.573 (0.512, 0.640) | 0.590 (0.436, 0.800) |
| Coast Guard | 0.740 (0.636, 0.855) | 0.678 (0.526, 0.857) | 0.940 (0.340, 2.598) | 1.055 (0.765, 1.413) | 0.521 (0.355, 0.734) | 0.631 (0.259, 1.540) | 0.752 (0.475, 1.191) | 0.325 (0.045, 2.353) |
| Marines | 0.675 (0.642, 0.710) | 0.590 (0.538, 0.646) | 0.763 (0.487, 1.197) | 0.820 (0.735, 0.913) | 0.518 (0.461, 0.579) | 0.512 (0.369, 0.712) | 0.563 (0.474, 0.669) | 0.434 (0.263, 0.717) |
| Navy | 0.759 (0.729, 0.789) | 0.709 (0.664, 0.757) | 1.000 (0.723, 1.385) | 0.902 (0.827, 0.984) | 0.782 (0.723, 0.846) | 0.769 (0.618, 0.958) | 0.532 (0.461, 0.614) | 0.503 (0.335, 0.753) |
| Rank | | | | | | | | |
| Enlisted | — | — | — | — | — | — | — | — |
| Officer | 0.827 (0.782, 0.876) | 0.960 (0.878, 1.050) | 1.296 (0.865, 1.941) | 0.767 (0.668, 0.879) | 0.963 (0.847, 1.095) | 1.192 (0.930, 1.528) | 1.253 (1.052, 1.491) | 0.932 (0.529, 1.640) |
| Education Level | | | | | | | | |
| Less than High School | — | — | — | — | — | — | — | — |
| **Variable** | **Chest Pain** | **Palpitations** | **Atrial Fibrillation** | **Syncope** | **Tachycardia** | **Heart Failure** | **Bradycardia** | **Myocarditis** |
| | **Adj IRR (95% CI)**[1,2] | | | | | | | |
| High School | 0.757 (0.539, 1.109) | 0.681 (0.397, 1.314) | 0.275 (0.067, 1.119) | 1.467 (0.564, 5.910) | 0.912 (0.423, 2.548) | 0.871 (0.122, 6.226) | 39,492 (0.000, 1.368e+85) | 0.193 (0.026, 1.406) |
| Some College | 0.691 (0.491, 1.013) | 0.669 (0.389, 1.293) | 0.186 (0.045, 0.775) | 1.202 (0.460, 4.852) | 0.804 (0.372, 2.250) | 0.972 (0.136, 6.970) | 39,612 (0.000, 1.372e+85) | 0.243 (0.033, 1.794) |
| Bachelor's Degree | 0.677 (0.481, 0.994) | 0.639 (0.371, 1.237) | 0.165 (0.039, 0.696) | 1.192 (0.455, 4.814) | 0.703 (0.324, 1.972) | 0.944 (0.131, 6.793) | 42,944 (0.000, 1.487e+85) | 0.143 (0.019, 1.093) |
| Advanced Degree | 0.667 (0.472, 0.983) | 0.634 (0.366, 1.233) | 0.222 (0.051, 0.958) | 1.180 (0.446, 4.793) | 0.720 (0.329, 2.032) | 0.882 (0.121, 6.420) | 43,137 (0.000, 1.494e+85) | 0.219 (0.027, 1.758) |
| Other/Unknown | 0.667 (0.466, 0.993) | 0.632 (0.356, 1.248) | 0.171 (0.032, 0.912) | 1.472 (0.545, 6.035) | 0.714 (0.317, 2.047) | 1.197 (0.158, 9.099) | 40,097 (0.000, 1.389e+85) | 0.271 (0.031, 2.396) |
| COVID-19 Symptomology | | | | | | | | |
| Asymptomatic | — | — | — | — | — | — | — | — |
| Symptomatic | 1.096 (1.066, 1.126) | 1.094 (1.043, 1.148) | 1.017 (0.804, 1.286) | 1.110 (1.045, 1.178) | 1.176 (1.108, 1.248) | 1.350 (1.156, 1.577) | 0.980 (0.889, 1.079) | 1.746 (1.291, 2.361) |
| COVID-19 Hospitalization | | | | | | | | |
| Not Hospitalized | — | — | — | — | — | — | — | — |

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| Hospitalized | 1.133 (1.011, 1.266) | 1.164 (0.961, 1.395) | 3.867 (2.305, 6.488) | 1.281 (1.017, 1.589) | 1.892 (1.575, 2.252) | 3.011 (2.168, 4.181) | 1.166 (0.789, 1.724) | 5.669 (3.472, 9.257) |
| COVID-19 Re-Infection Status | | | | | | | | |
| First Infection | — | — | — | — | — | — | — | — |
| Re-infection | 1.074 (1.022, 1.128) | 1.113 (1.024, 1.208) | 0.893 (0.569, 1.400) | 0.986 (0.885, 1.095) | 1.098 (0.994, 1.210) | 1.258 (0.975, 1.623) | 1.101 (0.925, 1.310) | 0.796 (0.428, 1.479) |
| COVID-19 Vaccination Status | | | | | | | | |
| Not Vaccinated | — | — | — | — | — | — | — | — |
| **Variable** | **Chest Pain** | **Palpitations** | **Atrial Fibrillatio** | **Syncope** | **Tachycardia** | **Heart Failure** | **Bradycardia** | **Myocarditis** |
| | **Adj IRR (95% CI)[1,2]** | | | | | | | |
| Vaccinated | 0.885 (0.841, 0.932) | 0.847 (0.774, 0.927) | 0.984 (0.631, 1.533) | 1.041 (0.928, 1.169) | 0.983 (0.878, 1.102) | 0.793 (0.606, 1.036) | 0.921 (0.764, 1.110) | 0.673 (0.422, 1.076) |
| COVID-19 Wave | | | | | | | | |
| Wild-type | — | — | — | — | — | — | — | — |
| Alpha | 1.033 (0.944, 1.127) | 1.069 (0.905, 1.253) | 1.327 (0.602, 2.922) | 1.184 (0.978, 1.420) | 1.096 (0.882, 1.345) | 1.398 (0.911, 2.148) | 1.137 (0.842, 1.536) | 0.752 (0.328, 1.724) |
| Delta | 1.109 (1.053, 1.167) | 1.181 (1.078, 1.293) | 1.394 (0.879, 2.211) | 1.087 (0.967, 1.221) | 1.287 (1.144, 1.445) | 1.337 (1.023, 1.747) | 0.994 (0.824, 1.199) | 1.118 (0.732, 1.707) |
| Omicron | 1.081 (1.020, 1.146) | 1.186 (1.071, 1.313) | 1.324 (0.795, 2.204) | 1.156 (1.015, 1.315) | 1.369 (1.202, 1.558) | 1.216 (0.895, 1.653) | 0.979 (0.794, 1.206) | 0.824 (0.485, 1.400) |
| COVID-19 Treatment | | | | | | | | |
| No Treatment/Unknow | — | — | — | — | — | — | — | — |
| Antivirals | 1.036 (0.781, 1.343) | 1.015 (0.668, 1.471) | 0.236 (0.031, 1.799) | 0.892 (0.460, 1.547) | 1.433 (0.933, 2.097) | 0.582 (0.229, 1.483) | 0.703 (0.259, 1.910) | 1.152 (0.262, 5.068) |
| Immune Modulators | 0.000 (0.000, 0.000) | 0.000 (0.000, 0.000) | 0.000 (0.000, Inf) | 0.000 (0.000, 0.000) | 0.000 (0.000, 0.000) | 0.000 (0.000, 2.870e+2 | 0.000 (0.000, Inf) | 0.000 (0.000, Inf) |
| Monoclonal Antibodies | 4.128 (0.686, 12.76) | 5.761 (0.954, 17.95) | 0.000 (0.000, Inf) | 0.000 (0.000, 0.000) | 0.000 (0.000, 0.000) | 0.000 (0.000, 8.933e+1 | 0.000 (0.000, Inf) | 0.000 (0.000, Inf) |
| Comorbidity | | | | | | | | |
| No Comorbidity | — | — | — | — | — | — | — | — |
| Has Comorbodity | 1.070 (1.011, 1.133) | 1.267 (1.157, 1.388) | 1.179 (0.781, 1.781) | 1.025 (0.907, 1.159) | 1.147 (1.032, 1.275) | 1.200 (0.927, 1.553) | 1.371 (1.116, 1.684) | 0.732 (0.417, 1.286) |

[1]IRR = Incidence Rate Ratio; [2]Adjusted for other risk factors displayed in this table

[3]Excludes diagnoses with insufficient numbers of incident cases, including blurred vision, fatigue, cognitive dysfunction, myocardial infarction, cerebral infarction, post exertional malaise, and pericarditis

## CHAPTER 5: Manuscript 2

Long COVID and Vaccination Status in the Active Component U.S. Military, 2020-2022

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### 5.1 Abstract

**Objective:** To identify whether COVID-19 vaccination and time since last dose impact the risk of long COVID in the U.S. military

**Methods:** Incidence of long COVID was measured in a cohort of active component U.S. servicemembers with confirmed COVID-19 between January 1, 2020, and December 31, 2022. COVID-19 vaccination and length of time since last vaccine dose were assessed as risk factors for long COVID using Cox proportional hazards regression with a step function for follow-up periods.

**Results:** Of 464,356 servicemembers with a confirmed COVID-19 event, 104,024 (22.4%) servicemembers developed long COVID within one year of follow-up. Being partially or fully vaccinated (aHR, 0.96; 95% CI, 0.94 to 0.98) and vaccination with one or more booster doses (aHR, 0.91; 95% CI, 0.88 to 0.94) prior to the COVID-19 event were associated with lower rates of long COVID compared to those who were unvaccinated, and results were strongest for those whose most recent dose was within 3 months of the COVID-19 event (aHR, 0.94; 95% CI, 0.91 to 0.97). However, significant reductions in long COVID risk were only seen for the first 3 months of follow-up, with insignificant differences between vaccinated and unvaccinated groups for the remainder of the follow-up period. Neurological (4 months of follow-up) and respiratory (7 months

of follow-up) symptoms showed significant decreases in diagnoses for vaccinated servicemembers vs unvaccinated for a longer duration compared to the overall long COVID outcome.

**Conclusions:** Vaccination against COVID-19 appears to provide modest reductions in risk of long COVID, and benefits for those vaccinated closer to their COVID-19 event may be even greater. However, the effect of vaccination on long COVID risk may wane over time, with the greatest reduction in risk in the first 3 months after infection. However, protection against individual diagnostic groups, like neurological and respiratory diagnoses, may be longer.

**Policy Implications:** Efforts to promote COVID-19 booster doses closer to peaks in COVID-19 activity may help prevent down-stream complications like long COVID. Additionally, the results of this study may indicate the need for booster doses with more robust and long-lasting protection, especially given the most to yearly booster doses.

### 5.2 Introduction

COVID-19 emerged at the end of 2019 in China, spreading globally and causing more than 775 million cases and over 7 million deaths as of June 2025[1–3,7]. Long COVID, or the presence of symptoms more than 4 weeks after the initial COVID-19 infection, was soon found in a large proportion of previous COVID-19 cases[29–34]. Symptoms of long COVID can include mental health, cardiac, respiratory, and neurological symptoms, with many studies highlighting fatigue, brain fog, anxiety, depression, and stroke as common symptoms[29–34].

Vaccination against COVID-19 prior to a COVID-19 infection has been shown to reduce the incidence of long COVID by approximately 30-50% in studies conducted within civilian populations[44–47]. Internal, unpublished analyses among active component servicemembers found that vaccination with any dose of a COVID-19 vaccine prior to a COVID-19 infection reduced the risk of long COVID by a more modest 5% after controlling for other risk factors, though mental health, respiratory, and cardiac symptoms were reduced by between 10-20% in the same study.

However, current research has been unclear about the role of boosters, individual vaccine types, and waning immunity on the risk of long COVID, and little research has been conducted to evaluate how vaccines affect risk of long COVID in the active component military population. U.S. active component servicemembers are provided free health insurance through the TRICARE program, which includes access to COVID-19 vaccines[85]. This study will aim to provide clarity on the role of COVID-19 vaccines against long COVID and individual symptoms of long COVID in this population using a large cohort of active component COVID-19 cases and linked medical records.

### 5.3 Methods

The protocol for this secondary analysis of existing data was approved by both the George Washington University Committee on Human Research, Institutional Review Board and the Component Office for Human Research Protections, Defense Health Agency Office of Research Protections.

### 5.3.1 Study Population

This study utilized a cohort of active component U.S. service members with a confirmed case of COVID-19 between January 1, 2020, and December 31, 2022. Active component includes full-time active duty servicemembers but excludes those who are reserves or in the National Guard. Data were taken from a registry of COVID-19 cases, defined as having either a positive SARS-CoV-2 nucleic acid or antigen test or a COVID-19 reportable medical event (RME) in the Disease Reporting System Internet (DRSi), maintained by the Armed Forces Health Surveillance Division (AFHSD). The registry includes information relevant to a service member's COVID-19 event, including the type and timing of all COVID-19 vaccine doses received, re-infection status, and hospitalization.

### 5.3.2 Exposures/Risk Factors

Demographic, comorbidity, and treatment information were taken from the Defense Medical Surveillance System (DMSS), a DoD-maintained database of health information which includes personnel, medical, immunization, pharmacy, health assessment, laboratory, and deployment data. Exposures of interest in this study focused on COVID-19 vaccination prior to the COVID-19 event. Exposures included COVID-19 vaccination status at the time of the COVID-19 event (unvaccinated, partially or fully vaccinated, one or more booster doses), the type of vaccine used for the initial vaccine series (unvaccinated or any vaccine), the type of vaccine used for the most recent vaccine dose prior to the COVID-19 event (unvaccinated, mRNA, other vaccine type), and the length of time between the most recent vaccine dose prior to the COVID-19 event and the date of the COVID-19 event (unvaccinated, <3 months, 3-6 months, >6 months). Partially

vaccinated was defined as receiving only one dose of the two-dose initial vaccine series available prior to booster doses, while those who received both initial series doses were considered fully vaccinated. Those who received a booster dose, regardless of whether they received an initial vaccine series, were included in the one or more booster dose category.

Additionally, risk factors identified in a previous study in this population were also used in this analysis, including sex, age, race/ethnicity, service branch, rank, education level, COVID-19 hospitalization status, COVID-19 re-infection status, wave of initial COVID-19 event, symptomology of initial COVID-19 event, COVID-19 treatment, and comorbidity status[5]. Symptomology of the initial COVID-19 event was assessed using the COVID-like illness (CLI) ICD-10 codes provided in Supplemental Table 5-2. Symptomatic COVID-19 was defined as having a CLI diagnosis in any diagnostic position within 10 days before or after the COVID-19 event date in an inpatient or outpatient setting. The list of COVID-19 treatment names used is included in Supplemental Table 5-3, and the list of comorbidities and corresponding ICD-10 codes is included in Supplemental Table 5-4. Additionally, the number of total encounters for each service member during the follow-up period was included as a proxy for healthcare-seeking behaviors. Data for these risk factors were taken from the master list of cases and DMSS.

### 5.3.3 Case Definition

The outcome of interest, long COVID, was assessed using the Post-Acute Sequelae of COVID-19 (PASC) definition developed by the Defense Centers for Public Health-

Portsmouth (DCPH-P). The definition requires a service member to have a confirmed COVID-19 event and an ICD-10 code of one of the mental health, neurological, cardiac, or respiratory defining diagnoses between 4 and 52 weeks after the COVID-19 event. The service member must not have a diagnosis for that specific defining diagnosis within one year prior to the COVID-19 event. Inpatient and outpatient datasets from DMSS were used to identify incidence of long COVID in this population. Prior history of each diagnostic group within the previous one year was noted to determine baseline status for each group.

### 5.3.4 Analyses

Descriptive statistics for each vaccination exposure and the other risk factors are presented, including frequencies and percentages for categorical variables and means and standard deviations for continuous variables. This study utilized Cox proportional hazards regression to evaluate whether the incidence of long COVID is associated with each of the vaccination exposure variables. Crude hazard ratios (HRs) and 95% confidence intervals are shown for each exposure variable. An adjusted analysis was also performed incorporating the additional risk factors listed above. The length of time between most recent vaccine dose and the COVID-19 event was also assessed as a potential effect modifier of the relationship between the other vaccination exposures and the outcome. Adjusted HRs, 95% confidence intervals, and p-values are presented. Each exposure variable was assessed on whether it meets the proportional hazards assumption using the “cox.zph” function from the “survival” package in R. If a variable violated the proportional hazards assumption, a step function was included to calculate different $\beta(t)$ coefficient for each specified follow-up time period using the “survSplit” function from

the “survival” package. Results are presented both with and without stratification by follow-up period. The analysis was also performed for each diagnostic group (mental health, neurological, cardiac, and respiratory), with adjustments made for baseline status for that specific diagnostic group. All statistical analyses were conducted using R (version 4.1, The R Foundation for Statistical Computing, Vienna, Austria), and an alpha (α) level of 0.05 was considered statistically significant.

### 5.4 Results

In total, 464,356 cases of COVID-19 in active component servicemembers were identified between 2020 and 2022. Among those cases, 104,024 (22.4%) were diagnosed with incident long COVID during the follow-up period. Descriptive statistics are shown in Table 5-1. The distribution of vaccination exposures was similar between cases and non-cases, while a larger proportion of cases were female, over 35 years of age, non-Hispanic Black, members of the Army, enlisted, have had a symptomatic COVID-19 event, have been hospitalized for COVID-19, been a re-infection of COVID-19, received treatment for COVID-19, and have at least one comorbidity.

As expected, vaccination exposures showed high levels of correlation with each other, with all correlation coefficients exceeding 0.73. All variables also had high variance inflation factors (VIFs), indicating possible collinearity, including initial vaccine type (21.20), most recent vaccine type (6.70), time since last vaccine dose (6.77), and vaccine category at time of COVID-19 event (5.30). Due to potential collinearity, each vaccination exposure was assessed separately using the additional risk factors as covariates in the adjusted models. Additionally, each of the exposure variables violated

the proportional hazards assumption, indicating the hazard rate was not constant throughout the follow-up period. Step functions were included for each of the exposure variables using monthly time intervals throughout the follow-up period (11 total periods: 28-60 days, 61-90, 91-120, 121-150, 151-180, 181-210, 211-240, 241-270, 271-300, 301-330, and 331-360).Use of a step function satisfied the proportional hazards assumption for both vaccine category at time of COVID-19 event (p=0.1585) and most recent vaccine type (p=0.2889), while the assumption was nearly satisfied for initial vaccine type (p=0.0449). The assumption was still violated for time since last vaccine dose (p=0.0063), indicating some variability in the hazard rate even within monthly time intervals.

Table 5-2 shows the results of the initial stratified and unstratified Cox regression models without the step functions. After adjusting for the other risk factors, being vaccinated at the time of the COVID-19 event was associated with a decreased risk of long COVID compared to being unvaccinated, with risk being lower for those vaccinated with one or more booster doses (aHR, 0.91; 95% CI, 0.88 to 0.94) than for those who were partially or fully vaccinated (aHR, 0.96; 95% CI, 0.94 to 0.98). Being vaccinated with an initial vaccine series, regardless of subsequent booster doses, was also associated with decreased incident long COVID compared to those who were unvaccinated (aHR, 0.96; 95% CI, 0.93 to 0.98). Both mRNA vaccines (aHR 0.96, 95% CI 0.94-0.98, p<0.001) and other types of COVID-19 vaccines (aHR, 0.94; 95% CI, 0.91 to 0.97) for the most recent vaccine dose were associated with a decreased risk of long COVID compared to those who were unvaccinated. And the effect of receiving a vaccine was strongest among those receiving a vaccine within 3 months prior to the COVID-19 event (aHR, 0.94; 95% CI,

0.91 to 0.97). The risk of long COVID in those vaccinated 3-6 months prior to their COVID-19 event (aHR, 0.96; 95% CI, 0.93 to 0.98) and those vaccinated more than 6 months prior (aHR, 0.96; 95% CI, 0.94 to 0.99) were also reduced, though not as much as the less than 3 month group. An interaction between vaccination status at the time of the COVID-19 event and time since last vaccine dose was statistically significant ($p<0.001$). Table 5-2 also shows the results of the stratified analysis. Being vaccinated with one or more booster doses was associated with decreased risk of PASC compared to the partially or fully vaccinated group in both those vaccinated within 3 months prior to the COVID-19 event (aHR, 0.88; 95% CI, 0.84 to 0.94) and those vaccinated within 3-6 months prior to the COVID-19 event (aHR, 0.94; 95% CI, 0.90 to 0.98). However, no significant association was seen among those vaccinated more than 6 months prior to the COVID-19 event (aHR, 1.00; 95% CI, 0.97 to 1.04).

Results of the adjusted analyses by diagnostic group without use of a step function are also shown in Table 5-2. Results were similar to the overall PASC definition for neurological, respiratory, and cardiac diagnoses, with reduced risk seen in those who were vaccinated with one or more booster doses and those who were vaccinated within 3 months of their COVID-19 event. Notably, being partially or fully vaccinated was associated with a small but significantly higher rate of mental health diagnoses compared to being unvaccinated (aHR, 1.05; 95% CI, 1.01 to 1.08), while being vaccinated with one or more booster dose was not associated with mental health diagnoses (aHR 1.01, 95% CI 0.97-1.05, $p=0.6$). In addition, rates of mental health diagnoses were higher, though not significantly, in those vaccinated within 3 months of their COVID-19 event compared to those who were unvaccinated (aHR, 1.03; 95% CI, 0.99 to 1.07), and

continued to increase for those vaccinated 3-6 months prior to their COVID-19 event date (aHR, 1.04; 95% CI, 1.00 to 1.08) and those vaccinated >6 months prior (aHR, 1.05; 95% CI, 1.02 to 1.09).

The results of the regression models with a step function included are shown in Table 5-3 and Figure 5-1. Results in Table 5-3 are shown for the 1st (28-60 days), 6th (181-210 days), and 11th (331-365 days) follow-up time strata, while results in Figure 5-1 are shown across all follow-up periods. Results for the 1st strata are similar to those in Table 5-2, with being partially or fully vaccinated at the time of the COVID-19 event (aHR, 0.88; 95% CI, 0.85 to 0.91), being vaccinated with one or more booster doses at the time of the COVID-19 event (aHR, 0.77; 95% CI, 0.73 to 0.81), receiving any initial COVID-19 vaccine series (aHR, 0.86; 95% CI, 0.83 to 0.89), receiving a mRNA (aHR, 0.87; 95% CI, 0.84 to 0.89) or other vaccine type (aHR, 0.82; 95% CI, 0.84 to 0.89) as the most recent vaccine, and most recent vaccination within 3 months (aHR, 0.87; 95% CI, 0.84 to 0.92), 3-6 months (aHR, 0.88; 95% CI, 0.84 to 0.92), and >6 months (aHR, 0.86; 95% CI, 0.83 to 0.89) showing significantly reduced rates of PASC compared to those who were not vaccinated. However, with the exception of receiving the most recent vaccine within 3-6 months of the COVID-19 event (aHR, 0.92; 95% CI, 0.86 to 0.99), no other group was significantly different from the unvaccinated/no vaccine groups at the 6th and 11th strata.

Results of the adjusted analyses using step functions for each diagnostic group are shown in Table 5-4 and Figure 5-2. Similar to the results for the overall PASC definition, neurological, respiratory, and cardiac diagnostic groups showed significantly reduced

rates of diagnosis across all vaccination categories compared to unvaccinated groups earlier in the follow-up period, with differences between vaccinated and unvaccinated groups becoming mostly non-significant by the end of the follow-up period. The neurological diagnostic group maintained significantly reduced rates among vaccinated groups (compared to unvaccinated) through the 4$^{th}$ time strata (up to 5 months after COVID-19 diagnosis), while the respiratory diagnostic group maintained the same feat through the 7$^{th}$ time strata (up to 8 months of follow-up) and the cardiac diagnostic group through only the 2$^{nd}$ time strata (up to 3 months of follow-up). At some later time strata, most notably for the neurological diagnostic group, higher rates of diagnoses were seen in those who were vaccinated compared to unvaccinated. The mental health diagnostic group showed the opposite pattern than the other diagnostic groups, with significantly higher rates of diagnosis in the first 2 time strata (up to 3 months of follow-up) in vaccinated individuals compared to unvaccinated, with results becoming non-significant for the remainder of the study period.

**5.5 Discussion**

Incidence of long COVID was high in a population of active component U.S. servicemembers, at 70.4 per 100,000 person-days of follow-up from 2020-2022. Being vaccinated against COVID-19 prior to the COVID-19 event significantly reduced the rate of long COVID compared to being unvaccinated, with receipt of one or more booster doses reducing the rate of long COVID by 9% and being partially or fully vaccinated reducing the rate by 4%. This matches previous research indicating that vaccination against COVID-19 reduces the risk of subsequent long COVID, and that additional doses of vaccine may reduce the risk even further[44,45,99]. Significant interaction was seen

between vaccination status and the length of time between the last vaccine received and the COVID-19 event, with the effect of additional vaccine doses decreasing as the time since last vaccine dose increased. Among those with a COVID-19 event within 3 months of being vaccinated, receiving one or more booster dose significantly reduced the rate of long COVID by 12% compared to those who were partially or fully vaccinated. That reduction fell to a still significant 6% decrease among those with a COVID-19 event between 3 and 6 months after their most recent vaccination, and further to no reduction (HR=1) for those with a COVID-19 event more than 6 months after their most recent vaccination.

However, the hazard ratios changed significantly throughout the follow-up period, with the highest benefit of vaccination occurring during the first few months of follow-up before leveling off towards the middle and end of the follow-up period. During the first month of follow-up, being vaccinated with one or more booster doses prior to the COVID-19 infection reduced the of PASC by 23% compared to those who were unvaccinated. By the $6^{th}$ and $11^{th}$ months of follow-up the results had shifted to a 5% reduction and 4% increase, respectively, neither of which was statistically significant. Similar results were observed for vaccine type and time since the most recent vaccination. Nearly one quarter of PASC cases in the study were diagnosed within the first month of follow-up, and over half within the first four months of follow-up. Therefore, even short-term benefits from vaccination could have outsize effects.

The results of vaccination were even greater when looking at neurological, respiratory, and cardiac diagnoses, where rates in servicemembers vaccinated with a booster dose

decreased by 19%, 23%, and 14%, respectively, compared to unvaccinated servicemembers. However, no significant difference was seen for mental health diagnoses and a small but significant 5% increase was seen for those who were partially or fully vaccinated but had not received a booster dose. Prior research has shown that COVID-19 vaccination may reduce the risk of cardiovascular disease in patients previously infected with SARS-CoV-2[99]. Risk of long COVID was lowest among those vaccinated within 3 months of the COVID-19 event compared to those who were unvaccinated for neurological (HR=0.87), respiratory (HR=0.80), and cardiac (HR=0.91) outcomes, with risk steadily increasing as the length of time between vaccination and COVID-19 event increased. Again, the benefits of vaccination were concentrated mostly within the first few months of follow-up for neurological and cardiac diagnoses, with those receiving a booster having 56% and 38% lower rates of diagnoses, respectively, compared to those who were unvaccinated. Receipt of a booster dose prior to the COVID-19 event was more robust for respiratory diagnoses, with 41% lower rates seen during the first month of follow-up and 28% lower rates seen during the 6$^{th}$ month of follow-up. This pattern is similar to the dynamics seen for COVID-19 infection and severe disease, with the effect of vaccination most pronounced early after receipt of vaccine and declining over time.

The strength of this study is the use of linked medical records and a large cohort of COVID-19 cases, as well as a validated case definition for PASC. This study builds upon prior efforts to characterize long COVID in the U.S. military by focusing on the effect vaccination may play in the development of long COVID. This study does, however, rely on passive surveillance through medical records. Servicemembers are not required to

report or to visit a provider for symptoms consistent with long COVID, and healthcare utilization may have differed throughout the study period due to demographic factors or because of lockdowns and other pandemic-related factors. Efforts were made to control for a large number of potential confounders that may be related to healthcare utilization, as well as the total number of encounters for each servicemember. However, residual confounding may be present. Another limitation is that the case definition allows for a servicemember to meet the criteria for multiple individual diagnoses. While this more closely resembles the general population, it may make it more difficult to interpret the results for individual symptoms. Additionally, the study period ended in December 2022, limiting the ability to determine the effect of vaccination during the Omicron wave and the effect of more widely available vaccine types. COVID-19 vaccination after COVID-19 infection but prior to PASC diagnosis was not assessed in this study. Previous research has suggested that one or two doses of vaccine after being infected with SARS-CoV-2 may reduce long COVID symptoms for at least two months after receipt of the vaccine[48].

While uncertainty remains about the role of waning vaccine-induced immunity, this study highlights the effective role of vaccinations in the prevention of long COVID, especially in the first few months after a COVID-19 diagnosis and for respiratory, neurological, and cardiac outcomes. Booster doses are critical to reducing the risk of long COVID, as is the timing of COVID-19 vaccinations. Receipt of vaccinations within 3 months of a COVID-19 event may be more effective than those administered further away, emphasizing the need to anticipate increases in COVID-19 activity and make booster doses available close to those windows to maximize their effect. Additional research could be aimed at

exploring these associations during the Omicron wave and into more current time periods, as well as further tease out the interaction between time and vaccination status.

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### 5.7 Acknowledgments

**Shauna Stahlman, PhD; Alexis McQuistan, MPH**

**Table 5-1. Characteristics of long COVID cases and non-cases, active component service members, 2020-2022**

| Characteristic | Cases | Non-Cases |
|---|---|---|
| | N = 104,024[1] | N = 360,332[1] |
| COVID-19 Vaccination Status | | |
| Not vaccinated | 39,040 (37.5%) | 133,597 (37.1%) |
| Partially or fully vaccinated | 53,165 (51.1%) | 186,252 (51.7%) |
| One or more booster doses | 11,819 (11.4%) | 40,483 (11.2%) |
| Initial COVID-19 Vaccination Type | | |
| No vaccine | 39,043 (37.5%) | 133,612 (37.1%) |
| Any vaccine | 64,981 (62.5%) | 226,720 (62.9%) |
| Most Recent COVID-19 Vaccination Type | | |
| No vaccine | 39,040 (37.5%) | 133,597 (37.1%) |
| mRNA | 59,341 (57.0%) | 205,345 (57.0%) |
| Other vaccine | 5,643 (5.4%) | 21,390 (5.9%) |
| Time Between COVID-19 Event and Last Dose Received (days) | 238.9 (130.4) | 236.7 (128.7) |
| Time Period Between COVID-19 Event and Last Dose Received | | |
| No vaccine | 39,040 (37.5%) | 133,597 (37.1%) |
| < 3 months | 7,988 (7.7%) | 27,939 (7.8%) |
| 3-6 months | 14,325 (13.8%) | 49,679 (13.8%) |
| > 6 months | 42,671 (41.0%) | 149,117 (41.4%) |
| Sex | | |
| Female | 31,107 (29.9%) | 66,007 (18.3%) |
| Male | 72,917 (70.1%) | 294,325 (81.7%) |
| Age (years) | 29.0 (7.9) | 27.7 (7.2) |
| Age Group | | |
| <20 | 5,879 (5.7%) | 25,347 (7.0%) |
| 20-24 | 32,683 (31.4%) | 124,972 (34.7%) |
| 25-29 | 23,816 (22.9%) | 87,534 (24.3%) |
| 30-34 | 15,548 (14.9%) | 56,962 (15.8%) |
| 35-39 | 14,230 (13.7%) | 38,734 (10.7%) |
| 40-44 | 7,608 (7.3%) | 17,504 (4.9%) |
| 45+ | 4,259 (4.1%) | 9,278 (2.6%) |
| Unknown/Missing | 1 (0.0%) | 1 (0.0%) |
| Race | | |
| Asian | 3,877 (3.7%) | 14,357 (4.0%) |
| Hispanic | 20,478 (19.7%) | 72,726 (20.2%) |
| Non-Hispanic Black | 21,888 (21.0%) | 59,613 (16.5%) |
| Non-Hispanic White | 49,549 (47.6%) | 184,803 (51.3%) |
| Other | 6,522 (6.3%) | 23,634 (6.6%) |
| Unknown | 1,710 (1.6%) | 5,199 (1.4%) |
| Service | | |
| Air Force | 29,121 (28.0%) | 98,098 (27.2%) |

| | | |
|---|---|---|
| Army | 43,248 (41.6%) | 139,184 (38.6%) |
| Coast Guard | 838 (0.8%) | 3,711 (1.0%) |
| Marines | 9,511 (9.1%) | 45,376 (12.6%) |
| Navy | 21,306 (20.5%) | 73,963 (20.5%) |
| Rank | | |
| Enlisted | 91,339 (87.8%) | 306,533 (85.1%) |
| Officer | 12,685 (12.2%) | 53,799 (14.9%) |
| Education Level | | |
| Less than High School | 120 (0.1%) | 332 (0.1%) |
| High School | 66,760 (64.2%) | 239,758 (66.5%) |
| Some College | 15,214 (14.6%) | 42,701 (11.9%) |
| Bachelor's Degree | 13,226 (12.7%) | 47,923 (13.3%) |
| Advanced Degree | 7,297 (7.0%) | 23,294 (6.5%) |
| Other/Unknown | 1,407 (1.4%) | 6,324 (1.8%) |
| COVID-19 Hospitalization | | |
| Not Hospitalized | 102,555 (98.6%) | 358,423 (99.5%) |
| Hospitalized | 1,469 (1.4%) | 1,909 (0.5%) |
| COVID-19 Re-Infection Status | | |
| First Infection | 95,187 (91.5%) | 335,190 (93.0%) |
| Re-infection | 8,837 (8.5%) | 25,142 (7.0%) |
| COVID-19 Wave | | |
| Wild-type | 27,946 (26.9%) | 97,163 (27.0%) |
| Alpha | 2,326 (2.2%) | 7,989 (2.2%) |
| Delta | 17,540 (16.9%) | 59,087 (16.4%) |
| Omicron | 56,212 (54.0%) | 196,093 (54.4%) |
| COVID-19 Symptomology | | |
| Asymptomatic | 46,262 (44.5%) | 177,195 (49.2%) |
| Symptomatic | 57,762 (55.5%) | 183,137 (50.8%) |
| COVID-19 Treatment | | |
| No Treatment/Unknown | 103,750 (99.7%) | 359,972 (99.9%) |
| Any treatment | 274 (0.3%) | 360 (0.1%) |
| Comorbidity | | |
| No Comorbidity | 66,417 (63.8%) | 263,081 (73.0%) |
| Has Comorbodity | 37,607 (36.2%) | 97,251 (27.0%) |
| Number of Encounters | | |
| 0 | 0 (0.0%) | 5,799 (1.6%) |
| 1 | 135 (0.1%) | 11,547 (3.2%) |
| 2 | 426 (0.4%) | 17,559 (4.9%) |
| 3 | 734 (0.7%) | 21,527 (6.0%) |
| 4 | 1,152 (1.1%) | 23,775 (6.6%) |
| >=5 | 101,577 (97.6%) | 280,125 (77.7%) |
| [1] n (%); Mean (SD) | | |

**Table 5-2a. Hazard rate of incident PASC and individual PASC diagnostic groups by risk factor, active component service members, 2020-2022**

| Variable | Overall PASC | | | | | Mental Health | | Neurological | | Respiratory | | Cardiac | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Cases | Rate | Crude HR (95% CI)[1] | Adj HR (95% CI)[1,2] | p-valu | Rate | Adj HR (95% CI)[1,2] | Rate | Adj HR (95% CI)[1,2] | Rate | Adj HR (95% CI)[1,2] | Rate | Adj HR (95% CI)[1,2] |
| COVID-19 Vaccination Status | | | | | | | | | | | | | |
| Not vaccinated | 39,040 | 71.3 | — | — | | 35.3 | — | 4.9 | — | 21 | — | 22.5 | — |
| Partially or fully vaccinated | 53,165 | 69.6 | 0.98 (0.96, 0.99) | **0.96 (0.94, 0.98)** | 0.001 | 42.1 | **1.04 (1.01, 1.08)** | 3.2 | 0.92 (0.83, 1.01) | 12.1 | **0.82 (0.78, 0.86)** | 21.5 | **0.92 (0.88, 0.96)** |
| One or more booster doses | 11,819 | 70.7 | 0.99 (0.97, 1.01) | **0.91 (0.88, 0.94)** | <0.001 | 42.2 | 1.01 (0.97, 1.05) | 3.4 | **0.81 (0.71, 0.93)** | 12.2 | **0.77 (0.72, 0.82)** | 21.5 | **0.86 (0.82, 0.91)** |
| Initial COVID-19 Vaccination Type | | | | | | | | | | | | | |
| No vaccine | 39,043 | 71.3 | — | — | | 35.3 | — | 4.9 | — | 21.0 | — | 22.5 | — |
| Any vaccine | 64,981 | 69.8 | 0.98 (0.97, 0.99) | **0.96 (0.93, 0.98)** | <0.001 | 42.2 | **1.04 (1.01, 1.08)** | 3.3 | 0.91 (0.82, 1.00) | 12.1 | **0.82 (0.78, 0.86)** | 21.5 | **0.91 (0.88, 0.95)** |
| Most Recent COVID-19 Vaccination Type | | | | | | | | | | | | | |
| No vaccine | 39,040 | 71.3 | — | — | | 35.3 | — | 4.9 | — | 21 | — | 22.5 | — |
| mRNA | 59,341 | 70.3 | 0.99 (0.97, 1.00) | **0.96 (0.94, 0.98)** | <0.001 | 42.5 | **1.04 (1.01, 1.08)** | 3.3 | 0.91 (0.83, 1.01) | 12.2 | **0.82 (0.78, 0.86)** | 21.7 | **0.92 (0.88, 0.96)** |
| Other vaccine | 5,643 | 64.8 | 0.91 (0.88, 0.93) | **0.94 (0.91, 0.97)** | <0.001 | 39.2 | 1.03 (0.98, 1.07) | 3 | 0.88 (0.76, 1.01) | 11.6 | **0.82 (0.76, 0.88)** | 20.1 | **0.89 (0.84, 0.94)** |
| Time Period Between COVID-19 Event and Last Dose Received | | | | | | | | | | | | | |
| No vaccine | 39,040 | 71.3 | — | — | | 35.3 | — | 4.9 | — | 21 | — | 22.5 | — |
| < 3 months | 7,988 | 69.6 | 0.98 (0.95, 1.00) | **0.94 (0.91, 0.97)** | <0.001 | 41.1 | 1.03 (0.99, 1.07) | 3.3 | **0.87 (0.77, 0.99)** | 12.8 | **0.80 (0.75, 0.85)** | 21.7 | **0.91 (0.86, 0.96)** |
| 3-6 months | 14,325 | 70.2 | 0.98 (0.96, 1.00) | **0.96 (0.93, 0.98)** | 0.002 | 41.6 | 1.04 (1.00, 1.07) | 3.2 | 0.90 (0.80, 1.02) | 12.8 | **0.84 (0.79, 0.89)** | 21.8 | **0.91 (0.87, 0.96)** |
| > 6 months | 42,671 | 69.7 | 0.98 (0.96, 0.99) | **0.96 (0.94, 0.99)** | 0.004 | 42.5 | **1.05 (1.02, 1.09)** | 3.3 | 0.93 (0.84, 1.03) | 11.8 | **0.82 (0.78, 0.86)** | 21.4 | **0.92 (0.88, 0.96)** |

[1]HR=Hazard Ratio, CI=Confidence Interval; [2]Adjusted individually for sex, age group, race/ethnicity, rank, education, COVID-19 symptoms, COVID-19 hospitalization, COVID-19 re-infection, COVID-19 treatment, COVID-19 wave, any comorbidity, and total encounters

**Table 5-2b. Hazard rate of incident PASC by risk factor, stratified by time between COVID-19 event and last dose received, active component service members, 2020-2022**

| Variable | Person-Days | Cases | Rate | Crude HR (95% CI)[1] | Adj HR (95% CI)[1] | p-value |
|---|---|---|---|---|---|---|
| **Unvaccinated** | | | | | | |
| COVID-19 Vaccination Status | | | | | | |
| 31.1:Not vaccinated | 54,724,712 | 39,040 | 71.3 | | | |
| **<3 months between COVID-19 Event and Last Dose Received** | | | | | | |
| COVID-19 Vaccination Status | | | | | | |
| 31.2:Partially or fully vaccinated | 5,360,939 | 3,934 | 73.4 | Ref | Ref | |
| 31.4:One or more booster doses | 6,118,444 | 4,054 | 66.3 | 0.90 (0.86, 0.94) | **0.88 (0.84, 0.94)** | <0.001 |
| **3-6 months between COVID-19 Event and Last Dose Received** | | | | | | |
| COVID-19 Vaccination Status | | | | | | |
| 31.2:Partially or fully vaccinated | 15,616,013 | 10,977 | 70.3 | Ref | Ref | |
| 31.4:One or more booster doses | 4,804,502 | 3,348 | 69.7 | 0.99 (0.95, 1.03) | **0.94 (0.90, 0.98)** | 0.007 |
| **>6 months between COVID-19 Event and Last Dose Received** | | | | | | |
| COVID-19 Vaccination Status | | | | | | |
| 31.2:Partially or fully vaccinated | 55,425,462 | 38,254 | 69.0 | Ref | Ref | |
| 31.4:One or more booster doses | 5,783,624 | 4,417 | 76.4 | 1.10 (1.07, 1.14) | 1.00 (0.97, 1.04) | 0.8 |

[1]*HR=Hazard Ratio, CI=Confidence Interval*

[2]*Adjusted individually for sex, age group, race/ethnicity, rank, education, COVID-19 symptoms, COVID-19 hospitalization, COVID-19 re-infection, COVID-19 treatment, COVID-19 wave, any comorbidity, and total encounters*

**Table 5-3a. Hazard rate of incident PASC by risk factor and follow-up periods, active component service members, 2020-2022**

| | 30-60 Days | | 61-90 Days | | 91-120 Days | | 121-150 Days | | 151-180 Days | | 181-210 Days | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Variable** | **Rate** | **Adj HR (95% CI)[1,2]** | **Rate** | **Adj HR (95% CI)[1,2]** | **Rate** | **Adj HR (95% CI)[1,2]** | **Rate** | **Adj HR (95% CI)[1,2]** | **Rate** | **Adj HR (95% CI)[1,2]** | **Rate** | **Adj HR (95% CI)[1,2]** |
| COVID-19 Vaccination Status | | | | | | | | | | | | |
| Not vaccinated | 96.9 | Ref | 94.7 | Ref | 81.3 | Ref | 71.4 | Ref | 64.1 | Ref | 63.7 | Ref |
| Partially or fully vaccinated | 85.8 | **0.88 (0.85, 0.91)** | 93.5 | 0.97 (0.93, 1.02) | 79.2 | 0.96 (0.92, 1.00) | 68.9 | **0.95 (0.90, 1.00)** | 63.8 | 0.98 (0.93, 1.03) | 64.4 | 1.00 (0.94, 1.05) |
| One or more booster doses | 79.9 | **0.77 (0.73, 0.81)** | 92.4 | **0.90 (0.84, 0.96)** | 79.7 | **0.90 (0.84, 0.97)** | 73.0 | 0.94 (0.87, 1.01) | 65.4 | 0.94 (0.87, 1.01) | 65.9 | 0.95 (0.88, 1.03) |
| Initial COVID-19 Vaccination Type | | | | | | | | | | | | |
| No vaccine | 96.9 | Ref | 94.7 | Ref | 81.3 | Ref | 71.4 | Ref | 64.0 | Ref | 63.7 | Ref |
| Any vaccine | 84.7 | **0.86 (0.83, 0.89)** | 93.3 | 0.96 (0.92, 1.01) | 79.3 | **0.95 (0.91, 1.00)** | 69.6 | 0.95 (0.91, 1.00) | 64.1 | 0.98 (0.93, 1.03) | 64.7 | 0.99 (0.94, 1.04) |
| Most Recent COVID-19 Vaccination Type | | | | | | | | | | | | |
| No vaccine | 96.9 | Ref | 94.7 | Ref | 81.3 | Ref | 71.4 | Ref | 64.1 | Ref | 63.7 | Ref |
| mRNA | 85.5 | **0.87 (0.84, 0.89)** | 93.7 | 0.96 (0.92, 1.01) | 79.6 | **0.95 (0.91, 1.00)** | 70.0 | 0.95 (0.91, 1.00) | 64.9 | 0.99 (0.94, 1.04) | 64.6 | 0.99 (0.94, 1.04) |
| Other vaccine | 76.6 | **0.82 (0.84, 0.89)** | 89.2 | 0.97 (0.89, 1.05) | 75.9 | 0.96 (0.88, 1.05) | 66.0 | 0.95 (0.86, 1.05) | 56.5 | 0.91 (0.82, 1.01) | 65.0 | 1.05 (0.95, 1.16) |
| Time Period Between COVID-19 Event and Last Dose Received | | | | | | | | | | | | |
| No vaccine | 96.9 | Ref | 94.7 | Ref | 81.3 | Ref | 71.4 | Ref | 64.1 | Ref | 63.7 | Ref |
| < 3 months | 86.5 | **0.87 (0.84, 0.92)** | 91.4 | 0.93 (0.86, 1.00) | 73.7 | **0.87 (0.81, 0.95)** | 67.9 | **0.92 (0.84, 1.00)** | 60.9 | 0.92 (0.84, 1.00) | 65.3 | 0.98 (0.90, 1.08) |
| 3-6 months | 86.4 | **0.88 (0.84, 0.92)** | 93.4 | 0.96 (0.91, 1.02) | 76.5 | **0.92 (0.86, 0.98)** | 70.8 | 0.97 (0.90, 1.03) | 64.1 | 0.97 (0.90, 1.05) | 60.5 | **0.92 (0.86, 0.99)** |
| > 6 months | 83.8 | **0.86 (0.83, 0.89)** | 93.6 | 0.97 (0.93, 1.02) | 81.2 | 0.98 (0.94, 1.03) | 69.5 | 0.96 (0.91, 1.01) | 64.7 | 1.00 (0.94, 1.05) | 66.0 | 1.02 (0.97, 1.08) |

[1]HR=Hazard Ratio, CI=Confidence Interval; [2]Adjusted individually for sex, age group, race/ethnicity, rank, education, COVID-19 symptoms, COVID-19 hospitalization, COVID-19 re-infection, COVID-19 treatment, COVID-19 wave, any comorbidity, and total encounters

**Table 5-3b. Hazard rate of incident PASC by risk factor and follow-up periods, active component service members, 2020-2022**

| | 211-240 Days | | 241-270 Days | | 271-300 Days | | 301-330 Days | | 331-360 Days | |
|---|---|---|---|---|---|---|---|---|---|---|
| **Variable** | **Rate** | **Adj HR (95% CI)[1,2]** | **Rate** | **Adj HR (95% CI)[1,2]** | **Rate** | **Adj HR (95% CI)[1,2]** | **Rate** | **Adj HR (95% CI)[1,2]** | **Rate** | **Adj HR (95% CI)[1,2]** |
| COVID-19 Vaccination Status | | | | | | | | | | |
| Not vaccinated | 63.7 | Ref | 56.9 | Ref | 54.8 | Ref | 50.9 | Ref | 49.0 | Ref |
| Partially or fully vaccinated | 63.2 | 0.98 (0.93, 1.03) | 59.1 | 1.02 (0.96, 1.08) | 57.4 | 1.03 (0.97, 1.09) | 54.7 | 1.05 (0.99, 1.12) | 51.1 | 1.03 (0.97, 1.09) |
| One or more booster doses | 65.2 | 0.94 (0.86, 1.01) | 65.1 | 1.04 (0.96, 1.13) | 62.1 | 1.03 (0.95, 1.13) | 58.6 | 1.05 (0.96, 1.15) | 55.7 | 1.04 (0.96, 1.13) |
| Initial COVID-19 Vaccination Type | | | | | | | | | | |
| No vaccine | 63.7 | Ref | 56.9 | Ref | 54.8 | Ref | 50.9 | Ref | 49.0 | Ref |
| Any vaccine | 63.6 | 0.97 (0.93, 1.03) | 60.1 | 1.03 (0.98, 1.09) | 58.2 | 1.04 (0.98, 1.09) | 55.4 | **1.06 (1.00, 1.12)** | 52.0 | 1.03 (0.98, 1.09) |
| Most Recent COVID-19 Vaccination Type | | | | | | | | | | |
| No vaccine | 63.7 | Ref | 56.9 | Ref | 54.8 | Ref | 50.9 | Ref | 49.0 | Ref |
| mRNA | 63.6 | 0.97 (0.92, 1.02) | 60.7 | 1.03 (0.98, 1.09) | 58.9 | 1.04 (0.99, 1.10) | 56.0 | **1.07 (1.01, 1.13)** | 52.6 | 1.04 (0.99, 1.10) |
| Other vaccine | 63.6 | 1.03 (0.93, 1.14) | 54.9 | 0.99 (0.89, 1.11) | 51.9 | 0.97 (0.87, 1.09) | 49.6 | 1.00 (0.89, 1.13) | 45.7 | 0.96 (0.85, 1.08) |
| Time Period Between COVID-19 Event and Last Dose Received | | | | | | | | | | |
| No vaccine | 63.7 | Ref | 56.9 | Ref | 54.8 | Ref | 50.9 | Ref | 49.0 | Ref |
| < 3 months | 64.2 | 0.97 (0.88, 1.05) | 62.8 | 1.06 (0.96, 1.16) | 58.2 | 1.02 (0.92, 1.12) | 56.6 | 1.07 (0.97, 1.18) | 53.5 | 1.05 (0.95, 1.16) |
| 3-6 months | 63.5 | 0.97 (0.90, 1.04) | 61.2 | 1.04 (0.96, 1.13) | 62.1 | **1.10 (1.02, 1.19)** | 56.0 | 1.07 (0.98, 1.16) | 52.8 | 1.05 (0.97, 1.13) |
| > 6 months | 63.5 | 0.98 (0.93, 1.04) | 59.3 | 1.02 (0.97, 1.09) | 56.9 | 1.02 (0.96, 1.08) | 54.9 | 1.06 (1.00, 1.13) | 51.4 | 1.03 (0.97, 1.09) |

[1]HR=Hazard Ratio, CI=Confidence Interval; [2]Adjusted individually for sex, age group, race/ethnicity, rank, education, COVID-19 symptoms, COVID-19 hospitalization, COVID-19 re-infection, COVID-19 treatment, COVID-19 wave, any comorbidity, and total encounters

**Table 5-4a. Hazard rate of incident PASC by risk factor and follow-up periods, stratified by time between COVID-19 event and last dose received, active component service members, 2020-2022**

| | 30-60 Days | | 61-90 Days | | 91-120 Days | | 121-150 Days | | 151-180 Days | | 181-210 Days | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Variable** | **Rate** | **Adj HR (95% CI)[1,2]** | **Rate** | **Adj HR (95% CI)[1,2]** | **Rate** | **Adj HR (95% CI)[1,2]** | **Rate** | **Adj HR (95% CI)[1,2]** | **Rate** | **Adj HR (95% CI)[1,2]** | **Rate** | **Adj HR (95% CI)[1,2]** |
| **Unvaccinated** | | | | | | | | | | | | |
| COVID-19 Vaccination Status | | | | | | | | | | | | |
| Not vaccinated | 96.9 | | 94.7 | | 81.3 | | 71.4 | | 64.1 | | 63.7 | |
| **<3 months between COVID-19 Event and Last Dose Received** | | | | | | | | | | | | |
| COVID-19 Vaccination Status | | | | | | | | | | | | |
| Partially or fully vaccinated | 93.9 | Ref | 98.0 | Ref | 76.7 | Ref | 72.2 | Ref | 66.9 | Ref | 65.3 | Ref |
| One or more booster doses | 79.9 | **0.84 (0.76, 0.92)** | 85.6 | **0.86 (0.76, 0.99)** | 71.2 | 0.91 (0.78, 1.06) | 64.1 | 0.87 (0.74, 1.02) | 55.7 | **0.81 (0.69, 0.96)** | 65.3 | 0.98 (0.83, 1.15) |
| **3-6 months between COVID-19 Event and Last Dose Received** | | | | | | | | | | | | |
| COVID-19 Vaccination Status | | | | | | | | | | | | |
| Partially or fully vaccinated | 89.7 | Ref | 96.2 | Ref | 76.3 | Ref | 70.7 | Ref | 63.8 | Ref | 59.7 | Ref |
| One or more booster doses | 75.7 | **0.82 (0.75, 0.90)** | 84.5 | **0.83 (0.74, 0.94)** | 77.1 | 0.95 (0.84, 1.08) | 71.2 | 0.95 (0.83, 1.09) | 65.1 | 0.96 (0.84, 1.11) | 63.3 | 1.00 (0.86, 1.16) |
| **>6 months between COVID-19 Event and Last Dose Received** | | | | | | | | | | | | |
| COVID-19 Vaccination Status | | | | | | | | | | | | |
| Partially or fully vaccinated | 83.8 | Ref | 92.4 | Ref | 80.2 | Ref | 68.0 | Ref | 63.6 | Ref | 65.7 | Ref |
| One or more booster doses | 83.2 | **0.90 (0.84, 0.97)** | 105.9 | 1.04 (0.95, 1.14) | 90.9 | 1.03 (0.94, 1.14) | 84.0 | **1.12 (1.01, 1.25)** | 76.0 | 1.09 (0.97, 1.21) | 68.8 | 0.95 (0.85, 1.07) |

[1]HR=Hazard Ratio, CI=Confidence Interval; [2]Adjusted individually for sex, age group, race/ethnicity, rank, education, COVID-19 symptoms, COVID-19 hospitalization, COVID-19 re-infection, COVID-19 treatment, COVID-19 wave, any comorbidity, and total encounters

**Table 5-4b. Hazard rate of incident PASC by risk factor and follow-up periods, stratified by time between COVID-19 event and last dose received, active component service members, 2020-2022**

| | 211-240 Days | | 241-270 Days | | 271-300 Days | | 301-330 Days | | 331-360 Days | |
|---|---|---|---|---|---|---|---|---|---|---|
| **Variable** | **Rate** | **Adj HR (95% CI)[1,2]** | **Rate** | **Adj HR (95% CI)[1,2]** | **Rate** | **Adj HR (95% CI)[1,2]** | **Rate** | **Adj HR (95% CI)[1,2]** | **Rate** | **Adj HR (95% CI)[1,2]** |
| **Unvaccinated** | | | | | | | | | | |
| COVID-19 Vaccination Status | | | | | | | | | | |
| Not vaccinated | 63.7 | | 56.9 | | 54.8 | | 50.9 | | 49.0 | |
| **<3 months between COVID-19 Event and Last Dose Received** | | | | | | | | | | |
| COVID-19 Vaccination Status | | | | | | | | | | |
| Partially or fully vaccinated | 71.0 | Ref | 62.3 | Ref | 57.1 | Ref | 59.4 | Ref | 54.2 | Ref |
| One or more booster doses | 58.2 | 0.80 (0.68, 0.95) | 63.2 | 0.99 (0.84, 1.17) | 59.1 | 1.01 (0.85, 1.21) | 54.3 | 0.89 (0.74, 1.07) | 52.8 | 0.95 (0.79, 1.13) |
| **3-6 months between COVID-19 Event and Last Dose Received** | | | | | | | | | | |
| COVID-19 Vaccination Status | | | | | | | | | | |
| Partially or fully vaccinated | 62.1 | Ref | 59.8 | Ref | 60.8 | Ref | 54.5 | Ref | 51.0 | Ref |
| One or more booster doses | 68.0 | 1.03 (0.89, 1.18) | 65.8 | 1.03 (0.89, 1.19) | 66.4 | 1.02 (0.88, 1.19) | 60.9 | 1.05 (0.90, 1.23) | 58.6 | 1.08 (0.93, 1.25) |
| **>6 months between COVID-19 Event and Last Dose Received** | | | | | | | | | | |
| COVID-19 Vaccination Status | | | | | | | | | | |
| Partially or fully vaccinated | 62.7 | Ref | 58.5 | Ref | 56.4 | Ref | 54.2 | Ref | 50.9 | Ref |
| One or more booster doses | 70.5 | 1.02 (0.91, 1.14) | 66.4 | 1.03 (0.91, 1.16) | 61.7 | 0.99 (0.87, 1.13) | 61.2 | 1.02 (0.90, 1.16) | 56.3 | 1.00 (0.89, 1.14) |

[1]HR=Hazard Ratio, CI=Confidence Interval; [2]Adjusted individually for sex, age group, race/ethnicity, rank, education, COVID-19 symptoms, COVID-19 hospitalization, COVID-19 re-infection, COVID-19 treatment, COVID-19 wave, any comorbidity, and total encounters

**Figure 5-1. Follow-up Time Group-Adjusted Hazard Ratio and 95% Confidence Interval by COVID-19 Vaccine Exposure, active component service members, 2020-2022**

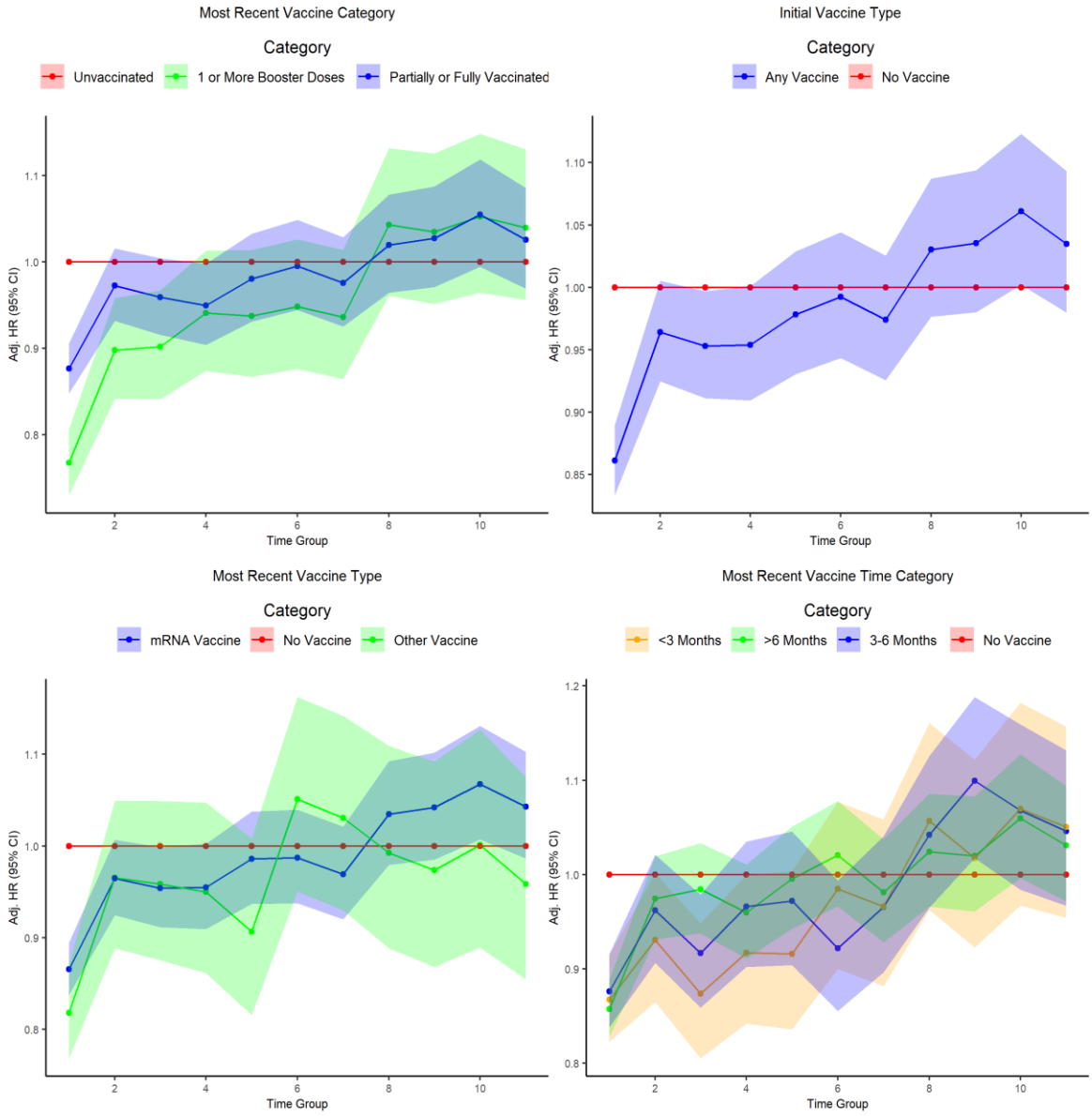


**Table 5-5. Hazard rate of incident PASC diagnostic groups by risk factor and by follow-up period, active component service members, 2020-2022**

| | A) Mental Health | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| **Variable** | 28-60 Days | 61-90 Days | 91-120 Days | 121-150 Days | 151-180 Days | 181-210 Days | 211-240 Days | 241-270 Days | 271-300 Days | 301-330 Days | 331-365 Days |
| | **Adj HR (95% CI)**[1,2] | | | | | | | | | | |
| COVID-19 Vaccination Status | | | | | | | | | | | |
| Not vaccinated | Ref | Ref | Ref | Ref | Ref | Ref | Ref | Ref | Ref | Ref | Ref |
| Partially or fully vaccinated | **1.10 (1.05, 1.15)** | **1.10 (1.03, 1.16)** | 1.05 (0.99, 1.12) | 1.04 (0.98, 1.11) | 1.00 (0.94, 1.07) | 1.04 (0.97, 1.11) | 1.01 (0.94, 1.08) | 1.05 (0.98, 1.12) | 1.01 (0.94, 1.09) | 1.01 (0.94, 1.09) | 0.94 (0.88, 1.01) |
| One or more booster doses | 0.98 (0.92, 1.05) | 1.07 (0.99, 1.17) | 0.98 (0.89, 1.07) | 1.04 (0.94, 1.14) | 0.98 (0.89, 1.09) | 1.03 (0.93, 1.13) | 1.02 (0.92, 1.12) | 1.06 (0.96, 1.18) | 1.04 (0.93, 1.15) | 0.97 (0.87, 1.09) | 0.98 (0.88, 1.09) |
| Initial COVID-19 Vaccination Type | | | | | | | | | | | |
| No vaccine | Ref | Ref | Ref | Ref | Ref | Ref | Ref | Ref | Ref | Ref | Ref |
| Any vaccine | **1.08 (1.04, 1.13)** | **1.10 (1.04, 1.16)** | 1.04 (0.98, 1.11) | 1.05 (0.98, 1.11) | 1.00 (0.94, 1.07) | 1.04 (0.97, 1.11) | 1.01 (0.95, 1.08) | 1.06 (0.99, 1.13) | 1.02 (0.95, 1.10) | 1.01 (0.94, 1.08) | 0.95 (0.89, 1.02) |
| Most Recent COVID-19 Vaccination Type | | | | | | | | | | | |
| No vaccine | Ref | Ref | Ref | Ref | Ref | Ref | Ref | Ref | Ref | Ref | Ref |
| mRNA | **1.09 (1.04, 1.14)** | **1.10 (1.03, 1.16)** | 1.04 (0.98, 1.10) | 1.05 (0.98, 1.12) | 1.01 (0.94, 1.08) | 1.03 (0.96, 1.10) | 1.01 (0.95, 1.08) | 1.06 (0.99, 1.13) | 1.03 (0.96, 1.10) | 1.01 (0.94, 1.09) | 0.96 (0.89, 1.03) |
| Other vaccine | 0.99 (0.91, 1.07) | 1.12 (1.00, 1.25) | 1.10 (0.98, 1.23) | 1.02 (0.90, 1.16) | 0.97 (0.85, 1.10) | **1.17 (1.04, 1.33)** | 1.05 (0.92, 1.19) | 1.05 (0.92, 1.20) | 0.98 (0.84, 1.13) | 1.00 (0.87, 1.16) | 0.91 (0.79, 1.05) |
| Time Period Between COVID-19 Event and Last Dose Received | | | | | | | | | | | |
| No vaccine | Ref | Ref | Ref | Ref | Ref | Ref | Ref | Ref | Ref | Ref | Ref |
| < 3 months | 1.06 (0.99, 1.14) | 1.07 (0.97, 1.18) | 0.99 (0.89, 1.10) | 1 (0.90, 1.12) | 0.90 (0.80, 1.02) | 1.07 (0.96, 1.20) | 1.08 (0.97, 1.21) | 1.08 (0.96, 1.21) | 1.03 (0.92, 1.17) | 0.95 (0.84, 1.08) | 0.95 (0.84, 1.07) |
| 3-6 months | 1.07 (1.00, 1.13) | 1.08 (1.00, 1.17) | 1.03 (0.94, 1.12) | 1.05 (0.96, 1.15) | 1.00 (0.91, 1.09) | 0.97 (0.88, 1.06) | 1.04 (0.95, 1.14) | 1.08 (0.98, 1.19) | 1.07 (0.97, 1.18) | 1.00 (0.90, 1.11) | 0.97 (0.88, 1.07) |
| > 6 months | **1.1 (1.05, 1.15)** | **1.11 (1.05, 1.18)** | 1.06 (1.00, 1.13) | 1.06 (0.99, 1.13) | 1.03 (0.96, 1.10) | 1.06 (0.99, 1.14) | 1.00 (0.93, 1.07) | 1.04 (0.97, 1.12) | 1.01 (0.93, 1.09) | 1.03 (0.95, 1.11) | 0.95 (0.88, 1.03) |

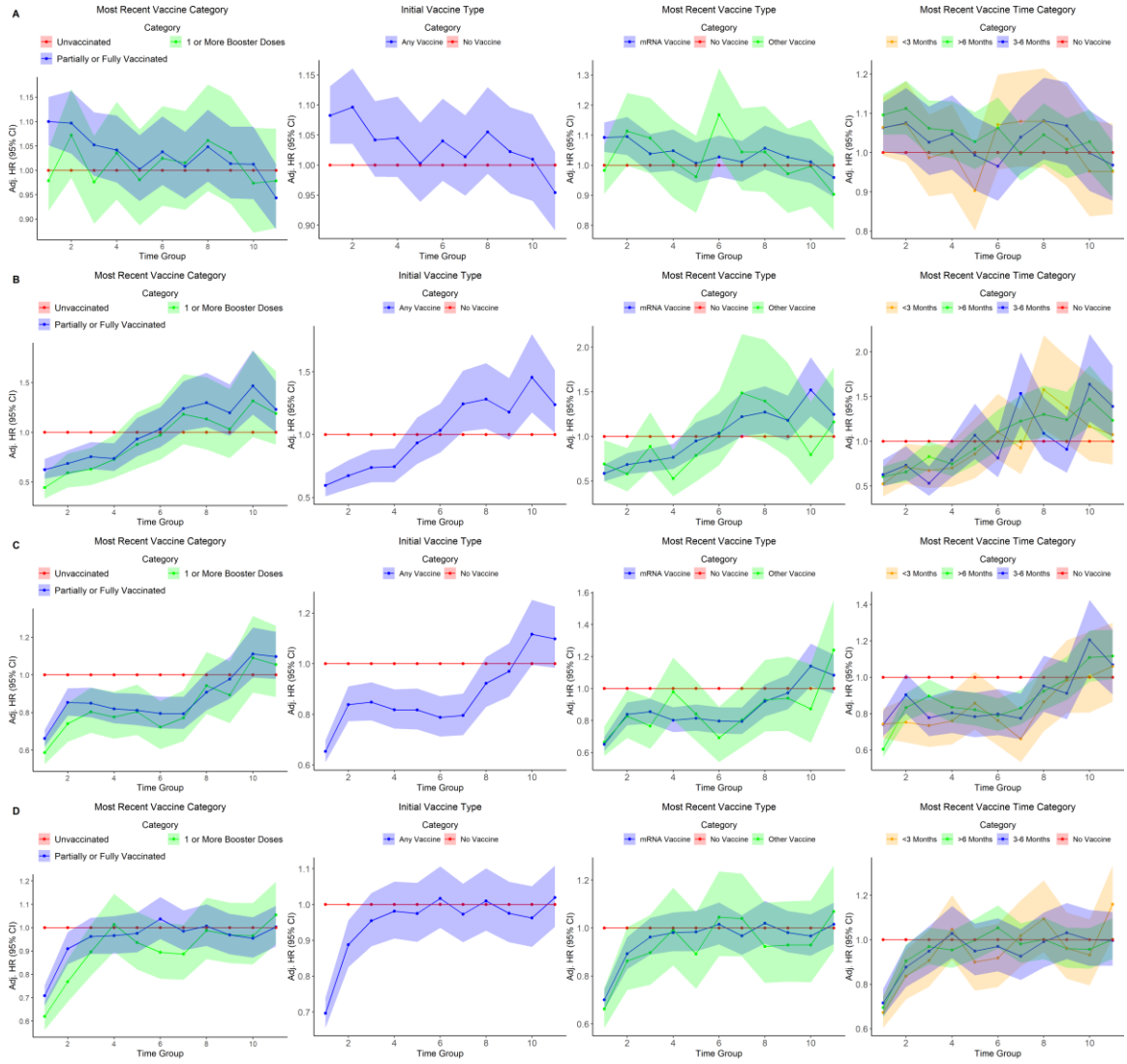
| | B) Neurological | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| **Variable** | 28-60 Days | 61-90 Days | 91-120 Days | 121-150 Days | 151-180 Days | 181-210 Days | 211-240 Days | 241-270 Days | 271-300 Days | 301-330 Days | 331-365 Days |
| | **Adj HR (95% CI)**[1,2] | | | | | | | | | | |
| COVID-19 Vaccination Status | | | | | | | | | | | |
| Not vaccinated | Ref | Ref | Ref | Ref | Ref | Ref | Ref | Ref | Ref | Ref | Ref |
| Partially or fully vaccinated | **0.62 (0.53, 0.73)** | **0.69 (0.58, 0.82)** | **0.75 (0.63, 0.90)** | **0.74 (0.61, 0.89)** | 0.93 (0.76, 1.14) | 1.03 (0.85, 1.25) | **1.24 (1.02, 1.51)** | **1.30 (1.05, 1.60)** | 1.20 (0.97, 1.48) | **1.47 (1.18, 1.83)** | 1.23 (1.00, 1.51) |
| One or more booster doses | **0.44 (0.34, 0.58)** | **0.59 (0.44, 0.78)** | **0.63 (0.47, 0.84)** | **0.73 (0.54, 0.97)** | 0.87 (0.64, 1.20) | 0.97 (0.72, 1.30) | 1.18 (0.88, 1.58) | 1.13 (0.82, 1.55) | 1.03 (0.74, 1.43) | 1.31 (0.95, 1.82) | 1.19 (0.88, 1.61) |
| Initial COVID-19 Vaccination Type | | | | | | | | | | | |
| No vaccine | Ref | Ref | Ref | Ref | Ref | Ref | Ref | Ref | Ref | Ref | Ref |
| Any vaccine | **0.59 (0.51, 0.69)** | **0.67 (0.57, 0.80)** | **0.74 (0.62, 0.88)** | **0.74 (0.62, 0.89)** | 0.93 (0.77, 1.14) | 1.03 (0.86, 1.24) | **1.24 (1.03, 1.51)** | **1.28 (1.05, 1.57)** | 1.18 (0.96, 1.45) | **1.45 (1.18, 1.80)** | **1.24 (1.01, 1.51)** |
| Most Recent COVID-19 Vaccination Type | | | | | | | | | | | |
| No vaccine | Ref | Ref | Ref | Ref | Ref | Ref | Ref | Ref | Ref | Ref | Ref |
| mRNA | **0.59 (0.50, 0.69)** | **0.69 (0.58, 0.82)** | **0.73 (0.61, 0.87)** | **0.77 (0.64, 0.92)** | 0.95 (0.78, 1.16) | 1.04 (0.86, 1.26) | **1.22 (1.01, 1.49)** | **1.27 (1.04, 1.57)** | 1.18 (0.96, 1.46) | **1.52 (1.23, 1.89)** | **1.25 (1.02, 1.53)** |
| Other vaccine | **0.69 (0.50, 0.95)** | **0.58 (0.39, 0.87)** | 0.88 (0.62, 1.26) | **0.53 (0.33, 0.84)** | 0.78 (0.49, 1.25) | 1.00 (0.67, 1.50) | **1.48 (1.02, 2.13)** | 1.39 (0.93, 2.07) | 1.18 (0.76, 1.81) | 0.79 (0.46, 1.38) | 1.16 (0.76, 1.77) |
| Time Period Between COVID-19 Event and Last Dose Received | | | | | | | | | | | |
| No vaccine | Ref | Ref | Ref | Ref | Ref | Ref | Ref | Ref | Ref | Ref | Ref |
| < 3 months | **0.53 (0.39, 0.72)** | **0.71 (0.52, 0.97)** | **0.67 (0.48, 0.95)** | 0.70 (0.50, 1.00) | 0.86 (0.59, 1.25) | 1.10 (0.80, 1.53) | 0.93 (0.63, 1.35) | **1.58 (1.14, 2.19)** | 1.38 (0.97, 1.95) | 1.17 (0.78, 1.74) | 1.07 (0.74, 1.56) |
| 3-6 months | **0.63 (0.50, 0.79)** | **0.73 (0.57, 0.94)** | **0.53 (0.39, 0.72)** | 0.79 (0.60, 1.04) | 1.07 (0.80, 1.42) | 0.81 (0.60, 1.10) | **1.53 (1.18, 1.99)** | 1.09 (0.79, 1.48) | 0.91 (0.65, 1.27) | **1.64 (1.22, 2.19)** | **1.39 (1.05, 1.84)** |
| > 6 months | **0.61 (0.51, 0.72)** | **0.66 (0.55, 0.79)** | 0.83 (0.69, 1.00) | **0.75 (0.61, 0.91)** | 0.92 (0.74, 1.14) | 1.11 (0.90, 1.35) | 1.23 (0.99, 1.51) | **1.30 (1.05, 1.62)** | 1.24 (0.99, 1.55) | **1.47 (1.17, 1.85)** | 1.23 (0.99, 1.54) |

| | C) Respiratory | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| **Variable** | 28-60 Days | 61-90 Days | 91-120 Days | 121-150 Days | 151-180 Days | 181-210 Days | 211-240 Days | 241-270 Days | 271-300 Days | 301-330 Days | 331-365 Days |
| | **Adj HR (95% CI)**[1,2] | | | | | | | | | | |
| COVID-19 Vaccination Status | | | | | | | | | | | |
| Not vaccinated | Ref | Ref | Ref | Ref | Ref | Ref | Ref | Ref | Ref | Ref | Ref |
| Partially or fully vaccinated | **0.66 (0.62, 0.71)** | **0.85 (0.78, 0.93)** | **0.85 (0.78, 0.93)** | **0.82 (0.74, 0.90)** | **0.81 (0.73, 0.90)** | **0.80 (0.72, 0.88)** | **0.79 (0.71, 0.88)** | 0.91 (0.81, 1.01) | 0.98 (0.87, 1.09) | 1.11 (0.99, 1.25) | 1.10 (0.98, 1.23) |
| One or more booster doses | **0.59 (0.53, 0.65)** | **0.74 (0.64, 0.85)** | **0.80 (0.69, 0.93)** | **0.78 (0.66, 0.91)** | **0.80 (0.68, 0.95)** | **0.72 (0.61, 0.86)** | **0.77 (0.65, 0.92)** | 0.94 (0.79, 1.12) | 0.89 (0.74, 1.07) | 1.09 (0.91, 1.31) | 1.05 (0.88, 1.26) |
| Initial COVID-19 Vaccination Type | | | | | | | | | | | |
| No vaccine | Ref | Ref | Ref | Ref | Ref | Ref | Ref | Ref | Ref | Ref | Ref |
| Any vaccine | **0.65 (0.61, 0.70)** | **0.84 (0.77, 0.91)** | **0.85 (0.78, 0.93)** | **0.82 (0.74, 0.90)** | **0.82 (0.74, 0.90)** | **0.79 (0.71, 0.87)** | **0.80 (0.72, 0.88)** | 0.92 (0.83, 1.03) | 0.97 (0.87, 1.08) | 1.12 (1.00, 1.25) | 1.10 (0.98, 1.23) |
| Most Recent COVID-19 Vaccination Type | | | | | | | | | | | |
| No vaccine | Ref | Ref | Ref | Ref | Ref | Ref | Ref | Ref | Ref | Ref | Ref |
| mRNA | **0.65 (0.61, 0.70)** | **0.84 (0.77, 0.91)** | **0.86 (0.78, 0.94)** | **0.80 (0.73, 0.88)** | **0.82 (0.74, 0.90)** | **0.80 (0.72, 0.88)** | **0.80 (0.72, 0.88)** | 0.92 (0.83, 1.03) | 0.97 (0.87, 1.09) | 1.14 (1.02, 1.28) | 1.08 (0.97, 1.21) |
| Other vaccine | **0.66 (0.58, 0.76)** | **0.83 (0.69, 0.99)** | **0.76 (0.62, 0.94)** | 0.98 (0.80, 1.19) | 0.84 (0.67, 1.05) | **0.69 (0.54, 0.88)** | 0.80 (0.63, 1.01) | 0.93 (0.73, 1.18) | 0.94 (0.73, 1.20) | 0.87 (0.66, 1.15) | 1.24 (0.99, 1.55) |
| Time Period Between COVID-19 Event and Last Dose Received | | | | | | | | | | | |
| No vaccine | Ref | Ref | Ref | Ref | Ref | Ref | Ref | Ref | Ref | Ref | Ref |
| < 3 months | **0.74 (0.67, 0.83)** | **0.75 (0.64, 0.88)** | **0.74 (0.62, 0.88)** | **0.76 (0.63, 0.91)** | 0.86 (0.71, 1.03) | **0.76 (0.63, 0.93)** | **0.66 (0.53, 0.82)** | 0.86 (0.70, 1.06) | 0.98 (0.80, 1.20) | 1.00 (0.81, 1.25) | 1.06 (0.86, 1.30) |
| 3-6 months | **0.74 (0.68, 0.81)** | 0.90 (0.80, 1.02) | **0.78 (0.68, 0.89)** | **0.80 (0.69, 0.93)** | **0.78 (0.67, 0.91)** | **0.80 (0.68, 0.93)** | **0.77 (0.66, 0.91)** | 0.95 (0.81, 1.12) | 0.91 (0.77, 1.08) | **1.20 (1.02, 1.42)** | 1.07 (0.90, 1.26) |
| > 6 months | **0.61 (0.56, 0.65)** | **0.83 (0.76, 0.91)** | **0.90 (0.81, 0.99)** | **0.84 (0.75, 0.93)** | **0.82 (0.74, 0.92)** | **0.79 (0.71, 0.88)** | **0.83 (0.74, 0.93)** | 0.92 (0.82, 1.04) | 0.99 (0.88, 1.11) | 1.11 (0.98, 1.26) | 1.12 (0.99, 1.26) |

| | D) Cardiac | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| **Variable** | 28-60 Days | 61-90 Days | 91-120 Days | 121-150 Days | 151-180 Days | 181-210 Days | 211-240 Days | 241-270 Days | 271-300 Days | 301-330 Days | 331-365 Days |
| | **Adj HR (95% CI)**[1,2] | | | | | | | | | | |
| COVID-19 Vaccination Status | | | | | | | | | | | |
| Not vaccinated | Ref | Ref | Ref | Ref | Ref | Ref | Ref | Ref | Ref | Ref | Ref |
| Partially or fully vaccinated | **0.71 (0.67, 0.75)** | **0.91 (0.84, 0.98)** | 0.96 (0.89, 1.04) | 0.97 (0.89, 1.05) | 0.98 (0.89, 1.06) | 1.04 (0.95, 1.13) | 0.98 (0.90, 1.07) | 1.01 (0.92, 1.10) | 0.97 (0.89, 1.06) | 0.95 (0.87, 1.04) | 1.00 (0.92, 1.09) |
| One or more booster doses | **0.62 (0.56, 0.68)** | **0.77 (0.68, 0.86)** | 0.90 (0.79, 1.01) | 1.01 (0.90, 1.14) | 0.94 (0.82, 1.07) | 0.89 (0.78, 1.02) | 0.89 (0.78, 1.01) | 0.99 (0.87, 1.13) | 0.97 (0.85, 1.11) | 0.96 (0.84, 1.10) | 1.05 (0.93, 1.20) |
| Initial COVID-19 Vaccination Type | | | | | | | | | | | |
| No vaccine | Ref | Ref | Ref | Ref | Ref | Ref | Ref | Ref | Ref | Ref | Ref |
| Any vaccine | **0.70 (0.66, 0.74)** | **0.89 (0.83, 0.96)** | 0.95 (0.88, 1.03) | 0.98 (0.91, 1.06) | 0.97 (0.90, 1.06) | 1.02 (0.93, 1.11) | 0.97 (0.89, 1.06) | 1.01 (0.93, 1.10) | 0.98 (0.89, 1.06) | 0.96 (0.88, 1.05) | 1.02 (0.94, 1.11) |
| Most Recent COVID-19 Vaccination Type | | | | | | | | | | | |
| No vaccine | Ref | Ref | Ref | Ref | Ref | Ref | Ref | Ref | Ref | Ref | Ref |
| mRNA | **0.70 (0.66, 0.75)** | **0.89 (0.83, 0.96)** | 0.96 (0.89, 1.04) | 0.98 (0.90, 1.06) | 0.98 (0.90, 1.07) | 1.02 (0.93, 1.11) | 0.97 (0.89, 1.05) | 1.02 (0.93, 1.11) | 0.98 (0.90, 1.07) | 0.97 (0.88, 1.06) | 1.02 (0.93, 1.11) |
| Other vaccine | **0.66 (0.58, 0.75)** | 0.86 (0.74, 1.00) | 0.90 (0.76, 1.05) | 0.99 (0.84, 1.17) | 0.89 (0.75, 1.06) | 1.04 (0.88, 1.23) | 1.04 (0.88, 1.22) | 0.92 (0.77, 1.10) | 0.93 (0.78, 1.11) | 0.93 (0.77, 1.11) | 1.07 (0.91, 1.26) |
| Time Period Between COVID-19 Event and Last Dose Received | | | | | | | | | | | |
| No vaccine | Ref | Ref | Ref | Ref | Ref | Ref | Ref | Ref | Ref | Ref | Ref |
| < 3 months | **0.67 (0.60, 0.75)** | **0.84 (0.73, 0.95)** | 0.91 (0.79, 1.04) | 1.05 (0.91, 1.20) | 0.90 (0.77, 1.05) | 0.92 (0.79, 1.07) | 1.02 (0.88, 1.18) | 1.09 (0.95, 1.27) | 0.96 (0.82, 1.12) | 0.93 (0.79, 1.09) | **1.16 (1.01, 1.33)** |
| 3-6 months | **0.72 (0.66, 0.78)** | **0.88 (0.79, 0.97)** | 0.95 (0.85, 1.06) | 1.03 (0.92, 1.15) | 0.95 (0.84, 1.07) | 0.97 (0.86, 1.10) | 0.93 (0.82, 1.05) | 0.99 (0.87, 1.12) | 1.03 (0.91, 1.16) | 1.00 (0.88, 1.13) | 1.00 (0.88, 1.12) |
| > 6 months | **0.70 (0.65, 0.74)** | **0.90 (0.84, 0.98)** | 0.97 (0.89, 1.05) | 0.95 (0.87, 1.04) | 1.00 (0.91, 1.09) | 1.05 (0.96, 1.15) | 0.98 (0.90, 1.07) | 1.00 (0.91, 1.10) | 0.96 (0.87, 1.05) | 0.96 (0.87, 1.05) | 1.00 (0.91, 1.10) |

[1]HR=Hazard Ratio, CI=Confidence Interval; [2]Adjusted individually for sex, age group, race/ethnicity, rank, education, COVID-19 symptoms, COVID-19 hospitalization, COVID-19 re-infection, COVID-19 treatment, COVID-19 wave, any comorbidity, and total encounters

**Figure 5-2. Follow-up Time Group-Adjusted Hazard Ratio and 95% Confidence Interval by COVID-19 Vaccine Exposure for Mental Health (A), Neurological (B), Respiratory (C), and Cardiac (D) Diagnoses, active component service members, 2020-2022**



## Supplemental Table 5-1. PASC Diagnostic Categories and ICD-10 Diagnosis

| Diagnostic Group | Diagnosis Description | ICD10 Codes |
|---|---|---|
| Mental Health | Anxiety | F4323, F419, F411, F418, F4322 |
| | Insomnia | G4700, F51 |
| | PTSD | F4312 |
| | Major Depression | F321, F329, F331, F332, F339, R45851 |
| Neurological | Headache | R51 |
| | Taste Loss | R430, R431, R432, R438, R439 |
| | Seizure | R5600, R5601, R569, G40001, G40009, G40011, G40019, G40101, G40109, G40111, G40119, G40201, G40209, G40211, G40219, G40301, G40309, G40311, G40319, G40401, G40409, G40411, G40419, G40501, G40509, G40801, G40802, G40803, G40804, G40811, G40812, G40813, G40814, G40821, G40822, G40823, G40824, G4089, G40901, G40909, G40911, G40919, G40A01, G40A09, G40A11, G40A19, G40B01, G40B09, G40B11, G40B19 |
| | Blurred Vision | H53 |
| | Fatigue | R53 |
| | Memory Loss | R413 |
| | Cognitive Dysfunction | R410, R411, R412 |
| | Vertigo | H8110, H8111, H8112, H8113, H8141, H8142, H8143, H8149 |
| Respiratory | Cough | R05 |
| | Short of Breath | R0602, R0600, R0609 |
| | Pulmonary Embolism | I2699 |
| | Asthma | J45909, J4520, J45901, J4530, R062 |
| Cardiac | Chest Pain | R079, R0789, R072 |
| | Palpitations | R002 |
| | Atrial Fibrillation | I4891, I480 |
| | Syncope | R55 |
| | Tachycardia | R000 |
| | Heart Failure | I509, I517 |
| | Bradycardia | R001 |
| | Myocardial Infarction | I21, I22 |
| | Cerebral infarction/Stroke | I63 |
| | Post Exertional Malaise | T733 |
| | Myocarditis | I40, I41, I514, B3322 |
| | Pericarditis | I30, I32, B3323 |
| Abbreviations: PASC, Post Acute Sequelae of COVID-19 | | |

**Supplemental Table 5-2. COVID-19 Treatment Names**

| Treatment | Category | Drug Name |
|---|---|---|
| Nirmatrelvir/Ritonavir | Antiviral | Paxlovid |
| Remdesivir | Antiviral | Veklury |
| Molnupiravir | Antiviral | Lagevrio |
| Tocilizumab | Immune Modulator | Actemra |
| Baricitinib | Immune Modulator | Olumiant |
| Anakinra | Immune Modulator | Kineret |
| Sotrovimab | Monoclonal Antibodies | Sotrovimab |
| Bamlanivimab/Etesevimab | Monoclonal Antibodies | Bamlanivimab and Etesevimab |
| Bebtelovimab | Monoclonal Antibodies | Bebtelovimab |

**Supplemental Table 5-3. ESSENCE COVID-Like Illness (CLI) Definition**

| Diagnosis Description | ICD-10 Codes |
|---|---|
| Coronavirus, unspecified | B34.2 |
| SARS-associated coronavirus as the cause of disease classified elsewhere | B97.21 |
| Other coronavirus as the cause of disease classified elsewhere | B97.29 |
| Acute nasopharyngitis; common cold | J00 |
| Acute upper respiratory infection, unspecified | J06.9 |
| Pneumonia due to SARS-associated coronavirus | J12.81 |
| Other viral pneumonia | J12.89 |
| Viral pneumonia unspecified | J16.8 |
| Pneumonia in diseases classified elsewhere | J17 |
| Bronchopneumonia, unspecified organism | J18.0 |
| Lobar pneumonia, unspecified organism | J18.1 |
| Other pneumonia, unspecified organism | J18.8 |
| Pneumonia, unspecified organism | J18.9 |
| Acute bronchitis due to other specified organisms | J20.8 |
| Acute bronchitis, unspecified | J20.9 |
| Unspecified acute lower respiratory infection | J22 |
| Bronchitis, not specified as acute or chronic | J40 |
| Acute respiratory distress syndrome | J80 |
| Idiopathic interstitial pneumonia not otherwise specified | J84.111 |
| Cough | R05 |
| Dyspnea | R06.0 |
| Dyspnea, unspecified | R06.00 |
| Shortness of breath | R06.02 |
| Acute respiratory distress | R06.03 |
| Other forms of dyspnea | R06.09 |
| Anosmia | R43.0 |
| Ageusia | R43.2 |
| Fever, unspecified | R50.9 |
| 2019-nCoV acute respiratory disease, COVID-19, virus identified | U07.1 |

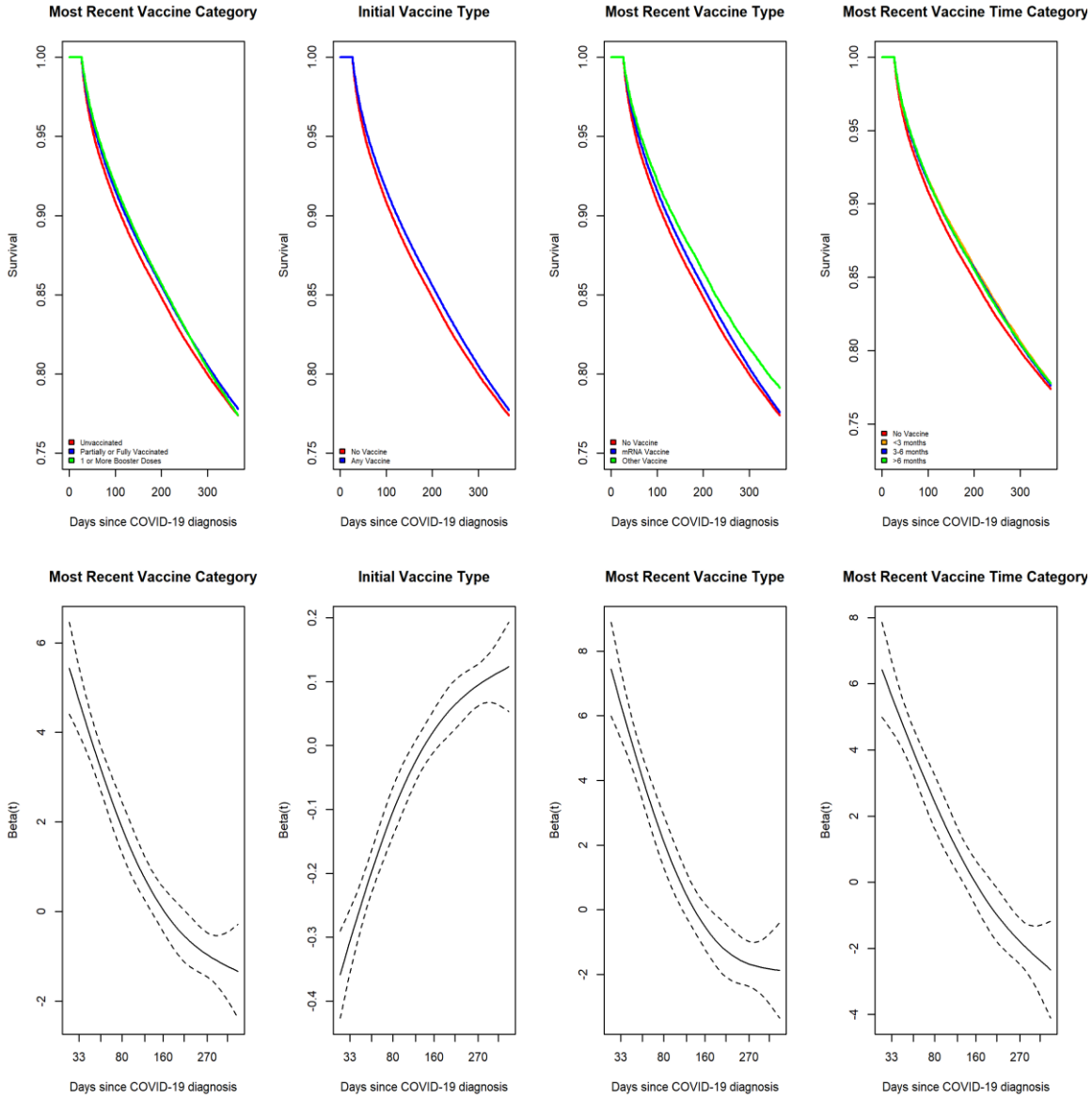
**Supplemental Table 5-4. Comorbidity Categories and ICD-10 Diagnosis**

| Diagnosis Description | ICD-10 Codes |
|---|---|
| Hypertension | I10*-I16*, O10*-O16* |
| Any cardiovascular disease | I05*-I89*, Z95* |
| Chronic lower respiratory disease | J40*-J44* |
| Asthma | J45* |
| Any lung disease | J40*-J99* |
| Metabolic disease | E08*-E13*, O24*, Z794*, E00*-E07*, E50*-E64*, E88.81 |
| Immune compromising conditions | B20, D55*-D77*, D80*-D89*, Z94*, Z795*, L40*, M04*-M08*, K50*-K52* |
| Substance use disorders (including nicotine dependence) | F10*-F16*, F18*-F19*, F17* |
| Chronic liver disease | K70*-K77*, B18* |
| Chronic kidney disease | N03*-N16*, N18*-N19* |
| Chronic neurologic disorders | G10*-G40* |
| Neoplasms | C00*-D49* |
| Obesity or overweight | E66.0*, E66.1, E66.2, E66.3, E66.8, E66.9, Z68.3*, Z68.4*, Z68.25- Z68.29 |
| HIV** | B20* |
| * Indicates all underlying ICD-10 codes are included | |
| **HIV is also included as part of the Immune Compromising Conditions category | |

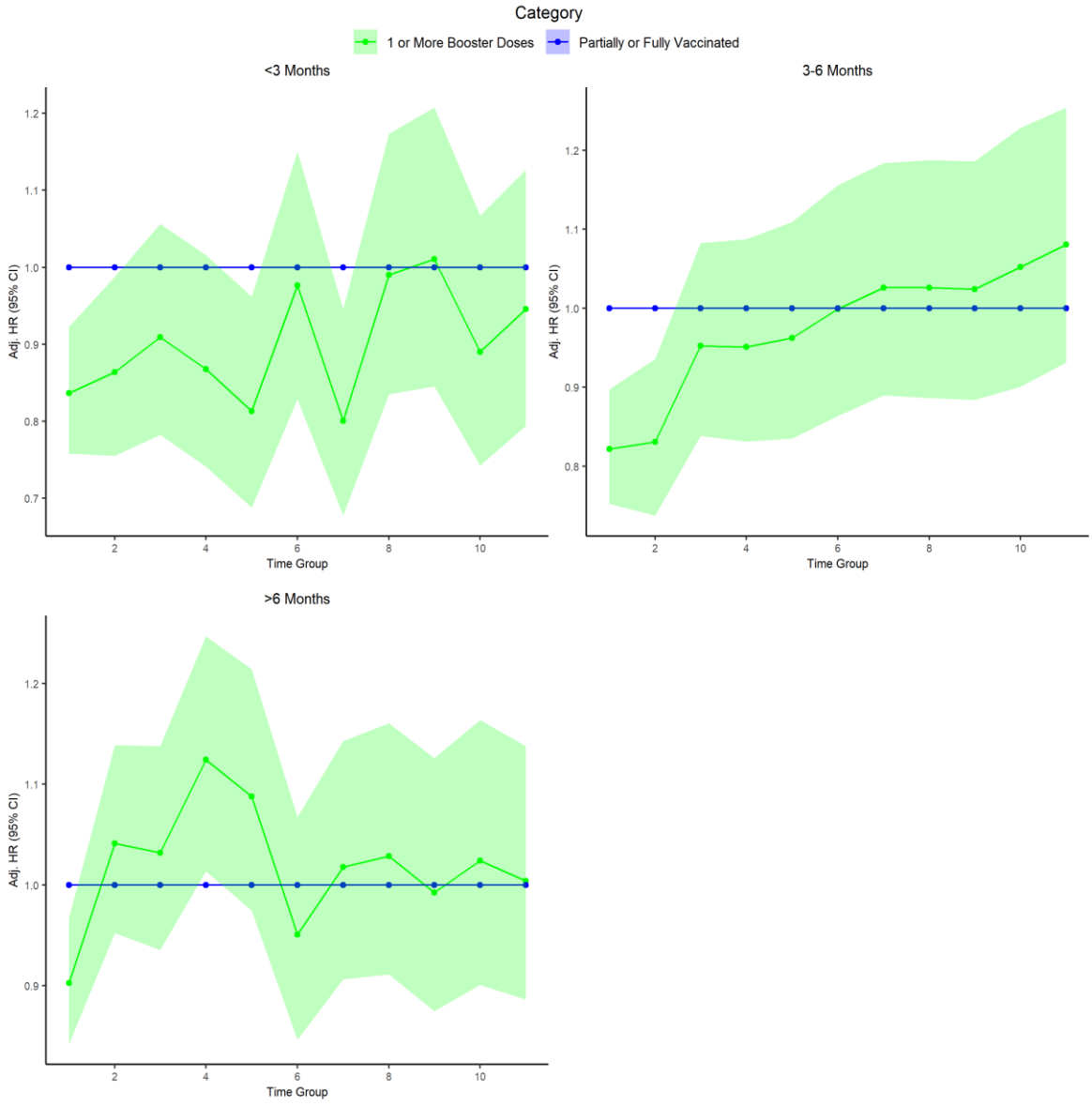
**Supplemental Table 5-5. Time to PASC diagnosis, active component service members, 2020-2022**

| Time | Cases (%) | Cumulative Cases (%) |
|---|---|---|
| | N = 104,024[1] | N = 104,024[1] |
| 28-60 days | 24,443 (23.5%) | 24,443 (23.5%) |
| 61-90 days | 12,207 (11.7%) | 36,650 (35.2%) |
| 91-120 days | 10,144 (9.8%) | 46,794 (45.0%) |
| 121-150 days | 8,713 (8.4%) | 55,507 (53.4%) |
| 151-180 days | 7,788 (7.5%) | 63,295 (60.8%) |
| 181-210 days | 7,666 (7.4%) | 70,961 (68.2%) |
| 211-240 days | 7,440 (7.2%) | 78,401 (75.4%) |
| 241-270 days | 6,765 (6.5%) | 85,166 (81.9%) |
| 271-300 days | 6,426 (6.2%) | 91,592 (88.0%) |
| 301-330 days | 5,959 (5.7%) | 97,551 (93.8%) |
| 331-365 days | 6,473 (6.2%) | 104,024 (100.0%) |
| [1] n (%) | | |

**Supplemental Figure 5-1. Kaplan-Meier Survival Curve and B(t) Estimate Over Time by COVID-19 Vaccine Exposure, active component service members, 2020-2022**



**Supplemental Figure 5-2. Follow-up Time Group-Adjusted Hazard Ratio and 95% Confidence Interval for Most Recent COVID-19 Vaccine Category Stratified by Most Recent COVID-19 Vaccine Time Category, active component service members, 2020-2022**



**Supplemental Table 5-6a. Hazard rate of incident PASC diagnostic descriptions by risk factor, active component service members, 2020-2022**

| **Variable** | Anxiety | Insomnia | PTSD | Major Depression | Headache | Taste Loss | Seizure | Memory Loss | Vertigo |
|---|---|---|---|---|---|---|---|---|---|
| | **Adj HR (95% CI)**[1,2] | **Adj HR (95% CI)**[1,2] | **Adj HR (95% CI)**[1,2] | **Adj HR (95% CI)**[1,2] | **Adj HR (95% CI)**[1,2] | **Adj HR (95% CI)**[1,2] | **Adj HR (95% CI)**[1,2] | **Adj HR (95% CI)**[1,2] | **Adj HR (95% CI)**[1,2] |
| COVID-19 Vaccination Status | | | | | | | | | |
| Not vaccinated | — | — | — | — | — | — | — | — | — |
| Partially or fully vaccinated | **1.09 (1.04, 1.13)** | 1.04 (0.99, 1.10) | 1.08 (0.97, 1.19) | 1.00 (0.95, 1.07) | 1.21 (0.81, 1.79) | **0.55 (0.45, 0.67)** | 0.94 (0.74, 1.19) | 1.08 (0.91, 1.29) | 1.17 (0.91, 1.51) |
| One or more booster doses | **1.07 (1.01, 1.12)** | 0.99 (0.92, 1.06) | 1.01 (0.89, 1.14) | **0.87 (0.80, 0.94)** | 1.16 (0.70, 1.90) | **0.48 (0.35, 0.66)** | 0.78 (0.56, 1.08) | 0.87 (0.70, 1.08) | 1.18 (0.87, 1.60) |
| Initial COVID-19 Vaccination Type | | | | | | | | | |
| No vaccine | — | — | — | — | — | — | — | — | — |
| Any vaccine | **1.08 (1.04, 1.13)** | 1.04 (0.98, 1.10) | 1.07 (0.97, 1.19) | 1.00 (0.94, 1.06) | 1.20 (0.81, 1.79) | **0.54 (0.45, 0.67)** | 0.93 (0.73, 1.18) | 1.05 (0.88, 1.26) | 1.17 (0.91, 1.51) |
| Most Recent COVID-19 Vaccination Type | | | | | | | | | |
| No vaccine | — | — | — | — | — | — | — | — | — |
| mRNA | **1.09 (1.05, 1.13)** | 1.04 (0.98, 1.10) | 1.08 (0.98, 1.20) | 1.00 (0.94, 1.06) | 1.20 (0.80, 1.79) | **0.54 (0.44, 0.66)** | 0.94 (0.74, 1.20) | 1.06 (0.89, 1.27) | 1.20 (0.93, 1.54) |
| Other vaccine | 1.06 (1.00, 1.12) | 1.05 (0.97, 1.13) | 0.98 (0.85, 1.13) | 0.98 (0.90, 1.07) | 1.22 (0.71, 2.10) | **0.62 (0.44, 0.85)** | 0.82 (0.57, 1.17) | 1.08 (0.85, 1.37) | 0.98 (0.68, 1.41) |
| Time Period Between COVID-19 Event and Last Dose Received | | | | | | | | | |
| No vaccine | — | — | — | — | — | — | — | — | — |
| < 3 months | **1.09 (1.03, 1.14)** | 1.03 (0.96, 1.10) | 1.02 (0.89, 1.15) | 0.96 (0.88, 1.03) | 1.20 (0.75, 1.92) | **0.55 (0.41, 0.73)** | 0.84 (0.61, 1.17) | 0.98 (0.79, 1.23) | 1.16 (0.85, 1.58) |
| 3-6 months | **1.08 (1.03, 1.13)** | 1.03 (0.97, 1.10) | 1.10 (0.98, 1.24) | 0.97 (0.91, 1.04) | 1.26 (0.80, 1.99) | **0.57 (0.44, 0.73)** | 0.94 (0.71, 1.24) | 1.02 (0.83, 1.25) | 1.23 (0.93, 1.63) |
| > 6 months | **1.09 (1.04, 1.13)** | 1.05 (0.99, 1.11) | 1.08 (0.97, 1.20) | 1.02 (0.96, 1.09) | 1.17 (0.77, 1.79) | **0.53 (0.43, 0.66)** | 0.95 (0.74, 1.23) | 1.11 (0.92, 1.34) | 1.15 (0.88, 1.50) |

[1]*HR = Hazard Ratio*

[2]*Adjusted individually for sex, age group, race/ethnicity, rank, education, COVID-19 symptoms, COVID-19 hospitalization, COVID-19 re-infection, COVID-19 treatment, COVID-19 wave, any comorbidity, and total encounters*

**Supplemental Table 5-6b. Hazard rate of incident PASC diagnostic descriptions by risk factor, active component service members, 2020-2022**

| **Variable** | Cough | Shortness of Breath | Pulmonary Embolism | Asthma |
|---|---|---|---|---|
| | **Adj HR (95% CI)**[1,2] | **Adj HR (95% CI)**[1,2] | **Adj HR (95% CI)**[1,2] | **Adj HR (95% CI)**[1,2] |
| COVID-19 Vaccination Status | | | | |
| Not vaccinated | — | — | — | — |
| Partially or fully vaccinated | **0.48 (0.39, 0.59)** | **0.83 (0.78, 0.87)** | **0.56 (0.41, 0.77)** | 0.96 (0.86, 1.06) |
| One or more booster doses | **0.44 (0.29, 0.67)** | **0.74 (0.69, 0.79)** | 0.70 (0.45, 1.09) | 0.96 (0.84, 1.09) |
| Initial COVID-19 Vaccination Type | | | | |
| No vaccine | — | — | — | — |
| Any vaccine | **0.48 (0.39, 0.58)** | **0.82 (0.78, 0.87)** | **0.57 (0.42, 0.79)** | 0.96 (0.87, 1.06) |
| Most Recent COVID-19 Vaccination Type | | | | |
| No vaccine | — | — | — | — |
| mRNA | **0.45 (0.36, 0.55)** | **0.82 (0.77, 0.86)** | **0.60 (0.43, 0.83)** | 0.97 (0.87, 1.08) |
| Other vaccine | **0.67 (0.48, 0.95)** | **0.83 (0.76, 0.90)** | **0.40 (0.22, 0.73)** | 0.87 (0.75, 1.02) |
| Time Period Between COVID-19 Event and Last Dose Received | | | | |
| No vaccine | — | — | — | — |
| < 3 months | **0.59 (0.45, 0.76)** | **0.79 (0.74, 0.85)** | 0.91 (0.61, 1.34) | 0.91 (0.80, 1.04) |
| 3-6 months | **0.50 (0.37, 0.66)** | **0.84 (0.79, 0.90)** | **0.53 (0.35, 0.80)** | 0.99 (0.88, 1.12) |
| > 6 months | **0.38 (0.29, 0.49)** | **0.82 (0.77, 0.87)** | **0.47 (0.33, 0.66)** | 0.96 (0.86, 1.07) |

[1]*HR = Hazard Ratio*

[2]*Adjusted individually for sex, age group, race/ethnicity, rank, education, COVID-19 symptoms, COVID-19 hospitalization, COVID-19 re-infection, COVID-19 treatment, COVID-19 wave, any comorbidity, and total encounters*

**Supplemental Table 5-6c. Hazard rate of incident PASC diagnostic descriptions by risk factor, active component service members, 2020-2022**

| **Variable** | Chest Pain | Palpitations | Atrial Fibrillation | Syncope | Tachycardia | Heart Failure | Bradycardia | Myocarditis |
|---|---|---|---|---|---|---|---|---|
| | **Adj HR (95% CI)**[1,2] | **Adj HR (95% CI)**[1,2] | **Adj HR (95% CI)**[1,2] | **Adj HR (95% CI)**[1,2] | **Adj HR (95% CI)**[1,2] | **Adj HR (95% CI)**[1,2] | **Adj HR (95% CI)**[1,2] | **Adj HR (95% CI)**[1,2] |
| COVID-19 Vaccination Status | | | | | | | | |
| Not vaccinated | — | — | — | — | — | — | — | — |
| Partially or fully vaccinated | **0.92 (0.87, 0.96)** | **0.88 (0.80, 0.95)** | 1.05 (0.68, 1.62) | 0.98 (0.88, 1.09) | 0.99 (0.89, 1.10) | 0.78 (0.60, 1.01) | 0.98 (0.82, 1.17) | **0.55 (0.35, 0.86)** |
| One or more booster doses | **0.83 (0.78, 0.89)** | **0.79 (0.70, 0.88)** | 1.07 (0.63, 1.81) | 0.93 (0.81, 1.08) | 0.90 (0.78, 1.04) | **0.63 (0.45, 0.89)** | 0.93 (0.74, 1.17) | 0.51 (0.26, 1.00) |
| Initial COVID-19 Vaccination Type | | | | | | | | |
| No vaccine | — | — | — | — | — | — | — | — |
| Any vaccine | **0.91 (0.87, 0.96)** | **0.87 (0.80, 0.94)** | 1.05 (0.69, 1.62) | 0.97 (0.87, 1.08) | 0.98 (0.88, 1.10) | **0.77 (0.59, 0.99)** | 0.97 (0.81, 1.17) | **0.55 (0.35, 0.86)** |
| Most Recent COVID-19 Vaccination Type | | | | | | | | |
| No vaccine | — | — | — | — | — | — | — | — |
| mRNA | **0.91 (0.87, 0.96)** | **0.87 (0.80, 0.95)** | 1.05 (0.68, 1.61) | 0.99 (0.89, 1.10) | 0.99 (0.89, 1.11) | **0.76 (0.58, 0.98)** | 0.98 (0.81, 1.17) | **0.53 (0.33, 0.84)** |
| Other vaccine | **0.91 (0.85, 0.98)** | **0.86 (0.76, 0.97)** | 1.10 (0.61, 1.98) | 0.88 (0.75, 1.03) | 0.90 (0.77, 1.06) | 0.81 (0.56, 1.18) | 0.95 (0.73, 1.23) | 0.67 (0.34, 1.33) |
| Time Period Between COVID-19 Event and Last Dose Received | | | | | | | | |
| No vaccine | — | — | — | — | — | — | — | — |
| < 3 months | **0.89 (0.83, 0.95)** | **0.83 (0.74, 0.93)** | 1.08 (0.64, 1.83) | 0.91 (0.79, 1.05) | 1.00 (0.87, 1.15) | 0.75 (0.54, 1.05) | 0.94 (0.75, 1.19) | 0.77 (0.43, 1.37) |
| 3-6 months | 0.94 (0.89, 1.00) | **0.89 (0.81, 0.98)** | 0.99 (0.60, 1.63) | 0.95 (0.84, 1.08) | 0.89 (0.79, 1.01) | 0.77 (0.57, 1.05) | 1.01 (0.82, 1.24) | **0.46 (0.26, 0.83)** |
| > 6 months | **0.90 (0.86, 0.95)** | **0.87 (0.80, 0.95)** | 1.07 (0.68, 1.68) | 1.01 (0.90, 1.14) | 1.02 (0.91, 1.14) | 0.77 (0.58, 1.01) | 0.97 (0.80, 1.17) | **0.51 (0.31, 0.83)** |

[1]*HR = Hazard Ratio*

[2]*Adjusted individually for sex, age group, race/ethnicity, rank, education, COVID-19 symptoms, COVID-19 hospitalization, COVID-19 re-infection, COVID-19 treatment, COVID-19 wave, any comorbidity, and total encounters*

## CHAPTER 6: Manuscript 3

### Strategies for Forecasting Long COVID in the Active Component U.S. Military

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***Disclaimer***

*The views expressed in this manuscript are those of the author and do not necessarily reflect the official policy or position of the Defense Health Agency, Department of Defense, nor the U.S. Government.*

## 6.1 Abstract

Long COVID represents a potentially serious threat to military readiness. Forecasts of future long COVID diagnoses could help prepare senior leaders for disruptions. However, few studies predicting the incidence of long COVID have been published to date. Using existing COVID-19 and long COVID diagnoses, as well as demographic and outpatient encounter data, 1- to 6-month ahead and full 6-month forecasts were generated using time series and machine learning models trained on various covariate data. Forecasting models generated accurate predictions of long COVID diagnoses up to 6 months ahead of the forecasted date. Several model and covariate combinations were within 5% of the observed number of diagnoses over the full 6-month testing period, and monthly forecasts of long COVID diagnoses had MAPE ranging from 3-10% for the best performing model combinations. Simple forecasting models and distribution-based forecasts that utilize existing clinical databases can provide accurate predictions of incident long COVID up to 6 months in advance and can be used to prepare for the burden of new long COVID diagnoses.

## 6.2 New Findings

Accurate predictions of long COVID cases over a 6-month period were made using existing COVID-19 case and outpatient encounter data from January 1, 2020, to December 31, 2022.

## 6.3 Impact

Long COVID symptoms could cause disruptions to military readiness and prevent a healthy force, especially after surges in COVID-19 cases. The ability to use existing data

streams to accurately predict future cases of long COVID allows senior leaders to anticipate and prepare for potential changes in the availability of servicemembers.

### 6.4 Introduction

Long COVID has been well studied in the general population, though it has not been well established in the U.S. military. Internal, not yet published Defense Medical Surveillance System (DMSS) data in active component servicemembers diagnosed with COVID-19 between January 2020 and December 2022 has indicated that symptoms of long COVID may be present in up to 20% of servicemembers, with cardiac symptoms in approximately 8% and respiratory symptoms in approximately 5% of servicemembers (**unpublished**). Another study in active duty servicemembers with COVID-19 diagnoses between March 2020 and November 2021 found cardiac symptoms in nearly 2% of servicemembers more than 30 days after being diagnosed with COVID-19[89]. At best, mild symptoms of long COVID could disrupt force readiness by causing unplanned training limitations and absences, while more severe symptoms could result in long-term disability or even death. It is therefore critical for senior U.S. Department of Defense (DOD) leaders to anticipate the burden of long COVID in advance to prepare for potential disruptions and to anticipate impacts on the military healthcare system resources.

Infectious disease forecasting, especially for influenza, has been around for decades. The Centers for Disease Control and Prevention (CDC) hosts annual forecasting challenges for influenza and COVID-19 aimed at predicting short-term incidence of cases and hospitalizations[80]. Various mechanistic, statistical, and time series models have been used

for forecasting, as well as combined ensemble models. CDC has found that ensemble models tend to be more stable and accurate across multiple forecasting locations and targets than individual models, including for COVID-19[81,100]. However, long COVID is a long-term, post-infectious process of COVID-19 and not a contagious process, and requires a person both be infected with COVID-19 and develop symptoms of long COVID after a specified period of time has passed. Traditional time series methods for forecasting short-term COVID-19 and other respiratory disease activity may not be useful for forecasting long COVID cases, and little research has been published to date on efforts to predict the incident number of long COVID diagnoses using existing case data, especially within the military population. Studies using clinical data in civilian populations found various models to be reasonably accurate, with AUROC values between 0.74 and 0.895[101–103]. Attempts have been made to use time series models to forecast incident cases of other diseases with long follow-up periods, such as Lyme disease, using clinical data, with mean absolute percentage errors around 8%[104]. The purpose of this study was to develop predictive models to forecast future long COVID diagnoses and to compare the predictions of each model against observed long COVID diagnoses. To achieve this, a cohort of COVID-19 cases, linked demographic and medical records, and longitudinal health encounter data were utilized.

### 6.5 Methods

The protocol for this study was approved by both the George Washington University Committee on Human Research, Institutional Review Board and the Component Office for Human Research Protections, Defense Health Agency Office of Research Protections.

### 6.5.1 Study Population

The study population included a cohort of 464,356 active component U.S. service members with a confirmed case of COVID-19 between January 1, 2020, and December 31, 2022 stationed at a U.S. military hospital or clinic. Active component includes full-time active duty service members but excludes those who are reserves or in the National Guard. Data were taken from a master list of COVID-19 cases, defined as having either a positive SARS-CoV-2 nucleic acid or antigen test or a COVID-19 reportable medical event (RME) in the Disease Reporting System Internet (DRSi), maintained by the Armed Forces Health Surveillance Division (AFHSD). The master list includes information relevant to a service member's COVID-19 event, including vaccinations, re-infection status, and hospitalization.

### 6.5.2 Exposures/Covariates

Covariates of interest in this study focused on measures of COVID-19 activity, including COVID-specific, COVID-like illness (CLI), and Post Acute Sequelae of COVID-19 (PASC) outpatient encounters, as well as risk factors for long COVID. Risk factors included sex, age, race and ethnicity, rank, COVID-19 hospitalization status, COVID-19 re-infection status, and COVID-19 vaccination status. Demographic information for each COVID-19 case in the Master Positive List were taken from the Defense Medical Surveillance System (DMSS), a DoD-maintained database of health information which includes personnel, medical, immunization, pharmacy, health assessment, laboratory, and deployment data. Monthly aggregated outpatient encounters by military hospital or clinic were downloaded from the DoD Electronic Surveillance System for the Early Notification of Community-based Epidemics (ESSENCE). COVID-specific encounters

were defined as any outpatient encounter with a discharge diagnosis containing the ICD-10 codes U07.1 or J12.81, while PASC encounters were defined as those containing the ICD-10 code U09.9. The CLI encounter definition is provided in Supplementary Table 6-2.

### 6.5.3 Case Definition

The outcome of interest, long COVID, was assessed using the Post-Acute Sequelae of COVID-19 (PASC) definition developed and validated by the Defense Centers for Public Health- Portsmouth (DCPH-P). Briefly, the definition requires a service member to have a positive SARS-CoV-2 nucleic acid test or a confirmed COVID-19 reportable medical event, and an International Classification of Diseases, 10th Revision (ICD-10) code of one of the mental health, neurological, cardiac, or respiratory diagnostic groups between 4 and 52 weeks after the COVID-19 event. Diagnostic groups and their ICD-10 codes are shown in Supplementary Table 6-1**.** The service member must not have a diagnosis for that specific diagnostic group within 1 year prior to the COVID-19 event. Inpatient and outpatient datasets from DMSS were used to identify incidence of long COVID in this population.

### 6.5.4 Analyses

This study focused on longitudinal forecasts of long COVID in the active component population. To facilitate time series forecasting, long COVID, COVID-19, and outpatient encounter datasets were converted into time series by aggregating the monthly number of cases and encounters. COVID-19 cases were additionally broken down by risk factor.

The number of monthly cases and encounters were plotted together to visualize the relationship between each metric and the outcome of long COVID.

The data were split into training and testing datasets. The training dataset included data between January 1, 2020, and June 30, 2022, and the testing dataset included data from July 1, 2022, to December 31, 2022. Three models were fit with long COVID diagnoses as the outcome using the training data, including autoregressive integrated moving average (ARIMA), neural network, and vector autoregressive (VAR), as well as an ensemble model which represented the average of the other three models. Different versions of each model were fit, 21 in total, featuring different data lags (unlagged, 3 month lag, and 6 month lag) and covariate data including PASC encounters, COVID-19 cases, COVID-specific encounters, CLI encounters, and demographics (age, sex, race/ethnicity, rank, re-infection status, hospitalization status, and vaccination status). All model and covariate combinations are shown in Table 6-2. Model fit statistics were assessed for the training period, including AIC, $sigma^2$ (variance of the forecast errors), root mean squared error (RMSE), and median absolute percent error (MAPE).

Models showing the best fit with the training data were selected for forecasting, including the models with all COVID-19 metrics and those with all metrics. The models using PASC encounters were also included for forecasting. Several baseline models were also created for comparison. First, a seasonal naïve was calculated using a 5-month lag of COVID-19 cases and 22% of COVID-19 cases being diagnosed with long COVID in the cohort. The lag parameter represented the average time in months from the COVID-19 event date to the long COVID diagnosis date in the cohort, and the long COVID incidence parameter represented the percentage of COVID-19 cases diagnosed with long

COVID in the sample. Second, the distribution of the time from the COVID-19 event date to the long COVID diagnosis date in the cohort was estimated to be a Weibull distribution with a shape parameter of 1.56 and scale parameter of 5.81. A distribution of diagnosis times was calculated using the Weibull parameters, the long COVID incidence parameter above, and a minimum diagnosis time of 1 month and maximum of 12 months. The calculated distribution was applied to the time series of COVID-19 cases to create an estimate of expected long COVID diagnoses by month. Similarly, an adjusted Weibull prediction was created using a long COVID incidence parameter that varied by risk factor. Based on factor-specific incidence of long COVID in the cohort, the parameter was estimated for sex (32% for females and 20% for males), race and ethnicity (21% for Asian, 22% for Hispanic, 27% for non-Hispanic Black, 21% for non-Hispanic White, and 22% for Other race), age group (19% for <20, 21% for 20-34, 27% for 35-39, 30% for 40-44, and 31% for 45+), rank (23% for enlisted and 19% for officers), COVID-19 re-infection status (22% for first infection, 26% for re-infection), and COVID-19 hospitalization status (22% for not hospitalized, 43% for hospitalized). The average calculated distribution was applied to the time series of COVID-19 cases to create an estimate of expected long COVID diagnoses by month. Lastly, an ensemble model was calculated as the average of all models for each covariate and lag combination as well as overall.

Two sets of forecasts were generated for each model combination. First, the number of long COVID diagnoses during the entire 6-month testing period was forecasted using the training dataset. Second, for each month during the testing period (July-December), forecasts were generated for each remaining month in the testing period (through

December 2022). Models used data through the end of the previous month for training. For example, data through July 31, 2022, were used to generate forecasts for August, September, October, November, and December 2022. Data through August 31, 2022 were used to generate forecasts for September, October, November, and December 2022. This continued through the end of the testing period. Seasonal NAÏVE and ensemble forecasts were generated in both quantile and point format to facilitate evaluation of the complete distribution of the forecasts. Forecasts using the Weibull distribution were only generated as a point forecast.

Forecasts were scored by comparing the predicted number of long COVID diagnoses in a period to the observed number. Monthly point forecasts were scored using a median absolute percent error (MAPE) and quantile forecasts were scored using a weighted interval score (WIS). Full 6-month point forecasts were scored using percent error. WIS has been used previously by the Centers for Disease Control and Prevention for scoring COVID-19 forecasting hub entries[95]. All statistical analyses were conducted using R (version 4.1, R Foundation for Statistical Computing, Vienna, Austria), and an alpha ($\alpha$) level of 0.05 was considered statistically significant.

### 6.6 Results

Table 6-1 shows demographic characteristics of COVID-19 cases in the training and testing datasets. Datasets were similar in regard to age, race/ethnicity, rank, and COVID-19 hospitalization, though a larger proportion of the testing dataset was comprised of females (24.3% vs 20.4%). COVID-19 re-infections were much more prominent in the testing dataset (19.2% vs 5.5%), though this is expected as the testing data occurred

nearly two years into the COVID-19 pandemic. Figure 6-1 shows the time series of observed data used for training and prediction in this study. As expected, incidence of COVID-19 was higher than PASC, with COVID-19 cases peaking each summer between 10,000 and 20,000 monthly cases and each winter between 25,000 and 100,000 monthly cases, while PASC cases peaked between 2,500 and 6,000 monthly cases. PASC peaks tended to follow peaks in COVID-19 activity by 2 to 3 months.

Table 6-2 shows model fit statistics for each combination of trained models during the training period. The lowest AIC was seen for the 3-month lagged model containing all covariates (-103.8). This model combination also had the lowest sigma$^2$ (0.0), RMSE (0.4), and MAPE (0.05%) compared to other combinations. Other model combinations with a MAPE below 10% were the unlagged COVID-19 case model (8.8%), 6-month lagged COVID-19 encounter model (9.8%), unlagged all COVID-19 metric model (8.3%), and the 6-month lagged all COVID-19 metric model (9.9%). Graphs of the median fitted predicted values for each model combination and lag compared to observed data are shown in Supplementary Figure 6-1. All models appeared to fit the observed data visually, though the models with all covariates and those with only demographic covariates appeared to fit the data the best.

Table 6-3 shows model scoring metrics for each ensemble and baseline model and forecasting horizon. Across all forecasting horizons, the ensemble model using PASC encounters had the lowest median MAPE (9.2%) and WIS (206.6), followed by the 3-month lagged ensemble model using all covariates (11.3% MAPE, 291.0 WIS), and the unadjusted Weibull model (MAPE 11.5%). Model performance varied between the 1-month ahead through 6-month ahead horizons. Figure 6-2 shows the observed compared

to predicted values for each model and horizon. Ensemble models tended to predict a later peak than what was observed for the 1-month ahead through 3-month ahead forecasts, though this was less severe for the ensemble model using PASC encounters at the 2-month and 3-month ahead horizons. Weibull forecasts were more stable than ensemble model forecasts.

Table 6-4 shows the results of the full 6-month forecasts. During the forecasting period from July through December 2022, 23,132 incident cases of PASC were observed. The 6-month lagged ensemble model using all covariates had the lowest percent error over the 6-month period at -0.8% (22,960 predicted cases), followed by the unlagged ensemble model using all covariates (+4.3%, 24,174 predicted cases), adjusted Weibull model (-4.7%, 22,093 predicted cases), and the ensemble model using PASC encounters (+5%, 24,353 predicted cases). The SNAIVE model had the highest percent error at -71.6%, predicting only 13,479 cases during the 6-month period.

### 6.7 Discussion

This study aimed to use various forecasting models, including time series and machine learning models, as well as simple time-based distributions to predict the number of incident long COVID diagnoses over a 6-month period using various case, outpatient encounter, and demographic data. Forecasts were generated at the beginning of the study period for the entire 6-month period, and 1- to 6-month ahead forecasts were generated for each month in the study period. Monthly forecasts ranged in accuracy, with the PASC encounter ensemble model having the lowest WIS across all forecasting horizons and a MAPE below 10%, as did the adjusted Weibull forecasts, which can be seen in Table 6-4

and Supplementary Figure 6-2. No pattern was seen across the 1- to 6-month ahead horizons, with some models performing better at earlier horizons and some performing better at later horizons. This contrasts with COVID-19 forecasts, which tend to perform worse as horizons increase[105].

As long COVID is not an infectious process, it may not be useful to generate monthly forecasts of long COVID diagnoses, but instead to generate forecasts for a specified period to assist senior leaders and public health practitioners with planning for the burden of expected cases. To this end, forecasts of the entire 6-month period may be most useful. The ensemble model using all covariates and a 6-month lag was the most accurate, with a percent error of just -0.8% (-172 cases) over the study period. This is not unexpected, as the average time to a long COVID diagnosis was 5 months, so lagging covariate data by 6 months is a reasonable choice. Other models also had a percent error within 5%, however, including the unlagged ensemble model using all covariates (+4.3%), the adjusted Weibull model (-4.7%), and the ensemble model using PASC encounters (+5.0%). These were similar to estimates of Lyme disease, another slow-developing disease, in a previous study[104]. Despite having the best model fit using the training data, the 3-month lagged all covariate ensemble model had a percent error of -10.2%, ranking only 6$^{th}$ best of the 8 models tested. This was not unexpected, as the lag in the full cohort was 5 months which is closer to the 6-month lagged model. However, it does not explain why the model performed worse than the unlagged ensemble model.

This study serves as a 'proof of concept' for long COVID forecasting. The study demonstrates how forecasting models can be used to predict incident long COVID cases up to 6 months in advance using clinical and demographic data. The study utilized

existing datasets and surveillance databases to accurately predict the number of long COVID diagnoses over a 6-month period. The study has several limitations. First, models were only trained on COVID-19 cases between January 1, 2020, and June 30, 2022, and therefore do not reflect trends in long COVID in later years. Second, the study was only carried out for the entire U.S., which may not be as useful as installation-level or regional forecasts, which could be a goal of future studies. Lastly, longer-term horizons, such as the 5-month and 6-month ahead forecasts, were limited to just one or two data points for each model, potentially limiting assessment of those horizons. Future research could focus on the utility of longer-term forecasts by expanding the study period to allow additional forecasts. Additional lag periods, such as the 5-month lag used for the baseline models, can be explored for the ensemble model forecasts.

This study demonstrates that accurate forecasting of long COVID incidence is possible using clinical, laboratory, and demographic data. Further research needs to be conducted to determine if results are consistent in more recent time periods, and whether additional or more complex models improve accuracy.

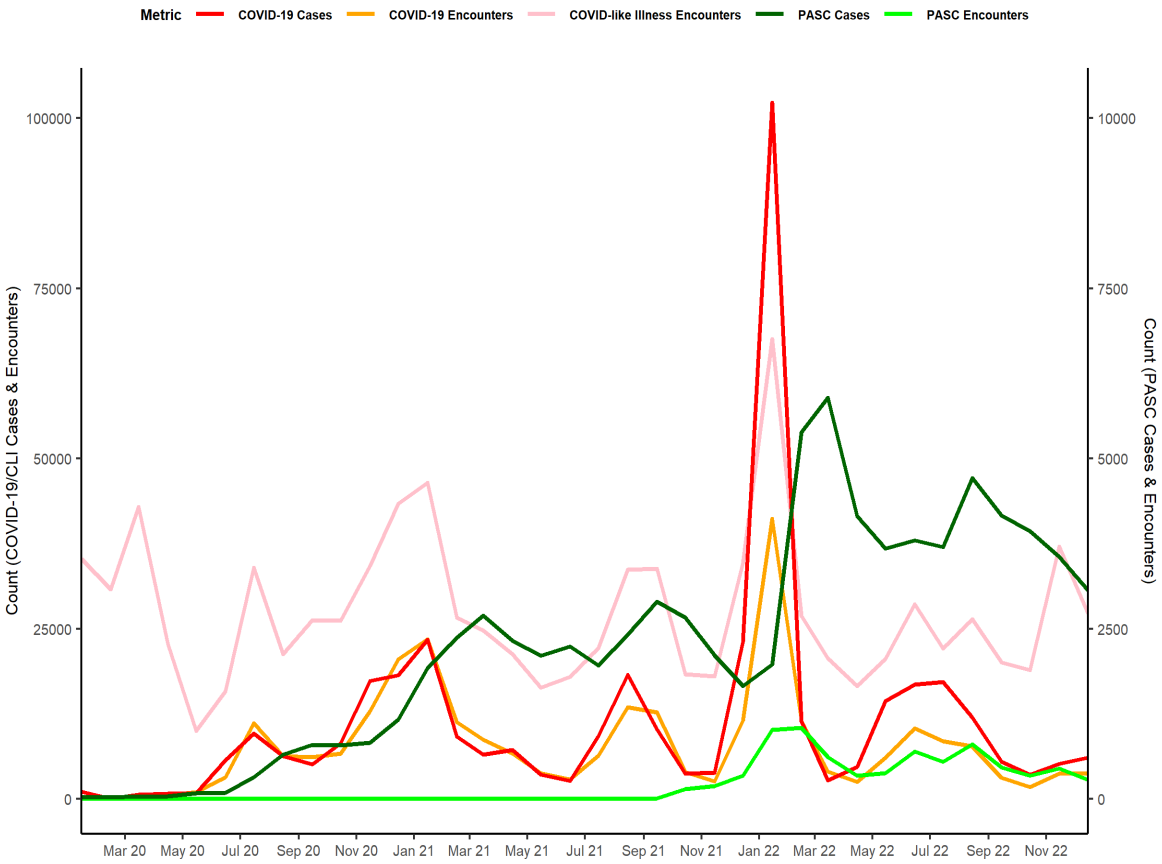
### 6.8 Acknowledgments

*Shauna Stahlman, PhD; Alexis McQuistan, MPH*

**Table 6-1. Demographic Characteristics of COVID-19 Cases During Training and Testing Periods**

| Variable | Cases (%) | |
|---|---|---|
| | **Training (n=402,352)** | **Testing (n=62,004)** |
| Age Group | | |
| <20 | 27,950 (6.9%) | 3,276 (5.3%) |
| 20-24 | 138,332 (34.4%) | 19,323 (31.2%) |
| 25-29 | 96,233 (23.9%) | 15,117 (24.4%) |
| 30-34 | 62,144 (15.4%) | 10,366 (16.7%) |
| 35-39 | 45,198 (11.2%) | 7,766 (12.5%) |
| 40-44 | 21,242 (5.3%) | 3,870 (6.2%) |
| 45+ | 11,251 (2.8%) | 2,286 (3.7%) |
| Sex | | |
| Female | 82,064 (20.4%) | 15,050 (24.3%) |
| Male | 320,288 (79.6%) | 46,954 (75.7%) |
| Race/Ethnicity | | |
| Asian | 15,462 (3.8%) | 2,772 (4.5%) |
| Hispanic | 80,899 (20.1%) | 12,305 (19.8%) |
| Non-Hispanic Black | 70,954 (17.6%) | 10,547 (17.0%) |
| Non-Hispanic White | 203,674 (50.6%) | 30,678 (49.5%) |
| Other | 25,311 (6.3%) | 4,845 (7.8%) |
| Unknown | 6,052 (1.5%) | 857 (1.4%) |
| Rank | | |
| Enlisted | 344,510 (85.6%) | 53,362 (86.1%) |
| Officer | 57,842 (14.4%) | 8,642 (13.9%) |
| COVID-19 Re-infection | | |
| First Infection | 380,256 (94.5%) | 50,121 (80.8%) |
| Re-infection | 22,096 (5.5%) | 11,883 (19.2%) |
| COVID-19 Hospitalization | | |
| Not Hospitalized | 399,367 (99.3%) | 61,611 (99.4%) |
| Hospitalized | 2,985 (0.7%) | 393 (0.6%) |

**Figure 6-1. Observed Monthly Number of Cases/Encounters by Metric, 2020-2022**




Observed COVID-19 cases and COVID-19/CLI encounters are shown using the left axis. PASC cases and encounters are shown using the right axis.

**Table 6-2. Median Model Fit Statistics by Training Covariates and Lagging**

| Combination | AIC* | Sigma$^2$** | RMSE | MAPE |
|---|---|---|---|---|
| Base (no covariates) | 331.5 | 250962.5 | 491.2 | 10.1 |
| PASC encounters | 427.9 | 267422.6 | 525.4 | 18.0 |
| COVID-19 Cases | | | | |
| No lag | 327.7 | 124189.8 | 313.6 | 8.8 |
| 3 month lag | 421.9 | 250262.5 | 645.6 | 19.6 |
| 6 month lag | 331.5 | 271967.1 | 528.5 | 11.5 |
| COVID-19 Encounters | | | | |
| No lag | 331.4 | 211062.8 | 445.8 | 11.0 |
| 3 month lag | 422.7 | 277948.1 | 643.0 | 20.1 |
| 6 month lag | 331.6 | 202544.6 | 441.7 | 9.8 |
| CLI Encounters | | | | |
| No lag | 331.6 | 217329.0 | 455.5 | 10.5 |
| 3 month lag | 421.4 | 258492.6 | 630.0 | 17.9 |
| 6 month lag | 420.5 | 254913.9 | 621.4 | 17.3 |
| COVID-19 Cases, COVID-19 Encounters, & CLI Encounters | | | | |
| No lag | 327.9 | 156411.2 | 392.1 | 8.3 |
| 3 month lag | 425.3 | 284716.0 | 610.4 | 16.3 |
| 6 month lag | 326.4 | 201484.5 | 431.9 | 9.9 |
| Demographics (age, sex, race/ethnicity, rank, re-infection status, hospitalization status) | 463.8 | 223839.5 | 210.1 | 14.9 |
| COVID-19 Cases, COVID-19 Encounters, CLI Encounters, & Demographics | | | | |
| No lag | 470.2 | 350118.4 | 262.6 | 75.8 |
| 3 month lag | 494.5 | 856769.3 | 391.9 | 93.3 |

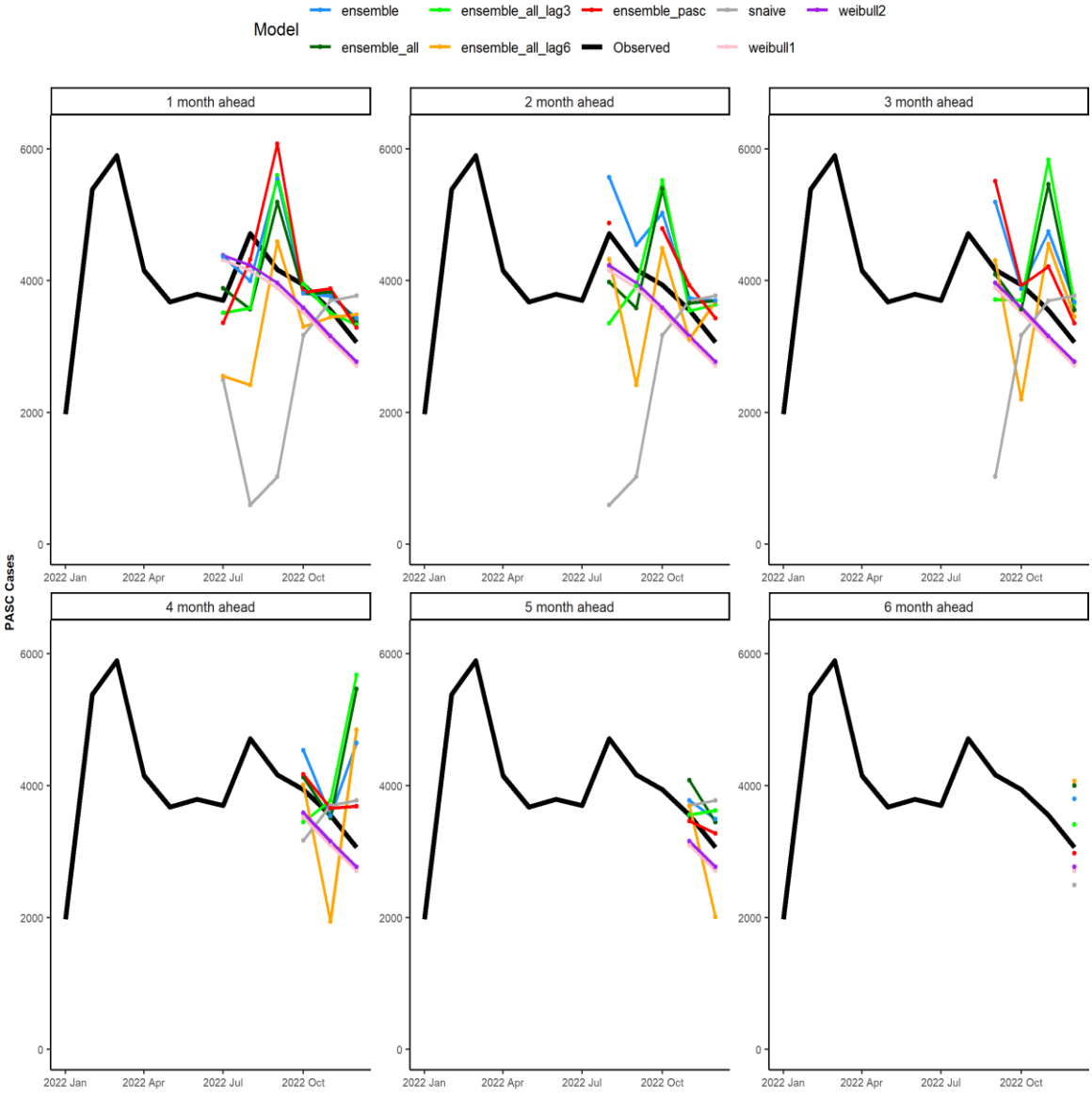
| **Combination** | **AIC*** | **Sigma$^2$**** | **RMSE** | **MAPE** |
|---|---|---|---|---|
| 6 month lag | 485.7 | 623760.20 | 334.1 | 112.3 |
| All (PASC Encounters, COVID-19 Cases, COVID-19 Encounters, CLI Encounters, & Demographics) | | | | |
| No lag | 465.1 | 299529.7 | 231.8 | 56.6 |
| 3 month lag | -103.8 | 0.0 | 0.4 | 0.05 |
| 6 month lag | 422.1 | 64483.4 | 108.0 | 85.7 |
| * Not available for the neural network (NNET) model | | | | |
| ** Not available for the vector autoregressive (VAR) model | | | | |

## Table 6-3. Median Model Scores by Selected Ensemble and Baseline Models

| All Horizons | | |
|---|---|---|
| **Combination** | **MAPE** | **WIS** |
| Ensemble | 15.3 | 322.8 |
| Ensemble (all covariates) | 13.9 | 265.9 |
| Ensemble (all covariates, 3 month lag) | 11.3 | 291.0 |
| Ensemble (all covariates, 6 month lag) | 16.2 | 363.8 |
| Ensemble (PASC encounters) | 9.2 | 206.6 |
| SNAIVE | 23.2 | 1098.3 |
| Weibull 1 | 11.5 | NA |
| Weibull 2 | 9.7 | NA |
| **1 month ahead** | | |
| **Combination** | **MAPE** | **WIS** |
| Ensemble | 13.6 | 263.9 |
| Ensemble (all covariates) | 8.8 | 155.6 |
| Ensemble (all covariates, 3 month lag) | 6.9 | 132.9 |
| Ensemble (all covariates, 6 month lag) | 15.0 | 319.6 |
| Ensemble (PASC encounters) | 8.8 | 180.3 |
| SNAIVE | 28.0 | 1082.2 |
| Weibull 1 | 11.7 | NA |
| Weibull 2 | 10.0 | NA |
| **2 months ahead** | | |
| **Combination** | **MAPE** | **WIS** |
| Ensemble | 18.1 | 332.9 |
| Ensemble (all covariates) | 15.5 | 378.1 |
| Ensemble (all covariates, 3 month lag) | 18.6 | 438.2 |
| Ensemble (all covariates, 6 month lag) | 14.0 | 326.7 |
| Ensemble (PASC encounters) | 12.0 | 217.3 |
| SNAIVE | 23.2 | 1077.4 |
| Weibull 1 | 11.5 | NA |
| Weibull 2 | 9.7 | NA |
| **3 months ahead** | | |
| **Combination** | **MAPE** | **WIS** |
| Ensemble | 22.4 | 410.2 |
| Ensemble (all covariates) | 12.7 | 231.2 |
| Ensemble (all covariates, 3 month lag) | 15.1 | 364.8 |
| Ensemble (all covariates, 6 month lag) | 20.4 | 472.3 |
| Ensemble (PASC encounters) | 14.0 | 277.9 |
| SNAIVE | 21.4 | 1087.8 |
| Weibull 1 | 11.1 | NA |
| Weibull 2 | 9.3 | NA |

| 4 months ahead | | |
|---|---|---|
| **Combination** | **MAPE** | **WIS** |
| Ensemble | 15.2 | 289.3 |
| Ensemble (all covariates) | 4.9 | 118.4 |
| Ensemble (all covariates, 3 month lag) | 12.6 | 327.5 |
| Ensemble (all covariates, 6 month lag) | 45.5 | 1488.2 |
| Ensemble (PASC encounters) | 5.8 | 206.6 |
| SNAIVE | 19.5 | 1101.5 |
| Weibull 1 | 11.5 | NA |
| Weibull 2 | 9.7 | NA |
| **5 months ahead** | | |
| **Combination** | **MAPE** | **WIS** |
| Ensemble | 10.2 | 227.9 |
| Ensemble (all covariates) | 13.7 | 249.4 |
| Ensemble (all covariates, 3 month lag) | 9.2 | 220.4 |
| Ensemble (all covariates, 6 month lag) | 19.2 | 505.8 |
| Ensemble (PASC encounters) | 4.7 | 200.0 |
| SNAIVE | 13.7 | 1113.7 |
| Weibull 1 | 12.2 | NA |
| Weibull 2 | 10.4 | NA |
| **6 months ahead** | | |
| **Combination** | **MAPE** | **WIS** |
| Ensemble | 23.9 | 368.8 |
| Ensemble (all covariates) | 30.5 | 632.3 |
| Ensemble (all covariates, 3 month lag) | 11.3 | 202.2 |
| Ensemble (all covariates, 6 month lag) | 32.8 | 797.0 |
| Ensemble (PASC encounters) | 2.9 | 191.7 |
| SNAIVE | 18.7 | 1326.7 |
| Weibull 1 | 11.5 | NA |
| Weibull 2 | 9.7 | NA |

**Figure 6-2. Observed vs Predicted Value by Selected Ensemble and Baseline Models and Forecasting Horizon**




Observed cases are shown in black. Solid, colored lines represent the point forecast for each model, while shaded areas represent the 95% confidence interval for each model.

**Table 6-4. Actual vs Predicted 6-Month PASC Cases by Selected Ensemble and Baseline Models**

| Month | Observed Cases | Predicted Cases (% Error) | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | Ensemble | Ensemble (all covariates) | Ensemble (all covariates, 3 month lag) | Ensemble (all covariates, 6 month lag) | Ensemble (PASC encounters) | SNAIVE | Weibull 1 | Weibull 2 |
| July 2022 | 3,702 | 4,368 (+15.2%) | 3,884 (+4.7%) | 3,510 (-5.5%) | 2,553 (-45%) | 3,359 (-10.2%) | 2,491 (-48.6%) | 4,311 (+14.1%) | 4,387 (+15.6%) |
| August 2022 | 4,712 | 5,567 (+15.4%) | 3,980 (-18.4%) | 3,352 (-40.6%) | 4,328 (-8.9%) | 4,874 (+3.3%) | 599 (-686.3%) | 4,152 (-13.5%) | 4,229 (-11.4%) |
| September 2022 | 4,163 | 5,191 (+19.8%) | 4,097 (-1.6%) | 3,710 (-12.2%) | 4,307 (+3.3%) | 5,509 (+24.4%) | 1,029 (-304.6%) | 3,889 (-7%) | 3,964 (-5%) |
| October 2022 | 3,938 | 4,537 (+13.2%) | 4,132 (+4.7%) | 3,444 (-14.4%) | 4,012 (+1.8%) | 4,168 (+5.5%) | 3,172 (-24.2%) | 3,516 (-12%) | 3,586 (-9.8%) |
| November 2022 | 3,553 | 3,777 (+5.9%) | 4,082 (+13%) | 3,557 (+0.1%) | 3,692 (+3.8%) | 3,466 (-2.5%) | 3,697 (+3.9%) | 3,096 (-14.8%) | 3,159 (-12.5%) |
| December 2022 | 3,064 | 3,797 (+19.3%) | 4,000 (+23.4%) | 3,409 (+10.1%) | 4,068 (+24.7%) | 2,976 (-2.9%) | 2,491 (-23%) | 2,711 (-13%) | 2,768 (-10.7%) |
| July-December 2022 | 23,132 | 27,237 (+15.1%) | 24,174 (+4.3%) | 20,982 (-10.2%) | 22,960 (-0.8%) | 24,353 (+5%) | 13,479 (-71.6%) | 21,675 (-6.7%) | 22,093 (-4.7%) |

## Supplemental Table 6-1. PASC Diagnostic Categories and ICD-10 Diagnosis

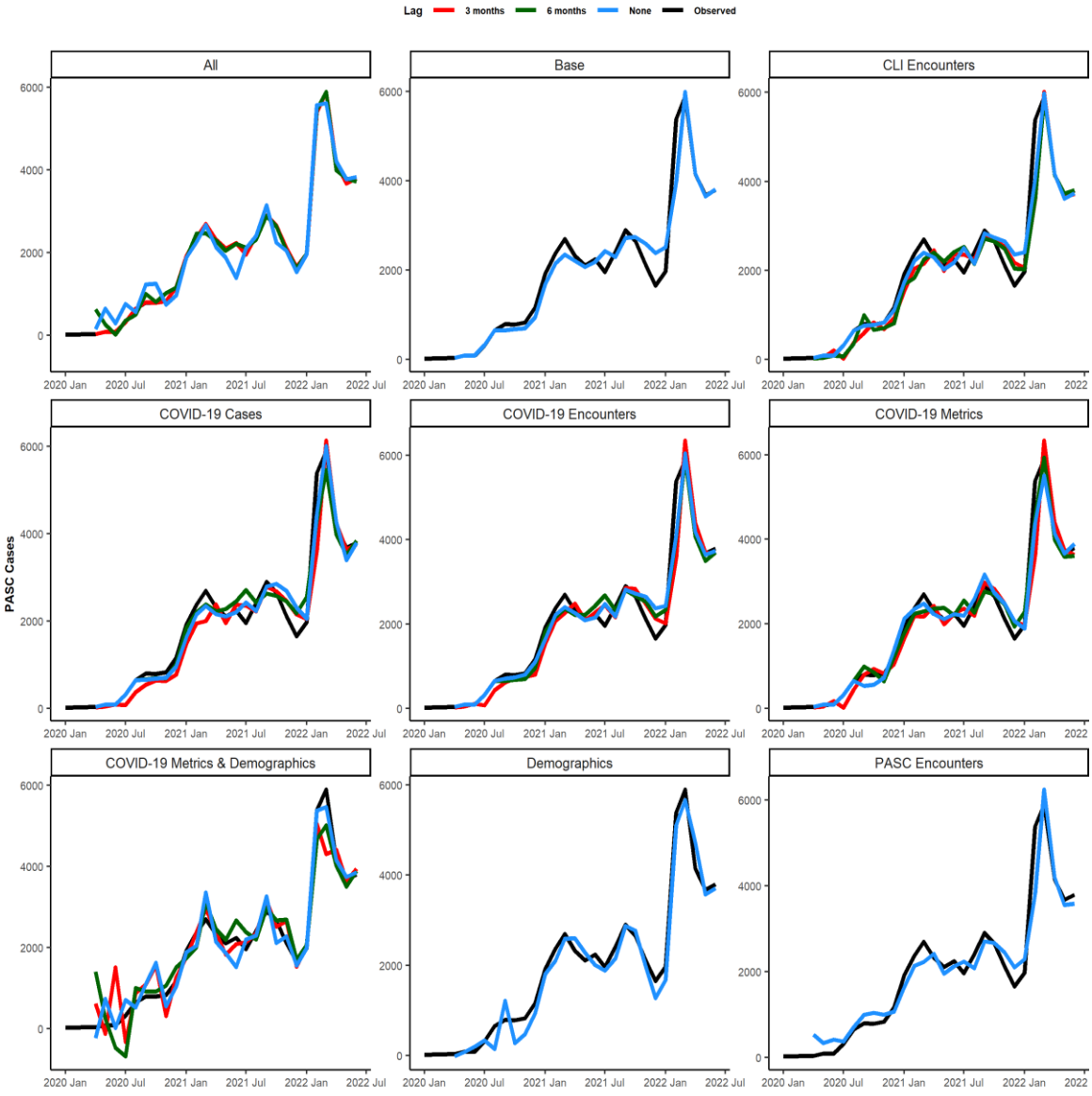
| Diagnostic Group | Diagnosis Description | ICD10 Codes |
|---|---|---|
| Mental Health | Anxiety | F4323, F419, F411, F418, F4322 |
| | Insomnia | G4700, F51 |
| | PTSD | F4312 |
| | Major Depression | F321, F329, F331, F332, F339, R45851 |
| Neurological | Headache | R51 |
| | Taste Loss | R430, R431, R432, R438, R439 |
| | Seizure | R5600, R5601, R569, G40001, G40009, G40011, G40019, G40101, G40109, G40111, G40119, G40201, G40209, G40211, G40219, G40301, G40309, G40311, G40319, G40401, G40409, G40411, G40419, G40501, G40509, G40801, G40802, G40803, G40804, G40811, G40812, G40813, G40814, G40821, G40822, G40823, G40824, G4089, G40901, G40909, G40911, G40919, G40A01, G40A09, G40A11, G40A19, G40B01, G40B09, G40B11, G40B19 |
| | Blurred Vision | H53 |
| | Fatigue | R53 |
| | Memory Loss | R413 |
| | Cognitive Dysfunction | R410, R411, R412 |
| | Vertigo | H8110, H8111, H8112, H8113, H8141, H8142, H8143, H8149 |
| Respiratory | Cough | R05 |
| | Short of Breath | R0602, R0600, R0609 |
| | Pulmonary Embolism | I2699 |
| | Asthma | J45909, J4520, J45901, J4530, R062 |
| Cardiac | Chest Pain | R079, R0789, R072 |
| | Palpitations | R002 |
| | Atrial Fibrillation | I4891, I480 |
| | Syncope | R55 |
| | Tachycardia | R000 |
| | Heart Failure | I509, I517 |
| | Bradycardia | R001 |
| | Myocardial Infarction | I21, I22 |
| | Cerebral infarction/Stroke | I63 |
| | Post Exertional Malaise | T733 |
| | Myocarditis | I40, I41, I514, B3322 |
| | Pericarditis | I30, I32, B3323 |

Abbreviations: PASC, Post Acute Sequelae of COVID-19

## Supplemental Table 6-2. ESSENCE COVID-Like Illness (CLI) Definition

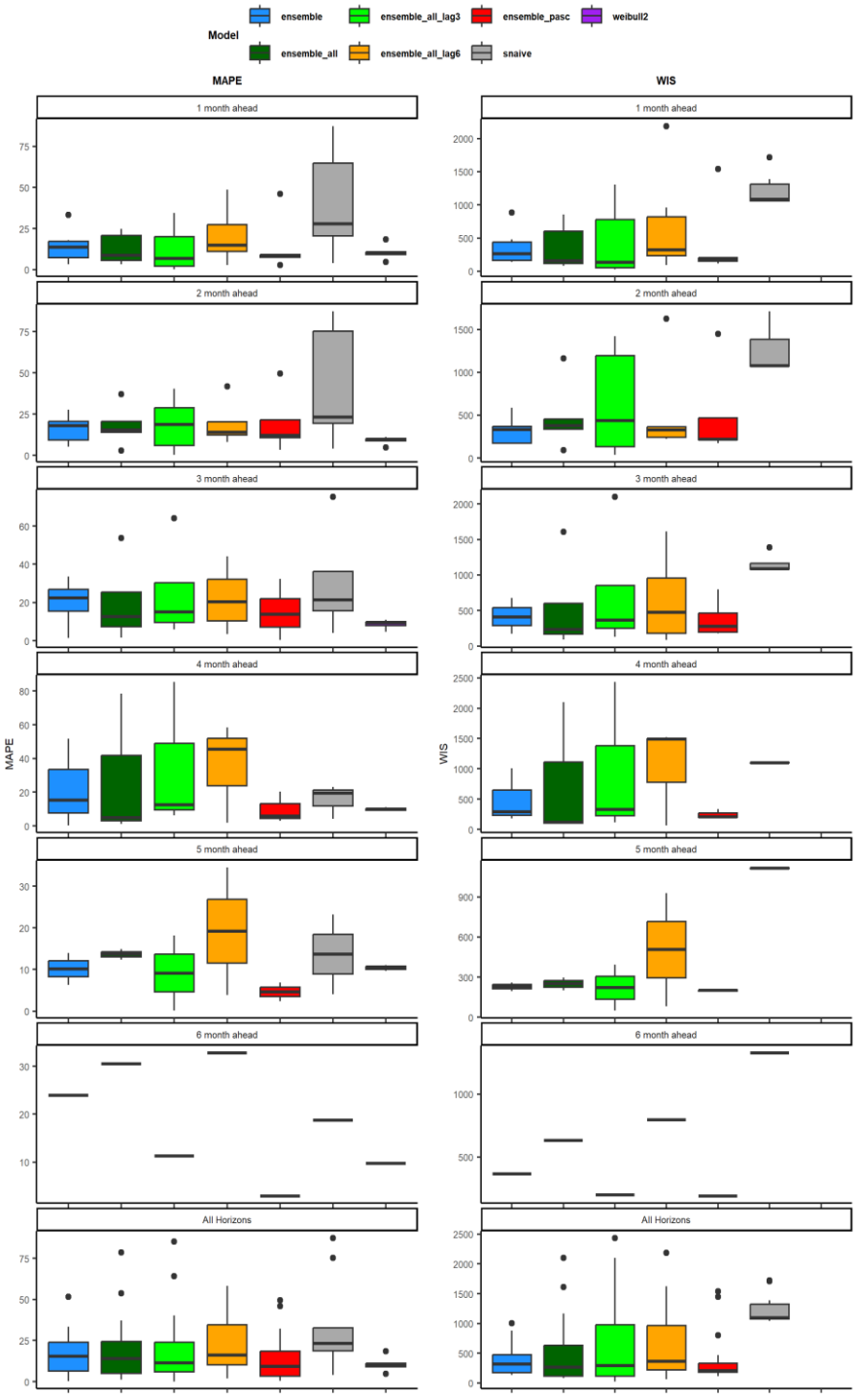
| Diagnosis Description | ICD-10 Codes |
|---|---|
| Coronavirus, unspecified | B34.2 |
| SARS-associated coronavirus as the cause of disease classified elsewhere | B97.21 |
| Other coronavirus as the cause of disease classified elsewhere | B97.29 |
| Acute nasopharyngitis; common cold | J00 |
| Acute upper respiratory infection, unspecified | J06.9 |
| Pneumonia due to SARS-associated coronavirus | J12.81 |
| Other viral pneumonia | J12.89 |
| Viral pneumonia unspecified | J16.8 |
| Pneumonia in diseases classified elsewhere | J17 |
| Bronchopneumonia, unspecified organism | J18.0 |
| Lobar pneumonia, unspecified organism | J18.1 |
| Other pneumonia, unspecified organism | J18.8 |
| Pneumonia, unspecified organism | J18.9 |
| Acute bronchitis due to other specified organisms | J20.8 |
| Acute bronchitis, unspecified | J20.9 |
| Unspecified acute lower respiratory infection | J22 |
| Bronchitis, not specified as acute or chronic | J40 |
| Acute respiratory distress syndrome | J80 |
| Idiopathic interstitial pneumonia not otherwise specified | J84.111 |
| Cough | R05 |
| Dyspnea | R06.0 |
| Dyspnea, unspecified | R06.00 |
| Shortness of breath | R06.02 |
| Acute respiratory distress | R06.03 |
| Other forms of dyspnea | R06.09 |
| Anosmia | R43.0 |
| Ageusia | R43.2 |
| Fever, unspecified | R50.9 |
| 2019-nCoV acute respiratory disease, COVID-19, virus identified | U07.1 |

**Supplemental Figure 6-1. Observed vs Median Fitted Predictions by Training Covariates and Data Lag**




Observed cases are shown in black. Solid, colored lines represent the fitted value for each covariate and data lag.

**Supplemental Figure 6-2. Median MAPE and WIS by Selected Ensemble and Baseline Models and Forecasting Horizon**




MAPE by model and forecasting horizon are shown on the left. WIS by model and horizon are shown on the right. Smaller values indicate more accurate model performance and more narrow boxplots indicate more precise forecasts.

## CHAPTER 7: Conclusions and Future Directions

The analyses conducted in this dissertation characterize long COVID in the military population, address gaps in long COVID research in this population, and provide a framework for predicting long COVID using available clinical data. The results were presented as three closely related manuscripts. The first analysis measured the rate of long COVID in U.S. servicemembers from 2020 to 2022 and identified risk factors for long COVID in a military setting. The second analysis built upon the first, looking specifically at the role of COVID-19 vaccinations in the risk of long COVID and exploring whether waning immunity could play a role in the development of long COVID. Analysis 3 used clinical data from the first analysis as well as syndromic surveillance data to develop predictive models of long COVID incidence up to 6 months in advance. The analyses presented in this dissertation indicate that, similar to the general public, risk factors for long COVID in the military population include increased age, female sex, having at least one comorbidity, and smoking, while vaccination against COVID-19 and antiviral treatment may reduce the risk of long COVID[38,39,41–46]. Additionally, this dissertation found that chest pain and shortness of breath were among the most commonly reported symptoms of long COVID, similar to previous studies[33,39]. However, unlike previous studies, the risk of long COVID was higher in servicemembers during the Omicron wave of SARS-CoV-2[79]. Differences in rates of long COVID were seen by service, with both the Coast Guard and Marines having the lowest adjusted IRR compared to the other services. Information about risk factors and symptoms of long COVID in this population can be leveraged to improve the health of service members in the future and ultimately improve troop readiness. Vaccination against COVID-19

reduced the overall risk of long COVID compared to servicemembers who were not vaccinated, with a greater reduction seen for those who had received one or more booster doses prior to being infected with SARS-CoV-2 compared to those who were partially or fully vaccinated but had not received a booster dose, which is in line with previous research[44,45,99]. Additionally, those vaccinated within 3 months of their COVID-19 event had the lowest risk of long COVID. However, the effect of vaccination decreased over the 11-month study period, with differences between vaccinated and unvaccinated servicemembers generally becoming insignificant after 3 months of follow-up. Longer-term reduction was seen for respiratory diagnoses (7 months) and neurological diagnoses (4 months). Understanding how vaccination, and particularly waning immunity, impacts risk for long COVID is crucial, especially with constantly changing vaccination schedules and recommendations. Providing booster doses as close to the observed peak of COVID-19 cases as possible could help prevent future reductions in troop readiness due to long COVID. Efforts to predict long COVID over a 6-month time period were largely successful, with predictions for several covariate combinations within 5% of the observed number of diagnoses over the forecasting period.

In analysis 1, we examined the risk of long COVID in active component U.S. servicemembers who were previously diagnosed with COVID-19, utilizing a large cohort of COVID-19 cases, along with linked medical records. The Defense Centers for Public Health – Portsmouth's Post Acute Sequelae of COVID-19 (PASC) definition was chosen as the long COVID definition as it was previously validated for use with DoD health encounter data. A cohort of 464,356 servicemembers with a confirmed COVID-19 event between 2020 and 2022 were included in the study, of which 104,024 (22.4%) were

subsequently diagnosed with long COVID, a rate of 70.4 per 100,000 person-days. This is in line with previous estimates of long COVID ranging from 10-60% in people who were previously diagnosed with COVID-19[5-10]. Potential risk factors were chosen for analysis due to their prior association with COVID-19 or long COVID, including demographics (sex, age, race/ethnicity), service-specific information (service branch, rank), education level, characteristics of their COVID-19 event (symptoms, hospitalization, re-infection, vaccination status, wave, treatment), and comorbidities. Similar to previous studies, higher rates of long COVID were seen with increasing age, female sex, having at least one comorbidity, and being unvaccinated at the time of the COVID-19 event[38,39,41–46,99]. Other significant risk factors identified included non-Hispanic Black race, symptomatic COVID-19 event, hospitalization for COVID-19, re-infection with SARS-CoV-2, and infection during the Alpha, Delta, and Omicron waves of the SARS-CoV-2 pandemic, while serving in the Coast Guard, Marines, and Navy as well as being an officer and increased levels of education were associated with reduced risk of long COVID in the study population. Additionally, antiviral treatment for COVID-19 lowered the rate of long COVID in the study population, which has been seen in previous studies[41–43]. Incidence of mental health symptoms was the highest of the four diagnostic groups, at 39.6 per 100,000 person-days while neurological symptoms were the lowest at 3.9 per 100,000 person-days. The most commonly reported symptoms in other studies have been shortness of breath, chest pain, and loss of smell[33,39].

Analysis 1 builds upon prior research in the general population to establish an estimate of long COVID in the military population. In addition, this analysis identifies risk factors for long COVID in this special population, some of which were not identified in previous

studies. Results indicated that individuals with more severe cases of COVID-19 may be at higher risk of long COVID, but tools used to combat COVID-19 may also be effective at reducing long COVID symptoms. Socioeconomic factors may also play into risk of long COVID, as both rank and education status were associated with long COVID. Mental health diagnoses were more prevalent in this analysis compared to prior studies, and more research is needed to determine if this is specific to the military. The analyses were only conducted using COVID-19 cases through the end of 2022, so future studies could explore whether the same associations are seen in more recent time periods. Overall, this analysis highlights the need to identify service-members with risk factors for long COVID, to prevent severe cases of COVID-19, and to provide timely vaccination and treatment in order to prevent long COVID and maintain troop readiness.

In analysis 2, the same cohort was used as in analysis 1, with the same outcome of long COVID and individual diagnostic groups. The analysis explored the effect of COVID-19 vaccination on the risk of long COVID, specifically the type of vaccine, number of doses received, and time between the most recent dose and the COVID-19 event. Due to violations of the proportional hazards assumption, the results were analyzed for each month of the 11-month follow-up period. Overall, vaccination reduced the risk of long COVID compared to those who were unvaccinated, with reductions of 4% and 9%, respectively for those who were partially or fully vaccinated and those with one or more booster dose. Those whose most recent vaccine dose was within 3 months of the COVID-19 event, regardless of vaccine type or category, had the largest reduction in risk of long COVID (6%) compared to the unvaccinated, versus 4% for those whose most recent dose was within 3-6 months and >6 months of the COVID-19 event. There was interaction

between vaccination category and time since last dose, with the difference between those who were partially or fully vaccinated and those with one or more booster doses being strongest at the <3 month time period compared to later time periods. The hazard ratios were not consistent throughout the study period, however, with decreases in long COVID among vaccinated groups mostly limited to the first 1-3 months of follow-up and becoming non-significant for the remainder of the study period.

Being partially or fully vaccinated was associated with a small increase in mental health diagnoses (aHR 1.05 vs unvaccinated), while one or more booster doses was not associated with mental health diagnoses (aHR 1.01). One or more booster doses was associated with larger decreases in neurological (aHR 0.81 vs unvaccinated), respiratory (0.77), and cardiac (0.86) diagnoses. Similar to the overall long COVID results, protection against individual diagnostic groups varied over time. The results were the most robust for respiratory diagnoses, with reduced risk extending through the 7$^{th}$ month of follow-up. Those receiving one or more booster doses had a 41% reduction in diagnoses after the first month of follow-up and a 23% reduction after the 7$^{th}$ month before becoming non-significant for the remainder of the study. Neurological diagnoses were reduced for the first 4 months of follow-up, before showing mixed results at later time periods. Cardiac diagnoses were reduced only for the first 2 months of follow-up, and mental health diagnoses were increased for the first 2 months before becoming non-significant.

Analysis 2 builds upon previous research showing that COVID-19 vaccination, and especially additional doses, is effective in reducing the risk of long COVID and cardiac

symptoms[44,45,99]. This analysis goes even further, exploring the effects of waning immunity by describing how the time between COVID-19 vaccination and the COVID-19 event, and the time between the COVID-19 event and long COVID diagnosis impact the risk of long COVID and individual diagnostic groups. Protection against long COVID wears off quickly after the initial months of follow-up. Future studies could explore the costs and benefits of providing booster doses during different times of the year to maximize the cost efficiency of COVID-19 vaccinations. This analysis excluded vaccinations received between the COVID-19 event and long COVID diagnosis, which could be explored further in future studies. Some evidence shows that receiving one or two doses of vaccine after being infected with SARS-CoV-2 may provide short-term protection against long COVID[48]. This analysis highlights the need to make booster doses available to service members, as well as the need to vaccinate as close to peaks in COVID-19 activity as possible. These strategies may be effective in preserving the health of the military population in the future and therefore troop readiness.

In analysis 3, the cohort from analyses 1 and 2 was used in conjunction with other data to develop predictive models of long COVID in the military population. COVID-19 cases and long COVID diagnoses were aggregated into monthly time series along with demographic information such as sex, race/ethnicity, and rank and clinical information such as hospitalization status, re-infection, and vaccination status. Additionally, monthly time series of COVID-19, COVID-like illness (CLI), and Post Acute Sequelae of COVID-19 (PASC) were downloaded and used as predictors in the models. Baseline seasonal NAÏVE model and Weibull distributions were used as comparisons against autoregressive integrated moving average (ARIMA), neural network (NNET), and vector

autoregressive (VAR) models for monthly and overall forecasts of long COVID diagnoses in a 6-month period from August through December 2022. Combinations of predictors were tested for model fit, with models using COVID-19 metrics and all possible covariates chosen for forecasting. For monthly forecasts of long COVID diagnoses, the most accurate ensemble models had a median absolute percent error (MAPE) within 15% of the observed number of diagnoses, while for full period forecasts the highest performing models were within 5% of the observed diagnoses.

This was one of the first analysis to predict cases of long COVID, both in the civilian population and within the military population. The analysis showed that available clinical and demographic data can be used to accurately predict future cases of long COVID. Both forecasting models and distribution-based forecasts were highly accurate at predicting the number of new long COVID cases over a 6-month period, though monthly forecasts were less accurate and less consistent between model and covariate combinations. This analysis was a "proof of concept" to determine the feasibility of forecasting a non-infectious process like long COVID. Future analyses could focus on improving monthly forecasts, predicting longer-term outcomes, and using more recent time periods for analysis. In addition to the limitations highlighted for each analysis in chapters 4-6, a few more are worth considering. First, the analyses were conducted using data from 2020-2022. Many changes have occurred with COVID-19 since that time, including expanded vaccine boosters and the end of the public health emergency. The results presented in this dissertation may not fully reflect the current state of long COVID. Analysis 3 provides a strategy for predicting new long COVID cases in the

future, which could be instrumental to senior DoD leaders as they plan for future disruptions to troop readiness.

These analyses may have been subjected to information bias, specifically misclassification of the exposure and outcome in each study. The analyses relied on ICD-10 codes and reporting of diagnostic codes in medical records, which may be inconsistent between locations and over time. Since service members are covered through TRICARE, ICD-10 coding within the DoD may differ from that in the civilian world as coding is not related to billing, which could result in more ambiguity when assigning codes to specific conditions. The long COVID outcome definition relied on a broad set of ICD-10 codes and may have excluded symptoms or diagnostic areas that would be of interest in long COVID research, while also including a combination of common, relatively mild symptoms as well as potentially rare and severe symptoms. These analyses were observational in nature and relied on previously collected medical and demographic information which may be incomplete, inaccurate, and/or inconsistent. This is especially true for race/ethnicity, education level, and occupation which are frequently collected at the beginning of a servicemembers time in service and not updated. The data were cross validated against multiple datasets within DMSS to improve completeness, but it was not possible to achieve full completeness of every variable. Another potential source of information bias in this cohort was the need to see a provider to receive a diagnosis of long COVID. This may have led to misclassification of service members who were sicker or those with better socioeconomic status and access to healthcare while underrepresenting those with more mild symptoms of long COVID. Attempts were made to control for a large number of demographic factors as well as the number of health

encounters for each person during the follow-up period to reduce the effect of health-seeking behavior on the results.

Additionally, COVID-19 hospitalization and vaccination status was assessed using multiple data sources and under different reporting requirements throughout the study period, potentially leading to differences in reporting based on when a servicemember was diagnosed with COVID-19. Hospitalization and/or vaccination may have occurred outside the military health system (outsourced care), leading to delays or underreporting that may not have been resolved prior to this study. Delays or gaps in reporting of outsourced care could have also affected the outcome and comorbidity classification as these definitions relied heavily on ICD-10 code reporting in DMSS. This may have impacted the COVID-19 symptomology exposure variable as well, which relied on a COVID-like illness ICD-10 code in an outpatient or inpatient medical encounter within a narrow time range around the COVID-19 event date. While outsourced encounters are received in DMSS, they are frequently delayed by up to or greater than six months. The CLI definition may be too broad based on changing understanding of COVID-19 symptoms, or symptoms may have been unrelated to the COVID-19 event itself.

Observational studies are also prone to selection bias, which may have affected the results of these analyses. The cohort consisted of servicemembers who tested positive or were diagnosed with COVID-19. Those who test for COVID-19 may be different than those who do not, potentially leading to the cohort not fully representing the overall military population. This study also lacked the ability to determine if a servicemember was lost to follow-up, whether because they chose not to see a provider or because they

left military service. Asymptomatic cases may have also resulted in selection bias, as those cases may not have been diagnosed with COVID-19 and included in the study population. This may have varied throughout the follow-up period due to the aforementioned differences in testing behaviors and changing symptomology of the infection itself over time. Lastly, this study did not include an external control group of healthy servicemembers without COVID-19, which could have strengthened the conclusions presented in this study.

Additionally, the analyses presented may be prone to type I errors. Analyses 1 and 2 may have benefited from corrections for multiple comparison tests, while the large sample size in the study may have increased the likelihood of a type I error rate. This study, while broadly generalizable to the military population, may not be generalizable to the general public due to demographic and other differences between the military and civilian populations.

Lastly, unmeasured confounding of clinical and demographic factors may have biased associations the analyses, notably analysis 1 and analysis 2. Additional confounding may also have been present due to differences in healthcare-seeking and reporting behaviors in the population. Service members who are vaccinated for COVID-19 or who choose to see a provider for long COVID symptoms may be different than those who are unvaccinated or do not report, though Active-Duty service members were required to be vaccinated for COVID-19 between August 24, 2021 and January 10, 2023 which may have reduced the effect of personal characteristics on vaccination. Efforts were made to control for demographic variables that may be related to a service member's behaviors, as well as

the number of health encounters during follow-up for each service member, however, the issue may persist. Propensity score matching for both vaccination and number of health encounters could have been used during this study to reduce bias from unmeasured confounding. Sensitivity analyses could also have been performed to measure the degree to which unmeasured confounding would need to be present to change the outcomes presented in the analyses.

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