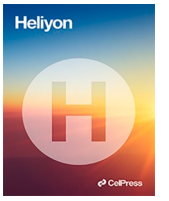
Heliyon 10 (2024) e27567

Contents lists available at ScienceDirect

Heliyon

journal homepage: www.cell.com/heliyon



Research article

Seroprevalence of SARS-CoV-2 IgG in people with cystic fibrosis

Kathleen Mahan [a,*], Sarah Kiel [a], Rebecca Freese [b], Nicholas Marka [b], Jordan Dunitz [a], Joanne Billings [a]

[a] University of Minnesota, Division of Pulmonary, Allergy, Critical Care and Sleep Medicine, USA
[b] Biostatistical Design and Analysis Center, Clinical and Translational Science Institute, University of Minnesota, USA

ARTICLE INFO

Keywords:
COVID-19
Cystic fibrosis
Seroprevalence
Antibody
Vaccination
Booster
Durability
Immunity
Natural
Induced

ABSTRACT

Background: When the first known US case of COVID-19 (Coronavirus Disease 2019) was reported in early 2020, little was known about the impact of this novel virus on the cystic fibrosis community. As the majority of individuals with CF have chronic lung disease, this population was initially considered to be at high risk for severe disease as infection with a multitude of viruses has proven to cause pulmonary exacerbation. SARS-CoV-2 virus has proven challenging to study given the multiple disease manifestations, range of severity, and wave-like phenomenon that varies geographically. People with CF who become infected with COVID-19 can be asymptomatic or have symptoms ranging from mild cough and congestion to full respiratory failure, similar to the manifestations seen in non-CF individuals. By studying the seroprevalence, clinical course, and antibody durability due to COVID-19 and vaccinations, we will be better equipped to provide appropriate and informed care to people with CF.

Methods: Between July 2020 and April 2021 we enrolled 123 people with CF (pwCF) who receive care at the MN CF Center. We monitored their serology every 6 months for SARS-CoV-2 immunoglobulins (nucleocapsid and spike IgG) for evidence of natural and induced immunity. Medication use, pulmonary function, exacerbation history, and hospitalizations were extracted via electronic medical record (EMR).

Results: 84% (101/120) of enrolled participants were vaccinated against SARS-CoV-2 during the study. Eighty three percent of the cohort showed evidence of either natural or induced "immunity." The average duration of antibody from induced immunity in participants was 6.1 months and from natural immunity was 7.4 months with an overall average duration of antibody of 6.8 months. Earliest antibody detected was 12 days after a single dose of the BNT162b2 vaccine and antibody was detectable across a span of 13 months. Eleven percent of vaccinated individuals did not have measurable IgG. 36% of non-responders (NRs) were solid organ transplant patients on chronic immunosuppressive therapy. Only 3 people within this cohort were hospitalized due to COVID pneumonia and all three survived.

Conclusion: To our knowledge, this is the first report on the seroprevalence and longevity of SARS-CoV-2 IgG to 1 year in adults with CF after the widespread availability of SARS-CoV-2 vaccinations. These data show that pwCF respond to the COVID vaccination and produce long-lasting antibodies similar to the general population.

* Corresponding author.
E-mail address: mahan023@umn.edu (K. Mahan).

https://doi.org/10.1016/j.heliyon.2024.e27567
Received 11 December 2023; Received in revised form 29 February 2024; Accepted 1 March 2024
Available online 7 March 2024

1. Introduction

The COVID-19 (Coronavirus Disease 2019) pandemic began with its first case documented in the United States in January 2020 [1]. As of January 2023, 101.5 million cases are reported with nearly 1.1 million deaths attributed to SARS-CoV-2 [2]. By January 5, 2023, the Cystic Fibrosis Foundation (CFF) has reported at least 7431 cases of COVID-19 in persons with cystic fibrosis (pwCF) in the United States with 32 associated deaths.

Cystic fibrosis (CF) is a genetic disorder caused by mutations in the cystic fibrosis transmembrane regulator (CFTR) gene resulting in disordered exchange of chloride ions within epithelial cells. Clinically, the disease manifests with multiple organ dysfunction, but CF is predominantly characterized by repeated respiratory infections and chronic inflammation leading to pulmonary decline [3,4]. There has been long-standing concern that mutations in the CFTR gene can alter both innate and adaptive immunity [5,6]. In a population with underlying chronic pulmonary disease, and dysregulated immunity to inhaled pathogens, the impact of SARS-CoV-2 is of particular interest.

In Europe, during the first wave of the pandemic, people with cystic fibrosis were more frequently hospitalized due to SARS-CoV-2 infection than the age matched general population [7], however, the underlying seroprevalence within the CF community has not been well described and infection fatality rate can only be poorly estimated [8,9]. In Italy, one study demonstrated 64 out of 434 CF patients >12 years of age had positive SARS-CoV-2 spike antibody levels (pre vaccine era) with over half of these patients being asymptomatic suggesting a much higher prevalence within the population than previously thought [10]. With the advent of COVID-19 vaccines, describing the prevalence of antibody formation within this population that relies on primary prevention is of utmost importance. With the wave-like release of COVID-19 vaccines through Emergency Use Authorization (EUA), identification of specific antibodies targeted to distinct regions of the SARS-CoV-2 virus (e.g. spike vs. nucleocapsid protein) allows for better understanding of serological results;

Table 1
Overall demographics, clinical characteristics, and transplant status of our patient population, n = 120. BMI – body mass index (kg/m^2), HBA1c – hemoglobin A1c (%), CFTR – cystic fibrosis transmembrane conductance regular, FEV_1 – forced expiratory volume in 1 s (in liters), Visit 1 – baseline, Visit 2 – 6 month follow-up, Visit 3 – 12 month follow-up, IQR – inter-quartile range.

Overall (# of patients)	120
Sex	
Female, N (%)	59 (49)
Male, N (%)	61 (51)
Age (years)	
Mean	35.6
range	13–70
Genotype, N (%)	
DF508 Homozygous	62 (52)
DF508 heterozygous	50 (42)
Other	8 (6)
BMI	
median	24
IQR (25th – 75th)	21.85–26.05
HbA1c	
median	5.5
(IQR) range	5.2–6
CFTR modulator, N (%)	
yes	96 (80)
No	24 (20)
Average FEV_1 (L)	
Visit 1	2.94
Visit 2	2.97
Visit 3	2.89
insulin use, N (%)	
Yes	49 (41)
No	71 (59)
Prednisone, N (%)	
Yes	18 (15)
No	102 (85)
Chronic oral antibiotic, N (%)	
Yes	71 (59)
No	49 (41)
Transplant	
lung, N (%)	12 (10)
pancreas, N (%)	2 (2)
kidney, N (%)	3 (3)

the presence of nucleocapsid antibody suggests viral infection whereas presence of spike antibody but lack of nucleocapsid antibody suggests prior vaccination.

To date, only two studies have described the seroprevalence or the impact of COVID19 vaccinations on seroprevalence within the CF population [9,11]. This current study aims to provide more insight regarding the seroprevalence of COVID-19, as well as document the longevity of antibody persistence, both induced and natural, in pwCF.

2. Results

Between July 2020 through April 2021, 123 participants were enrolled. Three participants withdrew from the study early. The first blood draw was completed in July 2020. Patient characteristics are shown in Tables 1 and 2.

Demographics: All patients received care at the MN CF center based in Minneapolis, MN. Participants lived in 90 distinct zip codes. 51% were male and the average age was 35.6 years with a range from 13 to 70 years. 52% had the DF508 homozygous genotype. At the time of screening the average BMI was 24.4 and average HbA1c was 5.8. Eighty percent of participants were taking a CFTR modulator at the time of enrollment; additionally, approximately 40% were taking insulin, 15% used chronic prednisone, and 59% used chronic oral antibiotics. The average FEV_1 was 2.9 L at the time of screening. Twelve patients were solid organ transplant recipients.

Vaccine data: The three major vaccinations available within the US were approved by EUA for use by early 2021. By the end of 2021, 84% of our enrolled patients were vaccinated (Table 3) with only 2% of patients not completing the full series. Over the following 12 months, 53% of our patients received at least one booster vaccine. This vaccination rate is higher than the rate currently seen in the general population in Minnesota, approximately 72% [12]. The majority of patients, 66%, received the Pfizer primary COVID vaccine series and 25% received Moderna as a primary series. The majority of COVID vaccinations, 68%, were obtained at a commercial pharmacy and only about 17% were received in the primary care setting. It is important to note that many clinics were operating via telehealth only visits at this time due to reduced in-person operations imposed from system administration due to the pandemic; this likely contributed to the low vaccination rate provided within the clinic setting.

IgG data: Within the first 6 months of the study, 8 out of 55 enrolled patients were identified to have SARS-CoV-2 IgG from natural infection either by the presence of nucleocapsid Ab or spike IgG Ab before vaccination. We term the presence of the antibody in this setting, "natural immunity." By the end of 2021, IgG Ab was detected in 17% of the patients due to natural infection. By July 2021, 27% of patients were identified to have "induced immunity" as indicated by the presence of spike IgG after vaccination and lack of nucleocapsid IgG. At the end of data collection for first year serology, 74% had induced immunity while 23% had natural immunity to COVID-19. Overall seroprevalence of SARS-CoV-2 IgG, either from natural infection or vaccination, was 83%. In comparison to data collected by CDC (Centers for Disease Control) that included a U.S. cohort of ~142,000 blood donors between April 2021 and

Table 2
Overall antibody detection grouped by patient characteristics: age, genotype, use of inhaled or oral steroids, CFTR modulator therapy, chronic NSAID use, or chronic antibiotic use. Columns 3–6 show antibody type (induced, natural, hybrid, none) and prevalence based on within-group (e.g., age 12–19, age 20–40, heterozygous DF508, homozygous DF508) patient characteristics. P-values for categorical variables from Fisher's exact tests and ANOVA for continuous variables. CFTR – cystic fibrosis transmembrane conductance regulator, NSAID – non-steroidal anti-inflammatory, Antibiotics – refers to oral antibiotics.

	Overall	Induced	Natural	Hybrid	No Antibodies	p-value
Overall, N (%)	120 (100)	71 (59.2)	11 (9.2)	17 (14.2)	21 (17.5)	
Age [years], N (%)						
12-19	7 (5.8)	1 (14.3)	0 (0)	2 (28.6)	4 (57.1)	
20-40	79 (65.8)	50 (63.3)	8 (10.1)	9 (11.4)	12 (15.2)	0.15
41-60	28 (23.3)	16 (57.1)	2 (7.1)	5 (17.9)	5 (17.9)	
>60	6 (5.0)	4 (66.7)	1 (16.7)	1 (16.7)	0 (0)	
CF Genotype, N (%)						
Heterozygous DF508	50 (41.7)	32 (64.0)	3 (6.0)	6 (12.0)	9 (18.0)	
Homozygous DF50	62 (51.7)	37 (59.7)	7 (11.3)	8 (12.9)	10 (16.1)	0.337
Other	8 (6.7)	2 (25.0)	1 (12.5)	3 (37.5)	2 (25.0)	
Inhaled Steroid, N (%)						
No	67 (55.8)	36 (53.7)	6 (9.0)	12 (17.9)	13 (19.4)	0.592
Yes	53 (44.2)	35 (66.0)	5 (9.4)	5 (9.4)	8 (15.1)	
Oral Prednisone, N (%)						
No	102 (85.0)	61 (59.8)	8 (7.8)	16 (15.7)	17 (16.7)	0.314
Yes	18 (15.0)	10 (55.6)	3 (16.7)	1 (5.6)	4 (22.2)	
CFTR Modulator, N (%)						
No	24 (20.0)	11 (45.8)	2 (8.3)	4 (16.7)	7 (29.2)	0.32
Yes	96 (80.0)	60 (62.5)	9 (9.4)	13 (13.5)	14 (14.6)	
NSAIDS, N (%)						
No	87 (72.5)	49 (56.3)	9 (10.3)	15 (17.2)	14 (16.1)	0.328
Yes	33 (27.5)	22 (66.7)	2 (6.1)	2 (6.1)	7 (21.2)	
Chronic Antibiotics, N (%)						
No	49 (40.8)	24 (49.0)	5 (10.2)	6 (12.2)	14 (28.6)	0.047
Yes	71 (59.2)	47 (66.2)	6 (8.5)	11 (15.5)	7 (9.9)	

Table 3
Vaccination data on enrolled patients, n = 120, including type of vaccine and location of vaccination. Data were self-reported and extracted from EMR.

	Overall
Overall, N	120
Vaccination Status, N (%)	
No	19 (15.8)
Yes	101 (84.2)
Vaccine Type, N (%)	
Pfizer	67 (66.3)
Moderna	25 (24.8)
Other	9 (8.9)
Vaccination Setting, N (%)	
Place of employment	11 (10.9)
Commercial Pharmacy	69 (68.3)
Primary Care	17 (16.8)
Other	4 (4.0)

September 2022, the overall seroprevalence of SARS-CoV-2 antibodies from previous infection or vaccination published in MMWR was higher than that seen in our population by May 2022 (96.4% vs. 83% in the CF population) [13]. 60% of pwCF had antibody due to induced immunity (vaccination), 8.3% from natural immunity (infection), and 15% with hybrid immunity (both induced and natural). In comparison, the CF population had higher antibody detection due to vaccination along with lower antibody detection from infection; these differences likely reflect the difference in long-standing practices engrained in the CF community to prevent viral spread such as hand-washing and distancing. The age group with the greatest hybrid immunity was age 20–40 years with the least hybrid immunity in the oldest age group, >60 years, similar to that seen in the Jones et al. study [13]. Natural infection rates varied by age group with the majority in the 12–40 year old age group (68%, n = 19 vs. n = 9), as shown in Table 2. This finding is consistent with many reports showing increasing exposure and spread of Covid-19 by the younger age groups [14]. The average age of those found to have natural infection is 33.6 years. The same young group (age 12–40) had the highest rate of no antibodies (n = 16 vs. n = 5), consistent with lower vaccination rates in this age range [15]. There were no significant associations between the following participant groups and SARS-CoV-2 antibody production: specific CF genotype, higher or lower BMI, mean FEV_1, HbA1c, chronic inhaled or oral corticosteroids, presence of CFTR modulator, chronic NSAID use, or chronic oral antibiotics.

Durability: In our patient population, induced IgG was measurable up to 15 months after vaccination and detected as early as 12 days after vaccination. Patients were resampled approximately 6 months later and antibodies persisted to that time point for all patients who made antibody in response to vaccination or infection (average 6.8 months). On serial blood draws, the range of Ab longevity for induced IgG was 3 months–13 months. The range of detection for natural IgG was 4 months–12 months. Fig. 1 provides patient examples delineating the establishment of "induced" vs. "natural" immunity based on serological data. In individuals who did not receive a booster vaccination, Abs were still detectable 9 months after completion of the initial vaccine series. These data suggest IgG durability that is comparable to that of the general population [16,17].

Eleven patients received vaccine but did not produce Abs on repeat measurement and are termed "non-responders" (NRs). The average age of the NRs is 33.7 years. Four of these are transplant recipients and thus receive chronic immunosuppressive therapy which directly affect immunoglobulin production, in particular antimetabolite immunosuppression [18]. 10 out of these 11 individuals had a positive rubeola IgG; one patient tested negative for IgG but had not previously been vaccinated for rubeola. Seven of the eleven NRs did not receive vaccine boosters at the time of Ab measurement. Of the 8 patients who received a solid organ transplant (SOT) and formed Abs, detectable antibody was measured upon resampling 1–9 months after the initial sample collection (average 5.9 months). The odds ratio for forming IgG Abs among transplanted patients as compared to those not transplanted is 0.37 [95% CI: (0.19, 0.73); p-value 0.14], as summarized in Table 4. This finding has been reported in several studies, notably most recently published by Barnes et al. [16,18,19].

Hospitalization data: Only 3 patients from the cohort were hospitalized for COVID-19 during the study (Table 5). One hundred percent had the DF508 heterozygous genotype. Average pre-hospitalization FEV_1 was 3.53 L. Average age was 50.7 years. Two of the individuals were vaccinated for COVID-19 at the time of hospitalization, one with Johnson & Johnson, and the other with the Pfizer vaccine. All were hypoxic (SpO2 <89%) and required supplemental oxygen during their illness. The average hospitalization length of stay (LOS) was 7 days; none required intensive care level treatment. Interestingly, the post-illness FEV_1 dropped by an average of 15% with none of the patients returning to the pre-hospitalization baseline greater than 1 year post-hospitalization. Only 1 of the 3 patients was on a CFTR modulator at the time of illness and one patient was initiated on HEMT (highly effective modulator therapy) post-hospitalization as lung function remained reduced several months after therapy for COVID-19. Chest CT imaging for this patient showed post-COVID pulmonary fibrosis.

3. Discussion

To our knowledge this is the only study reporting longitudinal monitoring of SARS CoV-2 IgG duration and presence in the adult CF population. Jaudszus et al. screened 156 patients over 13 months but only 83% of their patient cohort had a second blood draw and there is

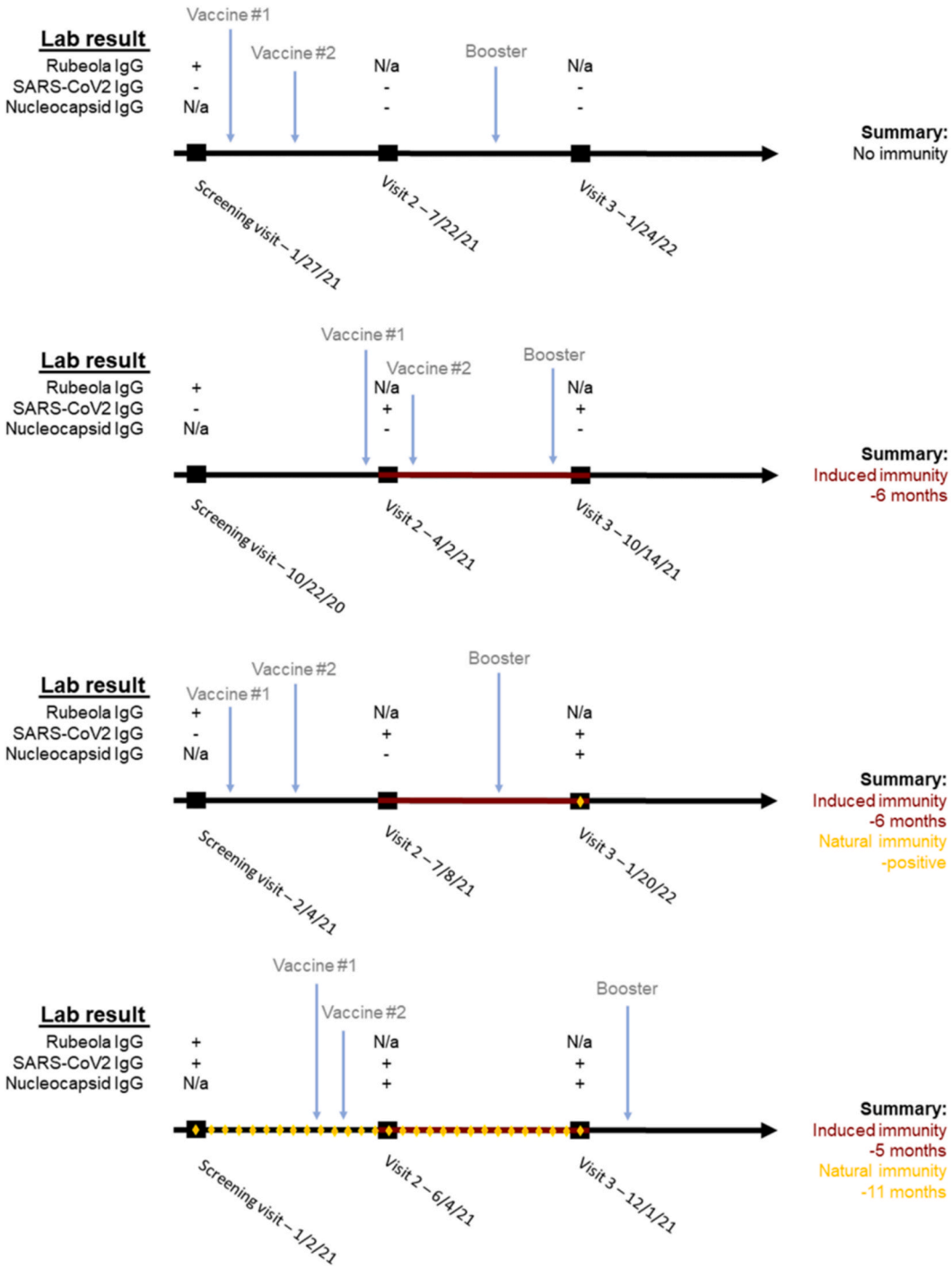


Fig. 1. Schematic showing patient visit dates, representative vaccination and boosters, and serological data (Rubeola IgG, SARS-CoV-2 Spike protein IgG, SARS-CoV-2 Nucleocapsid IgG). These 4 scenarios describe common serological data results used for antibody interpretation of "induced" vs. "natural" immunity.

no report on duration of antibody detection [20]. Strengths of our study include early enrollment and blood collection at the start of the COVID-19 pandemic, our patient cohort size (n = 120), and diverse patient population treated at a busy, metropolitan CF care center. Limitations are described below and include a necessary dynamic study design and implementation during a real-life pandemic with evolving regulations. Inherent to research during a pandemic are those associated with limiting exposure risk, internal institutional review board (IRB) restrictions, methodological adaptations required by emergency treatment measures such as approval of SARS-CoV-2 vaccines.

Table 4
SARS-CoV-2 IgG presence or absence in the 12 individuals who have received solid organ transplant (SOT). OR – odds ratio, CI – confidence interval.

ANTIBODY PRESENCE	NO TRANSPLANT N (%)	TRANSPLANT N (%)
OVERALL	108 (90)	12 (10)
NO	17 (15.7)	4 (33.3)
YES	91 (84.2)	8 (66.7)

ANTIBODY FORMATION OR = 0.37; 95% CI [0.19, 0.73], P-VALUE 0.14.

Table 5
Characteristics of the three individuals within the cohort who required hospitalization for COVID-19 infection. CFTRM – cystic fibrosis transmembrane conductance regulator modulator therapy, LOS - length of stay in days, DFEV1 - change in FEV_1 (pre-COVID $ppFEV_1$ - post-COVID $ppFEV_1$).

	Age	Vaccination status	Genotype	CFTRm	LOS (d)	$dFEV_1$ (%)
Patient 1	62	No	DF508/R117C	No	14	−33
Patient 2	44	Yes	DF508/CFTRDel21	Yes	1	−5
Patient 3	46	Yes	DF508del/3272-26A > G	No	5	−7

Additionally, relying on antibody assessment at set time intervals can lead to underestimation secondary to natural antibody decline over time, "non-responder" status, false negatives; identification of "natural infection" using this methodology is limited to the presence of SARS-CoV-2 nucleocapsid antibody and does not speak to recovery and then reinfection. Finally, while 120 patients enrolled is a fair representation of our entire CF center, inclusion of additional centers to increase the number of patients enrolled would provide additional power to the study. Despite these limitations, serological analysis is an essential method to study the epidemiology of respiratory viral illnesses, especially those which encompass such a wide range of symptoms. A meta-analysis by Ma et al., in 2021 reported that 40.5% of patients were asymptomatic despite confirmed positive testing for COVID-19 [21].

Our data show that patients less than 41 years of age had the highest rate of antibody formation (both induced from vaccination and natural infection). As the age distribution is skewed towards younger age in the CF population, this representative group was also the largest, n = 86 out of 120 (2021 CF Annual Data Report, CFF). A strength of the study is that our patient cohort spans seven decades with a maximum age of 70 years. Despite a relatively young population, this cohort was indeed vaccinated at a rate higher than the general population: MN, 68%; Iowa, 60%; ND, 51%; SD, 66.2%; and WI, 61.8% [2]. This effect may be secondary to long-standing exposure to and trust of the medical system.

People with CF have reliable vaccination, hand and respiratory hygiene practices which affect their exposure risk, and overall outcomes from COVID-19. Reports suggest that as a whole, pwCF have not had significant increased morbidity or mortality with COVID-19 as compared to the general population, though a subset of patients remain at high risk for severe disease [22,23]. These findings may be due to many reasons including HEMT (highly effective modulator therapy), differences in the pathophysiology of coronavirus in CF patients (altered ACE-2 expression), possible antiviral properties of chronic antimicrobials, effects of *Pseudomonas aeruginosa* colonization [24–26]. This population cohort represents a significant subset (n = 120) of our >600 total patients cared for at the MN CF Center; and while only 3 patients enrolled in the study (n = 120) were hospitalized with "severe" COVID there were a number of patients at our center who had "critical illness" COVID as classified by the World Health Organization (WHO). However, in all 3 individuals in the study hospitalized with COVID, lung function declined below baseline and had not recovered at 12 months post-hospitalization. This observation is not unique in that even those with "mild disease" who may be considered "COVID-recovered," may continue to suffer from ongoing symptoms despite the resolution of their primary disease process. "Long COVID" or PASC" (post-acute sequelae of COVID) is a disease entity which has been little studied in people with CF but certainly deserves attention given the significant associated morbidity [27,28].

As shown by this study, SARS-CoV-2 IgG vaccine response was robust amongst patients but we did not quantitatively measure Ab levels over time. Although the presence of antibody does not equal "immunity" and does not take into account the complexity of the human immune system (e.g. antigen presenting cells, lymphocytes, myeloid cells, etc.), it does represent an arm of the complex protection system so heavily relied upon in this pandemic; and, indeed, infusion of spike Ab (casirivimab, imdevimab, regdanvimab) only has proven effective treatment for people with CF [29]. Our data show persistent IgG after vaccination or natural infection in pwCF is detectable for up to 13 months. We will continue to monitor serology at 36 months and 48 months post-enrollment to better understand the durability of SARS-CoV-2 antibodies in pwCF.

4. Methods

People with CF who were 12 years of age and older from the Minnesota CF center who were due for regular lab monitoring were enrolled in the study. Enrollment began on July 8, 2020 and ended on April 15th, 2021.123 people were enrolled but 3 people ended the study early, 2 voluntarily withdrew and a third due to patient's death. Consent/assent was obtained for all individuals. This study was approved by the Institutional Review Board of the University of Minnesota. All participants completed a brief online survey

detailing possible exposures, symptoms of COVID-19. Surveys were repeated again at 6 and 12 months and included information regarding vaccination status, type of vaccine, booster information once these became available. Medications, lung function, and hospitalization data were extracted through the Electronic Medical Record (EMR). Blood samples were obtained at time points 0, 6, and 12 months to identify SARS-CoV-2 spike antibody, SARS-CoV-2 nucleocapsid antibody, and Rubeola (obtained at time point 0 only as a positive control) IgG. SARS-CoV-2 spike protein IgG only was measured at the start of the study but as vaccines were approved under Emergency Use Authorization (Pfizer-BioNTech on December 10, 2020, Moderna on December 17, 2020, and the Janssen vaccine on February 27, 2021), we additionally began testing for SARS-CoV-2 nucleocapsid protein antibody at the end of January 2021. Additional restrictions instituted by the University of MN required that we only collect bloodwork from individuals who were already undergoing phlebotomy for clinical purposes, e.g. liver function testing for highly effective modulator therapy (HEMT) monitoring. Serum antibody levels were measured using the *ELISA (enzyme-linked immunosorbent assay) Anti-Sars-CoV-2 assay* developed by Advanced Research and Diagnostics Laboratory (ARDL), a semi-quantitative serological assay (sensitivity: 96% and specificity: 100%). In April 2021 we switched to the *Elecsys Anti-SARS-CoV-2 S Reagent assay* and the *Elecsys Anti-SARS-CoV-2 Reagent assay* from Roche Diagnostics. All assays use a recombinant receptor binding domain (RBD) of the SARS-CoV-2 spike or nucleocapsid protein (sensitivity: 98.8%, 99.5% and specificity:100%, 99.8%). The assay targeting the spike protein (*Elecsys Anti-SARS-CoV-2 S Reagent assay)* is a semi-quantitative study and values > 0.8 U/mL were considered positive. Serological analysis were performed at the ARDL laboratory at the University of Minnesota and later sent out to Mayo Laboratory in Rochester, Minnesota per our clinical laboratory requirements. All assays used were approved by the FDA (U.S. Food and Drug Administration) for EUA. Participant demographics were summarized as means and standard deviations or medians and ranges for continuous factors as appropriate, and frequencies and percentages for categorical factors. Comparisons of demographic and clinical variables between antibody status groups was conducted using ANOVA or two-sample t-tests and Chi-square or Fisher's Exact test as appropriate for continuous and categorical factors respectively. All analyses were done at the 0.05 significance level using the R software (version 4.2.0).

5. Limitations

This study has many limitations. Monitoring antibody seroprevalence during a pandemic with multiple pandemic-era regulations (e.g., blood draws limited to those already planned), rolling availability of vaccinations under EUA, and the wave-like phenomenon associated with a respiratory viral illness which varies geographically have proven challenging to our study. As blood draws were set at 6 month intervals, the logic of "induced" vs. "natural" immunity were necessary but may not fully encompass all natural infections. The IgG that we are measuring has shown to be persistent up to 13 months, but may actually persist longer in some individuals; we are limited by only having time points out to 12 months ($\pm$ 3 months) at the time of manuscript preparation. Additionally, the number of blood draws varied by person with a goal of 3 blood draws but with an average of 2.5 blood draws per participant.

Declarations

Consent/assent was obtained for all individuals This study was approved by the Institutional Review Board of the University of Minnesota and the ethics committee: STUDY00009987.

Data availability statement

The data that support the findings of this study are available on request from the corresponding author, KM. The data are not publicly available due to their containing information that could compromise the privacy of research participants.

CRediT authorship contribution statement

Kathleen Mahan: Writing – review & editing, Writing – original draft, Validation, Methodology, Investigation, Funding acquisition, Formal analysis, Data curation, Conceptualization. **Sarah Kiel:** Writing – review & editing, Writing – original draft, Methodology. **Rebecca Freese:** Writing – review & editing, Validation, Formal analysis. **Nicholas Marka:** Writing – review & editing, Validation, Formal analysis. **Jordan Dunitz:** Writing – review & editing, Validation, Supervision, Methodology, Conceptualization. **Joanne Billings:** Writing – review & editing, Supervision, Resources, Methodology, Investigation, Formal analysis, Data curation, Conceptualization.

Declaration of competing interest

Authors certify that they have no affiliations with or involvement in any organization or entity with any financial interest in the subject matter or materials discussed in this manuscript.

Acknowledgements

The authors would like to thank the following: the University of MN Medical School COVID-19 Rapid Response Grant Initiative, the With One Breath Foundation, and the MN CF Center research team. We especially thank our patients with cystic fibrosis and their caregivers for participating in this study.

References

[1] M.L. Holshue, C. DeBolt, S. Lindquist, K.H. Lofy, J. Wiesman, H. Bruce, et al., First case of 2019 novel coronavirus in the United States, N. Engl. J. Med. 382 (10) (2020 Mar 5) 929–936.

[2] Centers for Disease Control and Prevention. CDC COVID Data Tracker Atlanta, GA: US Department of Health and Human Services. https://covid.cdc.gov/covid-data-tracker..

[3] C. Etherington, R. Naseer, S.P. Conway, P. Whitaker, M. Denton, D.G. Peckham, The role of respiratory viruses in adult patients with cystic fibrosis receiving intravenous antibiotics for a pulmonary exacerbation, J. Cyst. Fibros. 13 (1) (2014 Jan) 49–55.

[4] P.A.B. Wark, M. Tooze, L. Cheese, B. Whitehead, P.G. Gibson, K.F. Wark, et al., Viral infections trigger exacerbations of cystic fibrosis in adults and children: figure 1, Eur. Respir. J. 40 (2) (2012 Aug) 510–512.

[5] D. Ratner, C. Mueller, Immune responses in cystic fibrosis: are they intrinsically defective? Am. J. Respir. Cell Mol. Biol. 46 (6) (2012 Jun) 715–722.

[6] E.M. Bruscia, T.L. Bonfield, Update on innate and adaptive immunity in cystic fibrosis, Clin. Chest Med. 43 (4) (2022 Dec) 603–615.

[7] L. Naehrlich, A. Orenti, F. Dunlevy, I. Kasmi, S. Harutyunyan, A. Pfleger, et al., Incidence of SARS-CoV-2 in people with cystic fibrosis in Europe between february and june 2020, J. Cyst. Fibros. 20 (4) (2021 Jul) 566–577.

[8] S. Berardis, A. Verroken, A. Vetillart, C. Struyf, M. Gilbert, D. Gruson, et al., SARS-CoV-2 seroprevalence in a Belgian cohort of patients with cystic fibrosis, J. Cyst. Fibros. 19 (6) (2020 Nov) 872–874.

[9] G. Alicandro, V. Daccó, L. Cariani, M. Contarini, L.C. Morlacchi, C. Rosazza, et al., SARS-CoV-2 antibodies among people with cystic fibrosis prior to the vaccination campaign: a seroprevalence study in two specialized centres in Northern Italy, J. Cyst. Fibros. 21 (2) (2022 Mar) e113–e116.

[10] C. Colombo, G. Alicandro, V. Daccó, V. Gagliano, L.C. Morlacchi, R. Casciaro, et al., February-July 2020, in: A. Gaggar (Ed.), SARS-CoV-2 Infection in Cystic Fibrosis: A Multicentre Prospective Study with a Control Group, PLOS ONE, Italy, 2021 May 13 e0251527, 16(5.

[11] G.E. Hergenroeder, A.V. Faino, J.D. Cogen, A. Genatossio, S. McNamara, M. Pascual, et al., Seroprevalence and clinical characteristics of SARS-CoV-2 infection in children with cystic fibrosis, Pediatr. Pulmonol. 58 (9) (2023 Sep) 2478–2486.

[12] Mn Department of Health. COVID-19 Vaccine Data St. Paul, MN. https://www.health.state.mn.us/diseases/coronavirus/stats/vaccine.html..

[13] J.M. Jones, I.M. Manrique, M.S. Stone, E. Grebe, P. Saa, C.D. Germanio, et al., Estimates of SARS-CoV-2 seroprevalence and incidence of primary SARS-CoV-2 infections among blood donors, by COVID-19 vaccination status — United States, April 2021–september 2022, MMWR Morb. Mortal. Wkly. Rep. 72 (22) (2023 Jun 2) 601–605.

[14] K.E.N. Clarke, J.M. Jones, Y. Deng, E. Nycz, A. Lee, R. Iachan, et al., Seroprevalence of infection-induced SARS-CoV-2 antibodies — United States, september 2021–february 2022, MMWR Morb. Mortal. Wkly. Rep. 71 (17) (2022 Apr 29) 606–608.

[15] J. Diesel, N. Sterrett, S. Dasgupta, J.L. Kriss, V. Barry, K. Vanden Esschert, et al., COVID-19 vaccination coverage among adults — United States, december 14, 2020–may 22, 2021, MMWR Morb. Mortal. Wkly. Rep. 70 (25) (2021 Jun 25) 922–927.

[16] H. Ward, M. Whitaker, B. Flower, S.N. Tang, C. Atchison, A. Darzi, et al., Population antibody responses following COVID-19 vaccination in 212,102 individuals, Nat. Commun. 13 (1) (2022 Feb 16) 907.

[17] E.G. Levin, Y. Lustig, C. Cohen, R. Fluss, V. Indenbaum, S. Amit, et al., Waning immune humoral response to BNT162b2 covid-19 vaccine over 6 months, N. Engl. J. Med. 385 (24) (2021 Dec 9) e84.

[18] B.J. Boyarsky, W.A. Werbel, R.K. Avery, A.A.R. Tobian, A.B. Massie, D.L. Segev, et al., Antibody response to 2-dose SARS-CoV-2 mRNA vaccine series in solid organ transplant recipients, JAMA 325 (21) (2021 Jun 1) 2204.

[19] E. Barnes, C.S. Goodyear, M. Willicombe, C. Gaskell, S. Siebert, T. I De Silva, et al., SARS-CoV-2-specific immune responses and clinical outcomes after COVID-19 vaccination in patients with immune-suppressive disease, Nat. Med. 29 (7) (2023 Jul) 1760–1774.

[20] A. Jaudszus, M. Pavlova, M. Rasche, M. Baier, A. Moeser, M. Lorenz, One year monitoring of SARS-CoV-2 prevalence in a German cohort of patients with cystic fibrosis, BMC Pulm. Med. 22 (1) (2022 Dec) 101.

[21] Q. Ma, J. Liu, Q. Liu, L. Kang, R. Liu, W. Jing, et al., Global percentage of asymptomatic SARS-CoV-2 infections among the tested population and individuals with confirmed COVID-19 diagnosis: a systematic review and meta-analysis, JAMA Netw. Open 4 (12) (2021 Dec 14) e2137257.

[22] S.B. Carr, E. McClenaghan, A. Elbert, A. Faro, R. Cosgriff, O. Abdrakhmanov, et al., Factors associated with clinical progression to severe COVID-19 in people with cystic fibrosis: a global observational study, J. Cyst. Fibros. 21 (4) (2022 Jul) e221–e231.

[23] H.R. Mathew, M.Y. Choi, M.D. Parkins, M.J. Fritzler, Systematic review: cystic fibrosis in the SARS-CoV-2/COVID-19 pandemic, BMC Pulm. Med. 21 (1) (2021 Dec) 173.

[24] V. Bezzerri, V. Gentili, M. Api, A. Finotti, C. Papi, A. Tamanini, et al., SARS-CoV-2 viral entry and replication is impaired in Cystic Fibrosis airways due to ACE2 downregulation, Nat. Commun. 14 (1) (2023 Jan 10) 132.

[25] D. Peckham, M.F. McDermott, S. Savic, A. Mehta, COVID-19 meets Cystic Fibrosis: for better or worse? Gene Immun. 21 (4) (2020 Aug) 260–262.

[26] B.A. Stanton, T.H. Hampton, A. Ashare, SARS-CoV-2 (COVID-19) and cystic fibrosis, Am. J. Physiol. Lung Cell Mol. Physiol. 319 (3) (2020 Sep 1) L408–L415.

[27] M. Parotto, M. Gyöngyösi, K. Howe, S.N. Myatra, O. Ranzani, M. Shankar-Hari, et al., Post-acute sequelae of COVID-19: understanding and addressing the burden of multisystem manifestations, Lancet Respir. Med. 11 (8) (2023 Aug) 739–754.

[28] H.E. Davis, L. McCorkell, J.M. Vogel, E.J. Topol, Long COVID: major findings, mechanisms and recommendations, Nat. Rev. Microbiol. 21 (3) (2023 Mar) 133–146.

[29] I.V. Stan, V.D. Miron, I.A. Vangheli, R.M. Gheorghiu, A. Streinu-Cercel, O. Săndulescu, et al., First case of COVID-19 treated with monoclonal anti-spike antibodies in a patient with cystic fibrosis in Romania, Diagnostics 12 (1) (2022 Jan 7) 137.