COVID-19 Antibody Responses in Cystic Fibrosis

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Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Viral infectious disorders
Study type	Observational invasive

Summary

ID

NL-OMON56611

Source
ToetsingOnline

Brief title
CAR-CF

Condition

- Viral infectious disorders
- Inborn errors of metabolism
- Congenital respiratory tract disorders

Synonym
Coronavirus disease, COVID-19 infection

Research involving
Human

Sponsors and support

Primary sponsor: Erasmus MC, Universitair Medisch Centrum Rotterdam
Source(s) of monetary or material Support: Cystic Fibrosis Foundation en ECFS-CTN

Intervention

Keyword: COVID-19, Cystic Fibrosis, SARS-CoV-2, Seroprevalence

Outcome measures

Primary outcome

• Proportion of people with cystic fibrosis with at least 1 seropositive result over the 2-year period.

• Seroprevalence according to age group.

• Seroprevalence according to geographical area.

• Seroprevalence according to CF disease genotype and severity.

• Change in seroprevalence over time.

• Risk factors for infection in people with cystic fibrosis.

Secondary outcome

• Incidence of symptomatic COVID-19 over the 2 year study period and symptom severity.

• Proportion of seropositive people with cystic fibrosis with subsequent CF exacerbations compared to people with cystic fibrosis who are seronegative.

• Morbidity and mortality in people with cystic fibrosis with at least 1 seropositive result compared to people with cystic fibrosis who are seronegative.

• Levels and duration of anti-SARS-CoV-2 antibodies in pwCF following natural infection and vaccination SARS-CoV-2.

• Optional study objective: analysis of samples could include proteomic and genetic analysis and relating this to clinical outcome and antibody data

collected as part of main study.

Study description

Background summary

The symptoms of SARS-CoV-2 infection range from mild upper respiratory symptoms in the majority of cases to pneumonia and acute respiratory distress syndrome (ARDS) with overall case fatality rates of 1-5%.1 The diagnosis of SARS-CoV-2 infection is based on clinical symptoms and polymerase chain reaction (PCR) testing. However, given the asymptomatic nature of infection in a large proportion of cases, and the limitations of sampling the upper respiratory tract for PCR analysis, serologic assays may play a significant role in helping us to understand the epidemiology of SARS-CoV-2 infection. A seroprevalence study in California from community drawn samples in a non-CF population demonstrated a 4.06% prevalence of SARS-CoV-2 antibodies, with a population-weighted prevalence of 4.65%, significantly higher than the reported prevalence of SARS-CoV-2 infection in this region.2 Antibodies typically become detectable between 7-14 days following SARS-CoV-2 infection,3,4 but the degree and duration of immunity is not known. Antibody levels (titres) have been demonstrated to vary significantly between patients. Although animal models have suggested that antibody responses to SARS-CoV-2 can protect rhesus macaques from re-infection,5 it is not known whether this is true in humans. Re-infections with all seasonal coronaviruses are known to occur, often within three years, although the period of protective immunity is typically much shorter, lasting approximately 6-12 months.
Commercial serologic assays are in development, which test both IgG and IgA antibodies to the spike protein (S1 and S2) of SARS-CoV-2.7 However, additional research based serologic tests are also needed to detect antibody isotypes/subclasses (eg. IgG1, 2, 3, 4, IgA and IgM) and the specific region of the spike protein to which they bind (e.g. receptor binding domain) as these tests may be more predictive of future protection. Antibodies to the receptor binding domain (RBD) of SARS-CoV-2 may neutralize the virus more effectively than antibodies to other parts of the virus, as has previously been shown with SARS-CoV-1.8,9 The neutralizing capability of selected sera can be determined using a SARS-CoV-2 pseudo-virus neutralizing assay 9 using 293T cells engineered to express the SARS-CoV-2 receptor, ACE2 as target cells.
Many countries have focused on enhanced infection prevention recommendations to shield those populations perceived to be most at risk. Consequently, there has been limited testing in pwCF to date. Given this relative paucity of data of SARS-CoV-2 epidemiology in CF, and the potential increased risk due to underlying structural lung disease, serologic testing in combination with clinical assessment will be key to understand the impact on this population.
This study will be the first (to our knowledge) to assess the seroprevalence of

SARS-CoV-2 in the CF population on a longitudinal basis and may guide the risk assessment for pwCF during further peaks of outbreak. Furthermore, this study will be the first to assess IgG antibody responses and correlates of clinical disease in the CF population both according to severity and age. We hypothesize that pwCF will have a lower seroprevalence to SARS-CoV-2 compared to the general population due to their enhanced infection prevention practices; seroprevalence will be greater than the reported number of confirmed cases collected in the European CF Society (ECFS) Patient Registry.

Study objective

Our overall aim is to assess the seroprevalence of SARS-CoV-2 antibodies in an international population of pwCF and to examine associations between SARS-CoV-2 infection and clinical risk factors for infection, as well as subsequent clinical outcomes for pwCF.
We anticipate the seroprevalence of SARS-CoV-2 will be lower in people with CF than the general population. The benefit in the prospective longitudinal design of this study is that it provides a measure of baseline seroprevalence and subsequent change in prevalence as the pandemic progresses. We expect that the seroprevalence in this study will be higher than the number of cases reported to the national CF registries given that the registry data does not include all cases and asymptomatic cases are likely to be missed. This study also presents a unique opportunity to compare antibody responses in pwCF following natural infection with those produced following vaccination should a vaccine subsequently become available. Specifically this study enables a longitudinal comparison of the development of anti-SARS-CoV-2 antibodies post vaccination and post natural infection as well as comparison of the progression of anti-SARS-CoV-2 antibodies over time following these events.
Given the paucity of data surrounding SARS-CoV-2 infection and antibody responses in pwCF, we believe our international multi-centre study will provide critical knowledge about the risks to this vulnerable population and potentially inform clinical care and practice for subsequent SARS-CoV-2 surges and future pandemics.

Study design

CAR-CF is a prospective, longitudinal cohort study in pwCF with repeated serial sampling of participants. This study design was chosen to provide comprehensive information on SARS-CoV-2 seroprevalence changes over time and the subsequent clinical impact on people with Cystic Fibrosis.

Study burden and risks

This study is intended as a pragmatic study seeking to cause minimal additional disruption to enrolled patients and accordingly only serum samples will be taken alongside standard clinical samples without additional samples for

sputum, viral or other specimen collection. However, this study could generate an increased workload for data and blood sample collection.
As discussed previously, there is increasing evidence that antibody levels decrease rapidly post infection and therefore more frequent blood sampling may be required to avoid missing potential seroconversion amongst patients. However, the need for more frequent blood sampling needs to be balanced against the potential burden for enrolled patients with regards to blood-work that is additional to standard annual blood-work collection. This is particularly relevant for the paediatric CF cohort and could led to difficulty in patient recruitment and increased subject drop-out. Accordingly, at present we have included more frequent bloodwork on an opportunistic basis to be undertaken at any additional visits for routine blood-work outside of annual clinic visits.
We recognise this as a potential significant limitation for the study and will aim to strongly encourage sites to include these additional samples, particularly within adult cohorts.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age

Adolescents (12-15 years)
Adolescents (16-17 years)
Children (2-11 years)
Babies and toddlers (28 days-23 months)

Inclusion criteria

Consenting people with cystic fibrosis of any age, genotype, transplant status and disease severity will be eligible to participate in the study.

Exclusion criteria

There are no specific exclusion criteria other than refusal to give informed consent, or contraindication to blooddraw.

Study design

Design

Study type: Observational invasive

Masking:	Open (masking not used)
Control:	Uncontrolled
Primary purpose:	Basic science

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	06-10-2021
Enrollment:	50
Type:	Actual

Ethics review

Approved WMO

Date:	09-09-2021
Application type:	First submission

Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	04-01-2024
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

Other (possibly less up-to-date) registrations in this register

No registrations found.

In other registers

Register	ID
ClinicalTrials.gov	NCT04904445
CCMO	NL77380.078.21