Clinical features of COVID-19 in Pediatric Patients, long term effects (COPP2-study).

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primary objectives- To asses sequelae of COVID-19, at 4 to 12-months following a COVID-19 diagnosis among pediatric patients receiving care in the hospital or outpatient setting in the Netherlands.- To determine risk factors for long-COVID among...

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Immune disorders NEC
Study type	Observational invasive

Summary

ID

NL-OMON55281

Source
ToetsingOnline

Brief title
COPP-2

Condition

- Immune disorders NEC
- Viral infectious disorders
- Respiratory tract infections

Synonym
corona, SARS-CoV-2

Research involving
Human

Sponsors and support

Primary sponsor: Academisch Medisch Centrum

Source(s) of monetary or material Support: Ministerie van OC&W,subsidie-aanvragen lopen nog

Intervention

Keyword: COVID-19, follow-up, Pediatrics, pulmonary abnormalities

Outcome measures

Primary outcome

long-term morbidity, defined as:

o Frequency of symptoms, hospital readmission, emergency department or GP visits for symptoms, antibiotic courses for pulmonary infections or start of inhaled corticosteroids and/or b2-mimetics after admission for COVID-19 since diagnosis of COVID-19;

o The immunological profile of children at 4-12 months of follow-up after presenting to Dutch hospitals with COVID-19 or MIS-C

Secondary outcome

o Frequency of pulmonary symptoms in the month prior to the follow-up study visit.

o Quality of life score in all children and frequency of abnormalities in the neurocognitive profile of patient older than 6 years of age.

o Growth.

o Frequency of pulmonary function tests abnormalities, including exercise intolerance.

o Exhaled breath profiles (SpiroNose/GC-MS).

o Frequency and pattern of Chest CT abnormalities in patients with chronic pulmonary complaints and/or pulmonary function abnormalities.

o The longevity and quality of the humoral and cellular adaptive immune response in children with a history of COVID-19 or MIS-C.

o Complete normalization of hyperinflammatory cytokine profiles in children with COVID-19 or MIS-C after the infection with SARS-CoV-2

o Correlation between the immune response and cytokine profiles to detailed clinical parameters.

o Prevalence of olfactory dysfunction at long-term follow-up (4 to 12 months) in previously hospitalized children with COVID-19.

o Frequency and risk factors of increased fatigue (according to PROMIS pediatric fatigue) in children with a history of COVID-19 or MIS-C.

Study description

Background summary

Severe Acute Respiratory Syndrome coronavirus (SARS-CoV-2) is currently responsible for a severe pandemic. It was first reported in Wuhan, Hubei province in China in December 2019 (1). In the Netherlands, the first case was reported on February 27th, 2020. (RIVM). Currently, the United States of America, Spain, Italy and France are also major outbreak sites (date March 31st).
The infection leads to the disease known as Corona Virus Disease 2019 (COVID-19). Clinical features in adults range from mild non-specific respiratory symptoms (e.g. sore throat, cough, fatigue, mucus, myalgia, headache) to a more severe illness (e.g. fever, pneumonia, acute respiratory stress syndrome, septic shock and multi-organ failure.). In adults, an estimated 80% of infections follow a mild course, 13.8% of patients have severe complaints and 6.1% of patient suffer from a very severe disease. In China, the case fatality rate was estimated 2.3%, but the true case fatality rate may be lower if there are more mildly symptomatic cases that are not detected. (2-4).
The current data suggest that SARS-CoV-2 infection is less severe in children. The first data, summarized in a systematic review, show that children have accounted for 1-5% of diagnosed COVID-19 cases as well as have milder symptoms, where deaths are extremely rare. Clinical signs are similar to adults, but appear to arise much less frequently. (7) In the largest study to date, over

90% of 2.143 children with laboratory verified SARS-CoV-2 were asymptomatic or had mild to moderate disease, 5.2% had severe disease (dyspnoea, central cyanosis, oxygen saturation < 92%), and 0.6% had critical disease, needing ICU admittance, because of respiratory failure, ARDS, shock, or multi-organ failure. Those with critical disease had underlying health conditions. Severe disease was mostly seen in the children aged less than one year. (7-8)

In the US, 2572 children tested positive for SARS-CoV-2. Of these, signs and symptoms were known in 291 children: 56% showed fever, 54% cough, 13% shortness of breath, 23% myalgia, 7.2% a runny nose, 24% a sore throat, 28% headache, 11% nausea/vomiting, 5.8% abdominal pain, 13% diarrhea. Among 345 cchildren with information on underlying conditions 23% had at least one underlying condition, (50% asthma, 31% cardiovascular disease, 13% immunosuppression). Six patients were admitted to an ICU and, unfortunately, 3 children died. Review of these cases is ongoing to confirm COVID-19 as the likely cause of death. 32% occurred in children aged 15-17, 27% in children 10-14 years, 15% in children aged 5-9 years, 11% in children aged 1-4 year and 15% in children < 1 year. (21)
In a subgroup of children, chest CT scans were performed. Imaging features were normal, or showed mild abnormalities (up to 30% in PCR-confirmed COVID-19) (18, and data derived from a submitted study). Follow-up CTs improved in 30%, while 25% remained normal and only 12% showed deterioration.

During the current pandemic novel scientific information about COVID-19 in children emerges quickly. Although respiratory complaints remain the main reason for admittance, we also see a large group of especially young children with fever as main presenting symptom and a group of young teenagers with a systemic mucocutaneous-enteric illness, or diagnosis of Multisystem Inflammatory Syndrome in Children, (MIS-C C, frequently resulting in ICU admittance (11,12).). A survey by the Dutch Pediatric Society showed 10 additional patients who were diagnosed with PIMS-TSMIS-C, in the early months of the pandemic in 2020 (1412). However, by February 2021, we have already treated around 110 patients with MIS-C in Dutch Hospitals, about 50% was admitted to the paediatric intensive care unit, due to severe cardiogenic shock (data NVK webinar, 16-2-2021 and website COPP study https://www.covidkids.nl/scientific-dashboard/).

Long-COVID is the lay term for long term complaints in the period of weeks to months after COVID-19.In adults, many researchers have expressed their concern about the high frequency of long-term complaints after the active phase of COVID-19, resulting in persistent morbidity, reduced quality of life and inability to participate in family and working life. Recent literature describes a percentage of 10% of patients in the general population.
In the last couple of months multiple developments has led us to believe that *long COVID* in children deserves more attention than it currently gets. In scientific literature, case series of small cohorts of paediatric patients with complaints of long COVID are emerging. Our own research group performed a survey among Dutch paediatricians, revealing 89 cases of children, suspected of

long COVID, treated by Dutch paediatricians. All were not admitted in the hospital in the acute phase of COVID-19, but were suffering from long term complaints, like fatigue (87%), dyspnea (55%), concentration difficulties (45%), headaches (38%), thoracic pain complaints (35%), stomach ache (33%). 36% experienced severe limitations in daily functioning, like less or no school attendance. We suspect that these children are only the tip of the iceberg since some children with long-COVID may only be treated by the general practitioner. Furthermore, long-COVID is still an unknown phenomenon to many paediatricians, likely resulting in underdiagnosing.

The COPP and COPP-IMM study are two large multicenter, observational, prospective cohort studies in hospital-setting in the Netherlands, on pediatric COVID-19 and MIS-C.Currently, 53 of the 72 pediatric departments in the Netherlands are participating in COPP and 13 out of 72 will participate in COPP-IMM. From an international view this is an unique study in which national collaboration of most pediatric departments provides an excellent overview of the impact of COVID-19 in pediatric care. The COPP study and COPP-IMM study aim to include all pediatric cases in hospitals in the Netherlands, and collaborates closely with the Dutch Pediatric Society and researchers from all seven University Medical Centers in the Netherlands.
For COPP2, we aim to include all children with COVID-19 who were diagnosed in the outpatient department or were hospitalized, and who were included in the COPP study or COPP-IMM study, in which their clinical features were described. These study cohorts make it possible to give a scientific answer to our growing concerns about long-COVID in children. Therefore, we sought collaboration with different sections of the Dutch Pediatric Society. After consultation with specialists we developed an algorithm for clinical follow-up procedures based on symptoms or risk factors
In summary, next to follow-up of pulmonary sequela and quality of life, we will also investigate neurocognitive and olfactory morbidity, and the long-term immunological response in all patients. Depending on symptoms and risk factors of these children, nephrological, cardiac or thrombotic sequelae will be evaluated as standard care. We ask parents/caregivers and/or their children for permission to retrieve the results of these investigations from their medical file as part of our study.

Study objective

primary objectives
- To asses sequelae of COVID-19, at 4 to 12-months following a COVID-19 diagnosis among pediatric patients receiving care in the hospital or outpatient setting in the Netherlands.
- To determine risk factors for long-COVID among COVID-19 hospitalized and outpatient pediatric patients in the Netherlands.
- To obtain a detailed immunological profile of children at 4-12 months of follow-up after presenting to Dutch hospitals with COVID-19 or with SARS-CoV-2 related post-infectious inflammatory syndrome (MIS-C).

Secondary objectives
- To describe pulmonary function testing abnormalities in the follow-up of children with COVID-19.
- To describe exhaled breath profiles (SpiroNose/GC-MS) in children with a history of COVID-19.
- To describe CT abnormalities in patients with chronic respiratory complaints and/or pulmonary function test abnormalities and a history of COVID-19.
- To assess the quality of life in all children with a history of COVID-19.
- To assess parental perception of cognitive functioning and executive functioning in all children with a history of COVID-19
- To assess neurocognitive functioning in a consecutive sample of children with a history of COVID-19 (aged 6 or older)
- To correlate the immunological profiles with detailed clinical parameters
- To evaluate if at 4 to 12 months follow-up there is robust cellular and humoral immunity to SARS-CoV-2 in children who have presented to Dutch hospitals with COVID-19 related disease.
- To determine if there is a difference in the long-term cellular and humoral immunity to SARS-CoV-2 in children with COVID-19 COVID-19 related disease.
- To describe prevalence of olfactory dysfunction in children with a history of COVID-19.
• To identify frequency and risk factors of increased fatigue (according to PROMIS pediatric fatigue) in children with a history of COVID-19 or MIS-C.

Study design

Study design: This will be a multi-center, descriptive observational prospective cohort study.

Duration: Following an initial baseline registration as part of the COPP study or the COPP-IMM study, children and their caregivers will be requested to return for a follow-up visit at 4 to 12 months after COVID-19 or MIS-C diagnosis. We will enroll participants throughout a 1.5 year period.

Setting: Pediatric department. Children previously included at the COPP or the COPP-IMM study who provided consent to be approached for a possible participation in the COPP2 study. 53 hospitals are participating in the COPP study, from April 2020 through March 2021 over 169 patients were included. Seventeen COPP sites have currently expressed interest in participating in the COPP-IMM study, which is currently under review at the METC-LDD (NL76177.058.21). The exact number of children that will be included in both COPP and COPP-IMM depends on the course of the pandemic, but we expect to include at least 30 children in COPP-IMM, and at least 200 in COPP. Children from both the COPP and COPP-IMM study will be asked to participate in the COPP2 study.

Description: Children aged 0-17 years who were diagnosed with COVID-19 will be recruited from the COPP/COPP-IMM studies, if they gave permission to be

approached for follow-up studies.
Study measurements include: questionnaires and physical examination, growth measurements and immunological profile for all children and exhaled breath (SpiroNose/GC-MS), pulmonary function, exercise testing, odour identification testing, urine testing, cardiac and nefrological markers, neurocognitive evaluation and Chest CT scans in a subgroup of patients.

Study burden and risks

All participants will undergo:
- physical examination
- 5 questionnaires (1: pulmonary symptoms, 2: quality of life, 2: neurocognitive functioning)
- blood withdrawal

A subgroup of patiënt will undergo:
- pulmonary function testing
- excercise testing
- exhaled breath analysis
- odour identification testing
- neurocognitive functioning testing

This study includes only minors. Since COVID-19 in children in less severe than in adults, the long term effects cannot be deduced from future adult studies. In the future, the results of this study may lead to a better understanding for the need of follow-up of pediatric COVID-19 patients.
In the event that incidental findings are discovered, patients will be referred to their general pediatrician or pediatric pulmonologist.

Physical examination takes approximately 5 minutes to perform.
The questionnaires take about approximately 55 minutes to fill in.
Pulmonary function testing takes 1 hour, patients, older than 4 years of age, will be asked to breath in and out for several times. They will have a moutpiece in their mouth and a clamp on their nose. Burden is low.
Body pleghysmography will be conducted in patients older than 8 years of age. They will be asked to breath in and out for several times, with a mouthpiece in their mouth and a clamp on their nose. Burden is low .
Excercise testing will take about 1 hour to perform. Children from 6 years of age will be asked to excercise, also with a mouthpiece in their mouth. Burden is low.
The analysis of exhaled breath is also simple. The child will be asked to breath tidally through a mouthpiece into a breath sampling system, while watching cartoons. It can be performed by children from 2 years old on and does not cause any distress.
The Chest CT protocol consists of a CT without IV contrast, performed during the inspiratory phase. When children can follow instructions, an expiratory

phase will be added (>6yr). Anesthesia is not needed to perform the CT scan; young children will be held by a vacuum mattress, which holds them still, while being comfortable. The scan takes about 1 minute to perform, with preparation and explanation approximately 10 minutes in total time. a CT scan is only performed in patiënt with persisting respiratory symptoms or pulmonary function test abnormalities.
odour identification testing takes about 5 minutes and gives no burden.
bloodwithdrawal takes about 20 minutes and is a bit painful. We use positive language and topical anaesthetic medication to reduce the burden.

Contacts

Public
Academisch Medisch Centrum

Meibergdreef 9
Amsterdam 1105AZ
NL
Scientific
Academisch Medisch Centrum

Meibergdreef 9
Amsterdam 1105AZ
NL

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

Children age 0-17 years, in- or outpatient in Dutch hospitals with a medical history of COVID-19.
inclusion in COPP study

Exclusion criteria

- No evidence of COVID-19
- No consent from guardians and/or patient.

Study design

Design

Study type: Observational invasive

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

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	07-12-2020
Enrollment:	120
Type:	Actual

Ethics review

Approved WMO Date:	19-08-2020
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	27-10-2020

Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	02-06-2021
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	04-08-2021
Application type:	Amendment
Review commission:	METC Amsterdam UMC

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
CCMO	NL73696.018.20
Other	NL8926