COPP study ("Clinical features of COVID-19 in Pediatric Patients") and COPP-IMM study.
5.1.2e **and for collaborators: see www.covidkids.nl/over**
Project: The COPP-study is a nation-wide multicenter hospital-based prospective cohort study on pediatric COVID-19 and the post-infectious inflammatory condition Multi-system Inflammatory Syndrome in Children (MIS-C).
Current objectives: To determine the clinical features, course of disease, response to treatment and risk factors for severe disease in hospitalized and outpatient pediatric patients with COVID-19 and MIS-C in the Netherlands. In COPP-IMM, a detailed analysis of the immune system is done in addition to the collection of the clinical data.
Study population: ongoing inclusion, currently 296 patients included

COPP2 study ("Clinical features of COVID-19 in Pediatric Patients; long term effects")
5.1.2e

Project: The COPP2-study is the follow-up study of a nation-wide multicenter hospital-based prospective cohort study on pediatric COVID-19 and COVID-19 associated Multi-system Inflammatory Syndrome in Children (MIS-C) named COPP. Children in COPP will be followed after informed consent for a period of 12-18 months with a planned visit around 6-12 months after hospital admission or presentation and follow-up after 12-18 months by questionnaires. COPP2 study visits are in 3 hospitals; Emma Children's Hospital, AmsterdamUMC Amsterdam, Sophia Children's Hospital, ErasmusMC Rotterdam and Maastricht University Hospital Maastricht.
Current objectives: To describe long term morbidity, and immune response at 6 to 12 months following a COVID-19 diagnosis in children seeking care in either the outpatient or hospital setting in the Netherlands.
Study population: 120 children aged 0-17 years old, diagnosed with COVID-19 in the outpatient department or during hospitalization, and included in the previously approved pediatric study, named "clinical features of COVID-19 in pediatric patients" (also known as COPP), or in the upcoming study "COVID-19 in Pediatric patients: clinical and immunological features (COPP-IMM study). In these studies, the clinical features, course of disease, response to treatment and risk factors for severe disease in hospitalized and outpatient pediatric patients with COVID-19 in the Netherlands, are described. In COPP-IMM, a detailed immunological profile of children in the acute phase of COVID-19 will also be assessed.
Main study parameters/endpoints COPP2:
Primary endpoints:

- long-term morbidity (defined as frequency of long COVID symptoms, any hospital readmission, emergency or outpatient visit for long-COVID pulmonary symptoms, prescribed antibiotics for pulmonary infection since the diagnosis of COVID-19)
- the immunological profile during follow-up at 6-12 months after presenting to Dutch hospitals with COVID-19 or COVID-19 associated Multisystem Inflammatory Syndrome (MIS-C).

Secondary endpoints:

- measures of neurocognitive behavioral and school functioning (patients > 6 years)
- quality of life scores all ages (children and proxy)
- exhaled breath profiles
- frequency of pulmonary function test abnormalities, including exercise intolerance,
- the comparison of immunological profiles at diagnosis of COVID-19/MIS-C as obtained in COPP-IMM and the immunological profiles at follow-up in COPP-2
- frequency and pattern of CT-chest abnormalities

- the correlation between immunological profiles at follow-up and detailed clinical parameters.
- prevalence of olfactory dysfunction at long-term follow-up (6 to 12 months) in previously hospitalized children with COVID-19.
- To evaluate outcome of standard care concerning long term PICU, cardiac, hematological and nephrological evaluation after severe COVID-19 and/or MIS-C in children.

Current status: Over 200 children included in COPP and at this moment 25 children finished COPP2 study visit. Inclusion and follow-up COPP2 till September 2022.
Relevance to current call: This is the only pediatric study that investigates risk factors, clinical presentation, treatment, immune response and outcome (assessed with questionnaires, study visit and additional investigations) of children that presented to hospital or were admitted to the hospital in the Netherlands between March 2020 and September 2022. In children with persisting complaints suitable guidance will be arranged close to home.

PoCoCoChi study ("Post Corona Complaints in Children")

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Project: The acute phase of COVID-19 in children is commonly less severe than in adults. However, although not extensively investigated, long-term effects of COVID have also been shown in children, with the severe multisystem inflammatory syndrome in children (MIS-C) ranking highly in severity and scholarly attention.
The aim of this study is to prospectively evaluate the occurrence, severity, duration and limitations of post-corona complaints in children 0-17 years old, tested at Public Health Service (GGD) test locations in the region Kennemerland. Both parents of children and adolescents > 16 years old will be asked to participate and fill out a questionnaire within the first week after the corona test, after 4 weeks, 3 months, 6 months and 12 months. At 3, 6 and 12 months quality of life will also be assessed. We include participants with negative and positive test results. Impact of lockdown measures, especially in children, is enormous. By including children with a negative test result we will also be able to assess this aspect.
Children with a positive SARS-CoV-2 test result and complaints suggestive of long-COVID will be invited for evaluation at the POST-COVID kids out-patient department for extensive evaluation.
Current objectives/study parameters/endpoints
Primary objective
To evaluate the occurrence, type and duration of post-corona complaints in children from 0-18 years old in relation with the result of the SARS-CoV-2 test.
Secondary objective
To evaluate the impact of lockdown measures on possible complaints that children experience in relation with the result of the SARS-CoV-2 test.
Third objective
To evaluate the association of post corona complaints and ethnic background.
Study population: All children (0-17 years old) tested for SARS-CoV-2 at a GGD test location Kennemerland with a negative or positive test result.
Current status: Over 80 children included.
Relevance to current call: This study will give insight into occurrence, duration, possible risk factors (obesity, ethnic background and medical history) and limitations of post-covid/long-covid in children with mild disease in the acute phase. Children with persistent complaints will be referred to the POST-COVID children out-patient clinic for further evaluation and study (POCOS).

POCOS study ("Post-COVID Syndrome in children")

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Project:

Objective: We aim to describe long term morbidity, and immune response in children seeking care in the outpatient setting for post-COVID complaints at least 12 weeks after the acute phase of COVID-19 by referral of their general practitioner or pediatrician. Children with post-COVID enrolled in the PoCoCoChi, Long-COVID kids, SARSLIVA and COKIDS can also participate

Study Design: Prospective cohort study in AmsterdamUMC and Spaarne Gasthuis.

Study population: Children aged 0-17 years diagnosed with COVID-19 in their home environment, who are referred to our hospital for evaluation of post-COVID complaints, persisting for more than 12 weeks after the initial phase of disease. Children will be followed at 1 and 2 years after study visit.

Main study parameters/endpoints:

- long-term morbidity (defined as frequency of long COVID symptoms, any hospital readmission, emergency or outpatient visit for long COVID pulmonary symptoms))
- the immunological profile during evaluation of post-COVD syndrome
- the frequency of alternate diagnoses in the patients referred
- measures of neurocognitive behavioral and school functioning (patients > 6 years)
- quality of life scores
- exhaled breath profiles
- frequency of pulmonary function test abnormalities, including exercise intolerance
- immunological profiles in children with post-COVID syndrome, compared to COPP2 and adults
- frequency and pattern of CT-chest abnormalities in children with pulmonary abnormalities
- frequency and pattern of abnormalities on cardiac ultrasound
- the correlation between immunological profiles and detailed clinical parameters
- prevalence of olfactory dysfunction

Current status: Inclusion will start end of May 2021 for the period of one year and aim is to include at least 100 children.

Relevance to current call: This is the only pediatric study that investigates risk factors, clinical presentation, treatment, immune response and outcome (assessed with questionnaires, study visit and additional investigations) of children that present to the out-patient clinic with POST-COVID and initial mild acute disease. Depending on extent, burden and limitations suitable guidance will be arranged close to home.

CoKids study ("Coronavirus infections in kids")
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Project:
Objective: To obtain a detailed understanding of SARS-CoV-2 susceptibility and transmissibility profiles for pediatric age-groups. The CoKids study aims to quantify the role of children in SARS-CoV-2 transmission through a prospective household study in families with children in three different age-categories relevant to daycare and school closure policies.
Study Design: Prospective household study in regions Rotterdam and Haarlem/Hoofddorp. Households are prospectively monitored for occurrence of primary SARS-CoV-2 positive cases (both symptomatic and asymptomatic) in the community and the sequence of subsequent infections in household members is followed in detail.
Study population:
Households eligible for the study will be recruited from three ongoing birth cohort studies, each with a distinct age-profile of enrolled children:
RESCUE cohort (age 0-3 years);
RESCEU is a study funded by Innovative Medicines Initiative under H2020. The aim is to define the burden of respiratory syncytial virus infection.
MUIS-cohort (age 6-8 years)
The MUIS cohort consists of 120 term born children followed from pregnancy till their current age of 6 -7 years. These children have been monitored for respiratory microbiome and respiratory infections from birth onwards.
Generation-R cohort (age 14-17 years)
The Generation R Study is a population-based prospective cohort study from fetal life until adulthood. The study is designed to identify early environmental and genetic causes and causal pathways leading to normal and abnormal growth, development and health.
Main study parameters/endpoints:
1) To determine the susceptibility to, and transmissibility of SARS-CoV-2 infection by children of 3 different age-categories:
pre-school, elementary school, adolescents.
2. To describe the natural history of COVID- disease in children.
Specifically we investigate:
• the secondary infection rate and secondary clinical attack rate of SARS-CoV-2 infection among household contacts, as a function of age of the index case.
• the proportion of asymptomatic cases and symptomatic cases according to age-category
• SARS-CoV-2 virus and antibody kinetics in children
• the clinical course and severity of disease by age-category and clinical risk factors for COVID-19
• patterns of health-care seeking
Secondary:
1. To determine the susceptibility to, and transmissibility of SARS-CoV-2 infection in children relative to other key viral respiratory pathogens (RSV, influenza, rhinovirus…)
2. To describe household infection control measures in the context of a suspected or confirmed SARS-CoV-2 household outbreak and to identify measures most effective in reducing transmission.
3. To explore the role of prior non-SARS-CoV-2 coronavirus antibodies in susceptibility and transmissibility of SARS-CoV-2 and its clinical disease.
Current status: 305 households have been enrolled between August and December 2021. The initial follow-up period has been completed for ~80% of the cohort, extended follow-up runs until July 2021. To date, We have detected and mapped in detail about 40 household outbreaks of SARS-CoV-2 infections and > 100 outbreaks of RTI that were PCR negative for SARS-CoV2.
Relevance to current call: This cohort includes prospectively identified SARS-CoV-2 infections in children of different age-groups and their household members. It is representative of the full

spectrum of SARS-CoV-2 community infections, including asymptomatic, mildly symptomatic and moderate disease cases. Each infection is mapped in detail and longitudinal follow up has already been implemented (see POCOS study). In addition, the cohort offers access to well characterized control cases with non-COVID RTI matched on time for comparative analyses.