Research proposal

The role of children in the transmission of SARS-CoV-2 in daycare and schools

Project team (NIPH):

Brita Askeland Winje (lead)
Lin Brandal
Hinta Meijerink

Anja Kristoffersen
Ola Brynhildsrud
Karin Nygård

Margrethe Greve Isdahl
Hilde Marie Lund
Heidi Lange

Karoline Bragstad
Olav Hungnes
Rikard Rykkvin
Lisbeth Næss

Cathinka Halle Julin
Terese Bekkevold

Background

On 24 May 2020, a total of 8 352 individuals have tested positive for COVID-19 in Norway. Only 2.7% of the cases were 13 years or younger. The majority (63%) of pediatric cases were notified from Oslo and Viken counties.

A recently updated literature review on the role of children in transmission of SARS-CoV-2 reports evidence of viral transmission from children although there is no indication that children constitute a major source of infection.[1] Most children were infected from infectious adults.[2,3] In general, children with confirmed COVID-19have mild clinical manifestations and severe disease is rare.[4] Current knowledge shows that there might be spread among individuals that have mild disease or are asymptomatic.[5] Understanding the role of children in transmission of SARS-CoV-2 is essential for outbreak management and control.

In Norway, all children's daycare and schools were closed March 13th 2020. From April 20th 2020, re-opening started under strict recommendations with regards to social distancing, hygienic measures and absence when ill. In order to fulfill social distancing requirements, establishment of cohorts - small permanent groups of children and employees – with limited interaction between cohorts was advised. Limited evidence has been available to guide these decisions. The updated review calls for larger and well-conducted studies to assess the role of children in viral transmission in daycare and schools.

Two, long-term prospective NIPH population-based cohorts will invite children for prevalence studies. To our knowledge, no other national studies are focusing on transmission from children in daycare and school settings. The proposed study is complementing the ongoing study on household-transmission (Korona-hus study) in children above 12 years of age and adults.

In order to investigate the role of transmission between children in daycare and elementary school (grade 1 to 7) we propose a prospective cohort study among COVID-19 confirmed pediatric cases and their contacts in these settings. For the purpose of this study the term educational facility is used for both daycare and elementary school (grade 1-7).

Aims

To examine transmission of COVID-19 between children in educational facilities (including after school care) in order to gain more knowledge on the role of children in spread of COVID-19 in these settings.

Objectives

1. To estimate the extent of transmission in educational facility settings by estimating the secondary attack rate[1] for contacts of children in these settings.
2. To explore the transmission related to the level of exposure.
3. To calculate the prevalence and incidence of COVID-19 among contacts to child index cases in educational facility settings.
4. To characterize identified cases including the range of clinical presentation, risk factors for infection, and the fraction of asymptomatic infections.
5. To assess transmission in settings where adult contacts at educational settings are identified with COVID-19 at baseline compared to those where no adult contacts are identified as positive at baseline.
6. To examine the spread of SARS-CoV-2 within or between educational settings by whole genome sequencing
7. Compare results between nasopharyngeal swabs and saliva in index cases with confirmed COVID-19.
8. To assess mucosal antibody responses (including secretory IgA) against SARS-CoV-2 in children with confirmed COVID-19 and close contacts.
9. To assess whether presence of mucosal antibodies against SARS-CoV-2 in close contacts is related to protection against COVID-19.

[1]In this context the secondary infection rate (SIR) is defined as the frequency of new cases of COVID-19 infection among the daycare/school contacts of the index case in a defined period of time, as determined by a confirmed COVID-19 positive lab result. In simple terms: the proportion of daycare/school contacts of a primary case who subsequently become infected with COVID-19.

Study design

We will prospectively follow contacts of confirmed COVID-19 pediatric cases in daycare or elementary school settings.

Study population

Children (>2 years) attending an educational facility (daycare center or elementary school, grade 1-7) in which a pediatric COVID-19 case been confirmed.

Adults working in an educational facility (daycare or elementary school, grade 1-7) in which a pediatric COVID-19 case has been confirmed.

Setting

For the feasibility of collecting biological samples, we will preferably include pediatric cases from Oslo and Viken counties. We may expand the study to other counties if few pediatric cases are reported.

Selection process

For feasibility reasons, we will include the two first reported index cases per week to allow spread over time as well as manage resource needs both for this study and for local health authorities contact investigations.

Educational facilities that have previously been part of this study can only be included after 6 weeks since the last participating index case. The study will not include contact-tracing of secondary cases.

Exclusion criteria

Educational facilities with less than 20 children attending.

Definitions

Cases

Index case: all confirmed pediatric COVID-19 cases attending an educational facility

Primary cases: children or adults who are identified as COVID-19 positive at baseline are treated as primary cases with separate follow-up of contacts.

Secondary cases: children or adults who were COVID-19 negative at baseline and tested positive during follow-up.

Contacts

Contacts are defined as those who have been in contact with the index case in an educational facility within the last 48 hours prior to symptom start. For asymptomatic primary cases, the contacts are defined as those who have been in contact with the primary case within 48 hours prior to sampling date.

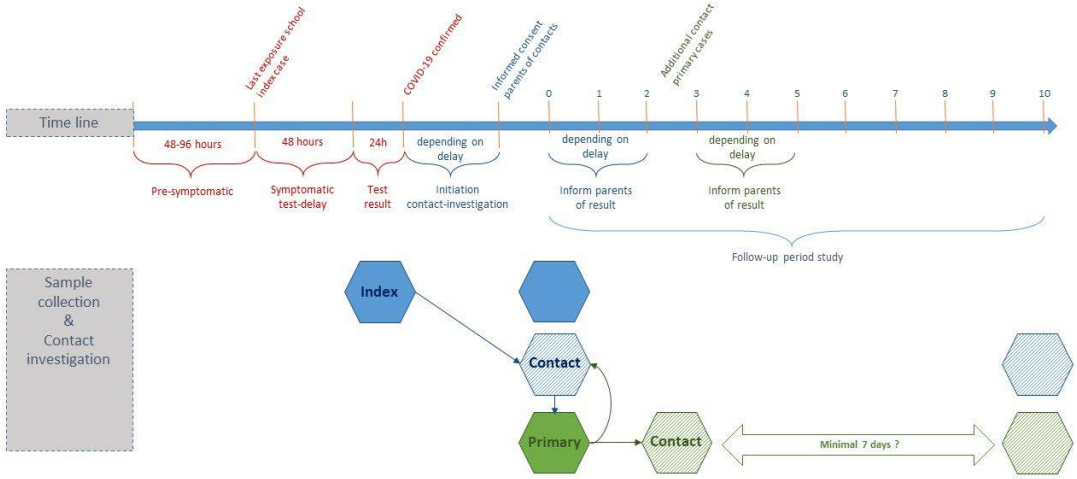
Close contact: (i) a child or adult who has been in the same room at the same time (< 2 meters distance for >=15 minutes), or (ii) other persons with direct physical contact with the case (at the educational setting).

Casual contact: (i) a child or adult who has been in the same room at the same time (but not meeting the definition of a close contact), (ii) a child or adult who has been in the same room at a different time, or (iii) a child who has shared the same defined outdoor space at the same time.

Follow-up of participants

The contacts will be followed 10 days after the first date the contacts were identified. Home sampling of saliva for SARS-CoV-2 testing is planned at baseline (as soon as possible) and day 10, see flow diagram of the study. Participants will complete a questionnaire at baseline (Form 1) and day 10 (Form 3) and report presence or absence of symptoms daily during the 10-day follow-up period (Form 2). If contacts develop symptoms or have concerns about COVID-19 during the follow-up period, they should contact their GP for diagnosis and follow-up.

Flow diagram study



The study team will communicate negative test results to participants when results are available. Positive test results will be communicated to municipal health doctors and MSIS according to routine for covid-19 reporting. Positive test results will be communicated to parents/contacts from the municipal health officer to ensure follow-up in line with national regulations.

Study period
Start date: June 10 2020
End date: Dec 31 2025

The recruitment period is estimated to take from 4 to 8 months depending on the number of eligible pediatric cases.

Sample size
Approximately 50 pediatric COVID-19 cases have been notified per month from Oslo and Viken counties. We plan to include 22 index cases for this study and will then evaluate whether this gives sufficient power for the study, or if more cases should be included. We estimate on average 40 contacts (80 tests) per index case in school (30 students and 10 adults per class, divided to two separate cohorts) and 30 contacts (60 tests) per index case in daycare (24 children and 6 adults, divided into four separate cohorts). We will use the cohorts as a gradient of exposure whenever possible. Primary cases will have their own contact tracing. However, since most contacts will be overlapping, we estimate a lower number of new contacts for the primary cases. Contacts outside of the educational facilities will not be traced as part of this study.

Based on these numbers we estimate the inclusion of 700-900 contacts, (1400-1800 tests) from the first 22 index cases.

We estimate a sample size of 22 index cases to estimate a secondary attack rate of 20% using the following data:

$$n = (z^2)\,(r)\,(1\text{-}r)\,(f)/\,(nc)\,(e^2) = (1.962)\,(0.1)\,(0.9)\,(2)/\,(35)\,(0.022) = 22$$

n is the sample size in terms of number of index cases to be selected
z is the statistic that defines the level of confidence desired; 1.96 for 95%CI

r is the estimated secondary attack rate; estimated on 20%
f is the sample design effect, assumed to be 2.0 (default value)
nc is the average number of contacts for each index case: estimated 35
e is the margin of error to be attained: 20% (of the outcome)

Recruitment

Local public health officials are responsible for the contact investigation as per national guideline. Municipal health officers will inform the project team by phone when they have a new pediatric COVID-19 case who has been attending an educational facility. A designated project phone will be staffed daily until 8 pm for this purpose. A designated person from the NIPH study team will assist local health authorities (on site or by digital meetings) in identifying contacts according to the study protocol. Local health authorities or educational facility administrators will ask parents/adult contacts if they may provide the study team at NIPH with contact-information (mobile number or e-mail). FHI will then send participants a sms with links to an invitation letter and informed consent. The coordinator will administer study material, including material for home-sampling of saliva, to consenting participant.

Data-collection

We will use Services for Sensitive Data (TSD) to obtain informed consent and collection of questionnaire data. This is a digital platform with an integrated solution for collecting sensitive data (Nettskjema). TSD is developed and operated by University of Oslo and complies with the norwegian privacy regulation. A two-step authentication is needed to gain access to the system. Parents will receive a sms with a link to TSD and may access the secure portal using BankID. They will be asked to respond to a baseline questionnaire at study start, a form for daily report of presence or absence of symptoms, and a questionnaire on outcome 10 days after baseline. They will have to use their BankID for each log in. Participants who prefer paper will have this option. All study material will be translated to english, somali, polish and arabic for non-Norwegian families. For the remaining non-Norwegians who do not understand Norwegian or any of the other languages, we will facilitate on-call translation services.

Parents of children/contacts in included daycares and schools will be invited to a digital meeting as soon as feasible, where they will be informed about the study (additional to written material), what they are expected to do and to ask questions. Further, they will be provided with a designated e-mail address where they may send their questions and concerns and in general receive same-day responses. The study will have a designated web-site at fhi.no where all the study material, contact-information and relevant links will be available.

Specimen sampling and testing

Self-collection of saliva[6,7] at baseline (as soon as possible) and at 10 days after date the contact was first identified (first saliva sample). Saliva samples will be collected from all participants irrespective of symptoms. Instructions for children and parents for self-collection of saliva will be provided, both as printed material and online guidance (animated film).

In both index cases and contacts, 1ml saliva (not sputum) will be collected in the morning, before eating, drinking or brushing teeth. Viral transport media will be added to the saliva to maintain the virus during transportation. The collection tube will be disinfected and regulatory embedded prior to transportation. Time of sample collection, details of transportation and time of arrival in the laboratory will be recorded for each specimen. Samples should reach the laboratory as soon as possible after collection. A NIPH project-coordinator will be available at specific pick-up sites close to

the educational facilities, in addition to offer residential pick-up services to ensure timely transportation and correct storage of the collected saliva samples.

Virological testing will take place at the national reference laboratory at NIPH, with established SARS-CoV-2 diagnostics. Whole genome sequencing (WGS) using Oxford Nanopore technology is planned for all index cases to look for variation in the SARS-CoV-2 between different educational settings. In some educational facilities, with primary cases detected, all COVID-19 cases will be selected for WGS to examine the heterogeneity of SARS-CoV-2 within the educational setting.

Half amount of the saliva samples will be stored in a freezer (-80^{o}C) for later anti body testing.

Data

From cases and contacts

All participants in the study will be asked to fill out a questionnaire at baseline, keep a daily journal with symptoms and fill out a questionnaire at the end of the follow-up. In addition, samples will be taken at baseline and end of follow-up period to be tested for COVID-19. Since it can be difficult for children, specifically the youngest, to express their distinct symptoms the daily journal is different for adults and children (Form 2a and b). The symptom list in a child's daily journal is amended to be observable for parents.

Baseline questionnaire includes (preferably in electronic format), (Form 1):

- Demographic data
  - Sex
  - Date of birth
  - Country of birth
  - Household size and composition in last week
- Clinical data (in last 14 days)
  - Identification of symptoms (yes/no)– if yes:
    - Date start
    - Number of days
  - Fever
  - Contact (in person or by phone/digital) with GP, COVID-19 clinic, hospital or emergency clinic
  - Tested for COVID-19? (No/Yes neg/Yes pos/Yes unknown)
    - If positive – how do you think you got infected?
  - Do you have hay fever?
- Risk factors (14 days)
  - International travel
  - Underlying diseases
  - Household member working as HCW in direct patient care?
  - How many days have you been in quarantine in the last 10 days (0 if none)?
  - Has anyone else in your household had respiratory symptoms in the last 7 days? Yes/No
  - Has anyone else in your household had fever in the last 7 days? Yes/No
  - Has anyone else in your household tested positive for COVID-19 in the last 7 days?
    - Yes/No/tested, but no result so far
  - Have you been in contact with a known case outside of daycare, school or household in the last 7 days? (Yes/No)

Daily journal for each participant (preferably electronic format) (Form 2):

- 2a, adult contacts: Check any if you have any of the following symptoms
  - Chills
  - Headache
  - Muscle and / or joint pain
  - Chest pain
  - More tired, or exhausted
  - Reduced or altered sense of taste
  - Reduced or altered sense of smell
  - Lack of appetite
  - Nausea
  - Vomiting
  - Diarrhea
  - Stomachache
  - Runny or stuffy nose
  - Sneezing
  - Sore throat
  - Shortness of breath
  - Cough; what type of cough?
  - Fever
  - Other, specify
- Contact with GP, COVID-19 clinic, hospital or emergency clinic?
- Tested for COVID-19? No/Yes neg/Yes pos/Yes unknown

- 2b, child contacts: Check any if you have any of the following symptoms
  - Fever
  - More tired, or exhausted
  - Sore throat
  - Cough
  - Runny or stuffy nose
  - Vomiting
  - Diarrhea
  - Stomach pain
  - Sneeze
  - Lack of appetite
  - Other, specify
- Contact with GP, COVID-19 clinic, hospital or emergency clinic?
- Tested for COVID-19? No/Yes neg/Yes pos/Yes unknown

Day 10 follow-up questionnaire (pref. electronic format) (Form 3)

- How many days have you been in quarantine in the last 10 days (0 if none)?
- Has anyone else in your household had respiratory symptoms in the last 10 days? Yes/No
- Has anyone else in your household had fever in the last 10 days? Yes/No
- Has anyone else in your household tested positive for covid-19 in the last 10 days?
  - No/Yes neg/Yes pos/Yes unknown

- Have you been in contact with a known case outside of school in the last 10 days?

From the educational facility (Form 4)
When a case is identified, the educational facility will be requested to provide information on the following (baseline data):

- Structure of educational facility including number of rooms, outdoor space, etc.
- Number of children per unit or class, number of employees in direct and indirect contact with children
- Infection prevention and control measures in place, including hand washing practice, environmental cleaning etc.

From teachers (Form 5)
Teachers or other adults in educational facilities with direct contact with the index case or another primary case are asked to describe the following at baseline:

- Size of the cohorts
- Daily routine of the cohort with the index/primary case
- Interactions between different cohorts that use the same room/indoor space
- Interactions between different cohorts outdoor

Data analysis
The data analyses will describe the prevalence and incidence of COVID-19 among contacts of positive pediatric cases in daycare and elementary schools by reporting:

- Number of primary COVID-19 cases at baseline
    - Number of positive children
    - Number of positive adults
- Number of secondary COVID-19 cases at 10-day follow-up
    - Number of positive children that were negative at baseline
    - Number of positive adults that were negative at baseline
- Secondary infection rate among contacts of index cases where no primary cases were identified
- Association between the secondary infection rate and level of exposure (close contacts, casual contacts, number of exposure cases, etc.)
- Correlation between the number of children and adults positive at baseline and those testing positive at follow-up
- Identification of factors associated with secondary COVID-19 cases
- Description of clinical presentation of pediatric COVID-19 positive cases, including factors associated with developing symptoms and asymptomatic infection
- Compare whole genome sequences among index cases in different educational facilities
- Describe transmission based on WGS within selected educational facilities
- Comparing mucosal antibody responses against SARS-CoV-2 in COVID-19 positive cases with contacts testing negative both at base line and at 14-day follow-up

Ethical clearance and informed consent
Ethical approval from the Regional Committees for Medical and Health Research Ethics (REC) in Norway will be sought and will comply with the general GDPR requirements (DPIA with institutional approval).

Parents will be informed about the study by trained members of the project team. Informed consent will be obtained from all cases and contacts willing to participate in the study before any procedure is

performed as part of the investigation. Consent for children under the age of 16 will be obtained from both parent(s) or legal guardian(s). Informed consent will seek approval to sample and store saliva, and demographic, epidemiological and clinical questionnaire data for the purpose of the study and to link these data with information from other National Health Registries.

Data will be stored in TSD and secure server at NIPH according to regulations at UiO and NIPH.

Timeliness

It is difficult to study transmission in populations that mix readily with the larger surrounding community. It is essential to distinguish primary cases (positive at baseline) from secondary cases (convert from negative to positive test). This requires timely response when pediatric COVID-19 cases are confirmed. Ideally, the baseline saliva test should be taken within the first two days after the index case is confirmed positive. Local health authorities are already at the limit of their capacity on infection control. We plan to restrict data-collection to maximum two outbreaks per week to ensure sufficient resources in the study implementation and laboratory capacity.

Timeline

The study will be implemented as soon as necessary capacity at local and NIPH (including laboratory capacity) level is established and approvals are in place, preferably before these settings are closing for summer vacation.

Funding

Norwegian Institute of Public Health

Data analyses plan

Outcome: COVID-19 positive individuals at 1. baseline and 2. follow-up

Outcome	Statistical test	Variables included	Population	Groups	Additional
% (95%CI)	One-Sample Proportion Test	Cohort Teacher	All baseline samples		Number of primary and secondary cases
N (%) Mean (95% CI)	Descriptives population	Age Gender Cohorts	All participants	Index Primary Secondary Contacts	Description population at baselines, potential compare groups
N (%)	Descriptives symptoms (t-tests?)	Symptoms last 14 days Underlying conditions	All participants	Index Primary Secondary Contacts	Description of reported symtoms per group
N (%)	Descriptive risk factors (t-tests?)	International travel Household HCW in household Contact cases	All participants	Index Primary Secondary Contacts	Description potential risk factors prior to study participation
PR (95%CI)	One-Sample Proportion Test	Adults Children Exposure level	All participants		Primary cases related to index case (prevalence ratio – is this the correct measure?)
AR (95%CI)	One-Sample Proportion Test	Adults Children Exposure level	Contacts **index case** Exclude primary cases		Secondary cases related to index case
AR (95%CI)	One-Sample Proportion Test	Adults Children Exposure level	Contacts **primary cases**		Secondary cases related to primary case
OR (95%CI)	Logistic regression	Exposure level	All participants	Primary cases Secondary cases	Relation between exposure level and risk primary /secondary cases
OR (95%CI)	Logistic regression	Number of cases at baseline Days in quarantine	All participants	Primary cases Secondary cases	Risk in relation to various exposure factors

		Number of adult contact Age Sex			
OR (95%CI)	Multiple logistic regression	Exposure level based on contact with index and primary cases Number of cases at baseline	All participants	Primary cases Secondary cases	Adjusted risk exposures
OR (95%CI)	Multiple logistic regression	Exposure level based Number of cases at baseline Number of adult cases Age Sex	All participants	Primary cases Secondary cases	Adjusted risk exposure and demographic factors
OR (95%CI)	Multiple logistic regression	Exposure level based Symptoms Risk factors	All participants	Primary cases Secondary cases	Adjusted risk exposure, demographic factors, symptoms and risk factors
No. of SNP differences	Phylogenetic analysis: SNP analysis using a reference genome		All index cases	Index cases	The spread of SARS-CoV-2 between educational settings
No. of SNP differences	Phylogenetic analysis: SNP analysis using a reference genome		All confirmed COVID-19 cases at selected educational settings	All confirmed COVID-19 cases within an educational setting	The spread of SARS-CoV-2 within educational settings

Appendices

Information/Invitation letter participants

- Study information, children attending daycare
- Study information, children in 1-4 grade in school
- Study information, children in 5-7 grade in school
- Study information and consent parent(s)/legal guardian(s)
- Study information and consent adult contacts

Questionnaires and interview guides

1. Form 1 – Baseline questionnaire
    a. Index
    b. Child contact
    c. Adult contact
2. Form 2 – Daily symptom reporting
    a. Child contact
    b. Adult contact
3. Form 3 - Outcome questionnaire (all participants)
4. Form 4 – Interview guide, administrative educational facilities
5. Form 5 – Interview guide, teachers educational facilities

References

1. Brurberg K. The role of children in the transmission of SARS-CoV-2 (COVID-19), 1st update. Oslo: Norwegian Institute of Public Health, 2020.
2. Cai J, Xu J, Lin D, Yang Z, Xu L, Qu Z. A Case Series of children with novel coronavirus infection: clinical abd epidemiological features. . *Clin Infect Dis* 2020.
3. Choi SH, Kim HW, Kang JM, Kim DH, Cho EY. Epidemiology and Clinical Features of Coronavirus disease 2019 in Children. *Clinical and experimental pediatrics* 2020.
4. Dong YM, Hu Y. Epidemiology of COVID-19 among children in China. *Pediatrics* 2020.
5. Furukawa NW, Brooks JT, Sobel J. Evidence Supporting Transmission of Severe Acute Respiratory Syndrome Coronavirus 2 While Presymptomatic or Asymptomatic. *Emerg Infect Dis* 2020.
6. To KK, Tsang OT, Chik-Yan Yip C, et al. Consistent detection of 2019 novel coronavirus in saliva. *Clin Infect Dis* 2020.
7. Williams E, Bond K, Bowen Z, Putland M, Williamson D. Saliva as a non-invasive specimen for detection of SARS-CoV-2. *J Clin Microbiol* 2020.