SARS-COV-2 Transmission and Disease in Children (CoKids-studie)

Samenvatting

The role of children in the transmission of SARS-CoV-2 remains unclear, and robust data for a consistent explanation for the markedly skewed age distribution of COVID-19 cases are not yet available. In mitigating the SARS-CoV-2 pandemic, governments have to weigh the public health benefit of interventions such as school closure against the significant societal and economic disruption they impose. To motivate the discussion of age-stratified social distancing measures, we propose to conduct a prospective household study in families with children in three different age-categories relevant to daycare and school closure policies. The study aims to quantify the role of children in SARS-CoV-2 transmission using a community-based surveillance approach that minimizes the risk of bias resulting from case identification conditional on healthcare usage. The results from the study will be used to inform models that estimate the impact of various age-structured social distancing interventions on the evolution of the SARS-CoV-2 epidemic.

Relevantie

The detection and spread of a novel emerging respiratory pathogen are accompanied by uncertainty over the key epidemiological, clinical and virological characteristics of the pathogen. This is the situation for the novel coronavirus SARS-CoV-2 and its disease (COVID-19), first detected in Wuhan city, China in December 2019, that rapidly developed into a pandemic with exponentially growing case numbers worldwide.

In the absence of a vaccine and available antiviral drugs, the spread of SARS-CoV-2 can only be mitigated via non-pharmaceutical interventions that reduce the risk of forward community transmission through social distancing. Communities are implementing combinations of social distancing measures to mitigate the spread of SARS-CoV-2, such as closure of bars and restaurants, cancellation of mass events and restrictions on public gatherings, school and university closures and even complete 'lock-downs'. The impact of each of these social distancing measures will depend on the role of different age-groups in transmission, a knowledge gap for SARS-CoV-2 that urgently needs to be addressed.

Contact tracing studies have found that children compared to other age-groups appear equally likely to be infected (1), but their clinical disease course is markedly different with mild or no symptoms predominating in the vast majority.(2) Governments are facing immense pressure to weigh the public health benefit of interventions such as school closure that are based on a thin evidence base, against the significant social and economic disruption that these closures impose.

The skewed age-distribution of COVID-19 cases contradicts with long known patterns for other respiratory viruses, where children typically encounter the highest attack rates and high viral loads, which make children the key transmitters of most common respiratory viruses in the community. Understanding why COVID-19 would deviate from this expectation is crucial for decision making on implementing, maintaining or relaxing appropriate interventions. If children are substantially contributing to transmission, then school and daycare closure is likely to be impactful in slowing the

spread of SARS-CoV-2. (3) If transmission is driven predominantly by adults, then focus should be on reducing their contacts.

Transmission within households is a key process driving the epidemic of many respiratory viruses such as influenza and Respiratory Syncytial Virus (RSV)(4). Household studies are therefore a useful approach to obtain insight into the main determinants of transmission and to derive estimates of transmission parameters. (4) By fully characterizing the critical process of SARS-CoV-2 household transmission, how they vary by patient and household characteristics and how SARS-CoV-2 transmission compares to transmission of other respiratory viruses, we will gain insight into the specific transmission dynamics of SARS-CoV-2 and in particular the role of children.

The crucial role of household studies in elucidating SARS-CoV-2 infection dynamics in the population has been recognized by the WHO and scientific community and already led to important research initiatives:

Rapid European COVID-19 Emergency Research response (RECOVER), is a project involving 10 international partners funded under the European Union Horizon 2020 research framework. RECOVER originates from partners of the PREPARE project (Platform for European Preparedness Against (Re-) and emerging Epidemics, see www.prepare-europe.eu; the EU Framework 7 (FP7) funded) and closely follows the PREPARE Outbreak Research Modes. As part of the current Mode 3 response, the RECOVER Household study on SARS-CoV-2 transmission will be launched within the next weeks. The objective of this study is to characterize onward household transmission by COVID-19 index cases identified in secondary care, and by SARS-CoV-2 positive healthcare workers identified through screening programmes. Similarly, the National Institute of Public Health and the Environment (RIVM) recently launched a household study, recruiting households of 100 COVID-19 index cases with families including children. However, by design, these studies will lack significant numbers of pediatric index cases, given COVID-19 disease is generally mild in children and often goes unrecognized.

To obtain a detailed understanding of SARS-CoV-2 susceptibility and transmissibility profiles for pediatric age-groups, household transmission studies should be unconditional on health-seeking behavior. (5) When recruitment depends on cases identified in healthcare, it means that index cases must have sufficiently severe symptoms to seek healthcare. This selection bias towards more severe and therefore more infectious cases may lead to overestimation of the probability of transmission compared with schools and daycare with mostly asymptomatic or mildly symptomatic children attending. Moreover, as severity is strongly associated with age for COVID-19, defining the transmission potential of children from such studies will be challenging.

A more comprehensive approach to household transmission requires prospective household monitoring for occurrence of primary SARS-CoV-2 positive cases in the community and careful recording of the sequence of subsequent infections in household members. Monitoring asymptomatic household infections and subsequent disease in a similar way may reveal its contribution to transmission.

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. By using a community-based surveillance approach, we minimize the risk of bias resulting from case identification conditional on healthcare usage. The study

will be aligned with the RIVM household study and RECOVER household studies to allow comparative studies and meta-analyses. Furthermore, by studying transmission of SARS-CoV-2 simultaneously with other respiratory viruses in the same households, we will gain further understanding of how SARS-CoV-2 transmission dynamics deviate from those of other common respiratory viruses.

Finally, the study data will feed into an age-structured transmission model that will be used to estimate the impact of age-stratified social distancing interventions in various stages of the epidemic.

Kennisoverdracht

Forecasting the effect of specific mitigation interventions as well as their joint impact on the epidemic evolution is challenging without in depth understanding of SARS-CoV-2 transmission dynamics. Similarly, once the epidemic starts to slow down, it is uncertain which interventions, at what stage of the epidemic and for what groups, can be relaxed to minimize economic disruption, while maintaining control over the epidemic. The CoKids study will be instrumental in these discussions, in particular on age-stratified social distancing measures. To expedite knowledge utilization, analysis of study data will be done on a continuous basis throughout the project as results start to accumulate. Results will be compared with those accumulating in the RECOVER and RIVM household studies at an ongoing basis. PIs of both projects are part of the CoKids study-team facilitating these collaborations. All results will be directly shared with to the COVID-19 Outbreak Management Team and the modeling group of the COVID-19 response team at the RIVM without delay. We will also inform public health agencies involved in COVID-19 response, such as the WHO and ECDC. Close ties with between members of our group and these institutes will be instrumental in delivering the evidence where it is most relevant. We anticipate that with 10-15 household outbreaks of SARS CoV-2 captured in the study, we will be able to conduct preliminary analysis. Results will become more robust as the study proceeds. The CoKids study will also help to identify differential transmission characteristics of SARS-CoV-2 in comparison to other common respiratory viruses, which is important for long-term projections on SARS-CoV-2 epidemiology in 'steady-state'.

To achieve maximal knowledge utilization in both policy and science, we will share the findings from this research through scientific publications, presentations and symposia on scientific conferences. For rapid dissemination and access to the results by the scientific community, manuscripts will be published on pre-print servers awaiting peer-review. In addition, we have ample experience in communicating science to the lay public by means of webinars, podcasts, online articles, and twitter. We will use this online media experience to disseminate the main research findings and their implications to the lay community.

Doelstelling

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 will 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

- the incubation period and the duration of infectiousness
- the serial interval of SARS-CoV-2 infection within households.
- the reproduction numbers: R0 and Re of SARS-CoV-2 within households
- 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.

Plan van Aanpak

This project consists of prospective follow-up of households with children, for the occurrence of SARS-CoV-2 household outbreaks. 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. Part of this study is an active surveillance study in which 189 infants were recruited over a 3-year period. Detailed clinical and socioeconomic characterization of these infants is available. Children are followed during every respiratory episode. This infant-oriented study can be expanded to a family-focused study. Parents have expressed great willingness to participate in subsequent studies as the study under proposal. The families live in the Hoofddorp region and are easily accessible by study staff. Parents are comfortable with infants swabbing.

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. Last follow-up moment was at age 5-6 years. Informed consent is in place to contact these families for further studies. Of the original 120 families, we can approach 110 families, there are additional children under 6 years of age in 51 families and children aged > 7yrs in 68 families.

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. This multidisciplinary study focuses on several health outcomes including also infectious disease and immunity. Main exposures of interest include environmental, endocrine, genomic (genetic, epigenetic, microbiome),

lifestyle related, nutritional and socio-demographic determinants. In total, 9778 mothers with a delivery date from April 2002 until January 2006 were enrolled in the study. Currently, approximately 6,000 children aged 13-17 years are still participating in the study.

The proposed recruitment procedure thus leverages the unique strengths of 3 different, well-characterized Dutch birth-cohorts and their households with highly motivated participants. Importantly, the study population will cover households in three essential age-categories relevant to priority public health questions on mitigation of the COVID-19 outbreak: closure of daycare, elementary and secondary schools.

The CoKids-study consists of **1)** a standard household follow-up scheme with repeated virological screening at 6-weeks intervals and longitudinal follow-up for occurrence of acute respiratory illness (ARI) covering a period of 23 weeks and **2)** a nested household outbreak study that is initiated once an index case is identified in the household.

CoKids standard household follow-up

For the duration of standard household follow-up, participants are instructed to report to the study team the onset of ARI in any of the household members. Compliance with reporting will be enhanced by regular emails, App messages and newsletters. Our birth-cohort participants are well experienced in study procedures as part of their regular study follow-up and we do not anticipate any difficulties with this method of reporting in the context of strong public awareness of the ongoing COVID-19 pandemic. Upon onset of ARI in any of the household members, the household outbreak study will be initiated. In addition, standard household follow-up includes routine SARS-CoV-2 virological testing every six week, irrespective of symptoms, for the duration of follow-up (Figure 1). Jointly, the continuous monitoring for ARI and intermittent virological screening at six-week intervals minimizes the risk that any household outbreak of SARS-CoV-2 would remain undetected. Routine screening for SARS-CoV-2 for an individual will end after a confirmed SARS-CoV-2 infection. This approach is acceptable since repeated SARS-CoV-2 infection in the same individual within a short time frame has not been confirmed so far, is immunologically implausible and because sampling can thus be minimized for those individuals no longer contributing to study endpoints.

CoKids household outbreak study

The nested household outbreak study (Figure 2) is initiated upon identification of an index case with suspected or confirmed SARS-CoV-2 infection. Household index cases are identified through **1)** a positive SARS-CoV-2 test during routine virological screening (confirmed case), or **2)** a reported case of ARI (suspected case).

At initiation of the household outbreak study all household members will undergo additional virological testing for SARS-CoV2. A blood sample for serological analysis will also be collected using finger-prick and dried-blood-spots. Virological testing is repeated whenever a next household member develops ARI symptoms. Serological testing is repeated at the end of the household outbreak follow-up period. Upon initiation of the household outbreak study, follow-up for ARI symptoms is temporarily intensified using daily symptom diaries. Daily follow-up continues until at least day 21 after identification of the index case, and is prolonged when additional ARI episodes occur in the household until 21 days after the last household ARI episode started. For the intense follow-up during the household outbreak study with daily reporting and frequent sampling, we will use an interactive diary App that has been proven successful in similar studies from our group.

Figure 1

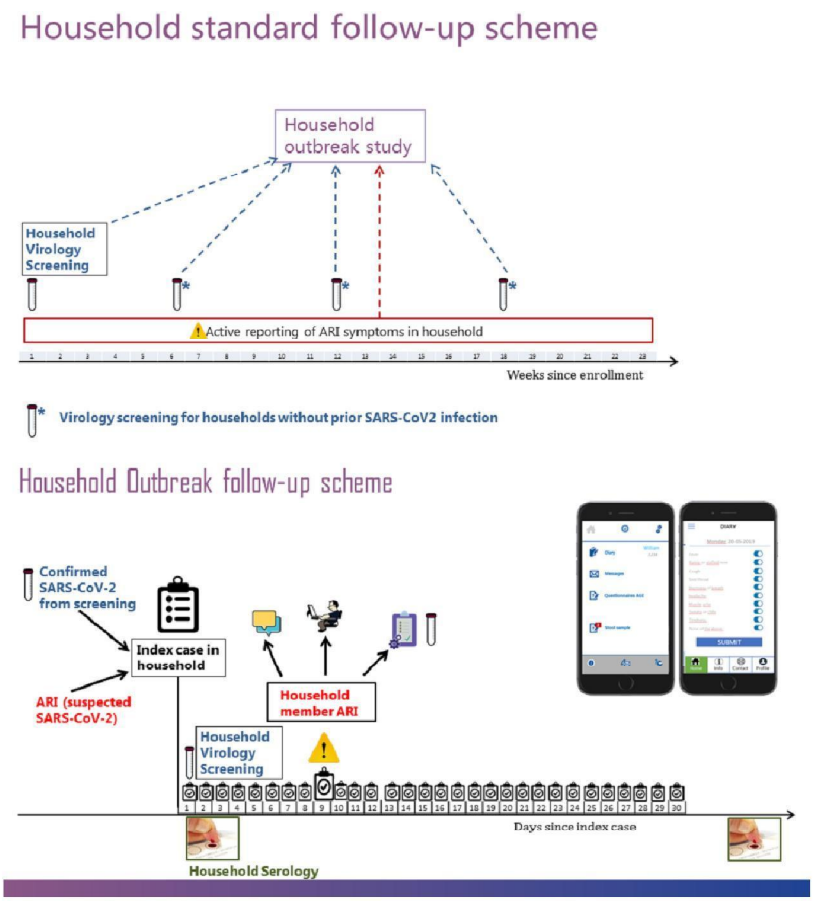


Figure 2

To minimize overall study burden for participants, households will participate no more than two times in the household outbreak study during the 23 weeks of follow-up. In case a previous COVID-19 had occurred the household is excluded from the study.

For study efficiency and for infection control purposes, we will encourage self-sampling by study participants as much as possible. Self-sampling is supported by providing written and video instructions in the App and telephone follow-up. For virological testing, we will use a combined

throat-nose swab and saliva, because these are easier to obtain and less invasive than nasopharyngeal swabs and have demonstrated good sensitivity.(6–8) Young children (not yet toilet-trained), fecal samples will also be collected. Similar procedures are used for self-collection of dry-blood-spots. If parents/caretakers are reluctant to take blood samples from a child, a study or home visit will be planned for this procedure.

Our household outbreak study is aligned with the WHO Household transmission investigation protocol for COVID-19(9), and with the RECOVER household study protocol. Furthermore, the RECOVER household protocol uses identical procedures for data collection, sampling, definitions and algorithms allowing datafiles to be merged at a later stage for joint analyses.

Microbiological and serological evaluations

Specimens will be tested for SARS-CoV-2 using an internationally extensively validated real-time reverse-transcription polymerase chain reaction (rRT-PCR) based on Corman et al. 2020.(10)

Testing for SARS-CoV-2 IgA and IgG antibodies in paired dried-blood-spot samples (at start and ending of a household outbreak) will help identify additional cases negative on rRT-PCR and will contribute to determining the final size of the household outbreak. Analysis will be done using multiplex-serology approach with simultaneous detection of antibodies to SARS-CoV-2 and other CoVs.(11) A random selection of negative and positive results will be confirmed by virus neutralization tests.

All collected and processed samples will be biobanked and available for additional virological and serological studies. These will be aligned with the ZonMw COVID-19 projects on SARS-CoV-2 whole genome sequencing and COVID-19 in healthcare workers as well as virological and immunological studies within RECOVER.

Sample size

No formal sample size can be calculated, but larger studies will undoubtedly permit more robust analysis of potential factors affecting susceptibility and infectivity, more precise estimation of the asymptomatic fraction, and more detailed characterization of the COVID-19 disease spectrum in children. In household studies performed in the context of 2009 pandemic influenza transmission, the number of households enrolled varied between 36 and 1547 with a majority of studies having less than 150 enrolled households.(12) We aim to enroll 80-120 households per age-category/birth-cohort study and a total number of 300 households. At an anticipated household outbreak rate of 20-30% (meaning that 20-30% of all households will experience introduction of SARS-CoV-2 at some point during follow-up), we expect data on 60-90 outbreaks to inform the transmission models (see below). Models can be further enriched with data from the RECOVER and RIVM household studies.

Statistical analyses and mathematical modelling

Secondary transmission rates and clinical attack rates will be calculated as the number of symptomatic and asymptomatic transmission events divided by the total number of household members at risk. In comparative analysis, we will assess how index case characteristics influence transmission and clinical attack rates.

Descriptive statistics will be used to asses the spectrum of disease severity of SARS-CoV-2 infections, proportion symptomatic and factors associated with the clinical disease course. Similarly, we will

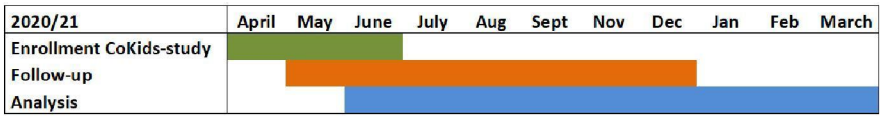
describe infection control and prevention practices and associations with within household transmission

Next, the data collected in the households will be used to inform a mathematical transmission model for the spread of SARS-CoV-2 in the population. For this purpose, the first step will be to analyse the household data by estimating key transmission parameters such as the serial interval, infectious periods, and transmissibility between household members of different types (e.g., age, parent, child). Methods to perform these analyses are up and running, based on earlier statistical analyses of household data.(13,14) By varying the model structure and comparing models, the effect of covariates on household transmission can be identified. The household analyses will feed into a transmission model at the population level. The model is a deterministic age-structured model, based on earlier models for transmission of virus infections (Rozhnova et al; submitted), and modified for SARS-CoV-2. The model will be fitted using Bayesian evidence synthesis, a statistical fitting procedure that enables fitting a model to several data sources simultaneously while taking the epidemiological relations between various types of data into account. Such an approach has been successfully applied to estimate various epidemiological characteristics of influenza.(15) The model will then be used to assess the impact of various interventions on the spread of SARS-CoV-2 in the Netherlands with an emphasis on elucidating the role of children in the spread of the virus. In earlier modelling analyses we have assessed the effectiveness of combinations of social distancing and contact tracing and isolation (Kretzschmar et al 2020, submitted) and the impact of various types of interventions on the epidemic peak and timing of the outbreak.(16) With the age-structured model now under development we will assess the contribution of school and daycare attendance to the incidence of SARS-CoV-2 in various stages of the epidemic. These results will provide guidance for policy makers on whether and when these measures can be lifted, or should be re-implemented.

The final dataset will be published in an open-access data repository (Dataverse) and will be shared with collaborating partners in the project for research purposes and the wider scientific community upon request.

Timeline

Given the urgency of the SARS-CoV-2 epidemic, an early start of the CoKids study is essential. We built on the existing research infrastructures of the birth-cohort studies and RECOVER household study to rapidly initiate recruitment, enrolment and data collection. We will start approaching cohort participants in week 15 and plan to enrol the first households in week 18.



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