CONSORTIUM AGREEMENT
For CoKids Project

Title of project proposal: **Kids and SARS-CoV-2 transmission and disease (CoKids-study)**

This Consortium Agreement (the "**Agreement**") is based on the General Terms and Conditions Governing Grants of ZonMw, version [Applicable as from 1 July 2013] and the Decision of ZonMw to award the Grant for this Project as communicated to the Main Applicant in a Grant Letter dated april 10th, 2020 with ZonMw file number **10150062010006** and shall come into effect on (the "**Effective Date**"):

Between:

1. Universitair Medisch Centrum Utrecht, having an address at Heidelberglaan 100, 3584 CX Utrecht, the Netherlands ("**UMC Utrecht**"), for the purposes of this Agreement lawfully represented by (10)(2e) and (10)(2e) (10)(2e) ; (10)(2e) (10)(2e) (10)(2e) and (10)(2e) ;

2. Streeklaboratorium Kennemerland, having an address at Boerhaavelaan 26, 2035 RC, Haarlem, the Netherlands ("**Streeklaboratorium Haarlem**"), for the purposes of this Agreement lawfully represented by (10)(2e) and (10)(2e) ;

3. **Erasmus University Medical Center Rotterdam**, an institution organized in accordance with public law of the Netherlands (section 1.13.2 Dutch Act on Higher Education and Scientific Research (WHW), acting exclusively for and on behalf of the Department of Peadiatrics, with its principal place of business at Dr. Molewaterplein 40, 3015 GD Rotterdam ("**Erasmus MC**", lawfully represented by (10)(2e) in his function as (10)(2e) ;;

4. The State of the Netherlands, represented by its Minister of Health, Welfare and Sport, on behalf of the Minister represented by (10)(2e) (10)(2e) (10)(2e) (10)(2e) (10)(2e) on behalf thereof for the (10)(2e) (10)(2e) (10)(2e) having its home office at Antonie van Leeuwenhoeklaan 9, 3721 MA Bilthoven, the Netherlands;

5. Spaarne Gasthuis, having an address at [Spaarnepoort 1 2134 TM Hoofddorp], the Netherlands ("**Spaarne Gasthuis**"), for the purposes of this Agreement lawfully represented by (10)(2e) ;

Hereinafter collectively referred to as "**Parties**" and individually referred to as "**Party**".

Considerations:

WHEREAS, the Parties are interested in evaluation of the role of children in the transmission of SARS-CoV-2 (hereinafter referred to as the '**Project**'), and have submitted a proposal dated April 1, 2020, dossier number: 50-55700-98-905 (the "**Full Project Proposal**", see Annex 1) to the funder ZonMw (the "**Funder**").

WHEREAS, the **Parties** have agreed to further formalize their cooperation concerning the Project (as defined below) in this Consortium Agreement and within the conditions described in the present Consortium Agreement.

Parties hereby agree as follows:

Clause 1 - Definitions

The terms hereafter shall have the following meaning:

Affiliates: means any company or other legal entity, of which a Party now or hereafter owns or controls directly or indirectly more than 50 % of the voting shares or by which the Party now or hereafter is owned or controlled directly or indirectly by more than 50 % of the voting shares, or any company or other legal entity which is under common control with a Party, but any such company shall be deemed to be an affiliated company only so long as such ownership or control exists.

Background IP: means the intellectual property rights and knowhow which is held by the Parties prior to the later of the Effective Date or the conclusion of the Grant Decision, including patents, copyrights or other intellectual property rights as well as applications for, or the issue of, patents, designs, supplementary protection certificates or similar forms of protection as set out in Annex 2.

Budget of the Project: means estimated cost incurred to carry out the Project tasks as defined in the Project Description.

Consortium Agreement: means the present contractual arrangement among the Parties set out herein including the annexes thereto, which annexes shall form an integral part of this Consortium Agreement.

Grant Decision: a formal decision issued by the Funder in response to an application for a grant indicating that the application has been successful whether in whole or in part.

Consortium: The group of organizations as described in the Project Description that participate in the Project.

Coordinator: means the Party identified in this Consortium Agreement who, in addition to its obligations as a Party, is obliged to carry out the specific coordination tasks provided for in this Consortium Agreement on behalf of the Parties to the Consortium Agreement.

Dissemination means the disclosure of Foreground IP by any appropriate means other than publication pursuant to the formalities for protecting the Foreground IP.

Effective Date means the date upon which the Parties shall commence the Consortium and start the joint development of the Foreground IP. The Effective Date (April 13th, 2020) will be communicated to the Parties by the Funder.

Funder: means ZonMw which provides a financial contribution to the Parties.

Foreground IP: means the intellectual property rights and knowhow arising directly from the performance of the Projects, including patents, copyrights or other intellectual property rights pertaining to such results following applications for, or the issue of patents, designs, supplementary protection certificates or similar forms of protection, excluding Background IP.

GDPR: means the General Data Protection Regulation (EU) 2016/679.

Parties: means each organisation that belongs to the Consortium.

Personal Data: means personal data as defined in the GDPR.

Project: means all the work within the CoKids-study as described in the Project Description.

Project Description: means the Full Project Proposal and the ZonMw decision to grant the Award as regards the Project, as attached as Annex 1 hereto, accepted by and, if applicable, as may be adjusted from time to time by the Parties after consultation with the Funder.

Clause 2 - Setting up of a Consortium

The Parties agree to set up a Consortium for the purpose of as further detailed in the Project Description.

In this agreement the relationship of the Parties within this Consortium will be further specified, in particular concerning the organisation of the work between the Parties, the management of the Project, and the rights and obligation of the Parties.

Nothing in this Consortium Agreement shall be deemed to create a partnership or agency or any formal business organization or legal entity among the Parties. This Consortium has not the purpose to exploit commercially the Foreground IP as a differentiated legal entity.

Clause 3 - Cooperation within the Project

Each Party who participates in this Project remains solely responsible for carrying out its relevant part of the Project.

The Parties have agreed to cooperate and carry out their tasks within the Project in accordance with the Project Description.

Clause 4 - Financial provisions

4.1 *Distribution of Funds*
UMC Utrecht (hereinafter: the 'Distributor') shall receive the funding from ZonMw according to the financial schedule in the Grant Decision. The Distributor shall distribute the funding according to the budget schedule included in Annex 2, provided that the Distributor shall not be obliged to distribute funding before having received such funding from ZonMw.

A Party shall be funded only for its tasks carried out in accordance with the Full Project Proposal and the Grant Decision.

4.2 *Justification of costs*
Each Party shall provide sufficient documentation to the Distributor, including an auditor's report at its own cost, to allow the Distributor to justify all spending of funding to ZonMw. In the event that the Distributor and/or ZonMw request additional documentation on how funding was spent, each Party shall be obliged to provide such additional documentation to the extent possible. Each Party shall be solely responsible for justifying its own costs with respect to the Project. In the event that ZonMw reclaims any funding for a particular section of the Project due to insufficiencies in the documentation provided, the Party concerned shall – if reasonable efforts to amend such insufficiencies have failed – repay the funding that is the subject of such claim, either to the Distributor or ZonMw directly. Neither the Distributor nor any of the other Parties shall in any way be liable or responsible for such justification of costs towards ZonMw.

4.3 *Reimbursement of actual duly justified eligible costs only*
A Party which spends less than its allocated share of the budget as set out in the Full Project Proposal will be funded in accordance with its actual duly justified eligible costs only. A Party that spends more than its allocated share of the budget as set out in the Full Project Proposal will be funded only in respect of duly justified eligible costs up to an amount not exceeding that share.

4.4 *Withholding of payments*
The Distributor is entitled to withhold any payments due to a Party identified by the Project Management Team to be in breach of its obligations under this Agreement or the Grant Decision. The Distributor is entitled to recover any payments related to such breach already paid to a defaulting Party. The Distributor is equally entitled to withhold payments to a Party when this is suggested by or agreed with ZonMw.

4.5 *VAT*
Since the funding was awarded to all Parties by ZonMw, Parties deem the payments to be VAT-free distribution of Grant funding. In case that the tax authorities deem otherwise, all mentioned amounts in this Agreement and its Annexes shall include any applicable VAT.

4.6 Leaving Party
A Party leaving the consortium will promptly transfer any unspent and uncommitted part of the Grant to the Party that is ultimately responsible for the application and use of the Grant.

Clause 5 - Operational structure and organization

5.1 The Coordinator

The main Party of the Project and hence the Coordinator is UMC Utrecht. Associate Professor P.C.J.Bruijning-Verhagen, Infectieziekten Epidemiologie, shall represent the Coordinator ("**Coordinator Representative**"). The Coordinator will act as the intermediary between the Parties and the Funder and shall, in addition to its obligations as a Party, execute all tasks assigned to it as described in the Grant Decision and hereunder.

5.2 The Management Board

The Parties shall form a Management Board composed of 1 representative of all Parties, except for UMC Utrecht that shall have 2 representatives. The Management Board will be chaired by P.C.J.L. Bruijning-Verhagen from UMC Utrecht, Division Julius Center, whereas J.G. Wildenbeest from UMC Utrecht, Division Pediatrics, B.L. Herpers from Streeklaboratorium Kennemerland, (10)(2e) from Erasmus MC, [illegible] (10)(2e) from RIVM-Cib and M.A. van Houten from Spaarne Gasthuis will be members.

The Management Board will be in charge of all relevant decisions regarding the Project, particularly for substantial shifts of tasks, responsibilities and budget or strategies regarding research parts and proposing the techniques and processes needed for the Project. In addition, it will resolve potential problems regarding technical choices and will provide for advice on scientific matters and commercialization, acting as advisor and arbitrator. Except as stated for in Clause 5.6 below, decisions will require consensus.

5.3 Meetings

The Management Board will meet once a quarter either in a telephone conference or in person, the latter at least once a year, at dates determined by the Coordinator Representative after consultation with other Management Board members, or as often as necessary if requirements from this Agreement, such as review of publications or communications pursuant to Clause 7, would necessitate more frequent meetings. Members of the Management Board will be noticed at least 30 days before the date about the meeting and its agenda.

5.4 Communication process

The Parties will intensively communicate throughout the life cycle of the Project, apart from the mentioned meeting schedule/procedure. Internet and e-mail will be used as the major mechanism for Project communication. For the convenience of Project administration, the Parties will use unified file formats for data and documentation exchange.

5.5 Coordination Team

The Coordination Team carry out the day-to-day management under the direction of the Management Board in the project management and communication between the Parties. The Coordination Team will be formed by a Coordinator Delegee (P. Bruijning-Verhagen) and the Project Manager (Marieke de Hoog), appointed by the Management Board from the staff of the Coordinator.

5.6 Decision making and conflict resolution
The Management Board will take the major decisions concerning the work plan, e.g. decisions dealing with a substantial shift of tasks, responsibilities and Budget of the Project as well as decisions regarding the strategies of one or more research parts and future use of research data. All members of a consortium body will have one vote. Decisions will normally be taken in consensus. In case of an important decision, notably concerning the protection of Foreground IP and the dissemination of Foreground IP/results, the Management Board will decide according to an absolute majority vote whereby the vote of the chairman is decisive in case of a tied vote.

Clause 6 - Intellectual Property

6.1 Ownership of Background IP
Each Party shall remain the owner and shall retain control of the Background IP owned by it. The Parties must – on a royalty-free basis – give access to the other Parties to Background necessary for their research activities under this Consortium Agreement.

6.2 Ownership of Foreground IP
Foreground IP are owned by the Party that generates them unless agreed otherwise between the Parties in a secondment agreement or Data Transfer Agreement (such as the standardized DTA for GenerationR data). For the avoidance of doubt, where researchers are seconded, the seconded researcher shall remain an employee of the Party with whom they were originally employed. The results produced by a seconded researcher shall become the property of the Party who's budget the work performed by the seconded researcher was concerned.

6.3 Protection, maintenance and costs of Foreground IP
Each Party is responsible for the application, acquisition and / or maintenance of its own Foreground IP and shall bear the costs relating to it.

In the event Parties jointly make the inventive step, or the creative step (in case of non-patent IP), carrying out the work generating that Foreground IP and where their respective share of the invention or the work as the case may be cannot be ascertained (hereafter: „**Joint Foreground IP**"), the Parties concerned together are responsible for the application, acquisition and / or maintenance of that Joint Foreground IP. These Parties shall own such Joint Foreground IP in equal parts and contribute in equal parts to the costs of application, acquisition and / or maintenance of the Joint Foreground IP.

In the event of Joint Foreground IP, Parties shall make additional arrangements with regard to strategy, tasks and costs of application, acquisition and / or maintenance of that Joint Foreground IP and may designate a lead Party considering the circumstances. The lead Party

shall timely discuss with the other Party or Parties applications, reports etc. in order to give the other Party or Parties the opportunity to comment thereon.

In the event of Joint Foreground IP each Party shall, and shall ensure that its employees, researchers, research fellows, individuals equivalent to those persons, give full cooperation and shall execute all documents, deeds and so forth as may reasonably be required in connection with the registration, protection and / or maintenance of that Joint Foreground IP.

6.4 Access rights Background IP
Parties hereby grant each other non-transferrable, non-exclusive, royalty free, fully paid up access rights to the Background IP contributed by it for the duration of the Project to the extent needed to enable the performance of such Project and to the extent each Party is authorized to grant such access rights (including based its own policy).

6.5 Access rights Foreground IP
Parties hereby grant each other non–transferrable, non-exclusive, royalty free, fully paid up access rights to the Foreground IP, to the extent necessary to enable the performance of the Project and to the extent each Party is authorized to grant such access rights.

6.6 Access rights Joint Foreground IP
Parties hereby grant to each of the Parties non–transferable, non-exclusive, royalty free, fully paid up access rights for research and educational purposes for non-commercial use to their Foreground IP and Joint Foreground IP.

6.7 Transfer rights Foreground IP
If for the commercial use of its Foreground IP, a Party needs access rights to Background IP, or another Party's part in such Party's Foreground IP, the owning Party or Parties, as the case may be, may grant that Party access rights on market terms and conditions as applicable in the relevant international market to be further determined in good faith at that time.

6.8 Transfer rights Joint Foreground IP
In the event of Joint Foreground IP, neither Party is entitled to grant access rights or transfer or assign or make available in any other way any Joint Foreground IP to any third party without prior written consent of the other owning Party, which shall not be unreasonably withheld. The Parties owning the Joint Foreground IP shall in good faith determine and negotiate the terms and conditions to grant access rights or transfer or assign or make available in any other way any Joint Foreground IP to that third party.

The aforementioned terms and conditions with that third party shall include arrangements with regard to publication, remuneration at international market conditions, research and educational license for each of the Parties and the obligation to further develop and / or commercialize the Joint Foreground IP.

Clause 7 - Publications

7.1 Each Party is and shall at all times be entitled to publish in written form, oral presentation or making public in any other form (including electronic publication on the internet) (the "**Publication**") all results of its own research under the Project, including but not limited to its own Foreground IP, both during the term of the Agreement as well as after the termination thereof, taking into account Clause 6 (Confidentiality). However, as the Project is a study in which all Parties shall participate, any publication based on the results obtained during the performance of the Project shall not be made before the first multi-party publication or presentation to which all Parties shall contribute, which shall be coordinated by Coordinator Representative.

7.2 The publishing Party shall inform the other Parties by sending a written notice (the "**Publication Notice**") including the draft Publication.

7.3 Within thirty (30) days of the date of the Publication Notice, the other Parties may request postponement of a maximum of sixty (60) days after the date of the Publication Notice, or alterations of the Publication by submitting a written notice (the "**Postponement Notice**") in order to protect any Foreground IP or to remove any Confidential Information under this Agreement of the other Parties. However, such interference must not infringe the scientific integrity (*wetenschappelijke integriteit*) of the publishing Party, nor unreasonably harm the scientific value of the publication.

7.4 If the publishing Party has not received a Postponement Notice within thirty (30) days of the date of the Publication Notice, the publishing Party is free to publish the Publication.

Clause 8 - Liabilities

8.1 No warranties
In respect of any information or materials (incl. Foreground IP and Background IP) supplied by one Party to another under the Project, no warranty or representation of any kind is made, given or implied as to the sufficiency or fitness for purpose nor as to the absence of any infringement of any proprietary rights of third parties.

Therefore:

- the recipient Party shall in all cases be entirely and solely liable for the use to which it puts such information and materials, and
- no Party granting access rights to Background IP shall be liable in case of infringement of proprietary rights of a third party resulting from any other Party (or its Affiliates) exercising such access rights.

8.2 Limitation and exclusion of contractual liability
No Party shall be responsible to any other Party for any indirect or consequential loss or similar damage such as, but not limited to, loss of profit, loss of revenue or loss of contracts, provided such damage was not caused by a wilful act or gross negligence

A Party's aggregate liability towards the other Parties collectively shall be limited to once that Party's share of the total costs of the Project as identified in the Grant Decision provided such damage was not caused by a wilful act or gross negligence.

The terms of this Consortium Agreement shall not be construed to amend or limit any Party's statutory liability

Clause 9 – Implementation of the Project

9.1 Allocation of work
The allocation of work to be performed within the Project is described in the Project Description. The Parties commit themselves to perform the work in accordance with the Project Description and to promptly inform the Coordinator Representative in case of defaulting. The Parties commit themselves to allocate adequate resources for the negotiations for the Grant Decision and to promptly inform the other Parties of any disagreement during such negotiations.

9.2 Contribution of each Party
For the contribution of each Party, see the Project Description, division of responsibilities (Annex 1).

9.3 Project timetable
The Parties will respect the Project timetable as described in the Project Description and notify the Coordinator Representative in case of any problems that might occur and may have an impact on the timely execution of the Project.

Clause 10 – Confidentiality

With respect to all information of whatever nature or form, whose confidential nature is specified at the time of disclosure or reasonably identifiable, relating in any manner to the business or affairs of another Party as is disclosed to a Party on a confidential basis by any other Party hereunder or otherwise in connection with the Project, whether pending or after execution of the Grant Decision, each Party undertakes to each of the other Parties that:

(a) It will not use any such information for any purpose other than in accordance with the terms of the Grant Decision and of the Consortium Agreement; and
(b) It will treat the same as (and use reasonable endeavour to procure that the same be kept) confidential and not disclose the same to any other person without the prior written consent of the disclosing Party in each case,

provided always that such undertaking shall not in any case be deemed to extend to any information, which the receiving Party can show:

(A) was at the time of receipt published or otherwise generally available to the public,
(B) has after receipt by the receiving Party been published or become generally available to the public otherwise than through any act or omission on the part of the receiving Party,
(C) was already in the possession of the receiving Party at the time of receipt without any restrictions on disclosure,
(D) was rightfully acquired from others without any undertaking of confidentiality imposed by the disclosing Party,

(E) was developed independently of the work under the Consortium Agreement by the receiving Party,
(F) is legally required to be disclosed by law, a government regulation or a court order.

Subject to the prior signature of similar confidentiality undertakings as contained in this Consortium Agreement, nothing in this clause shall prevent the communication of information to the Funder or to any Party or to any permitted third party insofar as necessary for the proper carrying out of the Project and/or this Consortium Agreement and/or the use of Foreground IP from the Project as provided for in this Consortium Agreement.

With respect to any permitted communication of any of the confidential information by the recipient Party to any other person, such Party will use reasonable endeavours to procure due observance and performance by such other person of all relevant undertakings in the Grant Decision or in this Consortium Agreement.
Each Party undertakes to take all appropriate steps on its own behalf as well as on behalf of its employees having to know the said results to consider and keep the latter as confidential.

Clause 11 – Data Protection

During the Project, Parties may provide to each other research data, which may constitute Personal Data ("**Data**"). Each Party receiving Data from another Party will conform to the following terms and conditions, unless otherwise agreed upon in a separate data transfer agreement ("**DTA**"):

a. Provider will retain all intellectual property rights in and to the Data provided under this agreement;

b. Parties shall comply with all applicable requirements of the GDPR including all local implementing legislation and shall give all reasonable assistance to each other where appropriate or necessary to comply with such duties;

c. Parties are joint data controllers in respect of all Personal Data processed pursuant to this Agreement,;

d. Receiving Party shall use received Data solely for the purposes of carrying out the Project;

e. Any transfer of Personal Data to countries that are not recognized as providing adequate protection measures for Personal Data processing outside the EU or the EEA will only be allowed if Parties have agreed on adequate safeguards;

f. Each Party ("**Indemnitor**") shall indemnify the other Party or Parties and hold them harmless for any claims or actions by third parties and for any fines imposed by the data protection authorities directly arising from (i) an attributable shortcoming on the part of Indemnitor or its processors in the fulfilment of its obligations under this Cause, or (ii) any violation by Indemnitor or its processors of the applicable legislation governing the processing of Personal Data;

g. Within 30 days of completion of the Project or termination of this Agreement, whichever is earlier, Parties shall destroy any received Personal Data in their possession or control..

Clause 12 - Coming into force – Duration – Early termination

This Agreement commences on the Effective Date and shall thereafter remain into force:

- until the fulfilment all requirements pursuing from the Project Description, complete discharge of all obligations of the Parties under the Grant Decision and/or under this Consortium Agreement as well as any amendment or extension thereof; or
- until this Consortium Agreement is terminated pursuant to this clause.

After a period of two (2) years in which this Agreement is in force the Parties will evaluate their collaboration.

Each Party may terminate this Agreement in relation to another Party prior to the Termination Date in the event of that other Party's bankruptcy (*faillissement*) or a moratorium of payments (*surseance van betaling*) or entering into a debt rescheduling arrangement (*schuldsaneringsregeling*) immediately upon the occurrence of the relevant event.

In case of breach of a Party of its substantial obligation as provided in the Grant Decision and/ or Consortium Agreement, if such breach is not remedied within 30 days from notice by the Coordinator - or by another Party designated by the Management Board in case the Coordinator is in breach - or is not capable of remedy, the other Parties shall have the right to request the termination of the participation of such defaulting Party in the Project, and decide within the Management Board on the re-allocation of tasks and funds to a new Party. Such re-allocation is subject to the agreement of the Funder office, which shall be duly informed, and object of the signature of a specific addendum to all relevant agreements.

This Consortium Agreement shall automatically terminate without any further demand and without liability of any Party to the others upon the first to occur of the following events:

- In case no Grant Decision is awarded;
- cancellation of the Project by the Funder;
- termination of the entire Grant Decision by the Funder;

Clause 13 - Consequences of termination

In case of withdrawal from the Consortium by a Party, another Party may take over the first Party's tasks as initially allocated as per the Project Description, subject to approval of all Parties. If no such take-over takes place within one (1) month from the date of said Party's withdrawal, all rights and obligations under the Grant Decision and this Consortium Agreement shall in good faith be re-allocated (work and funding) among the remaining Parties by the Management Board. No Party shall by reason of withdrawal or termination be relieved from:

- its responsibilities under this Consortium Agreement or the Grant Decision in respect of that part of that Party's work package which has been carried out (or which should have been carried out) up to the date of withdrawal or termination;

or

- any of its obligations or liabilities arising out of such withdrawal or termination.

The provisions of the clauses of this Consortium Agreement relating to liability, confidentiality (for five (5) years from termination), intellectual property rights and publications shall survive the term or termination of this Consortium Agreement for any reason whatsoever to the extent needed to enable the Parties to pursue the remedies and benefits provided for in those Clauses. For the avoidance of doubt, termination or withdrawal shall not affect any rights or obligations incurred prior to the date of the termination.

Clause 14 - Force majeure

No Party shall be considered to be in breach of this Consortium Agreement if such breach is caused by Force Majeure. Each Party will notify the Management Board of any Force Majeure as soon as possible. If the consequences of Force Majeure for the Project are not overcome within 6 weeks after such notification, the transfer of tasks of such Party – if any – to a new Party shall be considered and decided upon by the Management Board. Such decision should be subject to the agreement of the Funder, which shall be duly informed, and object of the signature of a specific addendum to all relevant agreements.

Clause 15 – Assignment

This Consortium Agreement and the rights and obligations provided for hereunder shall not be assigned by either Party to any other Party including Affiliates, except after prior written consent of the other Parties which consent shall imply the condition that such Affiliate or third Party first undertakes in writing to the other Parties to be bound by the terms of this Agreement.

Clause 16 – Notices

Formal notice under this Consortium Agreement shall be made by registered mail at the addresses of the Parties in the heading of this Consortium Agreement or to any other address subsequently designated by a Party by a written notification to the other Parties and to the Coordinator Representative.

Clause 17 - Dispute resolution

This Consortium Agreement shall be governed by the laws of the Netherlands. In the event the Parties have been unable to amicably resolve any dispute arising out of this Consortium Agreement the competent court of Midden-Nederland, location Utrecht shall have exclusive jurisdiction.

Annex 1 – Project Description
Annex 2 – Budget specifications
Annex 3 – Background IP

Signatures follow on next pages

This Consortium Agreement has been agreed and signed by:

Signature

For: **UMC UTRECHT**

Name: (10)(2e)

Title: (10)(2e)

Place:

Date:

Signature

For: **UMC UTRECHT**

Name: (10)(2e)

Title: (10)(2e)

Place:

Date:

Signature

For: **UMC UTRECHT**

Name: (10)(2e)

Title: (10)(2e)
(10)(2e)

Place:

Date:

Signature

For: **UMC UTRECHT**

Name: (10)(2e)

Title: (10)(2e)

Place:

Date:

Signature

For: **Streeklaboratorium Haarlem**

Name: (10)(2e)

Title: (10)(2e)

Place:

Date:

Signature

For: **Streeklaboratorium Haarlem**

Name: drs. F.F. Lamkamp

Title: CEO

Place:

Date:

Signature

For: **Erasmus MC**

Name:

Title:

Place:

Date:

Signature

For: **Erasmus MC**

Name:

Title:

Place:

Date:

Signature

For: **RIVM-Cib**

Name: Prof. dr. (10)(2e)

Title: (10)(2e)
(10)(2e)

Place:

Date:

Signature

For: **RIVM-Cib**

Name: Dr. (10)(2e)

Title: (10)(2e)
(10)(2e)

Place:

Date:

Signature

For: **Spaarne Gasthuis**

Name: prof.dr. I.N van Schaik

Title: voorzitter Raad van Bestuur

Place:

Date:

Signature

For: **Spaarne Gasthuis**

Name:

Title:

Place:

Date:

Annex 1

Project Description

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

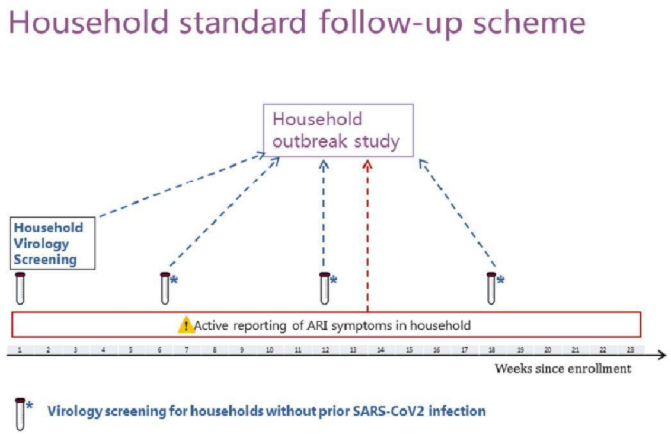
For the duration of standard household follow-up, participants are instructed to report to the study team the onset of ARI in any of the household members. Compliance with reporting will be enhanced by regular emails, App messages and newsletters. Our birth-cohort participants are well experienced in 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

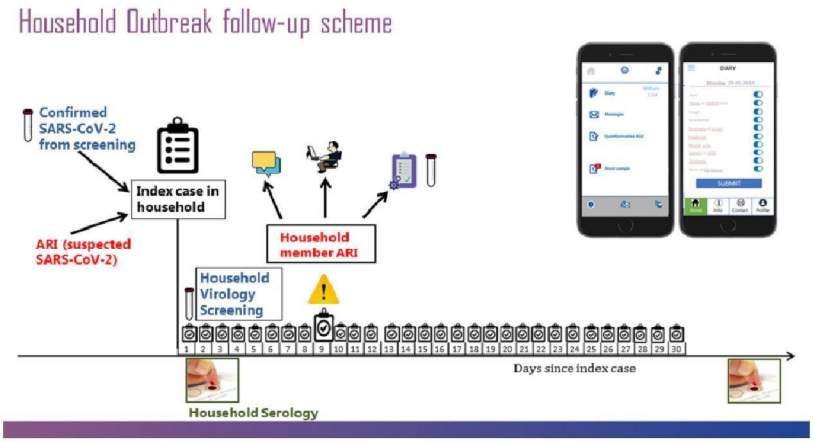


Figure 2
To minimize overall study burden for participants, households will participate no more than two times in the household outbreak study during the 23 weeks of follow-up. In case a previous COVID-19 had occurred the household is excluded from the study.
For study efficiency and for infection control 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.

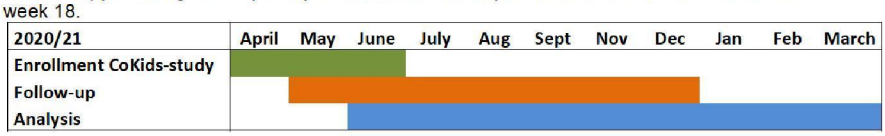
Descriptive statistics will be used to asses the spectrum of disease severity of SARS-CoV-2 infections, proportion symptomatic and factors associated with the clinical disease course. Similarly, we will describe infection control and prevention practices and associations with within household transmission

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.



Referenties

1. Bi Q, Wu Y, Mei S, Ye C, Zou X, Zhang Z, et al. Epidemiology and Transmission of COVID-19 in Shenzhen China: Analysis of 391 cases and 1,286 of their close contacts. medRxiv [Internet]. 2020 Mar 19 [cited 2020 Mar 27];2020.03.03.20028423. Available from: https://www.medrxiv.org/content/10.1101/2020.03.03.20028423v2
2. Dong Y, Mo X, Hu Y, Qi X, Jiang F, Jiang Z, et al. Epidemiological Characteristics of 2143 Pediatric Patients With 2019 Coronavirus Disease in China. Pediatrics [Internet]. 2020; Available from: http://www.ncbi.nlm.nih.gov/pubmed/32179660
3. Hay C, Haw DJ, Hanage WP, Jessica Metcalf CE, Mina Implications MJ. Implications of the Age Profile of the Novel Coronavirus [Internet]. Available from: https://github.com/jameshay218/age_implications
4. Cauchemez S, Ferguson NM, Fox A, Mai LQ, Thanh LT, Thai PQ, et al. Determinants of influenza transmission in South East Asia: insights from a household cohort study in Vietnam. PLoS Pathog [Internet]. 2014 Aug [cited 2014 Dec 18];10(8):e1004310. Available from: http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=4140851&tool=pmcentrez&rendertype=abstract
5. Quee FA, de Hoog MLA, Schuurman R, (10)(2e) (1)(c). Community burden and transmission of acute gastroenteritis caused by norovirus and rotavirus in the Netherlands (RotaFam): a prospective household-based cohort study. Lancet Infect Dis [Internet]. 2020 Feb [cited 2020 Mar 27]; Available from: https://linkinghub.elsevier.com/retrieve/pii/S147330992030058X
6. To KK-W, Tsang OT-Y, Leung W-S, Tam AR, Wu T-C, Lung DC, et al. Temporal profiles of viral load in posterior oropharyngeal saliva samples and serum antibody responses during infection by SARS-CoV-2: an observational cohort study. Lancet Infect Dis [Internet]. 2020 Mar 23 [cited 2020 Mar 31];0(0). Available from: http://www.ncbi.nlm.nih.gov/pubmed/32213337
7. Esposito S, Molteni CG, Daleno C, Valzano A, Tagliabue C, Galeone C, et al. Open Access SHORT REPORT Collection by trained pediatricians or parents of mid-turbinate nasal flocked swabs for the detection of influenza viruses in childhood. Virol J [Internet]. 2010 [cited 2017 Apr 5];7. Available from: http://www.virologyj.com/content/7/1/85
8. Woelfel R, Corman VM, Guggemos W, Seilmaier M, Zange S, Mueller MA, et al. Virological assessment of hospitalized cases of coronavirus disease 2019. medRxiv. 2020;2020.03.05.20030502.
9. World Health Organization (WHO). Household transmission investigation protocol for 2019-novel coronavirus (2019-nCoV) infection. 2020;2019(January):1–31. Available from: https://www.who.int/publications-detail/household-transmission-investigation-protocol-for-2019-novel-coronavirus-(2019-ncov)-infection
10. Corman VM, Landt O, Kaiser M, Molenkamp R, Meijer A, Chu DK, et al. Detection of 2019 novel coronavirus (2019-nCoV) by real-time RT-PCR. Eurosurveillance [Internet]. 2020 Jan 23 [cited 2020 Apr 1];25(3):2000045. Available from: https://www.eurosurveillance.org/content/10.2807/1560-7917.ES.2020.25.3.2000045
11. OKBA NMA, Muller MA, Li W, Wang C, GeurtsvanKessel CH, Corman VM, et al. SARS-CoV-2 specific antibody responses in COVID-19 patients. medRxiv [Internet]. 2020 Mar 20 [cited 2020 Apr 1];2020.03.18.20038059. Available from: https://www.medrxiv.org/content/10.1101/2020.03.18.20038059v1
12. Lau LLH, Nishiura H, Kelly H, Ip DKM, Leung GM, Cowling BJ. Household transmission of 2009 pandemic influenza A(H1N1): a systematic review and meta-analysis. Epidemiology [Internet]. 2012 [cited 2020 Apr 1];23(4):531. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3367058/
13. O'Neill P, Gareth RO. Bayesian Inference for Partially Observed Stochastic Epidemics : J R Stat Soc. 1999;Series A,(1):121–9.

14. Te Beest DE, Henderson D, van der Maas N a T, de Greeff SC, Wallinga J, Mooi FR, et al. Estimation of the serial interval of pertussis in Dutch households. Epidemics [Internet]. 2014 Jun [cited 2014 Dec 24];7:1–6. Available from: http://www.ncbi.nlm.nih.gov/pubmed/24928663
15. Presanis AM, Pebody RG, Paterson BJ, Tom BDM, Birrell PJ, Charlett A, et al. Changes in severity of 2009 pandemic A/H1N1 influenza in England: a Bayesian evidence synthesis. BMJ [Internet]. 2011 Sep 8 [cited 2020 Apr 1];343:d5408. Available from: http://www.ncbi.nlm.nih.gov/pubmed/21903689
16. Teslya A, Pham TM, Godijk NG, Kretzschmar ME, Bootsma MCJ, Rozhnova G. Impact of self-imposed prevention measures and short-term government intervention on mitigating and delaying a COVID-19 epidemic. medRxiv [Internet]. 2020 Mar 27 [cited 2020 Apr 1];2020.03.12.20034827. Available from: https://www.medrxiv.org/content/10.1101/2020.03.12.20034827v2

Division of responsibilities

CoKids study (ZonMw project 10150062010006)

Sites	**UMCU JC**	**Universitair Medisch Centrum Utrecht, Divisie Julius Centrum**
	UMC WKZ	**Universitair Medisch Centrum Utrecht, Divisie Kinderen**
	RIVM-CiB	**RijksInstituut voor Volksgezondheid en Milieu, Centrum voor Infectieziektenbestrijding**
	Erasmus MC	**Erasmus MC, Universitair Medisch Centrum Rotterdam**
	Spaarne	**Spaarne Gasthuis**
	Streeklab	**Streeklab Haarlem**

Contribution of each party

Study ACTIVITIES	**RESPONSIBILITY**					
	UMCU JC	**UMCU WKZ**	**RIVM CiB**	**Erasmus MC**	**Spaarne**	**Streeklab**
Regulatory Affairs						
IRB Creation and Review	C	R		R	R	
IRB Application preparation & submission		R		R	R	
EC/IRB Submissions/Management	C	R		R	R	
Local adaptation of essential documentation	C	R		R	R	
Clinical Monitoring						
Monitoring Management and Co-ordination	C					
Monitoring Plan	C	R		R	R	
Site Initiation Visits		R		R	R	
Site Monitoring Visits		R		R	R	
Site Closeout Visits		R		R	R	
Data Management						
Data Management Plan	R					
Data Management and cleaning	R					
Data Processing - export data	R		R			R
Data Transfer(s) to Other provider	R		R			R
Statistics						
Statistical Analysis Sample Size calculation	R					
Cohort tracking	C	R		R	R	
Statistical Analysis Plan	R					
Statistical Analysis	R					
Medical Writing						
Protocol writing	C	R		R	R	
Informed consent form	C	R		R	R	
Patient information sheet	C	R		R	R	

Clinical Study Report	R					
Data Capture (DC)						
CRF Design	R					
Database Design	R					
Management of database access	R					
Technology Management	R					
Database Hosting	R					
Uploading of non CRF data	R					
Database lock and archiving activities	R					
Quality Assurance						
Set up and control of study specific procedures (SSPs)	C	R	R	R	R	R
Inventory of project SOPs and controlled documents	C	R	R	R	R	R
Guideline for confidentiality and privacy of patient data	R					
Review and follow up of quality issues arising throughout study	R					
Regulatory Fees						
IRB Application Fees		R		R	R	
Participant recruitment and Follow-up						
Recruitment		R		R	R	
Study visits		R		R	R	
Sample Management						
Lab manual			R			R
Sampling materials	C		R			R
Sample shipment	C		R			R
Sample processing			R			R

C=coordinating
R=responsible

Annex 2

Budget Specifications

Annex 3

Background IP

University Medical Center Utrecht:

- Data resulting from clinical study with project title "[RECOVER Household study]"
- Your Research App for application "[COVApp]"

Erasmus MC, Universitair Medisch Centrum Rotterdam :

Socio-economic and -demographic data of subjects needed for objectives as described in Annex 1 (Project description) resulting from clinical study with project title "Generation R - CoKids"

Spaarne Gasthuis:

- Data resulting from clinical study with project title "[MUIS]"
- Data resulting from clinical study with project title "[RESCEU birth cohort]" in collaboration with UMCU