



Algemene gegevens / General Information

Programma / Programme : COVID-19 Programma
 Subsidierronde / Subsidy round : Bottom-up ronde COVID-19 aandachtsgebied 2
 Projecttitel / Project title : EarlyLife-COVID: SARS-CoV-2 carriage, disease and transmission among pregnant woman, children and families: A population-based, prospective household study focused on the first 1000 days of life
 Projecttaal / Project language : Engels / English
 Geplande startdatum / Planned start date : 15-07-2020
 Geplande duur / Planned duration : 24 maanden / months
 Datum indienen / Date of application : 14-05-2020
 Projecttype / Project type : Fundamenteel onderzoek / Fundamental research
 Vervolg eerder ZonMw-project / Continuation previously funded project : Nee / No
 ZonMw

Projectleden / Project members

Dr. (Main applicant)Functie / Position:  Opleiding / Education: 

Studierichting / Subject:

T: 06-  F: | E: @erasmusmc.nl

Erasmus MC
 Algemene Kindergeneeskunde
 Postbus 2060
 3000 CB ROTTERDAM

Dr. (Projectleader and secretary)Functie / Position:  Opleiding / Education: 

Studierichting / Subject:

T: 06-  F: | E: @erasmusmc.nl

Erasmus MC
 Algemene Kindergeneeskunde
 Postbus 2060
 3000 CB ROTTERDAM

Prof. dr.

Functie / Position: Hoogleraar Kindergeneeskunde - Epidemiologie | Opleiding / Education:

Studierichting / Subject:

T: 010-  F: | E: @erasmusmc.nl

Erasmus MC
 Postbus 2040
 3000 CA ROTTERDAM

Dr. Functie / Position:  Opleiding / Education: 

Studierichting / Subject:

T: 088-  F: | E: @umcutrecht.nl

Universitair Medisch Centrum Utrecht
 Julius Centre for Health Sciences and Primary Care
 Postbus 85500
 3508 GA UTRECHT

Dr. Functie / Position:  Opleiding / Education:

Studierichting / Subject:

Aanvraagformulier GGG_digitaal / Applicationform GGG_digital

Dossier nummer / Dossier number: 50-56300-98-676

DEFINITIEF

T: 010- (10)(2e) | F: | E: (10)(2e) @erasmusmc.nl

Erasmus MC
Postbus 2040
3000 CA ROTTERDAM

Dipl. (10)(2e) (10)(2e)
Functie / Position: (10)(2e) | Opleiding / Education: (10)(2e)
Studierichting / Subject:
T: 010- (10)(2e) | F: | E: (10)(2e) @rotterdam.nl

Gemeente Rotterdam
Beleidsontwikkeling Jeugd
Coolingsingel 40
3011 AD ROTTERDAM

Prof. dr. (10)(2e) (10)(2e) (10)(2e)
Functie / Position: (10)(2e) | Opleiding / Education:
Studierichting / Subject:
T: 010- (10)(2e) | F: | E: (10)(2e) @erasmusmc.nl

Erasmus MC
Postbus 2040
3000 CA ROTTERDAM

(10)(2e) (10)(2e)
Functie / Position: (10)(2e) | Opleiding / Education:
Studierichting / Subject:
T: 010- (10)(2e) | F: | E: (10)(2e) @erasmusmc.nl

Erasmus MC
Postbus 2040
3000 CA ROTTERDAM

Dr. (10)(2e) (10)(2e) (10)(2e)
Functie / Position: (10)(2e) | Opleiding / Education:
Studierichting / Subject:
T: 010- (10)(2e) | F: | E: (10)(2e) @rivm.nl

Rijksinstituut voor Volksgezondheid en Milieu
Postbus 1
3720 BA BILTHOVEN

Prof. (10)(2e) (Project commission member)
Functie / Position: (10)(2e) | Opleiding / Education:
Studierichting / Subject:
T: 010- (10)(2e) | F: | E: (10)(2e) @erasmusmc.nl

Erasmus MC
Postbus 2040
3000 CA ROTTERDAM

Projectgegevens / Project information

Aandachtsgebieden / Focus

- 2.1 Thema's aandachtsgebied 2
 - Transmissie en epidemiologie
- 2.3 Subthema's zorg en preventie voor kwetsbare burgers
 - Groepen met direct verhoogd risico en kwetsbaarheid
 - Middellange en langere termijn effecten
- 2.4 Subthema's transmissie en epidemiologie
 - Rol van en preventie op onderliggende aandoeningen op de COVID-19 epidemie
 - Verbeteren van het opvolgen van maatregelen en/of compliance
 - Verspreiding van virus in meest getroffen gebieden of bevolkingsgroepen
- 2.5 Sector
 - Jeugd(gezondheids)zorg
 - Preventie

Aanvraagformulier GGG_digitaal / Applicationform GGG_digital

Dossier nummer / Dossier number: 50-56300-98-676

DEFINITIEF

Samenvatting / Summary

The COVID-19 pandemic severely threatens the health and wellbeing of many individuals. The SARS-CoV-2 transmission patterns among pregnant women and children are not clear. Novel knowledge on SARS-CoV-2 and social distancing effects among pregnant women and their children has impact on: (1) public health strategies related to social distancing policies; (2) health care for pregnant women and specific risk groups and; (3) policies related to consequences for pregnancy outcomes and programming of long term disease in the offspring. This project will focus on the impact of SARS-CoV-2 and the social distancing on development, health and wellbeing in pregnant women and their children. The objectives are:

1. To identify patterns of carriage, disease and horizontal and vertical transmission of SARS-CoV-2 in pregnant woman and their children and families, and their role in building group immunity;
 2. To identify social, ethnic, lifestyle and health related risk factors, and immunological pathways related with SARS-CoV-2 carriage, transmission and disease;
 3. To examine the associations of subclinical and clinical SARS-CoV-2 disease during pregnancy on risks of miscarriage, pregnancy complications and embryonal, foetal and neonatal growth and development;
- This project will be embedded in the Generation R Next Study, an ongoing population-based prospective study from preconception onwards. This study included already 3000 participants enrolled in preconception/ early pregnancy. More than 1500 children have been born. We will enroll another 1000 participants in the next year (2020-2021). We will extend the data collection by: (1) monthly short-questionnaires on impact of virus and social measures in 3000 families (months 1-18); (2) household study in subgroup of 400 families. An impact and implementation team will be part of the project from the start to optimize translation of findings into policy.

Trefwoorden / Keywords

SARS=CoV-2, cohort, pregnancy, children

Samenwerking / Collaboration**Samenwerking tussen onderzoek en praktijk / Cooperation between research and practice:**

Ja / Yes

Organisaties

Gemeente Rotterdam

Postbus 70012

3000 KP ROTTERDAM

Rijksinstituut voor Volksgezondheid en Milieu

Postbus 1

3720 BA BILTHOVEN

Inhoud / Content**Disciplines / Disciplines**

- Infecties, parasitologie, virologie / Infections, parasitology, virology
- Gynaecologie en obstetrie / Gynaecology and obstetrics
- Kindergeneeskunde / Paediatrics
- Epidemiologie / Epidemiology

Aanvraagformulier GGG_digitaal / Applicationform GGG_digital

Dossier nummer / Dossier number: 50-56300-98-676

DEFINITIEF

Financiële gegevens / Financial data

ZonMw budget

Kostenpost	Jaar / Year								Totaal / Total
	1	2	3	4	5	6	7	8	
Personeel	110.000	115.000	0	0	0	0	0	0	0
Materieel	150.000	50.000	0	0	0	0	0	0	0
Implementatie	5.000	5.000	0	0	0	0	0	0	0
Apparatuur	10.000	10.000	0	0	0	0	0	0	0
Overig	0	0	0	0	0	0	0	0	0
Totaal / Total	275.000	180.000	0	0	0	0	0	0	0

(10)(2b)

Co-financiering / Cofinancing

Naam co-financier / Name of cofinancier	Bedrag / Amount	Status
Erasmus MC	225.000	Toegekend

Bijzondere gegevens / Additional information

Vergunningen / Permits

	Verklaring nodig / Statement required?		Status verklaring / Statement status		
	Ja / Yes	Nee / No	Verkregen / Acquired	Aangevraagd / Applied	Nog niet aangevraagd / Not applied yet
METC	X				X
DEC		X			
WBO		X			

Onderschrijvingen / Assents

	Ja / Yes	Nee / No	N.v.t. / N.A.
Code biosecurity / Code Biosecurity			X
Code openheid dierproeven / Code Transparency of Animal Testing			X

Andere vergunningen / Other permits

AANVRAAGFORMULIER PROJECTIDEE – BOTTOM-UP RONDE

COVID 19 programma

Deadline voor indiening: 14 mei 2020 (14:00 u)**LEES ALSTUBLIEFT ALLE INSTRUCTIES IN BIJLAGE "TOELICHTING
INDIENING PROJECTIDEE" VAN DE OPROEPTEKST ZORGVULDIG!**

Wanneer u het formulier heeft ingevuld:

1. Zet het formulier om naar een PDF file en controleer de details
 2. Upload het complete formulier als een bijlage bij uw indiening in Projectnet
(Let op: dit zijn twee verschillende links, gebruik maar 1 van de 2!)
- ProjectNet: [Aandachtsgebied 1 \(voorspellende diagnostiek en behandeling\)](#)
ProjectNet: [Aandachtsgebied 2 \(zorg en preventie\)](#)

NAAM VAN DE HOOFDAANVRAGER:

Dr. (10)(2e) / Prof.dr. (10)(2e) (10)

ORGANISATIE:

Erasmus MC

PROJECTTITEL:

EarlyLife-COVID: SARS-CoV-2 carriage, disease and transmission among pregnant woman, children and their families: A population-based, prospective household study focused on the first 1000 days of life

DATASTEWARD:

Wie is de datasteward die de open science en FAIR data planning in uw project ondersteunt? Zie de webinars op de [ZonMw website](#) om de datastewards te informeren en ondersteunen.☒ Ik betrek een datasteward bij mijn project:

Naam: Generation R Datamanagement

Instituut: Erasmus MC

E-mail: (10)(2e) @erasmusmc.nl

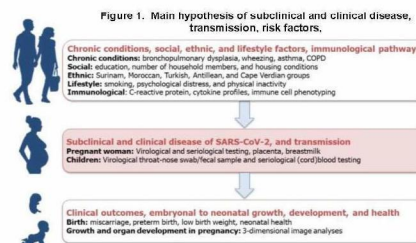
Was aanwezig bij de webinar: ☐ Ja ☒ Nee

The Generation R Data Management Group will be consulted for advice on data management and stewardship. Based on the needs and requirements of the research projects, we will involve specific expertise and support to (tools and services on data management and stewardship within the Erasmus MC.

1. PROBLEM AND OBJECTIVES

The COVID-19 pandemic severely threatens the health and wellbeing of people. Remarkably, COVID-19 seem less frequently and severely present among pregnant woman and young children. To date, only 55 pregnant woman with COVID-19 have been reported, and the reported presence of COVID-19 among children is approximately 1-2% (1, 2). For common respiratory viruses, young children are key transmitters. Also pregnant woman can vertically transmit viruses to their fetus. These transmission patterns are not yet clear for SARS-CoV-2 (1-4). **Knowledge on SARS-CoV-2 and social distancing effects among pregnant women and their children and families has import impact on: (1) public health strategies related to social distancing policies (day care, schools); (2) health care for pregnant women (specific risks for women and their offspring, caregivers protection) and; (3) policies for consequences for pregnancy outcomes and programming of long term health and disease in the offspring.** Therefore, we need to urgently address **current knowledge gaps on (Figure 1):**.

- Carriage, disease and horizontal and vertical transmission of SARS-CoV-2 in pregnant woman and their children and families, and their role in building group immunity;
- Effects of social, ethnic, lifestyle and health condition related factors, and immunological pathways;
- Effects of subclinical and clinical disease of SARS-CoV-2 during pregnancy or infancy on risks of miscarriage, pregnancy complications and embryonal, fetal and neonatal growth and development;



Typically, pregnant woman and children are more susceptible for respiratory viral infections due to the immunosuppressive state and physiological adaptations of pregnant woman, and the developing immune system of children. Factors that may play a role in the vertical transmission are the placenta and breastmilk. Also, pregnant woman and children may not have yet developed the known chronic conditions that are risk factors for COVID-19 in adults. However, obesity and subclinical cardio-metabolic and respiratory risk factors might be present (5, 6). In adults with severe COVID-19 typical immunological and inflammation markers are lymphocytopenia, increased C-reactive protein (CRP) levels, and a cytokine dysregulation with upregulation of pro-inflammatory cytokines (Interleukin-6 (IL-6), TNF- α) (7, 8). It is speculated that higher ACE2 receptor concentrations, trained immunity, and constitutional high lymphocyte counts partially explain the low occurrence rate and severity of COVID 19 of young children as compared to adults (8). Studying chronic conditions and their related social, ethnic, and lifestyle factors, and immunological pathways will identify important modifiable risk factors of the occurrence and transmission of SARS-CoV-2.

Previous studies reported that SARS-CoV-2 among pregnant women might have an increased risk of adverse clinical outcomes such as miscarriage, preterm birth, low birth weight, but results are inconclusive (2, 3). It is well known that adverse exposures during pregnancy, including viral exposures, may have severe and persistent effects on fetal and childhood growth and development. Therefore, the short and long term effects of SARS-CoV-2 during pregnancy need to be studied. Recently developed advanced, non-radiant 3-dimensional image analyses for studying embryo and fetal organ, and placental development in large-scale population-based studies enables identification of developmental programming effects, which may have long term consequences for childhood growth, development, and health. Against this background, **the EarlyLife-COVID project will focus on the impact of SARS-CoV-2 and the social distancing effects among pregnant women and their young children and families.**

The key objectives are:

1. To identify patterns of carriage, disease and horizontal and vertical transmission of SARS-CoV-2 in pregnant woman and their children and families, and their role in building group immunity;
2. To identify social, ethnic, lifestyle and health related risk factors, and immunological pathways related with SARS-CoV-2 carriage, transmission and disease;
3. To examine the associations of subclinical and clinical SARS-CoV-2 disease during pregnancy on risks of miscarriage, pregnancy complications and embryonal, foetal and neonatal growth and development;

2. WORKPLAN

The study will be embedded in the Generation R *Next* Study, an ongoing population-based prospective study from preconception onwards (9, 10). This study included already 3000 participants enrolled in preconception/early pregnancy (2018-2020). More than 1500 children have been born. We will enroll another 1000 participants in the next year (2020-2021). We will extend the data collection by: (1) monthly short-questionnaires on impact of virus and social measures in circa 3000 families (1-18 months); (2) household

study in subgroup of 400 families. **Embedding the project in this ongoing and successful cohort guarantees feasibility and availability of most necessary data and enables enrichment of the existing data collection with novel and innovative measurements.**

Objective 1. Carriage, disease and horizontal and vertical transmission of SARS-CoV-2.

First, we will use monthly short-questionnaires on impact of virus and social measures in circa 3000 families (months 1-18 months). Information includes socio-demographic data, financial impact, experienced stress, infection and disease, lifestyle, compliance to social distancing measures. **Second**, we will perform a **household study using** a similar protocol as the EU Horizon 2020-funded Rapid European COVID-19 Emergency Research response (RECOVER project), and the ZonMw-funded CoKids Study (UMCU, RIVM Erasmus MC). We will apply this protocol to a specific **new vulnerable group** of pregnant woman and young children (0-4 years). We will use a **standard follow-up scheme** with virological screening at bimonthly intervals during 12 months. Routine screening per subject will end after a confirmed SARS-CoV-2 infection. A **nested household outbreak scheme** will be initiated once an index case is identified in the household (positive SARS-CoV-2 test or COVID-19 symptoms). All household members will undergo additional testing, and serological blood samples collection using dried-blood-spots. Virological testing is repeated whenever a next household member develops symptoms. Serological testing is repeated at the end of the household outbreak follow-up period. Follow-up for symptoms is temporarily intensified using an app for daily symptom diaries until at least day 21. **Virological and serological specimens** will be tested for SARS-CoV-2 using an internationally extensively validated real-time reverse-transcription polymerase chain reaction (rRT-PCR)(11). Testing for SARS-CoV-2 IgA and IgG antibodies in paired dried-blood-spot samples will help identify additional cases negative on rRT-PCR (12). **Third**, we will assess **vertical transmission** (PCR SARS-CoV-2 and serology) by using cord blood and placental samples (maternal/fetal side) sampling at birth, and breast milk and fecal samples at age 4-6 weeks.

Objective 2. Social, ethnic, lifestyle and health related risk factors, and immunological pathways

First, information about social, ethnic, lifestyle and health related risk factors in pregnant woman, and their children and their families has been or will be collected by multiple longitudinally standardized or validated questionnaires and clinical examinations or medical records (preconception, 6-12 weeks and 30 weeks of gestation, birth, 1, 2, 3 and 4 years). **Second**, cord blood samples will be used for immunological measurements (high-sensitivity **C-reactive protein levels**, inflammatory and anti-inflammatory **cytokine profiles** (including IL-6, IFN- γ , TNF- α) will be determined (Milliplex® Human High Sensitivity Human T-cell multiplex kit), and **immune cell phenotyping** (absolute counts of peripheral blood CD19⁺ B lymphocytes, CD3⁺ T lymphocytes, and CD16/56⁺ NK lymphocytes, and subsets, obtained using a diagnostic lyse-no-wash protocol (BD Biosciences, San Jose, CA)(13).

Objective 3. Effects on miscarriage, pregnancy complications and foetal and neonatal growth

Recently, we developed embryonic ultrasound techniques, which enable growth and development measurements during embryonic life by using a virtual reality system (14). Embryonic-fetal size and body parts, and placental volume will be measured by repeated ultrasounds at 6, 9, 12, and 30 weeks (each maximal 20 minutes). The obtained 3-dimensional dataset will be analyzed off-line by using a virtual reality system, allowing depth perception and interaction with the projected images. At birth, information on gestational age, birth weight, and delivery will be obtained from medical or midwife records. Information about infant growth, development and behaviour will be collected yearly by standardized questionnaires.

Power and statistical analysis

Studies will be based on circa 3000 families (full group) or 400 (household studies). Clearly, the power depends on the incidence of new infections. Therefore, we will use a **full year in which we expect more than one “wave” of new cases**. In the full group, differences in the outcomes that can be detected range from at least 0.2 or 0.3 standard deviation (SD), and 1.3 or 1.7 relative risks for the substudy and full group study, respectively ($\alpha=0.05$, $\beta=0.2$, outcome incidence 10%). The number of households is larger than majority of household studies performed during the 2009 pandemic influenza transmission (range 36-1,547 households)(15). We expect data of 100-150 outbreaks (anticipated household outbreak rate of viral infections 20-30%). State-of-the-art statistical methods, both known and recently developed in the RECOVER and CoKids studies, will be used for the data analyses related to objective 1. For objectives 2 and 3, we will use univariate and multivariate (robust) linear and logistic linear mixed models. We apply Bonferroni or False Discovery Rate correction. Missing data may be imputed. Statistical techniques continue to develop and we will select the best and most state-of-the-art statistical method for each analysis.

3. FEASIBILITY

Time scheme

Year 1:

- Questionnaires on impact of virus and social measures (monthly, 3000 families during 12 months);
- Data collection for household study in subgroup of 400 families;

- High priority report on descriptive results for (1) impact of virus and measures; (2) carriage, disease and transmission among this group and risk social and ethnic groups;

Year 2:

- Follow up questionnaires (3000 families, at 18 months);
- Follow up measurements on pregnancy outcomes, fetal and infant outcomes and vertical transmission (placenta, cord blood, and, breast milk);
- Reports on impact of virus and social measures on family, pregnancy and infants, identification of risk groups, implementation strategy;

Motivation feasibility: The *EarlyLife-COVID* project will be embedded in the ongoing data collection of the Generation R *Next* Study, partially funded by ZonMw /Ministry of Health, Welfare and Sports. The logistics, data management, and biobank procedures are already available. We only request budget for a postdoc, research assistant and materials specifically needed for the additional SARS-CoV-2 /COVID studies. All other data already collected (information on genetics (GWAS), epigenetics (EWAS), lifestyle, diet, housing, families, pregnancy outcomes, fetal growth, infant development and behavior will be used.

4. RELEVANCE

The *EarlyLife-COVID* project is specifically focused on the burden of SARS-CoV-2 carriage, disease and transmission among pregnant woman, children and their families. The project links directly to the following **themes from the call**: (1) care and prevention for vulnerable groups (risk/ vulnerable groups; restrictive government measures effects; long term effects for youth and vulnerable families); and (2) transmission and epidemiology (spread in specific populations; role of underlying health problems; improvement of compliance to government measures). The **expected results** will include information about

- Incidence, carriage and transmission in pregnant women, their children and families;
- Specific risk social, ethnic, lifestyle, and health related risk factors;
- Impact on maternal, fetal and infant physical and mental health

We specifically look and **social and ethnic differences in carriage, transmission and compliance to government measures**. The direct deliverables for **most relevant** for families with young children and health workers for these groups.

5. STAKEHOLDER(S) (e.g. patients, professionals, etc.)

Planning, design and results of the study will be discussed every 3 to 6 months with parent and child cohort representatives, health care professionals (midwife, obstetrician, pediatrician, virologist) and the municipal healthcare workers (child health centers, center for youth and families), working together within the Rotterdam **Academic Center for Pregnancy & Childhood**. Additionally, this team, enriched with a implementation officers from Bernard van Leer foundation and RIVM, will function as **project specific implementation and impact team** that will be established in year one. **Implementation and impact team discussion will be focused on several issues including how to reach the different social and ethnic groups, how to identify specific risk groups and how to support vulnerable groups**. We have collaborations with the national programs *Healthy Pregnancy 4 All* and *Kansrijke Start* to share implementation knowledge and experience for our specific target group. In total € 5,000/year is included in the overall budget for implementation strategies (financial compensation for travelling implementation team, stakeholders, meeting organizations, materials such as app update).

6. LITERATURE

1. Wu Z, JAMA. 2020 Feb
2. Dashraath P, Am J Obstet Gynecol. 2020
3. Schwartz DA, Arch Pathol Lab Med. 2020
4. Zeng L, JAMA Pediatr. 2020
5. Jaddoe VV, Eur J Epidemiol. 2006.
6. Duijts L, 2014
7. Sarzi-Puttini P, Clin Exp Rheumatol. 2020
8. Cristiani L, Eur Respir J. 2020
9. Kooijman MN, Eur J Epidemiol. 2016
10. Kruitthof CJ, Eur J Epidemiol. 2014
11. Corman VM, Euro Surveill. 2020
12. OKBA NMA, medRxiv [Internet] 2020
13. Demers-Mathieu V, Nutrients. 2018
14. Rousian M, Placenta. 2018
15. Lau LL, Epidemiology. 2012