Influences of external determinants on the physiological development and composition of the infant microbiome in healthy infants from birth during the first 6 years of life using novel molecular techniques.
Subclinical and clinical disease, transmission, and risk factors of SARS-CoV-2 among children and their families: a household study within the "Microbiome Healthy Infant Study"

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Primary objectives:1. To study the development of the infant microbiome, defined as the microbial communities in the nasopharynx (transnasal), oral cavity (saliva), skin and gastro-intestinal tract (faeces), in healthy infants born by vaginal...

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Other condition
Study type	Observational invasive

Summary

ID

NL-OMON50226

Source
ToetsingOnline

Brief title
Microbiome healthy Infant Study

CoKids study

Condition

- Other condition
- Bacterial infectious disorders
- Bronchial disorders (excl neoplasms)

Synonym
carriage, microbial colonisation, SARS-CoV-2, transmission

Health condition

infecties, virale infectieziekten

Research involving
Human

Sponsors and support

Primary sponsor: Spaarne Gasthuis
Source(s) of monetary or material Support: ZonMW,De kosten voor het onderzoek komen ten laste van de verrichter en niet ten laste van de ziekenkostenverzekering

Intervention

Keyword: Atopy, Child, disease, Immune system, Microbiome, SARS-CoV-2, transmission

Outcome measures

Primary outcome

1. Comparison of the composition of infant microbiome between infants born

vaginally and infants born by caesarean section at several time points during

the first 12 months of life.

2. The dynamics of the infant nasopharyngeal and oral microbiome with age and

in periods of respiratory infections.

3. To study the human microbiome of children till age 6 in relation to health

status, life style and environmental factors

CoKids:

1. SARS-CoV-2 symptoms, infection, severity of disease and transmission

Secondary outcome

The secondary study parameters/endpoints:

1. The relation between nasopharyngeal, oral, gastrointestinal and skin microbiome.

2. The dynamics of the microbiome in periods of antibiotic consumption.

3. Comparison of the composition of the maternal microbiome and the child microbiome.

4. Comparison of the composition of the child microbiome between breastfed infants and formula fed infants.

5. The dynamics of the child microbiome in case of eczema/atopic diseases.

6. The dynamics of the child microbiome related to exposure and environment (father, siblings, day care).

7. The composition of breast milk in relation to the infant microbiome

8. The relation of microbiome to immunoglobulin and antibody development in saliva

9. The respiratory microbiome in relation to respiratory health, including medication over last six years and lung function parameters.

Exploratory end points

10. The dynamics of the early and childhood microbiome in relation to serum immunoglobulins, specific antibodies, immune IgE, T cell profile and

Th1/Th2/Treg/Th17 status.

11. Nutrition (including supplements like pre- and probiotics and vitamins) in relation to the oral, gut and respiratory microbiome.

12. The microbiome in relation to gastrointestinal complaints and weight development, length and blood pressure.

13. The distance of the residential address to an international airport in relation to the respiratory microbiome

14. The relationship of oral hygiene behaviour and the oral microbiome

15. The relationship of the oral microbiome and caries.

16. The relationship between sleep behaviour and physical exercise and the development of the respiratory, oral, gut and skin microbiome.

Study description

Background summary

The microbiome is defined as the ecological community of commensal, symbiotic, and pathogenic microbes that literally share our body space. Immediately after birth the body becomes populated with bacteria in various niches (e.g. nasopharynx, mouth, skin and gastrointestinal tract) of the human body and in time the so called human microbiome is being formed. During the first 12 months of life the composition of the microbiome changes rapidly due to external influences and host-related determinants like a maturing immune system. Suggested determinants are delivery mode, respiratory infections, age, antibiotics, maternal microbiome, nutrition, presence of eczema/ atopic disease and exposure to others (siblings, day care).
The composition of the microbiome of a niche may be relevant for health or susceptibility to disease. For instance, acquisition of a viral common cold may alter bacterial outgrowth of common colonizers of the nasopharynx like S. pneumoniae. Subsequently these bacteria may spread and cause acute otitis media or cause pneumonia. This development towards infectious disease by commensals like S. pneumoniae may however not only depend on viral acquisition, but also on the total microbial composition of which S. Pneumonia is part, that may counterbalance outgrowth and spread and this way determine susceptibility to

bacterial infections. It has already been shown that vaginal delivery or breastfeeding may have a protective role against respiratory infections at infant age. Vaginal delivery or breastfeeding may favour a microbiome that can control outgrowth of potential pathogenic bacteria for a long time. Better knowledge about favouring a protective microbiome for respiratory infections is relevant since respiratory tract infections are the most frequent infections in childhood for which physicians are consulted, antibiotics are prescribed and surgery like ventilator ear tubes and adenoidectomy is performed. Insight in optimal microbial composition may offer tools for future preventive strategies e.g. via pre- or probiotics. In a similar way, microbiome compositions of the oral cavity, skin and gastrointestinal tract may be associated with health or common diseases in childhood like atopic diseases. For example, atopic disease seems associated with an altered microbiome of the skin.

Up till now, detailed knowledge about the development of the infant microbiome after birth in the first year of life is scarce. Relations between the microbiome of the gastrointestinal tract, oral cavity, nasopharynx and skin are largely unknown. Most research on the microbiome is cross-sectional, and single niches have been described in literature. With this longitudinal study of these four niches, we aim to understand the effects of microbial community shifts and to relate this to infant*s health and disease (atopic, respiratory, gastro-intestinal).

Studies of the microbiome have become feasible with the development of molecular methods, since 40 to 80% of microbiome bacteria cannot be detected by conventional culture techniques. With novel molecular techniques as 454 pyrosequencing (DNA-sequencing), we can evaluate the bacterial microbiome composition. In the study we will focus on the development of the microbiome composition in the first year of life of four relevant niches (1) nasopharynx (2) oral cavity (saliva) (3) skin and (4) gastro-intestinal tract (faeces) using 454 pyrosequencing referred to as the infant microbiome. We will study the influence of external determinants on the infant microbiome. Since every child will develop at least 6-8 symptomatic respiratory infections that are likely to be initiated by viral acquisition, we will also study alterations in the nasopharyngeal and oral niche during a symptomatic clinical respiratory infection in these otherwise healthy infants.

The study population is observed until the age of 6. When the child nearly reaches the age of 5, parents receive an invitation to participate in an intensified protocol, called MUIS-5. In this study, the participants will be invited to the outpatient clinic for (1) additional microbiome sampling (2) physical examination, (3) saliva sampling for immunoglobines (4) an extended questionnaire. Optional tests will be: (1) blood test for immunoglobines, anti vaccine antibodies and T cell profiling, (2) lung function tests (spirometry and fractioned exhaled nitrous oxide test) (3, only optional voor non-follow-up-participants) nasopharyngeal microbiome sampling

CoKids:
The SARS-CoV-2 pandemic is a threat to the health and wellbeing of children and parents. The causes and contributing factors to this are unknown, as is the role of asymptomatic and symptomatic children in the spread of the virus and the development of herd immunity. The Ministry of Health, Welfare and Sport and ZonMw have approached a number of research groups to help answer questions related to the spread and transmission of the virus in specific groups. The UMCU/Erasmus MC and Spaarne Gasthuis in collaboration with the RIVM will study children in various age ranges, who are participating in ongoing cohort studies, to examine carriership and transmission in children and families. Given the impact and relevance of findings for public health decisions, we would like to contribute. Due to its prospective, longitudinal and detailed data collection in a large population and its existing infrastructure, the Microbiome Healthy Infant Study represents an excellent basis for studies into transmission and risk factors of SARS-CoV-2 in children and their families

Study objective

Primary objectives:
1. To study the development of the infant microbiome, defined as the microbial communities in the nasopharynx (transnasal), oral cavity (saliva), skin and gastro-intestinal tract (faeces), in healthy infants born by vaginal delivery or caesarean section, during the first 12 months of life using novel molecular techniques.
2. To study changes in the infant nasopharyngeal and oral microbiome during clinical respiratory infections in the first year of life.
3. To study the long-term effects of the infant respiratory, oral, (saliva) gut and skin microbiome on the respiratory and gastrointestinal and atopy health status of children till 6 years of age.
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Secondary objectives:
1. To study the influence of different determinants on the infant microbiome such as maternal conditions during labour (prolonged rupture of membranes, maternal fever (amnionitis) and antibiotics) nutrition (breastfeeding versus formula feeding), antibiotics, presence of eczema/ atopic disease and exposure to others (parents, siblings, day care).
2. To study the influence of life style and environmental factors on the human microbiome and the development of atopic, respiratory, and gastrointestinal complaints.
3. study the microbiome status (nasopharynx (transnasal), oral cavity (saliva), skin and gastro-intestinal tract (faeces)), at age 5 to mucosal immunoglobulins and anti vaccine antibodies.

Explorative:
1. To explore study the microbiome status (nasopharynx (transnasal), oral cavity (saliva), skin and gastro-intestinal tract (faeces)), at age 5 to serum immunoglobulins and anti vaccine antibodies and Tcel development.

CoKids:
1 To determine the incidence of overall, asymptomatic, mild and medically attended SARS-CoV-2 infection in children and their parents
2. To determine transmission patterns of SARS-CoV-2 within households with young children
3. To describe symptom severity in children

Study design

Observational prospective cohort study. The development of the infant microbiome during the first 12 months of life and the potential differences in the microbial composition between infants born vaginally and by caesarean section will be studied. During the follow-up children will be followed til the age of 6. At the age of 5, all MUIS participants will be invited for a one-off intensified protocol.

CoKids:
The project will be embedded in the Microbiome Healthy Infant Study, a population-based prospective study from birth onwards.

Study burden and risks

Participation in this study holds no more risks than negligible risk and no benefits to the infant or the mother, except for the venipuncture, were children could experience anxiety, we try to reduce anxiety by distracting and comforting the child. With local anaestetic EMLA cream we reduce pain levels. There is a 2% risk of developing a local hematoma.
We believe that the risk of this study is no more than negligible for all sampling methods are non-invasive and generally accepted as fully save. Sampling moments will take place during home visits to minimize burden and time spent for the study participants. There is no personal benefit for the infant or the mother.
We will follow the code of conduct relating to expressions of objection by minors participating in medical research, as stated by the CCMO.
Each sample moment will take 30 minutes of participant*s time. Also signing informed consents forms will take 30 minutes. Total time required for participation will be 7.5 hours. During follow-up, 10 visits will be performed over a time period of 5 years, each visit will take 30 minutes.
If parents participate in the MUIS-5 study, they are invited to visit the outpatient clinic for the different tests. This visit will take an estimated two to three hours. Parents receive an appropriate allowance for travelling and parking at the hospital.

CoKids: We believe that the risk of this study is no more than negligible for all sampling methods are non-invasive and generally accepted as fully save. Sampling moments will take place at home. There is no personal benefit for the

families.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adolescents (12-15 years)
Adolescents (16-17 years)
Adults (18-64 years)
Children (2-11 years)
Elderly (65 years and older)

Inclusion criteria

1. Neonates born after 37 weeks of gestational age
2. Born in the region Groot Kennemerland and Bollenstreek (draining on Spaarne hospital in Hoofddorp or Kennemer Gasthuis in Haarlem).

Inclusion criteria for COVID-19 related part:
1. Household member of participating children in the birth cohort study

(including participating children themselves)
2. Written informed consent obtained from parents
3. Parents ability and willingness to adhere to protocol-specified procedures.

Exclusion criteria

1.Severe perinatal/ neonatal/ maternal complications as asphyxia, resuscitation, transfer to neonatal intensive care unit etc.
2.Major congenital anomalies.
3.Language barrier.
4.Intention to move outside the research area.
5.Parents under the age of 18 years.
For CoKids study: None

Study design

Design

Study type: Observational invasive

Masking:	Open (masking not used)
Control:	Uncontrolled
Primary purpose:	Basic science

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	20-11-2012
Enrollment:	130
Type:	Actual

Ethics review

Approved WMO

Date:	09-09-2012
Application type:	First submission
Review commission:	METC Amsterdam UMC

Approved WMO Date:	03-06-2013
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	26-11-2013
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	16-04-2014
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	02-02-2016
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	13-12-2017
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	22-03-2018
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	29-05-2020
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	20-07-2020
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	14-08-2020
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO	

Date:	30-03-2021
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	13-07-2021
Application type:	Amendment
Review commission:	METC Amsterdam UMC

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

Other (possibly less up-to-date) registrations in this register

No registrations found.

In other registers

Register	ID
CCMO	NL38592.094.12