Protecting against Respiratory tract Infections through human Milk Analysis.

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Primary objective: 1. To identify the components in human milk (e.g. nutrients, oligosaccharides, fatty acids and (pathogen specific) immunoglobulins) that have a protective effect against respiratory tract infections during the first year of life....

Ethical review	Approved WMO
Status	Recruiting
Health condition type	Allergic conditions
Study type	Observational invasive

Summary

ID

NL-OMON51989

Source
ToetsingOnline

Brief title
PRIMA

Condition

- Allergic conditions
- Infections - pathogen unspecified

Synonym
pneumonia, Respiratory tract infection

Research involving
Human

Sponsors and support

Primary sponsor: Universitair Medisch Centrum Utrecht
Source(s) of monetary or material Support: Dit onderzoek wordt gefinancierd middels een grant van Nutricia Research BV.,Health~Holland TKI-LSH SIGNALERS project (UMCU + UU + Nestlé Research),Nutricia,Regio Deal Foodvalley

Intervention

Keyword: Antibodies, Human milk, Maternal diet, Oligosaccharides, Respiratory tract infections

Outcome measures

Primary outcome

The amount of medically attended respiratory tract infections during the first year of life.

Secondary outcome

1. The amount of medically attended respiratory tract infections for every quarter of a year during the first year of life.

2. The amount of prescribed antibiotic treatments for respiratory tract infections during the first year of life.

3. The total amount of respiratory tract infection periods during every quarter of a year for the first year of life.

4. Food allergies diagnosed by a physician during the first year of life.

5. Inhalation allergies diagnosed by a physician during the first year of life.

6. Eczema diagnosed by a physician during the first year of life.

7. Maternal diet.

8. Macro- and micronutrient composition of breast milk.

8. Microbiota composition in feces.

9. Antibody repertoire and viral genome in saliva.

10. Extracellular vesicle repertoire in breast milk.

Study description

Background summary

We aim to identify mechanisms by which breast feeding prevents respiratory tract infections. A healthy birth cohort (n=1000) will be set-up and studied during the first year of life. Human milk will be collected repeatedly and analysed to provide insights into the protective capacity of human milk components against (respiratory tract) infections and allergies. Saliva samples are collected from the infant at 3 and 12 months of age to study the immune development. Milk samples from a subgroup of 50 extra participants will be used to specifically investigate the role of extracellular vesicles in the protective effect of breast milk, using in vitro experiments with a focus on the development of the immune-liver-brain axis. Additionally, the vesicles will be characterised and the effect of milk processing will be studied. A subgroup will be further analyzed to obtain insight in transfer of maternal immunity to the child. By collecting additional cord blood, amniotic fluid and maternal blood samples, we will analyze the transfer of maternal immunity. In a sub-study (N=25), in addition, we will ask participating mothers to complete four dietary assessment questionnaires, and to collect some saliva and feces of their infant. With this, we can study the influence of the maternal diet on how well the breast milk protects their infant against respiratory tract infections and/or allergies. In the last decades, research shows the importance of the maternal diet on breast milk composition. However, the performed studies are often with too small study groups, and studies differ too much in study design to be able to compare them for meta-analyses. Lastly, there is no sufficient amount of studies/power to be able to draw conclusions.

Study objective

Primary objective: 1. To identify the components in human milk (e.g. nutrients, oligosaccharides, fatty acids and (pathogen specific) immunoglobulins) that have a protective effect against respiratory tract infections during the first year of life. Secondary objective: 2. The underlying mechanism of the components in human milk that offer protection from respiratory tract infections during the first year of life. 3. To identify the components in human milk (e.g. nutrients, oligosaccharides, fatty acids and (pathogen specific) immunoglobulins) that have offer from developing allergies during the first year of life and to identify the underlying mechanism of these components. 4. To study the alterations in human milk composition at various time points. 5. To gain insight in the transfer of maternal immunity to their child via human milk, amniotic fluid and the placenta.

6.To identify the long-term and short-term influence of the maternal diet on the breast milk composition.
7. Link the long-term and short-term influence of the maternal diet to the

clinical outcome of respiratory tract infection during the first year of life
8. To derive hypotheses about potential mechanisms if the maternal diet-influenced components in human milk are protective against respiratory tract infection during the first year of life.
9. To identify the association between long-term and short-term influence of the maternal diet on the microbiota composition of a 3-month old infant, and its consequence for the risk of developing respiratory tract infections in the first year of life.
10. To identify the antibody repertoire and viral genome in saliva samples from 3 and 12 month-old infants.
11. To link the antibody repertoire in saliva samples with antibody repertoire in feces and microbiota composition, and how this relates to the risk of developing respiratory tract infections in the first year of life.
12. To advance our understanding of the effect of human milk extracellular vesicles on the development of the immune-liver-brain axis, the impact of maternal factors on human milk extracellular vesicles and the preservation of their functionality after milk processing.

Study design

The study is designed as a prospective observational cohort study, including 1000 healthy mother-child pairs. Directly after birth we will collect data from all children enrolled through a questionnaire that is send to parents every 2 weeks. The questionnaires will be used to collect data about episodes of (respiratory tract) infections and already developed allergies during the first year of age. Meanwhile, we will collect human milk samples at four time points: within 1 week postpartum and after 1 month, 3 months and 6 months postpartum. By collecting human milk at these time points, we expect to collect samples from all relevant time-dependent types of human milk. The human milk samples will be stored until analysis at the biobank facility of the UMC Utrecht. After analysis of human milk composition is performed and clinical data collected, we will compare the two database in order to find beneficial profiles of human milk components. Additionally we will also collect additional samples to research what the influence of breastfeeding is on immune development compared to other routes that are enrolled in the transfer of maternal immunity to the neonate. This we will de in a subgroup of 20 mother-child dyads. The samples that we will collect are cord blood samples, a maternal blood sample and an amniotic fluid sample. Jacobino et al. showed that antibodies retrieved form human amniotic fluid protected mice pups against RSV-infections (JACOBINO2016). Very little is known about the protective value antibody titers in cord blood. Active placental transport of maternal antibodies to the neonatal blood has been described, but little is known about the effectiveness of these antibodies (KOHLER1966). To obtain more insight in the effect of the antibodies that are being transferred by breastfeeding, we will compare the effect of breastfeeding to the antibodies in cord blood and amniotic fluid. We will also collected saliva samples in the children enrolled n this subgroup at 1 week, 1, 3, 6, and 12 months postpartum. Saliva samples will be used to study immune development

in children.
Lastly, we will additionally (n=250) ask participating mothers to fill in four dietary assessment questionnaires, and to collect some saliva and feces from their infant when he/she is 3 months old.

Study burden and risks

Only parents will be burdened by participating in this study. Parents will be visited by researchers four times maximum. Children will not be affected by the collection of human milk samples, since they are a rather small fraction of the total amount of breastfeeding. Apart from human milk collection, parents will have to fill in questionnaires every 2 weeks that will take 1-2 minutes to complete. Additionally parents will have to fill in three more extensive questionnaires that will take about 300 minutes each to complete (i.e. baseline, midterm and end-of-study questionnaires). In total, the maximal estimated amount of hours will be 5-6 hours for each child. There is a minimal risk associated with the venipuncture. Although considered safe, rarely phlebitis, extravasation of blood, bruising and hematoma forming following venipuncture have been reported. However, since complications form venipunctures and expressing milk are rare, and we will decrease the risk of a data breach as best as we can with our DMP, we asses these risks for mothers acceptable. No risk is associated with the collection of amniotic fluid or saliva.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)
Babies and toddlers (28 days-23 months)
Newborns

Inclusion criteria

All healthy childen (and their parents) born at a minimal gestational age of 32 weeks.

Exclusion criteria

Exclusion criteria concerning the child: - Congenital heart defect. - Congenital lung disorder or other severe organ dysfunction. - (extreme) prematurtity (<32 weeks GA)., Concerning the parents: - Congenital or acquired immunodeficiency (except for allergies, eczema and hay fever). - Presence of a medical condition or use of medication in mothers that contraindicates breastfeeding. - Insufficient control of the Dutch Language (>B1 CEFR level).

Study design

Design

Study type: Observational invasive

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

Recruitment

NL

Recruitment status:	Recruiting

Start date (anticipated):	25-05-2021
Enrollment:	1000
Type:	Actual

Medical products/devices used

Registration:	No

Ethics review

Approved WMO Date:	10-09-2020
Application type:	First submission
Review commission:	METC NedMec
Approved WMO Date:	15-07-2021
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	09-03-2023
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	25-03-2025
Application type:	Amendment
Review commission:	METC NedMec

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

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

ID: 23847

Source: Nationaal Trial Register
Title:

In other registers

Register	ID
CCMO	NL74946.041.20