Protecting late-moderate preterm infants from respiratory tract infections and wheeze in their first yearsof life by using bacterial lysates.

Published: 07-01-2021
Last updated: 10-01-2025

This study has been transitioned to CTIS with ID 2024-518498-32-01 check the CTIS register for the current data. The project*s overarching aim is to diminish respiratory disease burden in moderate-late preterm born infants in their first year of…

Ethical review	Approved WMO
Status	Recruiting
Health condition type	Viral infectious disorders
Study type	Interventional

Summary

ID

NL-OMON55914

Source
ToetsingOnline

Brief title
PROTEA

Condition

- Viral infectious disorders
- Respiratory tract infections

Synonym
respiratory tract infections and wheezing

Research involving
Human

Sponsors and support

Primary sponsor: Franciscus Gasthuis & Vlietland
Source(s) of monetary or material Support: Franciscus Gasthuis & Vlietland,Longfonds Nederland,OM Pharma, Zwitserland/Portugal: bijdrage in de vorm van IMP en investigator initiated support,Ventica, Finland: bijdrage in de vorm van tijdelijke bruikleen van longfunctie apparatuur

Intervention

Keyword: prematurity, prevention, respiratory tract infection, wheezing

Outcome measures

Primary outcome

Doctor diagnosed lower RTI and wheezing episodes in the first year of life.

Time to first lower respiratory episodes in the second year of life.

Secondary outcome

• time to first lower RTI or wheezing episode

• total number of RTI

• total number of wheezing episodes

• distribution of viruses

• medication use (bronchodilators, corticosteroids, antibiotics)

• lung function as measured by expiratory variability index

• quality of life

• costs- and cost-effectiveness

• (serious) adverse events

• serum specific IgE (allergen sensitization) at 12 months

• infant vaccination titers at 12 months

• immune development trajectories; immune maturation

• gut and respiratory microbiome composition

• biomarkers predictive of high morbidity and/or treatment success

Study description

Background summary

Approximately 10% of all births occur prematurely; mostly between 30-36 weeks of pregnancy (*moderate-late* prematurity). Respiratory tract infections (RTI) and viral wheezing illnesses disproportionally affect preterms both early and later in life. Underdeveloped lungs, an unfavorable microbiome and aberrant immune maturation are considered causes of this increased RTI susceptibility in preterms. Moreover, they experience viral infections earlier in their life trajectory. Early- and severe RTI increase the likelihood of subsequent poor respiratory health and antibiotic prescriptions; further deviating microbiota development. There is a clear unmet clinical need for preventive therapies that decrease the burden of RTI and wheezing illnesses in young children.
Early childhood immune priming via gut microbial exposure is beneficial for the development of a healthy immune system. Oral bacterial lysates have shown effectiveness and safety in the prevention of recurrent RTI in pre-school children through Toll-like receptor engagement on epithelia and immune cells within the gut and the activation of beneficial innate- and regulatory immune responses. A recent trial showed that primary prevention and postponement of lower RTI was achieved with bacterial lysate administration in 3-6 month-old infants at risk for atopy. Studies using such bacterial lysates were exclusively performed on term children, while studies on preterms, the group with the highest respiratory disease burden, are lacking. In addition, the intervention was started at a time the first RTI might already have occurred. Therefore, we focus on moderate-late preterm infants and investigate whether we can achieve a reduction in first-years-of-life respiratory illnesses by early bacterial lysate administration, thereby probably optimizing chances for life-long respiratory health.
We hypothesize that early education of the neonatal immune system by daily stimulation with microbial elements leads to better protection against lower RTI and subsequent wheezing episodes. It enhances self-initiated immunity against pathogens by improved and accelerated immune maturation. This will lead to a significant health gain in preterm-born infants with enhanced risk for respiratory diseases.

Study objective

This study has been transitioned to CTIS with ID 2024-518498-32-01 check the CTIS register for the current data.

The project*s overarching aim is to diminish respiratory disease burden in

moderate-late preterm born infants in their first year of life.

We have formulated the following specific aims:
1. Determine whether bacterial lysates reduce the number and/or severity of lower RTI and wheezing episodes in the first year of life
2. To compare the efficacy of 1 versus 2-year bacterial lysate therapy for the prevention of lower respiratory episodes in moderate-late preterm infants in their first two years of life.
3. Analyze the impact of bacterial lysates on mucosal and systemic immune maturation and microbiome diversity and maturation
4. Identify biomarkers predicting development of early respiratory episodes (high risk group) and response to bacterial lysate administration in order to facilitate personalized treatment
5.To calculate cost-effectiveness of all bacterial lysate treatment regimens.

Study design

This multi-center randomized controlled trial includes 500 preterm infants (gestational age 30+0-35+6 weeks) without other significant morbidity. From age 6-8 weeks participants will receive blinded 3.5 mg OM-85 or placebo powder for 10 consecutive days per month till age 1 year, easily dissolved in breast- or formula milk. Clinical data (eg. RTI, medication use, health care visits, lung function) will be collected by e-Health and (live and digital) study visits. In case of a lower respiratory episode, the patient is seen by the local doctor and a nose swab will be taken by the parents or doctor. In a subset of patients (optional, N=250), biological samples (nasal fluid, swab, blood) will be collected at baseline, 6, and 12 months for immunological and microbiota typing. The patients having received OM-85 in the first year of life will be offered a follow-up study with new randomisation to OM-85 or placebo with otherwise identical treatment regimen in the 2nd year of life (N=206 patients needed). One optional study visit at 24 months for biosampling and/or lung function.

Intervention

OM-85 versus placebo

Study burden and risks

We expect a possible positive effect on respiratory health.
Safety is important in pediatric studies. Therefore, dosing and starting age were carefully considered; literature review, collegial and pharmaceutical consultation were performed. There are no known related safety issues when orally administering lysates (OM-85 and other) at a pediatric age. Lysates contain inactivated fragments of bacteria and cannot induce infections. Moreover, the oral route of application is the natural route for microbial

exposure and the gut filled with live microorganisms is designed to cope with these signals. In longer-term follow-up studies, the safety profile was good (see introduction).

Bacterial lysates have been given to infants from 6-12 weeks onwards without (short and longer term) side effects. The window of prevention might be small - before the start of first RTI. Moreover, repeated exposure seems to be needed to preserve the positive effect on RTI. Regular vaccinations are also administered from 6 weeks onwards; live-attenuated BCG-vaccine (also conferring aspecific immune protection) is even given immediately after birth. Therefore, we have decided to start early after birth and continue treatment till age 1 year; and in a subgroup till age 2 years.

Summarized, no important safety issues are expected. Nevertheless, a DSMB and individual physicians will regularly assess safety. Infants will be removed from the protocol if needed for well-being.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Premature newborns (<37 weeks pregnancy)

Inclusion criteria

Gestational age at delivery between 30+0 and 35+6 weeks
Postnatal age at least 6 weeks at randomization & postmenstrual age at least 37 weeks
Written informed consent by both parents or formal caregivers

Exclusion criteria

Underlying other severe respiratory disease such as broncho-pulmonary dysplasia (unexpected in this group); hemodynamic significant cardiac disease; immunodeficiency; severe failure to thrive; birth asphyxia with predicted poor neurological out-come; syndrome or serious congenital disorder.
Dysmaturity and/or weight < 2.5 kg at age of randomization.
Maternal TNF-alpha inhibitors or other immunosuppression during pregnancy and/or breastfeeding
Parents unable to speak and read Dutch/English language
Known allergic hypersensitivity to the active ingredients/substance or to any of the excipients.

Study design

Design

Study phase:	3
Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Double blinded (masking used)
Control:	Placebo
Primary purpose:	Prevention

Recruitment

NL

Recruitment status:	Recruiting
Start date (anticipated):	16-03-2022
Enrollment:	500
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Broncho-Vaxom
Generic name:	OM-85

Ethics review

Approved WMO Date:	07-01-2021
Application type:	First submission
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	31-05-2021
Application type:	First submission
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	13-01-2022
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	28-01-2022
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	17-11-2022
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)

Approved WMO Date:	21-11-2022
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	20-01-2023
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	28-01-2023
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	09-08-2023
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	30-08-2023
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	18-09-2023
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	12-12-2023
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	16-01-2024
Application type:	Amendment

Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	04-10-2024
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	14-10-2024
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)

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
EU-CTR	CTIS2024-518498-32-01
EudraCT	EUCTR2020-005868-67-NL
ClinicalTrials.gov	NCT05063149
CCMO	NL76165.100.20