Preterm Immune system development and response to Immunization

Published: 18-10-2022
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Primary objective is to study the antibody immune response to routine vaccinations in very preterm infants (GA

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

Summary

ID

NL-OMON56341

Source
ToetsingOnline

Brief title
Primi study

Condition

- Other condition
- Immunodeficiency syndromes
- Infections - pathogen unspecified

Synonym
immune system of preterm born infants, response to vaccination

Health condition

respons op vaccinaties

Research involving
Human

Sponsors and support

Primary sponsor: kindergeneeskunde
Source(s) of monetary or material Support: industrie,Merck

Intervention

Keyword: immune system, prematurity, vaccination

Outcome measures

Primary outcome

To measure blood IgG antibody concentrations against the antigen components of the hexavalent DTaP5-HB-IPV-Hib vaccine for the six preventable diseases (Diphtheria, Tetanus, Pertussis, Polio, Hepatitis-B, Haemophilus influenza type B) in preterm-born infants 4- 6 weeks after primary series of routine vaccinations in order to assess the proportion of children with IgG concentrations above international-defined thresholds for protection. This proportion will be compared with proportions in healthy term infants as known from literature. .

Secondary outcome

1. To assess the number and repertoire of blood antigen-specific memory B cells in term-born infants following routine vaccinations after primary series (age 6 months) and booster vaccination (age 12 months)

2. To assess number and repertoire of blood antigen-specific memory B cells in preterm-born infants following routine vaccinations after primary series (age 6 months) and booster vaccination (age 12 months) compared to term born infants

3. To assess blood IgG antibody concentrations against vaccine antigens in preterm-born infants following booster of routine vaccination with DTaP5-HB-IPV-Hib as a marker of immune maturation in premature children.

4. To assess blood IgG antibody geometrical mean concentrations in preterm infants compared to reference values in healthy term infants as known from literature following primary series and booster of routine vaccination with DTaP5-HB-IPV-Hib.

5. To assess blood IgG antibody concentrations against vaccine antigens in preterm-born infants following routine vaccinations with 10-valent pneumococcal conjugate vaccine after primary series and booster vaccination as a marker of immune maturation in premature children.

6. To assess blood IgG antibody concentrations against pertussis antigens at 2 months of age (before start of infant immunizations) in preterm-born infants after maternal Tdap vaccination and in infants whose mother did not receive maternal Tdap vaccination.

7. To assess blood IgG antibody concentrations against vaccine antigens in preterm-born infants before start of immunizations and following routine vaccinations after primary series and booster vaccination, in relation to maternal antibody concentrations against vaccine antigens.

Proportions of infants with IgG concentrations above the internationally defined threshold for protection and geometrical mean concentrations will be compared between preterm infants after maternal Tdap vaccination, preterm infants whose mothers did not receive Tdap vaccination and reference values in healthy term infants as known from literature.

Number and repertoire of antigen-specific memory B cells will be compared between preterm infants after maternal Tdap vaccination, preterm infants whose mothers did not receive Tdap vaccination and healthy term infants after maternal Tdap vaccination, who will be recruited for this study.

Study description

Background summary

Preterm infants are at increased risk of developing infections early in life due to a less mature immune system compared to full-term infants. Moreover, protection by the placental transfer of maternal antibodies in general and specifically against vaccine antigens has shown to be significantly lower in very preterm infants (gestational age (GA)< 32 weeks) compared to term infants. In this study we aim to investigate the immune system development of very preterm infants. Adequate immune response to vaccination is considered both clinically important as well as a functional test of the immune system. However, data on the antibody and Ag-specific memory B cell response to vaccination in preterm infants are limited.

Longitudinal data on the long-term memory B-cell response (antigen specific immune maturation) in healthy term infants is also sparse. To compare the long-term antigen specific memory B-cell response between preterm infants and healthy controls, Ag-specific memory B cell response to vaccination will be measured in 25 healthy term infants as well.

Study objective

Primary objective is to study the antibody immune response to routine

vaccinations in very preterm infants (GA<32 weeks). Secondary aim is to study the immune system more extensively using flow cytometry, ELISA and single cell transcriptomics to measure development of antigen (Ag)-specific memory B cells raised in response to vaccination, and by using proteomics, epigenetics, and microbiome studies.

Study design

Multicenter prospective observational cohort study of 120 very preterm infants (< GA 32 weeks) and their mothers and 25 healthy term infants. In preterm infants, antibody response to routine vaccinations as a readout for the development of the immune system will be measured before start of immunizations (age 2 months), after primary series (age 6 months) and after booster vaccination (12 months). To compare the long-term antigen specific memory B-cell response between preterm infants and healthy controls, Ag-specific memory B cell response to vaccination will be measured in 25 healthy term infants after primary series (age 6 months) and after booster vaccination (12 months).

Study burden and risks

The development of the immune system including antibody response to routine vaccinations will be measured before (age 2 months, in preterm infants) and after primary and booster vaccination (age 6 and 12 months respectively, in both preterm and full-term infants). Whenever possible, blood will be collected at the same time as routine blood draws, but extra blood draws may be needed for the study. In this case there will be some burden to the infant. For healthy controls, the study procedures are not part of regular care.
Longitudinal data on the long-term memory B-cell response in children (antigen specific immune maturation) is sparse. This information is therefore valuable in itself and for our study essential to compare the long-term antigen specific memory B-cell response between preterm infants and healthy controls. Previous studies have shown that maternal pertussis vaccination is highly effective in preventing pertussis in infants early in life. After implementation of this maternal pertussis vaccine the national immunization program was adjusted, and the first vaccination was delayed. However, it is not exactly known how high the protective antibodies are with this immunization schedule.
To ensure that the burden of blood draw is minimal we will administer sucrose and apply a topical anesthetic (lidocaine/prilocaine or lidocaine/ tetracaine) according to local guidelines. Blood volume restrictions will comply with the recommendations of the European Commission and the World Health Organization (WHO) guidelines.
There is no direct benefit of participation to the participant. However, knowledge and insight gained during this study contributes to knowledge on immune system development of premature infants and may aid to improve vaccine schedules and protection against vaccine-preventable diseases for preterm

infants in the future.
Given the aim of this study, it can only be performed in children and not in adults. Since this is an observational, non-interventional study, in which the response to routine vaccinations will be measured as a proxy for the immune maturation of premature children, the risk of participating in this study is considered negligible. The risk of this study procedure (blood draw) is considered very low.

Contacts

Public
Selecteer

P. Debyelaan 25
Maastricht 6229HX
NL
Scientific
Selecteer

P. Debyelaan 25
Maastricht 6229HX
NL

Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)
Babies and toddlers (28 days-23 months)
Newborns
Premature newborns (<37 weeks pregnancy)

Inclusion criteria

• Preterm infant born at gestational age less than 32 weeks (whose mothers did

or did not receive a T dap vaccination during pregnancy) OR healthy full-term infant whose mother received a Tdap vaccination during pregnancy
• Mothers of included preterm infants
•Parents/ guardians must have sufficient understanding of the Dutch language

Exclusion criteria

• Parents/guardians not able or willing to provide informed consent
• Infant with congenital anomaly which are more likely to cause adverse effects after immunization (for example hemodynamically significant congenital heart defect)
• Infant with a (possible) HIV infection, immunodeficiency or use of immunomodulating drugs
• Maternal use of immunosuppressive drugs during pregnancy
• Parental intention not to vaccinate according to the National Immunization Program

Study design

Design

Study type:	Observational invasive
Intervention model:	Other
Allocation:	Non-randomized controlled trial
Masking:	Open (masking not used)
Control:	Active
Primary purpose:	Prevention

Recruitment

NL

Recruitment status:	Recruiting
Start date (anticipated):	06-12-2022
Enrollment:	265
Type:	Actual

Ethics review

Approved WMO Date:	18-10-2022
Application type:	First submission
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)
Approved WMO Date:	23-03-2023
Application type:	Amendment
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)
Approved WMO Date:	12-06-2023
Application type:	Amendment
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)
Approved WMO Date:	22-11-2023
Application type:	Amendment
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)

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
Other	Clinical Trials.Gov
CCMO	NL80118.068.22