Detecting the antigen-specific B-cell-response to rabies vaccination.

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The goal of this study is to develop a flow-cytometric assay that is able detect antigen-specific B-cells to rabies vaccine.

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

Summary

ID

NL-OMON54645

Source
ToetsingOnline

Brief title
ASPERA

Condition

- Viral infectious disorders

Synonym
rabies

Research involving
Human

Sponsors and support

Primary sponsor: Leids Universitair Medisch Centrum
Source(s) of monetary or material Support: Ministerie van OC&W

Intervention

Keyword: Immunology, Rabies, Vaccination

Outcome measures

Primary outcome

Detection of rabies-specific B-cells in peripheral blood of hyperimmunized

volunteers.

Secondary outcome

Quantification and phenotypical characterization of rabies-specific B-cells.

Study description

Background summary

Rabies is a fatal disease that is still present globally, accounting for 59000 annual deaths. It is primarily transmitted via canine bite incidents, although other animals (such as bats) can be responsible for transmitting rabies as well. Adequate pre- and post-exposure treatments exist and have played a major role in decreasing the death rate of rabies. However, these treatments are not (financially) accessible universally. The cost of rabies vaccination can be lowered by decreased dosages per vaccination, or a shorter vaccination regimen. Current research is carried out to determine whether shorter, lower-dose vaccination schedules are equally effective to the current WHO-recommended schedules.
Effectivity of a vaccine/vaccination schedule is usually assessed through RVNA serology. A titer >0.5 IU/ml is considered protective against rabies. However, titers will drop eventually, and booster vaccinations need to be reapplied if titers have dropped below 0.5 IU/ml. To predict long-term protection, other parameters than serology might contain useful information. Some of these parameters can be assessed through cellular assays, such as flow cytometric assays. The quantity, velocity and diversity of the immune response might predict lasting memory. To assess whether this is the case, an antigen-specific assay against rabies vaccine needs to be developed.
More and more modern techniques have become available to detect immune cells. For other diseases, such as dengue or HPV, an antigen-specific cellular assay is already available. This is not yet the case for rabies. With such an assay, the composition of the response of B-memory-cells and plasma cells and the kinetics of the primary and secondary response can be described. Never before have they been described in such detail and antigen-specifically, and therefore they might contain useful, still unknown information for the field of vaccinology and immunology.
Rabies vaccine is the perfect agent for describing vaccination responses. As a

neo-antigen it can be used to assess both the primary and secondary response, whereas the primary response is harder to assess with other vaccines. Furthermore, the vaccine contains only virus particles and no adjuvants. The antigen-specific reaction will therefore always be targeted towards the virus particles and not to an additive.
This use of this assay is not limited to this. It can also be used to describe the antigen-specific primary and secondary immune response. These results can be used as reference values for diagnosing certain immune deficiencies. It can also be used in monitoring vaccination responses among immunocompromised patients, and could also provide a faster alternative to serological protection testing.
The possibilities are vast. Therefore, we would like to develop an assay that can detect antigen-specific B-cells to rabies vaccination.

Study objective

The goal of this study is to develop a flow-cytometric assay that is able detect antigen-specific B-cells to rabies vaccine.

Study design

This study consists of two phases, of which the first has been finished in 2022. The current study phase is phase II.
Phase I:
In a single cross-sectional visit of the researchers to the Wageningen Bioveterinary Research Institute in Lelystad and the LUMC in Leiden, blood will be drawn from 10 volunteers, 53,5 ml per person (including a 3,5 ml serum tube), after they have provided informed consent. The volunteers will fill in a short questionnaire on their rabies vaccination history as well.These volunteers have received multiple rabies vaccinations in the past, and will NOT be revaccinated for this study. This blood will be processed and frozen for future use.
The fresh and stored blood samples will be used to develop, validate and optimize the assay for flow-cytometric detection of antigen-specific B-cells against rabies vaccine. The acquired material (blood) is needed solely to develop and validate the assay. We expect that detection of rabies-specific B-cells will be possible in these hyperimmunized individuals due to their repeated previous exposure to (inactivated) rabies and gradual buildup of immunological memory. Rabies-naïve healthy controls will not have this memory as they have never been exposed: therefore we expect to see no rabies-specific B-cells in their blood. Control blood of people who have not been vaccinated against rabies will be collected from the employees of the departments of IHB, Infectious Diseases and Medical Microbiology of the LUMC. If they have been vaccinated against rabies at least three times, they are eligible to participate as part of the hyperimmunized group. Control blood can also be acquired from Leiden University students who have been recruited via a general

social media message.
For each blood sample, we will analyze leukocyte differential count and isolate peripheral blood mononuclear cells. For flow cytometric studies, we will incubate cells with rabies vaccine and detect vaccine-binding B-cells using CD19- and CD20-antibodies and an antibody against viral rabies proteins. We will perform multiple tests to find the optimal vaccine concentration and antibody clone and concentration. To test these parameters in different combinations, we need many cells, and therefore sufficient amounts of leukocytes from hyperimmunized donors will have to be collected. Once an optimal combination is found, we will validate this flow-cytometric assay among the blood of multiple hyperimmunized participants and blood of multiple rabies-naïve donors.

Phase II:
Participants are recruited via email (sent via the respective secretariats of the departments), posters or social media. They apply for one of the three groups(group 1: unvaccinated, will receive a single vaccination during study. group 2: unvaccinated, will not be vaccinated during study. group 3: previously vaccinated, will receive a single vaccination during study) via email to ASPERA@lumc.nl, from which they will receive their patient information forms. Study visits will be scheduled at the vaccination clinic in the LUMC and will take place on day 0, 7 and 28. After acquiring informed consent from the participant, the participant will be asked to complete a short questionnaire containing questions about general health and information on their (rabies) vaccination history. Only the participants who fulfill the inclusion criteria will be asked to participate. The information on rabies vaccination history, including the number of vaccinations, antibody titers, and the corresponding time frames, will help us interpret the findings. Each visit, peripheral blood samples (53.5 ml) will be collected and processed and cells and serum will be stored for future use. The fresh and stored blood samples will be used to develop, validate and optimize the assay for flow-cytometric/ELISPOT detection of antigen-specific B-cells against rabies vaccine. The two groups that receive one rabies vaccination, will receive this vaccination at their first visit.

Recruitment of the previously immunized group will consist of reapproaching participants of the PREPARE study (NL60550.056.17). They have recently been vaccinated in the light of this previous study and are therefore reasonably comparable. If insufficient participants can be recruited from this pool, a more general approach will be used to recruit participants for this study group.

Should technological developments allow antigen-specific B-cell detection, an additional study visit might be planned after the first visit for which participants can be reapproached. This is however completely dependent on the success of antigen-specific B-cell detection.

Intervention

Phase II: single intramuscular vaccination with Rabipur vaccine.

Study burden and risks

The burden of the study is limited and related to venipuncture and vaccination with a registered rabies vaccine. Risks include mild local or mild reversible systemic reactions.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)
Elderly (65 years and older)

Inclusion criteria

Phase I
Hyperimmunized:

- 18 years old or older.
- Received at least 3 rabies vaccinations.
- Able to provide informed consent.

Control:
- 18 years old or older.
- Never received rabies vaccinations.
- Able to provide informed consent.

Phase II
Previously immunized:
- 18-35 years old
- Received at least 2 rabies vaccinations.
- Able to provide informed consent.

Control:
- 18-35 years old
- Never received rabies vaccinations.
- Able to provide informed consent.

Exclusion criteria

- History of (pre)syncope associated with medical procedures involving needles
- Received any vaccination other than rabies within three months prior to inclusion.
- Administration of plasma or blood products within three months prior to inclusion
- Bleeding disorders or use of anticoagulants
- Any current infectious disease.
- Immunocompromised (due to medication, medical condition, or other)

Additional exclusion criteria for Phase II include:
- Known or suspected severe allergy against egg protein
- Known or suspected allergy against any of the other vaccine components
- History of unusual or severe reactions to any previous vaccination
- Pregnancy or breastfeeding
- Received any kind of vaccine in the month prior to inclusion
- Plans to receive any (rabies) vaccination(s) during the study (from day 0 to day 28)

Study design

Design

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

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	15-09-2020
Enrollment:	26
Type:	Actual

Ethics review

Approved WMO

Date:	27-05-2020
Application type:	First submission
Review commission:	METC Leiden-Den Haag-Delft (Leiden) metc-ldd@lumc.nl

Approved WMO

Date:	18-12-2020
Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden) metc-ldd@lumc.nl

Approved WMO

Date:	06-02-2021
Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden) metc-ldd@lumc.nl

Approved WMO Date:	13-10-2021
Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden) metc-ldd@lumc.nl

Approved WMO Date:	19-05-2022
Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden) metc-ldd@lumc.nl

Approved WMO Date:	23-02-2023
Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden) metc-ldd@lumc.nl

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	NL71756.058.20
Other	NL8404

Study results

Date completed:	26-06-2023
Actual enrolment:	26