A study of more time-efficient and cost-effective pre-exposure rabies vaccination schedules to secure timely adequate protection prior to military deployment

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1. To reduce the time required for pre-exposure rabies vaccination of military personnel2. To reduce costs of pre-exposure rabies vaccination of military personnel 3. To obtain a non-inferior immune response to a shortened, low-dosed scheme compared…

Ethical review	Approved WMO
Status	Will not start
Health condition type	Viral infectious disorders
Study type	Observational invasive

Summary

ID

NL-OMON39883

Source
ToetsingOnline

Brief title
Rabies vaccination study

Condition

- Viral infectious disorders

Synonym
Rabies

Research involving
Human

Sponsors and support

Primary sponsor: Academisch Medisch Centrum

Source(s) of monetary or material Support: Ministerie van Defenise

Intervention

Keyword: Low-dosed, Military, Rabies, Shortened, Vaccination

Outcome measures

Primary outcome

Percentage of vaccinees with RVNA's >0.5 IU/mL.

Measurement of Virus neutralizing antibodies:

Rabies virus neutralising antibodies (RVNAbs) will be determined in all blood samples by the rapid focus fluorescent inhibition assay (RFFIT), performed in the Erasmus Medical Centre in Rotterdam, the Netherlands. The RFFIT is currently the reference method, prescribed by the WHO. Briefly, a constant dose of previously titrated, cell culture adapted, challenge virus is incubated with serial dilution of the sera to be titrated. A reference serum of known titer is included in each test. The estimation of the percentage of infected cells for each dilution of the sera allows determination of the titer of the unknown sera by comparing with the reference serum. Titers of sera are expressed as International Units per milliliter (IU/ml). Sera with titers *0.5 IU/ml, the WHO recommended protective level, are considered as positive.

Secondary outcome

Adverse events follwong intradermal vaccination

Study description

Background summary

Rabies is a zoonosis transmitted through the bite or scratch from an infected animal (mainly wild or domestic canids). Infection, if left untreated, results in progressive neurologic illness followed by death in all cases affected. Illness and death can be averted by prompt cleaning of the wound and administration of post-exposure prophylaxis (PEP).
PEP aims at achieving high levels of virus neutralizing antibodies (VNAbs), >0.5 IU/mL preferably within 24 hours after exposure. This can be achieved in two ways.
The first is by administration of the standard pre-exposure prophylaxis (PreP) schedule which consists of 3 doses of the inactivated rabies vaccine on day 0,7,21 till 28, timely before deployment. In case of exposure, two inactivated rabies vaccinations with an interval of 2 days are required with the first given within 24 hours after exposure.
The second way, when no PreP has been administered, consists of administration of human anti-rabies immunoglobulin (HRIG) within 24 hours after exposure, followed by active immunization with five inactivated rabies vaccinations.

Usually, pre-exposure vaccination against rabies is advised to military personnel deemed at risk of exposure to rabies infection during deployment (i.e. in enzootic/epizootic areas).
Even though it is known that vaccination series induce long term immunologic memory, several problems for implementation of rabies prevention in the military setting exist. First, costs of the standard three-shot pre-exposure series (¤135-150) may prohibit implementation of pre-exposure vaccination in all situations where it is advised. Second, the pre-exposure vaccination using the standard 3-injection schedule on days 0, 7 and 28 often results in incomplete vaccination series prior to deployment, because vaccination is initiated too late or can not be completed due to competition with other pre-deployment preparation.
PEP with the use of HRIG and the 5-dose vaccination scheme, though effective, is problematic in three ways. First, maintenance of a cold chain is required, which can not always be achieved in operational settings. Also, the storage life of HRIG is around one year, which is limited and leads to increased cost of maintaining adequate supplies. Third, the 5-dose post-exposure vaccination scheme is intensive and lengthy.
The problems discussed above call for exploration of alternatives in the form of reduce-dosed, abbreviated pre-exposure vaccination schemes. Besides the logistic benefit of shortened schedules, the schemes we aim to study are also estimated to be less expensive than the above PEP scheme most often in use today. See appendix.

Recent studies have shown that four 0.1 ml intradermal vaccinations given simultaneously as a booster on day 0 elicit higher responses compared to the standard two 1 ml intramuscular boosters given on days 0 and 3 (Tantawichien

1999, Khawplod 2002). This method has recently been approved by WHO in the context of post-exposure boosting. We propose the use utilise this approach to boost responses in a low-cost pre-exposure vaccination schedule.

Study objective

1. To reduce the time required for pre-exposure rabies vaccination of military personnel
2. To reduce costs of pre-exposure rabies vaccination of military personnel
3. To obtain a non-inferior immune response to a shortened, low-dosed scheme compared to the standard scheme

Study design

Volunteers shall be randomly assigned to one of the study arms as depicted in the two tables below:

Group 1: (control group) 2 x 0.1 ID vaccination on days 0, 7, 28 and a booster at 1 year
Group 2: 2 x 0.1 cc ID vaccination on days 0, 7, 28 and a booster at 2 years
Group 3: 2 x 0.1 cc ID vaccination on days 0, 7 and a booster at 1 year
Group 4: 2 x 0.1 cc ID vaccination on days 0, 7 and a booster at 2 years
Group 5: 2 x 0.1 cc ID vaccination on days 0 and a booster at 1 year
Group 6: 2 x 0.1 cc ID vaccination on days 0 and a booster at 2 years

Study burden and risks

Previous studies have shown that local adverse events occur more often following intradermal vaccination compared to intramuscular vaccination. However, these effects are generally mild and self-limiting.
Potential risks of reduced schedules are that insufficient antibody titres are be reached prior to booster vaccination at 12 or 24 months and that participants may thus not be protected if deployed/travelling during the study period. Risks for participants will be precluded by:
1. Excluding personnel likely to be deployed to a rabies endemic area within the study period;
2. Providing full pre-exposure vaccination to participants for whom pre-exposure vaccination is indicated, for example due to intended travel to a rabies endemic area, if they have insufficient antibody responses at that moment;
3. All participants with inadequate antibody responses at the end of the study will be fully vaccinated.

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

> 18 years of age

Exclusion criteria

< 18 years of age;patential deployment to rabies endemic area

Study design

Design

Study type:	Observational invasive
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Open (masking not used)
Control:	Active
Primary purpose:	Prevention

Recruitment

NL

Recruitment status:	Will not start
Enrollment:	72
Type:	Anticipated

Medical products/devices used

Product type:	Medicine
Brand name:	Verorab Rabies vaccine

Ethics review

Approved WMO Date:	20-03-2013
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	14-02-2014
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
EudraCT	EUCTR2012-003166-40-NL
CCMO	NL41384.018.13