Safety and protective efficacy of BCG vaccination against controlled human malaria infection

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The primary objective is to determine the safety and tolerability BCG vaccination followed by controlled human malaria infection; and to determine the protective efficacy BCG vaccination against a controlled human malaria infection.

Ethical review	Approved WMO
Status	Completed
Health condition type	Protozoal infectious disorders
Study type	Interventional

Summary

ID

NL-OMON43394

Source
ToetsingOnline

Brief title
BCG-EHMI

Condition

- Protozoal infectious disorders

Synonym
Plasmodium falciparum; malaria

Research involving
Human

Sponsors and support

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

Intervention

Keyword: BCG vaccine, innate immunity, malaria, Plasmodium falciparum

Outcome measures

Primary outcome

Frequency and magnitude of adverse events in the study groups

Time to blood stage parasitemia detectable by qPCR after malaria challenge infection

Secondary outcome

Peripheral blood mononuclear cell (PBMC) and/or monocyte cytokine production after restimulation ex vivo

Peripheral blood plasma cytokine levels including IFN-γ, TNF-α, IL-6 and IL-1β

Phenotype and distribution of circulating immune cells after CHMI, including B cells, T cells, antigen presenting cells, NK cells and granulocytes

Study description

Background summary

The Bacillus Calmette-Guérin (BCG) vaccine, a live attenuated Mycobacterium bovis vaccine, has been used to prevent tuberculosis for almost a century, and it is still the most used vaccine in the world. There is also circumstantial and indirect evidence that BCG vaccination can protect against malaria. We hypothesize that BCG vaccination can offer protection against malaria in the Controlled Human Malaria Infection (CHMI) model.

Study objective

The primary objective is to determine the safety and tolerability BCG vaccination followed by controlled human malaria infection; and to determine the protective efficacy BCG vaccination against a controlled human malaria infection.

Study design

A total of 20 volunteers will participate in this randomized, single-blind clinical trial. Volunteers will be randomized to receive either BCG vaccination (BCG Vaccine, BB-NCIPD, Ltd, Sofia, Bulgaria) (group 1, n=10) or no treatment (group 2, n=10). Five weeks after vaccination of group 1 volunteers, all volunteers will undergo a CHMI administered by the bites of five P. falciparum infected Anopheles mosquitoes. All volunteers will attend the clinic for out-patient follow-up once daily on days 6-21 after the malaria challenge. These volunteers will be treated with a curative regimen of Malarone®, either at the time of detection of blood stage parasitemia or 21 days post-challenge. Throughout the study, blood will be collected from volunteers in both groups to analyse changes in innate and adaptive cellular responses.

Intervention

BCG vaccination (BCG Vaccine, BB-NCIPD, Ltd, Sofia, Bulgaria)

Study burden and risks

The study is associated with a single short period of intense clinical monitoring with daily site visits and blood examinations. As it is unpredictable when subjects will develop a positive qPCR, it is impossible to state the exact number of site visits and blood examinations. However, the maximum number of site visits and blood examinations for these volunteers will be 29. The maximum amount of collected blood over the period of ten weeks will be 500mL. Additionally, periodical physical examinations will be performed and the subject is asked to complete a diary.

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

1. Subject is aged >=18 and <=35 years and in good health.
2. Subject has adequate understanding of the procedures of the study and agrees to abide strictly thereby.
3. Subject is able to communicate well with the investigator and is available to attend all study visits.
4. The subject will remain within the Netherlands during the challenge period, not travel to a malaria-endemic area during the study period, and is reachable (2417) by mobile telephone throughout the entire study period.
5. Subject agrees to inform his/her general practitioner about participation in the study and to sign a request to release by the General Practitioner (GP), and medical specialist when necessary, any relevant medical information concerning possible contra-indications for participation in the study.
6. The subject agrees to refrain from blood donation to Sanquin or for other purposes throughout the study period and for a defined period thereafter according to current Sanquin guidelines.
7. For female subjects: subject agrees to use adequate contraception and not to breastfeed for the duration of study.
8. Subject agrees to refrain from intensive physical exercise (disproportionate to the subjects usual daily activity or exercise routine) during the malaria challenge period.
9. Subject has signed informed consent.

Exclusion criteria

1.Any history, or evidence at screening, of clinically significant symptoms, physical signs or abnormal laboratory values suggestive of systemic conditions, such as cardiovascular, pulmonary, renal, hepatic, neurological, dermatological, endocrine, malignant, haematological, infectious, immunodeficient, psychiatric and other disorders, which could

compromise the health of the volunteer during the study or interfere with the interpretation of the study results. These include, but are not limited to, any of the following.
1.1 Body weight <50 kg or Body Mass lndex (BM l) <18 or >30 kg/m2 at screening.
1.2 A heightened risk of cardiovascular disease, as determined by: an estimated ten year risk of fatal cardiovascular disease of >5% at screening, as determined by the Systematic Coronary Risk Evaluation (SCORE); history, or evidence at screening, of clinically significant arrhythmia's, prolonged QT-interval or other clinically relevant ECG abnormalities; or a positive family history of cardiac events in 1st or 2nd degree relatives <50 years old.
1.3 A medical history of functional asplenia, sickle cell traildisease, thalassaemia trait/disease or G6PD deficiency.
1.4 History of epilepsy in the period of five years prior to study onset, even if no longer on medication.
1.5 Screening tests positive for Human lmmunodeficiency Virus (HlV), or active Hepatitis B Virus (HBS) or Hepatitis C Virus (HCV).
1.6 Chronic use of i) immunosuppressive drugs, ii) antibiotics, iii) or other immune modifuing drugs within three months prior to study onset (inhaled and topical corticosteroids and oral anti-histamines exempted) or expected use of such during the study period.
1.7 Use of Non-steroidal Anti-lnflammatory Drugs (NSAIDs) in the four weeks prior to study start or expected use of NSAIDS during the study period.
1.8 History of malignancy of any organ system (other than localized basal cell carcinoma of the skin), treated or untreated, within the past 5 years.
1.9 Any history of treatment for severe psychiatric disease by a psychiatrist in the past year.
1.10 History of drug or alcohol abuse interfering with normal social function in the period of one year prior to study onset, positive urine toxicology test for cocaine or amphetamines at screening or prior to infection, or positive urine toxicology test for cannabis at inclusion.
2. For female subjects: positive urine pregnancy test at screening or at inclusion.
3. Any history of malaria, positive serology for P. falciparum, or previous participation in any malaria (vaccine) study.
4. Known hypersensitivity to or contra-indications (including co-medication) for use of chloroquine, Malarone or artemether-lumefantrine, or history of severe (allergic) reactions to mosquito bites.
5. Receipt of any vaccinations in the 3 months prior to the start of the study or plans to receive any other vaccinations during the study period or up to 90 days thereafter.
6. Participation in any other clinical study in the 30 days prior to the start of the study or during the study period.
7. Being an employee or student of the department of Medical Microbiology of the Radboudumc or the department of lnternal Medicine.
8. Previous BCG-vaccination; history of tuberculosis or positive Mantoux test; or positive whole blood IFN-γ response to restimulation with M. tuberculosis at screening.
9. Any other condition or situation that would, in the opinion of the investigator, place the subject at an unacceptable risk of injury or render the subject unable to meet the requirements of the protocol.

Study design

Design

Study phase:	2
Study type:	Interventional
Intervention model:	Other
Allocation:	Randomized controlled trial
Masking:	Single blinded (masking used)

Primary purpose: Prevention

Recruitment

NL

Recruitment status:	Completed
Start date (anticipated):	04-08-2016
Enrollment:	20
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	BCG Vaccine

Ethics review

Approved WMO Date:	13-01-2016
Application type:	First submission
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	29-03-2016
Application type:	First submission
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	02-06-2016

Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	07-06-2016
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	23-08-2016
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	07-09-2016
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)

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	EUCTR2015-005735-40-NL
ClinicalTrials.gov	NCT02692963
CCMO	NL56222.091.15

Study results

Date completed:	20-02-2017
Results posted:	27-02-2020

First publication
20-02-2019