The effects of BCG-vaccination on the immune response induced by influenza-vaccination in healthy volunteers. A pilot proof-of-principle study.

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Primary objective: The primary objective of the study is to determine the effects of BCG-vaccination on the immune response induced by subsequent influenza vaccination in healthy volunteers. This will be determined by measuring the Th1/Th2 response...

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Immunodeficiency syndromes
Study type	Interventional

Summary

ID

NL-OMON40818

Source
ToetsingOnline

Brief title
Effects of BCG on influenza-induced immune response

Condition

- Immunodeficiency syndromes
- Viral infectious disorders

Synonym
Influenza infection, the ""flu"

Research involving
Human

Sponsors and support

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

Intervention

Keyword: BCG, immunoscenescence, Influenza, Trained immunity

Outcome measures

Primary outcome

The primary study endpoint is the difference in influenza antibody titres 2 and 4 weeks (±2 days) after influenza vaccination between BCG-vaccinated subjects and subjects in the control group.

Secondary outcome

- Proportion of participants in each group who achieved seroprotection (defined by antibody titre >=1:40), 1, 2 and 4 weeks (±2 days) after influenza vaccination.

- Proportion of participants in each group who achieved seroconversion (defined by a >=4-fold rise in antibody titre), 1, 2 and 4 weeks ((±2 days) after influenza vaccination.

- IFN-gamma/IL-10 production (reflecting the Th1/Th2 immune response) of leukocytes ex vivo stimulated with inactivated influenza virus (0.1ug HA/ml), before BCG vaccination, before influenza vaccination, and 2 and 4 weeks after influenza vaccination.

- Production of Type 1 IFNs, IL-17 and IL-22 by leukocytes ex vivo stimulated with inactivated influenza virus (0.1ug HA/ml), before BCG vaccination, before influenza vaccination, and 2 and 4 weeks after influenza vaccination.

- Production of other inflammatory mediators (including TNFα, IL-1β, IFN-gamma, IL-10, IL-17, IL-22) by leukocytes ex vivo stimulated with m. tuberculosis (1ug/ml end protein concentration), s. aureus (1x10e6 microorganisms/ml), C. albicans (1x10e6 microorgansims/ml strain UC820), and inactivated influenza (0.1ug HA/ml) , before BCG vaccination, before influenza vaccination, and 2 and 4 weeks after influenza vaccination.
- The phenotype of circulating leukocytes (expression of surface markers, including, but not limited to CD45, CD3, CD4, CD8, CD56, CD14, CD11b, TLR4, TLR2), before BCG vaccination, before influenza vaccination, and 2 and 4 weeks after influenza vaccination.
- Inflammatory transcriptional pathways (by use of qPCR/microarrays) , before BCG vaccination, before influenza vaccination, and 2 and 4 weeks after influenza vaccination.
- Epigenetic changes in leukocytes, including H3K4 trimethylation, before BCG vaccination, before influenza vaccination, and 4 weeks after influenza vaccination.
- Subanalyses will include differences in all these parameters between young and older subjects.

Study description

Background summary

Influenza virus infection leads to millions of cases of severe illnesses worldwide and up to an estimated 500.000 deaths annually. The potential for the sudden emergence of pandemic influenza strains represents an incessant threat on even a larger scale. Seasonal influenza vaccination is the backbone of

influenza management. However, antibodies generated by vaccination, most often do not effectively neutralize emergent strains due to the high mutation rate of the influenza viral genome. In addition, although vaccination is effective in up to 85% of healthy adults, only 40-60% of the elderly are able to mount an protective antibody response due to an age-related decline in immune function (so-called immunoscenescence). As a result, the protective effects of influenza vaccination are limited, and strategies to improve host immune defenses against influenza virus infection per se, and following influenza vaccination, are highly warranted.
It is suggested that prior vaccination with Bacille Calmette-Guérin (BCG) could enhance resistance to other infectious diseases in addition to protection to tuberculosis (TBC) and, in mice, protection of prior BCG-vaccination against influenza infection was demonstrated long ago. However, only recently substantial evidence for these nonspecific beneficial effects of BCG-vaccination in humans has been provided by several randomized clinical trials. Considering these potentiating effects of BCG-vaccination, it could be a viable strategy to improve efficacy of influenza vaccination, and/or enhance immune defenses against influenza virus infection per se. If so, this would have an enormous impact on clinical practice.

Study objective

Primary objective:
The primary objective of the study is to determine the effects of BCG-vaccination on the immune response induced by subsequent influenza vaccination in healthy volunteers. This will be determined by measuring the Th1/Th2 response, and antibody titers induced by influenza vaccination in seronegative healthy volunteers who are, prior to influenza vaccination, vaccinated with either BCG or placebo in a double-blind randomized manner.

There are 6 secondary objectives:

1. To determine the effects of BCG-vaccination on ex vivo responsiveness of leukocytes to inactivated influenza virus before and after influenza vaccination.

2. To determine the effects of BCG-vaccination on ex vivo responsiveness of leukocytes to various not related inflammatory stimuli following influenza vaccination.

3. To determine the effects of BCG-vaccination on the phenotype of circulating leukocytes following influenza vaccination (e.g. expression pattern of cell-surface receptors by use of flow cytometry).

4. To determine the effects of BCG-vaccination on inflammatory transcriptional pathways (determined by qPCR/microarrays) following influenza vaccination.

5. To determine the effects of BCG-vaccination on epigenetic changes, including H3K4 trimethylation, in circulating immune cells following influenza vaccination.

6. To determine whether age influences the immune modulating effects of BCG-vaccination.

Study design

A randomized double-blind placebo-controlled pilot study in healthy human volunteers. In this pilot study, we will enrol 40 healthy young (>=18 and <=35 yrs) and 32 healthy older (>=65 yrs) male volunteers. Subjects will be randomized to receive either BCG-vaccination (n=20 young volunteers, n=16 old volunteers) or placebo (Saline, n=20 young volunteers, n=16 old volunteers) on day 1. Fourteen days later, all subjects will receive influenza vaccination. Blood will be withdrawn on 6 occasions to perform analyses.

Intervention

Placebo/BCG-vaccination followed by influenza vaccination.

Study burden and risks

The risks for participation in this study are low. BCG- and influenza vaccination are worldwide administered to millions of people, and are very well tolerated. In total, a maximum of 280 ml blood will be obtained over a period of 6 weeks, which is not expected to result in side effects. Therefore, we feel that the remaining risks are acceptable and do not outweigh the scientific and medical relevance of this study. Subjects will visit the research unit of the Intensive Care 6 times in total.

Contacts

Public
Universitair Medisch Centrum Sint Radboud

Geert Grooteplein-Zuid 10
Nijmegen 6525 GA
NL
Scientific
Universitair Medisch Centrum Sint Radboud

Geert Grooteplein-Zuid 10
Nijmegen 6525 GA

NL

Trial sites

Listed location countries

Netherlands

Eligibility criteria

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

Inclusion criteria

- Age >=18 and <=35 yrs or >=65 yrs
- Male
- Healthy

Exclusion criteria

- Prior exposure to *Influvac* influenza virus strains , measured by antibody titres. Previous exposure is defined by antibody titres >=1:40.
- History of influenza vaccination within the year prior to study entry
- History of BCG vaccination within 5 years prior to study entry
- History of Mantoux testing within the year prior to study entry
- Vaccination other than BCG or influenza, within 3 months prior to study or within study period
- Medical history of any disease associated with immune deficiency
- Clinically significant acute illness, including infections, within 4 weeks before vaccination
- Participation in a drug trial or donation of blood 3 months prior to study entry
- Use of recreational drugs within 21 days prior to experiment day
- Recent hospital admission or surgery with general anaesthesia (<3 months)
- Known chronic kidney or liver disease
- Latent or active tuberculosis infection

Study design

Design

Study phase:	2
Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Double blinded (masking used)
Control:	Placebo
Primary purpose:	Prevention

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	28-05-2014
Enrollment:	72
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Bacille Calmette Guérin (BCG)
Product type:	Medicine
Brand name:	Inactivated trivalent influenza vaccin (2013-2014)

Ethics review

Approved WMO Date:	09-04-2014
Application type:	First submission
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	30-05-2014
Application type:	First submission
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)

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	EUCTR2014-000966-23-NL
CCMO	NL48457.091.14
Other	volgt