# The effects of preceding human endotoxemia on the Fluenz-induced immune response, a explorative study

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Our primary objective is to investigate the effects of endotoxin-induced systemic inflammation and subsequent development of endotoxin tolerance on the inflammatory response following Fluenz® administration in vivo. To evaluate whether these effects...

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| **Ethical review** | Approved WMO |
| **Status** | Pending |
| **Health condition type** | Immune disorders NEC |
| **Study type** | Interventional |

## Summary

### ID

NL-OMON42371

**Source**
ToetsingOnline

**Brief title**
LPS-Fluenz

### Condition

- Immune disorders NEC

**Synonym**
Immunoparalysis / tolerance

**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:** endotoxemia, Fluenz, immune response

## Outcome measures

### Primary outcome

The main study parameter is to investigate the local inflammatory response, measured by IP-10 in nasal wash.

### Secondary outcome

Secondary endpoints include other parameters indicative of the local inflammatory response, including antibodies, immune cells, cytokines and local symptoms. Also, systemic inflammatory effects will be assessed, including circulating antibodies, immune cells and cytokines, lower respiratory tract and systemic symptoms and peak expiratory flow. Furthermore, viral load of influenza will be measured in nasal wash. Finally, changes in the mucosal microbiome will be assessed.

# Study description

### Background summary

A large proportion of ICU patients suffer from a systemic bacterial infection, called *sepsis*. This is often complicated by the reactivation of multiple viruses and secondary respiratory bacterial infections. Recent work has shown that a immunosuppressive state called *sepsis-induced immunoparalysis* accounts for this increased vulnerability. This condition renders the host unable to clear infections and/or increased vulnerability towards secondary infections. Influenza is one of the respiratory viruses that accounts for secondary respiratory infections in ICU patients. The Influenza virus is known for its severe course of infection and systemic effects. Influenza causes >250.000 deaths annually in the Western World with the highest attack rates among children and young adults.
Previous research in animals and humans has focused on the interaction of

influenza followed by a secondary bacterial agent, showing that influenza promotes susceptibility for secondary bacterial infections, and thereby worsening the prognosis.
However, the interaction of bacterial sepsis followed by influenza has only sparsely been investigated. However, because of the high mortality rates, it is of main importance to understand this mechanism for the development of putative preventive and therapeutic interventions in ICU patients.

The live, attenuated, trivalent influenza vaccine (LAIV) for intranasal administration *Fluenz® (Medimmune Vaccines)* is registered in the European Union for vaccination against influenza. It contains material from three different influenza strains recommended by national and international public health agencies as most likely to be protective against seasonal influenza in any given year. While inactivated influenza vaccines induce protective levels of serum antibodies to influenza hemaglutinine (HA) and neuraminidase (NA) surface proteins, these are strain specific and offer little protection against heterosubtypic influenza viruses. In contrast, LAIVs like Fluenz®, induce T-cell responses in addition to antibody responses against HA and NA surface proteins and vaccination protects against heterosubtypic influenza strains as well.

The human endotoxemia model consists of administration of lipopolysaccharide (LPS, a cell-wall compound of gram-negative bacteria) to healthy volunteers. It therefore represents a model of systemic inflammation caused by bacteria, which mimics some of the clinical and pathobiological hallmarks of sepsis. Among other things, we have shown that a second exposure to LPS within one or two weeks after the first results in a profoundly suppressed state of the immune system called endotoxin tolerance. This phenomenon, albeit mild, resembles sepsis-induced immunoparalysis.

In this study, we want to investigate the effects of preceding endotoxemia on the Fluenz®-induced inflammatory response. In this respect, human endotoxemia will serve as a model of Gram-negative sepsis and Fluenz® vaccination is used as a surrogate for an actual influenza infection.
As such, combining the experimental endotoxemia model with the administration of Fluenz® uniquely enables us to investigate crosstalk between bacterial and viral infections in humans in vivo. We hypothesize that the LPS-induced systemic endotoxin tolerance results in an altered inflammatory response, leading to an increased or decreased viral replication and inflammatory response upon vaccination with Fluenz®. This study will provide us with unique in vivo data on mechanistic interactions of systemic LPS followed by mucosal Fluenz®, which may not only be applicable to influenza infection, but also to other (respiratory) viruses commonly encountered in septic patients. As such, it can provide clues regarding the increased vulnerability towards viral infections in septic patients and open up new avenues to investigate therapeutic measures to prevent this. Furthermore, it provides important implications regarding the safety and applicability of the vaccine in

(post)septic or immunocompromised patients.

## Study objective

Our primary objective is to investigate the effects of endotoxin-induced systemic inflammation and subsequent development of endotoxin tolerance on the inflammatory response following Fluenz® administration in vivo. To evaluate whether these effects involve local and/or systemic inflammation, local inflammatory parameters are measured in nasal wash. Systemic inflammatory parameters are measured in blood. Furthermore, we want to evaluate whether preceding endotoxemia influences the viral load of influenza in nasal wash. Finally, changes in the mucosal microbiome will be assessed. For secondary objectives see page 14 of the C1 protocol.

## Study design

A parallel, randomized, open-label trial in which 10 subjects will receive a intravenous bolus of placebo (NaCl)and 10 subjects LPS (2 ng/kg E.coli lipopolysaccharide). After one week time, all subjects will be vaccinated with Fluenz® (spraying 0.1 mL into each nostril in supine position). Nasal wash, blood samples, temperature and symptom scores will be obtained at various time-points, and peak expiratory flow will be assessed.

## Intervention

Healthy volunteers who meet all inclusion criteria and none of the exclusion criteria that have given informed consent to participate in the study will be randomized to become either administered with an intravenous bolus of endotoxin (LPS derived from E coli O:113, 2 ng/kg) or placebo. After one week all subjects will be vaccinated with Fluenz® (spraying 0.1 mL into each nostril in supine position). Nasal wash, blood samples and symptom scores will be obtained at various time-points, and peak expiratory flow will be assessed.

## Study burden and risks

A medical interview and physical examination are part of this study. Subjects have to visit the hospital on a total of 9 occasions; during human endotoxemia or placebo one whole day, followed by 8 visits of about 10 minutes. During endotoxemia, volunteers will be monitored on the research unit of our medium care and receive an arterial line to facilitate blood pressure monitoring and blood sampling. The arterial line will be placed under local anaesthesia using 2% lidocaïne. Furthermore, a venous cannula will be placed for the administration of fluids and LPS.
The administration of LPS induces flu-like symptoms for approximately 4-6 hrs. This model of systemic inflammation has been applied for many years in various research centers in the world. LPS administration is considered safe and no

long-term effects have ever been documented.
Subjects have to keep a symptoms diary (scoring card) that they fill in at home. In total, maximally 400 mL of blood will be drawn (on 9 occasions via venapuncture). This is not associated with side effects (500 mL is also drawn at the blood bank without any side effects). Furthermore, 6 nasal washes will be performed, which can lead to slight irritation of the nasal mucosa but is not associated with risks. Fluenz® is registered for use within the European Union and has been administered to thousands of subjects. The most common solicited adverse reactions were mild and included: runny nose or nasal congestion, headache and sore throat. Large randomized trials have been performed to test the safety of Fluenz® and no serious adverse reactions have occurred

## 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

Age >=18 and <=35 years of age
Male
Healthy

## Exclusion criteria

-Pre-existent lung disease, including asthma
-A history of allergic rhinitis
-Use of any medication
-Use of alcohol > 5/day or >20/wk
-Use of any drugs
-Current smoker or more than 5 pack-year history
-Frequently have nosebleeds
-Recent nasal or otologic surgery
-Febrile illness or a common cold within four weeks before the LPS challenge
-Currently participating in another clinical trial or donation of blood 3 months prior to the LPS challenge.
-Previous spontaneous vagal collapse.
-History, signs or symptoms of cardiovascular disease.
-(Family) history of myocardial infarction or stroke under the age of 65 years.
-Cardiac conduction abnormalities on the ECG consisting of a 2nd degree atrioventricular block or a
complex bundle branch block.
-Hypertension (defined as RR systolic > 160 or RR diastolic > 90).
-Hypotension (defined as RR systolic < 100 or RR diastolic < 50).
-Renal impairment (defined as plasma creatinin >120 µmol/l).
-Liver enzyme abnormalities or positive hepatitis serology.
-Positive HIV serology or medical history of any other obvious disease associated with immune deficiency.
-History of allergic reaction to Fluenz®, eggs / gelatin / gentamicin
-History of Guillain-Barré Syndrome

# Study design

## Design

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| Study type: | Interventional |
| Intervention model: | Parallel |

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| Allocation: | Randomized controlled trial |
| Masking: | Open (masking not used) |
| Control: | Active |
| Primary purpose: | Diagnostic |

### Recruitment

NL

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|---|---|
| Recruitment status: | Pending |
| Start date (anticipated): | 01-01-2016 |
| Enrollment: | 0 |
| Type: | Anticipated |

### Medical products/devices used

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| Product type: | Medicine |
| Brand name: | live attenuated nasal influenza vaccin |

## Ethics review

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| Approved WMO Date: | 04-01-2016 |
| Application type: | First submission |
| Review commission: | CMO regio Arnhem-Nijmegen (Nijmegen) |
| Approved WMO Date: | 06-01-2016 |
| 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 | EUCTR 2015-004023-3-NL |
| CCMO | NL54870.091.15 |