

# Evaluation of the capacity of a drinkable vaccine against enterotoxicigenic *E. coli* diarrhoea to elicit immunological memory

<b>Submission date</b>	<b>Recruitment status</b>	<input type="checkbox"/> Prospectively registered
25/11/2013	No longer recruiting	<input type="checkbox"/> Protocol
<b>Registration date</b>	<b>Overall study status</b>	<input type="checkbox"/> Statistical analysis plan
16/12/2013	Completed	<input checked="" type="checkbox"/> Results
<b>Last Edited</b>	<b>Condition category</b>	<input type="checkbox"/> Individual participant data
07/10/2021	Infections and Infestations	

## Plain English summary of protocol

### Background and study aims

Infection with enterotoxicigenic *E. coli* bacteria (ETEC) is a common cause of diarrhoea among children in developing countries and in travellers to such countries. However, there is no vaccine available against ETEC disease. Our research team has developed a drinkable vaccine against ETEC infection which consists of killed bacteria and a toxin antigen (a protein from the bacteria). A first generation of our ETEC vaccine has been tested in several thousand people around the world. This ETEC vaccine was shown to provide protection against severe ETEC diarrhoea in adult travellers but did not protect young children in a developing country. We have now developed an improved vaccine against ETEC diarrhoea which was recently shown to be well tolerated and to produce robust intestinal immune responses when tested in 95 healthy Swedish adults. We will now assess whether the vaccinations in the previous study have given rise to immunological memory responses, i.e. responses that last for an extended time after immunization.

### Who can participate?

Adults aged between 18 and 47 years in good health who have been vaccinated with the new ETEC vaccine in the previous study, or individuals who have never been immunized with ETEC or cholera vaccines.

### What does the study involve?

All volunteers will be given one dose of the ETEC vaccine. The vaccine will be given as a drink. Participants will visit the vaccination unit four times over a period of 2-7 weeks for physical examination (two times) and to provide blood samples (four times). Participants will be asked to keep a diary in which they should report how they are feeling and whether they are taking any medicines throughout the study.

### What are the possible benefits and risks of participating?

Participants will receive a free medical check-up, and immunized participants may develop some protection against ETEC and cholera infection. Participation will promote the development of a new vaccine, which will hopefully diminish the risk for both children and adults of developing

ETEC diarrhoea in the future. The vaccine has been well tolerated when given in two oral doses in the previous study and similar ETEC vaccines have also been shown to be safe when given in three doses. Side effects are rare in adults, but if there are any they would consist of mild and transient diarrhoea, nausea, occasional vomiting, bloating and abdominal pain.

Where is the study run from?

Sahlgrenska University Hospital, Gothenburg, Sweden.

When is the study starting and how long is it expected to run for?

The study is planned to start in December 2013 and is due to end in June 2014.

Who is funding the study?

The Swedish Research Council and the Sahlgrenska University Hospital, Gothenburg, Sweden.

Who is the main contact?

Prof. Ann-Mari Svennerholm,

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## Contact information

**Type(s)**

Scientific

**Contact name**

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## Additional identifiers

**Clinical Trials Information System (CTIS)**

2013-003693-28

**Protocol serial number**

OEV-121A

## Study information

**Scientific Title**

A phase I study to evaluate the capacity of an oral inactivated tetravalent ETEC vaccine alone and in combination with dMLT adjuvant to induce immunological memory to toxin and colonization factor antigens in the vaccine

## **Study objectives**

We have recently developed a new oral inactivated tetravalent ETEC vaccine (TEV) which contains four different inactivated *E. coli* strains expressing the most prevalent ETEC colonization factors (CFs), i.e. CFA/I, CS3, CS5 and CS6, plus a LTB/CTB hybrid protein (LCTBA). This vaccine was recently shown to be safe and highly immunogenic when tested alone or together with two different dosages, i.e. 10 µg and 25 µg, respectively, of the mucosal adjuvant dmLT in adult Swedish volunteers (Study OEV-121, ISRCTN91363076). The aim of the present study is to evaluate if the TEV given alone or together with the lower dose of dmLT adjuvant in the OEV-121 trial has induced immunological memory.

### **Primary study hypothesis:**

Orally administered TEV, the non-adjuvanted and/or adjuvanted vaccine formulations, has induced mucosal memory responses to LTB and CFs that may be detected by accelerated, higher and/or more frequent circulating antibody secreting cell (antibodies in lymphocyte supernatants; ALS) responses to a single booster dose of TEV in previously vaccinated subjects than to a single dose of TEV in naive volunteers.

### **Secondary study hypotheses:**

1. The late booster dose and the single oral dose of TEV given to non-immunized subjects will be safe and not induce any serious adverse events or vaccine-related severe adverse events.
2. Orally administered TEV, the non-adjuvanted and/or adjuvanted vaccine formulations, has induced systemic memory responses that may be detected after immunization with a single dose of TEV given 1-2 years after the primary two-dose vaccinations.
3. The single late booster dose will induce antibody responses with higher avidity than the responses induced by the primary first or second vaccinations with TEV.
4. The primary vaccinations with TEV alone or together with dmLT have induced vaccine-specific memory B cells in the circulation that may be detected after 1-2 years.
5. Primary immunization with the dmLT adjuvanted vaccine has induced stronger immunological memory responses than the non-adjuvanted vaccine.

## **Ethics approval required**

Old ethics approval format

## **Ethics approval(s)**

Independent Ethics Committee in the Gothenburg region in Sweden, 07/11/2013 and 20/11/2013, ref no: 714-13

## **Study design**

Three-armed open-label non-randomised single-center phase I study

## **Primary study design**

Interventional

## **Study type(s)**

Treatment

## **Health condition(s) or problem(s) studied**

Enterotoxigenic *E. coli* (ETEC) diarrhoea

## **Interventions**

One oral dose of TEV will be given to healthy adult Swedes previously vaccinated with TEV ± dmLT adjuvant (10 µg) or age-matched non-vaccinated subjects. The vaccine consists of approximately 8x10e10 formalin-inactivated *E. coli* bacteria that over-express the colonization factors CFA/I, CS3, CS5 and CS6 and are combined with 1 mg LCTBA hybrid protein. The vaccine will be given orally in buffer.

The following three groups of totally 45-60 subjects will be immunized:

First group: previously non-vaccinated subjects (n = 15-20)

Second group: subjects previously given 2 doses of TEV alone (n = 15-20)

Third group: subjects previously given 2 doses of TEV + 10 ug dmLT (n = 15-20)

The follow up will be 7-8 days from immunization.

### **Intervention Type**

Drug

### **Phase**

Phase I

### **Drug/device/biological/vaccine name(s)**

Inactivated tetravalent ETEC vaccine

### **Primary outcome(s)**

To determine if primary vaccination with an inactivated tetravalent ETEC vaccine (TEV), given in two oral doses two weeks apart ± dmLT adjuvant to adult volunteers, has induced immunological memory responses against toxin (LTB) and colonization factor (CF) vaccine antigens.

Memory will be assessed as accelerated, higher and/or more frequent intestinally derived immune responses (antibodies in lymphocyte supernatants; ALS) to a single oral booster dose of TEV given to primed subjects vaccinated 1-2 years before than to a single dose of TEV given to naïve subjects.

### **Key secondary outcome(s)**

1. To evaluate the safety of a single booster dose of TEV given to subjects previously vaccinated with a primary 2-dose series of TEV alone or TEV + dmLT and to further evaluate the safety of a single dose of TEV given to naive subjects.
2. To evaluate if TEV previously given in two oral doses ± dmLT has induced systemic immunological memory as measured by accelerated and/or higher and/or more frequent serum IgA and /or IgG antibody responses against LTB to a single oral dose of TEV given after 1-2 years than to a single dose of TEV given to naive volunteers.
3. To evaluate if the avidity of the antibody responses induced by the late booster immunization with TEV is higher than the avidity of the responses induced by the first or the second primary vaccinations or after a single dose given to naive subjects.
4. To evaluate if primary vaccinations with TEV alone and/or TEV + dmLT have induced vaccine-specific memory B-cell responses that are detectable in the circulation (using polyclonal B-cell stimulation methods); this includes evaluating if there is a relationship between circulating memory B-cell responses prior to vaccination and memory antibody responses to a single booster dose determined by ALS analyses.
5. To evaluate if primary vaccination with TEV + dmLT adjuvant has induced accelerated, higher and/or more frequent immunological memory responses than priming with TEV.

Gastrointestinal and systemic adverse events will be assessed post-vaccination through day 7 using physical examination, vital signs and clinical laboratory tests, diary cards and interviews.

#### **Completion date**

30/06/2014

## **Eligibility**

#### **Key inclusion criteria**

1. Male or female aged 18-47 years
2. Healthy constitution as established by medical history, medical examination and clinical chemistry and haematology testing
3. Willing and able to communicate with the investigators/physicians and understand the requirements of the study
4. Give written informed consent to participate
5. Sexually active females should, unless being menopausal, agree to use reliable contraception during the study as assessed by the investigator/physician, and should have a negative urine pregnancy test at screening and also negative urine pregnancy tests before vaccination.
6. For recruitment to group A: has never received any ETEC vaccine
- For recruitment to group B: has received two doses of TEV in the OEV-121 study
- For recruitment to group C: has received two doses of TEV + 10 µg dMLT in the OEV-121 study

#### **Participant type(s)**

Patient

#### **Healthy volunteers allowed**

No

#### **Age group**

Adult

#### **Lower age limit**

18 years

#### **Upper age limit**

47 years

#### **Sex**

All

#### **Key exclusion criteria**

1. An acute or chronic medical condition that, in the opinion of the investigator/physician, would render ingestion of the investigational products unsafe or would interfere with the evaluation of responses. This includes, but is not limited to, gastrointestinal diseases and autoimmune diseases.
2. Gastroenteritis within two weeks prior to vaccination
3. Antibiotic therapy within six weeks prior to vaccination
4. Known hepatitis A, B, C and/or HIV infection
5. Concomitant intake of immune-modulating drugs during the study period or less than three months prior to the first immunization

6. Psychiatric symptoms and treatments during the last year deemed by the investigator/physician to be relevant for participation in the OEV-121A study.
7. Intends to receive any other vaccine during the study period, or within two weeks prior to trial vaccination
8. Any known hypersensitivity to any ingredient in the vaccines
9. Has received Dukoral or any other ETEC vaccine than the TEV
10. Brought up in ETEC-endemic areas (e.g., Central and South America, Caribbean, most countries in Asia, Africa, etc)
11. Has travelled to ETEC-endemic areas within the last 3 years or spent > two months in ETEC-endemic areas during the last 10 years
12. Known or suspected history of drug, chemical or alcohol abuse, as deemed by the investigator/physician
13. Receipt of any other investigational product in the month before study entry or during the study deemed by the investigator/physician to be relevant for the OEV-121 study
14. Concomitant participation in any other clinical study deemed by the investigator/physician to be relevant for the OEV-121A study
15. Blood donation less than two weeks before immunization until one month after immunization
16. Females who are pregnant
17. Females who are nursing
18. Unable to participate in all study visits
19. Any condition or circumstance which would make the subject unsuitable for participation in the study in the opinion of the investigator/physician

**Date of first enrolment**

02/12/2013

**Date of final enrolment**

30/06/2014

## Locations

**Countries of recruitment**

Sweden

**Study participating centre**

Dept. of Microbiology and Immunology

Gothenburg

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## Sponsor information

**Organisation**

Gothenburg University Vaccine Research Institute (GUVAX) (Sweden)

**ROR**

<https://ror.org/01tm6cn81>

## Funder(s)

### Funder type

Hospital/treatment centre

### Funder Name

Sahlgrenska University Hospital (ALF; Agreement on Medical Education and Research) (Sweden)

### Funder Name

Swedish Research Council (Sweden)

### Alternative Name(s)

Swedish Research Council, VR

### Funding Body Type

Government organisation

### Funding Body Subtype

National government

### Location

Sweden

## Results and Publications

### Individual participant data (IPD) sharing plan

#### IPD sharing plan summary

Not provided at time of registration

### Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
<a href="#">Results article</a>	results	08/06/2016	23/01/2019	Yes	No
<a href="#">Results article</a>		22/03/2021	07/10/2021	Yes	No
<a href="#">Participant information sheet</a>	Participant information sheet	11/11/2025	11/11/2025	No	Yes