Establishing colonisation with non-toxigenic Clostridioides difficile in healthy volunteers.

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Primary objective:- To evaluate the safety and tolerability of colonisation with non-toxigenic C. difficile.- To establish the effective protocol to obtain colonisation with non-toxigenic C. difficile in the majority of subjects.Secondary objective...

Ethical review	Approved WMO
Status	Recruiting
Health condition type	Gastrointestinal infections
Study type	Interventional

Summary

ID

NL-OMON56374

Source
ToetsingOnline

Brief title
CloDiCo

Condition

- Gastrointestinal infections
- Bacterial infectious disorders

Synonym
experimental human NTCD colonisation

Research involving
Human

Sponsors and support

Primary sponsor: Leids Universitair Medisch Centrum
Source(s) of monetary or material Support: Bontius Stichting en IMI2 JU (Innovative

Medicines Initiative 2 Joint Undertaking programme;a public-private partnership between the European Union and the European pharmaceutical industry)

Intervention

Keyword: C.difficile, Colonisation, Human, Non-toxigenic

Outcome measures

Primary outcome

- Number and grade of adverse events during the first month after ingestion of

spores of non-toxigenic C.difficile.

- The number of volunteers successfully colonised with non-toxigenic

C.difficile. Colonisation is defined as a positive PCR for C.difficile on stool

or a positive culture for C.difficile on at least two timepoints between three

days and two weeks after the last exposure day.

Secondary outcome

- Microbiota markers which are associated with successful C.difficile

colonisation.

Exploratory endpoints

- Identification of changes in microbiota components following C.difficile

colonisation.

- Identification of genetic changes in C.difficile after passage through the

human host.

Study description

Background summary

Clostridioides difficile (Cdiff or C.difficile) is the leading cause of healthcare-associated diarrhoea, with almost 190.000 cases a year and estimated health-cares costs of 3 billion euros yearly in the European Union. With a mortality rate of 5% and high relapse rates ranging from 20% after an initial episode and 60% after multiple prior recurrences the urge for new treatment strategies has become increasingly important.
The most important advancement in this area has been the prevention of recurrence by fecal microbiota transplantation (FMT) from a healthy donor. Host gut microbiota factors are of key importance in the pathology caused by C.difficile, as disturbances of the microbiota by antibiotics cause C.difficile to grow out and germinate into toxin-producing cells and thereby causing disease. Restoring these disturbances of the fecal microbiota with healthy microbiota through FMT, prevents colonisation of C.difficile. FMT has shown to have superior efficacy compared to standard treatments in particular for recurrent disease. However the essential components of FMT, as well as the specific markers which influence the microbiota susceptibility for colonisation of C.difficile are unknown. Our understanding of microbiota susceptibility markers and the components of FMT which effectively provide colonisation resistance, is urgently needed to find (new) strategies for prevention of C.difficile infection. Therefore we propose to develop a human model for colonisation with C.difficile, in which we can investigate colonisation resistance conferred by the (natural) microbiome. We propose to use a non-toxigenic strain of C.difficile (NTCD) which lacks the genetic locus for toxin production (PaLoc) and as such cannot cause C.difficile disease. In the healthy population asymptomatic colonisation of C.difficile is seen in 4-15%, of which a varying proportion (30-93%) does not carry toxin genes. Experimental colonisation with NTCD has been done before in healthy volunteers and was well tolerated.
In summary, with this trial we aim to investigate the safety, tolerability and dose needed to obtain colonisation with non-toxigenic C.difficile and investigate host microbiota factors associated with colonisation.

Study objective

Primary objective:
- To evaluate the safety and tolerability of colonisation with non-toxigenic C. difficile.
- To establish the effective protocol to obtain colonisation with non-toxigenic C. difficile in the majority of subjects.

Secondary objective:
- To determine factors in the host microbiota associated with successful colonisation.

Exploratory objectives:
- Determine changes in the host microbiota following colonisation.

- Investigate C. difficile in-vivo evolution and adaptation.

Study design

This will be an adaptive dose design, randomised double-blind controlled clinical trial investigating oral exposure to non-toxigenic C.difficile. The trial will consist of two or, if necessary, three different consecutive intervention phases. The second and third phase are dependent on results of the preliminary phases. In every phase one cohort volunteers will be randomised to different dose levels of NTCD spores or placebo.

Phase 1
In the first phase we will test two dose levels: 5 doses of 10E4 NTCD spores and 5 doses of 10E7 NTCD spores. These doses will be compared with placebo. 24 volunteers will be randomly divided over 3 groups; A, B and C (as scheduled below). Group A and B will consist of 10 volunteers each and group C (the control group) will consist of 4 volunteers. Group A will receive 5 doses of 10E4 NTCD spores on day 0 to day 4, group B will receive 5 doses of 10E7 NTCD spores on day 0 to day 4, and group C will receive 5 doses of placebo on day 0 to 4.

Phase 1 (N=24):
Group A (N=10): 5 doses 10E4 NTCD spores.
Group B (N=10): 5 doses 10E7 NTCD spores.
Group C (N=4): 5 doses of placebo.

Dose of the second phase will be based upon the colonisation results of the first phase. See the flow chart below (Figure 1). Progression to the second phase will be in consultation with the local safety monitor.

Phase 2
Depending on the outcome of phase 1, the dose given in phase 2 will either be reduced (if colonisation frequency in phase 1 is >60%) or the doses will be preceded by vancomycin pre-treatment (if the colonisation frequency in phase 1 is <60%) according to predefined criteria. 23 or 26 volunteers will be randomly divided over 3 groups: D, E and F (as scheduled below). Group D and E will consist of 10 volunteers each and group F (the control group) will consist of 3 or 6 volunteers. Depending on the results of colonisation of the first phase, there are three options for dosing schedules in the second phase.

Phase 2 (N=23 or 26)

Option 1 (N=26):
Group D (N=10): 3 doses 10E4 NTCD spores.
Group E (N=10): 1 dose 10E4 NTCD spores, 2 doses placebo.
Group F (N=6): 3 doses placebo.

OR

Option 2 (N=26):
Group D (N=10): 3 doses 10E7 NTCD spores.
Group E (N=10): 1 dose 10E7 NTCD spores, 2 doses placebo.
Group F (N=5): 3 doses placebo

OR

Option 3 (N-23):
Day -7: one day of vancomycin (4 times a day 250mg).
Group D (N=10): 5 doses 10E4 NTCD spores.
Group E (N=10): 5 doses 10E7 NTCD spores.
Group F (N=3): 5 doses placebo.

Escalation to the third phase will only be done if option 3 is selected in phase 2. Dosing of the third phase will be based upon the colonisation results of the second phase. Progression to the third phase will be in consultation with the local safety monitor.

Phase 3
Depending on the outcome of phase 2, the dose given in phase 3 will either be reduced (if colonisation frequency in phase 2 is >60%) or the vancomycin pre-treatment will be extended to five days (if the colonisation frequency in phase 2 is <60%) according to predefined criteria. 23 volunteers will be randomly divided over 3 groups: G, H and I (as scheduled below). Group G and H will consist of 10 volunteers each and group F (the control group) will consist of 3 volunteers. Depending on the results of colonisation of option 3 of the second phase, there are three options for dosing schedules in the second phase, which is scheduled below.

Phase 3 (N=23)

Option 1:
Day -7: 1 day vancomycin (4 times a day 250mg).
Group G (N=10): 3 doses 10E4 NTCD spores.
Group H (N=10): 1 dose 10E4 NTCD spores, 2 doses placebo.
Group I (N=3): 3 doses of placebo.

OR

Option 2:
Day -7: 1 day vancomycin (4 times a day 250mg).
Group G (N=10): 3 doses 10E7 NTCD spores.
Group H (N=10): 1 dose 10E7 NTCD spores, 2 doses placebo.
Group I (N=3): 3 doses of placebo.

OR

Option 3:
Day -11: 5 days vancomycin (4 times a day 250mg).
Group G (N=10): 5 doses 10E4 NTCD spores.
Group H (N=10): 5 doses 10E7 NTCD spores.
Group I (N=3): 5 doses of placebo.

All volunteers in all phases will visit the trial centre on the days of spores or placebo ingestion, with collection of feces prior to the ingestion. If phase 3 of the trial is needed, volunteers will also visit the trial centre twice between intake of vancomycin and spores/placebo ingestion for fecal sample collection. During the four follow-up weeks (after spores/placebo ingestion) volunteers will visit the trial centre three times a week for fecal sample collection, with a weekly follow-up visit for adverse events (AEs) registration on day 7, 14, 21 and 28. Safety blood tests will be performed on day 14 and 28. After three months (day 84) there will be a (final) follow-up visit, with collection of fecal samples and AEs. Should a volunteer still be positive for C.difficile at the three month timepoint, the volunteer is asked to return for follow-up every one to two months for fecal sample collection until the sample is negative for C.difficile, up till a maximum of one year after the start of the trial.

Intervention

Different dose levels (10E4 or 10E7) of NTCD spores or placebo for 1 or 5 days with optional vancomycin pre-treatment.

Study burden and risks

There is no direct benefit to the volunteers taking part. Since the strain used for colonisation is a non-toxigenic strain, it is not expected to cause any symptoms. In a previous double-blind placebo
controlled trial using a non-toxigenic strain gastro-intestinal complaints such as nausea, flatulence and cramping have been described. These AEs were all classified as mild and were comparable to those experienced by the placebo group. Because colonisation with NTCD is very common in the general population, NTCD colonisation will not be terminated with antibiotics. Rescue treatment for NTCD is available in case of unexpected adverse events. Antibiotics can be used to clear the NTCD. Additionally, FMT (using the fecal microbiota composition of a healthy donor) is available which can be used as a rescue treatment in case of persistent disturbances to the host microbiota. Based on prior published studies administering NTCD to healthy volunteers, the need for rescue treatment is not expected.
If volunteers in phase 2 or phase 3 will be pre-treated with oral vancomycin, they may experience gastro-intestinal side effects of vancomycin (i.e.

diarrhoea).
In order to limit the risk of transmission of the NTCD strain to household members, volunteers will be instructed to practice proper hygiene measures during the course of the trial and volunteers living with household member who are considered *vulnerable* will be excluded. Since non-toxigenic strains are present in the natural environment and asymptomatic colonisation with NTCD occurs in an estimated 4-15% of the healthy population, household members will experience a minimal added risk compared to the daily natural risk of exposure to NTCD.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)

Inclusion criteria

1. Subject is aged >= 18 and <= 45 years and in good health.
2. Subject has adequate understanding of the procedures of the study and is

able and willing to abide strictly thereby.
3. For female subjects: subject agrees to use adequate contraception and not to breastfeed for the duration of study.
4. Subject has signed informed consent.

Exclusion criteria

1. Any physical or psychiatric illness or conditions that could threaten or compromise the health of the subject during the study, influence their ability to participate in the trial or interfere with the interpretation of the study results, as determined by the trial physician.
2. Use of antibiotics (or other microbiota influencing products) within three months prior to inclusion.
3. Known immunosuppressive condition, including infection with Human Immunodeficiency Virus (HIV), use of systemic corticosteroids or other immune modifying drugs (with exception of antihistamines and topical steroids).
4. Regular use (defined by more than once weekly) of proton-pump inhibitors or H2- blockers during one month prior to inclusion.
5. The use of strong P-glycoprotein-inhibitors (like ciclosporin, ketoconazole, erythromycin, clarithromycin, verapamil and amiodaron).
6. Known allergy to vancomycin, metronidazole or fidaxomicin.
7. Known allergy to glycerol.
8. Known immunodeficiency disorders.
9. Known gastro-intestinal disease including but not limited to inflammatory bowel diseases (Crohn*s disease, Colitis Ulcerosa), recent gastro-intestinal surgery, constipation defined by bowel movements less than every second day.
10. Positive fecal PCR with Clostridiodes or SSYC (Salmonella, Shigella, Yersinia or Campylobacter spp.) at screening.
11. Any condition that would put household members at a greater risk for transmission e.g. no access or use of flush toilet, household members belonging to vulnerable populations such as persons who are immunocompromised, children younger than 2 years of age and elderly older than 70 years of age.
12. For women of child bearing potential: a positive urine pregnancy test before inclusion or lactating at screening / during the trial.
13. Being an employee or student of the Experimental bacteriology group or the controlled human infection center at LUMC.

Study design

Design

Study type:	Interventional

Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Double blinded (masking used)
Control:	Placebo
Primary purpose:	Basic science

Recruitment

NL

Recruitment status:	Recruiting
Start date (anticipated):	22-09-2023
Enrollment:	70
Type:	Actual

Ethics review

Approved WMO

Date:	08-09-2023
Application type:	First submission
Review commission:	METC Leiden-Den Haag-Delft (Leiden) metc-ldd@lumc.nl

Approved WMO

Date:	19-02-2024
Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden) metc-ldd@lumc.nl

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
ClinicalTrials.gov	NCT05693077
CCMO	NL83949.058.23