Subject information for participation in medical research

Dose-finding and safety study of a new *Shigella* vaccine combined with an adjuvant (=additive) in the Netherlands and Zambia

Phase Ia/b double-blind, placebo-controlled, dose escalating safety study of detoxified Shigella flexneri 2a Artificial Invasin Complex (Invaplex$_{AR\text{-}Detox}$) vaccine formulated with and without dmLT adjuvant given intramuscularly to healthy adults in the Netherlands and Zambia

Introduction

With this letter, we would like to ask you to take part in a medical research study.
Participation is voluntary.
You can read about the study in this information sheet, what it means for you, and what the pros and cons are. It is a lot of information. Can you please read the information and decide if you want to take part? If you want to take part, complete the form in **Appendix D**.

Ask your questions

You can make your decision based on the information in this information sheet. We also suggest that you do this:
- Ask questions to the investigator who gave you this information.
- Talk to your partner, family or friends about this study.
- Ask questions to the independent expert. For contact details, go to **Appendix A**.
- Read the information on www.rijksoverheid.nl/mensenonderzoek.
- Read the information on www.shigaplexim.eu.

1. General information

The Leiden University Medical Centre (LUMC) has set up this study. Below, we always call the LUMC the 'sponsor'.
Investigators, these can be doctors, research nurses and other personnel, conduct the study at the LUMC and at the Centre for Infectious Disease Research in Zambia (CIDRZ).

Participants in a medical research study are often called subjects. In this study, subjects are healthy participants.

This study needs 85 healthy adults from two different countries (Netherlands and Zambia). In the Netherlands, it is expected that 50 subjects will take part. In Zambia, 35 subjects are expected to participate.
The Central Committee on Medical Research with Human Subjects (in Dutch: *Centrale Commissie Mensgebonden Onderzoek*, CCMO) in the Netherlands and the National Ethics Committee in Zambia have approved this study.

2. What is the purpose of the study?

In this study, we look at how safe a new *Shigella* vaccine (Invaplex$_{AR\text{-}Detox}$) administered into the muscle is, with or without an adjuvant (dmLT). An adjuvant is a substance that is added to a vaccine to improve its efficacy. This study will also look at the the most optimal vaccine dose and the effect of the vaccine and the adjuvant on the immune system.
We compare the new vaccine and adjuvant with a placebo. A placebo is a product without the active ingredient: a 'fake medicinal product'.

3. What is the background of the study?

Worldwide, diarrhea is one of the leading causes of death among children below the age of five. A considerable part of the deadly diarrhea cases is caused by the *Shigella* bacteria, especially in low- and middle-income countries. Currently, the is no effective vaccine against *Shigella* available. An effective vaccine against *Shigella* could help prevent these cases of diarrheal disease. Our hope is that this new *Shigella* vaccine (Invaplex$_{AR\text{-}Detox}$) could be used for this in the future.

The new *Shigella* vaccine has been administered (without the adjuvant) to 46 human subjects before in a previous scientific study. In that previous study, the vaccine was safe and well tolerated. The adjuvant (dmLT) has already been administered to humans in multiple small scientific studies. In these studies, the adjuvant was safe and well tolerated.

In this current study we will investigate the new *Shigella* vaccine in combination with the adjuvant. The new *Shigella* vaccine has not been administered to humans before in combination with the adjuvant. The *Shigella* vaccine and adjuvant will first be tested in adult subjects in the Netherlands. In the Netherlands, we will gather information on side effects and how well the vaccine is tolerated. This is information is needed before we can test this vaccine and adjuvant in Zambia. After that, the *Shigella* vaccine and adjuvant will be tested in adult subjects in Zambia. If the vaccine and adjuvant are safe and have a good effect on the immune system, the next study will be organized to test the vaccine and adjuvant in children.

4. What happens during the study?

How long will the study take?
Are you taking part in the study? It will take about 32 weeks.

Step 1: are you eligible to take part?
If you consent to participate in this study, first, we want to know if you are eligible to take part. That is the reason that the investigator will do some checks during a screening visit in the LUMC. The screening visit will take about 1 hour. The following checks will be done:

- Physical examination. For example, the investigator can listen to your heart and lungs and measure your blood pressure and heart rate.

- Blood test. The investigator will take some blood from you. We will test this blood for HIV, Hepatitis B and Hepatitis C. We will tell you if you have any of these diseases.
- Register your medical history.

Please note: it is possible that you are not eligible for this study, even if you are healthy. The investigator will tell you more about this.

Step 2: if you participate in this study

We will vaccinate you three separate times. There will be a period of 4 weeks between every vaccination.

The vaccine will be given into the shoulder muscle. You will be asked to wait for at least 30 minutes after the vaccination at the research unit so that we can check if you are well before we let you go home.

For this study, we will have 3 cohorts (=main group), each consisting of 3 groups:

Cohort A (Netherlands)

- Group A1: 10 people in this group will get 2.5 mcg (microgram) vaccine.
- Group A2: 10 people in this group will get 2.5 mcg vaccine and 0.1 mcg adjuvant.
- Group A3: 5 people in this group will get a placebo.

Cohort B (Netherlands)

- Group B1: 10 people in this group will get 10 mcg vaccine.
- Group B2: 10 people in this group will get 10 mcg vaccine and 0.1 mcg adjuvant.
- Group B3: 5 people in this group will get a placebo.

Cohort C (Zambia)

- Group C1: 15 people in this group will get 10 mcg vaccine.
- Group C2: 15 people in this group will get 10 mcg vaccine and 0.1 mcg adjuvant.
- Group C3: 5 people in this group will get a placebo.

In the Netherlands, you will be recruited for one of the two first cohorts (A or B). You will know if you are in cohort A or B. A draw will decide to which group you will be allocated (1, 2 or 3). You and the investigator do not know which group you are in. But if it is important for your health, we can look this up.

Step 3: study measurements

For the study, you need to visit the LUMC 8 times (9 times when including the screening visit) in 32 weeks. There are different types of visits:

1) Screening (see step 1 above)
2) Vaccination. There are three vaccination visits that will take about 2 hours each. During a vaccination visit your body temperature and blood pressure will be measured and some of your blood will be drawn. After that, the vaccination will take place and

possible side effect will be registered Between every vaccination there is a 4 week period.

3) Control visits. A total of five control visits will take place that, will take about 15 minutes each.

We will carry out these checks:

- . You will keep a diary to keep track of side effects you experience after vaccination.
- Blood sampling. For this, the investigator takes about 2 to 8 tubes of blood at a time from your arm using a needle. In total, we will collect approximately 300 ml of blood from you. This amount does not cause any problems in adults. For comparison: if you give blood at the blood bank, you will give 500 ml of blood at a time. We will not take more than 500 ml blood in the entire study. With the blood samples, we test these things:
    - Are there changes in your general health? (e.g. kidney and liver function)
    - Does the vaccine induce antibodies?
    - Does the vaccine stimulate immune cells?

Appendix C has a list of the vaccinations and measurements we carry out during each visit.

5. What agreements do we make with you?

We want the study to go well. That is why we want to make the following agreements with you:

- You do not take part in any other medical research during this study.
- You go to every appointment.
- You should contact the investigator in these situations:
    - You want to start taking other medication. Also, if these are vaccines, homoeopathic remedies, natural remedies, vitamins or over-the-counter medicines.
    - You are hospitalized or get treatment in a hospital.
    - You suddenly have problems with your health.
    - You no longer want to take part in the study.
    - Your telephone number, address or email address changes.

Is it OK for you to get pregnant during the study?

Women who are pregnant or breastfeeding cannot take part in this study. Women should also not get pregnant up to 3 months after the last vaccine dose. This study can have consequences for an unborn child. The consequences are not known.
Therefore, you must use contraception during the study. The investigator will tell you how best to prevent pregnancy. Talk to your partner about this.

Pregnant after all?

If you do become pregnant during the study, inform the investigator immediately. In this case, you should stop participating in the study in consultation with the investigator.

6. What side effects, adverse effects or discomforts could you experience?

The vaccine and/or the adjuvant may cause side effects.

The following side effects are common:

- Pain at the vaccination site
- Redness at the vaccination site
- Swelling at the vaccination site
- Itch at the vaccination site
- Tiredness
- Malaise
- Headache
- Muscle ache
- Joint ache
- Chills
- Fever
- Loose/soft stools

The vaccine and/or the adjuvant can also have side effects that we do not know about at the moment.

What are the possible discomforts you may experience with checks or measurements during the study?

Taking a blood sample can be a little painful. You could get a bruise as a result.

7. What are the pros and cons if you take part in the study?

Taking part in the study can have pros and cons. We will list them below. Think about this carefully and talk to other people about it.

You yourself do not benefit from taking part in this study. But if you take part you will help the investigators to get more insight into *Shigella* vaccine development.

Taking part in the study can have these cons:

- You may experience side effects or adverse effects of the vaccine and/or adjuvant.
- There may be some discomfort from the blood draw during the study.
- Taking part in the study will cost you time.

You do not wish to participate in the study?

It is up to you to decide if you wish to participate in the study.

8. When does the study end?

The investigator will let you know if there is any new information about the study that is important to you. The investigator will then ask you if you want to continue to take part.

In these situations, the study will stop for you:

- All checks according to the schedule are finished.
- You have become pregnant.
- You want to stop participating in the study yourself. You can stop at any time and there will be no penalty. Report this to the investigator immediately. You do not have to explain why you want to stop. For your safety, the investigator may arrange one or more check-ups.
- The investigator thinks it is better for you to stop. The investigator will still invite you for one or more follow-up checks.
- One of the following authorities decides that the study should stop:
    - the sponsor,
    - an independent group of experts that review the study safety data
    - the government, or
    - the ethical review board.

What happens if you stop participating in the study?
The investigators use the data and blood samples that have been collected up to the moment that you decide to stop participating in the study.

The study as a whole is completed when all participants have had their last visit.

9. What happens after the study has ended?

Will you get the results of the study?
About 6 to 12 months after the study has ended, the investigator will inform you about the most important results of the study. The investigator may also tell you which group you were in. Do you prefer not to know? Please tell the investigator. They will not tell you in that case.

10. What will be done with your data and blood samples?

Are you taking part in the study? Then you also give your consent to collect, use and store your data and blood samples.

What data do we store?
We store these data:
- your name
- your gender
- your address and contact details
- your bank details (to transfer the financial compensation)
- your date of birth
- information about your health

- (medical) information that we collect during the study

We will also ask you to allow us to take a photograph of you so we can identify you at the clinic visits.

What body material do we store?
We collect, use and store blood samples.

Why do we collect, use and store your data and blood samples?
We collect, use and store your data and your blood samples to answer the questions of this study. And to be able to publish the results. Data and blood samples can be used by the sponsor and partners that help the sponsor with measurements on blood and analysis of the data.

How do we protect your privacy?

To protect your privacy, we give a code to your data and your blood samples. We only put this code on your data and blood. We keep the key to the code in a safe place in the research center. When we process your data and blood, we always use only that code. In reports or publications on the study, nobody will be able to see that you were in the study.

Who can see your data?
Some people can see your name and other personal information without a code. These are people checking whether the investigators are carrying out the study properly and reliably. These persons can access your data:

- Representatives of the sponsor e.g. monitors.
- Members of the committee that keeps an eye on the safety of the study.
- An auditor who is hired by the sponsor.
- National and international supervisory authorities.

These people will keep your information confidential. We ask you to give permission for this access. In the Netherlands, the Health and Youth Inspectorate can access your personal information without your permission.

For how long do we store your data and body material?
We store your data 25 years. We store your body materials at the research center. They will be stored for 25 years in order to be able to make new assessments related to this study. If no longer needed, we will destroy your body material.

Can we use your body material for other research?
No, your (remaining) blood will only be used for medical research regarding the currently researched *Shigella* vaccine.

What happens if there are coincidental findings?
It is possible that during the study we discover something that is not directly relevant to the study but is important to your health. In that case, the investigator will contact your general practitioner. You will then discuss what needs to be done with your doctor. With the form, you give consent to inform your general practitioner.

Can you take back your consent for the use of your data?
You can take back your consent for the use of your data at any time. Please tell the investigator if you wish to do so. This is applicable to this research and to the use in other research. Note: if you take back your consent and the researcher have already collected some of your data for the research? The researchers are then allowed to still use the data that they have already collected.

Do you want to know more about your privacy?

- Do you want to know more about your rights when processing personal data? Visit https://www.autoriteitpersoonsgegevens.nl/en

- Do you have questions about your rights? Or do you have a complaint about the processing of your personal data? Please contact the person who is responsible for processing your personal data. For the present, this is:
    - The LUMC, see **Appendix A** for contact details and website.
- If you have complaints about how your personal data is processed, we advise you to first discuss the matter with the research team. For further privacy-related information, refer to the privacy statement of the LUMC on the LUMC website: see **Appendix A**. You can also contact the Data Protection Officer at the LUMC. Alternatively, you can submit a complaint to the Dutch Data Protection Authority.

Where can you find more information about the study?
More information about the study can be found on the following website: www.clinicaltrialsregister.eu/ctr-search/search. After the study, the website may display a summary of the study results. You can find this study by searching for '2023-506394-35'.

This website will not include information that can identify you. At most, the website will include a summary of the results. You can search this website at any time.

11. Will you receive compensation if you participate in the study?

The testing for the study will not cost you anything. If you are eligible and you take part in this study, you will receive a reimbursement.

The reimbursement consists of:
- €50,- per control visit,
- €75,- per vaccination day

- a bonus of €100,- after the last follow-up visit.

The total reimbursements amounts to €625,-. For back-up study subjects who are on standby on the day of the first vaccination, the total reimbursement is €100,-. You do not receive separate compensation for travel costs.

If you are excluded from the study by the investigator due to a medical reason, you will receive the full reimbursement. If you quit the study before it is completed, you will receive less compensation.

The compensation for taking part in this study should possibly be declared to the Tax and Customs Administration as 'income from other work'. When needed, ask the National Tax Administration (in Dutch: *de Belastingdienst*) for more information.

12. Are you insured during the study?

Insurance has been taken out for everyone who takes part in this study. The insurance pays for damage caused by the study. But not for all damage. You can find more information about this insurance and any exceptions in **Appendix B**. It also says who you can report damage to.

13. We will inform your general practitioner

The investigator will send your general practitioner a letter to let them know that you are taking part in the study. This is for your own safety.

14. Do you have any questions?

You can ask questions about the study to the research team. Would you like to get advice from a neutral party? Then contact dr. Hetty Jolink. She knows a lot about the study but is not involved in it. You can find her contact details in **Appendix A**.

Do you have a complaint? Discuss it with the investigator. Would you prefer not to? Then please contact the complaints committee at the LUMC. **Appendix A** explains how you can do this.

15. How can I provide consent for the study?

You should first think carefully about this study. Then you tell the investigator if you understand the information and if you want to take part or not. If you want to take part, fill in the consent form that you can find with this information sheet during the screening visit. You will receive a validated copy of this consent form.

16. Appendices accompanying this information

A. Contact details
B. Information about the insurance
C. Overview of measurements
D. Consent form

Appendix A: Contact details

Principal investigator
Prof. Meta Roestenberg, MD, PhD
Department of Parasitology
Tel: 06-20942061
E-mail: vaccinonderzoek@lumc.nl

Independent expert
Hetty Jolink, MD, PhD
Department of Infectious Diseases LUMC
Tel: 071-52662613
E-mail: H.Jolink@lumc.nl

Complaints

If you have a complaint about the study, you can contact Team Klachten of the LUMC via e-mail: patientenservicebureau@lumc.nl. You can also contact the Patiëntenservicebureau by phone: 071-5262989, during office hours. They will process your complaint according to the applicable regulations.

Privacy & rights

If you have questions about the protection of your privacy, you can contact the data protection officer at the LUMC (In Dutch: *Functionaris Gegevensbescherming*) via privacy@lumc.nl. For more information about your rights, you can contact the LUMC.

Contact details LUMC

Albinusdreef 2
2333 ZA Leiden
Central telephone number: +31(0)71-5269111
For further information about your rights, please visit the website of the LUMC.
https://www.lumc.nl/12367/Deelnemers-wetenschappelijk-onderzoek/

Appendix B: Information about the insurance

The LUMC has taken out insurance for everyone who takes part in the study. The insurance pays for the damage you have suffered because you participated in the study. This concerns damage you suffer during the study or within 4 years after your participation in the study has ended. You must report damage to the insurer within 4 years.

Have you suffered damage due to the study? Please report this to this insurer:

The insurer for this study is:	
Name:	Centramed
Address:	Maria Montessorilaan 9, 2719 DB Zoetermeer
Telephone:	+31 (0)70-3017070
E-mail:	info@centramed.nl
Policy number:	624.530.305

The insurance will pay maximum €650,000 per person and €5,000,000 for the whole study (and €7,500,000 per year for all studies by the same client).

Please note that the insurance does **not** cover the following damage:

- Damage due to a risk about which we have given you information in this sheet. But this does not apply if the risk turned out to be greater than we previously thought. Or if the risk was very unlikely.
- Damage to your health that would also have happened if you had not taken part in the study.
- Damage that happens because you did not follow directions or instructions or did not follow them properly.
- Damage to the health of your children or grandchildren.
- Damage caused by a treatment method that already exists. Or by research into a treatment method that already exists.

These provisions can be found in the 'Besluit verplichte verzekering bij medisch-wetenschappelijk onderzoek met mensen 2015' ('Medical Research (Human Subjects) Compulsory Insurance Decree 2015'). This decision can be found in the Government Law Gazette (https://wetten.overheid.nl).

Appendix C: Overview of visits and measurements

Day	Approx. duration	Activity
Screening visit / visit 1	1 – 1,5 hours	Explanation about the study and possibility to ask questions. The informed consent form will be signed. You will be asked about your age, gender and medical history. The following tests and assessments will be carried out: - Temperature, blood pressure, heart rate; - Height and weight; - Physical examination; - Blood sampling (approximately 50 ml) and blood examination; - Only for women: pregnancy test.
Study day 1 / visit 2: **Vaccination 1**	2 hours	Draw to decide which group you are in (blinded). Administration of vaccine, vaccine & adjuvant or placebo (depending on the group you are in). The following tests and assessments will be carried out: - Temperature, blood pressure, heart rate; - Blood sampling (approximately 50 ml); - Assessment of side effects; - Physical examination when needed; - Only for women: pregnancy test.
Study day 8 / visit 3: Control visit	15 minutes	The following tests and assessments will be carried out: - Body temperature; - Assessment of side effects; - Blood sampling (approximately 40 ml) and blood examination.
Study day 29 / visit 4: **Vaccination 2**	2 hours	Administration of vaccine, vaccine & adjuvant or placebo (depending on the group you are in). The following tests and assessments will be carried out: - Temperature, blood pressure, heart rate; - Blood sampling (approximately 20 ml); - Assessment of side effects; - Physical examination when needed; - Only for women: pregnancy test.
Study day 36 / visit 5: Control visit	15 minutes	The following tests and assessments will be carried out: - Body temperature; - Assessment of side effects; - Blood sampling (approximately 5 ml) and blood examination.

Study day 57 / visit 6: **Vaccination 3**	2 hours	Administration of vaccine, vaccine & adjuvant or placebo (depending on the group you are in). The following tests and assessments will be carried out: - Temperature, blood pressure, heart rate; - Blood sampling (approximately 20 ml); - Assessment of side effects; - Physical examination when needed; - Only for women: pregnancy test.
Study day 64 / visit 7: Control visit	15 minutes	The following tests and assessments will be carried out: - Body temperature; - Assessment of side effects; - Blood sampling (approximately 60 ml) and blood examination.
Study day 85 / visit 8: Control visit	15 minutes	The following tests and assessments will be carried out: - Body temperature; - Assessment of side effects; - Blood sampling (approximately 20 ml) and blood examination.
Study day 225 / visit 9: **End of study visit**	15 minutes	The following tests and assessments will be carried out: - Body temperature; - Assessment of side effects; - Blood sampling (approximately 40 ml).

Appendix D: Consent form study subjects

Belonging to 'Dose-finding and safety study of a new Shigella vaccine combined with an adjuvant in the Netherlands and Zambia'

- I have read the information sheet. I was able to ask questions. My questions have been answered well enough. I know who to contact in case of future questions. I had enough time to decide if I wanted to take part.
- I know that taking part is voluntary. I also know that at any time I can decide not to take part in the study. Or to stop taking part. I do not have to explain why.
- I give consent to inform my general practitioner about my participation in this study and about accidental discoveries made during the study that are important for my health.
- I give consent to collect and use my data and body material (blood samples). The investigators only do this to answer the questions of this study.
- I give consent to take a picture of me to use as a means of identification during the study.
- I know that some people will be able to see all of my data to review the study. These people are mentioned in this information sheet. I give consent to let them see my data for this review.
- For women: I know that I cannot get pregnant until 3 months after the last vaccine administration.
- For women: The investigator discussed with me how I can best prevent becoming pregnant.

- I want to take part in this study.

My name is (participant):

Signature:

Date (DD/MMM/YYYY) : ____ / _____ / _____ Time __ : __ (24h notation)

I declare that I have fully informed this subject about the study mentioned.

If any information becomes known during the study that could influence the subject's consent, I will let this subject know in good time.

Investigator name (or their representative):

Signature:

Date (DD/MMM/YYYY) : ____ / _____ / _____ Time __ : __ (24h notation)

The participant will receive the entire subject information sheet, together with a certified copy of the signed informed consent form.