

Participant Information Sheet

Study title

Measuring responses to sublingual antigens

Invitation paragraph

We would like to invite you to take part in a research study. Before you decide you need to understand why the research is being done and what it will involve for you. Please take time to read the following carefully and discuss it with others if you wish.

Part 1 tells you the purpose of this study and what will happen to you if you take part

Part 2 gives you detailed information about the conduct of the study

If you would like any further information or if anything is not clear, please ask us. Take time to decide whether or not you wish to take part

Thank you for reading this.

Part 1

What is the purpose of the study?

The purpose of this study is to find out if "antigens" (in this case small proteins that can stimulate an immune response) can stimulate a measurable immune response when simply placed as drops under the tongue.

This route of delivery is called "sublingual". Studies in animals by other scientists have shown that sublingual delivery of antigens from viruses can not only stimulate antibodies and white blood cells (lymphocytes), but these can actually protect against infection. In humans, scientists have used some antigens made from bacterial toxins, and shown that they can stimulate antibodies when placed under the tongue, but these proteins are rather unusual and may be more powerful at provoking immune responses than "normal" proteins from viruses and bacteria. For many decades clinicians have safely used repeated sublingual applications of "allergens" (proteins such as grass pollen that stimulate unpleasant allergic immunity like hay fever) to change an unpleasant allergic type of immunity into a non-harmful type of immunity. However, this process (called "desensitisation") takes weeks of daily applications of huge amounts of the allergen. This is quite different to vaccines which use tiny amounts of antigens, given only a few times. The response to vaccines also tends to be "positive" in that it stimulates a protective immunity, whereas the response to desensitisation is rather negative in that it damps-down harmful allergic immunity.

Previously we have carried out studies in healthy volunteers where we have stimulated the immune system protecting the external surfaces of the respiratory, gut and reproductive tracts (called "mucosal immunity") and the immunity protecting our blood and internal organs (called "systemic immunity") by using purified proteins available in safe licensed vaccines. We have administered them into the nose or mouth, and explored how the systemic and mucosal immune systems appear to respond in different ways following these different routes of administration.

We now wish to extend these studies to discover whether sublingual delivery can provoke immune responses in humans, and if so whether this immunity resembles that seen after nasal, oral or injected delivery. If we can learn more about how the mucosal and systemic systems interact with each other it will further our knowledge and understanding of immune responses, and may help in designing new vaccines and the way we deliver them. There are many arguments to deliver vaccines in a way that does not require a needle, so swallowing them or letting the vaccine be absorbed under the tongue may be an alternative, and may provoke an immune response that is even more useful than injecting the antigens. Putting antigens sublingually may also (in theory) produce better responses in the genital tract, allowing us to design convenient vaccines against infection like HIV, chlamydia, etc. In addition by better understanding how mucosal and systemic immune systems "talk" to each other we may better understand certain types of arthritis that develop after gut or genital infections, and other "inflammatory" diseases.

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This study is part of a larger European collaboration investigating delivering vaccine antigens to mucosal surfaces. In order to find out whether the antigens are stable in the vagina we would like to collect undiluted vaginal secretions from you on one occasion only (at a time when you will already be attending the study site) to observe the stability of these antigens. This would require you to use the 'instead' cup collection method. It involves inserting a small soft plastic pliable cup into the vagina, leaving it there for 1-2 hours and removing it in private when attending your next visit. As this sample is not vital to this protocol, it is entirely optional if you wish to provide it and if you do not, it will not adversely affect your participation in this trial. There will not be any extra payment for this sample.

This is not a "clinical trial". We are not "testing" a new vaccine or route of vaccine delivery. We are using the Human Papilloma Virus (HPV) vaccine just because it is a safe and pure form of viral proteins. We are using it as a "model" to mimic other situations. We chose HPV because we already have tests that can measure immune responses to HPV, and we know it will stimulate good immune responses when injected. The results of this study will help our basic understanding of healthy human physiology, and maybe help design better vaccines in the future. But this is not part of a process to develop an HPV vaccine - it is just a convenient and safe system to adopt.

Why have I been invited?

Because we are especially interested in the way that the sublingual and female genital tract immune systems seem to be interconnected, we will be recruiting 18 *female* volunteers to this study. Those 18 will be in two groups: the first 6 to enter the study will receive three injections of the antigens. This will allow us to set-up and calibrate our tests, and try-out new tests for immunity to HPV. We will do these first as we already know that the HPV vaccine works very well by injection. After this we will recruit 12 subjects to receive the sublingual drops. We do this last as we don't know if sublingual delivery will provoke any response, and we want to run the "positive response" group first. We have selected these numbers as 6 will ensure we get a good amount of positive controls (around 100% will respond), and 12 is a manageable number given the resources and time we have available.

Because we want to study healthy human physiology we will check that people are in basically good health, and not affected by anything that could interfere with their normal immune responses. For those reasons you will be invited to this study if:

- You are aged between 18 to 35 years of age (we just want to keep the variation between people as small as possible to avoid the data being influenced by age, hormonal or other effects).
- You are in good health
- If of childbearing potential, must have a negative pregnancy test before each immunisation (this is a contraindication of the Gardasil vaccine, not because it is predicted to cause any harm, but because of a lack of information on its use in pregnancy).
- You have not donated blood during 3 months prior to study entry and agree to not donate for 3 months after the end of their participation in the study (because we will be taking blood samples as well).
- You have not received blood products or immunoglobulins 120 days prior to enrolment (as this could affect your immune responses)
- You are willing and able to read, understand and sign this consent
- You do not have a sensitivity to any of the components of the vaccine under investigation

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- All your tests done during the screening visits are normal including HIV, Hepatitis B or Hepatitis C tests (as these infections could affect your immune responses, and expose laboratory staff to risks of infection).
- You do not have a known or suspected history of lung, heart, liver, kidney diseases, blood disorders or problems with your immune system (as this could affect your immune responses).
- You do not regularly use oral or injected steroids (as this could affect your immune responses).
- You are not receiving any vaginal medication (as this could affect your immune responses).
- You do not have a history of alcohol or substance misuse or dependence (as this could affect your immune responses).
- You have not received another investigational medicinal product within 3 months prior to the start of the study (as this could interact with the vaccine in ways we can not predict).
- You do not have any tongue or piercings or oral jewellery that may interfere with sublingual delivery (as this could affect way the vaccine crosses the lining of the mouth).
- You agree to comply with the study requirements and you can make yourself available to attend the study site for all the study visits (as all the samples we collect are important in evaluating the immune responses, and we cannot predict which time we will see the best response).

Do I have to take part?

Participation in this study is entirely voluntary. It is up to you to decide whether or not to take part. If you do, you will be given this information sheet to keep and asked to sign a consent form. You are still free to withdraw at any time and without giving a reason. A decision to withdraw at any time or not take part will not affect the standard of care you receive from any healthcare organisation.

What will happen to me if I take part?

This study will be conducted over a period of up to 24 weeks. Initially we will take some blood tests and do a medical examination to check that you can enter the study. We have to do this within 28 days of the first dose of antigens. If these tests are all OK, we will then schedule you for the first dose of antigens. After the first dose the study lasts 20 weeks, and includes two more doses of antigens plus visits to the site to have some samples taken. On some time-points we will also perform a vaginal - cervical examination using a speculum to look inside the vagina. On the first visit this is just to check that there are no vaginal problems that could interfere with the study. On later occasions we will take some samples of the secretions inside the vagina, using a soft sponge (like a Q-tip - normally used to collect tears from the eyes).

This table shows the schedule of visits:

Visit no.	1	2	3	4	5	6	7	8	9
Study day no.	-28 to -2	0	7	28	35	56	112	119	140
Study week no.		0	1	4	5	8	16	17	20
Study month no.		0		1		2	4		5

The following paragraphs describe in detail the procedures we will perform at each visit:

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Visit 1 (Up to 28 days before the next visit):

- You will be asked for contact details, your NHS or National Insurance number, and for your GP so that we can inform him/her about your participation in this study. To take part you must give us your permission to let your GP know of your participation, so that he/she is aware of what you have received and can advise of any concerns they may have regarding your participation. We will also collect information about your past and current health and any medications, and we will record these together with information about your age.
- We will take blood (about 15 mL) and urine samples from you for a number of routine laboratory tests including tests for HIV and Hepatitis B and C infections. Before doing this the study nurse will have a pre-test discussion to discuss the issues around having an HIV test. Should your screening HIV or Hepatitis B or C tests return positive, the Principal Investigator, Dr David Lewis will personally inform you, in the strictest confidence. He will offer to arrange follow-up counselling and treatment should you wish to have it. If you would like the results to be communicated to your GP, we will do this in the strictest confidence. Any positive result will exclude you from the study.
- Another blood sample will also be collected for immunology tests to establish the state of your immune system before we give you the antigen so we can compare the results after administration of the antigen. This will help us analyse how your body is responding to it.
- You will be seen by a doctor who will record your medical history and examine you (this involves listening to your heart and lungs, feeling your abdomen, taking blood pressure and temperature). A nurse or doctor will also use a speculum to examine your vagina and cervix to check that it looks healthy. This involves gently inserting a speculum (a device that opens the vagina) so that we can see the cervix (the lower part of the womb) clearly. It will be very similar to having a cervical smear test done.
- Once the screening tests are completed, we will make arrangements for your next visit if everything is acceptable. If any of the tests are abnormal such that you cannot enter the study, we will let you know in confidence.

Visit 2, 4, 6 and 7 (On the day of the first dose of antigens, and 4 and 16 weeks later):

- At these visits, we will take a tiny sample of vaginal secretions using a soft sponge. A trained member of the study staff will always perform this. To collect the samples, we will insert a speculum and gently place the soft absorbent sponge against the cervix and vaginal wall to absorb some of the normal secretions.
- Blood will be taken from your arm for immune testing (about 55 mL) and a urine pregnancy test will be carried out.
- The antigens will be given on these visits except for visit 6. Initially the first six volunteers will receive the antigens as an injection in the non-dominant arm (i.e. the left arm if you are right-handed) into the bulky muscle of the upper, outer arm. The following twelve volunteers will receive the challenge antigens sublingually. This will be done by dripping 0.5mL (a few drops) under your tongue over a few seconds, while you hold your tongue up. We will place soft cotton pads inside your cheeks to absorb saliva. We will ask both groups to stay at the clinic for thirty minutes after the dosing to ensure that you are well.

Visits 3, 5, and 8 (1 week, five weeks, eight weeks and 17 weeks after the first dose of antigens on visit 2)

- During this visit only blood samples (about 25 mL) from the arm will be taken.

Visit 9 (20 weeks after the first dose of antigens)

- This will be your final visit during which blood (about 55 mL) and cervico-vaginal secretions will be collected for immunology tests.
- Vaginal sample collection using the 'instead' cup – optional
- Saliva sample - optional

In recognition of the time, inconvenience and some discomfort involved in taking part in this study you will receive a flat rate £100.00 compensation for each scheduled study visit actually

made. Reimbursement will be made after your last visit and blood results have been reviewed. The total amount you're likely to receive if you complete the study is £900.

What do I have to do?

This study does not require any specific lifestyle restrictions other than ensuring that you make yourself available for all study visits and comply with the instructions provided to you. There are some medications and vaginal treatments that may interfere with the study and if you need to take those we may have to withdraw you from the study. You should advise study staff of any changes to treatment or new treatments you begin during the study. You should not participate in any other clinical trial whilst being on this trial as the test substances may interact in ways we cannot predict, or interfere with our laboratory tests.

What are the antigens being used to challenge me?

The protein being used to stimulate your immune response is called L1 protein of Human Papilloma Virus (HPV). We have chosen the preparation of four individual L1 antigens present in the HPV vaccine "Gardasil". The safety of Gardasil been demonstrated in numerous clinical trials, and the UK Dept of Health is engaged in a mass HPV immunisation campaign in healthy young adult women. Gardasil reliably provoke serum and genital tract antibody responses in the majority of women after injection. We have selected Gardasil, not because we are particularly interested in HPV, but because it is a convenient, safe and effective way to stimulate immune responses that we can study.

Three applications of 0.5 mL of Gardasil will be given either:

- Intramuscularly on months 0, 1 and 4 - a schedule recommended in the Gardasil information leaflet.
- Or
- Sublingually on months 0, 1 and 4 to match the injected group.

What are the disadvantages and risks of taking part? What are the side-effects of any treatment received when taking part?

Gardasil does not contain thiomersal preservative. It does not contain live organisms and can not cause HPV infection or disease. The proteins contain no viral DNA, they can not infect cells, reproduce, or cause disease or cancer. It contains an "adjuvant: which is alum (aluminium hydroxide) present in many vaccines over many decades.

Gardasil is licensed for human use as an injected vaccine according to the dose and schedule we propose to use. Intramuscular injection is generally well tolerated and associated with the usual risks of alum-containing purified protein vaccines: fever, injection site inflammation or bruising being commonly reported. More serious complications such as bronchospasm (wheezing) and urticaria (rashes) are rare or very rare. Idiosyncratic (unexpected) reactions such as anaphylaxis (fainting and shock) may extremely rarely occur. In general, the adverse events reported with overdose was comparable to recommended single doses of Gardasil.

The risks associated with sublingual application has not be specifically evaluated, but is expected to be considerably less than after injection given the small amounts of protein expected to cross the lining of the mouth, compared with the dose delivered intramuscularly. Although local reactogenicity in the mouth has not been specifically studied, single-dose and repeated-dose toxicity and local tolerance studies of Gardasil revealed no special hazards to humans. Natural infection with HPV (which can also be oral) is initially without symptoms or signs and not associated with localised reactions to L1 viral surface proteins. The tiny (microgram) amounts of L1 protein and alum present no credible risk if swallowed, when compared with the huge (gram) amounts of protein (and other particulates such as toothpaste) swallowed daily. Any swallowed L1 or alum is expected to be immediately destroyed by gastric acid and digestive enzymes.

Taking blood may be associated with bruising, localised discomfort and fainting. Dedicated clinical facilities, including phlebotomy chairs will be used and staff must be trained and experienced. The blood volumes drawn over 20 weeks do not present a significant risk of causing anaemia in a healthy person, and you will be screened for anaemia before entry.

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Vaginal speculum examination can be uncomfortable, and staff will be experienced in the technique. Collection of secretions onto single-use, sterile, soft ophthalmic sponges (developed to collect tears) is painless and risk-free. A dedicated room complete with colposcopy couch, private changing and showering area, will be provided to minimise discomfort and ensure privacy.

The Full Blood Count, HIV and hepatitis tests, and medical examination may reveal illnesses you were not aware of. You will have a pre-test discussion before to discuss issues around HIV tests. We will give you all your results in confidence, and offer to inform your GP, and advise you about any follow-up or treatment of conditions that we discover - if you wish us to.

Pregnant women are recommended not to receive Gardasil as there is not yet enough information on its safety in pregnancy. Women who plan to become pregnant during the study should not take part. Women who could become pregnant will have regular pregnancy tests performed. Any woman who finds or suspects that she has become pregnant while taking part in the study should inform the study doctor immediately.

What are the possible benefits of taking part?

You will receive a free basic medical health check.

Nearly 100% of women who received Gardasil by injection develop immunity to the HPV strains represented in the vaccine. This level of immunity was associated with high levels of protection (approaching 100%) against cervical cancer lesions. Subjects already infected with HPV can expect to gain no benefit against the strain of virus with which they are infected, but will be protected against other strains. Subjects can expect to receive a high level of benefit in protection against HPV infection and associated cervical cancer or genital warts. Women over 18 are not eligible for the free NHS mass immunisation programme and so those receiving Gardasil by injection will benefit from a free vaccination with an effective vaccine against HPV.

No information is available for the level of immunity provoked by sublingual immunisation, this will be the first study to investigate this. However, it is expected that any immune responses induced will be low level and non-protective. You should therefore not expect to gain any benefit from inclusion in the group receiving sublingual administration.

What happens when the research study stops?

When the study stops you will not be required to do anything different from usual. Those who have completed three doses of intramuscular antigens will have completed the recommended course of Gardasil immunisation.

What if there is a problem?

Any complaint about the way you have been dealt with or any possible harm you might suffer will be addressed. The detailed information on this is given in part 2

Will my taking part in the study be kept confidential?

Yes, all the information about your participation in this study will be kept confidential. The details are in part 2.

This completes Part 1.

If the information in Part 1 has interested you and you are considering participation, please read the additional information in Part 2 before making any decision.

Part 2

What if relevant new information becomes available?

We will update you on any new developments and information related to the study that becomes available to us after you have signed this consent and which might affect your consent to participate. We will discuss with you whether you want to continue in the study. If you decide to withdraw from the study you may do so at any time without giving a reason. If you decide to continue in the study you may be asked to sign an updated consent form. The study doctors can at any time terminate your participation in the study or the whole study itself without your consent if it is in your best interests. If you are part-way through an intramuscular immunisation schedule we can advise you how to complete the course if appropriate.

What will happen if I don't want to carry on with this study?

You can withdraw at any time without giving a reason. Information collected may still be used. Any stored blood or tissue samples that can still be identified as yours will be destroyed if you wish.

What if there is a problem?

St Georges University of London has agreed that if you are harmed as a result of your participation in the study, you will be compensated, provided that, on the balance of probabilities, an injury was caused as a direct result of the intervention or procedures you received during the course of the study. These special compensation arrangements apply where an injury is caused to you that would not have occurred if you were not in the trial. These arrangements do not affect your right to pursue a claim through legal action.

Should you have a complaint you should discuss it with an appropriate member of the study staff and we would ask that you also put your complaint in writing.

Will my taking part in this study be kept confidential?

All information given to us by you and all the data we gain through tests is confidential. Strict rules apply with respect to the storage and use of all data which can be traced back to you personally. You can request a copy of all the personal data we hold about you at any time. We will ask your permission to contact your GP who will be informed that you are participating in a clinical trial.

You must not take part in too many studies because it's not good for you. So, we and other units like ours in the UK keep a database of healthy volunteers ("TOPS") and when they take part in studies. We'll enter into the database:

- your National Insurance number (if you're a UK citizen); or
- your passport number and country of origin (if you're not a UK citizen); and
- the date of your last dose of study antigens.

If you withdraw from the study before you receive any study antigens, the database will show that you never received a dose. Only staff at St George's and other medicines research units can use the database. We may call other units, or they may call us, to check your details. We'll keep your details for at least two years. If we need to contact you about the study after you've finished it, but we can't because you've moved or lost contact with your GP, we might be able to trace you through the information in the database.

Your personal and medical details will be held by the researcher in paper and electronic format for future reference for no longer than two years. Professor David Lewis will be the custodian of these details. This information may be made available to regulatory authorities for the purpose of inspecting and validating our work, and it may be disclosed on a strict 'need to know' basis in case of medical emergencies.

Identifying personal data (documents containing your name, address, phone number or other data allowing us to contact you) is held for your later identification related to this trial for as long this is required under currently applicable Good Clinical Practice guidelines and UK law, which is for at least the time the study is being carried out, but no longer than two years. We will also retain your identifying personal data for the same time in order to contact you at a later date either by e-mail, mail or telephone to supply or receive information including updates about future studies in which you may want to participate. You may instruct us not to contact you regarding future studies

All other personal data which will not identify you or include any information which may identify you will be processed for the purpose of the study, and for any additional scientific research, product registration purposes, research purposes in general, and for ensuring compliance with medical, ethical, and pharmaceutical laws and regulations may be kept indefinitely.

What will happen to any samples I give?

All samples will be given a unique number and letter code to make them anonymous. All samples will be kept and stored in secure facilities. Only staff members will be able to access them. The samples being taken will be treated as a 'gift', and you will not benefit financially if this research leads to the development of a new treatment or medical test. If we have to send samples or information to collaborators or other labs (including units overseas) we will "link-anonymise" the samples which means labelling them with the unique code that cannot be used to identify you, except by the study staff at St George's. As these clinical samples may be unique, if the results are promising we will seek permission to either conduct further analysis in a specific follow-on project, or enter them into an approved Tissue Bank to enable future research. However if neither is possible before ethical approval expires from this project they will be destroyed. If the results of this study are disappointing, and it is concluded that no useful further research on the samples is possible, they will be destroyed.

Will any genetic tests will be done?

No

What will happen to the results of the research study?

This research will help us better understand the basic mechanisms of the immune system. In order for us to share that information we may wish to publish the data in a scientific journal, or present it at meetings. Your identity will not be revealed at any time. If you wish to be kept informed of any publications or results, please do not hesitate to ask one of the researchers.

Who is organising and funding the research?

The study is being organised by St George's University of London. The study doctor is Professor David Lewis. The study has been funded by a grant from the Commission of the European Union.

Who has reviewed the study?

All research involving humans is looked at by an independent group of people called a Research Ethics Committee to protect your safety, wellbeing and dignity. This study has been reviewed and given a favourable opinion by Wandsworth Research Ethics Committee

Further Information and Contact Details

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