AANVRAAGFORMULIER PROJECTIDEE – BOTTOM-UP RONDE

COVID 19 programma

Deadline voor indiening: 14 mei 2020 (14:00 u)

LEES ALSTUBLIEFT ALLE INSTRUCTIES IN BIJLAGE ''TOELICHTING INDIENING PROJECTIDEE'' VAN DE OPROEPTEKST ZORGVULDIG!

Wanneer u het formulier heeft ingevuld:

1. **Zet het formulier om naar een PDF file en controleer de details**
2. **Upload het complete formulier als een bijlage bij uw indiening in Projectnet (Let op: dit zijn twee verschillende links, gebruik maar 1 van de 2!)**

ProjectNet: Aandachtsgebied 1 (voorspellende diagnostiek en behandeling)
ProjectNet: Aandachtsgebied 2 (zorg en preventie)

BASISGEGEVENS (voorpagina)

NAAM VAN DE HOOFDAANVRAGER:

5.1.2e 5.1.2e

ORGANISATIE:

Spaarne Gasthuis

PROJECTTITEL:

SARSLIVA:
utility of saliva in diagnosis, detecting co-infections, and evaluating household transmission in COVID-19

DATASTEWARD:

Wie is de datasteward die de open science en FAIR data planning in uw project ondersteunt? Zie de webinars op de ZonMw website om de datastewards te informeren en ondersteunen.

☐ Ik betrek een datasteward bij mijn project:
Naam: Klik of tik om tekst in te voeren.
Instituut: Klik of tik om tekst in te voeren.
E-mail: Klik of tik om tekst in te voeren.
Was aanwezig bij de webinar: ☐ Ja ☐ Nee

☒ Ik heb nog geen datasteward.

ONDERZOEKSVOORSTEL **max 3 pagina's A4** (inclusief literatuurreferenties)	(voorpagina met basisgegevens niet meegerekend - font type Arial 10 pts)

1. PROBLEEMSTELLING EN DOELSTELLING(EN):

In mitigating the SARS-CoV-2 pandemic, governments have to weigh the public health benefit of interventions such as school closure and closing of restaurants and theatres against the significant societal and economic disruption they impose. After opening up schools and public life, and restarting the economy, close monitoring of spread of the virus is a crucial tool for success of tracing the virus and SARS-CoV-2 spreading in the population. Recently, tracking the virus in saliva by molecular diagnostics was shown to be at least as sensitive as the most broadly used method of viral detection in nasopharyngeal (NP) swabs (Wyllie A et al, medRxiv; doi.org/10.1101/2020.04.16.20067835). Saliva sampling would be a very attractive way for large scale monitoring of SARS-CoV-2 spreading. However, saliva sampling has not yet been validated for a-symptomatic and pre-symptomatic SARS-CoV-2 infected individuals. If we can use saliva for early detection, containment of viral spread is made easier. Saliva is also not yet validated at lower viral density in the track of COVID-19 infection. This would allow to see whether persons, who we now know may remain symptomatic for a prolonged period of time (weeks to months), are still infectious.

Nasopharyngeal swabs are currently the specimen most often collected for SARS-CoV-2 detection. But good NP swabbing requires trained health-care professionals collecting these, wearing protective equipment to administer since swabbing induces coughing and sneezing. In contrast, collection of saliva is easy by self-sampling, causes no discomfort and this way avoids necessity of trained health care workers. Saliva collection can be done at home by COVID-19 patients in follow-up, and by members of household of COVID patients or by those who have been in contact with a case and need to be monitored.

In the study from Yale, saliva was collected by drooling in a sterile cup in the early morning, before tooth brushing and breakfast, and transported to the laboratory within 48 hours. In a direct comparison between 38 paired nasopharyngeal and saliva samples from COVID-19 patients, the Yale group found comparable or higher sensitivity and similar or higher SARS-CoV-2 loads in saliva than in nasopharyngeal swabs. Also 98 asymptomatic health-care worker were evaluated and SARS-CoV-2 was found in saliva of two health-care workers who had tested negative using the nasopharyngeal swabs. In an Italian study, saliva tested positive for all 25 COVID-19 patients, even on the day that upper respiratory swabs converted to negative. These findings suggest that saliva may be a valid sample for assessing the presence as well as the duration of SARS-CoV-2 infections.

Based on our own experience and published papers, a larger volume of saliva collected by drooling seems not only the simplest but possibly also the optimal approach in SARS-CoV-2 detection. Almost any modification, like using swabs or any other cotton- or dacron-based devices, with potential inhibitors and less volume of saliva, seem to harm rather than help (5.1.2e , one of authors of the "Brief Summary on Using Oral Fluids for CoV"). In children under 5 years of age, a sponge for saliva collection is required since drooling or spitting is too difficult. In the Netherlands, the currently ongoing FXX study by RIVM collects saliva with a ORACOL sponge, along with NP and OP swabs by trained research nurses at home visits. Saliva is immediately put on ice and samples are transported the same day to the RIVM laboratory. It was confirmed that with this protocol, results from saliva on SARS-CoV-2 detection are virtually in the same range as detection in NP and OP swabs (pers. Communication 5.1.2e , RIVM).

For large scale monitoring, home self-sampling without need of health care workers is preferred. Sampling and storage in home settings should also allow for a delay in transport to the lab for two or more days.
In this study we want to assess the sensitivity of self-sampling of saliva, in home situations, compared with NP and OP swabs in COVID-19 patients. Sampling and storage in home settings should also allow for a delay in transport to the lab for two or more days.

Next we like to assess whether saliva sampling is suitable for detecting lower viral loads and tracing SARS-CoV-2, not only in asymptomatic or pre-symptomatic persons who nevertheless may be shedding SARS-

CoV -2 and spreading the virus, but also in follow-up of COVID-19 patients for several weeks who may continua shedding via respiratory droplets.

In addition to SARS-CoV-2 detection, saliva may also be a good specimen for detecting emerging mucosal IgA and IgG antibodies against SARS-CoV-2.
Also, with molecular diagnostics, other respiratory viral and bacterial pathogens can be detected in saliva. Lastly, saliva may be a tool for oral microbiome and mycobiome analysis.

We therefore propose **a pilot study** which will allow us to determine:
Primary aims

1. The sensitivity of saliva collection for SARS-CoV-2 tracing, with home self-sampling, storage and transport to the laboratory.
2. The sensitivity of saliva in a- and pre-symptomatic persons of household members of COVID-19 patients
3. The emergence of IgA and IgG anti-SARS-CoV-2 specific antibodies in saliva

Secondary aims

4. Evaluation of tracing other respiratory viruses in saliva

Exploratory

5. Evaluation of potential bacterial pathogens by molecular diagnostics (PCR)
6. Evaluate the oral microbiome with 16S and mycobiome with 18S/28S/ITS dynamics

2. PLAN VAN AANPAK:

Descriptive study.

COVID-19 patients and follow-up
We will ask 75 patients, aged 1-75 years, referred to the Spaarne hospital for suspected COVID-19 and confirmed by diagnostics by NP/OP swabs, to collect saliva the next morning, before breakfast, drinks and tooth brushing. We ask for two samples in the morning, at day 1, 2 , 3 , 5, 7,11, 15, 18, 21, 28, 35, 42 after COVID diagnosis, together with a short questionnaire on symptoms.
For saliva collection we will use

a) ORACOL-sponge in case of children under 5 yrs of age, who cannot yet spit
b) Drooling into a sterile tube according to instructions for those > 5 yrs

Samples are immediately frozen and stored in the home freezer to be collected later by a courier to the laboratory. In these samples SARS-CoV-2 and SARS-CoV-2 viral loads will be evaluated as well as other respiratory viruses. Viruses may co-exist with SARS-CoV-2, or may lower SARS-CoV-2 acquisition. Viral interference will be explored. Short questionnaires on symptoms, vaccination status (seasonal influenza, pneumococcal vaccines) will be collected

We will ask for a second saliva sample *once a week* for 6 weeks with ORACOL sponge/ drooling into a tube with EDTA medium up to a volume of 2 ml and store at room temperature. In the EDTA medium saliva, IgA and IgG anti-SARS-CoV-2 specific antibodies in saliva will be determined. At 4-6 weeks after COVID-2 diagnosis of the index case, also a blood sample (capillary, dry blood spot) will be collected to compare serum and saliva antibody emergence.

A- and pre-symptomatic persons of household members of COVID-19 pts
Household contacts of confirmed COVID-19 patients will be asked to collect saliva by self-sampling according to the same procedure as asked from COVID-19 patients, *every day in the first week* after diagnosis of COVID in index case and twice per week for the following 5 weeks. EDTA saliva will be collected once/week. Parents will collect saliva specimens of kids under 5 years of age with the ORACOL sponge, older persons are asked to drool in a tube. SARS-CoV-2 and other respiratory viruses in saliva and antibodies in household members will be determined, together with short questionnaires on symptoms.

With respect to exploratory endpoints, we will explore **feasibility to determine presence potential bacterial pathogens**. We have ample experience with molecular (PCR) diagnostics in saliva for assessment of bacterial dynamics due to COVID-19 compared with other viruses like influenza.
We will also explore feasibility and changes in the oral microbiome with 16S and mycobiome with 18S/28S/ITS
This may be explored before and after COVID-19 infection for potential changes or fungal outgrowth like Aspergillus.
We have ample experience with molecular diagnostics in saliva and microbiome studies.

3. HAALBAARHEID VAN HET PROJECT:

TIJDSSCHEMA
We already have METC approval and have started the study. We aim to include 75 patients and families. In case we include 3 COVID-19 patients/week who are willing to participate and family members who are willing to participate, the study will take 25 weeks /6 months and cover the autumn and early winter respiratory season of 2020 (July 2020 to January 2021). This inclusion rate is feasible in the Spaarne hospital, but other hospitals will help when necessary. We have ample experience in large, complicated trials with home sampling and home visits, including films and instructions for home sampling, cold chain transport, short questionnaires. A whole trial infrastructure is ready at our Spaarne Gasthuis Academy, that exists since 2003 and has performed many large studies, with high qualified personnel which are trained at different times to achieve samples of high quality. We have a longstanding collaboration with Streeklaboratory Haarlem who will perform COVID-19 diagnostics. Streeklab will work together with the RIVM to perform all laboratory diagnostics according to the adjusted scheme. The projected tests are already implemented at the Streeklaboratory and the RIVM. Expertise on the datapoints and analysis is present. Together, stakeholders have ample experience in all aspects of the proposed study.

	Winter season 2020							Spring season 2021				
	July	Aug	Sept	Oct	Nov	Dec	Jan	Feb	March	April	May	June	July
Enrolment	x	x	x	x	x	x							
Follow-up of families	x	x	x	x	x	x	x						
LAB ANAYSIS		x	x	x	x	x	x	x					
Data analysis and reporting									x	x	x	x	x

4. RELEVANTIE VOOR DE PRAKTIJK:

In this PILOT, we are seeking proof that saliva self-sampling at home can be indeed utilized in monitoring SARS-CoV-2 tracing and spread in the population, also presymptomatic and in low viral loads. It would be an easy and non-invasive way of testing 5.1.2e a Nobel Prize-winning economist, believes that significantly boosting the number of tests is the only way out of the economic and health crises. A simpler collection device that uses spit instead of swabs would make it easier.

5. DEELNAME VAN DE STAKEHOLDER(S) (e.g. patiënten, zorgprofessionals, etc.):

RIVM:
-The viral diagnostic unit Dr 5.1.2e Dr 5.1.2e, supervising national viral and serology diagnostics for SARS-CoV-2.
- Dr 5.1.2e, molecular diagnostics and microbiome/mycobiome studies.
- Dr 5.1.2e Immunology/serology and 5.1.2e PIENTER CORONA study on SARS-CoV-2 serology
UMCU &RIVM: Molecular diagnostics (bacterial); dr 5.1.2e, collaborating with RIVM. Long standing experience with saliva as specimen for tracing bacterial infections.
UMCU WKZ & RIVM: Prof dr 5.1.2e 5.1.2e 5.1.2e at RIVM, experienced in large scale trials on respiratory infections and microbiome studies.
Streeklab Haarlem: 5.1.2e 5.1.2e of the Streeklaboratory Haarlem, 5.1.2e, epidemiologist
Spaarne Gasthuis: 5.1.2e Internist-infectious diseases and 5.1.2e pulmonologist