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

ORGANISATIE:

Spaarne

PROJECTTITEL:

SARSLIVA

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 (ref 5.1.2e. Saliva sampling would be a very attractive way for large scale monitoring of SARS-CoV-2 spreading.

Saliva is an obvious source for SARS-CoV-2 detection. The virus's ability to infect and actively reproduce in the upper respiratory tract was shown last month by Wendtner et al, who reported on experiments that virus from the throats of nine people with COVID-19 could be cultured, showing that the virus is actively reproducing and infectious there (ref). Saliva gland ducts also express the ACE2 receptor for the virus, as was shown in rhesus macaques. It has been shown that high viral loads were already present in the saliva of COVID-19 patients at the onset of disease, which could account for the fast-spreading nature of this epidemic (ref). Also, SARS-CoV-2 infection appears to shed viral particles from the throat into saliva even before symptoms start. Pre-symptomatic transmission was estimated to contribute to 48% (95%CI 32-67%) and 62% (95%CI 50-76%) of diagnosed COVID-19 cases in Singapore and in Tianjin, China, respectively (ref) Saliva may be therefore be the obvious tool to detect asymptomatic and presymptomatic individuals before actual symptoms present. If we can use saliva for early detection, containment of viral spread is made easier.

Nasopharyngeal swabs are currently the specimen most often colleced for SARS-CoV-2 detection (WHO en ref RIVM/ 5.1.2e stuk ?). 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. For this part however, one needs to confirm the best way of collecting and storing saliva, when not in a hospital or study setting and without specimens transported to the lab within 24-48 hours for diagnostics.

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. (ref) 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 (ref). These findings suggest that saliva may be a valid sample for assessing the presence as well as the duration of SARS-CoV-2 infections. There are some conflicting results however. Data from Australia on 522 paired saliva and nasopharyngeal swabs of COVID-19 suspected patients demonstrated inferior sensitivity of saliva (ref). Together, 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 (ref 5.1.2e For example, our pilot results already showed that adding RNA -protect hampered sensitivity compared with drooling a larger volume of saliva in a tube. (personal communication 5.1.2e .
In the Netherlands, the currently ongoing FXX study by RIVM collects saliva, along with NP and OP swabs, collected by trained research nurses at home visits. Saliva is collected with a ORACOL sponge at the same

time by trained research nurses, put on dry ice and samples are immediately transported to the RIVM laboratory. Laboratory procedures are performed within 48 hours. 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 (ref 5.1.2e bijvoegen?)

AIM:
For large scale monitoring, home self-sampling without need of health care workers is preferred. In this study we want to asses the best way of self-sampling of saliva, in home situations. Sampling and storage in home settings should also allow for a delay in transport to the lab for two or more days. Room temperature and sending samples by post would be preferred to cold chain transport.

Also we like to assess whether saliva sampling is suitable for detecting lower viral loads and tracing SARS-CoV-2 in asymptomatic or pre-symptomatic persons who nevertheless may be shedding SARS-CoV -2 and spreading the virus

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

1. The best method of saliva collection, storage and transport for self-sampling at home.
2. The sensitivity of saliva over time with lower viral loads in patients with COVID-2
3. Evaluate the sensitivity of saliva in a- and pre-symptomatic persons
4. The best method of saliva preservation for SARS-CoV-2 specific antibody detection

2. PLAN VAN AANPAK:

1. The best method of saliva collection, storage and transport for self-sampling at home.

The sampling with the ORACOL sponge as in the FXX study at RIVM and cold chain transport within 48 hours to the RIVM laboratory is considered the gold-standard in this study. Longer storage is not tested yet. Also, avoiding freezing samples at home and avoiding cold-chain transport and thawing of samples upon arrival in the laboratory would be of great benefit. Thawing will cause a likely loss of sensitivity for viral detection and antibodies due to the multitude of enzymes in saliva for monitoring specimens.

We will compare the FFX protocol with freezing and cold chain transport with collecting saliva in medium with inhibitors of RNA-ses with storage and transport at room temperature.

We will ask 30 patients, aged 1-90 years and admitted to the Spaarne hospital for COVID-19, confirmed by routine diagnostics by NP and OP swabs, to collect saliva the next morning, before breakfast, drinks and tooth brushing. We ask for two samples

1. The ORACOL XX sponge according to instructions and immediate freezing and storage at -20
2. Drooling into a tube with medium with RNA-protect up to a volume of 2 ml and store at room temperature.

In the laboratory, SARS-CoV-2 detection and viral load will be compared after storage for 24, 48 hours and 5 days. In case of children under 5 years of age, drooling and spitting in a tube is too difficult. We will ask parents to collect saliva by the ORACOL sponge and either freeze the specimen immediately or put the sponge in RNA-protect medium and store the specimen at room temperature

2. The sensitivity of saliva over time with lowering viral loads over time in COVID-19 patients.

After selecting the best method for saliva collection, we want to follow a total of 40 COVID-19 patients during 6 weeks upon discharge, at home to see how long we may detect SARS-CoV-2 in saliva. Patients will perform self-sampling at home (twice per week) and at least for 2 weeks after samples have become negative over a period of 6 weeks. Samples will be monitored for SARS-CoV-2 detection and changes in viral loads over the course of infection along with a short questionnaire about symptoms.
Of ???
We will ask discharged patients to prolong self-sampling at home with both the ORACOL sponge and the RNA-protect medium. SARS-CoV-2 detection and viral load will be determined at days .....

In case of children under 5 years of age, we will ask parents to collect saliva by the ORACOL sponge and either freeze the specimen immediately or put the sponge in RNA-protect medium and store the specimen at room temperature.

3. **Evaluation of detection of SARS-CoV-2 in saliva from a- or pre-symptomatic individuals**

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 patients. Parents will collect saliva specimens of kids under 5 years of age. Household members will be followed for 6 weeks after diagnosis of the index case with saliva sampling 2 times per week.

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4. **The best method of saliva preservation for SARS-CoV-2 specific antibody detection**

Since RNA-protect interferes with antibody detection like IgA-anti SARS-CoV-2 detection in saliva, we will ask for a second spit sample in EDTA medium, known to protect against loss of salivary immunoglobulins (ref). We will compare immunoglobulin data in raw saliva without medium with saliva collected in EDTA from 30 COVID-19 patients and 60 household members that either become symptomatic COVID-19 patients or remain asymptomatic over 6 weeks of time. A second sample with EDTA medium will be collected once per week.

3. HAALBAARHEID VAN HET PROJECT:

TIJDSSCHEMA
We already have METC approval and have started the study. We aim to include ….

In case COVID admission are low … …andere ziekenhuizen…
MOTIVATIE HAALBAARHEID
(ik zie niks over budget, toch indicatie doen?)

4. RELEVANTIE VOOR DE PRAKTIJK:

Onderbouw de relevantie aan de hand van de in de subsidieoproep benoemde relevantiecriteria
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. It would be an easy and non-invasive way of testing, 5.1.2e, a 5.1.2e 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 to supersize the nation's testing capacity, he said in an interview (ref nature).

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

1. RIVM 5.1.2e 5.1.2e 5.1.2e, 5.1.2e 5.1.2e, 5.1.2e 5.1.2e, 5.1.2e
2. UMCUtrecht 5.1.2e
3. Streeklaboratorium Haarlem 5.1.2e 5.1.2e 5.1.2e 5.1.2e
4. Kliniek interne etc

6. LITERATUURREFERENTIES (optioneel):

Nog invullen