AANVRAAGFORMULIER
UITGEWERKTE SUBSIDIEAANVRAAG
– BOTTOM-UP RONDE

COVID 19 programma

Deadline voor indiening: 15 juni 2020 (14:00 u)

LEES ALSTUBLIEFT ALLE INSTRUCTIES IN BIJLAGE ''TOELICHTING INDIENING SUBSIDIEAANVRAAG" 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)

NAAM VAN DE HOOFDAANVRAGER:

Dr. 5.1.2e pediatrician, PI Vaccination, Infection and Immunity

ORGANISATIE:

Spaarne Gasthuis

ENGELSE PROJECTTITEL:

SARSLIVA and utility of saliva in diagnosis for wide scale testing, including viral and SARS-CoV-2 antibody detection in pre- and asymptomatic persons and follow-up of infections in COVID-19 patient; a house hold study

NEDERLANDSE PROJECTTITEL:

SARSLIVA: studie naar speeksel als middel om betrouwbaar het COVID-19 virus en antistoffen hiertegen aan te tonen; onderzoek naar gevoeligheid van de test bij pre- en asymptomatische corona besmettingen en de duur van besmettelijk zijn bij COVID-19 patiënten.

ONDERZOEKSVOORSTEL **max 8 pagina's A4** (inclusief literatuurreferenties)	(voorpagina met basisgegevens niet meegerekend - font type Arial 10 pts)

1. PROBLEEMSTELLING, URGENTIE EN DOELSTELLING(EN)

Onderbouw probleemstelling, urgentie en doelstelling. Maak doelstelling SMART (specifiek, meetbaar, acceptabel, realistisch en tijdsgebonden)

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 by wide scale testing of spread of the virus is a crucial tool for success of tracing the virus and SARS-CoV-2 spreading in the population. Easy testing without causing too much discomfort and costs will help to keep (repeated) testing over time acceptable for both individuals and health care. 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 [1, 2,3,4]. Saliva sampling would be a very attractive way for large scale monitoring by self-sampling of SARS-CoV-2 spreading. However, saliva sampling has not yet been validated as single sampling specimen and for SARS-CoV-2 detection in a-symptomatic and pre-symptomatic SARS-CoV-2 infected individuals, who already may have high viral loads the days before becoming symptomatic. If we can use saliva for early detection, containment of viral spread is made a lot easier. Saliva is also not yet validated at lower viral density in the track of COVID-19 infection. This would allow to see how long 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 [1,3,4]. 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 and costs [1,5,6,7]. Saliva collection may be done at home by COVID-19 patients in follow-up, and by pre- and as yet asymptomatic members of household of COVID-19 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 [1]. 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 [3]. 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 [1,5]. 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 [4]. In the Netherlands, the currently ongoing FXX study by RIVM collects saliva with a single 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 in the same range as detection in NP and OP swabs (pers. Communication 5.1.2e, RIVM). In children under 5 years of age, a sponge for saliva collection is required since drooling or spitting is too difficult. In older children and in adults, a larger volume of saliva can be safely collected by self-sampling at home, by using all-in-one prefab saliva collector tubes [1,5].

For large scale monitoring, home self-sampling without need of health care workers would offer great advantages. After sampling, storage in home settings should also allow for a delay in transport to the lab for two or more days.
In this study we (1) 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 want to (2) 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 the follow-up of COVID-19 patients for several weeks, who may continue shedding via respiratory droplets. This will be done by screening household members of confirmed COVID-19 patients, and by follow-up of COVID-19 patients for several weeks.

In addition to SARS-CoV-2 detection, saliva may also be a good specimen for (3) detecting emerging mucosal IgA, IgM and IgG antibodies against SARS-CoV-2 [7,8]. This may provide additional information on recent contact or previous infections with SARs-CoV-2 virus (personal communication. dr. 5.1.2e 5.1.2e en dr. Marien de Jonge, RadboudMC together with dr. 5.1.2e, RIVM and co-applicant of this study)

Also, with molecular diagnostics, (4) other respiratory viral pathogens can be detected in saliva, that may enhance of inhibit SARS-CoV-2 infection and symptoms

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 at home and transport to the laboratory in COVID-19 patients during 3-6 weeks of follow-up.
2. The sensitivity of saliva in a- and pre-symptomatic persons of household members of COVID-19 patients
3. The emergence of IgA, IgM and IgG anti-SARS-CoV-2 specific antibodies in saliva

Secondary aims

4. Evaluation of tracing other respiratory viruses in saliva

2. LOPEND ONDERZOEK

Beschrijf beknopt gepubliceerd onderzoek EN lopend nationaal (en waar mogelijk internationaal) onderzoek op dit gebied en wat uw project daaraan toevoegt. Zie hier een lijst met mogelijke portals.

The current project is fully aligned with the FXX study by the National Institute of Public Health and the Environment (RIVM), with RIVM researchers as co-applicants of the SARSLIVA study. In the Dutch FFX study, saliva is collected together with NP and OP swabs (by trained research nurses), from household members of index-persons with proven COVID-19. The SARSLIVA study will add to the FFX: screening over time of COVID-19 index-patients and pre- and asymptomatic household members to (possibly) detect early infection in pre- and asymptomatic household members (by viral or antibody detection). In addition, the SARSLIVA study will follow-up index-patients and household members. This will add substantial additional data and power to the FXX study, and empower the use of saliva as single specimen to detect SARS-CoV-2 infection.
The SARSLIVA study will also add valuable data to the ZonMW financed CoKids study (nr 10150062010006), where RIVM investigators and several applicants of this study are co-investigators. In the CoKids study, there is limited follow-up of patients and household members, apart from registration of symptoms via the app, and saliva collection is not (as yet) included. We are looking for additional funding to also add saliva collection in the CoKids study. Investigators of the CoKids study are also involved in the SARSLIVA study. There is also a link with the European Rapid European COVID-19 Emergency Research response (RECOVER), a project involving 10 international partners funded under the European Union Horizon 2020 research framework. RECOVER originates from partners of the PREPARE project (Platform for European Preparedness Against (Re-) and emerging Epidemics, see www.prepare-europe.eu; the EU Framework 7 (FP7) funded) and closely follows the PREPARE Outbreak Research Modes. The objective of

this study is also to characterize onward household transmission by COVID-19 index cases identified in secondary care, and by SARS-CoV-2 positive healthcare workers identified through screening programs . In RECOVER, saliva collection is also not part of the study and self-sampling is performed by nasal and oral swabs. The PI of CoKids and several RIVM applicants are also involved in de RECOVER study, with several co-investigators from RIVM/SARSLIVA involved in all four studies. This ensures data sharing and working according to the same protocol, with similar procedures for data collection, sampling procedures, definitions and algorithms, allowing datafiles to be merged at a later stage for joint analyses.
The SARSLIVA household study is aligned with the WHO Household transmission investigation protocol for COVID-19 [9] In summary, SARSLIVA will provide informative new data for data sharing with the FXX, CoKIDS and RECOVER household study.

3. PLAN VAN AANPAK (ONDERBOUW KEUZES)

DESIGN
This will be an observational household cohort study, based on 75 index-cases with laboratory-confirmed COVID-19 and their household members.

STUDY POPULATION
We will invite index-patients and their families on the day they are diagnosed to participate in the SARSLIVA study. The index-patient is diagnosed to suffer from (laboratory-confirmed) COVID-19 by routine diagnostics using NP/OP swabs in either 1. the Spaarne hospital on referral because of COVID-19-like complaints, 2. the GP because of complaints, 3. municipal health services Kennemerland for testing because of SARS-CoV-2 contact or complaints, including health care workers at the Spaarne hospital, in case of screening or testing because of complaints. In case of consent from both index- patient and at least two household members (living in the same house), index-patients and household members will undergo the same study procedures. At enrolment, short questionnaires on subject characteristics such as medical history, medication use and vaccination status (seasonal influenza, pneumococcal vaccines) will be collected.

By recruitment of COVID-19 index-cases from different groups (hospital, GPs, and municipal health services Kennemerland), we ensure adequate enrolment rate of patients with varying disease severity.

Inclusion criteria:
- Age index case 0-65 years
- Laboratory-confirmed COVID-19 of index case
- Household living together with at least 3 individuals, including the index patient
- Informed consent of index-patient and at least 2 other household members

Exclusion criteria:
- Language barrier, or
- Living more than 50 km from the Spaarne Gasthuis Haarlem Zuid

COLLECTION OF SALIVA BY SELF-SAMPLING AT HOME AND EXTRA NP/OP SWABBING BY HEALTH CARE WORKER
We ask for saliva sampling in the morning the day after informed consent was provided from index-case and household members (at day 1 after diagnosis of index-case) followed by day 3, 5, 7, 10, 14, 21, 28, 35, 42 after COVID-19 diagnosis of the index-case, together with a short questionnaire on medical history and symptoms. This is done to assess the duration of SARS-CoV-2 positivity and the viral load over time in relation to symptoms and transmission to household members. Samples are collected most frequently in the first 2 weeks, the period we expect mostly emergence of SARS-CoV-2 in saliva in household members. On day 7, a research nurse will conduct a home visit, (with appropriate protective gear (gloves, mask, coat, glasses), to collect an additional NP and OP swab from all participants. This to investigate if SARS-CoV-2 is (still) detected in these NP/OP samples when compared with the saliva sample collected at this same day. In weeks 3-6, we aim to collect samples weekly, also to be able to trace mucosal antibody development through time.

SALIVA SAMPLE COLLECTION AND STORAGE

For saliva collection we will use:

a) 2 ORACOL-sponges in case of children under 5 yrs of age, who cannot spit. Two sponges are to ensure sufficient volume of saliva.
b) Drooling at least 2 ml of saliva into a sterile tube, according to instructions for those > 5 yrs. For drooling we will use a collection device with a funnel (Isohelix Genefix Saliva Collection without buffer) and instructions to ensure clean saliva collection.

Samples are immediately frozen and stored by participants in the home freezer to be collected later by a courier for transport to the laboratory (cold chain transport). For each time point of home sampling of saliva, a Safetybag (DaklaPack© Medical Packaging) is provided for safe storage of saliva collection tubes. The Safetybag is suitable as secondary liquid-tight packaging of Category B diagnostic samples. The bag is hermetically sealed simply by removing the covering strip, thereby minimizing the risk of contamination.
At day 7 following COVID-19 diagnosis, additional NP and OP swabs will be collected by a trained research nurse. NP/OP swabs in Amies medium will transported to the laboratory within 4-6 hours.
Finally, at 42 days after COVID-19 diagnosis, an optional blood sample (capillary) will be collected by a finger prick to compare serum (immunoglobulins IgM, IgG and IgA) with saliva antibody emergence.

LABORATORY DIAGNOSTICS

On arrival in the laboratory the samples will be stored at -80°C until testing. After thawing, samples will be aliquoted in two parts. In the first aliquot, SARS-CoV-2 and SARS-CoV-2 viral loads will be evaluated. Nucleic acid extraction is conducted via MagNA Pure96 (Roche) and reverse transcriptase quantitative PCR is performed on Lightcycler 480 system (Roche) targeting the E gene. The RNA extraction protocol uses dithiothreitol (DTT), that is frequently used as a mucolytic agent. Preliminary results from a pilot experiment show no issues so far with viscosity of saliva for viral load detection.
Presence of other respiratory viruses will be assessed using fast track PCR. This will be performed once for all index cases and once for all household members who develop respiratory symptoms during follow-up, which is estimated to happen in 50% of the household members.

In the other aliquot containing EDTA, salivary SARS-CoV-2 specific antibodies (immunoglobulins IgM, IgA and IgG anti SARS-CoV-2) will be measured to assess the development of (mucosal) immunity over time once per week. We have ample experience with antibody assessment in saliva. We commonly dilute the saliva in (EDTA) assay buffer for antibody detection, thereby also reducing the issues of viscosity.
Testing for SARS-CoV-2 IgA, IgM and IgG antibodies in saliva will also help identify additional cases negative on rRT-PCR and may contribute to determine contact with SARS-CoV-2 of household members.
SARS-CoV-2 specific antibodies (immunoglobulins IgG and IgM) will also be measured in serum collected at the end of the study period after 6 weeks. Antibodies will be measured using microarray to quantify the different types of immunoglobulins separately, and by Wantai ELISA to quantify IgM and the total immunoglobulin level. Both methods are complementary and will be used to obtain more insight.

All collected and processed, remaining sample materials will be biobanked and available for additional virological and serological studies, when applicable.

EXPECTED OUTCOME

We expect to find that saliva is as sensitive for SARS-CoV-2 tracing as nasal and/or oral swabs in COVID-19 cases, based on experience in the FFX study and some early results in literature [1, 3 ,7]. We also expect that the viral load of SARS-CoV-2 in saliva is at its highest the last few days before and at symptom onset, and thus that we may detect SARS-CoV-2 in saliva from household members who may be presymptomatic or even remain asymptomatic. This would provide a proof-of-concept that saliva is as good as nasal or oral swabs for diagnosing and monitoring the presence of SARS-CoV-2.
Regarding antibody detection, we expect to find that serum and salivary antibody levels (immunoglobulin G) against SARS-CoV-2 are correlated (based on experience with other pathogens and first results from the RadboudMC) [10-12], implying that saliva may also be a useful specimen to evaluate immunity against (IgG). Based on preliminary results from the RadboudMC, we expect that salivary IgA and IgM enable to detect contact with the SARS-CoV-2 virus. Furthermore, we expect that IgA and IgG salivary antibodies

against SARS-CoV-2 increase over time once infected, and that the timing of this increase in index cases and household members will be related to the timing of symptom onset. This may add important value to screening for SARS-CoV-2.

DATA-ANALYSE

Diagnostic performance of the SARS-CoV-2 PCR in saliva samples compared to nasal and/or oral swabs will be evaluated by assessing sensitivity, specificity, positive predictive value and negative predictive value of testing for SARS-CoV-2 in saliva using 2x2 contingency tables. 95% Confidence intervals will be calculated using the Score confidence interval (when the proportion is in the range [5%-95%], or with the Exact confidence interval, and compared using McNemar's tests. Comparisons of viral load of SARS-CoV-2 (Ct-values) from quantitative PCR between saliva, NP and OP swabs will be performed using Wilcoxon signed rank tests. Concordance of serum and salivary antibody levels and change over time will be evaluated using Wilcoxon signed rank test (matched samples) and Mann-Whitney U-test (between groups), and linear regression models. Viruses may co-exist with SARS-CoV-2, or may lower SARS-CoV-2 acquisition. Viral interference will be explored.

The final dataset will be published in an open-access data repository (Dataverse) and will be shared with collaborating partners in the project for research purposes and shared with the wider scientific community upon COVID 19 or other FAIR data point.

POWER CALCULATION

No formal sample size can be calculated, but larger studies will undoubtedly permit more robust analysis. We aim to enrol 75 households of at least 3 individuals who provide informed consent.
In order to address the primary objective, a total of 60-80 SARS-CoV-2 positive subjects will be required. This sample size is based on previous reports of tests for other infectious agents yielding comparable results in saliva as in NP and OP swabs [6,13-15]. Data can be further enriched with data from the RIVM FFX household studies. Data on children may be enriched by data from the CoKids study, when we have funding for additional saliva collection in the CoKids study.

4. PLAN VAN AANPAK (ONDERBOUW KEUZES)

TIME SCHEDULE

We plan to start enrolment in July 2020, and continue until January 2021. The scheme below shows our proposed schedule. We plan to run laboratory analyses in parallel with the recruitment and follow-up, so that first results will rapidly become available in Spring/Summer 2021.

MOTIVATIE HAALBAARHEID

	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	x						
Follow-up of families	x	x	x	x	x	x	x	x					
laboratory analysis		x	x	x	x	x	x	x	x	X			
Data analysis and reporting									x	x	x	x	x

We already have METC approval for saliva collection in COVID-19 patients recruited at Spaarne Gasthuis Haarlem Zuid and have started this study. Therefore, study protocols for saliva collection are already approved. We approached the general practitioners and municipal health services, and they are willing to participate. Information about additional saliva collection sampling moments, the extra NP/OP swabbing at day 7 and blood collection at day 42 by a finger prick will be added to the study protocol and the patient information leaflet that will be sent to the METC VUmc for review and approval.
In all, we aim to include 75 patients and families. between July 2020 to February 2021. At the moment, with low SARS-CoV-2 circulation we expect to include 2 families week. In the autumn, we expect this to increase to 3-4 households /week. This inclusion rate appears feasible, especially with the different study sites. We have ample experience in large, complicated trials with home sampling and home visits, and have instructions and video's for home sampling. The Spaarne Gasthuis academy has all required facilities for

cold chain transport up and running and the complete trial infrastructure is ready for the study, that exists since 2003 and has performed many large studies, with highly 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 and RIVM. The Streeklaboratory together with RIVM will perform all laboratory diagnostics. 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.

RECRUITMENT STRATEGY
We will recruit cases at different sites. In the Spaarne Gasthuis Haarlem Zuid, eligible patients will be invited by the treating physician, who will refer potential participants to the study team. COVID-19 cases presenting to the municipal health services Kennemerland, and to general practitioners, will at the time of testing, receive a leaflet with information on the study and contact details. When tested positive, the physician will ask them whether they might be willing to participate. Participants then contact the study team, who will provide all information. In case of informed consent, all study procedures will be explained by research physician and/or research nurses and materials will be delivered at home.

5. RELEVANTIE

OPROEP SPECIFIEKE RELEVANTIE CRITERIA
Given that saliva can be self-collected, leaving healthcare workers unexposed, and at home, without discomfort like nasal and oral swabs, this could have important implications for wide scale diagnostic testing.
In this PILOT in the area of diagnostics, 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. 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. In the Netherlands, wide scale sampling is now done by trained health care workers, with protective gear, by oral and/or nasal swabs that cause discomfort. Particularly in young children and teenagers, repeated testing will not be appreciated, once they underwent nasopharyngeal and throat swabbing. The procedure is time-consuming for COVID patients and contacts who have to arrange an appointment for sampling time during the day, and labour-intensive for health care workers at municipalities to arrange all this. A much simpler collection device that uses spit instead of swabs would make it easier. Home collection of spit would save a lot of time, is easy and cause no discomfort and saves a substantial amount of costs. When salivary antibodies also prove to be informative, this adds knowledge on contacts when the PCR for SARS-CoV-2 is no longer positive. The SARSLIVA study team will provide regular interim reports on data to the outbreak management team, to provide evidence on using saliva as a single test specimen and on the feasibility, sensitivity and robustness of the test in case home sampling and cold transport by couriers to the laboratory.
ZONMW ALGEMENE RELEVANTIE CRITERIA
This is a multidisciplinary collaboration between physicians, microbiologists, virologist, immunologists and epidemiologists with the innovative target of underpinning new diagnostics and sampling procedures for wide scale testing of SARS-CoV-2 viral infection. Modellers will benefit from the new data. Data sharing with other studies like FFX, CoKids and RECOVER and application of FAIR data will ensure maximal benefit for science and the community.

6. PROJECTGROEPLEDEN EN HUN ROLLEN

Onderbouw dat in de projectgroep relevante disciplines met de juiste expertise en beoogde einddoelgroep(en) zijn vertegenwoordigd. Maak helder welke deelnemers aan de projectgroep welke rol hebben. Geef bij voorkeur werkpakketten aan.

RIVM: Dr. 5.1.2e, Dr. 5.1.2e, The Viral Diagnostics Unit, supervising and responsible for viral and serology diagnostics for SARS-CoV-2 in the Netherlands.
Dr. 5.1.2e, molecular diagnostics and sample logistics.
UMCU WKZ & RIVM: Prof dr 5.1.2e, pediatrician at UMC Utrecht, and currently also Chief Science Officer at RIVM with special focus on immunology, vaccinology and infectious diseases and experienced in large scale trials on respiratory infections, immunology and microbiome studies; Study concept development and planning, logistics, study results analysis, and interpretation and reporting.Dr. 5.1.2e 5.1.2e, Senior Research Scientist/Associate Professor, Senior Scientific Consultant to RIVM, microbiologist, expert on diagnostics of respiratory pathogens and on surveillance of respiratory bacteria carriage with long-standing experience with saliva as a diagnostic specimen. Study concept development and planning, logistics, study results analysis, and interpretation.
Streeklab Haarlem: Dr. 5.1.2e, microbiologist director of the Streeklaboratory Haarlem,

Spaarne Gasthuis: Dr. 5.1.2e specialist Internal medicine & infectious diseases, coordinator COVID-19 care for department of internal medicine, member of COVID-19 expert panel of the Spaarne Gasthuis.
Dr. 5.1.2e pulmonologist, , coordinator COVID-19 care for department of pulmonology, member of COVID-19 expert panel of the Spaarne Gasthuis
Dr. 5.1.2e paediatrician at Spaarne Gasthuis and PI in infectious and vaccination studies and experienced in large scale trials on respiratory infections, immunology and microbiome studies; Study concept development and planning, logistics, supervises, study result analysis, and interpretation and reporting.

7. KENNISOVERDRACHT, IMPLEMENTATIE, BESTENDIGING

Beschrijf hoe u de kennis opgedaan in uw project gaat delen, en hoe u de resultaten en/of producten verder gaat brengen richting implementatie, bijvoorbeeld door toepassing in de praktijk, of bij het vormen van beleid.

Increasing knowledge on reliable and easy to perform diagnostic tools to detect and monitor circulation of SARS-CoV-2 is a crucial element in planning of specific mitigation interventions to control epidemic evolution. Data generated by the SARSLIVA study will be instrumental in this.
To expedite knowledge utilization, analysis of study data will be done on a continuous basis throughout the project as results start to accumulate. Results will be compared with those accumulating in the FFX RIVM household studies at an ongoing basis as well as with the ZonMW CoKIDS study. Investigators of different projects collaborate in the SARSLIVA study-team, facilitating these collaborations. All results will be directly shared with to the COVID-19 Outbreak Management Team and the modeling group of the COVID-19 response team at the RIVM without delay. We will also inform public health agencies involved in COVID-19 response, such as the WHO and ECDC. Close ties with between members of our group and these institutes will be instrumental in delivering the evidence where it is most relevant. Results will become more robust as the study proceeds.
To achieve maximal knowledge utilization in both policy and science, we will share the findings from this research through scientific publications, presentations and symposia on scientific conferences. For rapid dissemination and access to the results by the scientific community, manuscripts will be published on pre-print servers awaiting peer-review. In addition, we have ample experience in communicating science to the lay public by means of webinars, podcasts, online articles, and twitter. We will use this online media experience to disseminate the main research findings and their implications to the lay community.

8. DEELNAME VAN DE STAKEHOLDER(S)/EINDDOELGROEPEN

Beschrijf welke partijen (die mogelijk geen mede-aanvrager zijn, bijvoorbeeld patiënten, zorgprofessionals) op welke manier bij uw project worden betrokken.

Since study participants are important stakeholders in this study, we will inform them about the study with reports every 2 months . Upon request , we will inform them about their personal results (SARS-CoV-2 postive and/or saliva antibody titers during the study period) together with additional information on interpretation of the results. This will be done at the Spaarne hospital by the treating physician and for the GP and municipalities by the research physician, a few weeks after the last collection moment, when all samples have been analyzed. Next to that, the patients advisory council of the Spaarne hospital is involved and will share their thoughts on the study protocol. And in the end we will ask the participants to give some comments in joining the study.
Next to the study participant some other professionals from the RIVM are involved in the person of Dr Fiona vd Klis, she has outstanding knowledge of Immunology/serology and leading the PIENTER CORONA study on SARS-CoV-2 serology at this moment.
As described earlier the collaboration between the Spaarne Gasthuis with the Streeklaboratory can be described as excellent especially because of the aid of Dr. 5.1.2e, epidemiologist. He is capable to translate clinical questions to the laboratory and analyzes and reports this in an easy way.
The municipal health services Kennemerland, and the general practitioners are also important partners in this study and they will help to include participants.

9. LITERATUURREFERENTIES:

Vermeld hier de referenties die uw aanvraag inhoudelijk onderbouwen en vermijd opsommingen van publicaties van uw projectgroep(leden).

1. Wyllie AL, Fournier J, Casanovas-Massana A, et al. Saliva is more sensitive for SARS-CoV-2 detection in COVID-19 patients than nasopharyngeal swabs. medRxiv. April 2020:2020.04.16.20067835. doi:10.1101/2020.04.16.20067835

2. To KK-W, Tsang OT-Y, Leung W-S, et al. Temporal profiles of viral load in posterior oropharyngeal saliva samples and serum antibody responses during infection by SARS-CoV-2: an observational cohort study. Lancet Infect Dis. March 2020. doi:10.1016/s1473-3099(20)30196-1

3. Azzi L, Carcano G, Gianfagna F, et al. Saliva is a reilable too to detect SARS-Cov-2. J Infect. April 2020. doi:10.1016/j.jinf.2020.04.005

4. Williams E, Bond K, Zhang B, Putland M, Williamson DA. Saliva as a non-invasive specimen for detection of SARS-CoV-2. J Clin Microbiol. April 2020. doi:10.1128/jcm.00776-20

5. Wyllie AL, Chu MLJN, Schellens MHB, et al. Streptococcus pneumoniae in Saliva of Dutch Primary School Children. de Lencastre H, ed. PLoS One. 2014;9(7):e102045. doi:10.1371/journal.pone.0102045

6. Kim Y-G, Yun SG, Kim MY, et al. Comparison between Saliva and Nasopharyngeal Swab Specimens for Detection of Respiratory Viruses by Multiplex Reverse Transcription-PCR. J Clin Microbiol. 2017;55(1):226-233. doi:10.1128/JCM.01704-16

7. Sullivan PS, Sailey C, Guest JL, et al. Detection of SARS-CoV-2 RNA and Antibodies in Diverse Samples: Protocol to Validate the Sufficiency of Provider-Observed, Home-Collected Blood, Saliva, and Oropharyngeal Samples. JMIR Public Heal Surveill. 2020;6(2):e19054. doi:10.2196/19054

8. Niedrig M, Patel P, El Wahed AA, Schädler R, Yactayo S. Find the right sample: A study on the versatility of saliva and urine samples for the diagnosis of emerging viruses. BMC Infect Dis. 2018;18(1):707. doi:10.1186/s12879-018-3611-x

9 World Health Organization (WHO). Household transmission investigation protocol for 2019-novel coronavirus 2019-nCoV) infection. 2020;2019(January):1–31. Available from: https://www.who.int/publications-detail/household-transmission-investigation-protocol-for-2019-novel-coronavirus-(2019-ncov)-infection

10. Rodenburg GD, Sanders EA, van Gils EJ, et al. Salivary immune responses to the 7-valent pneumococcal conjugate vaccine in the first 2 years of life. PLoS One. 2012;7(10):e46916. doi:10.1371/journal.pone.0046916

11. van Ravenhorst MB, van der Klis FRM, van Rooijen DM, Sanders EAM, Berbers GAM. Use of saliva to monitor meningococcal vaccine responses: proposing a threshold in saliva as surrogate of protection. BMC Med Res Methodol. 2019;19(1):1. Published 2019 Jan 5. doi:10.1186/s12874-018-0650-3

12.Stoof SP, van der Klis FR, van Rooijen DM, et al. Salivary antibody levels in adolescents in response to a meningococcal serogroup C conjugate booster vaccination nine years after priming: systemically induced local immunity and saliva as potential surveillance tool. Vaccine. 2015;33(32):3933-3939. doi:10.1016/j.vaccine.2015.06.055

13. To et al. Additional molecular testing of saliva specimens improves the detection of respiratory viruses. Emerg Microbes Infect. 2017 Jun; 6(6): e49. doi: 10.1038/emi.2017.35

14. To et al. Saliva as a diagnostic specimen for testing respiratory virus by a point-of-care molecular assay: a diagnostic validity study. Clin Microbiol Infect 2019 Mar;25(3):372-378. doi: 10.1016/j.cmi.2018.06.009. Epub 2018 Jun 12.

15. To et al. Consistent Detection of 2019 Novel Coronavirus in Saliva. Clinical Infectious Diseases, ciaa149, https://doi.org/10.1093/cid/ciaa149