Brief summary of using oral fluid specimens for detection of SARS-CoV-2 infection in cases suspect for COVID-19

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[redacted], [redacted], [redacted], [redacted], [redacted], [redacted], [redacted], [redacted], [redacted], [redacted], [redacted], [redacted], [redacted], on behalf of the first few hundred study group

Centre for Infectious Disease Control, National Institute for Public Health and the Environment, Bilthoven, The Netherlands. Contact: [redacted] ([redacted]@rivm.nl)

Most frequently used specimens for SARS-CoV-2 detection are nasopharyngeal (NP) (or mid turbinate nasal) and oropharyngeal (OP) swabs, with NP (or midturbinate) in general more frequently and for a longer period positive than OP. Because of shortages of NP swabs, alternatives are sought. In The Netherlands for many years in the surveillance of mumps, measles and rubella and pneumococci oral fluid is being used for molecular detection of the virus or bacterium [1-4].

In the first few hundred COVID-19 cases study in the Netherlands with special attention for the involvement of young children in the transmission of SARS-CoV-2, oral fluid has been collected primarily for IgA detection and secondarily for studying the possibility of virus detection and contribution to transmission.

Oral fluid is collected by a simple device Oracol S10, Malvern Medical Developments (https://www.malmed.co.uk/saliva-collection/) (Figure 1).

Figure 1. Oral fluid collection system Oracol S10.

The procedure for use is simple. The device is designed to be used in a similar way to a toothbrush. Remove the cap from the tub, take out the sponge (Figure 2). Oral fluid is collected by rubbing the sponge swab firmly along the gum (at the base of the teeth if present) at both sides of the mouth until the sponge is wet; this takes about 1 minute. For SARS-CoV-2 investigation we use 2 minutes to be absolutely sure there is enough oral fluid collected. Once the sponge is sufficiently wet, replace the sponge back into the test tube and insert the cap (Figure 2 in reverse order.

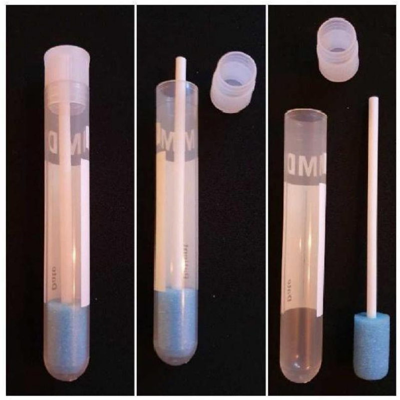

Figure 2. The sponge in the tube and when removed from the tube. Keep the cap clean. After oral fluid has been collected the sponge is put back in the tube in reverse order.

The oral fluid is extracted from the sponge using a centrifuge. Procedure 1) Remove the cap and remove the sponge from the tube and insert the sponge in the cap (Figure 3). Place the cap with sponge attached back on the tube (Figure 3). Centrifuge for 10 minutes 3,000 rpm in a table top centrifuge at room temperature, preferable with closed buckets. Remove the cap with sponge and discard as contaminated material. Remove the oral fluid used a pipette and aliquot as appropriate. Store at -80°C until use.

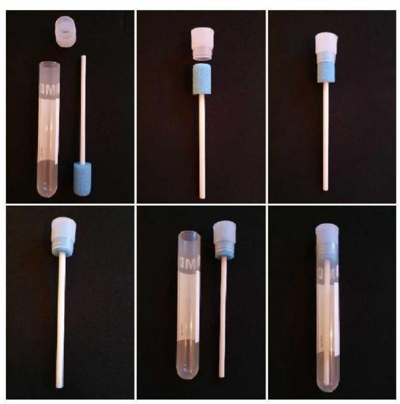

Figure 3. Sponge with oral fluid removed from the tube, inverted and sponge inserted in the cap and next the cap with sponge inserted in the tube for centrifugation.

Procedure 2) Alternatively, after opening the collection tube, with tweezers take the sponge, cut 3 cm from the shaft using scissors, invert the sponge and insert in the tube upside down. Close the tube with the cap and centrifuge for 8 minutes 800 *g* in a table top centrifuge at room temperature, preferable with closed buckets. Remove the cap and take the sponge out with tweezers and discard as contaminated material. Remove the oral fluid used a pipette and aliquot as appropriate. Store at -80°C until use.

For molecular detection we use Roche COBAS4800 with CT/NG kit extraction or Roche MagNApure extraction and in-house implementation of E-gene and RdRP-gene Corman et al. real-time RT-PCR on LC480 II using fast virus master mix chemistry [5]. For COBAS4800 extraction, 300 µl specimen is mixed with 300 µl CT/NG lysis buffer and 25 µl Equine Arteritis Virus (EAV) internal control; 400 µl is used for extraction and eluted in 100 µl. 10 µl is used in the PCR. Routinely we mix 200 µl specimen with 275 µl MagNApure blue extraction buffer with EAV internal control and yeast tRNA included; 450 µl is used for extraction and eluted in 50 µl. 5 µl is used in the PCR. If there is not enough oral fluid the volume is supplemented with DNAse/RNAse free physiological salt solution. However, in practice there is usually enough volume oral fluid.

A pilot was conducted using COBAS4800 or MagNApure extraction of oral fluid from 17 adults and 28 children. Two adults and 7 children were selected being negative in PCR for nasopharyngeal (NP) and oropharyngeal (OP) swab originating from families with members having COVID-19; oral fluid (OF) of all persons was negative in PCR for SARS-CoV-2. Twenty-one children (median age 12 range 2-16 years) and 15 adults (median age 46 range 18-61 years) were selected being positive in PCR for NP and/or OP swabs. For the 15 adults there is good concordance between OF and NP swab and OF and OP swab (Figure 4). The Ct values are however slightly to considerable higher in OF compared to those in NP and OP swabs (Figure 4). Nevertheless, only one patient who had a positive OP swab and negative NP swab, indicative for low viral load, was negative for OF.

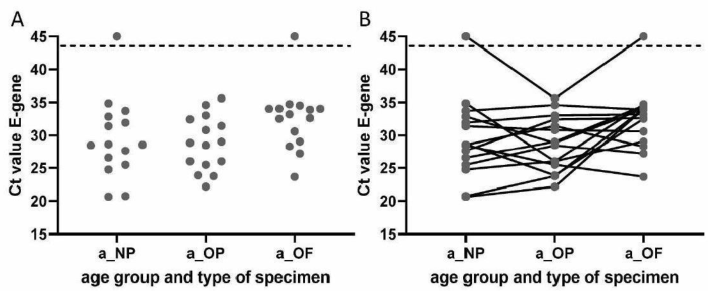

Figure 4. Comparison of Ct values for E-gene SARS-CoV-2 RT-PCR in oral fluid (OF) versus nasopharyngeal (NP) and oropharyngeal (OP) swab for adults (a). A. Distribution of Ct values by specimen type. B. Ct values for all specimen types connected by patient. Ct 45 = negative in PCR. For one patient only OP was positive.

For the 21 children the results were different (Figure 5). In total, of 13/21 (62%) children the OF specimen was positive. However, similar to the single adult, of 5/6 children with only one of NP or OP swabs being positive the OF specimen was negative. Of a further three children of whom the OF specimen was negative the NP and OP specimens had Ct values larger than approximately 29.

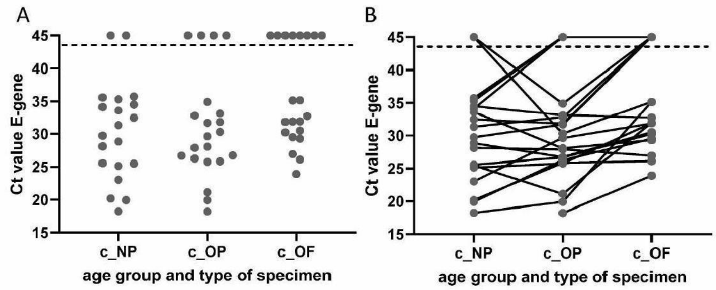

Figure 5. Relationship of SARS-CoV-2 E-gene RT-PCR Ct values in oral fluid (OF) versus nasopharyngeal (NP) and oropharyngeal (OP) swab for children (c). A. Distribution of Ct values by specimen type. B. Ct values for all specimen types connected by patient. Ct 45 = negative in PCR.

Of the 13 patients with positive OF specimen this specimen type had frequently a higher Ct compared to NP and OP swab (Figure 5B).

Self-collected deep throat saliva (posterior oropharyngeal saliva) was suggested as alternative to sputum and yielded positive PCR results in 11 out of 12 hospitalized COVID-19 patients in Hong Kong, as well as 3 positive and 2 negative virus cultures [6]. Further cohort of 23 patients with 173 deep throat saliva or endotracheal aspirate specimens studied by the same group found median viral loads of 5.2 log10 copies per mL (IQR 4.1–7.0) at presentation. The highest saliva viral loads were reported in the first week since symptoms onset for 20 patients, followed by gradual decline and prolonged detection of 20 days or more in 7 patients [7]. A pre-print study in the USA including 44 cases reported comparable or superior sensitivity of saliva to NP swabs and higher SARS-CoV-2 titers in saliva for 38 matched specimens [8]. A study in Italy analyzed saliva specimens of 25 confirmed COVID-19 patients and all were found PCR positive whilst two patients showed positive salivary results on the same days when their pharyngeal or respiratory swabs showed conversion to negative [9]. They reported the later two cases in more detail separately raising the concern of possible transmission when saliva is positive and upper respiratory tract specimens negative [10]. A study in Zhejiang, China confirmed SARS-CoV-2 infection in 96 patients by testing 668 sputum and 1178 saliva samples but did not specify positivity rates for the samples types separately. Taken together the positivity rates declined from 95% to 54% in the first 4 weeks since symptoms onset with a median virus shedding duration of 18 (IQR 13-29) days [11]. Fang and colleagues reported SARS-CoV-2 detection in saliva for 25 cases for a period of 13.33±5.27 days in mild cases and 16.50±6.19 days in ICU patients [12]. A study in Australia analyzed 522 paired saliva and NP swabs of COVID-19 suspect cases; 39 had positive NP swab of which 33 also positive saliva. Viral loads were lower in saliva compared to NP swab with both positive up to 21 days post symptom onset. Among 50 NP PCR-negative patients one had a positive saliva specimen [13].

A remark has to be made on the type of specimen reported as saliva. In the above studies it ranged from posterior oropharyngeal saliva collected by spitting or using the drooling technique collecting oral fluid after 1 to 2 minutes waiting and collecting it using a pipette or a sponge how we did it. Nevertheless, all techniques resulted in reliable detection of SARS-CoV-2 compared to upper or lower respiratory specimens. Sometimes with slightly higher and sometimes with slightly lower SARS-CoV-2 detection rates compared to NP swab.

In conclusion, taken into account recently published work and our preliminary findings, collection of OF instead of NP and OP swabs is a good alternative for SARS-CoV-2 detection in the upper respiratory tract. However, patients with low viral load NP and/or OP specimens will be missed when OF is collected alone.

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ZonMw programma second wave corona, april 2020

Projectvoorstellen met het CIb als hoofdaanvrager:

#	Indiener (centrum + naam)	Onderwerp	Korte beschrijving of abstract	Partners binnen RIVM	Partners buiten RIVM
1	[redacted] of andere MLUer	SARS-CoV-2 afvalwater surveillance	Nog veel is onduidelijk over de rol van kinderen bij SARS-CoV-2 transmissie, over een eventuele afname van de epidemie in de zomer of toename na de zomer, en over asymptomatische en presymptomatische transmissie. Met behulp van afvalwater surveillance kan in een gemeente worden gezien of het SARS-CoV-2 circuleert onder de bevolking. Ook kunnen trends worden waargenomen bijvoorbeeld of een bepaalde maatregel effectief is zoals het de social disctancing of welke gevolgen het weer opheffen van een maatregel heeft zoals het heropenen van de basisscholen. Of dat er een afname of toename optreedt in circulerend virus naarmate de seizoenen veranderen. Eerder hebben we laten zien dat afvalwater surveillance zinvol is om de afwezigheid van poliovirus te onderbouwen alsook vroegsignalering van poliovirus of andere enterovirussen. Ook circulatie van mazelen en influenza virus kan worden aangetoond. Naast typering met NGS en kweek om infectieuze virussen aan te tonen is ook kwantificering van belang om de gevoeligheid van de afvalwater surveillance aan te tonen, en de aanvullende waarde op andere nationale surveillance systemen.	Z&O [redacted], [redacted], etc. EPI [redacted], IIV [redacted], IDS [redacted], SIM [redacted], DMG [redacted]	Unie van Waterschappen, Waterschappen, Partners4UrbanWater, xxx
2	EPI ([redacted])	Role of the microbiome in COVID19 infections (susceptibility and effects)	Goal: The human microbiome plays an important role in human health, including maintenance of immune homeostasis and protection to pathogens invasion. Since the majority of infections occur without hospitalization, the goal of this project is to study the respiratory microbiome in susceptibility and symptoms of COVID-19 in a prospectively followed non-hospitalized population with pre and post COVID infection (defined serologically as well as by virus detection) respiratory samples available, among non-hospitalized people in open Dutch population. This is especially relevant also in relation to environmental factors like proximity to intensive livestock farming and air quality. Finally, the study will also give insight in the prevalence of COVID-19 virus in the open population in relation to serology and symptoms. Approach: we will make use of the currently active Pienter-	IDS ([redacted]), IIV ([redacted]), EPI ([redacted], [redacted])	[redacted] (UMCU/Edinburgh)?

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			COVID19 serology study to additionally collect saliva by self sampling , next to the dry blood spot collection, which will be checked for COVID-19 RNA and subsequently sequenced for microbiome composition. A previous comparison in the Triumph microbiome project showed that the microbiome composition of saliva is very similar to that of the oropharynx. Furthermore, initial studies show that COVID-19 can be detected in saliva. We will include saliva sampling in each upcoming repetition of the Pienter-COVID-19 blood-sampling, with the next round in August 2020, resulting in a prospective cohort study that provides the opportunity to study the role of the microbiome in susceptibility to infection since the project generates before and after infection data. In addition, for a subset of the study group we already obtained saliva or oropharynx microbiome composition as part of SPR Triumph. Overall, the combination of the COVID-19 serology (blood, done in Pienter-COVID-19), data regarding symptoms (Pienter-COVID-19 and the citizen-science project Infectieradar), COVID-19 testing (saliva, collaborating project) and microbiome (saliva, this project and TRIuMPH data from 3600 Pienter3 participants of which a part are included in the COVID Pienter follow up)) allows us to make inferences about the role of the microbiome in the infection dynamics of COVID-19. Relation to other (active) projects: : - Pienter-COVID-19 serology study started March 2020 - PIENTER CORONA saliva additional study - Infectieradar (inclusion platform Pienter-COVID-19) - SPR TRIuMPH (RIVM microbiome platform) Relatie naar zonmw calltekst: *Aandachtsgebied 2: zorg en preventie. Sub, onderzoek naar <u>verloop van individuele en groepsimmuniteit, zowel voor als na besmetting</u>, zowel virusfactoren als <u>gastheer(mens)factoren</u>.*		
3	[redacted] (IIV)	The gut microbiome in COVID-19 *Or broader:* *frailty/immunological biomarkers and induction of specific immunity*	<u>Rationale:</u> The growing aging population is at increased risk for infections, fact that has become increasingly evident in the current COVID-19 pandemic. Innovative strategies designed towards protection of this at risk population would therefore provide a major public health benefit. The gut microbiome plays a key role in protection against respiratory infections, modulating the immune system locally and at distal sites.	IIV ([redacted]), IDS ([redacted]), EPI ([redacted]), Z&O ([redacted])	WUR ([redacted])

			<u>Goal</u>: To identify microbiome and immune biomarkers for susceptibility (or as a result) to COVID-19 infection in older adults, in comparison to a young population. <u>Approach:</u> Within the project VITAL, we collected fecal samples in a cohort of 150 older adult individuals (>65 y.o.) in comparison with 150 healthy young participants (25-64 y.o.). A second sampling time is scheduled within the coming months. This provides a unique dataset of pre- and post-COVID-19 sampling times, with which we can address predisposing factors or susceptibility to disease. Furthermore, microbiome data will be combined with immunological and health data. Potential microbial biomarkers for susceptibility will be grown and tested in our in-vitro gut epithelial model, where we will study the downstream (innate) immune responses for the design of potential interventions. Relation to other (active) projects: : - SPR TRIuMPH (RIVM microbiome platform) - VITAL (vaccines and infections in the aging population) *Relatie naar zonmw calltekst:* *Aandachtsgebied 2: zorg en preventie. Sub, onderzoek naar verloop van individuele en groepsimmuniteit, zowel voor als na besmetting, zowel virusfactoren als gastheer(mens)factoren.*		
4	[redacted] [redacted] [redacted]IV)	Heeft COVID-19 infectie effect op vaccinatie response (en wat zijn daarin bepalende factoren)	Studie naar PPV23 vaccinatie bij ouderen die in najaar wordt uitgerold b(75-79 jaar) waarin we op baseline gezondheids parameters (voor identificeren kwetsbaarheid), als het kan baseline immunol biomarkers en eerdere exposure aan COVID (bewezen infectie en/of antistoffen) in kaart brengen en vervolgens na 1 maand de response (mn antistof) op de vaccinatie meten. In parallel of ter vergelijk kan hier de VITAL studie tegenaan gelegd worden. Die PCV13 vaccinatie gaan krijgen.	[redacted] [redacted]/ [redacted] [redacted] [redacted] [redacted] [redacted] [redacted], [redacted] [redacted] [redacted] [redacted]/ [redacted] [redacted] [redacted]	
5	[redacted] [redacted] (V&Z)/ [redacted] [redacted], [redacted]	Invloed van kwetsbaarheid op covid-19 infecties en afweer response	Gebruik makend van Doetinchem cohort waarin kwetsbaarheid goed is documenteerd mbv vragenlijsten en serologie nagaan wie ge-exposeerd is aan COVID-19 en zien welke	[redacted]	

	(IIV)		gezondheidsparameters van invloed zijn op kwetsbaarheid en mbv opgeslagen serum immunologische of andere biomarkers (metabolomics ed kan ook) identificeren die kwetsbaren identificeren.		
6	[redacted], Cib-Z&O [redacted], Cib-Z&O [redacted], Cib-IDS [redacted], Cib-EPI [redacted], IIV-IMM	The role of prior exposure to coronaviruses in severity of COVID-19 through antibody-dependent enhancement (ADE)	SARS-CoV-2 has not spread equally over the Netherlands and regional clusters exist. Interestingly, spatial analyses of confirmed COVID-19 cases indicate that also the severity of infection in confirmed cases shows regional differences, suggesting a spatial factor might be involved. Prior exposure to (especially animal) coronaviruses could be regionally distributed, and although antibodies are generally protective, antibody-dependent enhancement (ADE) is known to occur for coronaviruses. We hypothesize that prior exposure to (animal) corona viruses can induce ADE and thereby increase severity of COVID-19. We want to test this hypothesis by addressing the following research questions: - To which (animal) coronaviruses does (part of) the Dutch population have antibodies? - Do these antibodies to other coronaviruses cross-react with SARS-CoV-2 *in vitro*? - Is the presence of these antibodies to these other coronaviruses related to severity in COVID-19 patients? De focus hier ligt nu vooral op de coronavirussen in de veehouderij, maar ook humane coronavirussen (NL63 etc) worden meegenomen. Dit project heeft dus overlap met #7.	[redacted], Cib-Z&O [redacted], Cib-Z&O [redacted], Cib-IDS [redacted], Cib-EPI [redacted], IIV-IMM	[redacted], arts-microbioloog Deventer Ziekenhuis - [redacted] UU Faculteit Diergeneeskunde -...
7	IIV [redacted]	Role of crossreactive antibodies towards circulating coronaviruses in protection or ADE in humans	In ouderen hebben we in verschillende griepseizoenen infecties in kaart gebracht. Zowel in ouderen met bewezen Coronovirus infecties in deze seizoenen als ouderen met andere bewezen infecties of niet geïnfecteerden hebben we de serologie in kaart gebracht. Een subset van deze ouderen zit momenteel in het VITAL cohort, maar een aanvullend deel van eerdere deelnemers kunnen we benaderen om nu in de nieuwe pandemie de antistof response tegen het huidige coronavirus te relateren aan eerdere exposure van circulerende coronaviruses om te bepalen of deze beschermend of juist niet werken. Verdere karakterisatie van de antistoffen is mogelijk in in-vitro epitheelmodellen en zal uitwijzen of een vaccin dat antistoffen opwekt bescherming gaat bieden.		
8	[redacted]	Fretten model als COVID-ziekte	Fretten zijn een uitgelezen diermodel voor respiratoire infecties.	: [redacted],	

		model ter identificatie van immunologische processen en testen van vaccin concepten.	Het model kan gebruikt worden voor humoraal en cellulair immunologisch onderzoek en om verschillende vaccinconcepten in te testen. Het model met bijbehorende uitlees assays en parameters is reeds goed werkend voor influenza infecties. Deze unieke bestaande ervaring en beschikbare data vormen bij uitstek goed vergelijkingsmateriaal voor SARS-CoV-2 infecties. Studies zullen zich richten op meerdere stadia van de infectie en ziekte en de daarmee gepaard gaande humorale en cellulaire immuun responsen. Aangezien SARS-CoV-2 ook een enteraal virus lijkt te zijn is onderzoek naar de interactie met het microbioom een interessant onderzoeksthema. Deze interactie zou een rol kunnen spelen bij de inductie van een immuunrespons tegen het virus en de duur van uitscheiding via feces. Ook hiervoor zijn de technieken en analyses reeds opgezet en werkend. Gepaard aan fretten infectie studies, worden er infecties op humane primaire luchtweg epitheel cellen die de wand van de luchtwegen vormen uitgevoerd uit de neus en bronchiën. De reactie van de humane luchtweg epitheel cellen wordt vergeleken met wat er in het fretten diermodel gebeurt. Daarnaast kunnen deze epitheelculturen gebruikt worden om meer inzicht te krijgen in de werking van specifieke antistoffen tegen SARS-CoV-2.	[redacted], [redacted], [redacted], [redacted], [redacted] en [redacted].	
9	[redacted] (UMCG)/ [redacted] (UMCG)	Use of novel models to identify the role of antibodies and medication in protection against COVID-19	Using different model systems to test protective effect of antibodies, the working mechanisms of protection, immunomodulatory and blocking peptides and molecules to identify vaccine effectiveness and therapeutic agents		
10	zie partners, nog bepalen	The role of prior exposure to coronaviruses in severity of COVID-19 through antibody-dependent enhancement (ADE)	SARS-CoV-2 has not spread equally over the Netherlands and regional clusters exist. Interestingly, spatial analyses of confirmed COVID-19 cases indicate that also the severity of infection in confirmed cases shows regional differences, suggesting a spatial factor might be involved. Prior exposure to (especially animal) coronaviruses could be regionally distributed, and although antibodies are generally protective, antibody-dependent enhancement (ADE) is known to occur for coronaviruses. We hypothesize that prior exposure to (animal) corona viruses can induce ADE and thereby increase severity of COVID-19. We want to test this hypothesis by addressing the following research questions: - To which (animal) coronaviruses does (part of) the Dutch population have antibodies?	[redacted], Cib-Z&O [redacted], Cib-Z&O [redacted], Cib-IDS [redacted], Cib-EPI [redacted], IIV-IMM	[redacted], arts-microbioloog Deventer Ziekenhuis [redacted] UU Faculteit Diergeneeskunde -...

			- Do these antibodies to other coronaviruses cross-react with SARS-CoV-2 *in vitro*? - Is the presence of these antibodies to these other coronaviruses related to severity in COVID-19 patients?		
11	[redacted]/ [redacted] & [redacted]	Wellicht primair voor surveillance en niet ZonMW, mede afhankelijk van mogelijkheid tot saliva self samples vanaf augustis 2020	With opening of primary schools and gradually relaxing the lock down, the need to monitor circulation of SARS-CoV-2 virus in the open population is urgent. We now also want to follow viral circulation and mucosal immunity in the open community in saliva samples. To this aim we make use of the PIENTER CORONA study, that evaluates the immune status of 3500 individuals, aged 1-90 yrs to monitor herd protection. In this study, blood samples from around 3500 individuals, aged 1-90 yrs, in the open community are tested for IgM and IgG antibodies against SARS-CoV-2. Dry blood spots are collected by self sampling at home and dry blood spot cards sent by post to the RIVM for evaluation. The first results were that only 4% of the population had circulating antibodies in the blood against SARS-CoV-2 as of April 2020. Saliva was shown to be a representative sample to detect SARS-CoV-2 virus. Recently, saliva was shown to be an appropriate, and perhaps even more sensitive, alternative to nasopharyngeal swab (Wyllie et al) . In fact, saliva may even be more suitable for screening asymptomatic or pre-symptomatic SARS-CoV-2 infections, in particular when more volume is collected. In contrast to the current golden standard of nasopharyngeal swabs or viral detection, that is difficult and uncomfortable to self- collect, self-sampling of saliva is easy. When collected in the right test medium, this can be posted along with the dry blood spots and evaluated at RIVM. In addition to SARS-CoV-2 detection and the determination of the	[redacted] IIV [redacted], IDS [redacted], IDS Nog toevoegen anderen als: [redacted] (EPI) [redacted] IIV [redacted] for bacterial pathogens [redacted] for microbiome [redacted] for mycobiome [redacted], IDS	

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			viral load in saliva, salivary antibodies against SARS-CoV-2 as indicator for mucosal immunity, can be compared with detection of circulating antibodies in the blood as detected by the dry blood spots evaluation. For children, under 5 years of age, who cannot spit in test tubes, we will ask to collect saliva with a special sponge. We have ample experience with this way of collection of saliva and have found it easy, comfortable and participants are willing to repeat this non-invasive sampling repeatedly when required. For this reason we propose , in the next round of PIENTER-CORONA collection of dry blood spots, to invite participants also to provide saliva samples. Aims of study **Primary aim**: Determine SARS-CoV-2 prevalence in the open population between May and Dec 2020 in individuals aged 1-90 yrs **Secondary aims**: 1. determine local mucosal anti -SARd0CoV-2 antibodies in saliva 2. relate mucosal antibody presence and levels levels to circulating antibodies in the blood as determined in the dry blood spot study 3. determine circulation of other respiratory viruses in saliva for co-circulation or viral interference 4. future microbiome and mycobiome studies by molecular diagnostics 5. future determination by PCR of bacterial pathogens and load like Streptococcus pneumoniae, H. influenzae and Staphylococcus and meningococcus. **Approach:** Recent findings demonstrate that saliva is a viable and sensitive alternative to nasopharyngeal swabs for SARS-CoV-2 detection and enables at-home self-administered sample collection for accurate large-scale SARS-CoV-2 testing (Wyllie et al.) Saliva samples will be self-collected by the participant Participants (age…) are invited to participate in the saliva study next to the dry blood spot collection. Upon waking in the morning, participants		

			are asked to repeatedly spit in in a test tube until roughly up till 2 ml (without bubbles) before taking food, water and brushing of teeth. Saliva will be collected in RNA-protect medium that allows detection of SARS-CoV-2 and other respiratory viruses and viral load. Then the cup is securely closed. A second tube with EDTA medium is filled likewise, for mucosal serology i.e. IgA, and IgG anti SARS-CoV-2 antibody determination All samples are stored at room temperature and posted together with the dry blood spots to the research lab at RIVM The study will start at the next round of PIENTER CORONA scheduled in August 2020 and depending on the number of cycles and course of the pandemic end in February 2021. Data will be communicated after each round and wrapped up in 2021		
	(10)(2e) 10)(2e 0)(2e 0)(2e	Determinants of susceptibility to SARS-Cov-2 in open population in the upcoming next respiratory illness season	Within the ongoing PIENTER Corona study serum and data from questionnaire is collected from the start of the Corona outbreak to at least 1,5 year thereafter. Much data is available already from the former PIENTER 3 study and will be expanded with the epi and serological data from the present study. This PIENTER Corona study therefore is an unique opportunity to investigate the susceptibility to respiratory infectious diseases (SARS-Cov-2, seasonal corona's, other respiratory seasonal pathogens) in the upcoming next season. We question whether SARS-Cov-2 positive participants are more/less prone to infection with respiratory illnesses. For this we include all serology data (with concentrations of antibodies against SARS-Cov-2, seasonal corona's among othersl, demografic, risk factors, no/ mild/severe symtoms.	IIV en EPI	

Projectvoorstellen met een andere partij als hoofdaanvrager en het CIb als partner:

#	Indiener (naam + organisatie)	Onderwerp	Toelichting	Partners binnen RIVM	Partners buiten RIVM
1	[redacted] (TNO), [redacted] en [redacted] (Hubrecht institute)	Opschaling detectie SARSCOV-2 met behulp van LAMP technologie	Om grootschalige bevolkingstesten mogelijk te maken zijn gespecialiseerde testcentra nodig die ten tijde van crisis ad hoc kunnen worden geactiveerd. Het veilig en efficiënt uitvoeren van tienduizenden testen per dag vereist het herdefiniëren en optimaliseren van alle stappen in het testproces: swab afname en virus-inactivatie, geautomatiseerde sample handling tot data verwerking. Met de kennis en materialen van een groot consortium kan een prototype centrum binnen 2-3 maanden mogelijk gemaakt worden waarbij bedrijven de swabs, andere consumables en automatisering leveren en het Hubrecht Institute en TNO een modulaire moleculaire test inrichten die testen mogelijk maakt op grond van zowel de LAMP assay als versimpelde RT-PCR methoden. Beoogde betrokkenheid van het RIVM is bij validatie van de detectie en virus-inactivatie.	[redacted], [redacted] (ZNO), [redacted] (IDS)	TNO, Hubrecht institute, UMC Utrecht CMM en Klinische Microbiologie, DSM, Sopachem, Genmab, SCD.
2	UMCG	Serologische response in lifelines tijdens pandemie	- What is the total number of SARS CoV-2 infected (exposed) individuals among the LifeLines participants (seroprevalence)? - Is there a relationship between the magnitude of the SARS CoV-specific antibody titer and disease severity (as retrieved from the questionnaires)? - Is there a relationship between antibody titers to other human coronaviruses and the titers to SARS CoV-2? (positive: enhanced susceptibility to (coronavirus) infections?; negative: (partial) cross-protection?) - Is there a relationship between infection with SARS CoV-2 and the general immune status (measured as total amount of IgG, if possible also pro-inflammatory cytokines etc)? - How did coronavirus-specific and total IgG develop over time? > comparison with earlier taken samples > can changes predict disease outcome?	[redacted]	[redacted] (UMCG) [redacted] (UMCG)
3	UMCU/Radboud/LUMC/RIVM [redacted]	Immunological responses in the BCG vaccination trial	1500 health care workers were vaccinated with BCG (and currently trial in elderly ongoing) to induce an innate memory state that may partially protect individuals from (severe) disease.	[redacted] LUMC [redacted] Radboud, [redacted]	

			From these participants blood samples will be taken to look at innate immune profiles (Radboud), BCG specific induced immune changes (transcriptomics? LUMC) and immune phenotypes, antibody and T cell profiles (UMC/RIVM), to understand the potential working mechanisms of BCG OVID disease.	[redacted] UMCU, [redacted] IIV	
4	AUMC sponsor	Covid-19 in autoimmune disorders: prevalence, disease course, risk factors and immunity	RIVM is currently partner in the Health Holland consortium T2B (Target2B), investigating aberrant B cell immunity underlying B cell autoimmunities and B cell oncologies. In the ongoing collaboration RIVM shares knowledge, data and (limited) samples from Pienter studies as healthy controls in the Dutch population. In the present call Target2B proposes a study to investigate the impact of immunological frailty or treatment on Covid-19 immunity to enable advices on daily life restrictions and choice of immunosuppressive treatments in patients with various autoimmune diseases and guidance of future immunization strategies. The T2B infrastructure with close collaboration between different university hospitals, RIVM and Sanquin provides a unique opportunity to perform in depth analysis of Covid-19 immunity in both patients and healthy controls.	IMS ([redacted]), IMM ([redacted])	AUMC, LUMC, MUMC, UMCG, EUR, [redacted]
5	UMCU/RIVM [redacted] / [redacted] / [redacted]	Classification of COVID-19 patient based on inflammatory protein profiles , dominant immune signatures and memory formation	Identification and treatment of hyper-inflammation using existing, approved therapies with proven safety profiles is an important strategy to address the immediate clinical need for reducing morbidity and mortality of COVID-19 infected patients. We therefore propose classification of COVID-19 patients based on (1) their inflammatory protein profiles and (2) dominant immune cell signatures in blood (3) Humoral and cellular immune responses (antibodies as well as T and B cell memory levels. By comparing hospitalized (IC or cohort-department) patients at UMCU/VUMC and infected persons at home with mild symptoms/asymptomatic or uninfected, we will see difference in inflammatory profiles and induction of immunity which will help to classify COVID-19 patients and identify pathogenic and protective immune mechanisms of disease. 2 paths to follow: broad analysis of inflammatory pathways with O-link platform and specific analysis of pro-inflammatory markers and antiviral cytokines using a sensitive approach: Quanterix platform (VUMC)	[redacted]	[redacted] (UMCU) [redacted] (VUMC)