

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	(10)(2e) (10)(2e) (10)(2e) (10)(2e) (10)(2e) 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 distancing 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 typing 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 (10)(2e) (10)(2e) (10)(2e) (10)(2e) (10)(2e), etc. EPI (10)(2e) (10)(2e) (10)(2e) IIV (10)(2e) (10)(2e) (10)(2e) IDS (10)(2e) (10)(2e) SIM (10)(2e) (10)(2e) DMG (10)(2e) (10)(2e) (10)(2e)	Unie van Waterschappen, Waterschappen, Partners4UrbanWater, xxx
2	EPI (10)(2e) (10)(2e)	Role of the microbiome in COVID19 infections (susceptibility and effects)	<u>Goal:</u> 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. <u>Approach:</u> we will make use of the currently active Pienter-	IDS (10)(2e) (10)(2e) (10)(2e) (10)(2e) IIV (10)(2e) (10)(2e) (10)(2e) (10)(2e) (10)(2e) (10)(2e) EPI (10)(2e) (10)(2e) (10)(2e) (10)(2e) (10)(2e)	(10)(2e) (10)(2e) (UMCU/Edinburgh)?

			<p><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.</p> <p><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.</p> <p>Relation to other (active) projects: :</p> <ul style="list-style-type: none"> - SPR TRIuMPH (RIVM microbiome platform) - VITAL (vaccines and infections in the aging population) <p><i>Relatie naar zonnw caltekst:</i> <i>Aandachtsgebied 2: zorg en preventie. Sub, onderzoek naar verloop van individuele en groepsimmuniteit, zowel voor als na besmetting, zowel virusfactoren als gastheer(mens)factoren.</i></p>		
4	(10)(2e) (10)(2e) (10)(2e) (IIV)	Heeft COVID-19 infectie effect op vaccinatie response (en wat zijn daarin bepalende factoren)	<p>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.</p>	(10)(2e) (10)(2e) (10)(2e) (10)(2e) (10)(2e) (10)(2e) (10)(2e) (10)(2e) (10)(2e) (10)(2e) (10)(2e)	
5	(10)(2e) (10)(2e) (V&Z) (10)(2e) (10)(2e)	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	(10)(2e) (10)(2e) (10)(2e) (10)(2e)	

(IIV)		gezondheidsparameters van invloed zijn op kwetsbaarheid en mbv opgeslagen serum immunologische of andere biomarkers (metabolomics ed kan ook) identificeren die kwetsbaren identificeren.		
6	<p>(10)(2e), (10)(2e), Cib-Z&O (10)(2e), (10)(2e), Cib-Z&O (10)(2e), (10)(2e), Cib-IDS (10)(2e), (10)(2e), Cib-EPI (10)(2e), (10)(2e), IIV-IMM</p>	<p>The role of prior exposure to coronaviruses in severity of COVID-19 through antibody-dependent enhancement (ADE)</p>	<p>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:</p> <ul style="list-style-type: none"> - To which (animal) coronaviruses does (part of) the Dutch population have antibodies? - Do these antibodies to other coronaviruses cross-react with SARS-CoV-2 <i>in vitro</i>? - Is the presence of these antibodies to these other coronaviruses related to severity in COVID-19 patients? <p>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.</p>	<p>(10)(2e), (10)(2e), Cib-Z&O (10)(2e), (10)(2e), Cib-Z&O (10)(2e), (10)(2e), Cib-IDS (10)(2e), (10)(2e), Cib-EPI (10)(2e), (10)(2e), IIV-IMM</p> <p>(10)(2e), (10)(2e), arts-microbioloog Deventer Ziekenhuis -Berend (10)(2e), (10)(2e), UU Faculteit Diergeneeskunde "..."</p>
7	<p>IIV (10)(2e) (10)(2e) (10)(2e)</p>	<p>Role of crossreactive antibodies towards circulating coronaviruses in protection or ADE in humans</p>	<p>In ouderen hebben we in verschillende griepseizoenen infecties in kaart gebracht. Zowel in ouderen met bewezen Coronavirus 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.</p>	
8	(10)(2e), (10)(2e)	Fretten model als COVID-ziekte	Fretten zijn een uitgelezen diermodel voor respiratoire infecties.	: (10)(2e), (10)(2e)

			<ul style="list-style-type: none"> - Do these antibodies to other coronaviruses cross-react with SARS-CoV-2 <i>in vitro</i>? - Is the presence of these antibodies to these other coronaviruses related to severity in COVID-19 patients? 	
11	<p>(10)(2e) & (10)(2e) (10)(2e)</p> <p>Wellicht primair voor surveillance en niet ZonMW, mede afhankelijk van mogelijkheid tot saliva self samples vanaf augustus 2020</p>	<p>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.</p> <p>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.</p> <p>In addition to SARS-CoV-2 detection and the determination of the</p>	<p>(10)(2e) IIV (10)(2e) (10)(2e), IDS (10)(2e) (10)(2e), IDS</p> <p>Nog toevoegen anderen als: (10)(2e) (10)(2e) (10)(2e) (EPI)</p> <p>(10)(2e) (10)(2e) (10)(2e) IIV</p> <p>(10)(2e) & (10)(2e) (10)(2e) for bacterial pathogens</p> <p>(10)(2e) (10)(2e) (10)(2e) (10)(2e) (10)(2e) for microbiome</p> <p>(10)(2e) (10)(2e) for mycobiome</p> <p>(10)(2e) (10)(2e), IDS</p>	

			<p>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.</p> <p>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.</p> <p>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.</p> <p>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</p> <p>Secondary aims:</p> <ol style="list-style-type: none"> 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. <p>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</p>		
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			<p>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.</p> <p>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.</p> <p>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.</p> <p>Data will be communicated after each round and wrapped up in 2021.</p>		
		<p>Determinants of susceptibility to SARS-Cov-2 in open population in the upcoming next respiratory illness season</p>	<p>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.</p> <p>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 others), demographic, risk factors, no/ mild/severe symptoms.</p>	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	(10)(2e) TNO, (10)(2e) en (10)(2e) (Hubrecht institute)	Opschaling detectie SARSCOV-2 met behulp van LAMP technologie	<p>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.</p> <p>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.</p>	(10)(2e) (10)(2e) (10)(2e) (ZNO), (10)(2e) (IDS)	TNO, Hubrecht institute, UMC Utrecht CMM en Klinische Microbiologie, DSM, Sopachem, Genmab, SCD.
2	UMCG	Serologische response in lifelines tijdens pandemie	<ul style="list-style-type: none"> - 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? 	(10)(2e) (10)(2e) (10)(2e) (10)(2e) (10)(2e) (10)(2e)	(10)(2e) (UMCG) (10)(2e) (10)(2e) (UMCG)
3	UMCU/Radboud/LUMC/RIVM (10)(2e)	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.	(10)(2e) LUMC (10)(2e) Radboud, (10)(2e)	

			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.	(10)(2e) JMCU, (10)(2e) (10)(2e) 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 (10)(2e) (10)(2e) (10)(2e) (10)(2e) (10)(2e) (10)(2e) (10)(2e) IMM (10)(2e) (10)(2e) (10)(2e) (10)(2e) (10)(2e)	AUMC, LUMC, MUMC, UMCG, EUR, Sanquin
5	UMCU/RIVM (10)(2e) (10)(2e) (10)(2e) / (10)(2e) (10)(2e) (10)(2e) (10)(2e)	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)	(10)(2e) (10)(2e) (10)(2e) (10)(2e) (10)(2e)	(10)(2e) (UMCU) (10)(2e) (VUMC)

<p>6</p>	<p>Amsterdam UMC: <small>(10)(2e)</small> <small>(10)(2e)</small> (Verloskunde en prenatale diagnostiek) <small>(10)(2e)</small> <small>(10)(2e)</small></p>	<p>‘Real-time’ monitoring the seroprevalence of SARS-CoV-2 antibodies (IgG/IgM immunity) in relation to lockdown and open-up measures in the Netherlands, by using residual blood samples from the Dutch antenatal screening program.</p>	<p>The Netherlands is one of the few countries that adopted an ‘intelligent’ lockdown strategy based on the idea of herd immunity. As this intelligent lockdown differs from stricter approaches in most other countries, ‘real-time’ monitoring of changes in the immunity of the Dutch population in relation to the lockdown and open-up measures is of highest priority.</p> <p>We aim to provide an estimate on the number of people with antibodies (IgG/IgM immunity) against SARS-CoV-2 virus in the Netherlands and its changes over time, by using second trimester residual blood samples of pregnant women as a proxy for the general population.</p> <p>Research questions:</p> <ol style="list-style-type: none"> 1) Is the seroprevalence of antibodies among pregnant women different from that in other projects (blood donors, Pienter-Corona) in the same period? 2) Do seroprevalence rates differ between women with and without children? 3) How does seroprevalence change in relation to the intelligent lockdown measures over time? (February/March) 4) How does seroprevalence change in relation to the intelligent open-up measures over time? (May/June) 5) How does seroprevalence change over time in women with and without children in relation to childcare/school lockdown and open-up measures (Feb/June) 	<p>RIVM-Cib: <small>(10)(2e)</small> <small>(10)(2e)</small> <small>(10)(2e)</small> <small>(10)(2e)</small></p>	<p>Sanquin: <small>(10)(2e)</small> (Experimental Immunohematology) <small>(10)(2e)</small> <small>(10)(2e)</small> <small>(10)(2e)</small></p>
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