Algemene gegevens / General Information

Programma / Programme	:	**COVID-19 Programma**
Subsidieronde / Subsidy round	:	**Bottom-up ronde COVID-19 aandachtsgebied 1**
Projecttitel / Project title	:	**Pre-symptomatic host response markers of respiratory viral infection in health care workers?**
Projecttaal / Project language	:	**Nederlands / Dutch**
Geplande startdatum / Planned start date	:	**01-07-2020**
Geplande duur / Planned duration	:	**12 maanden / months**
Datum indienen / Date of application	:	**14-05-2020**
Projecttype / Project type	:	**Toegepast onderzoek / Applied research**
Vervolg eerder ZonMw-project / Continuation previously funded project ZonMw	:	**Nee / No**

Projectleden / Project members

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Projectgegevens / Project information

Aandachtsgebieden / Focus

1.1 Thema's aandachtsgebied 1
- Diagnostiek van besmetting

1.3 Setting
- Anders
- Ziekenhuiszorg

Samenvatting / Summary

Problem: Early diagnosis of respiratory viral infection is relevant to contain an outbreak. It is estimated that SARS-CoV-2 infectiousness peaks at 0–2 days before symptom onset and about half of secondary infections occur during the pre-symptomatic stage. Detecting asymptomatic infection would be an effective intervention to contain a future outbreak if COVID-19 re-enters. In addition, in a future viral outbreak caused by an unknown or mutated virus, before pathogen specific PCR tests are developed, a readily available test that is able to detect any pre-symptomatic virus may make the difference between the ability to contain the virus or not before it spreads globally. We will develop a commercially available diagnostic to identify pre-symptomatic virally infected individuals, including health care workers in order to limit in-hospital transmission.

Design: We will prospectively follow 666 healthcare workers without symptoms of infection, who have a high risk of infection for 2 weeks. A respiratory swab and blood sample will be taken three times per week. In blood biomarkers (TRAIL and IP-10) will be determined. Respiratory samples will be collected for PCR analysis to detect viral pathogens, including COVID-19. At study start and 3-4 weeks after the last biomarker sample, an additional serology sample will be taken to detect any asymptomatic infection.

Primay outcome: sensitivity of TRAIL and/or IP-10 measured in pre-symptomatic subjects (Index test) for PCR confirmed viral infections including COVID-19.

Analysis: As the most promising application of the test will be early identification of subjects who are infected, sensitivity - meaning the percentage of positive test results in the presence of the target disorder – should be sufficiently high. Cut-off points will be selected that approximate 50, 70 and 90% sensitivity. Specificity will also be calculated, and for both 95% confidence intervals will be constructed.

Trefwoorden / Keywords

Diagnostic test, biomarker, point-of-care, virus, COVID-19, sensitvity

Samenwerking / Collaboration

Samenwerking tussen onderzoek en praktijk / Cooperation between research and practice:

Nee / No

Inhoud / Content

Disciplines / Disciplines

- Infecties, parasitologie, virologie / Infections, parasitology, virology
- Longziekten / Pulmonology
- Epidemiologie / Epidemiology

Financiële gegevens / Financial data

ZonMw budget

	Jaar / Year								
Kostenpost	*1*	*2*	*3*	*4*	*5*	*6*	*7*	*8*	**Totaal / Total**
Personeel	210.000	0	0	0	0	0	0	0	210.000
Materieel	144.000	0	0	0	0	0	0	0	144.000
Implementatie	19.000	0	0	0	0	0	0	0	19.000
Apparatuur	0	0	0	0	0	0	0	0	0
Overig	18.500	0	0	0	0	0	0	0	18.500
Totaal / Total	**391.500**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**391.500**

Co-financiering / Cofinancing

Naam co-financier / Name of cofinancier	Bedrag / Amount	Status

Bijzondere gegevens / Additional information

Vergunningen / Permits

	Verklaring nodig / Statement required?		Status verklaring / Statement status		
	Ja / Yes	Nee / No	Verkregen / Acquired	Aangevraagd / Applied	Nog niet aangevraagd / Not applied yet
METC	X				X
DEC		X			
WBO		X			

Onderschrijvingen / Assents

	Ja / Yes	Nee / No	N.v.t. / N.A.
Code biosecurity / Code Biosecurity		X	
Code openheid dierproeven / Code Transparency of Animal Testing		X	

Andere vergunningen / Other permits

CE mark for the test.

Pilot study was approved by METC.

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:

Wilhelmina Kinderziekenhuis, UMC Utrecht

PROJECTTITEL:

Pre-symptomatic host response markers of respiratory viral infection in health care workers

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):

Need for early and rapid detection of viral infection at the point of care

We will develop a **commercially available diagnostic** to identify **pre-symptomatic virally infected individuals,** including health care workers in order to limit in-hospital transmission. Controlling a respiratory viral outbreak like the current one requires early detection of infection. Early diagnosis of respiratory viral infection is relevant to contain an outbreak, especially if an infected person is contagious before onset of symptoms. It is estimated that SARS-CoV-2 infectiousness peaks at 0–2 days before symptom onset and about **half of secondary infections occur during the pre-symptomatic stage**.[1] Detecting asymptomatic infection would be an effective intervention to contain a future outbreak if COVID-19 re-enters The Netherlands. In addition, in a future viral outbreak caused by an unknown or mutated virus, before pathogen specific PCR tests are developed, a readily available test that is able to detect any pre-symptomatic virus may make the difference between the ability to contain the virus or not before it spreads globally. Individuals unaware of their own (pre-symptomatic) infection can inadvertently put others at risk of infection, especially if the virus is contagious at a pre- or early symptomatic stage. Identifying an infected pre-symptomatic individual as early as possible, isolating them and providing them with treatment if applicable, may be able to help to combat the outbreak. This may be especially useful if it is difficult to longer-term isolate persons at (low) risk of infection, for example in elderly homes, persons who have difficulty understanding the situation and/or applying the distance rules (persons with dementia or mental or physical handicaps), persons in crucial jobs including healthcare workings. Such a test may also be used before entering necessary long-distance flights. The gold standard for detection of COVID-19 is PCR, which has acceptable sensitivity between 1-5 days after start of symptoms, although the accuracy of the test before onset of symptoms has not been described yet. Even if the test would be able to identify viral infection before start of symptoms, the current shortage of PCR testing material and facilities, as well as the impossibility to use this test at the point of care make a time-consuming PCR test impractical. Currently, molecular diagnostics require several days. There is an urgent need for a **scalable, point of care test that detects pre-symptomatic viral infection at acceptable cost**.

A blood test that may be able to fill this gap involves measurement of host-proteins, integrated into an immune-signature. Such a test was developed by MeMed diagnostics to distinguish between bacterial and viral infections. The test is based on measurement of biomarkers TRAIL, IP-10 and CRP, immune-proteins that are upregulated in response to different viral infections including coronavirus OC43 and COVID-19. The test is CE marked. We recently showed that the test has a sensitivity and specificity over 90%, with a negative predictive value >98% across multiple pathogens and irrespective of time of symptom onset.[2,3] The increase in IP10 and TRAIL concentrations may not be virus-specific. However, low-circulation of other viruses in the summer results in an increased likelihood that a pre-symptomatic identified viral infection is a COVID-19. We are currently performing a pilot study, which shows study feasibility. Results are not known yet.

Need for early treatment

Markers used in this test may be indicative of the severity of disease, becoming very important once effective antivirals are identified, eventually combined with other biomarkers.[4] There is evidence that Remdesivir improves outcome of COVID patients, which is why EMA has currently approved expanded compassionate use. **Antivirals are most effective when applied at an early stage in the disease**, when the viral load is still low and the immune cascade is not yet fully unleashed. For example oseltamivir is no longer effective in reducing influenza symptoms applied 48 hours after onset of symptoms.[5] In addition, most antivirals have potentially severe side-effects, including cardiac side-effects, and may need to be administered intravenously. If it would be possible to assess how likely a person is to exhibit severe infection symptoms at this stage, it will allow for an informed decision on the expected risks and benefits of treatment in this individual. The blood test developed by Memed may also predict course of disease. This additional characteristic will allow further tailoring antiviral treatment to patients with the highest need.

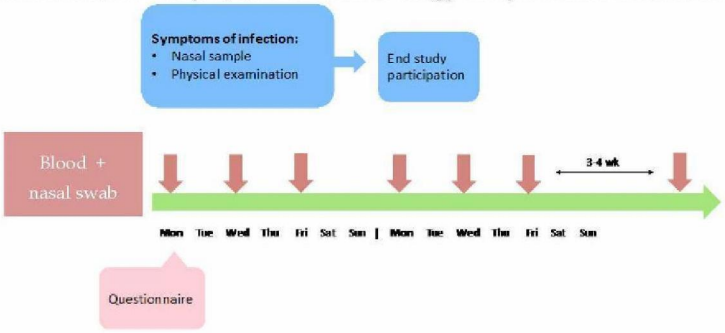
Objectives

In this study we aim to evaluate whether the levels of TRAIL and/or IP-10, alone or in combination, are a sign of viral infection at a stage before symptoms arise. We will assess the diagnostic value of these two biomarkers separately, or in combination.

2. PLAN VAN AANPAK:

Design: We will prospectively follow healthcare workers without symptoms of infection, who have a high risk of infection. Subjects will be followed for two weeks during the pandemic. Severity of disease will be determined in case of respiratory findings.

Diagnostic test: In all participating health workers a respiratory swab and blood sample will be taken three times per week, followed by an observational period of 48-72 hours to observe the development of respiratory symptoms. If respiratory symptoms occur, we will measure symptoms, blood biomarkers (TRAIL and IP-10) and viral load daily for four consecutive days. Blood will be used to measure biomarkers and for RNA analysis. Respiratory samples will be collected in symptomatic participants and during the sixth study visit for PCR analysis to detect viral pathogens, including COVID-19. At study start and 3-4 weeks after the last biomarker sample, an additional serology sample will be taken to detect any asymptomatic infection.



Study Population: Adult healthcare workers who have a high risk of exposure to respiratory viral infection (defined as bedside care for patients), will be eligible for inclusion. General practitioners may also be included. Inclusion criteria are no symptoms of acute infection at time of enrollment or in the previous two weeks.

Sample size. 666 subjects will be followed for 2-3 weeks. For the intended use to contain a future outbreak at an early stage, we aim to be able to estimate the sensitivity with sufficient precision. At cut-points of 50-70-90% sensitivity, the confidence interval around the estimated sensitivity as well as specificity will be calculated. With a conservative estimated 4% of respiratory episode in 2-3 weeks in this group, this will lead to N=20 subjects with a respiratory viral infection. We anticipate n=4 who will not have a blood sample drawn 48 hours before onset of symptoms. If the observed sensitivity will be as high as 90% the confidence interval will be 65% to 99%. If the sensitivity is 70% in the sample, inclusion of 16 virally infected subjects, produce a two-sided 95% confidence interval from 43% to 90%. If the outbreak wanes to an estimated <1% infections in the study population, the study will be halted and restarted when the infection rates rise to an estimated 3% or at the start of winter season.

Endpoints:
Primary: sensitivity of TRAIL and/or IP-10 measured in pre-symptomatic subjects (Index test) for PCR confirmed viral infections including COVID-19.
Secondary:

- sensitivity and specificity of TRAIL and/or IP-10 in early symptomatic healthcare workers.
- sensitivity and specificity of TRAIL and/or IP-10 in all healthcare workers measured maximum 48 hours before symptom onset.
- sensitivity and specificity of TRAIL and/or IP-10 in all healthcare workers measured every 24 hours
- sensitivity and specificity of TRIAL and/or IP-10 in symptomatic healthcare workers related to disease severity

Explorative: levels of TRAIL and/or IP-10 in severely ill patients.

Analysis: As the most promising application of the test will be early identification of subjects who are infected, sensitivity - meaning the percentage of positive test results in the presence of the target disorder – should be sufficiently high. Cut-off points will be selected that approximate 50, 70 and 90% sensitivity. Specificity will also be calculated, and for both 95% confidence intervals will be constructed. The results of the pilot study and this study will be pooled, for an overall estimate of accuracy over both studies.

3. HAALBAARHEID VAN HET PROJECT:

TIME SCHEDULE
Start month July end month November 2020
Week 1 : Study preparations. Rapid start as IRB permission is available.
Week 2-6 : Recruitment. Based on the Heracles pilot study, we expect full recruitment within one month.
Week 6-11 : Follow-up, the study ends with COVID serology for the last participant.
Week 12-14 : Lab analysis of blood biomarkers, nasal swabs, serology.
Week 15-16 : Statistical analysis

MOTIVATIE HAALBAARHEID
To capture a sufficient number of blood samples at a pre-symptomatic stage is a challenge, as sample sizes will be determined by the number of viral infected persons. If the epidemic wanes, more persons need to be sampled to capture the same number of virally infected persons. Therefore, for efficiency it is extremely important to capture samples during the epidemic. In our feasibility study in April 2020, we have shown this is possible, with an over 50% positive response rate resulting in a recruitment of **75 health workers per week for 6 blood draws per person within 14 days**, streamlined collaboration between the clinical and the lab teams and institutional review board approval within one week. If the outbreak wanes to an estimated <1% infections in the study population, the study will be halted and restarted when the infection rates rise to an estimated 3% or at the start of winter season.

Our group combines expertise from all required fields in already existing collaborations, making it possible to quickly start-up a good quality study.

- Immunology and infectious disease studies: Louis Bont
- Epidemiology and statistics of infectious diseases: Katrien Oude Rengerink
- Diagnostic test studies and prediction: Hans Reitsma, Ewoud Schuit
- Public health: if the proposal will be successful input will be provided by and attuned with the RIVM, in collaboration with 5.1.2e
- Test development and test expertise: MeMed diagnostics

Our group has experience with use and validation of the test, published in Lancet infectious disease.[2]

4. RELEVANTIE VOOR DE PRAKTIJK:

The test could be relevant in practice:

1. Directly after proven usefulness: SARS-CoV-2 infectiousness peaks at 0–2 days before symptom onset and about half of secondary infections occur during the pre-symptomatic stage.[1] Detecting asymptomatic infection would be an effective intervention to contain a future outbreak if COVID-19 re-enters The Netherlands. Identifying an infected pre-symptomatic individual as early as possible, isolating them and providing them with treatment if applicable, may be able to help to combat the outbreak. This may be especially useful if it is difficult to longer-term isolate persons at risk of infection, for example in elderly homes, persons who have difficulty understanding the situation and/or applying the distance rules (persons with dementia or mental or physical handicaps), persons with essential professions including healthcare workings.
2. In the future: viral outbreak caused by an unknown or mutated virus, before pathogen specific PCR tests are developed, a readily available test that is able to detect any pre-symptomatic virus may make the difference between the ability to contain the virus or not before it spreads globally.

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

Physicians and nurses will be asked to participate in this study. They are members of the project group. In addition, input has been asked from physicians and nurses outside the study group to tailor the study design and provide insight into perceived relevance and feasibility (perceived relevance of research question, number of blood draws, frequency of blood draws, barriers and motivators for participation.
Prof Louis Bont, project member, is member of the COVID crisis team of the University Medical Center Utrecht and chairs the IRB..

6. LITERATUURREFERENTIES (optioneel):

1. He, X. Temporal dynamics in viral shedding and transmissibility of COVID-19. Nat Med 2020..
2. Van Houten. Host-protein based assay differentiate bacterial and viral infections. Lancet Infect Dis 2018
3. Van Houten. Update of a clinical prediction model for bacterial infection. BMJ Pediatr open 2019
4. Wyants. Prediction models for diagnosis and prognosis covid-19 infection: systematic review. BMJ 2020.
5. Treanor. Efficacy and safety Oselatmivir. JAMA 2000