STUDY PROTOCOL

EVALUATION OF A SARS-COV-2 RAPID ANTIGENTEST:
TEST PERFORMANCE AND POTENTIAL AS A PRE-SCREENING DIAGNOSTIC.

PROTOCOL TITLE : Evaluation of a SARS-CoV-2 rapid antigen test: Test performance and Potential as a pre-screening diagnostic.

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Sponsor (in Dutch: verrichter/opdrachtgever)	Amphia Hospital Breda
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Enrolling sites	GGD West-Brabant testcentrum Breda/Etten-Leur/ Roosendaal
Laboratory sites	Microvida Laboratory for Medical Microbiology, Roosendaal/Breda
Pharmacy	Not applicable.

SUMMARY

Rationale: Good and rapid diagnostics are essential for the treatment and control of COVID-19. The current test used to establish active COVID-19 infection is real-time reverse transcriptase PCR (RT-PCR). The capacity to perform this highly sensitive and specific test has been progressively scaled up in the Netherlands, but a further increase, up to 3 times the current capacity, will be needed to satisfy growing test demand during fall and winter. This greatly pressurises microbiological laboratories and logistic and administrative challenges intrinsic to turn-over time and the need for a specialised laboratory setting lead to substantial reporting delays of the results. There is a need for a rapid diagnostic test that can be performed at the point of care or at home.

We propose a two-tired study to evaluate the 'BD Veritor System for Rapid Detection of SARS-CoV-2' (VRD) test-performance compared to RT-PCR and the potential applicability as a pre-screening diagnostic for specific test groups in the Netherlands.

Objective: Primary objective is to determine the overall test sensitivity and specificity of the VRD antigen test performed on a superficial nasal/throat specimen compared to RT-PCR on nasal/throat specimen. Secondary objectives are to determine sensitivity and specificity stratified by Ct-value category (Ct-value 25 or less, 25 to 30 and 30 or higher) and to evaluate practical applicability of the VRD as a pre-screening diagnostic in the Netherlands.

Study design: Prospective validation study.

Study population: In part 1 of the study we aim to include a minimum of 350 adults (≥18 years) presenting at a selected GGD West-Brabant test centre for a COVID-19 test within the study period who are willing to participate in the study. In the concurrently performed part 2 of the study 200 adults who had a positive RT-PCR during the study period and who are able and willing to give verbal informed consent will be included. The sample size may be adjusted based on the results that are obtained.

Main study parameters/endpoints: Sensitivity and specificity of VRD performed on nasal/throat specimen compared to RT-PCR performed on nasal/throat specimen overall and stratified by Ct-value group (Ct-value 25 or less, 25 – 30, positive RT-PCR with Ct-value higher than 30, negative RT-PCR).

Nature and extent of the burden and risks associated with participation, benefit and group relatedness: Participation in this study poses a negligible risk and the burden is considered minimal. Nasal/throat swabs are commonly used methods for collecting test samples for respiratory viral infection. Swabbing may be mildly uncomfortable as it may cause momentary gagging. Discomfort and risk will be minimised by having experienced personnel take the swabs. There is no direct benefit to the subjects.

1. INTRODUCTION AND RATIONALE

Good diagnostics are essential for the treatment and control of COVID-19. The current test used to establish active COVID-19 infection is real-time reverse transcriptase PCR (RT-PCR). The capacity to perform this highly sensitive and specific test has been progressively scaled up in the Netherlands up to 30.000 tests per day at present. It is anticipated that the daily number of tests will increase up to 100.000 per day later this year. This however greatly pressurises microbiological laboratories and is not sufficient to answer the increasing test demand as test indications keep on expanding (asymptomatic contacts of infected patients, asymptomatic returning travellers etc.). Furthermore, RT-PCR has a turnover time of several hours and can only be performed in highly specialised laboratories. Due to subsequent logistic and administrative challenges, delays in reporting can currently rise up to 4-5 days. In order to further increase test capacity, relieve pressure on microbiological laboratories and increase willingness to get tested amongst the population, there is an urgent need for a rapid diagnostic test that can be performed at the point of care or at home.
We plan to evaluate the 'BD Veritor System for Rapid Detection of SARS-CoV-2' (VRD), a chromatographic immunoassay for the qualitative detection of nucleocapsid antigens in respiratory specimen. The VRD can be performed point of care by trained personnel and results are available within 15 minutes. The manufacturer reports a test specificity of 100% and a sensitivity of 84% compared to RT-PCR as a gold standard during the first 5 days after disease onset. (1) Although this is a substantial loss of sensitivity, we believe that the short turn-around time and the possibility to test at point of care potentially outweigh the loss of laboratory sensitivity for specific test indications. In predefined groups in which pre-test probability is low and for who consequences of a (rare) false negative test result would be relatively manageable, the increased willingness of testing and speed of reporting will outweigh the decrease in test-sensitivity.

We propose a two-tired study protocol to evaluate VRD test-performance compared to RT-PCR and the potential applicability for pre-screening of specific test groups in the Netherlands in the immediate future.

1. OBJECTIVES

1.1 Part 1

- Primary Objective:
  To determine the overall test specificity of the 'BD Veritor System for Rapid Detection of SARS-CoV-2' (VRD) antigen test performed on nasal/throat specimen compared to semi-quantitative real-time reverse transcriptase PCR (RT-PCR) on nasal/throat specimen.

- Secondary Objectives:
  To evaluate the practical applicability of the VRD antigen test for use as a pre-screening diagnostic in the Netherlands.
  To determine the overall test sensitivity of the VRD antigen test performed on nasal/throat specimen compared to RT-PCR on nasal/throat specimen.
  To determine the test sensitivity and specificity of the VRD antigen test on nasal/throat specimen compared to RT-PCR on nasal/throat specimen stratified by Ct-value category (Ct-value 25 or less, 25 to 30 and 30 or higher, negative).
  To determine VRD sensitivity and specificity when the results are visually read compared to analysis with the 'BD Veritor Plus Analyzer'.
  To quantify the difference in turnaround time (moment of presentation at the test centre until results ready for communication to the GGD) between the RT-PCR and the VRD.

1.2 Part 2

- Primary Objective:
  To determine the test sensitivity of the VRD antigen test on nasal/throat specimen compared RT-PCR on nasal/throat specimen overall and stratified by Ct-value category (Ct-value 25 or less, 25 to 30 and 30 or higher, negative).

- Secondary Objectives:
  To evaluate the practical applicability of the VRD antigen test for use as a pre-screening diagnostic in the Netherlands.
  To determine VRD sensitivity and specificity when the results are visually read compared to analysis with the 'BD Veritor Plus Analyzer'.

2. STUDY DESIGN

We plan a prospective validation study.

3. SETTING

Currently COVID-19 testing of non-hospitalised patients in the Netherlands is coordinated by the Municipal Health Service (GGD). A person with a test indication makes an appointment to be tested at a GGD test centre. Nasopharyngeal swabs are performed by trained GGD personnel and sent to the regional laboratory for RT-PCR. Laboratories electronically report test results within 24 hours to the GGD trough a digital communication system, the tested individual will thereafter be informed digitally or by a GGD employee. Individuals that have a positive test are approached with a questionnaire for the purpose of source- and contact-tracing.
The GGD of the region West-Brabant currently has 3 test centres operational with a total maximum capacity of 1200 tests daily. The majority of specimen of all test locations are currently sent to and analysed at a Microvida microbiology laboratory. In the first week of September 2020 2-3% of individuals presenting at a West Brabant GGD tested positive (personal communication).

4. STUDY POPULATION

4.1 Part 1

All adults (≥18 years) presenting at the selected West-Brabant GGD test centre for a COVID-19 test within the study period who give verbal informed consent to participate in the study, will be included.
We aim to include at least 300 RT-PCR negative individuals. As a 2-3% positivity is to be expected (cfr. Setting), at least 350 participants will be included. An analysis will be performed and it may be concluded to extend the sample size based on the results.

4.2 Part 2

All adults (≥18 years) who presented at a GGD West-Brabant test centre for a COVID-19 test and had a positive RT-PCR during the study period, who are able and willing to give verbal informed consent will be included. We aim to include 200 participants.

5. TREATMENT OF SUBJECTS WITH INVESTIGATIONAL OR NON-INVESTIGATIONAL PRODUCTS

Not applicable.

6. METHODS

6.1 Study parameters/Endpoints

6.1.1 Part 1

- Main outcome measures:
  Overall specificity of VRD performed on nasal/ throat specimen compared to RT-PCR performed on nasal/ throat specimen.

  Secondary outcome measures:
  Specificity and sensitivity of VRD performed on nasal/ throat specimen compared to RT-PCR performed on nasal/ throat specimen stratified by Ct-value category (Ct-value 25 or less, 25 – 30, positive RT-PCR with Ct-value higher than 30, negative RT-PCR).
  Qualitative evaluation of logistics, communication and workability of the use of the VRD at the GGD test-centre in the shape of a unstructured interview with GGD and laboratory representatives.
  Sensitivity and specificity of VRD when the results are visually read compared to analysis with the 'BD Veritor Plus Analyzer'.

6.1.2 Part 2

- Main outcome measures:
  Overall sensitivity of VDR performed on nasal/ throat specimen compared to RT-PCR performed on nasal/ throat specimen.

- Secondary outcome measures:
  Sensitivity of VDR performed on nasal/ throat specimen compared to RT-PCR performed on nasal/ throat specimen for RT-PCR stratified by Ct-value category (Ct-value 25 or less, 25 – 30, positive RT-PCR with Ct-value higher than 30, negative RT-PCR).
  Sensitivity and specificity of VRD when the results are visually read compared to analysis with the 'BD Veritor Plus Analyzer'.

6.2 Randomisation, blinding and treatment allocation

Not applicable.

6.3 Study Procedures

6.3.1 Part 1

- Enrollment
  Adults presenting at the selected test centre will be verbally informed about the study and the need for an additional nasal swab/ throat swab. They will be asked for verbal informed consent. Individuals who agree will be directed to a test lane for double sampling.

- Sampling and Test procedure
  A routine nasal/throat swab will be obtained by a GGD employee and sent to the regional laboratory for routine RT-PCR in accordance with the Dutch national COVID-19 test protocol.
  In addition to and directly following the routine nasal/throat swab, the GGD employee will obtain a second superficial (2.5 cm up the nostril) nasal/throat swab. The specimen will be transferred to a trained laboratory technician, who will perform the VRD in accordance with the manufacturer's operating procedure.
  Additionally to analysis with the 'BD Veritor Plus Analyzer' as prescribed by the manufacturer, visual bands on the test device will be interpreted as positive, negative, control invalid or not interpretable by an independent technician. The participants will not be informed about the VRD test results.

- RT-PCR positive individuals

  Individuals who have a positive RT-PCR are routinely contacted by the GGD in context of source- and contact tracing. Part of the standard questionnaire are questions on whether or not the individual was symptomatic, what the time of symptom onset was and what the indication for testing had been. The answers to these questions will be subtracted from the GGD-files (HP-Zone).

- Post-project evaluation of the implementation of VRD at GGD test-centres
  In an unstructured interview, representatives of the involved GGD and laboratories will be asked about their vision on the VRD and its applicability (workability, logistics, possible obstacles) for point of care testing at GGD test centres.

6.3.2 Part 2

- Enrollment
  Adults that presented for a COVID-19 test at a GGD West-Brabant test centre and had a positive RT-PCR are routinely contacted by the GGD for the purpose of source- and contact-tracing. During this conversation the GGD employee will inform the potential participant about the study and ask permission for obtainment of an additional nasal/throat swab during a home visit.

- Sampling and Test procedure
  A trained professional will visit the participants' homes within 72 hours after obtainment of the specimen for RT-PCR. After confirmation of the verbal informed consent, the laboratory technician wearing personal protective equipment will obtain a standard nasal/throat swab and an additional superficial nasal/throat. The first specimen will be transported to the laboratory for RT-PCR, the latter specimen will be analysed with VRD in accordance with the manufacturer's operating procedure.
  Additionally to analysis with the 'BD Veritor Plus Analyzer' as prescribed by the manufacturer, visual bands on the test device will be interpreted as positive, negative, control invalid or not interpretable by an independent technician. The participants will not be informed about the VRD test results.

6.4 Withdrawal of individual subjects and replacement or follow-up after withdrawal

Not applicable.

6.5 Premature Termination of the Study

There are no predefined reasons to terminate this study prematurely. In case the study is terminated prematurely, the coordinating investigator will notify the accredited METC and the competent authority (CA) within 15 days, including the reasons for the premature termination.

7. SAFETY REPORTING

7.1 Temporary halt for reasons of subject safety

In accordance to section 10, subsection 4, of the WMO, the sponsor will suspend the study if there is sufficient ground that continuation of the study will jeopardise subject health or

safety. The sponsor will notify the accredited METC without undue delay of a temporary halt including the reason for such an action. The study will be suspended pending a further positive decision by the accredited METC. The investigator will take care that all subjects are kept informed.

7.2 AEs, SAEs and SUSARs

7.2.1 Adverse events (AEs)

Nasal/throat swabs are currently performed in routine diagnosis. The study involves an additional superficial (2.5 cm up the nostril) nasal/throat swab. Due to the negligible risk of this procedure, no adverse events will be reported.

7.2.2 Serious adverse events (SAEs)

Nasal/throat swabs are currently performed in routine diagnosis. The study involves an additional superficial (2.5 cm up the nostril) nasal/throat swab. Due to the negligible risk of this procedure, no serious adverse events will be reported.

7.3 Annual safety report

Not applicable.

7.4 Follow-up of adverse events

Not applicable.

7.5 Data Safety Monitoring Board (DSMB) / Safety Committee

Not applicable

8. STATISTICAL ANALYSIS

Test sensitivity and specificity compared to RT-PCR will be calculated overall and stratified by CT-value group (Ct-value 25 or less, 25 – 30, positive RT-PCR with Ct-value higher than 30, negative RT-PCR).

Positive and negative predictive values will be calculated as observed and with varying prevalence as they depend on the pre-test probability in specific test populations.

9. ETHICAL CONSIDERATIONS

9.1 Regulation Statement

The study will be conducted according to the principles of the Declaration of Helsinki, amended at the 64th General Assembly (Fortaleza, Brazil, October 2013) and in accordance with the Medical Research Involving Human Subjects Act (WMO) and the Code Goed Gebruik (2011).

9.2 Recruitment and Conscent

9.2.1 Part 1

Individuals presenting at the test centre will be verbally informed about the study and the accompanying extra nasal/throat swab. Furthermore, information signs will be placed at the participating test centre and the study will be announced in local media and trough GGD communication channels. A full participant information letter will be available on the GGD West-Brabant website. A verbal informed consent will be obtained of every participant. No written informed consents will be obtained as the study procedure has a negligible risk and this would compromise the strictly needed high flow of individuals being tested in the test centres. Currently the test time per person is 3 minutes.

9.2.2 Part 2

Participants will be informed about the study and the need for two additional nasal/throat swabs a first time by telephone. Subsequently a verbal informed consent will be obtained during the home visit. Furthermore, participants will be guided to the full participant information letter on the website of the GGD West-Brabant.

9.3 Objection by Minors or Incapacitated Subjects

Not applicable.

9.4 Benefits and risks assessment, group relatedness

Participation in this study poses a negligible risk and the burden is considered minimal. Nasal/throat swabs are commonly used methods for collecting test samples for respiratory viral infection. Swabbing may be mildly uncomfortable as it may cause momentary gagging.

Discomfort and risk will be minimised by having experienced personnel take the swabs. There is no direct benefit to subjects.

9.5 Compensation for injury

The sponsor/investigator has a liability insurance which is in accordance with article 7 of the WMO. Given the negligible risk of the study-related procedures, exemption from the WMO human subject insurance is granted by the METC.

9.6 Incentives

Subjects will not be compensated for participating in this study.

10. ADMINISTRATIVE ASPECT, MONITORING AND PUBLICATION

10.1 Handling and storage of data and documents

Data will be handled confidentially in compliance with the EU General Data Protection Regulation and the Dutch Act on Implementation of the General Data Protection Regulation (in Dutch: Uitvoeringswet AVG, UAVG).

10.2 Monitoring and Quality Assurance

To guarantee correct sample management and performance of the VRD a trained laboratory technician of the Microvida Amphia microbiology lab will be onsite during the study period.

10.3 *Public disclosure and* publication policy

The investigators will disclose the results of the study unreservedly at the end of the study or earlier in case result impact policy making. The study will be registered in the Netherlands Trial Register before the first subject is recruited.

11. STRUCTURED RISK ANALYSIS

Not applicable. / This study has a low risk according to the NFU risk-classification.

12. REFERENCES

(1)BD ; https://www.fda.gov/media/139755/download