STUDY PROTOCOL

Evaluation of SARS-CoV-2 Antigen Rapid Diagnostic Test: increasing testing capacity in screening of SARS-CoV-2 (SARA)

This protocol is based on the first evaluation of 5 Ag RDTs and the advise for antigen testing by OMT-12-10-2020.

Version(date)

Abbreviations

Ag	Antigen
COVID-19	CORonavirus Infectious Disease
RT-PCR	Reverse transcriptase Polymerase Chain Reaction
RDT	Rapid DiagnosticTest
SARS-CoV-2	SARS Coronavirus 2
WHO	World Health Organization
GGD	Municipal Health Center

Version(date)

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1. Introduction

1.1. Rationale

Good and rapid diagnostics are essential for the treatment and control of COVID-19. The current testing regimes relies on active case finding of COVID-19 infection using real-time reverse transcriptase PCR (RT-PCR). RT-PCR is highly sensitive and specific with results obtained within 24 hours.

The measures to control the COVID-19 pandemic rely heavily on fast and accurate testing of (suspected) COVID-19 cases and their contacts. SARS-CoV-2 testing is intended to identify current infection in individuals and is generally performed when a person has signs or symptoms consistent with COVID-19, or when a (asymptomatic) person has been in contact with a SARS-CoV-2 positive case or identified by a SARS-CoV-2 positive case through contact tracing.

However, control of the pandemic has required countries to drastically scale up their testing capacities in the first wave of the COVID-19 pandemic. Nonetheless the capacity is not enough as the current testing regimes takes at least 24-48 hours from sample to result and this time increases in high prevalent regions.

As such there is an increasing need and demand for rapid test currently being marketed to be used. Reliable rapid diagnostic tests could reduce the pressure on laboratories, GGD and expand testing capacities. However data is limited on the performance of these assays in GGD test lanes.

Rapid testing will allow for more rapid and informed quarantine guidelines, in particular for priority professions. These tests will also enable alleviation of containment measures enabling (partial) restoration of high societal and economic impact the pandemic has had.

The aim of this protocol is asses usefulness of Antigen Rapid Diagnostic tests (RDTs) with regards to clinical performance in the field for diagnostic and screening purposes. The Antigen RDTs selected should fit the WHO criteria (sensitivity of ≥80%, specificity ≥97%) as reported by the manufacturer.

1.2. Objectives

1.2.1. primary objective

To determine the diagnostic performance on sensitivity and specificity of the RAT compared to RT-PCR regarding usefulness in COVID19 diagnostic and screening.

- As a bias in sensitivity and specificity of the RT-PCR exist depending on the manufacturer, target region and laboratory setting. To ensure comparison between test data, a standard inactivated SARS-CoV-2 will be analyzed in all laboratories involved.

1.2.2. Secondary objectives

Secondary objectives are to determine the diagnostic performance of sensitivity and specificity compared to RT-PCR stratified by viral load/Ct values (ct<25, ct<30, ct <35), disease stage (< and > 7 days), symptomatic versus asymptomatic, sample type, prevalence of SARS-CoV-2 in population tested, age and sex.

2. Study design

2.1. Diagnostic purpose

The study design for diagnostic purposes relies on (mild) symptomatic cases visiting GGD test lanes (general population) which include (mild) symptomatic cases who have been in contact with confirmed COVID-19 cases (contact tracing/corona-app)

2.1.1. Study population

The sample size depend on the number of cases tested in GGD test lane but should be aimed at analyzing at least 100 RT-PCR positive cases and 300 RT-PCR negative cases per test.

- Other diagnostic purpose settings include GP-posts and ER departments.

2.1.2. Study procedure

Enrolment

- All persons visiting the test lane will be given asked to participate within the study and given a clinical enquiry questionnaire is given to be filled in to collect symptom information.
  - Informed consent is given verbally and confirmed with a second swab being taken.

Sampling and testing:

- One nasopharyngeal swab and one oropharyngeal swabs for RT-PCR and one nasopharyngeal swab or nasal swab (depending on kit specifics) for Ag-RDT are performed by trained GGD personnel.
- Samples for RT-PCR are sent to the regional laboratory for testing.
- Samples for Ag-RDT are tested on site in as separate test site by trained personal in PPE or are sent to the regional laboratory for testing.
  - In case Ag-RDTs are not reported in Coron-IT samples should be manually linked to RT-PCR labnumber
  - All Ag-RDT specimens shall be destroyed after testing as contaminated waste.

Reporting

- Laboratories electronically report RT-PCR test results to the GGD trough a digital communication system, the tested individual will thereafter be informed by a GGD employee of the RT-PCR results.
- Results for Ag-RDT are not reported to the person as the results are under evaluation and will not provide additional information to the person.

2.2. Screening purpose

The study design for screening purposes relies on (mild) symptomatic cases who have been in contact with confirmed COVID-19 cases (contact tracing/corona-app) or are part of a cluster. The aim is to implement public health measures as soon as possible.

2.2.1. Study population

The sample size depends on the number of cases tested for contact tracing or within a cluster.

2.2.2. Study procedure

Enrolment

- All persons are asked to participate within the study and given a clinical enquiry questionnaire is given to be filled in to collect symptom information
  - Informed consent is given verbally and confirmed with a second swab being taken.

Sampling and testing:

- One nasopharyngeal swab and one oropharyngeal swabs for RT-PCR and one nasopharyngeal swab or nasal swab (depending on kit specifics) for Ag-RDT are performed by trained GGD personnel.
- Samples for RT-PCR are sent to the regional laboratory for testing.
- Samples for Ag-RDT are tested on site in as separate test site by trained personal in PPE or are sent to the regional laboratory for testing.
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    - All Ag-RDT specimens shall be destroyed after testing as contaminated waste.

Reporting
- Laboratories electronically report RT-PCR test results to the GGD trough a digital communication system, the tested individual will thereafter be informed by a GGD employee of the RT-PCR results.
- Results for Ag-RDT are not reported to the person as the results are under evaluation and will not provide additional information to the person.

2.3. Asymptomatic screening

The study design for asymptomatic relies on continuous monitoring of asymptomatic cases with and without known exposure, screening of asymptomatic visitors of a nursing home or other short term exposure risk), and screening of asymptomatic cases of travelers from high endemic countries.

2.3.1. Study population

unknown

2.3.2. Study procedure

Enrolment

- All persons are asked to participate within the study
    - Informed consent is given verbally and confirmed with a second swab being taken.

Sampling and testing:
- One nasopharyngeal swab and one oropharyngeal swabs for RT-PCR and one nasopharyngeal swab or nasal swab (depending on kit specifics) for Ag-RDT are performed by trained GGD personnel.
- Samples for RT-PCR are sent to the regional laboratory for testing.
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- Results for Ag-RDT are not reported to the person as the results are under evaluation and will not provide additional information to the person.

2.4. Implementation study

When Ag test has been evaluated and meet testing criteria, the test can be implemented (implementation-study period) for all cases where double swabs are routinely taken. Positive results can be reported immediately. Negative results should be confirmed by RT-PCR before reporting. Confirmation by RT-PCR should be evaluated

3. Evaluation

Data should be evaluated according to the objectives specified.
The data includes categorical values and will be presented as quantitative data using standard statics for categorical data. Data points that are undetermined result shall be excluded.
It is recommended to report the 95 % confidence interval for the estimates of both the diagnostic sensitivity and the diagnostic specificity (https://ec.europa.eu/docsroom/documents/40805.).

4. Data collection, management and ethics

The clinical performance study shall be conducted so as to ensure accountability, traceability, suitability and quality of all specimens during the steps of the clinical performance study, from collection through testing and result reporting. All relevant information should be documented and maintained for the duration of the study to ensure accuracy and reliability of the clinical performance study data.

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). Data are owned by the laboratory or GGD that shared them.
Results should be stored in the laboratory information system.

Only aggregated data will be reported to funding bodies. Data will be stored for 20 years after the completion of this study according to WGBO (wet geneeskundige behandelingsovereenkomsten) article 4.6/ 8.1.7.

The study is non-WMO under number 20-606 (METC Urecht) for evaluation in GGD test lanes. Evlaution in other settint should be reported as amendment to 20-606

5. Literature

Dinnes J, Deeks JJ, Adriano A, Berhane S, Davenport C, Dittrich S, Emperador D, Takwoingi Y, Cunningham J, Beese S, Dretzke J, Ferrante di Ruffano L, Harris IM, Price MJ, Taylor-Phillips S, 5.1.2e, Leeflang MM, Spijker R, Van den Bruel A; Rapid, point-of-care antigen and molecular-based tests for diagnosis of SARS-CoV-2 infection. Cochrane COVID-19 Diagnostic Test Accuracy Group. Cochrane Database Syst Rev. 2020 Aug 26;8:CD013705. doi: 10.1002/14651858.CD013705. PMID: 32845525