Evaluation of the accuracy of saliva rapid antigen self-testing for SARS-CoV-2 infection

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SUMMARY

Rationale: The Dutch public SARS-CoV-2 testing programme considers the introduction of self-collected saliva antigen-detecting rapid diagnostic tests (Ag-RDT) for the detection of SARS-CoV-2 infection. If sufficiently accurate, as compared to the prevailing reference test (reverse transcriptase polymerase chain reaction; RT-PCR), a saliva Ag-RDT can be introduced as preferred self-test since saliva tests are less invasive and easier to use than the currently available self-collected nasal swab Ag-RDT. This study is very timely since almost all countries are facing the re-opening of societies and public life, with self-testing likely becoming an integral part of our lives. However, before wide scale implementation of self-collected saliva SARS-CoV-2 Ag-RDT in asymptomatic or symptomatic individuals, quantification of the accuracy of each candidate saliva Ag-RDT (notably its sensitivity and negative predictive value) using the RT-PCR as reference, and with a head-to-head comparison with the prevailing self-collected nasal swab Ag-RDT, is warranted. Also, evidence of the diagnostic accuracy of the self-collected saliva Ag-RDT across symptom presence, vaccination status, and regarding virus variants is urgently needed.

Objective: To sequentially quantify the diagnostic accuracy of various self-collected saliva Ag-RDTs with RT-PCR as the reference standard, and a head-to-head comparison with the prevailing self-collected nasal swab Ag-RDT (Biosensor test (Roche Diagnostics)) in presymptomatic or asymptomatic, and symptomatic tested individuals.

Study design: Prospective cross-sectional diagnostic test accuracy study. Each individual scheduled for a routine SARS-CoV-2 test at one of the participating Dutch public health service test sites who is interested in study participation will subsequently receive a testkit with two Ag-RDT self-tests to apply at home according to the manufacturers' instructions after haven provided digital informed consent. The testkit contains the self-collected saliva Ag-RDT (the Ag-RDT type will be determined by the Ministry of Health, Welfare and Sport, independent to the research team) and the Biosensor self-collected nasal swab Ag-RDT (The Biosensor test is currently the prevailing nasal self-test in The Netherlands and has a specific manufacturers' instruction for self-use). Participants will also be asked to complete a short online baseline and follow-up (after 10 days) questionnaire.

If feasible, viral culturing will be performed on all positive RT-PCR specimens of the Erasmus MC Viroscience diagnostic laboratory and whole genome sequencing of the SARS-CoV-2 virus in all cases with positive RT-PCR specimens but negative self-collected Ag-RDT (test-discordant cases).

Study population: Individuals aged 16 years and older presenting for routine SARS-CoV-2 testing (regardless of test indication, symptomatology, and COVID-19 vaccination status at test request) at one of the participating Dutch public health service test sites (West-Brabant (location Roosendaal), Hart voor Brabant (location Tilburg), Rotterdam Rijnmond (location Zuidland), and other public health service testing sites to be determined).

Main study parameters/endpoints: The diagnostic accuracy (sensitivity, specificity, positive and negative predictive values) of the three self-collected saliva Ag-RDT as well as the Biosensor self-collected nasal swab Ag-RDT will be assessed using RT-PCR as reference standard. As reference test result we will use both the standard RT-PCR test result as well as the RT-PCR test result stratified for the viral load cut-off above which 95% of RT-PCR positives have a positive viral culture as a proxy of infectiousness. In secondary analyses, the test accuracy of the self-collected saliva Ag-RDTs will be stratified according (but not limited) to age groups, gender, indication for testing, presence of symptoms at testing, having had a positive SARS-CoV-2 test previously, having been vaccinated (and with which COVID-19 vaccine), and SARS-CoV-2 variant.

Nature and extent of the burden and risks associated with participation, benefit and group relatedness: There is no direct personal benefit in participation. The participant will undergo the standard swab for RT-PCR testing, followed by self-collection of saliva for the saliva Ag-RDT and a self-collected nasal swab for the nasal Biosensor Ag-RDT. The additional burden of the self-tests is negligible; they are minimally invasive and pose no risk to the health of the participant.

1. INTRODUCTION AND RATIONALE

In the current phase of the global COVID-19 pandemic, all countries are facing the re-opening of societies and public life, with SARS-CoV-2 self-testing likely becoming an integral part of daily life. The Dutch public SARS-CoV-2 testing programme is considering the introduction of self-collected saliva antigen-detecting rapid diagnostic self-tests (Ag-RDT) for the detection of SARS-CoV-2 infection. If sufficiently accurate, as compared to the prevailing reference test (reverse transcriptase polymerase chain reaction; RT-PCR) and the currently available self-collected nasal swab Ag-RDT, a saliva Ag-RDT could be introduced as preferred self-test since saliva is less invasive and easier to collect than a nasal swab. However, before wide scale implementation of self-collected saliva SARS-CoV-2 Ag-RDT in asymptomatic or symptomatic individuals, quantification of their accuracy (notably their sensitivity and negative predictive value) using the RT-PCR as reference, and with a head-to-head comparison versus the currently available self-collected nasal swab Ag-RDT, is warranted.

Also, evidence of the diagnostic accuracy of the self-collected saliva Ag-RDT across symptom presence, vaccination status, and if possible virus variants is urgently needed.

In the Netherlands, the Biosensor test (Roche Diagnostics) is the prevailing self-collected nasal swab Ag-RDT since it has a high specificity and relatively high sensitivity to identify individuals with a high probability of infectiousness, and has a specifically developed self-test manual and kit.[1]

A wide range of self-collected saliva SARS-CoV-2 Ag-RDT are increasingly becoming available but robust evidence on their diagnostic accuracy is lacking.[2] We have established a successful research collaboration and infrastructure embedded within the Dutch public health service test sites[3] which allows us to efficiently determine diagnostic accuracies of self- and rapid tests compared to RT-PCR. The aim of this particular study is to sequentially quantify the diagnostic accuracy of various self-collected saliva Ag-RDTs, and head-to-head comparison of each of the saliva Ag-RDTs with the Biosensor self-collected nasal swab Ag-RDT using the RT-PCR as the reference standard in presymptomatic or asymptomatic, and symptomatic individuals presenting for routine SARS-CoV-2 testing at Dutch public health service test sites.

2. OBJECTIVES

Primary objective:

To sequentially quantify the diagnostic accuracy of various self-collected saliva Ag-RDTs with RT-PCR as the reference standard.

Secondary objectives:

- To sequentially quantify the diagnostic accuracy of various self-collected saliva Ag-RDTs with a viral load cut-off above which 95% of RT-PCR positives have a positive culture as a proxy of infectiousness as the reference standard.
- To perform a head-to-head comparison of the diagnostic accuracy of each self-collected saliva Ag-RDT with the Biosensor self-collected nasal swab Ag-RDT, again using the RT-PCR as reference (using both types of RT-PCR outcomes).
- To assess the diagnostic accuracies of each self-collected saliva Ag-RDT across (if data allow for):
    1. Age and gender strata.
    2. prior SARS-CoV-2 infection status.
    3. COVID-19 vaccination status (including type of vaccine received).
    4. indication for testing: known close contact of an individual with a confirmed SARS-CoV-2 infection with or without symptoms at the time of sampling or symptomatic individuals seeking testing independent of contact-tracing.
    5. absence or presence (and duration) of COVID-19 like symptoms at the time of sampling.
    6. SARS-CoV-2 variants
    7. the saliva test was used according to the instruction (yes vs no) - as indicated by participant in questionnaire.
- To explore the usability of the self-collected saliva Ag-RDT and the Biosensor self-collected nasal swab Ag-RDT.
- To assess the prevalence of COVID-19 like symptoms and SARS-CoV-2 infection within 10 days after initial negative RT-PCR test result.

3. STUDY DESIGN

We will perform a prospective cross-sectional diagnostic test accuracy study, where in each study participant the reference test (RT-PCR) is conducted at the Dutch public health service testing site by trained healthcare professionals, followed (within three hours) by self-testing with two index tests: the self-collected saliva Ag-RDT and the Biosensor self-collected nasal swab Ag-RDT.

The nasopharyngeal swab for routine RT-PCR test will be taken at the participating public health service test site. Next, the study participant will receive two Ag-RDT self-tests to apply at home: a self-collected saliva Ag-RDT (the Ag-RDT type will have CE-marking and will be determined by the Ministry of Health, Welfare and Sport, independent to the research team; various types will be sequentially tested during the study) and the Biosensor self-collected nasal swab Ag-RDT. The reading of both self-tests will be done by direct visual interpretation by the study participant.

Participants will also be asked to complete a short online baseline questionnaire at the day of inclusion (Appendix A), and a follow-up questionnaire 10 days later (Appendix B) to determine whether a negative RT-PCR test result was followed by a positive SARS-CoV-2 test (to determine the proportion of missed infections, which is notably important in individuals at an early stage of an infection at the time of initial testing).

If feasible, viral culturing will be performed on all positive RT-PCR specimens of the Erasmus MC Viroscience diagnostic laboratory and whole genome sequencing of the SARS-CoV-2 virus in *all* cases (irrespective of laboratory) with positive RT-PCR specimens but negative self-collected Ag-RDT (test-discordant cases).

4. STUDY POPULATION

4.1 Population (base)

The study will be embedded in the routine national public health SARS-CoV-2 testing programme. Participating public health service sites include West-Brabant (location Roosendaal) and Hart voor Brabant (location Tilburg), Rotterdam Rijnmond (location Zuidland) and other public health testing sites when needed. The need to add more sites will mainly depend on the number of tests performed daily per site during the course of the study.

4.2 Inclusion criteria

To be eligible to participate in this study, a person must meet all of the following criteria:

- Aged 16 years or older.
- Scheduled for a SARS-CoV-2 RT-PCR test at participating public health service site.
- Willing to provide written informed consent for study participation.

4.3 Exclusion criteria

A person will be excluded if one of the following criteria are met:

- Aged <16 years.
- Visiting the test facilities to obtain travel-related negative test certificates
- Unable or unwilling to complete the informed consent in the Dutch language.

4.4 Sample size consideration

Previous Ag-RDTs performance studies in symptomatic individuals found sensitivities around 85%.[4] and when used as a self-test around 80%.[1] A recent accuracy study in The Netherlands that quantified the accuracy of saliva Ag-RDT performed by healthcare professionals (i.e. not by self-collection), found an overall sensitivity of 66% and around 89% when using cycle threshold <30 cut-off.[2] We therefore base our sample size calculation on an expected sensitivity of 80% for the self-collected saliva Ag-RDT, with a margin of error of 7%, type I error of 5% and power of 80%. Hence, we aim for approximately 140 positive RT-PCR tests. In the current situation (June 2021), we anticipate a SARS-CoV-2 prevalence (based on RT-PCR) in our target population of around 5% in the tested populations, but we will closely monitor the RT-PCR test positivity rate in our study population over time and prolong recruitment if needed. We expect to need 8 to 10 weeks for patient recruitment.

5. METHODS

5.1 Study endpoints

5.1.1 Main study endpoint

Diagnostic accuracy (sensitivity, specificity, positive and negative predictive values) of the individual self-collected saliva Ag-RDT, with RT-PCR as the reference standard. The Roche cobas platforms for RT-PCR testing were used according to the manufacturer's instructions; amplification curves and cycle threshold values were interpreted using the manufacturer's interpretation algorithms, which complied with the European in-vitro diagnostic devices directive.

5.1.2 Secondary study endpoints

- Diagnostic accuracy (sensitivity, specificity, positive and negative predictive values) of the individual self-collected saliva Ag-RDT, with the viral load cut-off above which 95% of RT-PCR positives have a positive culture as a proxy of infectiousness as the reference standard.
- Head-to-head comparison of diagnostic accuracy parameters (sensitivity, specificity, positive and negative predictive values) of the self-collected saliva Ag-RDT, and the Biosensor self-collected nasal swab Ag-RDT, with RT-PCR as reference standard (using both types of RT-PCR outcomes).
- Diagnostic accuracy (sensitivity, specificity, positive and negative predictive values) of the self-collected saliva Ag-RDT stratified by (if data allow for):
    1. demographic variables (gender, age).
    2. prior SARS-CoV-2 infection status.
    3. COVID-19 vaccination status (and type of vaccine received).
    4. indication for testing: known close contact of an individual with confirmed SARS-CoV-2 infection with or without symptoms at the time of sampling or symptomatic individuals seeking testing independent of contact-tracing.
    5. absence or presence (and duration) of COVID-19 like symptoms at the time of sampling.
    6. SARS-CoV-2 variants
    7. the saliva test was used according to the instruction (yes vs no) - as indicated by participant in questionnaire.
- User opinions regarding the difficulty of using of the saliva and nasal swab test
- Prevalence of COVID-19 like symptoms and SARS-CoV-2 infection within 10 days after an initial negative RT-PCR test.

5.2 Study procedures

Triage at the public health service test sites

Participants will be recruited consecutively at the participating public health service test sites. Verbal triage will take place at the public health service test sites when potential participants present themselves. To verify eligibility, potential participants will be asked whether they:

1. are aged 16 years or above.
2. are willing to participate in the study.
3. Are visiting the site for regular test purposes (travel-related testing visitors excluded from the study due to low a priori risk of a positive test)

Only if the answer to all these questions is "yes", individuals will receive a participant information letter, and will complete a contact information form to provide contact details (name, phone number, and email address). Participants will have sufficient time to think about participation and to read the study information.

Tests at the public health service test site

Study participants will be sampled for a routine RT-PCR, by trained public health service personnel. For the RT-PCR, a nasopharyngeal swab will be taken placed directly in universal transport media (HiViralTM or HiViralTM + lysis buffer), and shipped to the participating diagnostic laboratories (Microvida location Bravis for West-Brabant and Hart voor Brabant Erasmus MC Viroscience diagnostic laboratory in Rotterdam; and other laboratories affiliated to the other participating public health testing sites). Routine RT-PCR testing will be performed in virus transport medium using the cobas® SARS-CoV-2 test on the cobas 6800® platform (Roche Diagnostics International, Rotkreuz, Switzerland) in Erasmus MC Viroscience diagnostic laboratory and cobas 8800® platform (Roche Diagnostics International, Rotkreuz, Switzerland) in Microvida location Bravis. A barcode sticker with the CoronIT ID (=sample number) is put on the sample tube as well as on the contact information form.

Self-sampling and testing

Upon consent from the participant, public health service personnel will enter the participant's contact information written on the contact information form (name, email address, telephone number and CoronIT number) in SLIM. This information is needed for sending the url that will guide participants to the digital informed consent form and the baseline and follow-up questionnaires (Appendices A and B). Furthermore, it will allow us to contact the study participant in case the baseline questionnaire and self-collected saliva and nasal swab Ag-RDT results have not been recorded in Research Online (RO) within 3 hours after the RT-PCR test was taken. The online questionnaires will be designed in RO, and the coded data will be stored on a secure central server of the Julius Center, UMC Utrecht (see also section 8.1).

Study participants will receive a self-test kit from the public health service personnel including all necessary materials needed for applying at home (within 3 hours) the self-collected saliva Ag-RDT and the Biosensor self-collected nasal swab Ag-RDT. Both Ag-RDT self-tests have CE-marking and will be performed according to the manufacturers' instructions.
Finally, participants will be asked to complete a short follow-up questionnaire using again Research Online 10 days later to determine whether a negative RT-PCR test result was followed by symptoms and/or a positive test (to determine the proportion of missed infections).

Virus culture and viral load calculation
If feasible, samples of participants with a positive RT-PCR test result at the Erasmus MC Viroscience diagnostic laboratory, will be inoculated onto Vero cells, and incubated for a maximum of 14days or until cytopathic effects are observed. Once cytopathic effects will be visible, the presence of SARS-CoV-2 virus will be confirmed with immunofluorescent detection of nucleocapsid protein (Rabbit polyclonal antibody Sino Biological inc., Eschborn, Germany).
A standard curve has been created by testing dilutions of a specific quantified E-gene transcript (primary standard) available from the European Virus Archive (EVAg3) with the RT-PCR described by Corman et al.[5] and by linear regression analysis. Based on this calibration curve, a secondary standard derived from cell-cultured virus was prepared and quantified. Based on this standard all participating laboratories, will provide a calibration curve to be able to convert CT-values into viral loads that can be directly compared between laboratories.
Any differences in initial sample volume and subsequent sample dilution by the various laboratories will be taken into account. In line with previous studies, the infectiousness viral load cut-off will be defined as the viral load above which 95% of RT-PCR positives collected in Rotterdam showed in vitro infectivity in cell culture.[3]

Viral sequencing
In all cases with positive RT-PCR specimens but negative self-collected Ag-RDT (test-discordant cases) whole genome sequencing of the virus isolate will be performed to determine the SARS-CoV-2 variant. The laboratory that will conduct the whole genome sequencing will be selected after all samples have been collected.

Results of tests
Study participants will be informed about the result of the SARS-CoV-2 RT-PCR test within 24 hours after testing. They are also explicitly informed that the result of the RT-PCR test is the leading test result and to act according to health service's instructions (based on the RT-PCR test). Participants will not be notified about the viral culture or sequencing results.

6. STATISTICAL ANALYSIS

Descriptive statistics will be used to describe the demographics of our study population as well as the prevalence of SARS-CoV-2 infection (based on RT-PCR) both from initial testing as well as after 10 day follow-up. The number of missing values is expected to be low, especially for the primary analyses that focus on the diagnostic accuracy. Therefore, no a priori details to account for missing values are provided.
In primary analyses, the results of the self-collected saliva Ag-RDT (positive vs. negative) will be compared to the reference test RT-PCR (positive vs. negative) by calculating the sensitivity, specificity, positive and negative predictive values with corresponding 95% Cis.
In secondary analyses, the results of the self-collected saliva Ag-RDT (positive vs. negative) will be compared to the reference test RT-PCR (positive vs. negative) by calculating the sensitivity, specificity, positive and negative predictive values with corresponding 95% Cis, stratified for the viral load cut-off above which 95% of RT-PCR positives have a positive culture as a proxy of infectiousness conform previous studies. The same is done for the Biosensor self-collected nasal swab Ag-RDT and the diagnostic accuracy of the self-collected saliva Ag-RDT will be compared to that of the Biosensor self-collected nasal swab Ag-RDT.

Also, we will calculate the sensitivity, specificity, positive and negative predictive values with corresponding 95% CIs of the self-collected saliva Ag-RDT (with RT-PCR as the reference standard), according to the following subgroup characteristics (if sufficient numbers):

- demographic variables (gender, age).
- prior SARS-CoV-2 infection status.
- COVID-19 vaccination status.
- indication for testing.
- absence or presence (and duration) of COVID-19 like symptoms at the time of sampling.
- SARS-CoV-2 variants
- saliva test was used according to the instruction (yes vs no) – as indicated by participant in questionnaire.

Finally, we will describe user opinions regarding the difficulty of using of the saliva and nasal swab test and determine revalence of COVID-19 like symptoms and SARS-CoV-2 infection within 10 days after an initial negative RT-PCR test.

7. ETHICAL CONSIDERATIONS

7.1 Regulation statement

This 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 EU GDPR (General Data Protection Regulation), the "AVG (UAVG) and "Gedragscode Gezondheidsonderzoek". The medical research ethics committee (METC) Utrecht has reviewed our study and concluded that ethics approval was not required because the study is outside the scope of the Dutch Medical Research Involving Human Subjects Act (WMO) (METC Utrecht protocol number: 21/xxx).

7.2 Recruitment and consent

At the public health service test site, eligible participants will be asked to consent to participate in our study. Participants will be informed about the study by the same person who performs the triage and receive a participant information letter and a contact information form. After given verbal consent, participants will share their contact details and receive a testkit to bring home. After, they will receive an email with a participation link, and enough time to think about participation and to read the study information prior to providing digital informed consent if they are willing to participate in the study.

8. ADMINISTRATIVE ASPECTS AND PUBLICATION

8.1 Handling and storage of data and documents

For this study, a research collaboration agreement will be signed between the UMC Utrecht and RIVM.

Part of the data used in our study will be collected as part of the nationwide testing policy. This means data will be collected by the public health service and communicated with the RIVM following the General Data Protection Regulation (GDPR; https://gdpr-info.eu/). RIVM will sign research agreements with participating public health service test sites regarding test results and sample analyses.

The UMC Utrecht will sign research agreements with participating health service test sites regarding the recruitment of participants and collecting their contact details.

GGD Hart voor Brabant will be responsible for the follow-up of research participants; this specific role will be included and outlined in the signed research agreement between the UMC Utrecht and GGD Hart voor Brabant will sign a this specific role.

Per participant the following information will be collected:

- Digital informed consent form (Research Online)
- Contact information of study participant including name, email address and telephone number (entered in SLIM by public health service test site personnel)
- Baseline and follow-up short questionnaire information (online by study participant in RO)
- Demographics age, gender; public health service test site (CoronIT)
- RT-PCR test result (local laboratories)
- Self-collected saliva Ag-RDT and Biosensor self-collected nasal swab Ag-RDT results (online by study participants in RO)
- If applicable, virus culture (laboratory Erasmus MC) and whole genome sequencing results (local laboratories)

The informed consent forms will be initially stored at the participating public health service test sites. After enrolment of the final participant, the informed consent forms will be transported to the UMC Utrecht for final storage.

Public health service test site personnel will place barcode stickers containing a study participant code (the CoronIT ID) on the nasopharyngeal sample taken for RT-PCR. These nasopharyngeal samples will be destroyed at the end of the study according to the standard operating procedures of the participating local laboratories. The same CoronIT ID will be

placed on the contact information form and stored in a separate secure database (SLIM). The survey results are stored with a study number (study ID) in a separate database (Research Online). Merging the PCR results with the survey data will be done with SAS syntax. The CoronIT ID will only be temporarily used for merging purposes and will not be used in the analysis datasets.

The data management department of the Julius Center, UMC Utrecht will be responsible for the data management of this study. GDRP proof systems including SLIM and RO will be used. Study participants will be asked to complete the baseline and follow-up short questionnaire and the self-collected saliva and nasal swab Ag-RDT results in RO.

In addition, demographic data from the public health service (CoronIT) will be linked to participants' RT-PCR test results from the local laboratories by the RIVM using the CoronIT ID. Once these data have been assembled, a pseudonymised database will be sent by the RIVM via a secure transfer (e.g. Surf filesender or Surfdrive) to the UMC Utrecht. These data will be added to the UMC Utrecht database derived from RO and the combined dataset will then be used for final analysis. The pseudonymised dataset will be stored in a study folder on a central drive of the Julius Center for 15 years. The database will only be accessible to assigned members of the research team and a data manager of the Julius Center, UMC Utrecht.

8.2 Systems

Research Online

The Electronic Data Capture (EDC) system 'Research Online' guarantees a correct, complete and consistent data collection.

SLIM

Based on the principles that research data should be managed separately from personal data of subjects, SLIM offers the researchers to register, communicate include, exclude and invite subjects to take part in a (clinical) study. It also offers to automatically invite subjects to fill in forms in RO after subjects have fulfilled certain criteria, such as signing an informed consent and being included in a study. Using specific roles, access to personal data is limited for strict user purposes or to research related identifiers.

8.3 Systems security

Research Online and SLIM

Data from Research Online and SLIM will be transferred over the internet using secured data communication protocols. All data will be stored automatically and regularly back-ups will

make sure that data will never be lost. Databases and web servers of these systems will be hosted in a ISO/IEC 27001:2013 certified data center in the EU. Security is assured by ISAE 3402 type 2 and SOC 1 type 2 reports.
The servers are actively monitored (including memory, storage and CPU usage and network connections). When an incident occurs in the servers, the support desk is alerted and will resolve the issue.
To keep RO running smoothly, updates and fixes are required. Therefore server/database maintenance is scheduled outside office hours monthly in combination with a new software version. Any required scheduled downtime is limited to approximately 10 minutes. Major updates which require more than a 30-minute window will be planned and communicated to all involved study teams. Exceptions can be made for urgent security updates or issues that are causing high priority production issues.

A backup of all data (model and database) is made daily for the user acceptance testing and production environment. Backups are stored in secured locations that are geographically dispersed. The duration of storage is as follows:

- Nightly Backups: 2 weeks
- Sunday Backups: 3 months
- Monthly Backups (1st Sunday of each month): 1 year

RO and SLIM meet all ICH-GCP, EMA (annex 11) and FDA (21CFR part 11) guidelines for electronic data collection in terms of protecting data integrity and securing the information collected. This means, among other things, that users will get role-based access to the system after they have logged-in using their own username and password. The system will log all data entry steps with timestamps, update reasons and user information. Role-based access to the system will avoid unauthorized data access and prevents users from taking actions for which they are not authorized.

Development
RO and SLIM are developed in MENDIX. This state-of-the-art development platform enables very flexible and fast development of new functionalities to the system. A full DTAP (Development, Test, Acceptance, Production) approach is used to develop, test and deploy new releases of the software in a controlled way. An automatic test environment including hundreds of test cases is used for full regression testing of RO before new releases will be placed into production environment.

8.4 Amendments

Amendments are changes made to the research after an ethical committee gave an advice non-WMO. Any change that may cause the investigation to fall within the scope of the WMO is submitted to the ethical committee that gave the non-WMO advice.

9. REFERENCES

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APPENDIX A

Online baseline vragenlijst voor deelnemers

1. Wat was de uitslag van de speekseltest?
□ Negatief
□ Positief
□ Weet ik niet ik kon de test niet uitvoeren
□ Weet ik niet: ik kon de test niet aflezen
□ Anders, nl: (open tekst)

2. Wat was de uitslag van de neuswat test?
□ Negatief
□ Positief
□ Weet ik niet ik kon de test niet uitvoeren
□ Weet ik niet: ik kon de test niet aflezen
□ Anders, nl: (open tekst)

3. Waarom heeft u een corona-test aangevraagd bij de GGD?
(meerdere antwoorden mogelijk)
□ Ik heb of had zelf corona-gerelateerde klachten
□ Ik heb contact gehad met iemand met corona:
- Het laatste contact was op: ___ /____ (dd/mm)
Ik ben daarachter gekomen want (meerdere antwoorden mogelijk):
- Deze persoon is een huisgenoot □ Ja / □ Nee
- Ik kreeg een melding via de CoronaMelder app □ Ja / □ Nee
- Een GGD BCO medewerker nam contact met me op □ Ja / □ Nee
- De persoon die positief getest was nam contact met me op □ Ja / □ Nee
- Op een andere manier, namelijk: ……
□ Ik kreeg het advies van de huisarts om me te laten testen
□ Ik ben naar het buitenland geweest
□ Ik heb een zelftest gedaan en had een positieve testuitslag
Ja? Wat was de datum van de positieve zelftest: ___ /____ (dd/mm)
□ Geen van bovenstaande, maar: ……

4. Bent u gevaccineerd tegen COVID-19?
□ Nee
□ Ja:
Met welk vaccin? □ Pfizer □ Moderna □ AstraZeneca □ Janssen □ onbekend

Hoe vaak? □ 1x □ 2x
Wat is de datum van de laatste vaccinatie? … / … / ….. (dd/mm/jjjj)

5. Heeft u al eens eerder een positieve coronatest gehad?
□ Nee
□ Ja:
Hoelang geleden? □ <2 maanden □ 2-6 maanden □ 6-12 maanden □ >12 maanden

6. Heeft u op dit moment COVID-gerelateerde symptomen of klachten (zie volgende vraag voor lijst aan klachten)?
□ Nee → Ga naar vraag 9
□ Ja

7. Welke klachten heeft u op dit moment? (meerdere antwoorden mogelijk)
   - □ Verkoudheidsklachten (neusverkoudheid, loopneus, niezen, keelpijn)
- □ Benauwdheid of kortademigheid
- □ Koorts of verhoging
   - □ Hoesten
   - □ Plotseling verlies van reuk en/of smaak (zonder neusverstopping)
   - □ Erge spierpijn
- □ Ik heb andere klachten, namelijk: ……

8. Sinds wanneer heeft u deze klachten?

□ Vandaag □ Gisteren □ Eergisteren □ ≥ 3 dagen geleden

9. Wat is uw hoogst genoten opleidingsniveau?

□ Basisonderwijs
□ VMBO, HAVO, MBO
□ HBO/WO bachelor
□ HBO/WO-master, doctor

10. De instructie van de speekseltest geeft aan 30 min niet eten, drinken, roken, tanden poetsen of kauwgom kauwen, heeft u zich daaraan gehouden?

□ Ja
□ Nee, ik had (meerdere antwoorden mogelijk):
- □ Gegeten
- □ Gedronken
- □ Gerookt
- □ Mijn tanden gepoetst
- □ Kauwgom gekauwd

11. Hoe moeilijk vond u het om de speekseltest zelf af te nemen, op een schaal van 1 tot 5?

Heel makkelijk 1 2 3 4 5 Heel moeilijk

12. Hoe moeilijk vond u het om het speeksel testresultaat af te lezen, op een schaal van 1 tot 5?

Heel makkelijk 1 2 3 4 5 Heel moeilijk

13. Hoe moeilijk vond u het om de neuswat test zelf af te nemen, op een schaal van 1 tot 5?

Heel makkelijk 1 2 3 4 5 Heel moeilijk

14. Hoe moeilijk vond u het om het neuswat testresultaat af te lezen, op een schaal van 1 tot 5?

Heel makkelijk 1 2 3 4 5 Heel moeilijk

15. Bent u het eens met de volgende uitspraken?

De gebruiksaanwijzing van de speekseltest was duidelijk
eens twijfel oneens

Ik weet zeker dat ik de speekseltest goed heb afgenomen
eens twijfel oneens

Ik zou deze speekseltest thuis gebruiken als dat kon
eens twijfel oneens

16. Heeft u een voorkeur voor de speekseltest of de neuswat test?

□ Nee
□ Ja, voorkeur voor speekseltest
□ Ja, voorkeur voor neuswat

Indien ja, waarom: …..[open antwoord]

17. Heeft u suggesties voor verbetering van de gebruiksaanwijzing van de speekseltest of andere suggesties?
[open antwoord]

APPENDIX B

Online follow-up vragenlijst voor deelnemers met RT-PCR negatieve testuitslag

1. Heeft u na uw laatste corona test van 10 dagen geleden COVID-gerelateerde symptomen of klachten ontwikkeld (zie volgende vraag voor lijst aan klachten)?

☐ Nee
☐ Ja

2. Welke klachten waren dat? (meerdere antwoorden mogelijk)

☐ Verkoudheidsklachten (neusverkoudheid, loopneus, niezen, keelpijn)
☐ Benauwdheid of kortademigheid
☐ Koorts of verhoging
☐ Hoesten
☐ Plotseling verlies van reuk en/of smaak (zonder neusverstopping)
☐ Erge spierpijn
☐ Ik heb andere klachten, namelijk: ……

3. Sinds wanneer heeft u deze klachten?

… / … / ….. (dd/mm/jjjj)

4. Heeft u in de afgelopen 10 dagen, nadat u de corona test bij de GGD en de speeksel- en neustesten in studieverband bij uzelf heeft afgenomen, nog een corona-test laten doen of bij uzelf gedaan?

☐Nee → EINDE VRAGENLIJST
☐Ja

Indien Ja, wat voor soort test heeft u gehad?

☐ Test bij de GGD
☐ PCR
☐ Antigeen / sneltest
☐ Weet ik niet

☐ Test bij een commerciële aanbieder
☐ PCR
☐ Antigeen / sneltest
☐ Weet ik niet

□ Zelftest die ik zelf gekocht heb
□ Anders, namelijk (open tekst)

5. Wat was de reden voor het aanvragen van de nieuwe corona-test? (meerdere antwoorden mogelijk)

□ Ik heb of had zelf corona-gerelateerde klachten
□ Ik heb contact gehad met iemand met corona:
- Het laatste contact was op: : ___ /____ (dd/mm)

Ik ben daarachter gekomen want (meerdere antwoorden mogelijk):
- Deze persoon is een huisgenoot □ Ja / □ Nee
- Ik kreeg een melding via de CoronaMelder app □ Ja / □ Nee
- Een GGD BCO medewerker nam contact met me op □ Ja / □ Nee
- De persoon die positief getest was nam contact met me op □ Ja / □ Nee
- Op een andere manier, namelijk: ……

□ Ik kreeg het advies van de huisarts om me te laten testen
□ Ik ben naar het buitenland geweest
□ Ik heb een zelftest gedaan en had een positieve test-uitslag
Ja? Wat was de datum van de positieve zelftest: ___ /____ (dd/mm)
□ Geen van bovenstaande, maar: ……

6. Wat was de uitslag van deze coronatest?

□ Positief (SARS-CoV 2 infectie aanwezig)
□ Negatief
□ Geen uitslag (test mislukt)