International Platform of Registered Systematic Review and Meta-analysis Protocols

INPLASY

Clinical Performance of SARS-CoV-2 Rapid Antigen Tests: A Systematic Review andMeta-Analysis

INPLASY2023100033
doi: 10.37766/inplasy2023.10.0033
Received: 08 October 2023
Published: 08 October 2023

Germic, N[1]; Hayer, J[2]; Feng, Q[3].

Corresponding author:
Qian Feng

qian.feng.qf1@roche.com

Author Affiliation:
Roche Diagnostics.

ADMINISTRATIVE INFORMATION

Support - Roche Diagnostics.

Review Stage at time of this submission - Completed but not published.

Conflicts of interest - QF is an employee of Roche Diagnostics International Ltd and she holds stocks in F. Hoffmann-La Roche Ltd.

INPLASY registration number: INPLASY2023100033

Amendments - This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 08 October 2023 and was last updated on 08 October 2023.

INTRODUCTION

Review question / Objective We conducted a meta-analysis of 86 studies including 166,561 samples for RAT diagnostic accuracy for SARS-CoV-2 infections, and evaluated test sensitivity versus the presence of symptoms, days post symptom onset (DPSO), sample viral load, and sample type (i.e. direct swabs versus specimens stored in transport media).

Rationale RATs played a critical role during the COVID-19 pandemic. Comprehensive understanding of the capabilities and limitations of RATs for SARS-CoV-2 diagnosis is crucial to assess their utility in an endemic setting. Varying clinical performance has been reported for SARS-CoV-2 RATs from different manufacturers and among diverse patient populations on a global scale. The SARS-CoV-2 Rapid Antigen Test manufactured by SD Biosensor and distributed by Roche Diagnostics (equivalent to the STANDARD Q COVID-19 Ag Test) was broadly used internationally during the pandemic, both in professional point-of-care settings and as a self-test. To evaluate the diagnostic accuracy of the Roche/SDB RAT, we performed an unbiased literature search including studies across 36 different countries. Our meta-analysis of 86 studies shows that RAT performance supports near-patient testing for early COVID-19 diagnosis, with reliable sensitivity in those with relatively high viral load.

Condition being studied SARS-CoV-2 infection.

METHODS

Search strategy This meta-analysis was performed according to the Preferred Reporting

Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.[13] SURUS, a custom-built natural language processing (NLP) Engine (Medstone Science B.V.) was used to conduct query-based searches for relevant papers from January 2020 through March 2022. The databases MEDLINE, and preprint servers MedRixv and BioRxiv were initially searched for clinical performance studies of a commercial SARS-CoV-2 RAT with the following search strings: ("SARS-CoV-2" OR "Rapid antigen test" OR "point of care" or "lateral flow assay" or "Roche/SD Biosensor/ Standard Q") AND ("nasopharyngeal" OR "nasal" OR "oro-nasopharyngeal" OR "oropharyngeal" OR "viral culture") AND ("Sensitivity" OR "Specificity" OR "Accuracy" OR "PPA" OR "NPA" OR "PPV" OR "NPV" OR "LOD" OR "TCID"). Only papers that evaluated the Roche/SDB RAT performance with any of the specified parameters were considered if results were reported at the manufacturer level. If the Roche/SDB RAT was compared with one of the 9 other antigen tests of interest (Abbott, Acon, BD, Biosynex, Boson, Laihe, MP BIO, Siemens, Quidel), the data from these tests were included as well.
In addition to the machine-learning approach, a manual search including FIND (The Foundation for Innovative New Diagnostics [FIND], 2020) was conducted.

Participant or population Symptomatic and asymptomatic patients diagnosed with SARS-CoV-2 via RT-PCR.

Intervention N/A.

Comparator N/A.

Study designs to be included Clinical performance studies of Roche SDB Rapid Antigen Test versus RT-PCR testing in 100 or more patients.

Eligibility criteria We considered 7 quality parameters that are known to affect test performance, including 1) whether the patient sample represented the target population; 2) whether patient selection criteria were clearly described; 3) whether the time interval between the reference test and RAT was appropriately brief; 4) whether RAT execution was described in sufficient detail for test replication; 5) whether reference test execution was described in sufficient detail for test replication; 6) whether blinded interpretation of RAT results occurred; and 7) whether patient withdrawals and sample exclusion were explained.

Information sources SURUS, a custom-built natural language processing (NLP) Engine (Medstone Science B.V.) was used to conduct query-based searches for relevant papers from January 2020 through March 2022. The databases MEDLINE, and preprint servers MedRixv and BioRxiv were initially searched. In addition to the machine-learning approach, a manual search including FIND (The Foundation for Innovative New Diagnostics [FIND], 2020) was conducted.

Main outcome(s) This global systematic review and meta-analysis presents an overview of the key confounders across studies that report the sensitivity and specificity of commercially available SARS-CoV-2 RATs. Altogether, 97 articles investigating the use of RATs from 10 different manufacturers across 166,561 samples presented findings based on Ct and DPSO ranges, for direct swabs versus samples stored in transport media, and for symptomatic versus asymptomatic patients. The performance of RATs was calculated as relative sensitivity and specificity against RT-PCR results. Overall sensitivity of RATs among different manufacturers and study cohorts varied between 36.0% (95% CI: 24.0-50.1) and 79.4% (95% CI: 64.8-89.0). Roche/SDB RATs demonstrated competitive performance with a pooled (including off-label use) sensitivity of 70.0%, and nearly 100% specificity in included studies. The Roche/SDB RATs exhibited reliable sensitivity in patients with a relatively high viral load (96.6% [95% CI: 95.2-98.2] for Ct≤25). Roche/SDB RATs were more sensitive in symptomatic patients within the first 7 DPSO (85.5% [95% CI: 81.2-88.4]), and when used to test direct swabs (74.4% [95% CI: 69.7-80.3]). RATs were typically more sensitive for symptomatic patients, when used less than 7 days after symptom onset, and when using direct swabs. The Roche/SDB RAT performed competitively based on the studies assessed, and we found significant differences in test performance across RATs in various studies, though the sample size for some RATs was very small.

Additional outcome(s) The variation in test sensitivity observed across studies may have been caused by the heterogeneity of study populations, with different disease severity levels and sampling at different time points. The use of different sample types, extraction methods and RT-PCR reference tests may also have contributed to this variation.

Quality assessment / Risk of bias analysis We considered 7 quality parameters that are known to affect test performance, including 1) whether the patient sample represented the target population;

2) whether patient selection criteria were clearly described; 3) whether the time interval between the reference test and RAT was appropriately brief; 4) whether RAT execution was described in sufficient detail for test replication; 5) whether reference test execution was described in sufficient detail for test replication; 6) whether blinded interpretation of RAT results occurred; and 7) whether patient withdrawals and sample exclusion were explained.
For qualitative analysis, studies were excluded if:
a) the total number of analyzed samples was 24 hours".
Ninety-seven records were identified for qualitative analysis.
For quantitative analysis (meta-analysis), studies were excluded if no discernible numbers of true positive (TP) and false negative (FN), or true negative (TN) and false positive (FP) values could be manually extracted from the presented data in the eligible studies. Eighty-six records were identified for quantitative analysis.

Strategy of data synthesis As confidence intervals (CIs) reported in the publications were calculated using differing methods, all confidence intervals were recalculated using the exact Clopper–Pearson method for better comparability. Due to the heterogeneity in sub-groups and the small number of studies available for some RATs, we report the differences between tests descriptively rather than statistically. Relative sensitivity and specificity of RATs were calculated in relation to RT-PCR results as the gold standard (based on the number of TP, TN, FP, and FN values extracted from eligible studies).
The meta-analysis of the performance results of RATs against RT-PCR reference methods was performed using the statistical software R (R Foundation for Statistical Computing, 2020).
For overall clinical performance, we undertook the statistical pooling of estimates across all manufacturers namely Abbott, Acon, BD, Biosynex, Boson, Laihe, MP BIO, Roche, Siemens, and Quidel. The metaprop function from the "meta" package was used to calculate the effect size for each individual test and pooled overall in a forest plot.

Subgroup analysis The stratified analyses were depicted as forest plots which showed the individual results of each study. Due to the high heterogeneity of the results in the different studies, rather than the mean, the median and a corresponding CI were used in the result descriptions. The CIs were calculated using a Wald interval on the ranks. In case the sample size was not sufficient for the calculations, the minimal and maximal study result per condition (and manufacturer) was used as a proxy for confidence limits.
A bivariate model was fitted as a linear mixed model, and variance components were estimated by restricted maximum likelihood, using the reitsma function from the "mada" package for each system investigated in five or more studies. The results are presented as a summary receiver operating characteristic (SROC) curve plot. The summary estimates, SROC curves, and confidence regions are depicted when a sufficient number of studies was available (>5 studies for SROC curves, >3 studies for summary estimates and confidence regions).

Sensitivity analysis Not performed. We are aware that the results are robust only as far as supported by the corresponding confidence intervals, therefore the statement: "Due to the heterogeneity in sub-groups and the small number of studies available for some RATs, we report the differences between tests descriptively rather than statistically." All results have their respective confidence intervals, so one should be able to evaluate the robustness of the results.

Country(ies) involved Switzerland, Germany, United States.

Keywords SARS-CoV-2, COVID-19, clinical performance, rapid antigen test, lateral flow assay, point-of-care, in vitrodiagnostics.

Contributions of each author
Author 1 - Nina Germic.
Email: nina.germic@roche.com
Author 2 - Johannes Hayer.
Email: johannes.hayer@roche.com
Author 3 - Qian Feng.
Email: qian.feng.qf1@roche.com