ESCMID COVID-19 Guidelines: Diagnostic testing for SARS-CoV-2

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Abstract

Scope: The objective of these guidelines is to identify the most appropriate diagnostic test and/or diagnostic approach for SARS-CoV-2. The recommendations are intended to provide guidance to clinicians, clinical microbiologists, other health care personnel, and decision makers.

Methods: An ESCMID COVID-19 guidelines task force was established by the ESCMID Executive Committee. A small group was established, half appointed by the chair, and the remaining selected with an open call. Each panel met virtually once a week. For all decisions, a simple majority vote was used. A list of clinical questions using the PICO (population, intervention, comparison, outcome) format was developed at the beginning of the process. For each PICO, two panel members performed a literature search focusing on systematic reviews with a third panelist involved in case of inconsistent results. Quality of evidence assessment was based on the GRADE-ADOLOPMENT approach.

Questions addressed by the guideline and recommendations: A total of 43 PICO questions were selected that involve the following types of populations: 1) patients with signs and symptoms of COVID-19; 2) travelers, healthcare workers, and other individuals at risk for exposure to SARS-CoV-2; 3) asymptomatic individuals and 4) close contacts of patients infected with SARS-CoV-2. The type of diagnostic test (commercial rapid nucleic acid amplification tests, and rapid antigen detection), biomaterial, time since onset of symptoms/contact with an infectious case, age, disease severity, and risk of developing severe disease are also taken into consideration.

Keywords: SARS-CoV-2, COVID-19, diagnosis, guidelines, testing.
Scope

The present guideline has the objective of identifying the most appropriate diagnostic test and/or diagnostic/screening approach for 1) patients with signs and symptoms of COVID-19; 2) travelers from areas with low and high COVID-19 prevalence, healthcare workers, and other individuals at risk for exposure to SARS-CoV-2; 3) asymptomatic individuals (including general population) and 4) those with close contact with a person infected with SARS-CoV-2; and 5) symptomatic individuals following re-infection and/or vaccination. However, evidence for re-infection and post-vaccination testing approach was scarce when the literature search for the index guidelines was performed. Hence, associated PICO(s) could not be addressed. Additional considerations include the type of biomaterial, time since onset of symptoms/contact with infectious case, age, disease severity, and risk of developing severe disease. The document is intended to provide guidance to clinicians, clinical microbiologists, other health care personnel, and decision makers.

Context

The ongoing COVID-19 pandemic has severely disrupted human life worldwide and represents an unprecedented challenge to public health [1]. As stated in the first paper of the newly-developed ESCMID guidelines for COVID-19 [2], ESCMID did not develop recommendations at the start of the pandemic. However, given the time passed and the rapid growth in evidence upon which to base recommendations, in January 2021 the ESCMID Executive Committee (EC) decided to launch a new initiative to develop ESCMID guidelines on several COVID-19-related issues. The present guideline provides recommendations for diagnostic testing for SARS-CoV-2, which is of particular relevance given the high incidence of both infections and deaths. This is further complicated by circulating mutations of SARS-
CoV-2 and potential implications for diagnostic testing. Thus, a smart and effective approach to testing and screening is required to minimize spread of the virus.

Consensus guideline development

The general principles and methodology adopted have been described in the first paper in the ESCMID guidelines for COVID-19 related clinical topics [2]. Herein, the panel members proposed a list of diagnostic PICO questions to the panel Chair, who in turn selected the most clinically relevant questions and compiled a set of 55 priority PICO questions that reached consensus within the panel. Considering the available evidence, a total of 43 PICO questions were used for the development of the present guidelines. The PICO questions that were excluded are listed in Supplementary Appendix 1 along with additional details on the methods used.

Quality of evidence assessment

The quality of the body of evidence was evaluated following the GRADE approach. Accordingly, five factors for rating down the quality of evidence (risk of bias, inconsistency of results, indirectness of evidence, imprecision, and publication bias) and three for rating it up (large magnitude of effect, direction of plausible confounding, dose-response gradient) were assessed. Adaptation of the quality assessment factors was applied by the panel for the Diagnostic Guidelines, as described below.

Risk of bias

The risk of bias of each study was assessed using the QUADAS-2 tool for diagnostic accuracy studies. The QUADAS-2 tool includes four key domains that discuss patient selection, index test, reference standard, and flow of patients through the study and timing of the index tests and reference standard. The QUADAS-2 assessment of studies included in the original systematic review was adopted, whereas two panel members independently assessed the
QUADAS-2 for any new study retrieved during the evidence syntheses update, if performed (see Supplementary Methods). The risk of bias was judged very serious or serious if all or more/equal than a half of studies, respectively, have high or unclear concern regarding all or one to three QUADAS-2 domains. The risk of bias was judged not serious in any other case.

**Indirectness**

Indirectness was judged for all studies based on QUADAS-2 tool concerns for applicability for patient selection, index test, and reference standard. The QUADAS-2 applicability assessment of studies included in the original systematic review was adopted; two panel members independently assessed the QUADAS-2 applicability for any new study retrieved during the systematic review update, if performed. The indirectness was judged very serious or serious if all or more/equal than half of studies, respectively, have high or unclear concern regarding all or one to two QUADAS-2 domains for applicability concern. The indirectness was judged not serious in any other case. Furthermore, evidence was judged indirect if marked differences in population respect to the review question were suspected.

**Inconsistency**

Heterogeneity of results was assessed statistically by the $I^2$ test. We searched for a plausible source of heterogeneity by subgroup analyses according to the most plausible reason of heterogeneity, i.e. the type of samples, the type of test and the quality of the studies. These sub-analyses were performed only if subgroups included at least 4 or more studies. If a plausible explanation for heterogeneity was not identified, the quality of evidence was downgraded.

Inconsistency was judged very serious if high and unexplained heterogeneity ($I^2>90\%$) was detected. Inconsistency was judged not serious if either low ($I^2<50\%$) or otherwise explained through subgroup analyses. The inconsistency was judged serious in any other case.

**Imprecision**
We downgraded the evidence for imprecision if the boundaries of the 95% confidence intervals (CI) of all or ≥50% of studies included a threshold of sensitivity or specificity for which the panel agreed that the estimate was adequate to support the decision. The panel agreed to set the threshold of sensitivity or specificity for all the diagnostic tests encompassed by the guidelines at 80% or 90%, respectively.

Publication bias

Linear regression of log odds ratios on inverse root of effective sample sizes test was used to assess the presence of publication bias when 3 or more studies were available [3, 4]. Publication bias was strongly suspected if the p value of the test was <0.10. Publication bias was considered as “strongly suspected” when less than 3 studies informed the outcome and could not be excluded.

Definitions of tests

Rapid nucleic acid amplification tests (NAAT) were considered as those having the capacity to be performed at the ‘point of care’ or in a ‘near patient’ setting. This means decentralized testing requiring minimal equipment, sample preparation, and biosafety considerations to be performed near a patient and outside of central laboratory testing [5]. Rapid antigen tests were considered all commercially available tests including both point of care testing, defined as above, and 'in lab' testing [6]. However, only one study provided information about in-lab testing [7].

Questions addressed by the guideline

In developing the guidelines for diagnosis of SARS-CoV-2, focus has been placed on testing by using commercial NAAT and rapid antigen detection. The performance characteristics of these tests depends on the population being examined, viral prevalence in the community, and biomaterial used. Furthermore, the resources required to apply any of these tests and approaches
depends on the local infrastructure of the individual setting and healthcare system facilities. This includes trained personnel, properly equipped diagnostic laboratories, and the types of tests being covered or reimbursed by the local healthcare system. Regarding particular recommendations for (or against) a specific diagnostic approach, the main beneficial outcomes considered were: i) reduction of mortality, facilitation of early treatment (if deemed to play a critical role), ii) reduction of viral transmission, iii) minimizing unnecessary treatment and/or isolation, iv) reduction of anxiety of patients/potentially exposed persons, and v) burden to healthcare systems with consequences for health inequality.

Recommendations

The 43 PICO questions selected were divided according to the target population into: A, patients with signs and symptoms of COVID-19 (Table 1); B, travelers from areas with low COVID-19 prevalence, healthcare workers, and asymptomatic individuals at risk for exposure (5 questions; (Table 2); C, asymptomatic individuals and those with close contact with an infected person (Table 3). PICO questions in group A were further divided according to the type of test: A1, commercial rapid NAAT vs. standard NAAT (9 questions); A2, rapid antigen testing vs. standard NAAT (10 questions); A3, saliva sampling vs. nasopharyngeal swabs for NAAT (7 questions). PICO questions in group C were further divided into: C1, rapid antigen testing vs. NAAT (6 questions); C2, NAAT in saliva samples vs. nasopharyngeal swabs (6 questions). A full summary of the evidence for each PICO question is presented in Supplementary Appendices 2-4.

A: Patients with signs and symptoms of COVID-19

Rapid NAAT
The quality of the available evidence for all PICOs prioritized for patients with signs and symptoms compatible with COVID-19 was very low. Along these lines, the strength of recommendation was almost always weak except for cases where disease severity and/or risk of developing severe disease was considered of utmost importance. Diagnosis of COVID-19 with rapid NAAT will reduce the required time from sample acquisition to results. Extrapolation from studies looking into rapid NAATs for the detection of other respiratory viruses would suggest that early isolation is beneficial [8]. In general, rapid NAAT is suggested due to the high accuracy of the test, the low risk of anticipated harm, and its feasible implementation. However, the anticipated benefits are likely to depend on the different risk factors for hospitalization, mortality, and associated morbidity.

Rapid antigen testing

Diagnosis of COVID-19 with rapid antigen testing will reduce the required time from sample acquisition to results as well as reduce potential health inequities as antigen tests are (usually) readily available, easy to perform, and feasible to implement in various settings. This in turn, will reduce the potential consequences of a delayed COVID-19 diagnosis or even the ability to perform COVID-19 testing when access is limited due to restricted resources. However, current data suggest that antigen tests are not as accurate as the reference standard NAAT tests.

Saliva sampling

Laboratory-based NAAT in nasopharyngeal samples is the reference standard test for the diagnosis of COVID-19. The accuracy of other than nasopharyngeal samples, like saliva, is being investigated. Saliva sampling is easier to perform with essentially no adverse events. However, saliva processing may be challenging unless collected in appropriate media, since it has also been associated with aerosol generation [9, 10]. Especially in some subgroups of patients, like children, saliva might be preferred over nasopharyngeal swabs. Nevertheless,
children may not always be able to produce saliva on demand, and in such cases nasopharyngeal samples are still preferred. Notwithstanding, the available data suggest that the accuracy of saliva NAAT is not as high as nasopharyngeal NAAT.

B: Travelers from areas with low and high COVID-19 prevalence, healthcare workers, and asymptomatic individuals at risk for exposure

The quality of the available evidence for all PICOs prioritized for individuals at high risk of exposure to COVID-19 was very low. Therefore, the strength of recommendation for all PICOs in this section is weak. NAAT driven by questioning for contact history or high-risk exposure is very inaccurate, with very low sensitivity. Despite the very low quality of evidence, the panel recommended against the use of NAAT driven by questioning for contact history or exposure in returning travelers from areas of low and high prevalence of COVID-19, healthcare workers, and asymptomatic individuals at risk for exposure instead of universal NAAT testing.

C: Asymptomatic individuals and close contact of an infected person

As for all previous PICOs, quality of available evidence for asymptomatic individuals and close contacts was very low; thus all recommendations are weak.

Rapid antigen testing

In asymptomatic individuals and those with close contact with an infected person, the use of laboratory-based NAAT should be preferred over rapid antigen testing for diagnosis of COVID-19. The panel based its recommendations regarding rapid antigen testing on evidence from studies examining mainly the accuracy of first- and second-generation antigen tests that are not as accurate as the third-generation ones [11].
NAAT in saliva samples

In asymptomatic children <12 years old (with or without close contact), NAAT in saliva samples was recommended over NAAT on nasopharyngeal swab samples for diagnosis of COVID-19 considering the accuracy of the test, the large anticipated benefits and small harm, low amount of resources, small incremental cost relative to net benefits, acceptability, and feasibility of the test. In patients ≥12 years old, NAAT on nasopharyngeal samples should be preferred, also considering that young children may not produce saliva on command.

Future considerations

It is worthwhile noting that several gaps remain regarding the evidence for diagnostic testing in several areas. These include infection following vaccination or previous infection (re-infection); performance of newer generation antigen tests in different patient populations and samples; correlation of viral nucleic acid or antigen detection with contagiousness; accuracy of different diagnostic tests in different populations and non-nasopharyngeal samples; the accuracy of different diagnostic tests in asymptomatic individuals and the general population. Moreover, there is a paucity of data regarding costs and/or resource modelling studies, patient values, preferences and beliefs, definition of ‘feasibility’ of various tests, stakeholders’ opinion regarding acceptability, and assessment criteria on the potential implications of interventions on health inequities. The lack of objective criteria to judge the priority of clinically-relevant questions should also be highlighted, and very little data is available regarding the clinical impact (treatment, isolation, hospitalization) of these tests.

It is further noted that several methodological challenges were encountered that could be improved upon. Firstly, literature databases specific for COVID-19 are not user friendly and are difficult to navigate. Especially for diagnostic testing, there was a lack of exportable literature. The ongoing pandemic also posed considerable time constraints for development of
guidelines given the large amount of new information, need for regular updates, and revision
of recommendations, all within a context with limited resources for guideline development.

Among the limitations of the present guidelines is the very low quality of evidence and
lack of dedicated resources to update specific evidence syntheses. Furthermore, poorly
disclosed methodological details in relevant meta-analyses did not allow reproducibility of
literature searches. We also included reagents for SARS-CoV-2 testing independently of the
biomaterial for which they were optimized. We may thus not exclude the possibility that any
unfavorable performance of a group of tests (e.g. pooled sensitivity of antigen tests) is due to
diluting the favorable performance of tests, which are indeed optimized for one or another
biomaterial. We also did not distinguish between different saliva samples, which may perform
differently, and thus cannot draw more specific conclusions in this regard. In addition, it should
be mentioned that this is not a systematic review, but rather guideline recommendations based
on GRADE ADOLOPMENT methodology, which by definition is based on updating (if
applicable) existing moderate to high quality already (or preprint) published evidence
syntheses. Lastly, consensus was reached by a simple majority vote and not through consensus
software/application such as the Delphi technique, as suggested by the ESCMID Guidelines
Committee. However, its strengths include the multidisciplinary expertise of the writing group
and the transparent, structured, thorough, and sound methodological approach adopted.

Contribution of individual authors:

Panel members: Chrysanthi Skevaki (clinical microbiology, virology, infection epidemiology
and laboratory medicine), Paraskevi C. Fragkou (internal medicine, infectious diseases), Giulia
De Angelis (clinical microbiology, infection epidemiology, infectious diseases), Giulia
Menchinelli (clinical microbiology), Florence Morfin (clinical virology), Federico Garcia
(clinical microbiology, infectious diseases), Fusun Can (clinical microbiology).
Conceptualization and co-ordination of the overall scope of the guidelines: CS, PCF. First manuscript draft (scope/context, methodology, discussion, etc.): CS, PCF. Initial screening for available evidence synthesis: PCF, DD, EM. Information extraction/summary of existing relevant literature on methodological aspects: PCF, GDA, GM. Literature search for update of existing evidence syntheses: PCF, GDA, GM, DD, EM, AG. Data extraction: PCF, GDA, GM, FC, FG, FMS, DD, AdS. Additional meta-analyses: GDA, GM. Creation of SOFs: GDA, GM. First draft of final recommendations (completed summary templates of panel consensus): PCF, DD. PICO formulation and final selection, recommendations, finalization of associated recommendations summary templates: CS, PCF, GDA, GM, FMS, FG, FC. Methodological consultation: TL, LS.

Updating: the panel will meet once a month to assess the need for further updates.

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Conflicts of interest:

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PCF, GDA, GM, FM, FC, ADS, AG, TL, DD, FG, and EM declare no conflicts of interest.
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17 [18] Moore NM, Li H, Schejbal D, Lindsley J, Hayden MK. Comparison of Two Commercial Molecular Tests and a Laboratory-Developed Modification of the CDC 2019-


[24] Filgueiras, Priscilla; Corsini, Camila; Almeida, Nathalie BF; Assis, Jessica; Pedrosa, Maria Luysa; de Oliveira, Alana; Amorim, Raquel NH; de Miranda, Daniel AP; COVID-19 Rapid Antigen Test at hospital admission associated to the knowledge of individual risk factors allow overcoming the difficulty of managing suspected patients in hospitals COVID-19 Rapid Antigen Test facilitates the management of suspected patients on hospital admission medRxiv 2021.01.06.21249282.


Table 1. PICO questions and recommendations in patients with signs and symptoms of COVID-19.

<table>
<thead>
<tr>
<th>PICO question</th>
<th>Recommendation</th>
<th>Strength of recommendation*</th>
<th>Overall certainty of the evidence**</th>
<th>References</th>
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<tbody>
<tr>
<td><strong>Rapid NAAT</strong></td>
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</tr>
<tr>
<td>1 In patients with signs and symptoms compatible with mild or moderate COVID-19, should commercial rapid NAAT be used, compared with standard NAAT (commercial and/or in house) for diagnosis of COVID-19?</td>
<td>In patients with signs and symptoms compatible with mild or moderate COVID-19, we suggest the use of rapid NAAT versus laboratory based NAAT testing for the diagnosis of COVID-19.</td>
<td>Weak for Very low</td>
<td>[12-23].</td>
<td></td>
</tr>
<tr>
<td>2 In patients with signs and symptoms compatible with severe or critical COVID-19, should commercial rapid NAAT testing be used, compared with standard NAAT (commercial and/or in house) testing for diagnosis of COVID-19?</td>
<td>In patients with signs and symptoms compatible with severe or critical COVID-19, we suggest the use of rapid NAAT versus laboratory based NAAT for the diagnosis of COVID-19.</td>
<td>Strong for Very low</td>
<td>[12-23]</td>
<td></td>
</tr>
<tr>
<td>3 In patients with signs and symptoms compatible with COVID-19, should commercial rapid NAAT be used, compared with standard NAAT (commercial and/or in house) for diagnosis of COVID-19 in nasopharyngeal samples?</td>
<td>In patients with signs and symptoms compatible with COVID-19, we suggest the use of rapid NAAT in nasopharyngeal samples versus laboratory based NAAT in nasopharyngeal samples for the diagnosis of COVID-19.</td>
<td>Weak for Very low</td>
<td>[13, 15, 16, 18, 20, 22, 23]</td>
<td></td>
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<tr>
<td>4 In patients with signs and symptoms compatible with COVID-19, should commercial rapid NAAT be used, compared with the standard NAAT (commercial and/or in house)</td>
<td>In patients with signs and symptoms compatible with COVID-19, we suggest the use of rapid NAAT in samples other than nasopharyngeal swab versus laboratory based NAAT in samples</td>
<td>Weak for Very low</td>
<td>[12, 14, 15, 17, 21, 23]</td>
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</table>
In patients with signs and symptoms compatible with COVID-19 of equal or less than 7 days-onset, should commercial rapid NAAT be used, compared with standard NAAT (commercial and/or in house) for diagnosis of COVID-19? Weak for Very low [12-22]

In patients with signs and symptoms compatible with COVID-19 of more than 7 days-onset, should commercial rapid NAAT be used, compared with standard NAAT (commercial and/or in house) for diagnosis of COVID-19? Weak for Very low [12-23]

In children <12 years old with signs and symptoms compatible with COVID-19, should commercial rapid NAAT be used, compared with standard NAAT (commercial and/or in house) for diagnosis of COVID-19? Weak for Very low [12, 15, 17-20, 22, 23]

In patients ≥12 years old with signs and symptoms compatible with COVID-19, should commercial rapid NAAT be used, compared with standard NAAT (commercial and/or in house) for diagnosis of COVID-19? Weak for Very low [13, 14, 16, 21, 23]

In patients with signs and symptoms compatible with other than nasopharyngeal swab for the diagnosis of COVID-19, when allowed by regulatory boards and manufacturer's instructions. Weak for Very low [12-23]
COVID-19 at risk for severe illness, should commercial rapid NAAT be used, compared with standard NAAT (commercial and/or in house) for diagnosis of COVID-19?

**Rapid antigen testing**

<table>
<thead>
<tr>
<th>Weak against</th>
<th>Strong against</th>
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<tr>
<td>Very low</td>
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</table>

10 In patients with signs and symptoms compatible with **mild** or moderate COVID-19, should rapid antigen detection testing be used, compared with standard NAAT (commercial and/or in house) for diagnosis of COVID-19?

In patients with mild and moderate COVID-19, we suggest the use of laboratory-based NAAT versus rapid antigen detection testing for diagnosis of COVID-19.

Weak against **Very low** [6, 23-34]

11 In patients with signs and symptoms compatible with **severe** or critical COVID-19, should rapid antigen detection testing be used, compared with standard NAAT (commercial and/or in house) testing for diagnosis of COVID-19?

In patients with severe or critical COVID-19, we recommend the use of laboratory-based NAAT versus rapid antigen detection testing for diagnosis of COVID-19.

Strong against **Very low** [6, 7, 23, 30, 35-88]

12 In patients with signs and symptoms compatible with COVID-19, should rapid antigen detection testing be used, compared with the standard NAAT (commercial and/or in house) for diagnosis of COVID-19 in **nasopharyngeal samples**?

In patients with signs and symptoms compatible with COVID-19, we suggest the use of laboratory-based NAAT in nasopharyngeal samples versus rapid antigen detection testing in nasopharyngeal samples for diagnosis of COVID-19.

Weak against **Very low** [6, 7, 23, 24, 26-29, 32-36, 38, 39, 41-43, 45-52, 55-64, 69, 72, 73, 75-77, 80, 81, 85, 86, 89]

13 In patients with signs and symptoms compatible with COVID-19, should rapid antigen detection testing be used, compared with standard NAAT (commercial and/or in house) for diagnosis of COVID-19?

In patients with signs and symptoms compatible with COVID-19, we suggest the use of laboratory-based NAAT in saliva.

Weak against **Very low** [6, 7, 23, 30, 40]
compared with standard NAAT (commercial and/or in house) for diagnosis of COVID-19 in saliva samples?

14 In patients with signs and symptoms compatible with COVID-19, should rapid antigen detection testing be used, with standard NAAT (commercial and/or in house) testing for diagnosis of COVID-19 in samples other than nasopharyngeal sample and saliva?

In patients with signs and symptoms compatible with COVID-19, we suggest the use of laboratory-based NAAT in samples other than nasopharyngeal and saliva samples versus rapid antigen detection testing in samples other than nasopharyngeal and saliva samples for diagnosis of COVID-19.


15 In patients with signs and symptoms compatible with COVID-19 of equal or less than 7 days-onset, should rapid antigen detection testing be used, compared with standard NAAT (commercial and/or in house) for diagnosis of COVID-19?

In patients with signs and symptoms compatible with COVID-19 of equal or less than 7 days-onset, we suggest the use of laboratory-based NAAT versus rapid antigen detection testing for diagnosis of COVID-19.

Weak against Very low [6, 7, 23, 25, 28, 30, 33, 41, 49, 52, 59, 60, 68, 71-73, 78, 82, 84-86, 88]

16 In patients with signs and symptoms compatible with COVID-19 of more than 7 days-onset, should rapid antigen detection testing be used, compared with standard NAAT (commercial and/or in house) for diagnosis of COVID-19?

In patients with signs and symptoms compatible with COVID-19 of more than 7 days-onset, we suggest the use of laboratory-based NAAT versus rapid antigen detection testing for diagnosis of COVID-19.

Weak against Very low [6, 7, 23, 25, 28, 30, 49, 59, 60, 71, 73, 78, 84, 85]

17 In children <12 years with signs and symptoms compatible with COVID-19, should rapid antigen detection testing be used, compared with standard NAAT (commercial and/or in samples versus rapid antigen detection testing in saliva samples for diagnosis of COVID-19.

In children <12 years old with signs and symptoms compatible with COVID-19, we suggest the use of laboratory-based NAAT versus rapid antigen detection testing for diagnosis of COVID-19.

Weak against Very low [6, 23, 52, 71, 79, 86]
In patients ≥12 years old with signs and symptoms compatible with COVID-19, should rapid antigen detection testing be used, compared with standard NAAT (commercial and/or in house) for diagnosis of COVID-19?

**Saliva sampling**

In patients with signs and symptoms compatible with severe or critical COVID-19, should saliva sampling be used, compared with nasopharyngeal swab sampling for diagnosis of COVID-19 with NAAT?

In patients with signs and symptoms compatible with severe or critical COVID-19, for the diagnosis of COVID-19 infection, we suggest the use of NAAT in nasopharyngeal swab samples versus NAAT in saliva samples for diagnosis of COVID-19.

In patients with signs and symptoms compatible with mild or moderate COVID-19, should saliva sampling be used, compared with nasopharyngeal swab sampling for diagnosis of COVID-19 with NAAT?

In patients with signs and symptoms compatible with mild or moderate COVID-19, we suggest the use of NAAT in nasopharyngeal swab samples versus NAAT in saliva samples for diagnosis of COVID-19.
COVID-19 of equal or less than 7 days onset, should saliva sampling be used, compared with nasopharyngeal swab sampling for diagnosis of COVID-19 with NAAT? COVID-19 of equal or less than 7 days-onset, we suggest the use of NAAT in saliva samples versus NAAT in nasopharyngeal swab samples for diagnosis of COVID-19.

23 In patients with signs and symptoms compatible with COVID-19 of more than 7 days onset, should saliva sampling be used, compared with nasopharyngeal swab for diagnosis of COVID-19 with NAAT? In patients with signs and symptoms compatible with COVID-19 of more than 7 days-onset, we suggest the use of NAAT in nasopharyngeal swab samples versus NAAT in saliva samples for diagnosis of COVID-19.

Weak against Very low [95, 98, 104, 108]

24 In children <12 years old with signs and symptoms compatible with COVID-19, should saliva sampling be used, compared with nasopharyngeal swab for diagnosis of COVID-19 with NAAT? In children <12 years old with signs and symptoms compatible with COVID-19, we suggest the use of NAAT in nasopharyngeal swab samples versus NAAT in saliva samples for diagnosis of COVID-19.

Weak against Very low [90, 94, 95, 99, 103, 107, 108, 114, 115, 117]

25 In patients ≥12 years old with signs and symptoms compatible with COVID-19, should saliva sampling be used, compared with nasopharyngeal swab sampling for diagnosis of COVID-19 with NAAT? In patients ≥12 years old with signs and symptoms compatible with COVID-19, we suggest the use of NAAT in nasopharyngeal swab samples versus NAAT in saliva samples for diagnosis of COVID-19.

Weak against Very low [13, 91-93, 96-98, 100-102, 104-106, 109-113, 115, 116, 118]

26 In patients with signs and symptoms compatible with COVID-19 at risk for severe illness, should saliva sampling be used, compared with nasopharyngeal swab sampling for diagnosis of COVID-19 with NAAT? In patients with signs and symptoms compatible with COVID-19 at risk for severe illness, we suggest the use of NAAT in nasopharyngeal swab samples versus NAAT in saliva samples for diagnosis of COVID-19.

Weak against Very low [13, 90-118]

1 *Strength of recommendation (strong against, weak against, in research only, weak for, strong for).

2 **Overall certainty of the evidence (high, moderate, low, very low).
Table 2. PICO questions and recommendations in travellers, healthcare workers, and asymptomatic individuals at risk for exposure.

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<thead>
<tr>
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<th>PICO question</th>
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<th>Strength of recommendation**</th>
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<td>2</td>
<td><strong>In travelers from areas with high prevalence</strong>, should surveys for contact history with known or suspected exposures to infected people followed by NAAT be used compared to universal NAAT to diagnose COVID-19?</td>
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<td>In <strong>healthcare workers</strong>, should surveys for contact history with known or suspected exposures to infected people followed by NAAT be used compared to universal NAAT to diagnose COVID-19?</td>
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<td>4</td>
<td><strong>In asymptomatic populations at risk for exposure</strong>, should surveys for contact history with known or suspected exposures within less than 7 days to infected people followed by NAAT be used compared to universal NAAT to diagnose COVID-19?</td>
<td>In asymptomatic populations at risk for exposure, we suggest the use of universal NAAT versus survey for contact history with known or suspected exposures within less than 7 days in addition to NAAT for diagnosis of COVID-19.</td>
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<td><strong>In asymptomatic populations at risk for exposure</strong>, should surveys for contact history with known or suspected exposures above 7 days to infected people followed by NAAT be used compared to universal NAAT to diagnose COVID-19?</td>
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infected people followed by NAAT be used compared to universal NAAT to diagnose COVID-19? Known or suspected exposures above 7 days in addition to NAAT for diagnosis of COVID-19.

1 *Strength of recommendation (strong against, weak against, in research only, weak for, strong for).
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3
Table 3. PICO questions and recommendations in asymptomatic individuals and those with close contact with an infected person.

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<td>2</td>
<td>In asymptomatic patients ≥12 years old without risk factors for severe COVID-19 should rapid antigen tests be used, as compared to laboratory-based NAAT to diagnose COVID-19?</td>
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<td>In asymptomatic people of any age with any risk factor(s) for severe COVID-19 (including age &lt;3 or ≥65 years) should rapid antigen tests be used, as compared to laboratory-based NAAT to diagnose COVID-19?</td>
<td>In asymptomatic people of any age with any risk factor(s) for severe COVID-19 (including age &lt;3 months old or ≥65 years old), we suggest the use of laboratory based NAAT versus antigen testing for diagnosis of COVID-19.</td>
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<td>In asymptomatic people should rapid antigen test be used as compared to laboratory-based NAAT in nasopharyngeal samples to diagnose COVID-19?</td>
<td>In asymptomatic people, we suggest the use of laboratory-based NAAT in nasopharyngeal samples versus rapid antigen testing in nasopharyngeal samples for diagnosis of COVID-19.</td>
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test be used as compared to laboratory based NAAT in non-nasopharyngeal/non-saliva samples to diagnose COVID-19?

6 In asymptomatic people should rapid antigen tests be used in saliva samples as compared to laboratory based NAAT to diagnose COVID-19? In asymptomatic people, we suggest the use of laboratory-based NAAT in saliva samples versus rapid antigen testing in non-nasopharyngeal/non-saliva for diagnosis of COVID-19. Weak against Very low [6, 23, 30, 40]

**NAAT in saliva samples**

7 In asymptomatic children<12 years, should NAAT in saliva samples be used, as compared to nasopharyngeal samples to diagnose COVID-19? In asymptomatic children<12 years, we suggest the use of NAAT in saliva samples versus NAAT in nasopharyngeal swab samples for diagnosis of COVID-19. Weak for Very low [108, 115, 123, 124]

8 In asymptomatic patients ≥12 years, should NAAT test in saliva samples be used, as compared to nasopharyngeal samples to diagnose COVID-19? In asymptomatic patients ≥12 years, we suggest the use of NAAT in nasopharyngeal swab samples versus NAAT in saliva samples for diagnosis of COVID-19. Weak against Very low [96, 97, 105, 115, 125]

9 In close contacts asymptomatic children <12 years, should NAAT in saliva samples be used, as compared to nasopharyngeal samples to diagnose COVID-19? In close contact asymptomatic children<12 years, we suggest NAAT in saliva samples be used compared to NAAT testing in nasopharyngeal swab samples for diagnosis of COVID-19. Weak for Very low [126]

10 In close contacts asymptomatic patients ≥12 years, should NAAT in saliva samples be used, as compared to nasopharyngeal samples to diagnose COVID-19? In close contact asymptomatic patients ≥12 years, we suggest the use of NAAT in nasopharyngeal swab samples versus NAAT in saliva samples for diagnosis of COVID-19. Weak against Very low [96, 105, 115, 124, 125]
11 In close contacts asymptomatic children <12 years with less than 7 days since contact, should NAAT in saliva samples be used, as compared to nasopharyngeal samples to diagnose COVID-19?

In close contacts asymptomatic children <12 years with less than 7 days since contact, we suggest the use of NAAT in saliva samples versus NAAT in nasopharyngeal swab samples for diagnosis of COVID-19. Weak for Very low [108, 115, 123, 124]

12 In close contacts asymptomatic patients ≥12 years with less than 7 days since contact, should NAAT in saliva samples be used, as compared to nasopharyngeal samples to diagnose COVID-19?

In close contact asymptomatic patients ≥12 years with less than 7 days since contact, we suggest the use of NAAT in nasopharyngeal swab samples versus NAAT in saliva samples for diagnosis of COVID-19. Weak against Very low [96, 97, 105, 115]

1 *Strength of recommendation (strong against, weak against, in research only, weak for, strong for).

2 **Overall certainty of the evidence (high, moderate, low, very low).
Table 1. PICO questions and recommendations in patients with signs and symptoms of COVID-19.

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<td><strong>Rapid NAAT</strong></td>
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<td>1</td>
<td>In patients with signs and symptoms compatible with mild or moderate COVID-19, should commercial rapid NAAT be used, compared with standard NAAT (commercial and/or in house) for diagnosis of COVID-19?</td>
<td>In patients with signs and symptoms compatible with mild or moderate COVID-19 we suggest the use of rapid NAAT versus laboratory based NAAT testing for the diagnosis of COVID-19.</td>
<td>Weak for</td>
<td>Very low</td>
<td>[12-23].</td>
</tr>
<tr>
<td>2</td>
<td>In patients with signs and symptoms compatible with severe or critical COVID-19, should commercial rapid NAAT testing be used, compared with standard NAAT (commercial and/or in house) testing for diagnosis of COVID-19?</td>
<td>In patients with signs and symptoms compatible with severe or critical COVID-19 we suggest the use of rapid NAAT versus laboratory based NAAT for the diagnosis of COVID-19.</td>
<td>Strong for</td>
<td>Very low</td>
<td>[12-23]</td>
</tr>
<tr>
<td>3</td>
<td>In patients with signs and symptoms compatible with COVID-19, should commercial rapid NAAT be used, compared with standard NAAT (commercial and/or in house) for diagnosis of COVID-19 in nasopharyngeal samples?</td>
<td>In patients with signs and symptoms compatible with COVID-19 we suggest the use of rapid NAAT in nasopharyngeal samples versus laboratory based NAAT in nasopharyngeal samples for the diagnosis of COVID-19.</td>
<td>Weak for</td>
<td>Very low</td>
<td>[13, 15, 16, 18, 20, 22, 23]</td>
</tr>
<tr>
<td>4</td>
<td>In patients with signs and symptoms compatible with COVID-19, should commercial rapid NAAT be used, compared with the standard NAAT (commercial and/or in house) for diagnosis of COVID-19 in samples other than nasopharyngeal swab?</td>
<td>In patients with signs and symptoms compatible with COVID-19 we suggest the use of rapid NAAT in samples other than nasopharyngeal swab versus laboratory based NAAT in samples other than nasopharyngeal swab for the diagnosis of COVID-19, when allowed by regulatory boards and manufacturer's instructions.</td>
<td>Weak for</td>
<td>Very low</td>
<td>[12, 14, 15, 17, 21, 23]</td>
</tr>
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</table>
5 In patients with signs and symptoms compatible with COVID-19 of equal or less than 7 days-onset, should commercial rapid NAAT be used, compared with standard NAAT (commercial and/or in house) for diagnosis of COVID-19? We suggest the use of rapid NAAT versus laboratory based NAAT for the diagnosis of COVID-19.

6 In patients with signs and symptoms compatible with COVID-19 of more than 7 days-onset, should commercial rapid NAAT be used, compared with standard NAAT (commercial and/or in house) for diagnosis of COVID-19? We suggest the use of rapid NAAT versus laboratory based NAAT for the diagnosis of COVID-19.

7 In children <12 years old with signs and symptoms compatible with COVID-19, should commercial rapid NAAT be used, compared with standard NAAT (commercial and/or in house) for diagnosis of COVID-19? We suggest the use of rapid NAAT versus laboratory based NAAT for the diagnosis of COVID-19.

8 In patients ≥12 years old with signs and symptoms compatible with COVID-19, should commercial rapid NAAT be used, compared with standard NAAT (commercial and/or in house) for diagnosis of COVID-19? We suggest the use of rapid NAAT versus laboratory based NAAT for the diagnosis of COVID-19.

9 In patients with signs and symptoms compatible with COVID-19 at risk for severe illness, should commercial rapid NAAT be used, compared with standard NAAT (commercial and/or in house) for diagnosis of COVID-19? We suggest the use of rapid NAAT versus laboratory based NAAT for the diagnosis of COVID-19.

Rapid antigen testing

10 In patients with signs and symptoms compatible with mild or moderate COVID-19, should rapid antigen detection testing be used, compared with standard NAAT? We suggest the use of laboratory-based NAAT versus rapid antigen detection testing for diagnosis of COVID-19.
In patients with signs and symptoms compatible with severe or critical COVID-19, should rapid antigen detection testing be used, compared with standard NAAT (commercial and/or in house) testing for diagnosis of COVID-19?

Strong against Very low [6, 7, 23, 30, 35-88]

In patients with signs and symptoms compatible with COVID-19, should rapid antigen detection testing be used, compared with standard NAAT (commercial and/or in house) for diagnosis of COVID-19 in nasopharyngeal samples?

Weak against Very low [6, 7, 23, 24, 26-29, 32-36, 38, 39, 41-43, 45-52, 55-64, 69, 72, 73, 75-77, 80, 81, 85, 86, 89]

In patients with signs and symptoms compatible with COVID-19, should rapid antigen detection testing be used, compared with standard NAAT (commercial and/or in house) for diagnosis of COVID-19 in saliva samples?

Weak against Very low [6, 7, 23, 30, 40]

In patients with signs and symptoms compatible with COVID-19, should rapid antigen detection testing be used, with standard NAAT (commercial and/or in house) testing for diagnosis of COVID-19 in samples other than nasopharyngeal and saliva?


In patients with signs and symptoms compatible with COVID-19 of equal or less than 7 days-onset, should rapid antigen detection testing be used, compared with standard NAAT (commercial and/or in house) for diagnosis of COVID-19?

Weak against Very low [6, 7, 23, 25, 28, 30, 33, 41, 49, 52, 59, 60, 68, 71-73, 78, 82, 84-86, 88]
In patients with signs and symptoms compatible with COVID-19 of more than 7 days-onset, should rapid antigen detection testing be used, compared with standard NAAT (commercial and/or in house) for diagnosis of COVID-19?  

**Weak against Very low [6, 7, 23, 25, 28, 30, 49, 59, 60, 71, 73, 78, 84, 85]**

In children <12 years with signs and symptoms compatible with COVID-19, should rapid antigen detection testing be used, compared with standard NAAT (commercial and/or in house) for diagnosis of COVID-19?  

**Weak against Very low [6, 23, 52, 71, 79, 86]**

In patients ≥12 years old with signs and symptoms compatible with COVID-19, should rapid antigen detection testing be used, compared with standard NAAT (commercial and/or in house) for diagnosis of COVID-19?  

**Weak against Very low [6, 23, 26, 29, 30, 32, 36, 45-47, 54-56, 68, 71, 76, 84, 88]**

In patients with signs and symptoms compatible with COVID-19 at risk for severe illness, should rapid antigen detection testing be used, compared with standard NAAT (commercial and/or in house) for diagnosis of COVID-19?  

**Strong against Very low [6, 23, 46, 60]**

Saliva sampling

In patients with signs and symptoms compatible with mild or moderate COVID-19, should saliva sampling be used, compared with nasopharyngeal swab sampling for diagnosis of COVID-19 with NAAT?  

**Weak against Very low [90-97]**

<table>
<thead>
<tr>
<th>In patients with signs and symptoms compatible with COVID-19 of more than 7 days-onset, should rapid antigen detection testing be used, compared with standard NAAT (commercial and/or in house) for diagnosis of COVID-19?</th>
<th>Weak against Very low</th>
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<td>In children &lt;12 years with signs and symptoms compatible with COVID-19, should rapid antigen detection testing be used, compared with standard NAAT (commercial and/or in house) for diagnosis of COVID-19?</td>
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<td>In patients ≥12 years old with signs and symptoms compatible with COVID-19, should rapid antigen detection testing be used, compared with standard NAAT (commercial and/or in house) for diagnosis of COVID-19?</td>
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<td>In patients with signs and symptoms compatible with COVID-19 at risk for severe illness, should rapid antigen detection testing be used, compared with standard NAAT (commercial and/or in house) for diagnosis of COVID-19?</td>
<td>Strong against Very low</td>
<td>[6, 23, 46, 60]</td>
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<td>In patients with signs and symptoms compatible with mild or moderate COVID-19, should saliva sampling be used, compared with nasopharyngeal swab sampling for diagnosis of COVID-19 with NAAT?</td>
<td>Weak against Very low</td>
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21 In patients with signs and symptoms compatible with severe or critical COVID-19, should saliva sampling be used, compared with nasopharyngeal swab sampling for diagnosis of COVID-19 with NAAT?

22 In patients with signs and symptoms compatible with COVID-19 of equal or less than 7 days onset, should saliva sampling be used, compared with nasopharyngeal swab sampling for diagnosis of COVID-19 with NAAT?

23 In patients with signs and symptoms compatible with COVID-19 of more than 7 days onset, should saliva sampling be used, compared with nasopharyngeal swab for diagnosis of COVID-19 with NAAT?

24 In children <12 years old with signs and symptoms compatible with COVID-19, should saliva sampling be used, compared with nasopharyngeal swab for diagnosis of COVID-19 with NAAT?

25 In patients ≥12 years old with signs and symptoms compatible with COVID-19, should saliva sampling be used, compared with nasopharyngeal swab sampling for diagnosis of COVID-19 with NAAT?

26 In patients with signs and symptoms compatible with COVID-19 at risk for severe illness, should saliva sampling be used, compared with nasopharyngeal swab sampling for diagnosis of COVID-19 with NAAT?

In patients with signs and symptoms compatible with severe or critical COVID-19 for the diagnosis of COVID-19 infection, we suggest the use of NAAT in nasopharyngeal swab samples versus NAAT in saliva samples for diagnosis of COVID-19.

Weak against Very low [13, 92, 98-116]

In patients with signs and symptoms compatible with COVID-19 of equal or less than 7 days-onset, we suggest the use of NAAT in nasopharyngeal swab samples versus NAAT in saliva samples for diagnosis of COVID-19.

Weak for Very low [90, 95, 104, 108, 109, 113, 114]

In patients with signs and symptoms compatible with COVID-19 of more than 7 days-onset, we suggest the use of NAAT in nasopharyngeal swab samples versus NAAT in saliva samples for diagnosis of COVID-19.

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In children <12 years old with signs and symptoms compatible with COVID-19, we suggest the use of NAAT in nasopharyngeal swab samples versus NAAT in saliva samples for diagnosis of COVID-19.

Weak against Very low [90, 94, 95, 99, 103, 107, 108, 114, 115, 117]

In patients ≥12 years old with signs and symptoms compatible with COVID-19, we suggest the use of NAAT in nasopharyngeal swab samples versus NAAT in saliva samples for diagnosis of COVID-19.

Weak against Very low [13, 91-93, 96-98, 100-102, 104-106, 109-113, 115, 116, 118]

In patients with signs and symptoms compatible with COVID-19 at risk for severe illness, we suggest the use of NAAT in nasopharyngeal swab samples versus NAAT in saliva samples for diagnosis of COVID-19.

Weak against Very low [13, 90-118]

*Strength of recommendation (strong against, weak against, in research only, weak for, strong for).
Overall certainty of the evidence (high, moderate, low, very low).
Table 2. PICO questions and recommendations in travellers, healthcare workers, and asymptomatic individuals at risk for exposure.

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</table>
5. In asymptomatic people should rapid antigen test be used as compared to laboratory based NAAT in non-nasopharyngeal/non-saliva samples to diagnose COVID-19?

6. In asymptomatic people should rapid antigen tests be used in saliva samples as compared laboratory based NAAT to diagnose COVID-19?

NAAT in saliva samples

7. In asymptomatic children <12 years, should NAAT in saliva samples be used, as compared to nasopharyngeal samples to diagnose COVID-19?

8. In asymptomatic patients ≥12 years, should NAAT test in saliva samples be used, as compared to nasopharyngeal samples to diagnose COVID-19?

9. In close contacts asymptomatic children <12 years, should NAAT in saliva samples be used, as compared to nasopharyngeal samples to diagnose COVID-19?

10. In close contacts asymptomatic patients ≥12 years, should NAAT in saliva samples be used, as compared to nasopharyngeal samples to diagnose COVID-19?

11. In close contacts asymptomatic children <12 years with less than 7 days since contact, should NAAT in

In asymptomatic people, we suggest the use of laboratory-based NAAT in non-nasopharyngeal/non-saliva samples versus rapid antigen testing in non-nasopharyngeal/non-saliva for diagnosis of COVID-19.

In asymptomatic people, we suggest the use of laboratory-based NAAT in saliva samples versus rapid antigen testing in saliva for diagnosis of COVID-19.

In asymptomatic children <12 years, we suggest the use of NAAT in saliva samples versus NAAT in nasopharyngeal swab samples for diagnosis of COVID-19.

In asymptomatic patients ≥12 years, we suggest the use of NAAT in nasopharyngeal swab samples versus NAAT in saliva samples for diagnosis of COVID-19.

In close contact asymptomatic children <12 years, we suggest NAAT in saliva samples be used compared to NAAT testing in nasopharyngeal swab samples for diagnosis of COVID-19.

In close contact asymptomatic patients ≥12 years, we suggest the use of NAAT in nasopharyngeal swab samples versus NAAT in saliva samples for diagnosis of COVID-19.

In close contacts asymptomatic children <12 years with less than 7 days since contact, we suggest the use of NAAT in saliva samples versus NAAT in nasopharyngeal swab samples for diagnosis of COVID-19.

Weak against Very low [6, 23, 31, 40, 67, 74, 78, 79, 83]

Weak against Very low [6, 23, 30, 40]

Weak for Very low [108, 115, 123, 124]

Weak against Very low [96, 97, 105, 115, 125]

Weak for Very low [126]

Weak against Very low [96, 105, 115, 124, 125]

Weak for Very low [108, 115, 123, 124]
saliva samples be used, as compared to nasopharyngeal samples to diagnose COVID-19?

In close contacts asymptomatic patients ≥12 years with less than 7 days since contact, should NAAT in saliva samples be used, as compared to nasopharyngeal samples to diagnose COVID-19?

In close contact asymptomatic patients ≥12 years with less than 7 days since contact, we suggest the use of NAAT in nasopharyngeal swab samples versus NAAT in saliva samples for diagnosis of COVID-19.

1 *Strength of recommendation (strong against, weak against, in research only, weak for, strong for).

2 **Overall certainty of the evidence (high, moderate, low, very low).