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Guidelines

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 panellist involved in case of inconsistent results. Quality of evidence assessment was based on the GRADE-ADOLOPMENT (Grading of Recommendations Assessment, Development and Evaluation - adoption, adaptation, and de novo development of recommendations) approach.

Recommendations: A total of 43 PICO questions were selected that involve the following types of populations: (a) patients with signs and symptoms of COVID-19; (b) travellers, healthcare workers, and other individuals at risk for exposure to SARS-CoV-2; (c) asymptomatic individuals, and (d) 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

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infectious case, age, disease severity, and risk of developing severe disease are also taken into consideration. **Paraskevi C. Fragkou, *Clin Microbiol Infect* 2022;28:812**

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Scope

The present guidelines have the objective of identifying the most appropriate diagnostic test and/or diagnostic/screening approach for (a) patients with signs and symptoms of COVID-19; (b) travellers from areas with low and high COVID-19 prevalence, health care workers, and other individuals at risk for exposure to SARS-CoV-2; (c) asymptomatic individuals (including the general population); (d) those with close contact with a person infected with SARS-CoV-2; and (e) symptomatic individuals after reinfection and/or vaccination.

However, evidence on reinfection and postvaccination testing approach was scarce when the literature search for the index guidelines was performed. Hence, associated patient/population, intervention, comparison and outcomes (PICO) 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. This document is intended to provide guidance to clinicians, clinical microbiologists, and other health care personnel, as well as 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 European Society of Clinical Microbiology and Infectious Diseases (ESCMID) guidelines for COVID-19 [2], ESCMID did not develop recommendations at the start of the pandemic. However, given the time that has passed and the rapid growth in evidence upon which to base recommendations, in January 2021 the ESCMID Executive Committee 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 the 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 PICOs that reached consensus within the panel. Considering the available evidence, a total of 43 PICOs were used for the development of the present guidelines. The PICOs that were excluded are listed in [Appendix S1](#), along with additional details on the methods used.

Quality of evidence assessment

The quality of the body of evidence was evaluated per 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 in the following.

Risk of bias

The risk of bias of each study was assessed using the Quality Assessment of Diagnostic Accuracy Studies 2 (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, and two panel members independently assessed the QUADAS-2 for any new study retrieved during the evidence syntheses update, if performed (Methods S1). The risk of bias was judged to be very serious or serious if all or more/equal than a half of studies, respectively, had 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. Indirectness was judged to be very serious or serious if all or more/equal than half of studies, respectively, had high or unclear concern regarding all or one to two QUADAS-2 domains for applicability concerns. Indirectness was judged not serious in any other case. Furthermore, evidence was judged indirect if marked differences in the population with respect to the review question were suspected.

Inconsistency

Heterogeneity of results was assessed statistically with the I^2 test. We searched for a plausible source of heterogeneity by subgroup analyses according to the most plausible reason for heterogeneity (i.e. type of samples, type of test, and quality of studies). These subanalyses were performed only if subgroups included four 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. Inconsistency was judged serious in any other case.

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

| A | PICO question | Recommendation | Strength of recommendation ^a | Overall certainty of evidence ^b | References |
|----|---|--|---|--|------------------------|
| | Rapid NAAT | | | | |
| 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? | 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. | Weak for | Very low | [12–23] |
| 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 testing (commercial and/or in house) for diagnosis of COVID-19? | 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. | Strong for | Very low | [12–23] |
| 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? | 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. | Weak for | Very low | [13,15,16,18,20,22,23] |
| 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) for diagnosis of COVID-19 in samples other than nasopharyngeal swabs? | 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 swabs for the diagnosis of COVID-19, when allowed by regulatory boards and manufacturer instructions. | Weak for | Very low | [12,14,15,17,21,23] |
| 5 | In patients with signs and symptoms compatible with COVID-19 of ≤7 days' onset , should commercial rapid NAAT 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 ≤7 days' onset, we suggest the use of rapid NAAT versus laboratory-based NAAT for the diagnosis of COVID-19. | Weak for | Very low | [12–22] |
| 6 | In patients with signs and symptoms compatible with COVID-19 of >7 days' onset , should commercial rapid NAAT 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 >7 days' onset, we suggest the use of rapid NAAT versus laboratory-based NAAT for the diagnosis of COVID-19. | Weak for | Very low | [12–23] |
| 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? | In children <12 years old with signs and symptoms compatible with COVID-19, we suggest the use of rapid NAAT versus laboratory-based NAAT for diagnosis of COVID-19. | Weak for | Very low | [12,15,17–20,22,23] |
| 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? | In patients ≥12 years old with signs and symptoms compatible with COVID-19, we suggest the use of rapid NAAT versus laboratory-based NAAT for diagnosis of COVID-19. | Weak for | Very low | [13,14,16,21,23] |
| 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? | In patients with signs and symptoms compatible with COVID-19 at risk for severe disease, we suggest the use of rapid NAAT versus laboratory-based NAAT for diagnosis of COVID-19. | Weak for | Very low | [12–23] |
| | 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 | 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] |

Table 1 (continued)

| A | PICO question | Recommendation | Strength of recommendation ^a | Overall certainty of evidence ^b | References |
|----|---|---|---|--|---|
| | (commercial and/or in house) for diagnosis of COVID-19? | | | | |
| 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 | [6,7,23,30,35–55, 56–88] |
| 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 saliva samples ? | In patients with signs and symptoms compatible with COVID-19, we suggest the use of laboratory-based NAAT in saliva samples versus rapid antigen detection testing in saliva samples for diagnosis of COVID-19. | Weak against | Very low | [6,7,23,30,40] |
| 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. | Weak against | Very low | [6,23,25,31,40,44,49,54,65–68,71,74,78,79,84,88] |
| 15 | In patients with signs and symptoms compatible with COVID-19 of ≤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 ≤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 >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 >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 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? | 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] |
| 18 | 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? | In patients ≥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 | [6,23,26,29,30,32,36,45–47,54–56,68,71,76,84,88] |
| 19 | 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? | In patients with signs and symptoms compatible with COVID-19 at risk for severe illness, we recommend the use of laboratory-based NAAT versus rapid antigen detection testing for diagnosis of COVID-19. | Strong against | Very low | [6,23,46,60] |
| 20 | In patients with signs and symptoms compatible with mild or moderate COVID-19, should saliva sampling be used, compared with | In patients with signs and symptoms compatible with mild or moderate COVID-19, we suggest the use of NAAT in nasopharyngeal swab samples versus | Weak against | Very low | [90–97] |

(continued on next page)

Table 1 (continued)

| A | PICO question | Recommendation | Strength of recommendation ^a | Overall certainty of evidence ^b | References |
|----|---|---|---|--|--|
| 21 | nasopharyngeal swab sampling for diagnosis of COVID-19 with NAAT? 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? | NAAT in saliva samples for diagnosis of COVID-19. 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] |
| 22 | In patients with signs and symptoms compatible with COVID-19 of ≤7 days' onset , 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 of ≤7 days' onset, we suggest the use of NAAT in saliva samples versus NAAT in nasopharyngeal swab samples for diagnosis of COVID-19. | Weak for | Very low | [90,95,104,108,109,113,114] |
| 23 | In patients with signs and symptoms compatible with COVID-19 of >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 >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] |

NAAT, rapid nucleic acid amplification test; PICO, patient/population, intervention, comparison and outcome.

^a Strength of recommendation (strong against, weak against, in research only, weak for, strong for).

^b Overall certainty of the evidence (high, moderate, low, very low).

Imprecision

We downgraded the evidence for imprecision if the boundaries of the 95% CIs 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 diagnostic tests encompassed by the guidelines at 80% or 90%, respectively.

Publication bias

Linear regression of log ORs on the inverse root of an effective sample-sizes test was used to assess the presence of publication bias when three 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 strongly suspected when less than three studies informed the outcome and could not be excluded.

Definitions of tests

Rapid nucleic acid amplification tests (NAATs) were tests considered to have the capacity to be performed at the point of care or in a near-patient setting. This is decentralized testing requiring minimal equipment, sample preparation, and biosafety

considerations that can be performed near a patient and outside of central laboratory testing [5]. Rapid antigen tests were defined as all commercially available tests, including both point of care (as defined above) and in-laboratory testing [6]. However, only one study provided information about in-laboratory testing [7].

Questions addressed by the guideline

In developing the guidelines for diagnosis of SARS-CoV-2, focus was placed on testing with commercial NAATs and rapid antigen detection. The performance characteristics of these tests depends on the population 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 health care system facilities, including trained personnel, properly equipped diagnostic laboratories, and the types of tests being covered or reimbursed by the local health care system. Regarding particular recommendations for or against a specific diagnostic approach, the main beneficial outcomes considered were (a) reduction of mortality and facilitation of early treatment (if deemed to play a critical role), (b) reduction of viral transmission, (c) minimizing unnecessary

treatment and/or isolation, (d) reduction of anxiety of patients/potentially exposed persons, and (e) burden to health care systems with consequences for health inequality.

Recommendations

The 43 PICO questions selected were divided according to the target population: (A) patients with signs and symptoms of COVID-19 (Table 1); (B) travellers from areas with low COVID-19 prevalence, health care workers, and asymptomatic individuals at risk for exposure (5 questions; Table 2); and (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 versus standard NAAT (nine questions); (A2) rapid antigen testing versus standard NAAT (ten questions); and (A3) saliva sampling versus nasopharyngeal swabs for NAAT (seven questions). PICO questions in group C were further divided into (C1) rapid antigen testing versus NAAT (six questions) and (C2) NAAT in saliva samples versus nasopharyngeal swabs (six questions). A full summary of the evidence for each PICO question is presented in Appendices S2 through 4.

Group 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 (Table 1). 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 suggests that early isolation is beneficial [8]. In general, rapid NAAT is suggested due to the high accuracy of the test, low risk of anticipated harm, and 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 and will reduce potential health inequities because 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 NAATs (Table 1).

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, such as 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 because it has also been associated with aerosol generation [9,10]. Especially in some subgroups of patients, such as children, saliva might be preferred over nasopharyngeal swabs (Table 1). Nevertheless, children may not

Table 2

PICO questions and recommendations in travellers, health care workers, and asymptomatic individuals at risk for exposure

| B | PICO question | Recommendation | Strength of recommendation ^a | Overall certainty of evidence ^b | References |
|---|--|--|---|--|------------|
| 1 | In travellers from areas with low prevalence , should surveys for contact history with known or suspected exposures to infected people followed by NAAT be used compared with universal NAAT to diagnose COVID-19? | In returning travellers from areas with low prevalence of COVID-19, we suggest the use of universal NAAT versus survey for contact history with known or suspected exposures in addition to NAAT for diagnosis of COVID-19. | Weak against | Very low | [119–121] |
| 2 | In travellers from areas with high prevalence , should surveys for contact history with known or suspected exposures to infected people followed by NAAT be used compared with universal NAAT to diagnose COVID-19? | In returning travellers from areas with high prevalence of COVID-19, we suggest the use of universal NAAT versus survey for contact history with known or suspected exposures in addition to NAAT for diagnosis of COVID-19. | Weak against | Very low | [121,122] |
| 3 | In health care workers , should surveys for contact history with known or suspected exposures to infected people followed by NAAT be used compared with universal NAAT to diagnose COVID-19? | In health care workers, we recommend the use of universal NAAT versus survey for contact history with known or suspected exposures in addition to NAAT for diagnosis of COVID-19. | Strong against | Very low | [119,121] |
| 4 | In asymptomatic populations at risk for exposure , should surveys for contact history with known or suspected exposures within <7 days to infected people followed by NAAT be used compared with universal NAAT to diagnose COVID-19? | 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 <7 days in addition to NAAT for diagnosis of COVID-19. | Weak against | Very low | [119–122] |
| 5 | In asymptomatic populations at risk for exposure , should surveys for contact history with known or suspected exposures >7 days to infected people followed by NAAT be used compared with universal NAAT to diagnose COVID-19? | In asymptomatic populations at risk for exposure, we suggest the use of universal NAAT versus survey for contact history with known or suspected exposures >7 days in addition to NAAT for diagnosis of COVID-19. | Weak against | Very low | [119–122] |

NAAT, rapid nucleic acid amplification test; PICO, patient/population, intervention.

^a Strength of recommendation (strong against, weak against, in research only, weak for, strong for).

^b Overall certainty of the evidence (high, moderate, low, very low).

Table 3
PICO questions and recommendations in asymptomatic individuals and those with close contact with an infected person

| C | PICO question | Recommendation | Strength of recommendation ^a | Overall certainty of evidence ^b | References |
|----|---|---|---|--|---|
| | Rapid antigen testing | | | | |
| 1 | In asymptomatic children <12 years old without risk factors for severe COVID-19, should rapid antigen tests be used compared with laboratory-based NAAT to diagnose COVID-19? | In asymptomatic children <12 years old without risk factors for severe COVID-19, we suggest the use of laboratory-based NAAT versus rapid antigen testing for diagnosis of COVID-19. | Weak against | Very low | [6,23,30,33,40,51,62,67,79,83] |
| 2 | In asymptomatic patients ≥12 years old without risk factors for severe COVID-19, should rapid antigen tests be used compared with laboratory-based NAAT to diagnose COVID-19? | In asymptomatic patients ≥12 years old without risk factors for severe COVID-19, we suggest the use of laboratory-based NAAT versus rapid antigen testing for diagnosis of COVID-19. | Weak against | Very low | [6,23,26,27,31,45,46,48,54–57,60,74,75,82] |
| 3 | In asymptomatic people of any age with any risk factor(s) for severe COVID-19 (including age <3 months or ≥65 years) should rapid antigen tests be used compared with laboratory-based NAAT to diagnose COVID-19? | In asymptomatic people of any age with any risk factor(s) for severe COVID-19 (including age <3 months or ≥65 years), we suggest the use of laboratory-based NAAT versus antigen testing for diagnosis of COVID-19. | Weak against | Very low | [6,23,26,27,30,31,33,40,45,46,48,51,54–57,60,62,67,74,75,77–79,82,83] |
| 4 | In asymptomatic people, should rapid antigen test be used compared with laboratory-based NAAT in nasopharyngeal samples to diagnose COVID-19? | 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. | Weak against | Very low | [6,23,26,27,33,45,46,48,51,54–57,60,62,75,77,82,89] |
| 5 | In asymptomatic people, should rapid antigen test be used compared with laboratory-based NAAT in non-nasopharyngeal/non-saliva samples to diagnose COVID-19? | 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. | Weak against | Very low | [6,23,31,40,67,74,78,79,83] |
| 6 | In asymptomatic people, should rapid antigen tests be used in saliva samples compared with 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 saliva for diagnosis of COVID-19. | Weak against | Very low | [6,23,30,40] |
| 7 | In asymptomatic children <12 years old , should NAAT in saliva samples be used compared with nasopharyngeal samples to diagnose COVID-19? | In asymptomatic children <12 years old, 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 old , should NAAT test in saliva samples be used compared with nasopharyngeal samples to diagnose COVID-19? | In asymptomatic patients ≥12 years old, 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-contact asymptomatic children <12 years old , should NAAT in saliva samples be used compared with nasopharyngeal samples to diagnose COVID-19? | In close-contact asymptomatic children <12 years old, we suggest that NAAT in saliva samples be used compared with NAAT testing in nasopharyngeal swab samples for diagnosis of COVID-19. | Weak for | Very low | [126] |
| 10 | In close-contact asymptomatic patients ≥12 years old , should NAAT in saliva samples be used compared with nasopharyngeal samples to diagnose COVID-19? | In close-contact asymptomatic patients ≥12 years old, 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-contact asymptomatic children <12 years old with <7 days since contact, should NAAT in saliva samples be used compared with nasopharyngeal samples to diagnose COVID-19? | In close-contact asymptomatic children <12 years old with <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-contact asymptomatic patients ≥12 years old with <7 days since contact, should NAAT in saliva samples be used compared with nasopharyngeal samples to diagnose COVID-19? | In close-contact asymptomatic patients ≥12 years old with <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] |

NAAT, rapid nucleic acid amplification test; PICO, patient/population, intervention.

^a Strength of recommendation (strong against, weak against, in research only, weak for, strong for).

^b Overall certainty of the evidence (high, moderate, low, very low).

always be able to produce saliva on demand, and nasopharyngeal samples are still preferred in such cases. Notwithstanding, the available data suggest that the accuracy of saliva NAAT is not as high as nasopharyngeal NAAT.

Group B: Travellers from areas with low and high COVID-19 prevalence, health care 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 (Table 2). 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 travellers from areas of low and high prevalence of COVID-19, health care workers, and asymptomatic individuals at risk for exposure instead of universal NAAT.

Group C: Asymptomatic individuals and close contact of an infected person

As for all previous PICOs, the 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 a diagnosis of COVID-19 (Table 3). 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 third-generation ones [11].

NAAT in saliva samples

In asymptomatic children <12 years old (with or without close contact), NAAT of 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 (Table 3). 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 to note that several gaps remain regarding the evidence for diagnostic testing in several areas. These include infection after vaccination or previous infection (reinfection), 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, and 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, definitions 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 few data are available regarding the clinical impact (treatment, isolation, hospitalization) of these tests.

Furthermore, several methodological challenges were encountered that could be mitigated. First, 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 the development of guidelines, given the large amount of new information, as well as the need for regular updates and revisions 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 for 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 unfavourable performance of a group of tests (e.g. pooled sensitivity of antigen tests) is due to diluting the favourable 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; thus, we 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 the GRADE ADOLOPMENT methodology, which, by definition, is based on updating (if applicable) existing moderate-to-high quality already published (or preprint) 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.

Transparency declaration

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Author contributions

Giulia De Angelis and Giulia Menchinelli contributed equally to this work. Fusun Can, Federico Garcia, and Florence Morfin-Sherpa contributed equally to this work.

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Conceptualization and coordination of the overall scope of the guidelines: CS, PCF. First manuscript draft (e.g. scope/context, methodology, discussion): 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, and finalization of associated recommendations summary templates: CS, PCF, GDA, GM, FMS, FG, FC. Methodological consultation: TL, LS.

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

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Appendix A. Supplementary data

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