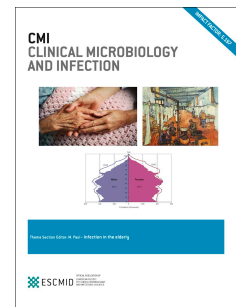# Journal Pre-proof

ESCMID COVID-19 guidelines: diagnostic testing for SARS-CoV-2

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

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18

1 **Abstract**

2 **Scope**: The objective of these guidelines is to identify the most appropriate diagnostic test

3 and/or diagnostic approach for SARS-CoV-2. The recommendations are intended to provide

4 guidance to clinicians, clinical microbiologists, other health care personnel, and decision

5 makers.

6 **Methods**: An ESCMID COVID-19 guidelines task force was established by the ESCMID

7 Executive Committee. A small group was established, half appointed by the chair, and the

8 remaining selected with an open call. Each panel met virtually once a week. For all decisions,

9 a simple majority vote was used. A list of clinical questions using the PICO (population,

10 intervention, comparison, outcome) format was developed at the beginning of the process. For

11 each PICO, two panel members performed a literature search focusing on systematic reviews

12 with a third panelist involved in case of inconsistent results. Quality of evidence assessment

13 was based on the GRADE-ADOLOPMENT approach.

14 **Questions addressed by the guideline and recommendations**: A total of 43 PICO questions

15 were selected that involve the following types of populations: 1) patients with signs and

16 symptoms of COVID-19; 2) travelers, healthcare workers, and other individuals at risk for

17 exposure to SARS-CoV-2; 3) asymptomatic individuals and 4) close contacts of patients

18 infected with SARS-CoV-2. The type of diagnostic test (commercial rapid nucleic acid

19 amplification tests, and rapid antigen detection), biomaterial, time since onset of

20 symptoms/contact with an infectious case, age, disease severity, and risk of developing severe

21 disease are also taken into consideration.

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

23

1 **Scope**

2   The present guideline has the objective of identifying the most appropriate diagnostic test

3 and/or diagnostic/screening approach for1) patients with signs and symptoms of COVID-19; 2)

4 travelers from areas with low and high COVID-19 prevalence, healthcare workers, and other

5 individuals at risk for exposure to SARS-CoV-2; 3) asymptomatic individuals (including

6 general population) and 4) those with close contact with a person infected with SARS-CoV-2;

7 and 5) symptomatic individuals following re-infection and/or vaccination. However, evidence

8 for re-infection and post-vaccination testing approach was scarce when the literature search for

9 the index guidelines was performed. Hence, associated PICOs could not be addressed.

10 Additional considerations include the type of biomaterial, time since onset of symptoms/contact

11 with infectious case, age, disease severity, and risk of developing severe disease. The document

12 is intended to provide guidance to clinicians, clinical microbiologists, other health care

13 personnel, and decision makers.

14

15 **Context**

16   The ongoing COVID-19 pandemic has severely disrupted human life worldwide and

17 represents an unprecedented challenge to public health [1]. As stated in the first paper of the

18 newly-developed ESCMID guidelines for COVID-19 [2], ESCMID did not develop

19 recommendations at the start of the pandemic. However, given the time passed and the rapid

20 growth in evidence upon which to base recommendations, in January 2021 the ESCMID

21 Executive Committee (EC) decided to launch a new initiative to develop ESCMID guidelines

22 on several COVID-19-related issues. The present guideline provides recommendations for

23 diagnostic testing for SARS-CoV-2, which is of particular relevance given the high incidence

24 of both infections and deaths. This is further complicated by circulating mutations of SARS-

1   CoV-2 and potential implications for diagnostic testing. Thus, a smart and effective approach

2   to testing and screening is required to minimize spread of the virus.

3

4   **Consensus guideline development**

5   The general principles and methodology adopted have been described in the first paper

6   in the ESCMID guidelines for COVID-19 related clinical topics [2]. Herein, the panel members

7   proposed a list of diagnostic PICO questions to the panel Chair, who in turn selected the most

8   clinically relevant questions and compiled a set of 55 priority PICOs that reached consensus

9   within the panel. Considering the available evidence, a total of 43 PICOs were used for the

10   development of the present guidelines. The PICOs that were excluded are listed in

11   Supplementary Appendix1 along with additional details on the methods used.

12   *Quality of evidence assessment*

13   The quality of the body of evidence was evaluated following the GRADE approach.

14   Accordingly, five factors for rating down the quality of evidence (risk of bias, inconsistency of

15   results, indirectness of evidence, imprecision, and publication bias) and three for rating it up

16   (large magnitude of effect, direction of plausible confounding, dose-response gradient) were

17   assessed. Adaptation of the quality assessment factors was applied by the panel for the

18   Diagnostic Guidelines, as described below.

19   *Risk of bias*

20   The risk of bias of each study was assessed using the QUADAS-2 tool for diagnostic

21   accuracy studies. The QUADAS-2 tool includes four key domains that discuss patient selection,

22   index test, reference standard, and flow of patients through the study and timing of the index

23   tests and reference standard. The QUADAS-2 assessment of studies included in the original

24   systematic review was adopted, whereas two panel members independently assessed the

1 QUADAS-2 for any new study retrieved during the evidence syntheses update, if performed

2 (see Supplementary Methods). The risk of bias was judged very serious or serious if all or

3 more/equal than a half of studies, respectively, have high or unclear concern regarding all or

4 one to three QUADAS-2 domains. The risk of bias was judged not serious in any other case.

5 *Indirectness*

6 Indirectness was judged for all studies based on QUADAS-2 tool concerns for

7 applicability for patient selection, index test, and reference standard. The QUADAS-2

8 applicability assessment of studies included in the original systematic review was adopted; two

9 panel members independently assessed the QUADAS-2 applicability for any new study

10 retrieved during the systematic review update, if performed. The indirectness was judged very

11 serious or serious if all or more/equal than half of studies, respectively, have high or unclear

12 concern regarding all or one to two QUADAS-2 domains for applicability concern. The

13 indirectness was judged not serious in any other case. Furthermore, evidence was judged

14 indirect if marked differences in population respect to the review question were suspected.

15 *Inconsistency*

16 Heterogeneity of results was assessed statistically by the I^2 test. We searched for a

17 plausible source of heterogeneity by subgroup analyses according to the most plausible reason

18 of heterogeneity, i.e. the type of samples, the type of test and the quality of the studies. These

19 sub-analyses were performed only if subgroups included at least 4 or more studies. If a plausible

20 explanation for heterogeneity was not identified, the quality of evidence was downgraded..

21 Inconsistency was judged very serious if high and unexplained heterogeneity ($I^2 > 90\%$) was

22 detected. Inconsistency was judged not serious if either low ($I^2 < 50\%$) or otherwise explained

23 through subgroup analyses. The inconsistency was judged serious in any other case.

24 *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

1   depends on the local infrastructure of the individual setting and healthcare system facilities.

2   This includes trained personnel, properly equipped diagnostic laboratories, and the types of

3   tests being covered or reimbursed by the local healthcare system. Regarding particular

4   recommendations for (or against) a specific diagnostic approach, the main beneficial outcomes

5   considered were: i) reduction of mortality, facilitation of early treatment (if deemed to play a

6   critical role), ii) reduction of viral transmission, iii) minimizing unnecessary treatment and/or

7   isolation, iv) reduction of anxiety of patients/potentially exposed persons, and v) burden to

8   healthcare systems with consequences for health inequality.

9

10   **Recommendations**

11   The 43 PICO questions selected were divided according to the target population into:

12   A, patients with signs and symptoms of COVID-19 (Table 1); B, travelers from areas with low

13   COVID-19 prevalence, healthcare workers, and asymptomatic individuals at risk for exposure

14   (5 questions; (Table 2); C, asymptomatic individuals and those with close contact with an

15   infected person (Table 3). PICO questions in group A were further divided according to the

16   type of test: A1, commercial rapid NAAT vs. standard NAAT (9 questions); A2, rapid antigen

17   testing vs. standard NAAT (10 questions); A3, saliva sampling vs. nasopharyngeal swabs for

18   NAAT (7 questions). PICO questions in group C were further divided into: C1, rapid antigen

19   testing vs. NAAT (6 questions); C2, NAAT in saliva samples vs. nasopharyngeal swabs (6

20   questions). A full summary of the evidence for each PICO question is presented in

21   Supplementary Appendices 2-4.

22

23   **A: Patients with signs and symptoms of COVID-19**

24   *Rapid NAAT*

1   The quality of the available evidence for all PICOs prioritized for patients with signs

2   and symptoms compatible with COVID-19 was very low. Along these lines, the strength of

3   recommendation was almost always weak except for cases where disease severity and/or risk

4   of developing severe disease was considered of utmost importance. Diagnosis of COVID-19

5   with rapid NAAT will reduce the required time from sample acquisition to results.

6   Extrapolation from studies looking into rapid NAATs for the detection of other respiratory

7   viruses would suggest that early isolation is beneficial [8]. In general, rapid NAAT is suggested

8   due to the high accuracy of the test, the low risk of anticipated harm, and its feasible

9   implementation. However, the anticipated benefits are likely to depend on the different risk

10   factors for hospitalization, mortality, and associated morbidity.

11   *Rapid antigen testing*

12   Diagnosis of COVID-19 with rapid antigen testing will reduce the required time from

13   sample acquisition to results as well as reduce potential health inequities as antigen tests are

14   (usually) readily available, easy to perform, and feasible to implement in various settings. This

15   in turn, will reduce the potential consequences of a delayed COVID-19 diagnosis or even the

16   ability to perform COVID-19 testing when access is limited due to restricted resources.

17   However, current data suggest that antigen tests are not as accurate as the reference standard

18   NAAT tests.

19   *Saliva sampling*

20   Laboratory-based NAAT in nasopharyngeal samples is the reference standard test for

21   the diagnosis of COVID-19. The accuracy of other than nasopharyngeal samples, like saliva, is

22   being investigated. Saliva sampling is easier to perform with essentially no adverse events.

23   However, saliva processing may be challenging unless collected in appropriate media, since it

24   has also been associated with aerosol generation [9, 10]. Especially in some subgroups of

25   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].

1   *NAAT in saliva samples*

2   In asymptomatic children <12 years old (with or without close contact), NAAT in saliva

3   samples was recommended over NAAT on nasopharyngeal swab samples for diagnosis of

4   COVID-19 considering the accuracy of the test, the large anticipated benefits and small harm,

5   low amount of resources, small incremental cost relative to net benefits, acceptability, and

6   feasibility of the test. In patients ≥12 years old, NAAT on nasopharyngeal samples should be

7   preferred, also considering that young children may not produce saliva on command.

8

9   **Future considerations**

10   It is worthwhile noting that several gaps remain regarding the evidence for diagnostic

11 testing in several areas. These include infection following vaccination or previous infection (re-

12 infection); performance of newer generation antigen tests in different patient populations and

13 samples; correlation of viral nucleic acid or antigen detection with contagiousness; accuracy of

14 different diagnostic tests in different populations and non-nasopharyngeal samples; the

15 accuracy of different diagnostic tests in asymptomatic individuals and the general population.

16 Moreover, there is a paucity of data regarding costs and/or resource modelling studies, patient

17 values, preferences and beliefs, definition of 'feasibility' of various tests, stakeholders' opinion

18 regarding acceptability, and assessment criteria on the potential implications of interventions

19 on health inequities. The lack of objective criteria to judge the priority of clinically-relevant

20 questions should also be highlighted, and very little data is available regarding the clinical

21 impact (treatment, isolation, hospitalization) of these tests.

22   It is further noted that several methodological challenges were encountered that could be

23 improved upon. Firstly, literature databases specific for COVID-19 are not user friendly and

24 are difficult to navigate. Especially for diagnostic testing, there was a lack of exportable

25 literature. The ongoing pandemic also posed considerable time constraints for development of

1   guidelines given the large amount of new information, need for regular updates, and revision

2   of recommendations, all within a context with limited resources for guideline development.

3   Among the limitations of the present guidelines is the very low quality of evidence and

4   lack of dedicated resources to update specific evidence syntheses. Furthermore, poorly

5   disclosed methodological details in relevant meta-analyses did not allow reproducibility of

6   literature searches. We also included reagents for SARS-CoV-2 testing independently of the

7   biomaterial for which they were optimized. We may thus not exclude the possibility that any

8   unfavorable performance of a group of tests (e.g. pooled sensitivity of antigen tests) is due to

9   diluting the favorable performance of tests, which are indeed optimized for one or another

10   biomaterial. We also did not distinguish between different saliva samples, which may perform

11   differently, and thus cannot draw more specific conclusions in this regard. In addition, it should

12   be mentioned that this is not a systematic review, but rather guideline recommendations based

13   on GRADE ADOLOPMENT methodology, which by definition is based on updating (if

14   applicable) existing moderate to high quality already (or preprint) published evidence

15   syntheses. Lastly, consensus was reached by a simple majority vote and not through consensus

16   software/application such as the Delphi technique, as suggested by the ESCMID Guidelines

17   Committee. However, its strengths include the multidisciplinary expertise of the writing group

18   and the transparent, structured, thorough, and sound methodological approach adopted.

19

20   **Contribution of individual authors:**

21   **Panel members**: Chrysanthi Skevaki (clinical microbiology, virology, infection epidemiology

22   and laboratory medicine), Paraskevi C. Fragkou (internal medicine, infectious diseases), Giulia

23   De Angelis (clinical microbiology, infection epidemiology, infectious diseases), Giulia

24   Menchinelli (clinical microbiology), Florence Morfin (clinical virology), Federico Garcia

25   (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.

6

7 **Conflicts of interest:**

8 For CS: Consultancy and research funding, Hycor Biomedical, BencardAllergie and Thermo

9 Fisher Scientific; Research Funding, Mead Johnson Nutrition (MJN).

10 PCF, GDA, GM, FM, FC, ADS, AG, TL, DD, FG, and EM declare no conflicts of interest.

11

12

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

2 19.

A	PICO question	Recommendation	Strength of recommendation*	Overall certainty of the evidence**	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 (commercial and/or in house) testing 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	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	Weak for	Very low	[12, 14, 15, 17, 21, 23]

	house) for diagnosis of COVID-19 **in samples other than nasopharyngeal swab?**	other than nasopharyngeal swab for the diagnosis of COVID-19, when allowed by regulatory boards and manufacturer's instructions.			
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?	In patients with signs and symptoms compatible with COVID-19 of equal or less than 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 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?	In patients with signs and symptoms compatible with COVID-19 of more than 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	In patients with signs and symptoms compatible with	Weak for	Very low	[12-23]

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	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**	COVID-19 at risk for severe disease, we suggest the use of rapid NAAT versus laboratory-based NAAT for diagnosis of COVID-19.			
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,	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**?	samples versus rapid antigen detection testing in saliva samples for diagnosis of COVID-19.			
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 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	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]

	house) for diagnosis of COVID-19?			
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]

Saliva sampling

20	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 NAATin saliva samples for diagnosis of COVID-19.	Weak against	Very low	[90-97]
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?	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	In patients with signs and symptoms compatible with	Weak for	Very low	[90, 95, 104, 108,

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	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.			109, 113, 114]
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).

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1   Table 2. PICO questions and recommendations in travellers, healthcare workers, and

2   asymptomatic individuals at risk for exposure.

B	PICO question	Recommendation	Strength of recommendation*	Overall certainty of the evidence**	References
1	In **travelers from areas with low prevalence**, 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?	In returning travelers 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 **travelers from areas with high prevalence**, 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?	In returning travelers 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 **healthcare workers**, 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?	In healthcare 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 less than 7 days** to infected people followed by NAAT be used compared to 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 less than 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 above 7 days** to	In asymptomatic populations at risk for exposure, we suggest the use of universal NAAT versus survey for contact history with	Weak against	Very low	[119-122]

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).

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

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infected people followed by NAAT be used compared to universal NAAT to diagnose

known or suspected exposures above 7 days in addition to NAAT for diagnosis of COVID-19.

1 Table 3. PICO questions and recommendations in asymptomatic individuals and those with

2 close contact with an infected person.

C	PICO question	Recommendation	Strength of recommendation*	Overall certainty of the evidence**	References
	Rapid antigen testing				
1	In asymptomatic **children<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?	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, as compared to 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 or ≥65 years)** should rapid antigen tests be used, as compared to 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 old or ≥65 years old), 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 as compared to 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	In asymptomatic people, we suggest the use of	Weak against	Very low	[6, 23, 31, 40,

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	test be used as compared to laboratory based NAAT in **non-nasopharyngeal/non-saliva samples** to diagnose COVID-19?	laboratory-based NAAT in non-nasopharyngeal/non-saliva samples versus rapid antigen testing in non-nasopharyngeal/non-saliva for diagnosis of COVID-19.			67, 74, 78, 79, 83]
6	In asymptomatic people should rapid antigen tests be used **in saliva samples** as compared 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]
	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]

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11	In close contacts asymptomatic **children <12 years** with **less than7days 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).

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

A	PICO question	Recommendation	Strength of recommendation*	Overall certainty of the evidence**	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 (commercial and/or in house) testing 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 swab?**	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.	Weak for	Very low	[12, 14, 15, 17, 21, 23]

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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?	In patients with signs and symptoms compatible with COVID-19 of equal or less than 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 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?	In patients with signs and symptoms compatible with COVID-19 of more than 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? **Rapid antigen testing**	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]
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]

(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, 35-88]
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 equal or less than 7 days-onset**, should rapid antigen detection testing be used, compared with	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	Weak against	Very low	[6, 7, 23, 25, 28, 30, 33, 41, 49, 52, 59, 60, 68, 71-73, 78, 82, 84-86, 88]

standard NAAT (commercial and/or in house) for diagnosis of COVID-19? versus rapid antigen detection testing for diagnosis of COVID-19.

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 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]
	Saliva sampling				
20	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 NAATin saliva samples for diagnosis of COVID-19.	Weak against	Very low	[90-97]

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?	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 equal or less than 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 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.	Weak for	Very low	[90, 95, 104, 108, 109, 113, 114]
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).

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

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1   Table 2. PICO questions and recommendations in travellers, healthcare workers, and asymptomatic individuals at risk for exposure.

B	PICO question	Recommendation	Strength of recommendation*	Overall certainty of the evidence**	References
1	In **travelers from areas with low prevalence**, 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?	In returning travelers 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 **travelers from areas with high prevalence**, 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?	In returning travelers 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 **healthcare workers**, 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?	In healthcare 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 less than 7 days** to infected people followed by NAAT be used compared to 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 less than 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 above 7 days** to infected people followed by NAAT be used compared to 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 above 7 days in	Weak against	Very low	[119-122]

addition to NAAT 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).

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1 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*	Overall certainty of the evidence**	References
	Rapid antigen testing				
1	In asymptomatic **children<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?	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, as compared to 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 or ≥65 years)** should rapid antigen tests be used, as compared to 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 old or ≥65 years old), 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 as compared to 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]

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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?	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** as compared 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]

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 than7days since contact**, should NAAT in	In close contacts asymptomatic children <12 years with less than 7 days since contact, we suggest the use of NAAT in saliva samples versus	Weak for	Very low	[108, 115, 123, 124]

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	saliva samples be used, as compared to nasopharyngeal samples to diagnose COVID-19?	NAAT in nasopharyngeal swab samples for diagnosis of COVID-19.			
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).

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