Philippine COVID-19 Living Clinical Practice Guidelines
Institute of Clinical Epidemiology, National Institutes of Health, UP Manila
In cooperation with the Philippine Society for Microbiology and Infectious Diseases
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EVIDENCE SUMMARY

Should the 14-day symptom-based test be used in screening for COVID-19 infection in apparently healthy adults and children?

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RECOMMENDATION

We suggest to do an initial screening for ANY influenza-like illness, typical and atypical COVID-19 symptoms* within the past 14 days in apparently healthy adults and children, especially for individuals with known exposure to a laboratory-confirmed case of COVID-19. *(Very low certainty of evidence; Weak recommendation)*

**Symptoms include but not limited to: fever/chills, cough, shortness of breath/dyspnea, sore throat, runny nose, myalgia, headache, fatigue/malaise, diarrhea, nausea/vomiting, abdominal pain, anosmia, ageusia, wheezing, chest pain, altered mental status, seizures, rash, pink eye*

Consensus Issues
A weak recommendation was made based on evidence including studies that were conducted prior to the new variant of concern, Omicron, which was noted to present symptoms not typical of previous variants. Additionally, majority of the studies were on adults while one study was on the pediatric population. The panelists emphasized that the list of symptoms is not exhaustive and that presence of any of the symptoms would warrant further investigation through a follow-up confirmatory diagnostic test.

PREVIOUS RECOMMENDATION

We suggest an initial screening for COVID-19 by checking for any influenza-like illness symptoms and typical COVID-19 symptoms* within the past 14 days in apparently healthy adults. *(Low quality of evidence; Conditional recommendation)*

Symptoms include: fever, cough, sore throat, runny nose, myalgia, headache, fatigue/malaise, diarrhea, nausea/vomiting, anosmia, ageusia, shortness of breath/dyspnea

Previous Consensus Issues
The 14-day symptom-based test is a screening strategy wherein the presence of any influenza-like illness symptoms within the past 14 days is designated as presumptive for COVID-19. It should be noted that since the recommendation is for initial screening, a follow-up confirmatory diagnostic test should be done.

What's new in this version?

- This version includes evidence on the diagnostic accuracy of 14-day symptom-based tests for both adult and pediatric populations.
- Sensitivity and specificity of individual COVID-19 symptoms, symptom combinations, and existing case definitions were also assessed in this version.

Key Findings

- Evidence on the accuracy of 14-day symptom-based testing was found from three observational studies (n=8,475). This symptom-based test had a wide range of sensitivity (2.2-100%) and specificity (29-99%) in detecting COVID-19 among adults and children. Variability in accuracy appeared to be associated with heterogeneity in the populations tested and the characteristics of the index test.
- The diagnostic accuracy of individual symptoms differed depending on the exposure history of the populations where the test was applied. For those with unclear exposure, individuals had excellent specificity (>90%) but poor sensitivity (<50%). For close contacts of confirmed COVID-19 cases, nasal congestion/rhinorrhea, headache, cough, sore throat, were the individual symptoms that had at least 70% sensitivity. For children, accuracy was highest for headache, nasal congestion or rhinorrhea, fever or chills, and sore throat.
- Combining individual symptoms can increase the specificity to as high as 99.9% but with no substantial improvements in sensitivity. The Centers for Disease Control (CDC) symptom list showed the highest sensitivity (100%) but lowest specificity (21-45%) in both adults and children population while influenza-like illness showed the highest specificity (86-96%) but lowest sensitivity (43-54%).

Introduction

Earlier local and international recommendations using symptom-based screening were based on the incubation period of COVID-19. It is hypothesized that if a 14-day symptom strategy for screening adults or children was to be implemented and the suspected individuals and their exposed contacts follow quarantine protocols, the resources needed to do serial or repeated testing will be reduced.

An earlier rapid review on this topic pooled two cohorts (n=234) and estimated the sensitivity or proportion of symptomatic SARS-CoV-2 positive cases who developed symptoms within 14 days to be at 92.8% (95% CI 89.5-96.1%).[1] The previous review also used indirect evidence from an influenza vaccine study on elderly patients and found that the development of influenza-like illness within 14 days had a specificity of 98.3% (95% CI 97.2-99.2).

This review aimed to update the evidence base on 14-day symptom-based testing for COVID-19 screening.

Review Methods

An updated systematic search was done from June 9, 2020 until October 20, 2021 through several electronic databases (MEDLINE, Cochrane CENTRAL, and HERDIN Plus), preprint servers (medRxiv and bioRxiv) and trial registries (ClinicalTrials.gov, WHO ICTRP, and ChiCTR) for studies investigating the accuracy of a 14-day symptom-based test in adults and children to screen for SARS-CoV-2 infection or COVID-19. Search terms included the following and their variations: influenza-like illness, influenza symptoms, COVID-19, SARS-CoV-2, monitoring, and surveillance and COVID-19 symptom checklist. We excluded studies that did

not specify a 14-day timeframe for symptoms, those involving hospital workers and studies with small sample sizes (n<30).

Results

Characteristics of included studies

Appendix 3 summarizes the characteristics of the three included studies. In this review update, one new study [4] was added to the two studies previously included.[2,3] Two studies [3,4] involved populations with possible or confirmed exposure to a confirmed COVID-19 case, while the remaining study included patients with unclear exposure history.[2] One study [4] reported diagnostic accuracy data specific to children. All three studies used RT-PCR with nasopharyngeal swab specimens as reference standard.[2-4] One study [3] used oropharyngeal swab (OPS) in addition to NPS while another study used anterior nares swabs.[4] All studies used symptoms found in COVID-19 and influenza-like illnesses, with varying case definitions or symptom criteria (i.e., WHO or CDC [2], CDC [3], or other [4]).

One cross-sectional study (n=8,214) in the United States evaluated the diagnostic performance of individual symptoms and various symptom combinations against a positive RT-PCR test[1].[2] Patients were 12 years or older who sought testing in statewide open-testing sites in Indiana, USA. All participants were screened for the presence of the following symptoms within the last 14 days using a standardized checklist: anosmia, ageusia, fever, chills, chest pain, vomiting, myalgia, cough, shortness of breath, sore throat, diarrhea, fatigue, headache, and runny nose. NPS specimens were collected by trained personnel using Dacron swabs during the same encounter as the symptom screening and were sent to laboratories in Indianapolis, IN. Blinding of those who interpreted the RT-PCR test was not specified. Of these, 4,772 (58%) participants were asymptomatic in the past two weeks. There were 368 (4.6%) individuals with a positive RT-PCR result and 91 (24.7%) were asymptomatic.

Another smaller cross-sectional study (n=76) investigated residents in a long-term skilled nursing facility in a Washington county where a COVID-19 outbreak occurred.[3] All consenting participants were screened for both typical (fever, cough, and shortness of breath) and atypical (malaise, nausea, sore throat, increased confusion, dizziness, diarrhea, rhinorrhea, myalgia, headache, and chills) symptoms of COVID-19 by records review and clinician interview. The study considered patients as asymptomatic if they had no symptoms and with only stable, chronic symptoms. The presence of at least one typical or atypical COVID-19 symptom was considered positive for the symptom-based test. NPS for all, and OPS for some participants were collected at the time of screening and sent for one-step real-time RT-PCR assay using the SARS-CoV-2 CDC assay protocol (Washington State Public Health Laboratory). A Ct value <40 cycles was the threshold for a positive result. Participants with positive RT-PCR test results and were asymptomatic at the time of testing were re-evaluated and assessed for any development of symptoms after one week. Those who developed new symptoms were re-categorized as pre-symptomatic. There were 53 residents (69.7%) considered as asymptomatic and 13 (24.5%) of them tested positive on RT-PCR. One week after testing, 10 of those 13 asymptomatic participants who had positive RT-PCR developed new symptoms while three remained asymptomatic. The most common symptoms that developed were fever, malaise, and cough.

A study done (n=185) in Wisconsin and Utah, United States assessed the diagnostic performance of existing case definitions of COVID-19 using symptoms reported from household

[1] Lilly Clinical Diagnostics Lab SARS-CoV-2 test, Luminexon NxTAG CoV Extended Panel or Roche cobas SARS-CoV-2 test, unspecified Ct value

contacts to a PCR-confirmed case of COVID-19.[4] Of the 185 (median age=22 yrs), 122 (66%) were adults and 63 (34%) were children. Among children, nine (14%) were less than 5 years, 19 (30%) were 5-9 years, and 35 (56%) were 10-17 years of age. Participants were assessed for the presence of COVID-19 symptoms by listing a symptom diary during the 14 days prior to enrollment and during 1-14 days after enrollment. NPS and anterior nares swabs were collected from participants on day 0 and day 14. An interim swab was also collected if any of the household contacts of participants had newly developed or had worsening symptoms of COVID-19. The study enrolled 199 household contacts of index patients with laboratory-confirmed SARS-CoV-2 infections.

Benefits and Harms of Screening

No studies that documented the effectiveness or harms of implementing a universal 14-day symptom-based screening strategy in reducing SARS-CoV2 transmission, mortality, or other patient-centered outcomes were found. These outcomes were also not evaluated in the three studies included in this review.

Diagnostic Accuracy

The sensitivity of the 14-day symptom-based test ranged from 2.2 to 100% while specificity ranged from 29 to 99.9%. Summary sensitivity and specificity estimates were not derived as studies had heterogeneous populations with variable exposure history, as well as varied index test characteristics (defining a “positive” test as either the presence of individual symptoms, symptom combinations, or fulfilment of a particular case definition/symptom criteria). These are briefly discussed in the following sections.

A. Individual symptoms

Two studies [2,4] reported the sensitivity and specificity of individual symptoms. Results differed between the two studies and may suggest that the diagnostic accuracy/performance of a 14-day symptom-based test differs when applied in populations with varying exposure history.

Nasal congestion/rhinorrhea, headache, and cough were the individual symptoms that had at least 70% sensitivity according to the study that involved adults and children with known exposure history to a COVID-19 case.[4] For children, accuracy was highest for headache (Sn 86%, Sp 80%) and nasal congestion or rhinorrhea (Sn 86%, Sp 63%), fever or chills (Sn 64%, Sp 86%), and sore throat (Sn 64%, Sp 86%).

Another study that involved patients above 12 years old with unknown exposure history reported different findings. All the individual symptoms exhibited a sensitivity of <50%, but high specificity (<90%).[2]

Table 1 shows the diagnostic accuracy of the top ten individual symptoms reported within 14 days for both adults and children.

Table 1. Diagnostic accuracy of the top ten individual symptoms reported within 14 days for both adults and children (2 studies)

Individual symptoms reported within 14 days	Dixon 2020 (> 12 y.o., unknown exposure history)		Reses 2021 (adult and children, household contacts exposed to a confirmed COVID-19 case)	
	Sn (%)	Sp (%)	Sn (%)	Sp (%)
Cough	47.60%	87.30%	74%	76%
Sore throat	24.50%	91.90%	55%	71%
Headache	39.10%	81.90%	86%	63%
Fever	35.10%	98.10%	63%	83%
Nasal congestion/rhinorrhea/runny nose	24.50%	85.30%	90%	49%
Myalgia	31.80%	92.60%	57%	85%
Shortness of breath	17.40%	94.20%	27%	92%
Anosmia	25.50%	98.90%	63%	96%
Aguesia	28.50%	98.70%		
Wheezing	-	-	10%	98%

B. Symptom combinations

Combining individual symptoms can increase the specificity to as high as 99.9%. However, it can also decrease its sensitivity.[2] The study by Kimball et al. [3] involving adults in nursing facility with possible exposure found low sensitivity but high specificity estimates with at least 1 typical (Sn 38.1%, Sp 81.6%) or 1 atypical COVID-19 symptom (Sn 13.3%, Sp 90.9%).

C. Case definitions

One study (n=185) compared the sensitivity and specificity of individual symptoms of different COVID-19 case definitions (e.g., US CDC COVID-19 like-illness, CDC symptom list, influenza-like illness, and WHO acute respiratory infection) and its combinations.[4] Existing case definitions used to classify COVID-19 showed sensitivity of 51 to 100% and specificity of 29 to 90%. The CDC symptom list showed the highest sensitivity (100%) but lowest specificity (21-45%) in both adults and children population, while influenza-like illness showed the highest specificity (86-96%) but lowest sensitivity (43-54%).

Table 2 shows the diagnostic accuracy of symptom combinations or case definitions reported within 14 days for both adults and children.

Certainty of evidence

The overall certainty of evidence for the diagnostic accuracy estimates was rated very low. Downgrading occurred due to risk of bias in two studies (patient selection, independence of index test interpretation), serious inconsistency, and serious imprecision.

Table 2. Diagnostic accuracy of symptom combinations or case definitions reported within 14 days for both adults and children (2 studies)

Symptom combinations	**Kimball 2020** [3] *(adults in nursing facility, with possible exposure to confirmed COVID-19 case)*		**Reses 2021** [HYPERLINK "https://forms.gle/UCm7gh4QdAXQ4Pdw6" *to a confirmed COVID-19 case)*	
	Sn (%)	**Sp (%)**	**Sn (%)**	**Sp (%)**
At least one typical COVID-19 symptoms (fever, cough, shortness of breath)	38.1%	81.6%	-	-
At least one atypical COVID-19 symptoms (chills, malaise, sore throat, confusion, rhinorrhea, nasal congestion, myalgia, dizziness, headache, nausea, diarrhea)	13.3%	90.9%	-	-
CDC symptom list[a]	-	-	100%	29%
WHO acute respiratory infection (ARI)[b]	-	-	96%	38%
U.S. CDC COVID-19-like illness (CLI)[c]	-	-	86%	68%
Influenza-like illness (ILI)[d]	-	-	51%	90%

[a]CDC symptom list include fever or chills, cough, shortness of breath or difficulty breathing, fatigue, muscle or body aches, headache, new loss of taste or smell, sore throat, congestion or runny nose, nausea or vomiting, diarrhea. Presence of at least 1 symptom may have COVID-19. This symptom list was last updated on 13 May 2020.
[b]World Health Organization (WHO) acute respiratory infection (ARI) definition for community-based respiratory syncytial virus (RSV) surveillance. At least one of the following: shortness of breath or cough, sore throat, or coryza. Last updated 04 February 2020.
[c]U.S. Centers for Disease Control and Prevention (CDC) COVID-19-like illness definition: fever AND/OR cough or shortness of breath. This definition was used to guide early diagnostic testing strategies from 17 January 2020 to 08 March 2020.
[d]Influenza-like-illness criteria include fever AND cough and/or sore throat

Evidence to Decision

The 14-day symptom-based test can be easily administered to anyone who needs to be screened for COVID-19 without spending any amount. There were no economic evaluation studies or other similar research evidence found on using a 14-day symptom testing strategy to screen for COVID-19 among adults and children.

Recommendations from Other Groups

Local societies forming the Healthcare Professionals Alliance Against COVID-19, including PSMID, PCCP, PCP, PSGIM and PCOOM, produced unified clinical decision algorithms that consider individuals without COVID-19 symptoms in the past 14 days as non-COVID-19 cases in November 2020.[6]

The WHO (2020 Dec 16) definition for suspected cases of SARS-CoV-2 infection includes the development of symptoms and meeting exposure criteria within 14 days before symptom onset.[5] The latest WHO Living Guidance (2021 Jan 25) recommends screening symptoms for all persons at the first point of contact with the health system (e.g., emergency unit, primary care clinic, community, telemedicine). A simple set of questions with symptoms including fever, cough, fatigue, anorexia, shortness of breath and other nonspecific symptoms should be used.[7]

The US Centers for Disease Control and Prevention (CDC, 2020 Oct 21) recommends SARS-CoV-2 diagnostic (molecular or antigen) testing in patients with symptoms of COVID-19. The CDC does not routinely recommend SARS-CoV-2 testing "if you do not have COVID-19 symptoms and have not been in close contact with someone known to have SARS-CoV-2 infection (meaning being within 6 feet of an infected person for at least 15 minutes)."[8]

Research Gaps

There are no ongoing trials specifically investigating the accuracy of the 14-day symptom-based test in detecting SARS-CoV-2 infection. However, it is suggested that the performance of symptom-based tests may increase if separate tests are developed for adults and children as symptoms or clinical manifestations of COVID-19 may differ between these two groups.[4]

References

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[9] Centers for Disease Control and Prevention. Overview of Testing for SARS-CoV-2 [Internet]. Vol. 2. 2021 [cited 2021 Feb 16]. Available from: https://www.cdc.gov/coronavirus/2019-ncov/hcp/testing-overview.html#print

Appendix 1. Evidence to Decision

Table 1. Summary of initial judgements prior to the panel discussion (N = 8)

FACTORS	JUDGEMENT					RESEARCH EVIDENCE/ADDITIONAL CONSIDERATIONS
Problem	No	Yes (8)				Understanding symptoms of COVID-19 in pre-clinical and community-based populations may assist in clinical screening and pandemic control.
Certainty of Evidence	High	Moderate (1)	Low (3)	Very low (4)		The overall certainty of evidence was rated as very low due to risk of bias in patient selection, inconsistency, and imprecision.
Accuracy	Very Accurate	Accurate (4)	Inaccurate (3)	Very Inaccurate	Uncertain (1)	This symptom-based test had a wide range of sensitivity (2.2 to 100%) and specificity (29-99%) in detecting COVID-19 among adults and children. Variability in accuracy appeared to be associated with heterogeneity in the populations tested and the characteristics of the index test.The diagnostic accuracy of individual symptoms appear to differ depending on the exposure history of the populations where the test is applied. For those with unclear exposure, individuals had excellent specificity (> 90%) but poor sensitivity (< 50%). For close contacts of confirmed COVID-19 cases, nasal congestion/rhinorrhea, headache, cough, sore throat, were the individual symptoms that had at least 70% sensitivity. For children, accuracy was highest for headache, nasal congestion or rhinorrhea, fever or chills, and sore throat. Combining individual symptoms can increase the specificity as high as 99.9% but with no substantial improvements in sensitivity. The CDC symptom list showed the

FACTORS	JUDGEMENT						RESEARCH EVIDENCE/ADDITIONAL CONSIDERATIONS
							highest sensitivity (100%) but lowest specificity (21-45%) in both adults and children population while Influenza-like illness showed the highest specificity (86-96%) but lowest sensitivity (43-54%).
Values	Important uncertainty or variability (1)	Possibly important uncertainty or variability (5)	Possibly NO important uncertainty or variability (2)	No important uncertainty or variability			No research evidence found
Resources Required	Uncertain (3)	Large cost	Moderate Cost (1)	Negligible cost (3)	Moderate savings	Large savings (1)	No research evidence found
Certainty of evidence of required resources	No included studies (6)	Very low	Low (2)	Moderate	High		No research evidence found
Cost effectiveness	No included studies (5)	Favors 14-day test (12)	Does not favor 14-day test or the comparator (1)	Favors comparator			No research evidence found
Equity	Uncertain (5)	Reduced	Probably no impact (1)	Increased (2)			No research evidence found
Acceptability	Uncertain (4)	No	Yes (4)				No research evidence found
Feasibility	Uncertain (3)	No	Yes (5)				No research evidence found

Appendix 2. Search Yield and Results

Database	Search Strategy / Search Terms	Date and Time of Search	Results	
			Yield	Eligible
MEDLINE	((influenza-like illness) OR (influenza symptoms)) AND (COVID-19) AND ((monitoring) OR (surveillance)) AND (COVID-19 symptom checklist)	10/13/21 09:05 PM	754	1
Cochrane	((COVID-19) OR (SARS-CoV-2)) AND ((influenza-like illness) OR (influenza symptoms))	09/29/21 12:13 PM	1 review 99 trials 1 editorial	0
medRxiv	((COVID-19) OR (SARS-CoV-2)) AND ((influenza-like illness) OR (influenza symptoms))	09/29/21 01:20 PM	136	0
bioRxiv	((COVID-19) OR (SARS-CoV-2)) AND ((influenza-like illness) OR (influenza symptoms))	09/29/21 01:51 PM	14	0
ClinicalTrials.gov	Condition: COVID-19 Other terms: influenza symptoms	09/29/21 01:57 PM	94	0
WHO ICTRP	((COVID-19) OR (SARS-CoV-2)) AND ((influenza-like illness) OR (influenza symptoms))	10/20/21 01:36 PM	14	0
ChiCTR	Target disease: COVID-19 Intervention: symptom	10/20/21 01:41 PM	12	0
HERDIN Plus	"COVID-19" OR "SARS-CoV-2" AND "influenza-like illness"	09/29/21 02:11 PM	18	0

Appendix 3. Characteristics of Included Studies

Characteristics	Dixon 2020	Kimball 2020	Reses 2021
Sample Size (N)	8,214	76	185
Population/ Setting	≥ 12 years old, exposure to confirmed case of COVID-19 unknown	Residents in a long-term skilled nursing facility in with a possible exposure to a confirmed case of COVID-19	Household contacts (adult or child) exposed to a PCR-confirmed case of COVID-19 (adult or child)
Index Test	Any symptom within 14 days on standardized symptom checklist (WHO or CDC)	Any typical (fever, cough, SOB) or atypical (malaise, nausea, sore throat, increased confusion, dizziness, diarrhea, rhinorrhea, myalgia, headache, chills) symptom within 14 days (CDC)	Individual COVID-19 symptoms Existing COVID-19 case definitions
Reference Standard	RT-PCR (NPS)	RT-PCR (NPS for all and OPS for some)	RT-PCR (NPS and anterior nares swabs)
Outcome	Diagnosis of SARS-CoV-2 infection	Diagnosis of SARS-CoV-2 infection	Diagnosis of SARS-CoV-2 infection
Time interval between 14-day symptom based test (index test) and RT-PCR test (reference standard)	Symptom screening and RT PCR test done on same day	On day of testing and preceding 14 days For those classified as pre-symptomatic, 1 week after testing	Testing done on day 0 and day 14 of enrollment; or interim if closed contact developed new symptoms or had worsening condition

Appendix 4. Study Appraisal

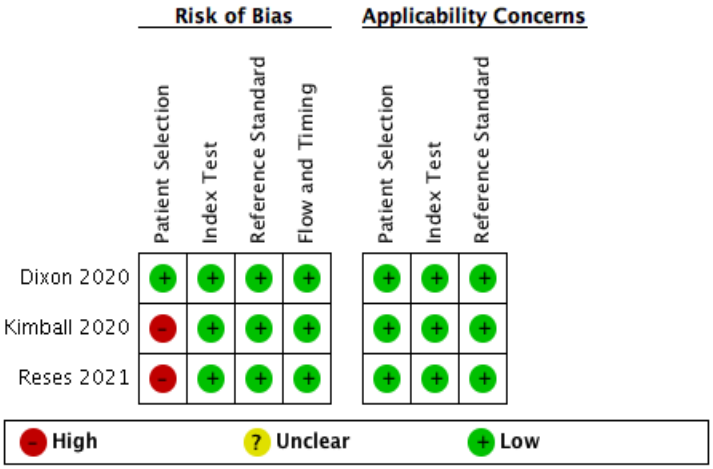

Figure 1. Summary of risk of bias and applicability concerns

Table 1. Study characteristics

Study characteristics	Dixon 2020 [2]	Kimball 2020 [3]	Reses 2021 [4]
Patient sampling	*Purpose:* To identify key symptoms and symptom combinations of COVID-19 in a community-based population *Design:* cross-sectional *Participant recruitment:* random and non-random sampling *Number of patients/samples:* 8214 *Inclusion criteria:* Indiana residents age 12 years old and above *Exclusion criteria:* not mentioned	*Purpose:* To evaluate the utility of symptom screening for identification of COVID-19 *Design:* cross-sectional *Participant recruitment:* convenience sampling *Number of patients/samples:* 76 *Inclusion criteria:* skilled nursing facility residents *Exclusion criteria:* not mentioned	*Purpose:* To assess the diagnostic performance of existing case definitions using symptoms reported from contacts to a PCR-confirmed case of COVID-19 *Design:* cross-sectional *Participant recruitment:* convenience sampling *Number of patients/samples:* 185 *Inclusion criteria:* household contacts of patients with laboratory confirmed SARS-CoV2 infection *Exclusion criteria:* contacts who was not living in the home on the day of enrollment, who was hospitalized at enrollment and who did not consent to have specimens collected; contacts that had negative RT-PCR and positive serology test results
Patient characteristics and setting	*Location:* Indiana *Dates:* end of April 2020 and beginning of June 2020 *Demographics:* 55.6% Females, 44.4% Males, 80.3% Whites, 19.7% Non-whites, 7.9% Hispanics, 92.1% Non-Hispanics *Exposure history:* unknown *Onset of symptoms:* not specified	*Location:* King County, Washington *Dates:* March 2020 *Demographics:* 63% female, 37% male *Exposure history:* with a possible exposure to a confirmed case of COVID-19 *Onset of symptoms:* not specified	*Location:* Utah, United States *Dates:* March 22 to April 22, 2020 *Demographics:* includes both adult and children *Exposure history:* yes *Onset of symptoms:* 10 days
Index tests	Any symptom within 14 days on standardized symptom checklist (WHO or CDC)	Any typical (fever, cough, SOB) or atypical (malaise, nausea, sore throat, increased confusion, dizziness, diarrhea, rhinorrhea, myalgia, headache, chills) symptom within 14 days (CDC)	Individual COVID-19 symptoms and existing COVID-19 case definitions
Reference standards	RT-PCR (NPS)	RT-PCR (NPS for all and OPS for some)	RT-PCR (NPS and anterior nares swabs)
Flow and timing	Symptom screening and RT PCR test done on same day	On day of testing and preceding 14 days For those classified as pre-symptomatic, 1 week after testing	Testing done on day 0 and day 14 of enrollment

Table 2. Detailed appraisal of studies

Methodological quality	Dixon 2020 [2]	Kimball 2020 [3]	Reses 2021 [4]

Item	Authors' judgment	Risk of bias	Applica-bility concerns	Authors' judgment	Risk of bias	Applica-bility concerns	Authors' judgment	Risk of bias	Applica-bility concerns
DOMAIN 1: Patient Selection									
Was a consecutive or random sample of patients enrolled?	Yes			No			No		
Was a case-control design avoided?	Yes			Yes			Yes		
Did the study avoid inappropriate exclusions?	Unclear			Unclear			Yes		
Could the selection of patients have introduced bias?		Low risk			High risk			High risk	
Are there concerns that the included patient and setting do not match the review question?			Low concern			Low concern			Low concern
DOMAIN 2: Index Test									
Were the index test results interpreted without knowledge of the reference standard?	Yes			Yes			Yes		
If a threshold was used, was it pre-specified?	Unclear			Unclear			Unclear		
Could the conduct or interpretation of the index test have introduced bias?		Low risk			Low risk			Low risk	
Are there concerns that the index test, its conduct, or interpretation differ from the review question?			Low concern			Low concern			Low concern
DOMAIN 3: Reference Standard									
Is the reference standards likely to correctly classify the target condition?	Yes			Yes			Yes		
Were the reference standard results interpreted without knowledge of the results of the index tests?	Yes			Yes			Yes		
Could the reference standard, its conduct, or its interpretation have introduced bias?		Low risk			Low risk			Low risk	
Are there concerns that the target condition as defined by the reference standard does not match the question?			Low concern			Low concern			Low concern
DOMAIN 4: Flow and TIming									
Was there an appropriate interval between index test and reference standard?	Unclear			Unclear			Unclear		
Did all patients receive the same reference standard?	Yes			Yes			Yes		
Were all patients included in the analysis?	Yes			No			No		
Could the patient flow have introduced bias?		Low risk			Low risk			Low risk	

Appendix 5. Study Results

Table 1. Results of Reses 2021 (adults and children) [4]

	Adults & Children		Adults		Children	
SYMPTOM COMBINATIONS	**Sn (%)**	**Sp (%)**	**Sn (%)**	**Sp (%)**	**Sn (%)**	**Sp (%)**
CDC symptom list	100%	29%	100%	21%	100%	45%
WHO acute respiratory infection	96%	38%	100%	29%	86%	55%
US CDC COVID-19 like illness	86%	68%	91%	61%	71%	82%
Influenza-like illness	51%	90%	54%	86%	43%	96%
INDIVIDUAL SYMPTOMS	**Sn (%)**	**Sp (%)**	**Sn (%)**	**Sp (%)**	**Sn (%)**	**Sp (%)**
Nasal congestion or rhinorrhea	90%	49%	91%	40%	86%	63%
Headache	86%	63%	86%	54%	86%	80%
Cough	74%	76%	86%	68%	43%	90%
Taste and/or smell dysfunction	63%	96%	71%	95%	43%	96%
Fever or chills	63%	83%	63%	82%	64%	86%
Fatigue	59%	69%	63%	59%	50%	88%
Myalgia	57%	85%	63%	79%	43%	96%
Sore throat	55%	71%	51%	61%	64%	88%
Diarrhea	37%	79%	40%	82%	29%	76%
Abdominal pain	31%	88%	37%	89%	14%	88%
Chest pain	29%	90%	34%	84%	14%	100%
Shortness of breath	27%	92%	29%	89%	21%	98%
Discomfort while breathing	25%	97%	29%	95%	14%	100%
Wheezing	10%	98%	11%	97%	7%	100%

Table 2. Results of Dixon 2021 (adults and children) [2]

INDIVIDUAL SYMPTOMS	**Sn (%)**	**Sp (%)**
Cough	47.60%	87.30%
Headache	39.10%	81.90%
Fever	35.10%	98.10%
Fatigue	34.50%	86.00%
Myalgia	31.80%	92.60%
Ageusia	28.50%	98.70%
Anosmia	25.50%	98.90%
Sore throat	24.50%	91.90%
Runny nose	24.50%	85.30%
Chills	22.00%	97.40%
Chest pain	17.70%	96.60%
Shortness of breath	17.40%	94.20%
Diarrhea	16.00%	93.70%
Vomiting	3.30%	99.30%
SYMPTOM COMBINATIONS	**SENSITIVITY (%)**	**SPECIFICITY (%)**
Fever & Ageusia	17.10%	99.70%
Fever & Anosmia	14.40%	99.70%
Cough & Fever & Ageusia	13.30%	99.80%
Fever & Headache & Ageusia	12.80%	99.70%
Fever & Ageusia & Myalgia	12.50%	99.80%
Fever & Anosmia & Ageusia	12.20%	99.80%
Fever & Headache & Anosmia	11.40%	99.80%
Fatigue & Fever & Ageusia	11.40%	99.80%
Cough & Fever & Anosmia	11.10%	99.80%
Fever & Anosmia & Myalgia	10.10%	99.80%
Fatigue & Fever & Anosmia	9.80%	99.80%
Chills & Fever & Ageusia	9.80%	99.80%
Chills & Fever & Anosmia	7.10%	99.90%
Diarrhea & Fever & Ageusia	6.20%	99.90%
Anosmia & Vomiting	2.20%	99.90%

Appendix 6. GRADE Evidence Profile

Should 14-day symptom-based test be used to diagnose COVID-19 in apparently healthy adults and children?

Pooled sensitivity: 0.02 to 1.00
Pooled specificity: 0.29 to 1.00

Outcomes	No of studies (patient)	Study design	Factors that may decrease certainty of evidence					Effect per 1,000 patients tested			Test Accuracy CoE
			Risk of bias	Indirectness	Inconsistency	Imprecision	Publication Bias	Pre-test probability of 5%	Pre-test probability of 10%	Pre-test probability of 20%	
True positives (patients with COVID-19)	3 studies 440 patients	cross-sectional (cohort type accuracy study)	serious[a]	not serious	serious[b]	serious[c]	none	1 to 50	2 to 100	4 to 200	⊕◯◯◯ Very Low
False negatives (patients incorrectly classified as not having COVID-19)								0 to 49	0 to 98	0 to 196	
True negatives (patients without COVID-19)	3 studies 7839 patients	cross-sectional (cohort type accuracy study)	serious[a]	not serious	serious[b]	serious[c]	none	275 to 949	261 to 899	232 to 799	⊕◯◯◯ Very Low
False positives (patients incorrectly classified as having COVID-19)								1 to 675	1 to 639	1 to 568	

Explanations
a. Downgraded due to possible bias in patient selection
b. Downgraded due to inability to determine independence of test performance
c. Downgraded due to wide confidence interval