EVIDENCE SUMMARY

RESEARCH QUESTION: **Among patients suspected to have COVID-19, should the 14-day symptom-based test be used in screening for COVID-19 infection?**

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RECOMMENDATIONS

Recommendations	Certainty of Evidence	Strength of Recommendation
We recommend the use of a 7-day symptom-based* test, instead of 14 days, to assess for possible COVID-19 infection among adults and children.** * Symptoms listed in the WHO Case Definition: acute onset of fever AND cough (ILI) OR acute onset of ANY THREE OR MORE of the following signs or symptoms: fever, cough, general weakness/fatigue, headache, myalgia, sore throat, coryza, dyspnea, nausea/diarrhea/anorexia ***Please refer to previous recommendation on testing using RTPCR and Rapid Antigen Tests*	Very low	Strong

Consensus Issues

The Panel considered feasibility, acceptability, cost-effectiveness, and practicality in determining the strength of this recommendation. While certainty of evidence is very low, the Panel decided a strong recommendation is warranted due to its beneficial impact to public health. Additionally, this recommendation was based focused on studies dealing with the Omicron variant. The Panel acknowledges that there may be a need to revisit recommendations when considering past and future COVID-19 variants.

KEY FINDINGS

- We found three observational studies, two of which included patients with and without COVID-19, presenting with and without the usual symptoms. Most of the symptoms showed a pooled sensitivity below 60%. Only cough had a sensitivity above 60%. The lowest sensitivities (10% and below) were seen with myalgia, shortness of breath, nausea/vomiting, diarrhea, and loss of smell or taste.
- Pooled specificity 60% and above was seen with fever, cough, fatigue, headache, myalgia, sore throat, runny nose/congestion, shortness of breath, nausea/vomiting, diarrhea and loss of smell or taste.
- Cough was the only symptom with both pooled sensitivity and pooled specificity above 60%.
- The third observational study compared the number of days spanned until resolution of symptoms in omicron-infected and delta-infected patients, and reported that the duration of acute symptoms was longer for delta (8.89 days; 95% CI 8.61-9.17) than omicron (6.87 days;

95%CI 6.58–7.16). This difference was statistically significant (MD 2.02 days lower with omicron, 95%CI 1.62 lower to 2.42 lower). This shorter period was even more marked in individuals who had received three doses of the vaccine.

WHAT'S NEW IN THIS VERSION

- This current update focuses on the use of the 14-day symptom-based test in the time of Omicron predominance, and includes evidence from studies 1) done in the time of Omicron predominance and 2) allowed the comparison with non-Omicron times.

PREVIOUS RECOMMENDATIONS
As of 29 November 2021

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 with 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.

INTRODUCTION

In the early months of the pandemic, the relative unavailability of widespread testing and immediate results called for other means to identify individuals who potentially had COVID-19. The recommendations from local and international groups regarding symptom-based screening were founded on the incubation period of the SARS-CoV-2 variants at the time. If a 14-day symptom check could identify sick persons, they could be isolated and their exposed contacts quarantined, possibly averting testing that requires healthcare resources.

Since then, the evolving face of the pandemic has seen the arrival of vaccines, the availability of various testing means, and the changes in predominant SARS-CoV-2 variants. The last review for this question, done in November 2021, synthesized the evidence from three cohort studies that included adult and pediatric populations before Omicron became the widely-circulating variant [1]. It reported a wide range of sensitivity (2.2-100%) and specificity (29-99%) of the 14-day symptom-based test in detecting COVID-19.

Our current update focuses on its use in this time of Omicron variant predominance, looking at the accuracy of the 14-day symptom-based test for screening and diagnosing COVID-19 in children and adults. We will also review the evidence to inform decisions for the duration of symptoms (i.e., 14 days versus other durations).

REVIEW METHODS

We performed a systematic search on April 18, 2023 using PubMed for MEDLINE, Cochrane CENTRAL, HERDIN Plus, the preprint servers MedRxiv and bioRxiv, as well as the trial registry ClinicalTrials.gov using the following search terms and synonyms: (("influenza-like illness") OR ("influenza-like symptoms") OR ("influenza symptoms") OR ("symptom-based")) AND (("COVID-19") OR ("COVID 19") OR ("COVID19") OR ("COVID 2019") OR ("COVID-2019")) AND ((diagnosis) OR (screening) OR (screen) OR (screenings) OR (screened)). We applied the filters of publication date, November 2021 (coinciding with the announcement of Omicron recognition) up to the present. We also conducted a free internet search using these same terms, and updated the search on May 9, 2023. Appendices 1 and 2 show the detailed search strategy and the yield from the databases, and the PRISMA Flow Diagram, respectively.

Relevant study data were extracted and risk of bias assessment was done using Newcastle Ottawa scale for cohort studies and for cross-sectional studies. RevMan was used to compute for the difference in mean duration till resolution of symptoms. Pooled sensitivity, pooled specificity and heterogeneity were generated using Meta-DiSc 2.0 (https://ciberisciii.shinyapps.io/MetaDiSc2/). The certainty of evidence was assessed using GRADE PRO.

RESULTS

Characteristics of included studies

This update includes a total of three observational studies that were 1) done in the time of Omicron predominance and 2) allowed the comparison with non-Omicron times. The summary is presented in Appendix 3. Two of the studies were cross-sectional in design [3,4] and one was a prospective longitudinal cohort [5]. Two studies included pediatric populations and one enrolled only adults. The given numbers from two studies allowed the calculation of individual, as well as pooled, sensitivity and specificity of distinct single symptoms compared to testing (which included one or a combination of polymerase chain reaction and antigen kit/rapid antigen test). The third study compared the mean duration till symptom resolution of omicron-infected and delta-infected patients.

Diagnostic accuracy

The study of Inaba et al. reported that the most common symptom identified in patients with COVID-19 was sore throat (67.3% of patients), followed by cough (62.0% of patients), and this was approximately twice as common in patients with COVID than those without [3]. Marquez et al. reported similar findings, in that the most common symptoms during the Omicron BA.1 period were cough (2044/3032 [67.4%]), sore throat (1316/3032 [43.4%]), congestion (1177/3032 [38.8%]), and headache (1075/3032 [35.5%]); whereas loss of smell or taste (160/3032 [5.3%]) and diarrhea (144/3032 [4.8%]) were least commonly reported [4].

Most of the symptoms showed a pooled sensitivity below 60%. Only cough had a sensitivity above 60%. The lowest sensitivities (10% and below) were seen with myalgia, shortness of breath, nausea/vomiting, diarrhea, and loss of smell or taste.

Pooled specificity 60% and above was seen with fever, cough, fatigue, headache, myalgia, sore throat, runny nose/congestion, shortness of breath, nausea/vomiting, diarrhea and loss of smell or taste.

Cough was the only symptom with both pooled sensitivity and pooled specificity above 60%.

Below is a summary of single symptom presentation and their individual and pooled sensitivity and specificity.

Table 1. Single symptom with individual and pooled sensitivity Sn) and specificity (Sp)

Symptom		Inaba et al.	Marquez et al.	Pooled estimate
Fever	Sn	59% (95%CI 54-64)	30% (95%CI 29-32)	44% (95%CI 26–64) i2 0.99
	Sp	54% ((95%CI 52-56)	86% (95%CI 84-87)	73% (95% CI 46-89) i2 0.99
Cough	Sn	62% (95%CI 57-67)	67% (95%CI 66-69)	66% (95% CI 62-69) i2 0.79
	Sp	70% (95%CI 68-72)	49% (95%CI 48-51)	60% (95%CI 45-73) i2 0.99
Fatigue	Sn	25% (95%CI 21-30)	20 (95%CI 18-21)	22% (95%CI 18-26 i2 0.85
	Sp	74% (95%CI 72-76)	83% (95%CI 82-84)	79% (95%CI 72-84) i2 0.99
Headache	Sn	37% (95%CI 32-42)	35% (95%CI 34-37)	36% (95%CI 34-37) i2 0
	Sp	65% (95%CI 63-67)	70% (95%CI 69-71)	68%(95%CI 64-71) i2 0.94
Myalgia	Sn	3% (95%CI 2-5)	29% (95%CI 27-30)	10% (95%CI 2-40)

				i2 0.98
	Sp	98% (95%CI 97-98)	93% (95%CI 75-99)	82% (95%CI 81-83 i2 0.99
Sore throat	Sn	67% (95%CI 63-72)	43% (95%CI 42-45)	55% (95%CI 39-71) i2 0.99
	Sp	62% (95%CI 60-64)	63% (95%CI 61-64)	62% (95%CI 61-64) i2 0
Runny nose/ congestion	Sn	33% (95%CI 29-38)	39% (95%CI 37-41)	37% (95%CI 33-41) i2 0.79
	Sp	67% (95%CI 65-69)	65% (95%CI 64-67)	66% (95%CI 65-67) i2 0.26
Shortness of breath	Sn	4% (95%CI 2-7)	8% (95%CI 7-9)	6% (95%CI 4-10) i2 0.86
	Sp	93% (95%CI 92-94)	94% (95%CI 93-94)	94% (95%CI 93-94) i2 0.14
Nausea/ vomiting	Sn	4% (95%CI 3-7)	5% (95%CI 4-6)	5% (95%CI 4-6) i2 0
	Sp	85% (95%CI 83-86)	94% (95%CI 94-95)	91% (95%CI 82-96) i2 0.99
Diarrhea	Sn	5% (95%CI 3-7)	5% (95%CI 4-6)	5% (95%CI 4-6) i2 0
	Sp	85% (95%CI 83-86)	95% (95%CI 94-95)	91% (95%CI 82-96)
Loss of smell or taste	Sn	3% (95%CI 1-5)	5% (95%CI 5-6)	4% (95%CI 3-7) i2 0.80
	Sp	97% (95%CI 97-98)	97% (95%CI 96-97)	97% (95%CI 97-98 i2 0.14

Duration of symptoms

Menni et al. compared data from patients who tested positive in the period of delta variant dominance in the UK (June 1 to Nov 27, 2021) and those who did when the omicron variant was widely circulating (Dec 20, 2021, to Jan 17, 2022, prevalence >70%) [5]. Participants were matched as to age, sex and vaccination doses. Comparing 1530 matched patients in each of the groups, the investigators reported that regarding the number of days spanned until resolution of acute symptoms, the duration of acute symptoms was longer for delta than omicron overall (delta mean duration 8.89 days, 95% CI 8.61–9.17 versus omicron mean duration 6.87 days, 95%CI 6.58–7.16. This difference was statistically significant (MD 2.02 days lower with omicron, 95%CI 1.62 lower to 2.42 lower).

This shorter period was even more marked in individuals who had received three doses of the vaccine (delta mean duration 7.71 days, 95%CI 7.26–8.15 versus omicron mean duration 4.40 days, 95%CI 3.98 –4.82).

Certainty of evidence

The overall certainty of evidence was judged to be very low because of serious risk of bias, very serious inconsistency and serious imprecision.

RECOMMENDATIONS FROM OTHER GROUPS

In July 2022, the WHO definition for suspected cases of SARS-CoV-2 infection named specific symptoms. These include (a) development of acute onset of fever and cough or (b) acute onset of any three or more of the following: fever, cough, general weakness/fatigue, headache, myalgia, sore throat, coryza, dyspnea, nausea/diarrhea/anorexia, or (c) severe acute respiratory illness with onset within the last 10 days. No time interval of development of symptoms was specified for symptoms not part of the severe acute respiratory illness definition [6].

The WHO Living Guidance in September 2022 recommended screening symptoms for all persons at the first point of contact with the health system (e.g., emergency unit, primary care clinic, community, telemedicine) using a simple set of questions. The guideline lists the following symptoms associated with COVID-19: fever, cough, fatigue, anorexia, shortness of breath and other nonspecific symptoms (i.e., sore throat, nasal congestion, headache, diarrhea, nausea and vomiting), anosmia, ageusia, and other neurologic manifestations (i.e., dizziness, agitation, weakness, seizures, or findings suggestive of stroke) [7].

The US Centers for Disease Control and Prevention as of September 2022 recommends SARS-CoV-2 diagnostic (molecular or antigen) testing immediately in patients with symptoms of COVID-19 [10]. CDC lists the following possible symptoms of COVID-19: fever or chills, cough, shortness of breath or difficulty of breathing, fatigue, muscle or body aches, headache, new loss of taste or smell, sore throat, congestion or runny nose, nausea or vomiting, diarrhea. These may change with new COVID-19 variants and can vary depending on vaccination status [8].

ONGOING STUDIES AND RESEARCH GAPS

We found no ongoing studies investigating the 14-day symptom-based test for screening and diagnosis of COVID-19.

ADDITIONAL CONSIDERATIONS FOR EVIDENCE TO DECISION (ETD) PHASE

We found no studies that evaluated the cost of the 14-day symptom-based test in relation to other testing.

As to acceptability by patients,Liu et al.(2022) investigated patient experience and gathered feedback after patients they were made to use an Electronic Health Record–Integrated COVID-19 Symptom Checker [9]. Overall, the respondents across all demographics reported high satisfaction, giving with a median rating of 8 out of 10. Almost half of the respondents gave a rating of 9 or 10 out of 10

REFERENCES

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APPENDICES

Appendix 1: Preliminary Evidence to Decision

Table 1. Summary of initial judgements prior to the panel discussion (N=6/9)

FACTORS	JUDGEMENT												RESEARCH EVIDENCE/ADDITIONAL CONSIDERATIONS
Problem	No	Yes (N=6)	Varies		Uncertain								The 14-day symptom-based test was used early in the pandemic when testing was not widely available. Since then, the world has seen the arrival of vaccines, the availability of various testing means, and the changes in predominant SARS-CoV 2 variants. The current update seeks to synthesize the evidence for the use of the 14-day symptom-based test in this time of Omicron variant predominance, and to review the evidence to inform decisions for the duration of symptoms (i.e., 14 days versus other durations).
Benefits	Large	Moderate (N=3)	Small	Trivial	Varies	Uncertain (N=3)							No studies found
Harms	Large	Moderate (N=1)	Small (N=1)	Trivial (N=1)	Varies	Uncertain (N=3)							No studies were found discussing harms of the 14-day symptom-based test.
Balance of Benefits and Harms	Favors diagnostic/ treatment (N=1)	Probably favors diagnostic/treatment	Does not favor diagnostic/treatment or no diagnostic/treatment (N=1)	Probably favors no diagnostic/treatment (N=1)	Favors no diagnostic/treatment	Varies	Don't know (N=1)						No studies found

		(N=3)						
Certainty of Evidence	No included studies	Very low (N=3)	Low (N=3)	Moderate	High			For the diagnostic accuracy of individual symptoms, certainty of evidence was Very Low (because of serious risk of bias, very serious inconsistency, and serious imprecision). For the duration of symptom check: Low
Accuracy	Very Accurate	Accurate	Inaccurate	Very Inaccurate	Varies (N=4)	Don't Know		
Values	Important uncertainty or variability (N=1)	Possibly important uncertainty or variability (N=2)	Possibly NO important uncertainty or variability (N=2)	No important uncertainty or variability				No studies found
Resources Required	Don't Know	Varies (N=1)	Large costs	Moderate costs (N=1)	Negligible costs or savings (N=1)	Moderate savings (N=1)	Large savings (N=2)	Others: Undecided (N=1)	No studies found
Certainty of evidence of required resources	No included studies (N=3)	Very low (N=1)	Low (N=1)	Moderate		Others: Undecided (N=1)			No research evidence

Cost effectiveness	No included studies (N=1)	Favors the comparator	Probably favors the comparator (N=2)	Does not favor either the intervention or the comparator	Probably favors the intervention (N=2)	Favors the intervention	Varies	Others: Undecided (N=1)	No studies found
Equity	Uncertain	Varies	Reduced	Probably reduced (N=1)	Probably No Impact (N=1)	Probably Increased (N=4)	Increased		No research evidence was found
Acceptability	Don't Know	Varies (N=1)	No		Probably no	Probably yes (N=5)	Yes		Liu et al.9 (2022) investigated patient experience and gathered feedback after patients they were made to use an Electronic Health Record–Integrated COVID-19 Symptom Checker. Overall, the respondents across all demographics reported high satisfaction, giving with a median rating of 8 out of 10. Almost half of the respondents gave a rating of 9 or 10 out of 10.
Feasibility	Don't Know	Varies (N=1)	No		Probably no	Probably yes (N=1)	Yes (N=4)		No studies found

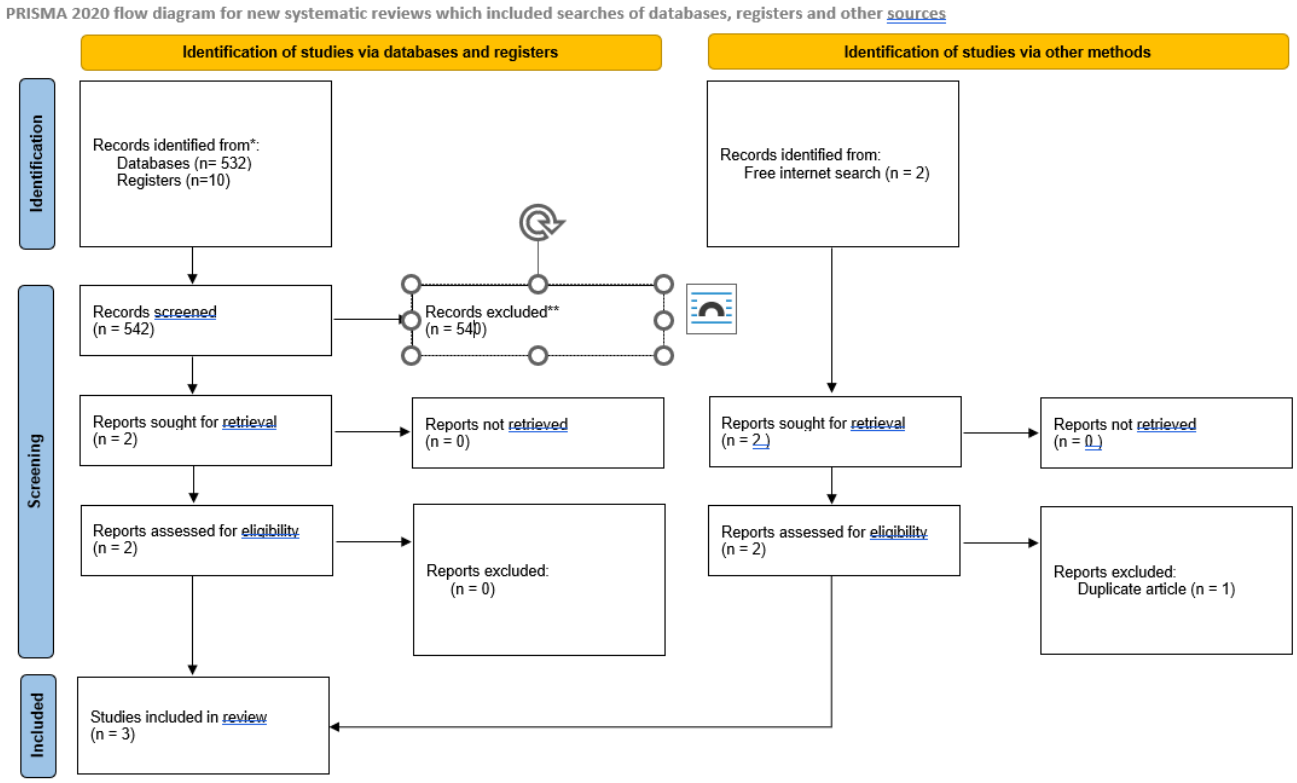
Appendix 2. Search strategy

Step	Query	Results
1	"COVID-19"[tw] OR "COVID 19"[tw] OR "COVID19"[tw] OR "COVID2019"[tw] OR "COVID 2019"[tw] OR "COVID-2019"[tw] OR "novel coronavirus"[tw] OR "new coronavirus"[tw] OR "novel corona virus"[tw] OR "new corona virus"[tw] OR "SARS-CoV-2"[tw] OR "SARSCoV2"[tw] OR "SARS-CoV2"[tw] OR "2019nCoV"[tw] OR "2019-nCoV"[tw] OR "2019 coronavirus"[tw] OR "2019 corona virus"[tw] OR "coronavirus disease 2019"[tw] OR "severe acute respiratory syndrome coronavirus 2"[nm] OR "severe acute respiratory syndrome coronavirus 2"[tw] OR "sars-coronavirus-2"[tw] OR "coronavirus disease 2019"[tw] OR "COVID-19"[Mesh] OR "corona virus disease 2019"[tw]	352,875
2	"symptom-based"[All Fields]	2,270
3	"influenza-like illness"[All Fields] OR "influenza-like symptoms"[All Fields] OR "influenza symptoms"	4,493
4	#2 OR #3	6,755
5	"diagnosis" [Subheading]	4,123,245
6	"diagnosis"[All Fields]	4,166,155
7	"screening"[All Fields] OR "screen"[All Fields] OR "screenings"[All Fields] OR "screened"[All Fields] OR "screens"[All Fields]	1,048,345
8	"mass screening"[MeSH Terms]	143,465
9	"mass"[All Fields] AND "screening"[All Fields]	163,478
10	"mass screening"[All Fields]	118,993
11	#5 OR #6 OR #7 OR #8 OR #9	5,874,284
12	#1 AND #4 AND #11	234

Database	Search Strategy / Search Terms	Results	
		Yield	Eligible
MEDLINE	((influenza-like illness) OR (influenza symptoms)) AND (COVID-19) AND ((monitoring) OR (surveillance)) AND (COVID-19 symptom checklist)	234	2
CENTRAL	((COVID-19) OR (SARS-CoV-2)) AND ((influenza-like illness) OR (influenza symptoms))	23	0
medRxiv and bioRxiv	((COVID-19) OR (SARS-CoV-2)) AND ((influenza-like illness) OR (influenza symptoms))	163	0
ClinicalTrials.gov	Condition: COVID-19 Other terms: influenza symptoms, symptom-based test	10	0

HERDIN Plus	"COVID-19" OR "SARS-CoV-2" AND "influenza-like illness" OR “symptom-based test”	112	0
Free internet search	“symptom-based test for COVID-19;” “14-day symptom check”		2

Appendix 3 : PRISMA Flow Diagram of Literature Search



Appendix 4. Characteristics of Included Studies

	Population	Index Test	Comparator	Outcomes (Reported by study or generated for this review
Inaba et al. Japan March 2023	COVID-19 (+) and (-) patients who visited outpatient fever clinic and tested for COVID-19 from 4/2021 to 5/2022 (n=2579; 87% in Omicron time)	Individual symptoms	PCR and/or antigen kit, using nasopharyngeal swabs	Sensitivity Specificity
Marquez et al. October 2022	Children and adults seeking testing for RAT in a clinic in San Francisco, USA from 1/2021 to 1/2022 (n=7283 from Omicron time)	Individual symptoms	Rapid antigen test (Binax Now) on bilateral anterior nares	Sensitivity Specificity
Menni et al. UK April 2022	Participants 16–99 years with a body-mass index between 15 and 55 kg/m2, who had at least two doses of any SARS-CoV-2 vaccine, were symptomatic, and logged a positive symptomatic PCR or lateral flow antigen test (LFAT) for SARS-CoV-2 between June 1, 2021, and Jan 17, 2022 Use of the ZOE Covid App; self-reports	Omicron predominance	Delta predominance	Likelihood of developing a given symptom (from the 32 monitored in the app) within 7 days before or after the positive LFAT or PCR Symptom duration

Appendix 5. Critical Appraisal of Included Studies

Assessment of quality of a cohort study – Newcastle Ottawa Scale

Menni C, Valdes AM, Polidori L, Antonelli M, Penamakuri S, Nogal A, et al. Symptom prevalence, duration, and risk of hospital admission in individuals infected with SARS-CoV-2 during periods of omicron and delta variant dominance: a prospective observational study from the ZOE COVID Study. The Lancet [Internet]. 2022 Apr 7;399(10335). Available from: https://www.sciencedirect.com/science/article/pii/S0140673622003270

Selection (tick one box in each section)/appraisal feature highlighted		
1. Representativeness of the intervention cohort		
a) truly representative of the average, elderly, community-dwelling resident	★	☒
b) somewhat representative of the average, elderly, community-dwelling resident	★	☐
c) selected group of patients, e.g. only certain socio-economic groups/areas		☐
d) no description of the derivation of the cohort		☐
2. Selection of the non intervention cohort		
a) drawn from the same community as the intervention cohort	★	☒
b) drawn from a different source		☐
c) no description of the derivation of the non intervention cohort		☐
3. Ascertainment of intervention		
a) secure record (eg health care record)	★	☐
b) structured interview	★	☒
c) written self report		☐
d) other / no description		☐
4. Demonstration that outcome of interest was not present at start of study		
a) yes	★	☐
b) no		☒
Comparability (tick one or both boxes, as appropriate)		
1. Comparability of cohorts on the basis of the design or analysis		
a) study controls for age, sex, marital status	★	☒
b) study controls for any additional factors (e.g. socio-economic status, education)	★	☒
Outcome (tick one box in each section)		
1. Assessment of outcome		
a) independent blind assessment	★	☐
b) record linkage	★	☒
c) self report		☐
d) other / no description		☐
2. Was follow up long enough for outcomes to occur		
a) yes, if median duration of follow-up >= 6 month	★	☐
b) no, if median duration of follow-up < 6 months		☒
3. Adequacy of follow up of cohorts		
a) complete follow up: all subjects accounted for	★	☐
b) subjects lost to follow up unlikely to introduce bias: number lost <= 20%, or description of those lost suggesting no different from those followed	★	☒
c) follow up rate < 80% (select an adequate %) and no description of those lost		☐
d) no statement		☐

Appendix 6. GRADE Evidence Profile

For single symptom check

Fever

Question: Should the 14-day symptom-based test (FEVER) be used to diagnose COVID-19 in adults and children?

Sensitivity	0.44 (95% CI: 0.26 to 0.64)
Specificity	0.73 (95% CI: 0.46 to 0.89)

Prevalences	2%	3.5%	5%

Outcome	№ of studies (№ of patients)	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 of2%	pre-test probability of3.5%	pre-test probability of5%	
True positives (patients with COVID-19)	2 studies 3429 patients	cross-sectional (cohort type accuracy study)	serious[a]	not serious	very serious[b]	serious[c]	none	9 (5 to 13)	15 (9 to 22)	22 (13 to 32)	⨁◯◯◯ Very low
False negatives (patients incorrectly classified as not having COVID-19)								11 (7 to 15)	20 (13 to 26)	28 (18 to 37)	
True negatives (patients without COVID-19)	2 studies 6412 patients	cross-sectional (cohort type accuracy study)	serious[a]	not serious	very serious[d]	serious[c]	none	715 (451 to 872)	704 (444 to 859)	694 (437 to 845)	⨁◯◯◯ Very low
False positives (patients incorrectly classified as having COVID-19)								265 (108 to 529)	261 (106 to 521)	256 (105 to 513)	

Explanations

a. Variable methods of ascertainment/reference standard (rapid antigen test in one, RT-PCR and/or antigen kit in the other
b. Very high i2 for sensitivity

Cough

Question: Should 14-day symptom check (COUGH) be used to diagnose COVID-19 in adults and children?

Sensitivity	0.66 (95% CI: 0.62 to 0.69)
Specificity	0.60 (95% CI: 0.45 to 0.73)

Prevalences	2%	3.5%	5%

Outcome	№ of studies (№ of patients)	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 of2%	pre-test probability of3.5%	pre-test probability of5%	
True positives (patients with COVID-19)	2 studies 3442 patients	cross-sectional (cohort type accuracy study)	serious[a]	not serious	very serious[b]	not serious	none	13 (12 to 14)	23 (22 to 24)	33 (31 to 34)	⨁◯◯◯ Very low
False negatives (patients incorrectly classified as not having COVID-19)								7 (6 to 8)	12 (11 to 13)	17 (16 to 19)	
True negatives (patients without COVID-19)	2 studies 6420 patients	cross-sectional (cohort type accuracy study)	serious[a]	not serious	very serious[c]	serious[d]	none	588 (441 to 715)	579 (434 to 704)	570 (428 to 694)	⨁◯◯◯ Very low
False positives (patients incorrectly classified as having COVID-19)								392 (265 to 539)	386 (261 to 531)	380 (256 to 522)	

Explanations

a. Variable methods of ascertainment/reference standard (rapid antigen test in one, RT-PCR and/or antigen kit in the other
b. Very high i2 for sensitivity
c. Very high i2 for specificity
d. Wide confidence interval

Fatigue

Question: Should 14-day symptom check (FATIGUE) be used to diagnose COVID-19 in adults and children?

Sensitivity	0.22 (95% CI: 0.18 to 0.26)
Specificity	0.79 (95% CI: 0.72 to 0.84)

Prevalences	2%	3.5%	5%

Outcome	№ of studies (№ of patients)	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 of2%	pre-test probability of3.5%	pre-test probability of5%	
True positives (patients with COVID-19)	2 studies 3442 patients	cross-sectional (cohort type accuracy study)	serious[a]	not serious	very serious[b]	not serious	none	4 (4 to 5)	8 (6 to 9)	11 (9 to 13)	⨁◯◯◯ Very low
False negatives (patients incorrectly classified as not having COVID-19)								16 (15 to 16)	27 (26 to 29)	39 (37 to 41)	
True negatives (patients without COVID-19)	2 studies 6420 patients	cross-sectional (cohort type accuracy study)	serious[a]	not serious	very serious[c]	not serious	none	774 (706 to 823)	762 (695 to 811)	751 (684 to 798)	⨁◯◯◯ Very low
False positives (patients incorrectly classified as having COVID-19)								206 (157 to 274)	203 (154 to 270)	199 (152 to 266)	

Explanations

a. Variable methods of ascertainment/reference standard (rapid antigen test in one, RT-PCR and/or antigen kit in the other
b. Very high i2 for sensitivity
c. Very high i2 for specificity

Headache

Question: Should 14-day symptom check (HEADACHE) be used to diagnose COVID-19 in adults and children?

Sensitivity	0.36 (95% CI: 0.34 to 0.37)
Specificity	0.68 (95% CI: 0.64 to 0.71)

Prevalences	2%	3.5%	5%

Outcome	№ of studies (№ of patients)	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 of2%	pre-test probability of3.5%	pre-test probability of5%	
True positives (patients with COVID-19)	2 studies 3442 patients	cross-sectional (cohort type accuracy study)	serious[a]	not serious	not serious	not serious	none	7 (7 to 7)	13 (12 to 13)	18 (17 to 19)	⊕⊕⊕◯ Moderate
False negatives (patients incorrectly classified as not having COVID-19)								13 (13 to 13)	22 (22 to 23)	32 (31 to 33)	
True negatives (patients without COVID-19)	2 studies 6420 patients	cross-sectional (cohort type accuracy study)	serious[a]	not serious	very serious[b]	not serious	none	666 (627 to 696)	656 (618 to 685)	646 (608 to 675)	⊕◯◯◯ Very low
False positives (patients incorrectly classified as having COVID-19)								314 (284 to 353)	309 (280 to 347)	304 (275 to 342)	

Explanations

a. Variable methods of ascertainment/reference standard (rapid antigen test in one, RT-PCR and/or antigen kit in the other
b. Very high i2 for specificity

Myalgia

Question: Should 14-day symptom check (MYALGIA) be used to diagnose COVID-19 in adults and children?

Sensitivity	0.10 (95% CI: 0.02 to 0.40)
Specificity	0.93 (95% CI: 0.75 to 0.99)

Prevalences	2%	3.5%	5%

Outcome	№ of studies (№ of patients)	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 of2%	pre-test probability of3.5%	pre-test probability of5%	
True positives (patients with COVID-19)	2 studies 3442 patients	cross-sectional (cohort type accuracy study)	serious[a]	not serious	very serious[b]	serious[c]	none	2 (0 to 8)	4 (1 to 14)	5 (1 to 20)	⨁◯◯◯ Very low
False negatives (patients incorrectly classified as not having COVID-19)								18 (12 to 20)	31 (21 to 34)	45 (30 to 49)	
True negatives (patients without COVID-19)	2 studies 6420 patients	cross-sectional (cohort type accuracy study)	serious[a]	not serious	very serious[d]	serious[c]	none	911 (735 to 970)	897 (724 to 955)	884 (712 to 941)	⨁◯◯◯ Very low
False positives (patients incorrectly classified as having COVID-19)								69 (10 to 245)	68 (10 to 241)	66 (9 to 238)	

Explanations

a. Variable methods of ascertainment/reference standard (rapid antigen test in one, RT-PCR and/or antigen kit in the other
b. Very high i2 for sensitivity
c. Wide confidence interval
d. Very high i2 for specificity

Sore throat

Question: Should 14-day symptom-based test (SORE THROAT) be used to diagnose COVID-19 in adults and children?

Sensitivity	0.55 (95% CI: 0.39 to 0.71)
Specificity	0.62 (95% CI: 0.61 to 0.64)

Prevalences	2%	3.5%	5%

Outcome	№ of studies (№ of patients)	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 of2%	pre-test probability of3.5%	pre-test probability of5%	
True positives (patients with COVID-19)	2 studies 3442 patients	cross-sectional (cohort type accuracy study)	serious[a]	not serious	very serious[b]	serious[c]	none	11 (8 to 14)	19 (14 to 25)	28 (20 to 36)	⨁◯◯◯ Very low
False negatives (patients incorrectly classified as not having COVID-19)								9 (6 to 12)	16 (10 to 21)	22 (14 to 30)	
True negatives (patients without COVID-19)	2 studies 6420 patients	cross-sectional (cohort type accuracy study)	serious[a]	not serious	not serious	not serious	none	608 (598 to 627)	598 (589 to 618)	589 (580 to 608)	⨁⨁⨁◯ Moderate
False positives (patients incorrectly classified as having COVID-19)								372 (353 to 382)	367 (347 to 376)	361 (342 to 370)	

Explanations

a. Variable methods of ascertainment/reference standard (rapid antigen test in one, RT-PCR and/or antigen kit in the other
b. Very high i2 for sensitivity
c. Wide confidence interval

Runny nose/congestion

Question: Should the 14-day symptom-based test (RUNNY NOSE/CONGESTION) be used to diagnose COVID-19 in adults and children?

Sensitivity	0.37 (95% CI: 0.33 to 0.41)
Specificity	0.66 (95% CI: 0.65 to 0.67)

Prevalences	2%	3.5%	5%

Outcome	№ of studies (№ of patients)	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 of2%	pre-test probability of3.5%	pre-test probability of5%	
True positives (patients with COVID-19)	2 studies 3442 patients	cross-sectional (cohort type accuracy study)	serious[a]	not serious	serious[b]	not serious	none	7 (7 to 8)	13 (12 to 14)	19 (17 to 21)	⨁⨁◯◯ Low
False negatives (patients incorrectly classified as not having COVID-19)								13 (12 to 13)	22 (21 to 23)	31 (29 to 33)	
True negatives (patients without COVID-19)	2 studies 6420 patients	cross-sectional (cohort type accuracy study)	serious[a]	not serious	serious[c]	not serious	none	647 (637 to 657)	637 (627 to 647)	627 (617 to 637)	⨁⨁◯◯ Low
False positives (patients incorrectly classified as having COVID-19)								333 (323 to 343)	328 (318 to 338)	323 (313 to 333)	

Explanations

a. Variable methods of ascertainment/reference standard (rapid antigen test in one, RT-PCR and/or antigen kit in the other
b. High i2 for sensitivity
c. High i2 for specificity

Shortness of breath

Question: Should the 14-day symptom-based test (SHORTNESS OF BREATH) be used to diagnose COVID-19 in adults and children?

Sensitivity	0.36 (95% CI: 0.34 to 0.37)
Specificity	0.68 (95% CI: 0.64 to 0.71)

Prevalences	2%	3.5%	5%

Outcome	№ of studies (№ of patients)	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 of2%	pre-test probability of3.5%	pre-test probability of5%	
True positives (patients with COVID-19)	2 studies 3442 patients	cross-sectional (cohort type accuracy study)	serious[a]	not serious	serious[b]	not serious	none	7 (7 to 7)	13 (12 to 13)	18 (17 to 19)	⨁⨁◯◯ Low
False negatives (patients incorrectly classified as not having COVID-19)								13 (13 to 13)	22 (22 to 23)	32 (31 to 33)	
True negatives (patients without COVID-19)	2 studies 6420 patients	cross-sectional (cohort type accuracy study)	serious[a]	not serious	not serious	not serious	none	666 (627 to 696)	656 (618 to 685)	646 (608 to 675)	⨁⨁⨁◯ Moderate
False positives (patients incorrectly classified as having COVID-19)								314 (284 to 353)	309 (280 to 347)	304 (275 to 342)	

Explanations

a. Variable methods of ascertainment/reference standard (rapid antigen test in one, RT-PCR and/or antigen kit in the other
b. High i2 for sensitivity

Nausea/vomiting

Question: Should the 14-day symptom-based test (NAUSEA/VOMITING) be used to diagnose COVID-19 in adults and children?

Sensitivity	0.05 (95% CI: 0.04 to 0.06)
Specificity	0.91 (95% CI: 0.82 to 0.96)

Prevalences	2%	3.5%	5%

Outcome	№ of studies (№ of patients)	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 of2%	pre-test probability of3.5%	pre-test probability of5%	
True positives (patients with COVID-19)	2 studies 3442 patients	cross-sectional (cohort type accuracy study)	serious[a]	not serious	not serious	not serious	none	1 (1 to 1)	2 (1 to 2)	3 (2 to 3)	⊕⊕⊕◯ Moderate
False negatives (patients incorrectly classified as not having COVID-19)								19 (19 to 19)	33 (33 to 34)	47 (47 to 48)	
True negatives (patients without COVID-19)	2 studies 6420 patients	cross-sectional (cohort type accuracy study)	serious[a]	not serious	serious[b]	not serious	none	892 (804 to 941)	878 (791 to 926)	864 (779 to 912)	⊕⊕◯◯ Low
False positives (patients incorrectly classified as having COVID-19)								88 (39 to 176)	87 (39 to 174)	86 (38 to 171)	

Explanations

a. Variable methods of ascertainment/reference standard (rapid antigen test in one, RT-PCR and/or antigen kit in the other
b. Very high i2 for specificity

Diarrhea

Question: Should the 14-day symptom-based test (DIARRHEA) be used to diagnose COVID-19 in adults and children?

Sensitivity	0.05 (95% CI: 0.04 to 0.06)
Specificity	0.91 (95% CI: 0.82 to 0.96)

Prevalences	2%	3.5%	5%

Outcome	№ of studies (№ of patients)	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 of2%	pre-test probability of3.5%	pre-test probability of5%	
True positives (patients with COVID-19)	2 studies 3442 patients	cross-sectional (cohort type accuracy study)	serious[a]	not serious	not serious	not serious	none	1 (1 to 1)	2 (1 to 2)	3 (2 to 3)	⨁⨁⨁◯ Moderate
False negatives (patients incorrectly classified as not having COVID-19)								19 (19 to 19)	33 (33 to 34)	47 (47 to 48)	
True negatives (patients without COVID-19)	2 studies 6420 patients	cross-sectional (cohort type accuracy study)	serious[a]	not serious	very serious[b]	not serious	none	892 (804 to 941)	878 (791 to 926)	864 (779 to 912)	⨁◯◯◯ Very low
False positives (patients incorrectly classified as having COVID-19)								88 (39 to 176)	87 (39 to 174)	86 (38 to 171)	

Explanations

a. Variable methods of ascertainment/reference standard (rapid antigen test in one, RT-PCR and/or antigen kit in the other
b. Very high i2 for specificity

Loss of smell or taste

Question: Should the 14-day symptom-based test (LOSS OF SMELL OR TASTE) be used to diagnose COVID-19 in adults and children?

Sensitivity	0.04 (95% CI: 0.03 to 0.07)
Specificity	0.97 (95% CI: 0.97 to 0.98)

Prevalences	2%	3.5%	5%

Outcome	№ of studies (№ of patients)	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 of2%	pre-test probability of3.5%	pre-test probability of5%	
True positives (patients with COVID-19)	2 studies 3442 patients	cross-sectional (cohort type accuracy study)	serious[a]	not serious	serious[b]	not serious	none	1 (1 to 1)	1 (1 to 2)	2 (2 to 4)	⨁⨁◯◯ Low
False negatives (patients incorrectly classified as not having COVID-19)								19 (19 to 19)	34 (33 to 34)	48 (46 to 48)	
True negatives (patients without COVID-19)	2 studies 6420 patients	cross-sectional (cohort type accuracy study)	serious[a]	not serious	not serious	not serious	none	951 (951 to 960)	936 (936 to 946)	922 (922 to 931)	⨁⨁⨁◯ Moderate
False positives (patients incorrectly classified as having COVID-19)								29 (20 to 29)	29 (19 to 29)	28 (19 to 28)	

Explanations

a. Variable methods of ascertainment/reference standard (rapid antigen test in one, RT-PCR and/or antigen kit in the other
b. High i2 for sensitivity

For duration of symptom check

Author(s): Maria Teresa S. Tolosa, MD, D Clin Epi
Question: Should the 14-day symptom-based test be used to screen for COVID-19 in adults and children?
Setting:
Bibliography: Menni C, Valdes AM, Polidori L, Antonelli M, Penamakuri S, Nogal A, et al. Symptom prevalence, duration, and risk of hospital admission in individuals infected with SARS-CoV-2 during periods of omicron and delta variant dominance: a prospective observational study from the ZOE COVID Study. The Lancet [Internet]. 2022 Apr 7;399(10335). Available from: https://www.sciencedirect.com/science/article/pii/S0140673622003270

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations			Relative (95% CI)	Absolute (95% CI)		
Mean duration to resolution of symptoms, omicron versus delta (follow-up: mean 21 days)												
1	observational study (3060 participants)	serious[a]	not serious	serious[b]	not serious	none	1530	1530	-	MD **2.02 days lower** (1.62 lower to 2.42 lower)	⨁⨁◯◯ Low	CRITICAL

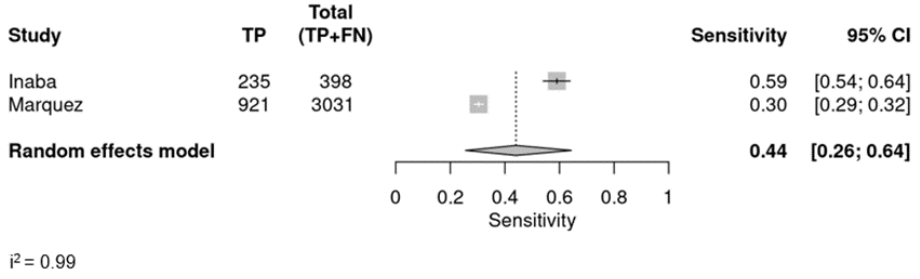
CI: confidence interval; **MD:** mean difference

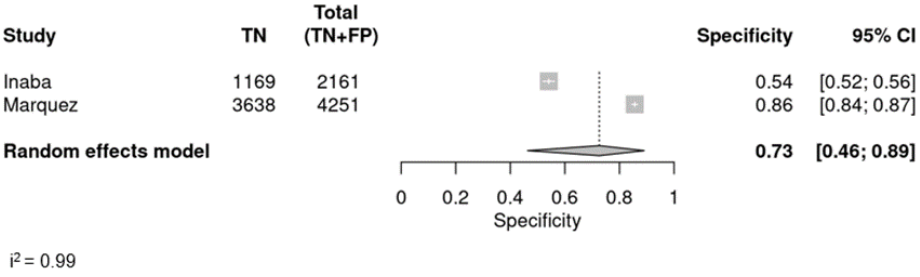
Explanations

a. Data for analysis was generated from self-reports and use of the ZOE COVID-19 app.
b. This study enrolled individuals aged 16-99 and did not include the entire spectrum of pediatric ages.

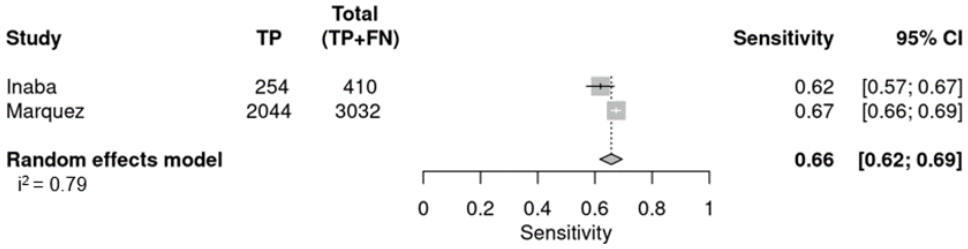
Appendix 7: Forest Plots

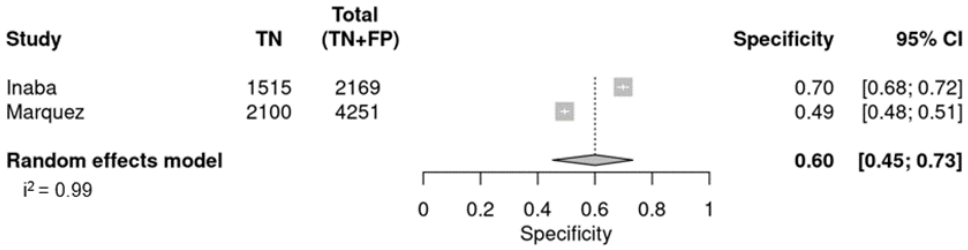
Fever



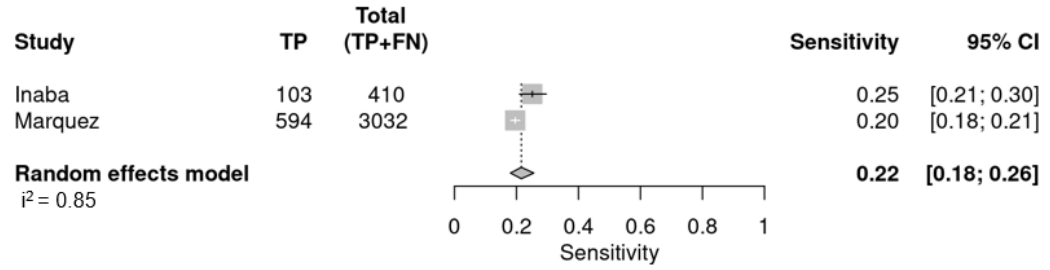


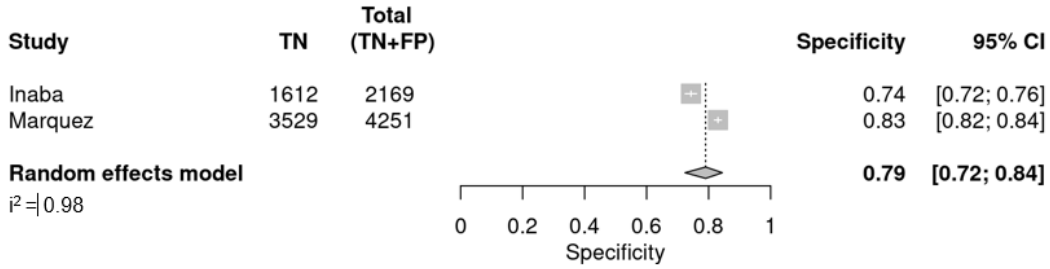
Cough



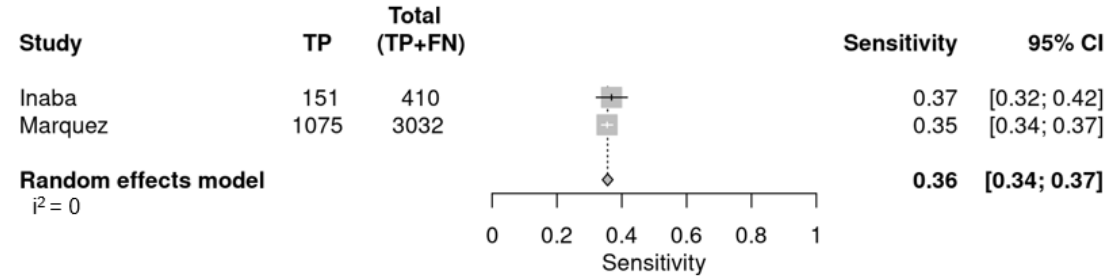


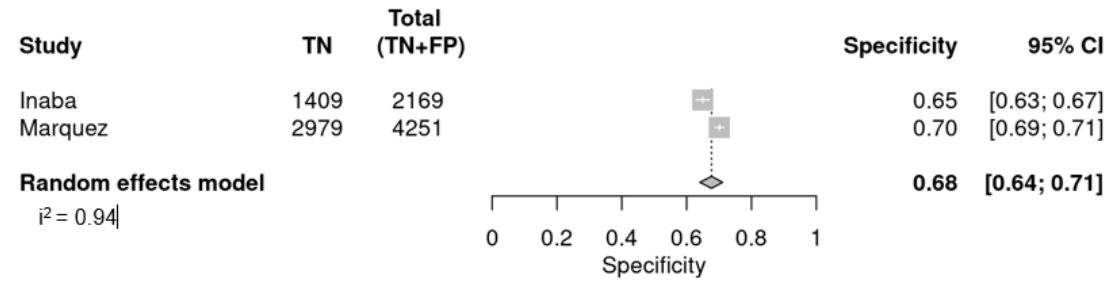
Fatigue



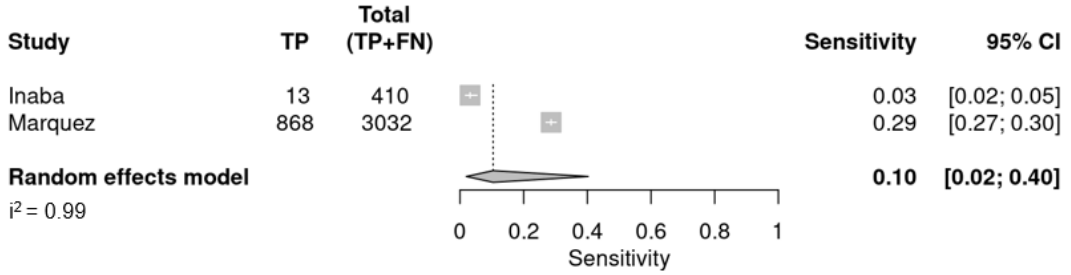


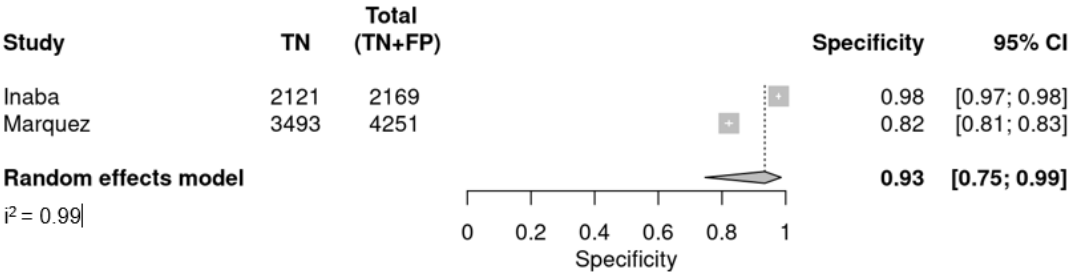
Headache



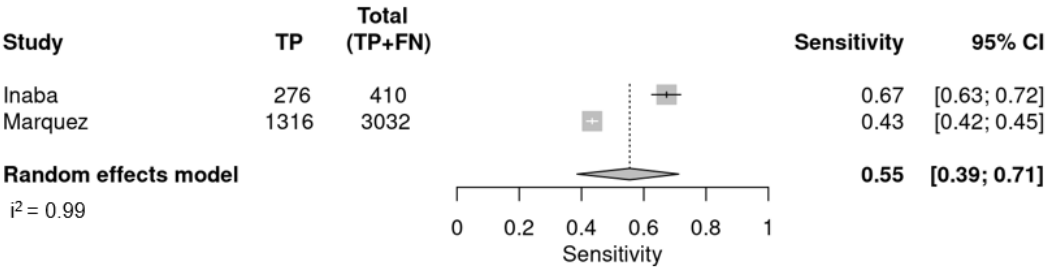


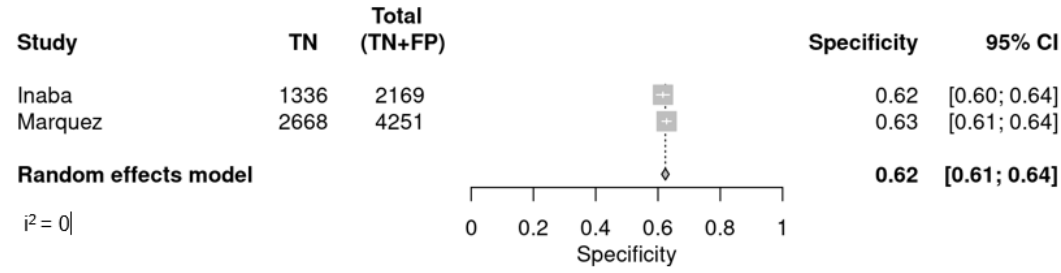
Myalgia



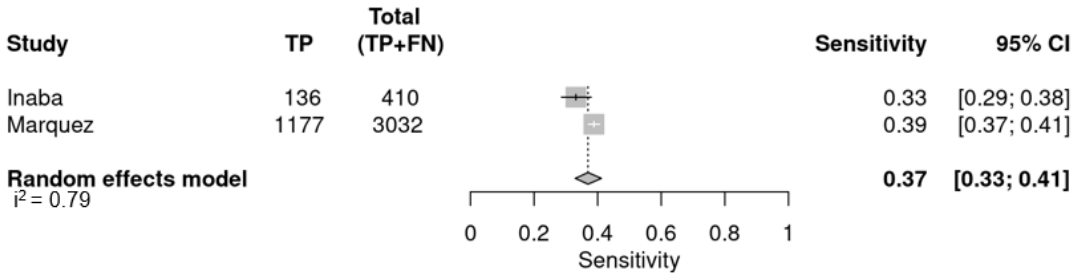


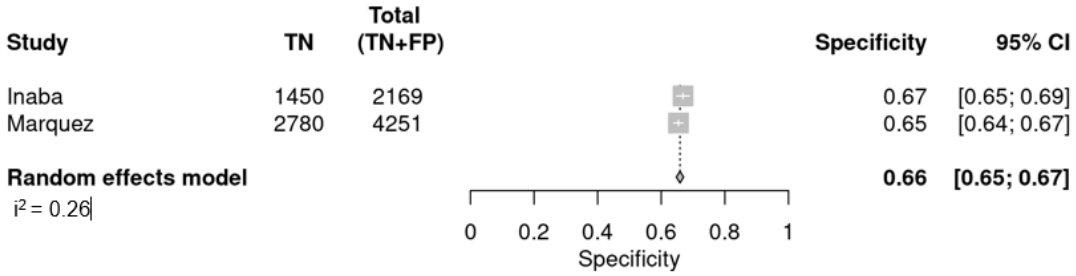
Sore throat



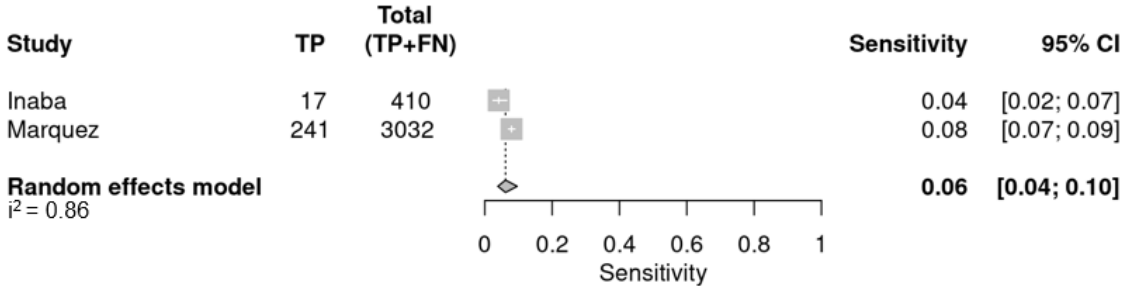


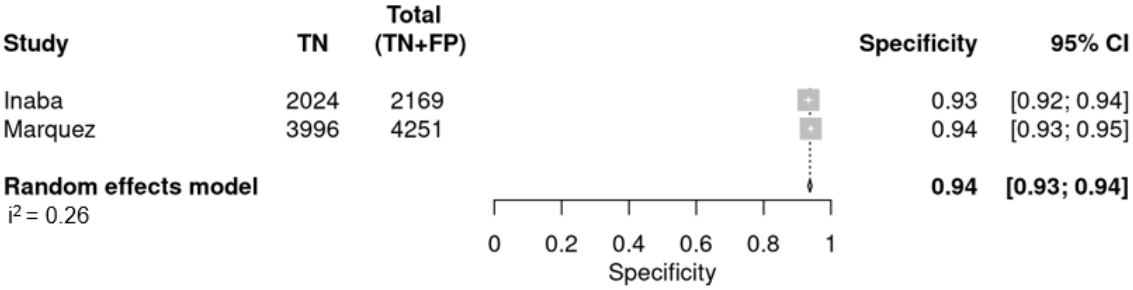
Runny nose/nasal congestion



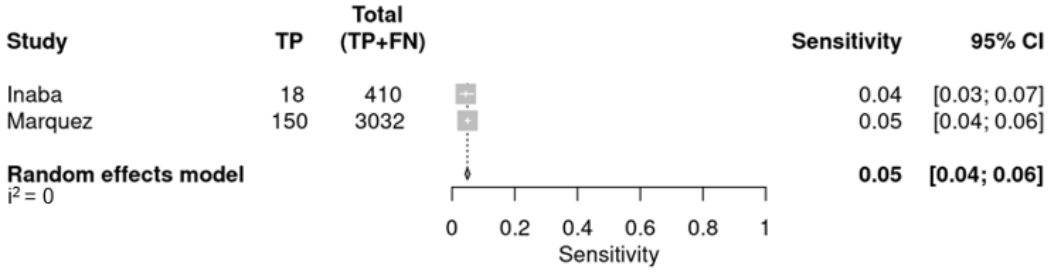


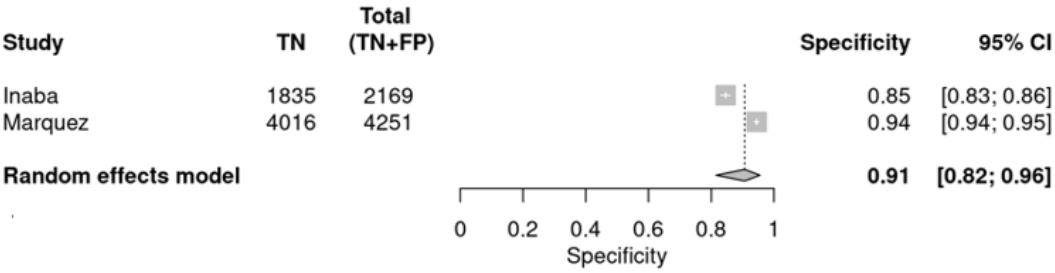
Shortness of breath



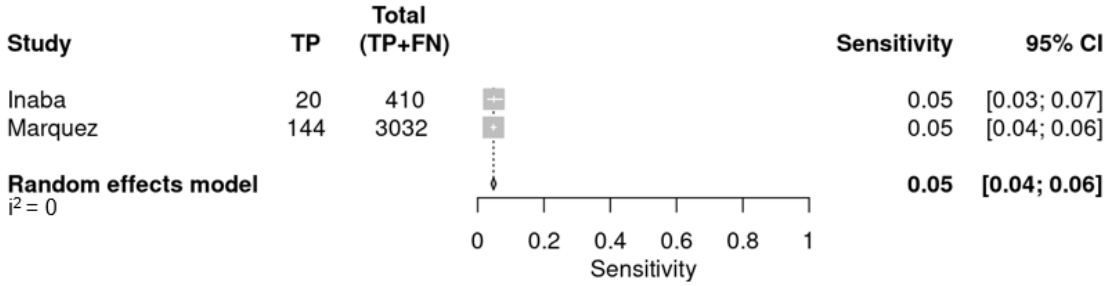


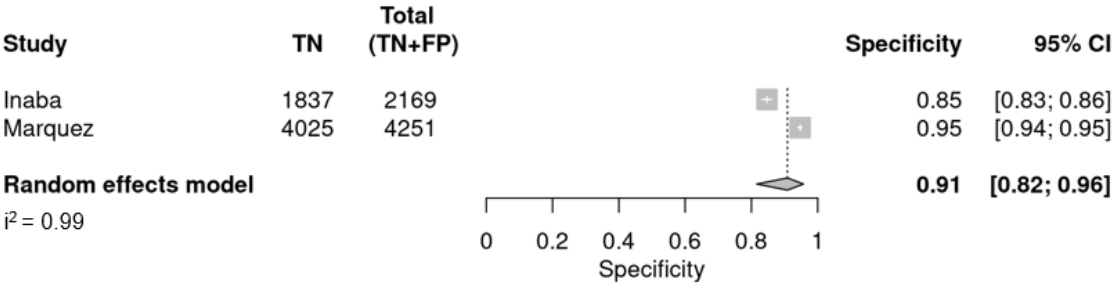
Nausea/vomiting





Diarrhea





Loss of smell or taste