EVIDENCE SUMMARY

Which clinical specimens can be used as an alternative to nasopharyngeal swab RT-PCR for the diagnosis of COVID-19 infection in children?

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Recommendations

As an alternative specimen to nasopharyngeal swab, we recommend the use of saliva specimen for RT-PCR* among non-hospitalized children suspected of COVID-19 infection.

**Nasopharyngeal swab is the specimen of choice for RT-PCR for the diagnosis of COVID-19 infection in children. The use of three specific saliva RT-PCR assays is recommended: Allplex 2019-nCOV assay, Cobas 6800, or QuantStudio 7 system.*

Certainty of evidence: Moderate
Strength of recommendation: Strong

Consensus Issues
There were no consensus panel issues noted.

As an alternative specimen to nasopharyngeal swab, we suggest the use of mid-turbinate swab for RT-PCR* for among non-hospitalized children suspected of COVID-19 infection.

**Nasopharyngeal swab is the specimen of choice for RT-PCR for the diagnosis of COVID-19 infection in children. The use of two specific mid-turbinate RT-PCR assays is recommended: RealStar SARS-CoV-2 RT-PCR kit or Aptima SAR-CoV-2 Assay.*

Certainty of evidence: Moderate
Strength of recommendation: Weak

Consensus Issues
There were no consensus panel issues noted.

We suggest against the use of nasopharyngeal aspirate as an alternative clinical specimen among non-hospitalized children suspected of COVID-19 infection.

Certainty of evidence: Low
Strength of recommendation: Weak

Consensus Issues
This recommendation is based on one study performed in children however, due to the low certainty of evidence and issues on availability of the test, the panel voted against the use of the nasopharyngeal aspirate in children.

Key findings

Seven cross-sectional studies on the use of saliva specimen were retrieved however, only three studies were appraised to have no serious risks of bias. Pooled analysis was done for the three studies to check for diagnostic accuracy. Saliva RT-PCR had a sensitivity: 0.87 (95% CI 0.81, 0.91) and specificity: 0.98 (95% CI 0.97, 0.99). Predictive values (PV) ranged from 91.7% - 96.8% and likelihood ratios (LR) for positive result was 45 and 0.13 for a negative result. These accuracy estimates had moderate certainty of evidence. The following assays were used: 1) Allplex 2019-nCoV assay, 2) Cobas 6800, and 3) QuantStudio 7 system

One study each on using mid-turbinate swab and nasopharyngeal aspirate (NPA) both showed moderate sensitivity but wide confidence interval and high specificity. Other PV and LR accuracy estimates were interpreted moderate to high among non-hospitalized and hospitalized children suspected of COVID-19, respectively. However, while mid-turbinate swab evidence was moderate in certainty of evidence, NPA RT-PCR was based on a study with low certainty of evidence.

No studies in children were seen using the following specimens: oropharyngeal swab, pharyngeal swab, nasal swab, and sputum for RT-PCR.

Introduction

The RT-PCR of the nasopharyngeal swab (NPS) is the current reference standard for diagnosis of SARS-CoV-2 infection [1]. However, NPS collection causes difficulty and discomfort in children as it is invasive, requires trained healthcare personnel, and the use of protective personal equipment (PPE). Recommended alternative specimens like nasal swab, oropharyngeal/ pharyngeal swab, mid-turbinate swab, and saliva are based on studies in adults [1-3]. Saliva sample collection is easy, non-invasive, and can be performed by non-healthcare professionals or individuals themselves who are properly instructed.

Recent studies have evaluated several alternative specimens to NPS for RT-PCR in children. The sensitivity of these specimens has shown considerable variability compared with NPS, ranging from 0.60 to 0.93 [4,5]. Reported heterogeneity is likely to reflect differences in sampling techniques, symptom duration, type of population being tested and assay kit. This review was conducted to determine the diagnostic performance of alternative specimens that may be easier and safer to collect in children.

Review Methods

We searched Medline through PubMed, Cochrane CENTRAL, ChinaXiv.org, MedRxiv.org, BioRxiv, COVID-19 Open Living Evidence, Living Evidence on COVID-19, and UptoDate on January 05, 2022 (Appendix 1) using free text and MeSH terms. Our inclusion criteria may be found in Table 1. We excluded studies with incomplete data on the accuracy of the index tests, with less than 30 participants. Included studies were appraised using QUADAS 2 tool and Joanna Briggs Criteria for the study on safety of obtaining saliva specimen. Subgroup analysis was planned for age group, symptomatology (symptomatic/ asymptomatic), setting (hospital/outpatient), method of specimen collection, and type of assay kit. (Appendix 4E-4M). However, data was unavailable for subgroup analysis on age group and symptomatology (symptomatic/asymptomatic).

Table 1. PICO criteria for alternative clinical specimen.

Population	Children with COVID-19
Intervention/Exposure	Alternative clinical specimen for RT-PCR for the diagnosis of COVID-19
Comparison	Nasopharyngeal RT-PCR
Outcomes	Accuracy, true positives, false positives, false negatives, true negatves, adverse events

Results

Summary of characteristics of included studies

Out of the 1, 404 studies screened, we included 9 observational studies in this review [4-12] (Appendix 2A).

Saliva RT-PCR

Seven studies were retrieved but only three studies with no serious risk for bias were included in the meta-analysis to determine the diagnostic accuracy of using saliva specimen in the diagnosis of COVID-19. These three studies included 1,043 non-hospitalized children 1 month to18 years old suspected of COVID-19 based on the presence of symptoms or history of exposure to confirmed COVID-19 individuals. Saliva was collected either by a healthcare professional, a caregiver or self-collected under supervision. The studies used different assays, namely 1) Allplex 2019-nCoV assay 2) Cobas 6800, and 3) QuantStudio 7 system.

Mid-turbinate swab RT-PCR

One study included 569 non-hospitalized symptomatic children suspected of COVID-19, median age was 5 years (range 1 month to < 18 y/o), and with a median time between symptom onset and specimen collection of 4 days (range 1 to 14 days). Specimen were collected by trained clinical staff. They used either RealStar SARS-CoV-2 RT-PCR kit or Aptima SARS-CoV-2 Assay [12].

Nasopharyngeal aspirate RT-PCR

One study evaluated the diagnostic performance of NPA on 136 hospitalized children suspected of COVID-19 provided 300 paired NPS/NPA specimens for analysis. They used either AllplexTM 2019-nCoV assay or GeneFinder COVID-19 Plus RealAmp Kit [9].

Methodological quality

Saliva RT-PCR

The three studies were without serious risk of bias with outcomes having moderate certainty of evidence due to imprecision (Appendix 4).

Mid-turbinate swab

The certainty of evidence for mid-turbinate swab RT-PCR was rated moderate due to imprecision (Appendix 4).

Nasopharyngeal aspirate

The certainty of evidence for the sensitivity of nasopharyngeal aspirate RT-PCR was low. There was a serious risk of bias due to timing of specimen collection, and imprecision (Appendix 4).

Diagnostic accuracy (Appendices 5 & 6)

Saliva RT-PCR

Three studies were pooled to check for diagnostic accuracy of saliva as specimen. Pooled sensitivity was 0.87 (95% CI 0.81, 0.91) with wide confidence interval and specificity of 0.98 (95% CI 0.97, 0.99). It demonstrated high positive PV of 91.75% (95% CI 87.02, 94.86) and negative PV of 96.82% (95% CI 95.41, 97.81). The LRs for a positive and a negative saliva RT-PCR were 45.48 (95% CI 40.17, 51.49) and 0.13 (95% CI 0.12, 0.14), respectively. (moderate certainty of evidence).

Mid-turbinate swab RT-PCR

One study on mid-turbinate RT-PCR showed a sensitivity of 0.82 (95% CI 0.74, 0.89) (n= 569) while its specificity was high at 1.00 (95% CI 0.99, 1.00). The positive and negative PVs were 100% (95% CI 96, 100) and 96% (95% CI 94, 97), respectively and the LR for a negative test was 0.18 (95% CI 0.16, 0.19*)* (n= 569). The certainty of evidence was moderate.

Nasopharyngeal aspirate RT-PCR

One study on NPA RT-PCR showed sensitivity: 0.81 (95% CI 0.63, 0.93) (n = 136 with 300 paired specimen). Its specificity was high: 0.93 (95% CI 0.90, 0.94*)*. Its positive and negative PVs were 58% (95% CI 43, 72) and 98% (95% CI 95, 99). The LR was 12 (95% CI 11, 14) for a positive test and 0.21 (95% CI 0.15, 0.29) for a negative test (n = 136 with 300 paired specimens. The certainty of evidence was low.

Adverse events

There were no reported adverse events with saliva specimen collection among hospitalized children (n= 156, one study, low certainty of evidence) (Appendix 4). There were no studies that reported adverse events on the use of mid-turbinate swab and NPA specimens.

Harms associated with false negative and false positive saliva RT-PCR results

With a sensitivity of 81-91%, saliva RT-PCR will detect 81-91 out of every 100 with COVID-19, but 9-19 will be missed as they will have false negative test. With a specificity of 97-99 %, out of every 100 individuals without COVID-19, 1-3 will be wrongly diagnosed as having COVID-19.

Other Considerations (Evidence to Decision)

Table 2. Evidence to Decision Considerations

Cost	Philhealth benefit package rates for COVID-19 testing: a) plate-based NPS RT-PCR: Php 800- 2,800 b) cartridge-based NPS RT-PCR: Php 500- 2, 450 [14]. There is no Philhealth benefit package for saliva, NPS and mid-turbinate for RT-PCR [14]. Philippine Red Cross offers saliva RT-PCR test for Php 2,000 [15].
Availability	There are FDA-approved, available test kits for saliva RT-PCR, mid-turbinate swab and nasopharyngeal aspirate RT-PCR. For saliva RT-PCR, these are Allplex, Argene SarsCoV-2 R gene, Molaccu and TaqPath CE-IVD. For mid-turbinate swab RT-PCR, these are Xpert Xpress, 1 copy qPCR 4plex, TaqPath FluA FluB combo kit and TaqPath CE-IVD. For NPA RT-PCR, these are Opti, Aptima, Triplex RT qPCR, CoviPath and

	TaqPath CE-IVD. Of these kits, only the saliva RT-PCR Allplex assay was used in the study by Trobajo-San Martin.
Patient's Values or Preferences; Social Impact	398 (77%) children preferred saliva specimen collection to NPS/ OPS/ mid turbinate swab/ throat swab specimens. These included 2- 11 y/o suspected to have COVID-19 and among asymptomatic children attending school day care centers. (n=516, from three cross-sectional studies, low certainty of evidence) [16-18].
Factors to Impact Acceptability or Compliance	**Saliva:** In 2,088 children, 97% provided adequate saliva samples for RT-PCR. These included hospitalized children suspected of COVID-19 (n=461) and asymptomatic school children (n= 1,627) from four cross-sectional studies, very low certainty of evidence) [17, 19-21]. The minimum age for adequate saliva sample collection was 5 y/o in hospitalized children suspected to have COVID-19 (n= 461, one cross sectional preprint, very low certainty [20]. With a sensitivity of 81-91%, saliva RT-PCR will detect 81-91 out of every 100 with COVID-19, but 9-19 will be missed as they will have false negative test. With a specificity of 97-99 %, out of every 100 individuals without COVID-19, 1-3 will be wrongly diagnosed as having COVID-19. **Mid-turbinate swab**: Among 67 children 2 years and older with influenza-like illness, a median discomfort score of 1 was obtained for mid-turbinate specimen collection compared with a score of 3 for NPS specimen. (validated 6-point Faces Pain scale with zero being no discomfort and 6 being worst imaginable) [22]. **NPA:** In 86 adult patients with URTI, 26% complained that NPA procedure was very uncomfortable, majority (69%) said it was mildly uncomfortable and only 6% patients reported no discomfort. On a 10-point-scale, the median discomfort was 4 [23].

Recommendations from Other Groups

The US-CDC (28 Dec 2021), American Academy of Pediatrics (AAP) (17 Nov 2021) and the Philippine Pediatric Society (PPS) (08 Jan 2022) along with the Pediatric Infectious Disease Society of the Philippines (PIDSP) recommend nasal mid turbinate, nasopharyngeal aspirate, and saliva as alternative specimens to NPS in the diagnosis of COVID-19 using RT-PCR [1-3].

The Infectious Disease Society of America (IDSA) (06 May 2021) suggests mid turbinate swab, and saliva as alternative specimens to NPS in the diagnosis of COVID-19 using RT-PCR [24].

The World Health Organization (WHO) (11 Sept 2020) does not recommend the use of saliva as the sole specimen type for routine clinical diagnostics. Due to a large variety of collection methods and processing steps, WHO recommends that laboratories must collect their own performance data linked to the local method of collection and in the relevant population for testing [25].

European CDC states that further clinical studies are warranted on the sensitivity of saliva for RT-PCR for symptomatic and asymptomatic children, and to standardize the sampling collection [26].

Research Gaps

As of January 2022, there are no ongoing studies. Further studies on the sensitivity of saliva, nasopharyngeal aspirate and mid-turbinate swab specimens for RT-PCR for COVID-19 diagnosis in children are needed, stratified by age, illness duration, setting, type of assay, and method of specimen collection. Studies on other specimens like oropharyngeal, pharyngeal or nasal swab and sputum are also recommended.

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Appendix 1. Search Yield and Results

Table 1. Search Yield and Results from different databases

Database	Search Strategy	Search Yield
Medline through PubMed	(((COVID-19) AND ((pediatric) OR (children))) AND (((((((saliva) OR (nasal swab)) OR (oropharyngeal swab)) OR (throat swab)) OR (nasopharyngeal)) OR (nasopharyngeal swab)) OR (upper respiratory tract))) AND (((((sensitivity) OR (accuracy)) OR (concordance)) OR (cost effectiveness)) OR (acceptability)) 19 AND 20	248
Cochrane CENTRAL database https://clinicaltrials.gov/ https://www.who.int/clinical-trials-registry-platform PubMed Embase	COVID-19 as Population (PICO search, Advanced Search) **Search Results** There are 11 results for your search on MeSH descriptor: COVID-19 Nucleic Acid Testing Explode all trees	24
ChinaXiv.org	Abstract: (COVID-19) AND Subjects::(“Medicine, Pharmacy” OR “Clinical Medicine”)	9
MedRxiv.org (with BioRxiv)	for term "COVID-19 AND (pediatric OR children) AND RT-PCR AND (Sensitivity OR accuracy OR cost-effectiveness OR feasibility)" and posted between "01 Jan, 2020 and 05 Jan, 2022"	376
Cross-referencing	Hoch	12
http://www.chictr.org.cn/searchproj en.aspx	COVID-19	0
COVID-19 Open Living Evidence Synthesis		0
Living Evidence on COVID-19 zika	COVID-19	736
Australia: https://covid19evidence.net.au/		0

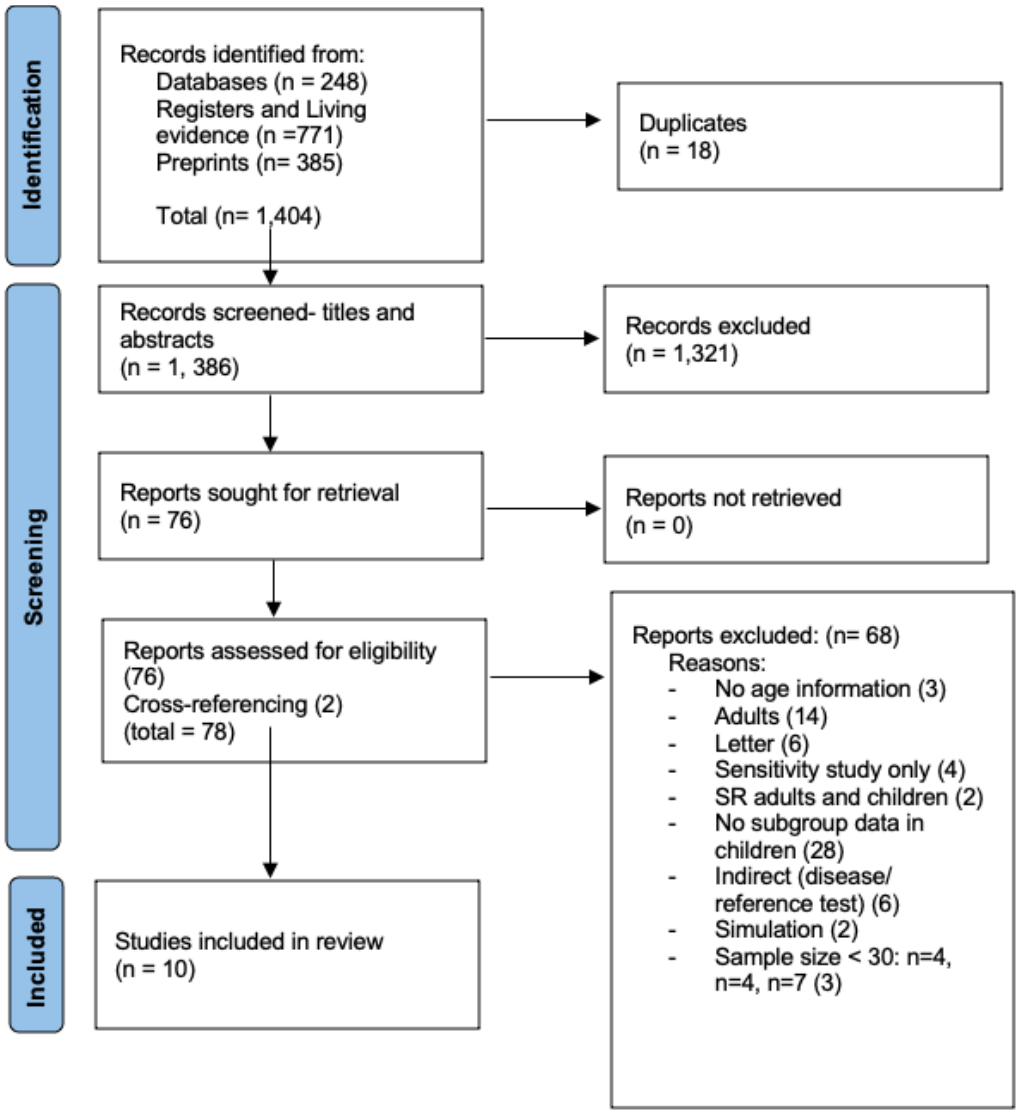

Figure 1. PRISMA flow diagram

Appendix 2A. Characteristics of Included Studies

Author	Study design	Population	Index test Assay	Reference standard	Outcome
Al-Suwaidi 2021 UAE	Cross-sectional	476 suspected COVID-19 Mean age 10.8 y/o SD 3.9 years (range 3- 18 y/o) • Outpatient	Saliva RT-PCR Allplex 2019-nCoV assay (Seegene, Seoul, South Korea)	NPS RT-PCR	Sn Sp
Fougere 2021 Switzerland	Cross-sectional	397 suspected COVID-19 • Outpatient	Saliva RT-PCR Cobas 6800 (Roche, Basel, Switzerland) or QuantStudio 7 system (Applied Biosystems, Waltham, United States)	NPS RT-PCR	Sn Sp
Huber 2021 Switzerland	Cross-sectional	170 suspected COVID-19 Median age -13 (range 5-17 y/o) Median days of symptoms 2 days (range 1-21 days) • Outpatient	saliva RT-PCR Cobas SARS- CoV-2 IVD test (Roche) on a Cobas 6800	NPS RT-PCR	Sn Sp
Felix 2021 Brazil	Cross-sectional	50 suspected COVID-19 Mean 10.24 (+- 3.52 years) Mean days of symptoms 4.76 (+- 1.31 days) • Outpatient	Saliva RT-PCR Altona Realstar Kit	NPS RT-PCR	Sn Sp
Alenquer 2021 Portugal	Cross-sectional	85 suspected COVID-19 and causes unrelated to COVID-19 (other medical pathologies or surgeries) (1- 10 y/o) Saliva collected within 48 hours from NPS collection • Hospital	Saliva RT-PCR iTaq Universal Probes One-Step Kit (BIORAD, #12013250)	NPS RT-PCR	Sn Sp
Banerjee 2021 USA	Cross-sectional	109 suspected COVID-19 Mean age 10.8 years (range 5-14 y/o) • Outpatient	Saliva RT-PCR Aptima SARS-CoV-2-Assay	NPS RT-PCR	Sn Sp
Trobajo-Sanmartin 2021 Spain	Cross-sectional	103 suspected of COVID-19 (subgroup) • Outpatient	Saliva RT-PCR AllplexTM 2019-nCoV assay (Seegene, Seoul, Korea)	NPS RT-PCR	Sn Sp
Sahni 2021 USA	Cross-sectional	569 children suspected COVID -19 median age 5 y/o (range 1 month to <18 y/o) Median onset of symptoms 2 days (range 0-13 days) • Outpatient	Mid turbinate swab RealStar SARS-CoV-2 Rt-PCR kit (Germany) or Aptima SARS-CoV-2 Assay on the Hologic Panther System (Massachusetts)	NPS RT-PCR	Sn Sp
Di Pietro 2021 Italy	Cross-sectional	136 suspected COVID-19 children (600 paired specimens) • Hospital	nasopharyngeal aspirate AllplexTM 2019-nCoV assay with Seegene NIMBUS & STARlet instrument (C_t cut-off value for a positive test was *≤ 40)* *or* GeneFinder COVID-19 Plus RealAmp Kit adapted to the ELITe InGenius® (ELITechGroup) (C_t cut-off value for a positive test was *≤ 45)*	NPS RT-PCR	Sn Sp

Appendix 2B. Method of Saliva Collection for RT-PCR

Study	Saliva collection
Alenquer 2021	1 ml of saliva collected with the help of a healthcare worker, after food and water abstinence for 30 minutes, by pooling saliva in the mouth and gently spitting it into a sterile container without coughing or clearing their throats For < 1 y/o- saliva was aspirated from the mouth with a suction tube
Al Suwaidi 2021	1- 3 ml of self-collected saliva, after food and water abstinence, by pooling saliva in the mouth for 1-2 minutes and spitting into a sterile container.
Banerjee 2021	2 ml of self-collected saliva, after food and water abstinence for 30 minutes by pooling saliva in the mouth and using a straw to fill the collection tube. A saliva collection kit was provided with a straw and 10 ml conical tube.
Felix 2021	The children were asked to spit into a sterile container for a collection of about 1 ml of saliva.
Fougere 2021	Saliva was either self-collected or collected by a healthcare professional or caregiver by asking the child to drool at least 10 uL of saliva in a tube.
Huber 2021	Participants were asked to clear their throat thoroughly and collect 0.5 - 1 ml of saliva (approximately a teaspoon full) one or two times into the same tube
Trobajo-Sanmartin 2021	Self-collection of saliva after 1 hour of food and water abstinence by pooling saliva in the mouth for a few seconds, and expelling the saliva into a sterile tube amounting to approximately one finger has been collected. If the amount is less, you should generate more saliva and expel it into the same tube.
Sahni 2021	The MT swab was inserted into one naris by trained clinical staff (medical assistants, licensed vocational nurses, registered nurses, and respiratory therapists). Age specific swab was used (pediatric size for < 2 y/o and adult size for > 2 y/o). The head of the child is tilted to an angle of 70 degrees and the personnel gently insert the swab into the nares, rotating the swab 2-3 times then holding the swab in place for 5 seconds. The swab is then inserted into the viral transport medium.
Di Pietro 2021	The nasopharyngeal aspirates were collected from both nostrils using a standard protocol and the Medicoplast mucus extractor 440- ch08.

Appendix 3. Detailed Study Appraisal

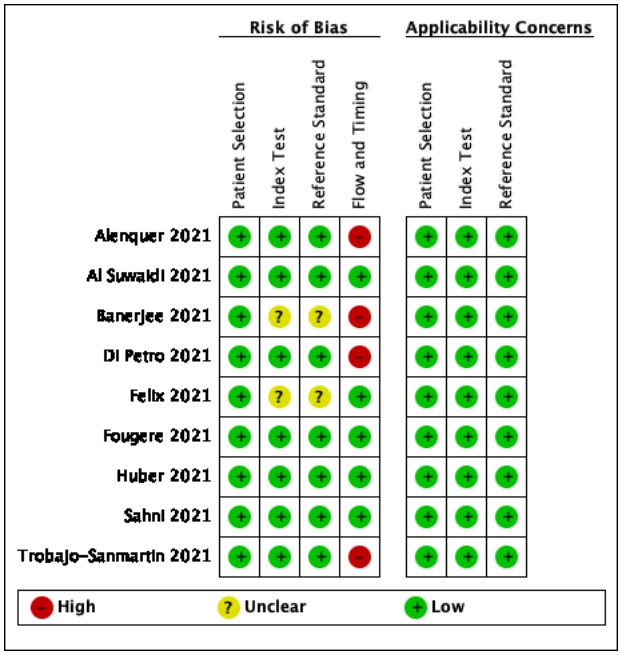

Figure 1. Risk of bias and applicability concerns summary of the included studies (QUADAS-2).

Table 1. Appraisal of studies using Joanna Briggs Critical Appraisal Instrument for Studies Reporting Prevalence Data

	Guzman-Ortiz
1. Was the sample frame appropriate to address the target population?	Yes
2. Were study participants sampled in an appropriate way?	Yes
3. Was the sample size adequate?	Yes
4. Were the study subjects and the setting described in detail?	Yes
5. Was the data analysis conducted with sufficient coverage of the identified sample?	Yes
6. Were valid methods used for the identification of the condition?	Yes
7. Was the condition measured in a standard, reliable way for all participants?	Yes
8. Was there appropriate statistical analysis?	Yes
9. Was the response rate adequate, and if not, was the low response rate managed appropriately?	Yes
Overall appraisal	Include

Appendix 4A. GRADE Evidence Profile: Saliva RT-PCR

Author(s): Eva I. Bautista, MD, Ma. Lucila M. Perez, MD, Maria Teresa S. Tolosa, MD
Question: Should Saliva RT-PCR be used to diagnose COVID-19 in children?
Setting: Hospital and Outpatient

Sensitivity	0.85 (95% CI: 0.76 to 0.91)	Prevalence	8 %*	33%**
Specificity	0.99 (95% CI: 0.97 to 0.99)			

Outcome	*№ of studies (№ of patients)*	*Study design*	*Factors that may decrease certainty of evidence*					*Effect per 1,000 patients tested*		*Test accuracy CoE*	*Importance*
			Risk of bias	*Indirectness*	*Inconsistency*	*Imprecision*	*Publication bias*	*pre-test probability of8%*	*pre-test probability of33%*		
True positives *(patients with COVID-19)*	*7 studies 364 patients*	*cross-sectional (cohort type accuracy study)*	*serious[1,2,3,a,b]*	*not serious*	*serious[2,4,c]*	*serious[2,3,4,5,d,e]*	*none*	*68 (61 to 73)*	*281 (251 to 300)*	⨁◯◯◯ *Very low*	*Critical*
False negatives *(patients incorrectly classified as not having COVID-19)*								*12 (7 to 19)*	*49 (30 to 79)*		*Critical*
True negatives *(patients without COVID-19)*	*7 studies 1027 patients*	*cross-sectional (cohort type accuracy study)*	*serious[1,2,4,a,b,d]*	*not serious*	*not serious*	*not serious*	*none*	*911 (892 to 911)*	*663 (650 to 663)*	⨁⨁⨁◯ *Moderate*	*Critical*
False positives *(patients incorrectly classified as having COVID-19)*								*9 (9 to 28)*	*7 (7 to 20)*		*Critical*

Outcome	№ of studies (№ of patients)	Study design	Factors that may decrease certainty of evidence					Effect per 1,000 patients tested		Test accuracy CoE	Importance
			Risk of bias	Indirectness	Inconsistency	Imprecision	Publication bias	pre-test probability of8%	pre-test probability of33%		
Positive Predictive Value	*7 studies 325 patients*	*cross-sectional (cohort type accuracy study)*	*serious[1,2,3,a,b]*	*Not serious*	*serious [3,4,,5, f]*	*Not serious*	*none*	*94% (95% CI 91, 96)*		⨁⨁◯◯ *Low*	*Critical*
Negative Predictive Value	*7 studies 1066 patients*	*cross-sectional (cohort type accuracy study)*	*serious[1,2,3,a,b]*	*Not serious*	*serious [3,4,,5,6, f]*	*Not serious*	*none*	*94% (95% CI 92, 96)*		⨁⨁◯◯ *Low*	*Critical*
Likelihood ratio for a (+) test	*7 studies 1391 patients*	*cross-sectional (cohort type accuracy study)*	*serious[1,2,3,a,b]*	*Not serious*	*serious [1, 5, f]*	*Not serious*	*none*	*48 (95% CI 43, 53)*		⨁⨁◯◯ *Low*	*Critical*
Likelihood ratio for a (-) test	*7 studies 391 patients*	*cross-sectional (cohort type accuracy study)*	*serious[1,2,3,a,b]*	*Not serious*	*serious [1, 5, 7, f]*	*Not serious*	*none*	*0.16 (95% CI 0.16, 0.17)*		⨁⨁◯◯ *Low*	*Critical*

Explanations
a. Saliva specimen was collected within 24-48 hours from NPS collection
b. 109/ 335 (33%) children were analyzed.
c. High heterogeneity (I2 = 77 %). Differences in the methods of specimen collection, setting, type of assay.
d. Wide confidence interval
e. small sample size
References
1.Banerjee D, et al. 2021;
2.Trobajo-Sanmartín C, et al. 2021;
3. Alenquer M, et al. 2021;
4.Felix AC, et al. 2021;
5.Huber M, et al. 2021.
6. Al Suwaldi, 2021
7. Fougere, 2021

* 8 % pretest probability of COVID-19 among children 0-14 y/o. [27]
**33% pretest probability of ICU admission among hospitalized COVID-19 children [28,29]

Appendix 4B. GRADE Evidence Profile: Saliva RT-PCR in studies without serious risk of bias

Author(s): Eva I. Bautista, MD, Maria Teresa S. Tolosa, MD, Ma. Lucila M. Perez, MD
Question: Should saliva RT-PCR be used to diagnose COVID-19 in children based on studies without serious risk of bias?
Setting: Ambulatory

Sensitivity	*0.87 (95% CI: 0.81 to 0.91)*	*Prevalence*	*8% **	*33% ***
Specificity	*0.98 (95% CI: 0.97 to 0.99)*			

Outcome	*№ of studies (№ of patients)*	*Study design*	*Factors that may decrease certainty of evidence*					*Effect per 1,000 patients tested*			*Test accuracy CoE*	*Importance*
			Risk of bias	*Indirectness*	*Inconsistency*	*Imprecision*	*Publication bias*	*pre-test probability of8%*	*pre-test probability of33%*	*pre-test probability of0%*		
True positives *(patients with COVID-19)*	*3 studies 205 patients*	*cross-sectional (cohort type accuracy study)*	*not serious*	*not serious*	*not serious*	*serious[1,a]*	*none*	*70 (65 to 73)*	*287 (267 to 300)*	*0 (0 to 0)*	⊕⊕⊕◯ *Moderate*	*Critical*
False negatives *(patients incorrectly classified as not having COVID-19)*								*10 (7 to 15)*	*43 (30 to 63)*	*0 (0 to 0)*		*Critical*
True negatives *(patients without COVID-19)*	*3 studies 838 patients*	*cross-sectional (cohort type accuracy study)*	*not serious*	*not serious*	*not serious*	*not serious*	*none*	*902 (892 to 911)*	*657 (650 to 663)*	*980 (970 to 990)*	⊕⊕⊕⊕ *High*	*Critical*
False positives *(patients incorrectly classified as having COVID-19)*								*18 (9 to 28)*	*13 (7 to 20)*	*20 (10 to 30)*		*Critical*

Outcome	№ of studies (№ of patients)	Study design	Factors that may decrease certainty of evidence					Effect per 1,000 patients tested			Test accuracy CoE	Importance
			Risk of bias	Indirectness	Inconsistency	Imprecision	Publication bias	pre-test probability of8%	pre-test probability of33%	pre-test probability of0%		
Positive Predictive Value	*3 studies 194 patients*	*cross-sectional (cohort type accuracy study)*	*Not serious*	*Not serious*	*Serious* [1,2, b]	*Not serious*	*none*	*92 % (95% CI 87, 95)*			⊕⊕⊕◯ *Moderate*	*Critical*
Negative Predictive Value	*3 studies 849 patients*	*cross-sectional (cohort type accuracy study)*	*Not serious*	*Not serious*	*Not serious*	*Not serious*	*none*	*97% (95% CI 95, 98)*			⊕⊕⊕⊕ *High*	*Critical*
Likelihood ratio for a (+) test	*3 studies 1043 patients*	*cross-sectional (cohort type accuracy study)*	*Not serious*	*Not serious*	*Serious* [1,2, b]	*Not serious*	*none*	*45 (95% CI 40, 51)*			⊕⊕⊕◯ *Moderate*	*Critical*
Likelihood ratio for a (-) test	*3 studies 1043 patients*	*cross-sectional (cohort type accuracy study)*	*Not serious*	*Not serious*	*serious* [1,2, b]	*Not serious*	*none*	*0.13 (95% CI 0.12, 0.14)*			⊕⊕⊕◯ *Moderate*	*Critical*

Explanations
a. wide confidence interval
References
1.Huber M, et al. 2021.
2. Fougere, 2021
3. Al Suwaldi, 2021

* 8 % pretest probability of COVID-19 among children 0-14 y/o. [27]
**33% pretest probability of ICU admission among hospitalized COVID-19 children [28,29]

Appendix 4C. GRADE Evidence Profile: Mid-turbinate swab RT-PCR

Author(s): Eva I. Bautista, MD, Ma. Lucila M. Perez, MD, Maria Teresa S. Tolosa, MD
Question: Should mid-turbinate RT-PCR be used to diagnose COVID-19 in children?
Setting: Ambulatory

Sensitivity	*0.82 (95% CI: 0.74 to 0.89)*	*Prevalence*	*8%**	*33% ***
Specificity	*1.00 (95% CI: 0.99 to 1.00)*			

Outcome	*№ of studies (№ of patients)*	*Study design*	*Factors that may decrease certainty of evidence*					*Effect per 1,000 patients tested*		*Test accuracy CoE*	*Importance*
			Risk of bias	*Indirectness*	*Inconsistency*	*Imprecision*	*Publication bias*	*pre-test probability of8%*	*pre-test probability of33%*		
***True positives** (patients with COVID-19)*	*1 study 114 patients*	*cross-sectional (cohort type accuracy study)*	*not serious*	*not serious*	*not serious*	*serious[1,a]*	*none*	*66 (59 to 71)*	*271 (244 to 294)*	⊕⊕⊕◯ *Moderate*	*Critical*
***False negatives** (patients incorrectly classified as not having COVID-19)*								*14 (9 to 21)*	*59 (36 to 86)*		*Critical*
***True negatives** (patients without COVID-19)*	*1 study 453 patients*	*cross-sectional (cohort type accuracy study)*	*not serious*	*not serious*	*not serious*	*not serious*	*none*	*920 (911 to 920)*	*670 (663 to 670)*	⊕⊕⊕⊕ *High*	*Critical*
***False positives** (patients incorrectly classified as having COVID-19)*								*0 (0 to 9)*	*0 (0 to 7)*		*Critical*
Positive Predictive Value	*1 study 94 patients*	*cross-sectional (cohort type accuracy study)*	*Not serious*	*Not serious*	*Not serious*	*Not serious*	*none*	*100 % (95% CI 96, 100)*		⊕⊕⊕⊕ *High*	*Critical*

Outcome	№ of studies (№ of patients)	Study design	Factors that may decrease certainty of evidence					Effect per 1,000 patients tested		Test accuracy CoE	Importance
			Risk of bias	Indirectness	Inconsistency	Imprecision	Publication bias	pre-test probability of8%	pre-test probability of33%		
Negative Predictive Value	*1 study 473 patients*	*cross-sectional (cohort type accuracy study)*	*Not serious*	*Not serious*	*Not serious*	*Not serious*	*none*	*96% (95% CI 94, 97)*		⊕⊕⊕⊕ *High*	*Critical*
Likelihood ratio for a (+) test	*1 study 567 patients*	*cross-sectional (cohort type accuracy study)*	*Not serious*	*Not serious*	*Not serious*	*Not serious*	*none*	*undefined*			*Critical*
Likelihood ratio for a (-) test	*1 study 567 patients*	*cross-sectional (cohort type accuracy study)*	*Not serious*	*Not serious*	*Not serious*	*Not serious*	*none*	*0.18 (95% CI 0.16, 0.19)*		⊕⊕⊕⊕ *High*	*Critical*

Explanations
a. Wide confidence interval
References
1.DiPietro GM, et al.;2021

* 8 % pretest probability of COVID-19 among children 0-14 y/o. [27]
**33% pretest probability of ICU admission among hospitalized COVID-19 children [28,29]

Appendix 4D. GRADE Evidence Profile: Nasopharyngeal aspirate RT-PCR

Author(s): Eva I. Bautista, MD, Ma. Lucila M. Perez, MD, Maria Teresa S. Tolosa, MD
Question: Should NPA RT-PCR be used to diagnose COVID-19 in children?
Setting: Hospital

Sensitivity	*0.81 (95% CI: 0.63 to 0.93)*
Specificity	*0.93 (95% CI: 0.90 to 0.94)*

Prevalence	*8 %**	*33%***	

Outcome	*№ of studies (№ of patients)*	*Study design*	*Factors that may decrease certainty of evidence*					*Effect per 1,000 patients tested*		*Test accuracy CoE*	*Importance*
			Risk of bias	*Indirectness*	*Inconsistency*	*Imprecision*	*Publication bias*	*pre-test probability of8%*	*pre-test probability of33%*		
***True positives** (patients with COVID-19)*	*1 studies 31 specimens*	*cross-sectional (cohort type accuracy study)*	*serious[1,a]*	*not serious*	*not serious*	*serious[1,b]*	*none*	*65 (50 to 74)*	*267 (208 to 307)*	*⨁⨁◯◯ Low*	*Critical*
***False negatives** (patients incorrectly classified as not having COVID-19)*								*15 (6 to 30)*	*63 (23 to 122)*		*Critical*
***True negatives** (patients without COVID-19)*	*1 studies 269 specimens*	*cross-sectional (cohort type accuracy study)*	*serious[1,a]*	*not serious*	*not serious*	*not serious*	*none*	*856 (828 to 865)*	*623 (603 to 630)*	*⨁⨁⨁◯ Moderate*	*Critical*
***False positives** (patients incorrectly classified as having COVID-19)*								*64 (55 to 92)*	*47 (40 to 67)*		*Critical*

Outcome	№ of studies (№ of patients)	Study design	Factors that may decrease certainty of evidence					Effect per 1,000 patients tested		Test accuracy CoE	Importance
			Risk of bias	Indirectness	Inconsistency	Imprecision	Publication bias	pre-test probability of8%	pre-test probability of33%		
Positive Predictive Value	*1 study 43 specimens*	*cross-sectional (cohort type accuracy study)*	*serious[1,a]*	*Not serious*	*Not serious*	*Not serious*	*none*	*58% (95% CI 43, 72*		⊕⊕⊕◯ *Moderate*	*Critical*
Negative Predictive Value	*1 study 257 specimens*	*cross-sectional (cohort type accuracy study)*	*serious[1,a]*	*Not serious*	*Not serious*	*Not serious*	*none*	*98% (95% CI 95, 99)*		⊕⊕⊕◯ *Moderate*	*Critical*
Likelihood ratio for a (+) test	*1 study 567 specimens*	*cross-sectional (cohort type accuracy study)*	*serious[1,a]*	*Not serious*	*Not serious*	*Not serious*	*none*	*undefined*		⊕⊕⊕◯ *Moderate*	*Critical*
Likelihood ratio for a (-) test	*1 study 567 specimens*	*cross-sectional (cohort type accuracy study)*	*serious[1,a]*	*Not serious*	*Not serious*	*Not serious*	*none*	*0.18 (95% CI 0.16, 0.19)*		⊕⊕⊕◯ *Moderate*	*Critical*

Explanations
a. Timing of specimen collection. NPS was either collected before NPA collection or after NPA collection on follow-up.
b. wide Confidence Interval
References
1.DiPietro GM, et al.; 2021

* 8 % pretest probability of COVID-19 among children 0-14 y/o. [27]
**33% pretest probability of ICU admission among hospitalized COVID-19 children [28,29]

Appendix 4E. GRADE Evidence Profile: Saliva RT-PCR among hospitalized children

Author(s): Eva I. Bautista, MD, Ma. Lucila M. Perez, MD, Maria Teresa S. Tolosa, MD
Question: Should saliva RT-PCR be used to diagnose COVID-19 in hospitalized children?
Setting: Hospital

Sensitivity	0.85 (95% CI: 0.71 to 0.94)	Prevalence	8% *	33% *
Specificity	1.00 (95% CI: 0.91 to 1.00)			

Outcome	*№ of studies (№ of patients)*	*Study design*	*Factors that may decrease certainty of evidence*					*Effect per 1,000 patients tested*		*Test accuracy CoE*	*Importance*
			Risk of bias	*Indirectness*	*Inconsistency*	*Imprecision*	*Publication bias*	*pre-test probability of8%*	*pre-test probability of33%*		
True positives *(patients with COVID-19)*	*1 study 46 patients*	*cross-sectional (cohort type accuracy study)*	*serious[1,a]*	*not serious*	*not serious*	*serious[1,b]*	*none*	*68 (57 to 75)*	*281 (234 to 310)*	⊕⊕◯◯ *Low*	*Critical*
False negatives *(patients incorrectly classified as not having COVID-19)*								*12 (5 to 23)*	*49 (20 to 96)*		*Critical*
True negatives *(patients without COVID-19)*	*1 study 39 patients*	*cross-sectional (cohort type accuracy study)*	*serious[1,a]*	*not serious*	*not serious*	*not serious*	*none*	*920 (837 to 920)*	*670 (610 to 670)*	⊕⊕⊕◯ *Moderate*	*Critical*
False positives *(patients incorrectly classified as having COVID-19)*								*0 (0 to 83)*	*0 (0 to 60)*		*Critical*

Outcome	№ of studies (№ of patients)	Study design	Factors that may decrease certainty of evidence					Effect per 1,000 patients tested		Test accuracy CoE	Importance
			Risk of bias	Indirectness	Inconsistency	Imprecision	Publication bias	pre-test probability of8%	pre-test probability of33%		
Positive Predictive Value	*1 study 39 patients*	*cross-sectional (cohort type accuracy study)*	*serious[1,a]*	*Not serious*	*Not serious*	*Not serious*	*none*	*100% (95% CI 91, 100*		⊕⊕⊕◯ *Moderate*	*Critical*
Negative Predictive Value	*1 study 46 patients*	*cross-sectional (cohort type accuracy study)*	*serious[1,a]*	*Not serious*	*Not serious*	*serious[b]*	*none*	*85% (95% CI 72, 92)*		⊕⊕◯◯ *Low*	*Critical*
Likelihood ratio for a (+) test	*1 study 85 patients*	*cross-sectional (cohort type accuracy study)*	*serious[1,a]*	*Not serious*	*Not serious*	*Not serious*	*none*	*undefined*			*Critical*
Likelihood ratio for a (-) test	*1 study 85 patients*	*cross-sectional (cohort type accuracy study)*	*serious[1,a]*	*Not serious*	*Not serious*	*Not serious*	*none*	*0.15 (95% CI 0.12, 0.20)*		⊕⊕⊕◯ *Moderate*	*Critical*

Explanations
a. Saliva specimen was collected within 24-48 hours from
b. Wide confidence interval
References
1.Alenquer M, et al. 2021
* 8 % pretest probability of COVID-19 among children 0-14 y/o. [27]
**33% pretest probability of ICU admission among hospitalized COVID-19 children [28,29]

Appendix 4F. GRADE Evidence Profile: Saliva RT-PCR among non-hospitalized children

Author(s): Eva I. Bautista, MD, Ma. Lucila M. Perez, MD, Maria Teresa S. Tolosa, MD
Question: Should saliva RT-PCR be used to diagnose COVID-19 in children in outpatient setting?
Setting: Ambulatory

Sensitivity	0.85 (95% CI: 0.75 to 0.92)	Prevalence	8% *	33 %**
Specificity	0.98 (95% CI: 0.97 to 0.99)			

Outcome	*№ of studies (№ of patients)*	*Study design*	*Factors that may decrease certainty of evidence*					*Effect per 1,000 patients tested*		*Test accuracy CoE*	*Importance*
			Risk of bias	*Indirectness*	*Inconsistency*	*Imprecision*	*Publication bias*	*pre-test probability of8%*	*pre-test probability of33%*		
***True positives** (patients with COVID-19)*	*6 studies 318 patients*	*cross-sectional (cohort type accuracy study)*	*serious[1,a]*	*not serious*	*serious[2,3,b]*	*serious[3,c,d]*	*none*	*68 (60 to 74)*	*281 (248 to 304)*	⨁◯◯◯ *Very low*	*Critical*
***False negatives** (patients incorrectly classified as not having COVID-19)*								*12 (6 to 20)*	*49 (26 to 82)*		*Critical*
***True negatives** (patients without COVID-19)*	*6 studies 988 patients*	*cross-sectional (cohort type accuracy study)*	*serious[1,a]*	*not serious*	*not serious*	*not serious*	*none*	*902 (892 to 911)*	*657 (650 to 663)*	⨁⨁⨁◯ *Moderate*	*Critical*
***False positives** (patients incorrectly classified as having COVID-19)*								*18 (9 to 28)*	*13 (7 to 20)*		*Critical*

Outcome	№ of studies (№ of patients)	Study design	Factors that may decrease certainty of evidence					Effect per 1,000 patients tested		Test accuracy CoE	Importance
			Risk of bias	Indirectness	Inconsistency	Imprecision	Publication bias	pre-test probability of8%	pre-test probability of33%		
Positive Predictive Value	*6 studies 286 patients*	*cross-sectional (cohort type accuracy study)*	*serious[1,a]*	*not serious*	*serious[2,3,d]*	*Not serious*	*none*	*94% (95% CI 90, 96)*		⊕⊕◯◯ *Low*	*Critical*
Negative Predictive Value	*6 studies 1020 patients*	*cross-sectional (cohort type accuracy study)*	*serious[1,a]*	*Not serious*	*Serious [1, 2, d]*	*Not serious*	*none*	*95% (95% CI 93, 96)*		⊕⊕◯◯ *Low*	*Critical*
Likelihood ratio for a (+) test	*6 studies 1306 patients*	*cross-sectional (cohort type accuracy study)*	*serious[1,a]*	*Not serious*	*Serious [1, 4, d]*	*Not serious*	*none*	*46 (95% CI 41, 51)*		⊕⊕◯◯ *Low*	*Critical*
Likelihood ratio for a (-) test	*6 studies 1306 patients*	*cross-sectional (cohort type accuracy study)*	*serious[1,a]*	*Not serious*	*Serious [1, 2, 4, d]*	*Not serious*	*none*	*0.17 (95% CI 0.16, 0.17)*		⊕⊕◯◯ *Low*	*Critical*

Explanations
a. 109 (33%) participants were included in the analysis out of 335 included children.
b. I2= 80 %
c. small sample size
References
1.Banerjee D, et al. 2021
2.Trobajo-Sanmartín, et al. 2021
3.Felix AC, et al. 2021

* 8 % pretest probability of COVID-19 among children 0-14 y/o. [27]
**33% pretest probability of ICU admission among hospitalized COVID-19 children [28,29]

Appendix 4G. GRADE Evidence Profile: Self-collected saliva for RT-PCR

Author(s): Eva I. Bautista, MD, Ma. Lucila M. Perez, MD, Maria Teresa S. Tolosa, MD
Question: Should self-collected saliva for RT-PCR be used to diagnose COVID-19 in children?
Setting: Ambulatory

Sensitivity	*0.83 (95% CI: 0.77 to 0.88)*	*Prevalence*	*8% **	*33% ***
Specificity	*0.98 (95% CI: 0.97 to 0.99)*			

Outcome	*№ of studies (№ of patients)*	*Study design*	*Factors that may decrease certainty of evidence*					*Effect per 1,000 patients tested*		*Test accuracy CoE*	*Importance*
			Risk of bias	*Indirectness*	*Inconsistency*	*Imprecision*	*Publication bias*	*pre-test probability of8%*	*pre-test probability of33%*		
True positives *(patients with COVID-19)*	*5 studies 219 patients*	*cross-sectional (cohort type accuracy study)*	*serious[1,2,a]*	*not serious*	*serious[1,2,3,4,5, b, d]*	*serious[4,c]*	*none*	*66 (62 to 70)*	*274 (254 to 290)*	⨁◯◯◯ *Very low*	*Critical*
False negatives *(patients incorrectly classified as not having COVID-19)*								*14 (10 to 18)*	*56 (40 to 76)*		*Critical*
True negatives *(patients without COVID-19)*	*5 studies 690 patients*	*cross-sectional (cohort type accuracy study)*	*serious[1,2,a]*	*not serious*	*not serious*	*not serious*	*none*	*902 (892 to 911)*	*657 (650 to 663)*	⨁⨁⨁◯ *Moderate*	*Critical*
False positives *(patients incorrectly classified as having COVID-19)*								*18 (9 to 28)*	*13 (7 to 20)*		*Critical*

Outcome	№ of studies (№ of patients)	Study design	Factors that may decrease certainty of evidence					Effect per 1,000 patients tested		Test accuracy CoE	Importance
			Risk of bias	Indirectness	Inconsistency	Imprecision	Publication bias	pre-test probability of8%	pre-test probability of33%		
Positive Predictive Value	*5 studies 195 patients*	*cross-sectional (cohort type accuracy study)*	*serious[1,2,a]*	*not serious*	*serious[1,2,3,4,5,b,d]*	*serious[4,c]*	*none*	*93% (95% CI 89, 96*		⨁◯◯◯ *Very low*	*Critical*
Negative Predictive Value	*5 studies 714 patients*	*cross-sectional (cohort type accuracy study)*	*serious[1,a]*	*Not serious*	*Serious 1, 2, 5, d*	*Not serious*	*none*	*95% (95% CI 93, 96)*		⨁⨁◯◯ *Low*	*Critical*
Likelihood ratio for a (+) test	*5 studies 909 patients*	*cross-sectional (cohort type accuracy study)*	*serious[1,a]*	*Not serious*	*Serious 2, 5, , d*	*Not serious*	*none*	*44 (95% CI 38, 51)*		⨁⨁◯◯ *Low*	*Critical*
Likelihood ratio for a (-) test	*5 studies 909 patients*	*cross-sectional (cohort type accuracy study)*	*serious[1,a]*	*Not serious*	*Serious 1, 2. 5, d*	*Not serious*	*none*	*0.17 (95% CI 0.16, 0.18)*		⨁⨁◯◯ *Low*	*Critical*

Explanations
a. non-inclusion of some children in the analysis
b. different RT-PCR assays used
c. small sample size
References
1.Trobajo-Sanmartín, et al. 2021;
2.Banerjee D, et al. 2021.;
3.Huber M, et al. 2021.;
4.Felix AC, et al. 2021.
5.Alenquer, et al. 2021.

* 8 % pretest probability of COVID-19 among children 0-14 y/o. [27]
**33% pretest probability of ICU admission among hospitalized COVID-19 children [28,29]

Appendix 4H. GRADE Evidence Profile: HCW/Caregiver-collected saliva for RT-PCR

Author(s): Eva I. Bautista, MD, Ma. Lucila M. Perez, MD, Maria Teresa S. Tolosa, MD
Question: Should saliva collected by healthcare worker or caregiver for RT-PCR be used to diagnose COVID-19 in children?
Setting: Hospital

Sensitivity	*0.85 (95% CI: 0.71 to 0.94)*	*Prevalence*	*8% **	*33% ***
Specificity	*1.00 (95% CI: 0.91 to 1.00)*			

Outcome	*№ of studies (№ of patients)*	*Study design*	*Factors that may decrease certainty of evidence*					*Effect per 1,000 patients tested*		*Test accuracy CoE*	*Importance*
			Risk of bias	*Indirectness*	*Inconsistency*	*Imprecision*	*Publication bias*	*pre-test probability of8%*	*pre-test probability of33%*		
True positives *(patients with COVID-19)*	*1 studies 46 patients*	*cross-sectional (cohort type accuracy study)*	*serious[1,a]*	*not serious*	*not serious*	*serious[1,b]*	*none*	*68 (57 to 75)*	*281 (234 to 310)*	⊕⊕◯◯ *Low*	*Critical*
False negatives *(patients incorrectly classified as not having COVID-19)*								*12 (5 to 23)*	*49 (20 to 96)*		*Critical*
True negatives *(patients without COVID-19)*	*1 studies 39 patients*	*cross-sectional (cohort type accuracy study)*	*serious[1,a]*	*not serious*	*not serious*	*not serious*	*none*	*920 (837 to 920)*	*670 (610 to 670)*	⊕⊕⊕◯ *Moderate*	*Critical*
False positives *(patients incorrectly classified as having COVID-19)*								*0 (0 to 83)*	*0 (0 to 60)*		*Critical*

Outcome	№ of studies (№ of patients)	Study design	Factors that may decrease certainty of evidence					Effect per 1,000 patients tested		Test accuracy CoE	Importance
			Risk of bias	Indirectness	Inconsistency	Imprecision	Publication bias	pre-test probability of8%	pre-test probability of33%		
Positive Predictive Value	*1 study 39 patients*	*cross-sectional (cohort type accuracy study)*	*serious[1,a]*	*not serious*	*not serious*	*Not serious*	*none*	*100% (95% CI 91, 100*		⊕⊕⊕◯ *Moderate*	*Critical*
Negative Predictive Value	*1 study 46 patients*	*cross-sectional (cohort type accuracy study)*	*serious[1,a]*	*Not serious*	*Not serious*	*serious[b]*	*none*	*85% (95% CI 72, 92)*		⊕⊕◯◯ *Low*	*Critical*
Likelihood ratio for a (+) test	*1 study 85 patients*	*cross-sectional (cohort type accuracy study)*	*serious[1,a]*	*Not serious*	*Not serious*	*Not serious*	*none*	*undefined*			*Critical*
Likelihood ratio for a (-) test	*1 study 85 patients*	*cross-sectional (cohort type accuracy study)*	*serious[1,a]*	*Not serious*	*Not serious*	*Not serious*	*none*	*0.15 (95% CI 0.12, 0.20)*		⊕⊕⊕◯ *Moderate*	*Critical*

Explanations

a. Saliva specimen was collected 24-48 hours after NPS collection.

b. wide confidence interval

References

1.Alenquer M, et al. 2021

* 8 % pretest probability of COVID-19 among children 0-14 y/o. [27]

**33% pretest probability of ICU admission among hospitalized COVID-19 children [28,29]

Appendix 4I. GRADE Evidence Profile: Saliva Allplex nCoV assay

Author(s): Eva I. Bautista, MD, Ma. Lucila M. Perez, MD, Maria Teresa S. Tolosa, MD
Question: *Should saliva Allplex nCoV assay be used to diagnose COVID-19 in children?*
Setting: Outpatient

Sensitivity	*0.76 (95% CI: 0.68 to 0.83)*	*Prevalence*	*8% **	*33% ***
Specificity	*0.99 (95% CI: 0.97 to 1.00)*			

Outcome	*№ of studies (№ of patients)*	*Study design*	*Factors that may decrease certainty of evidence*					*Effect per 1,000 patients tested*		*Test accuracy CoE*	*Importance*
			Risk of bias	*Indirectness*	*Inconsistency*	*Imprecision*	*Publication bias*	*pre-test probability of8%*	*pre-test probability of33%*		
True positives *(patients with COVID-19)*	*2 studies 122 patients*	*cross-sectional (cohort type accuracy study)*	*serious[1,a]*	*not serious*	*Serious[1,2,b]*	*not serious*	*none*	*61 (54 to 66)*	*251 (224 to 274)*	⊕⊕◯◯ *Low*	*Critical*
False negatives *(patients incorrectly classified as not having COVID-19)*								*19 (14 to 26)*	*79 (56 to 106)*		*Critical*
True negatives *(patients without COVID-19)*	*2 studies 457 patients*	*cross-sectional (cohort type accuracy study)*	*serious[1,a]*	*not serious*	*not serious*	*not serious*	*none*	*911 (892 to 920)*	*663 (650 to 670)*	⊕⊕⊕◯ *Moderate*	*Critical*
False positives *(patients incorrectly classified as having COVID-19)*								*9 (0 to 28)*	*7 (0 to 20)*		*Critical*
Inconclusive	*0 studies patients*	-	-	-	-	-	-			-	
Complications	*0 studies patients*									-	

Explanations
a. Unclear in the number of patients excluded in the analysis
b. 95 % confidence intervals do not overlap.
References
1.Trobajo-Sanmartín C, et al. 2021.
2. Al-Suwaidi H, et al. 2021
* 8 % pretest probability of COVID-19 among children 0-14 y/o. [27]
**33% pretest probability of ICU admission among hospitalized COVID-19 children [28,29]

Appendix 4J. GRADE Evidence Profile: Cobas 6800 assay

Author(s): Eva I. Bautista, MD, Ma. Lucila M. Perez, MD, Maria Teresa S. Tolosa, MD
Question: *Should saliva Cobas 6800 assay be used to diagnose COVID-19 in children?*
Setting: Outpatient

Sensitivity	*0.93 (95% CI: 0.78 to 0.99)*	*Prevalence*	*8% **	*33% ***
Specificity	*0.96 (95% CI: 0.92 to 0.99)*			

Outcome	*№ of studies (№ of patients)*	*Study design*	*Factors that may decrease certainty of evidence*					*Effect per 1,000 patients tested*		*Test accuracy CoE*	*Importance*
			Risk of bias	*Indirectness*	*Inconsistency*	*Imprecision*	*Publication bias*	*pre-test probability of8%*	*pre-test probability of33%*		
True positives *(patients with COVID-19)*	*1 studies 101 patients*	*cross-sectional (cohort type accuracy study)*	*not serious*	*not serious*	*not serious*	*serious[1,a]*	*none*	*74 (62 to 79)*	*307 (257 to 327)*	⨁⨁⨁◯ *Moderate*	*Critical*
False negatives *(patients incorrectly classified as not having COVID-19)*								*6 (1 to 18)*	*23 (3 to 73)*		*Critical*
True negatives *(patients without COVID-19)*	*1 studies 296 patients*	*cross-sectional (cohort type accuracy study)*	*not serious*	*not serious*	*not serious*	*not serious*	*none*	*883 (846 to 911)*	*643 (616 to 663)*	⨁⨁⨁⨁ *High*	*Critical*
False positives *(patients incorrectly classified as having COVID-19)*								*37 (9 to 74)*	*27 (7 to 54)*		*Critical*
Inconclusive	*0 studies patients*	-	-	-	-	-	-			-	
Complications	*0 studies patients*									-	

Explanations
a. wide Confidence Interval
References
1.Fougere, et al. 2021.

* 8 % pretest probability of COVID-19 among children 0-14 y/o. [27]
**33% pretest probability of ICU admission among hospitalized COVID-19 children [28,29]

Appendix 4K. GRADE Evidence Profile: Altona Realstar Kit assay

Author(s): Eva I. Bautista, MD, Ma. Lucila M. Perez, MD, Maria Teresa S. Tolosa, MD
Question: *Should saliva Altona Realstar kit assay be used to diagnose COVID-19 in children?*
Setting: Outpatient

Sensitivity	*0.80 (95% CI: 0.44 to 0.97)*	*Prevalence*	*8% **	*33% ***
Specificity	*1.00 (95% CI: 0.91 to 1.00)*			

Outcome	*№ of studies (№ of patients)*	*Study design*	*Factors that may decrease certainty of evidence*					*Effect per 1,000 patients tested*		*Test accuracy CoE*	*Importance*
			Risk of bias	*Indirectness*	*Inconsistency*	*Imprecision*	*Publication bias*	*pre-test probability of8%*	*pre-test probability of33%*		
True positives *(patients with COVID-19)*	*1 studies 10 patients*	*cross-sectional (cohort type accuracy study)*	*serious[1,a]*	*not serious*	*not serious*	*serious*	*none*	*64 (35 to 78)*	*264 (145 to 320)*	⨁⨁◯◯ *Low*	*Critical*
False negatives *(patients incorrectly classified as not having COVID-19)*								*16 (2 to 45)*	*66 (10 to 185)*		*Critical*
True negatives *(patients without COVID-19)*	*1 studies 40 patients*	*cross-sectional (cohort type accuracy study)*	*serious[1,a]*	*not serious*	*not serious*	*not serious*	*none*	*920 (837 to 920)*	*670 (610 to 670)*	⨁⨁⨁◯ *Moderate*	*Critical*
False positives *(patients incorrectly classified as having COVID-19)*								*0 (0 to 83)*	*0 (0 to 60)*		*Critical*
Inconclusive	*0 studies patients*	-	-	-	-	-	-			-	
Complications	*0 studies patients*									-	

Explanations
a. unclear if reference test was interpreted independently from the index test
References
1.Felix AC, et al. 2021.

* 8 % pretest probability of COVID-19 among children 0-14 y/o. [27]
**33% pretest probability of ICU admission among hospitalized COVID-19 children [28,29]

Appendix 4L. GRADE Evidence Profile: ITaq Universal Probes assay

Author(s): Eva I. Bautista, MD, Ma. Lucila M. Perez, MD, Maria Teresa S. Tolosa, MD
Question: Should saliva Itaq Universal Probes assay be used to diagnose COVID-19 in children?
Setting: Hospital

Sensitivity	*0.85 (95% CI: 0.71 to 0.94)*	*Prevalence*	*8% **	*33% ***
Specificity	*1.00 (95% CI: 0.91 to 1.00)*			

Outcome	*№ of studies (№ of patients)*	*Study design*	*Factors that may decrease certainty of evidence*					*Effect per 1,000 patients tested*		*Test accuracy CoE*	*Importance*
			Risk of bias	*Indirectness*	*Inconsistency*	*Imprecision*	*Publication bias*	*pre-test probability of8%*	*pre-test probability of33%*		
True positives *(patients with COVID-19)*	*1 studies 46 patients*	*cross-sectional (cohort type accuracy study)*	*serious[1,a]*	*not serious*	*not serious*	*serious[1,b]*	*none*	*68 (57 to 75)*	*281 (234 to 310)*	⊕⊕◯◯ *Low*	*Critical*
False negatives *(patients incorrectly classified as not having COVID-19)*								*12 (5 to 23)*	*49 (20 to 96)*		*Critical*
True negatives *(patients without COVID-19)*	*1 studies 39 patients*	*cross-sectional (cohort type accuracy study)*	*serious[1,a]*	*not serious*	*not serious*	*not serious*	*none*	*920 (837 to 920)*	*670 (610 to 670)*	⊕⊕⊕◯ *Moderate*	*Critical*
False positives *(patients incorrectly classified as having COVID-19)*								*0 (0 to 83)*	*0 (0 to 60)*		*Critical*
Inconclusive	*0 studies patients*	-	-	-	-	-	-			-	
Complications	*0 studies patients*									-	

Explanations
a. Timing of specimen collection. Saliva specimen was collected 24- 48 hours after NPS collection.
b. small sample size
References
1.Alenquer M, et al. 2021.
* 8 % pretest probability of COVID-19 among children 0-14 y/o. [27]
**33% pretest probability of ICU admission among hospitalized COVID-19 children [28,29]

Appendix 4M. GRADE Evidence Profile: Aptima SARS-CoV-2-Assay

Author(s): Eva I. Bautista, MD, Ma. Lucila M. Perez, MD, Maria Teresa S. Tolosa, MD
Question: *Should saliva Aptima SARS-CoV-2 assay be used to diagnose COVID-19 in children?*
Setting: Outpatient

Sensitivity	*0.93 (95% CI: 0.83 to 0.98)*	*Prevalence*	*8% **	*33% ***
Specificity	*0.96 (95% CI: 0.87 to 1.00)*			

Outcome	*№ of studies (№ of patients)*	*Study design*	*Factors that may decrease certainty of evidence*					*Effect per 1,000 patients tested*		*Test accuracy CoE*	*Importance*
			Risk of bias	*Indirectness*	*Inconsistency*	*Imprecision*	*Publication bias*	*pre-test probability of8%*	*pre-test probability of33%*		
True positives *(patients with COVID-19)*	*1 studies 57 patients*	*cross-sectional (cohort type accuracy study)*	*serious[1,a]*	*not serious*	*not serious*	*Serious [b]*	*none*	*74 (66 to 78)*	*307 (274 to 323)*	⨁⨁◯◯ *Low*	*Critical*
False negatives *(patients incorrectly classified as not having COVID-19)*								*6 (2 to 14)*	*23 (7 to 56)*		*Critical*
True negatives *(patients without COVID-19)*	*1 studies 53 patients*	*cross-sectional (cohort type accuracy study)*	*serious[1,a]*	*not serious*	*not serious*	*not serious*	*none*	*883 (800 to 920)*	*643 (583 to 670)*	⨁⨁⨁◯ *Moderate*	*Critical*
False positives *(patients incorrectly classified as having COVID-19)*								*37 (0 to 120)*	*27 (0 to 87)*		*Critical*
Inconclusive	*0 studies patients*	-	-	-	-	-	-			-	
Complications	*0 studies patients*									-	

Explanations
a. non-inclusion of other participants in the analysis
b. wide Confidence Interval
References
1.Banerjee D, et al. 2021.
* 8 % pretest probability of COVID-19 among children 0-14 y/o. [27]
**33% pretest probability of ICU admission among hospitalized COVID-19 children [28,29]

Appendix 4N. GRADE Evidence Profile: Adverse events of saliva RT-PCR

Author(s): Eva I. Bautista, MD, Ma. Lucila M. Perez, MD, Maria Teresa S. Tolosa, MD
Question: Should Saliva for RT-PCR compared to NPS/OPS RT-PCR be used to diagnose COVID-19?
Setting: Hospitalized

Certainty assessment							Impact	Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations			
Adverse events									
1	observational studies	not serious	not serious	not serious	not serious	none	There were no reported adverse events in 156 hospitalized children suspected of COVID-19 who had saliva and NPS/OPS RT-PCR. [1]	⨁⨁◯◯ Low	IMPORTANT

Reference

1. Guzman-Ortiz AL, et al. 2021

Appendix 5. Forest Plots

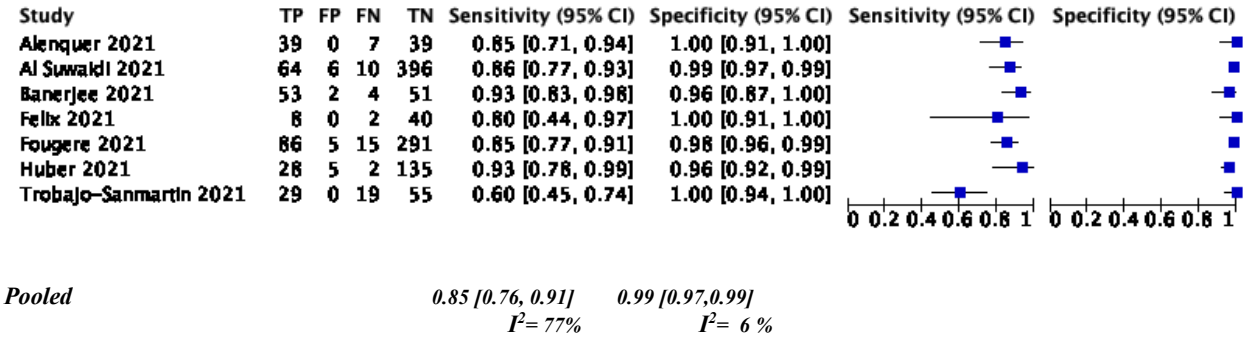

Figure 1. Forest plot of the sensitivity and specificity of saliva RT-PCR

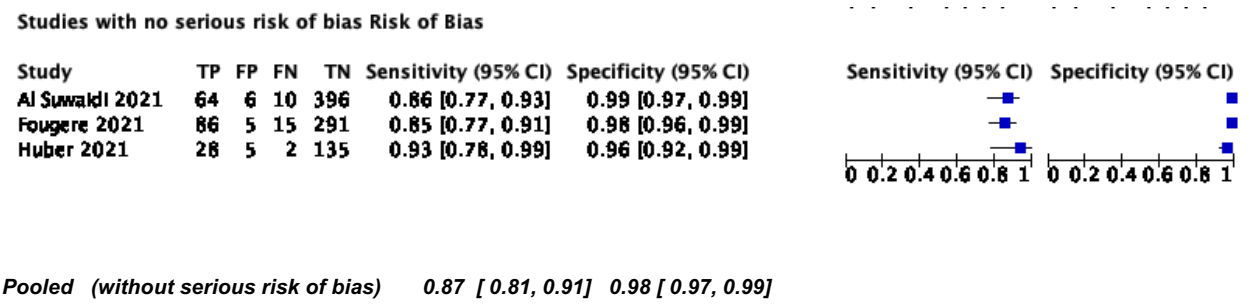

Figure 2. Forest plot of the sensitivity analysis of saliva RT-PCR: Studies with no serious risk of bias

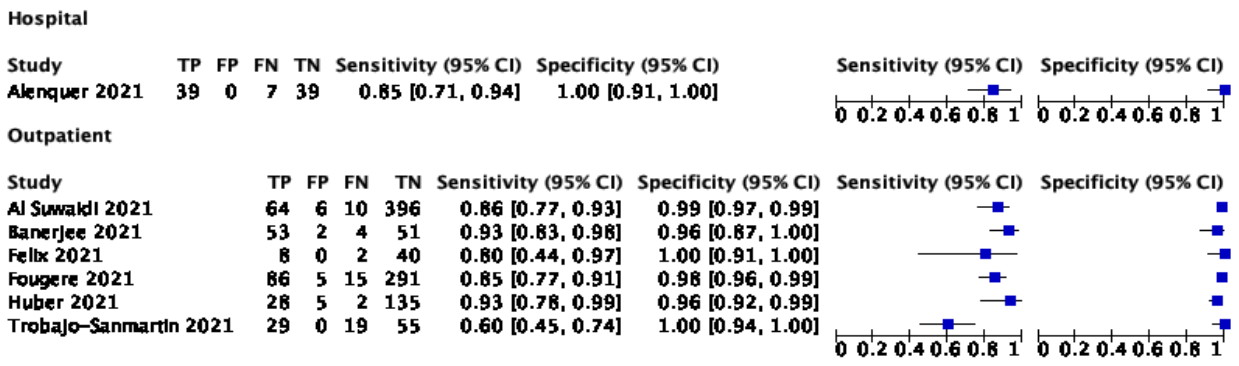

Figure 3. Forest plot of the sensitivity and specificity of saliva RT-PCR according to setting (hospital vs outpatient)

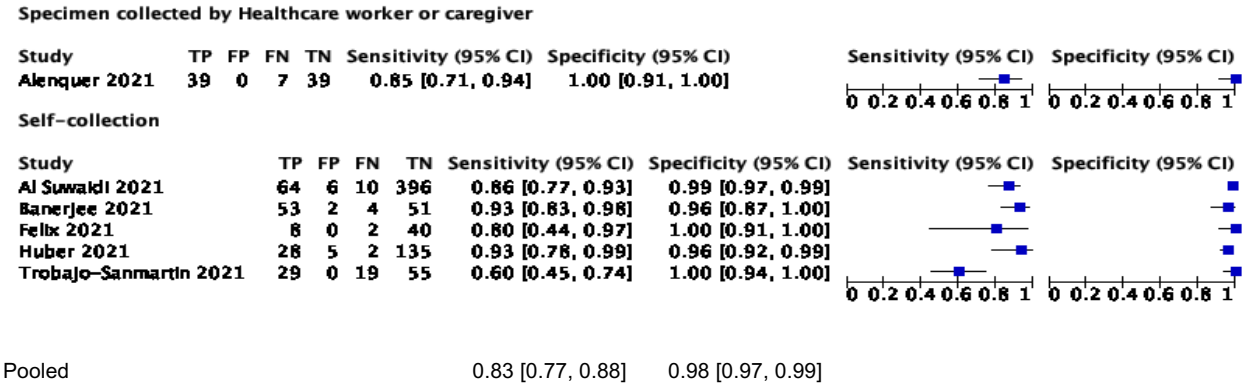

Figure 4. Forest plot of the sensitivity and specificity of saliva RT-PCR by method of collection

Appendix 6. Evidence to Decision Framework

Table 1. Summary of initial judgements prior to the panel discussion (N = 10)

FACTORS	JUDGEMENT (N = 10)							RESEARCH EVIDENCE/ADDITIONAL CONSIDERATIONS
Problem	No	Yes (10)		Varies		Uncertain		
Benefits	Large (1)	Moderate (9)	Small	Trivial	Varies	Uncertain		• Saliva specimen is preferred by majority of children 2-11 years old
Harm	Large	Moderate	Small (10)	Trivial	Varies	Uncertain		• Median score: 4/10 for discomfort
Certainty of evidence	High	Moderate (6)		Low (4)		Very low		• Saliva: moderate • Mid-turbinate: moderate • NPA: low
Balance of effects	Favors test (5)	Probably favors test (5)	Does not favor test or no test	Probably favors no test	Favors no test	Varies	Uncertain (8)	
Accuracy	Very accurate	Accurate (7)	Inaccurate	Very inaccurate	Varies	Uncertain (3)		• Saliva and mid-turbinate: moderate Sn, high Sp, wide CI • Insufficient for NPA
Values	Important uncertainty or variability (1)	Possibly important uncertainty or variability (3)		Probably no important uncertainty or variability (6)		No important uncertainty or variability		
Resources required	Uncertain (1)	Varies	Large costs (2)	Moderate costs (7)	Negligible costs or savings	Moderate savings	Large savings	
Certainty of evidence of resources required	No included studies (9)		Very low	Low (1)	Moderate	High		
Cost-effectiveness	No included studies (9)	Varies	Favors the comparison (1)	Probably favors the comparison	Does not favor the comparison or the intervention	Probably favors the intervention	Favors the intervention	
Equity	Uncertain (1)	Varies (2)	Reduced	Probably reduced (4)	Probably no impact	Probably increased (3)	Increased	
Acceptability	Uncertain (3)	Varies (1)	No	Probably no	Probably yes (5)	Yes (1)		
Feasibility	Uncertain (3)	Varies	No	Probably no	Probably yes (6)	Yes (1)		

Additional Comments

- Equity, acceptability and feasibility depend on whether there will be enough Philhealth/government support to shoulder these costs.