The Sensitivity and Costs of Testing for SARS-CoV-2 Infection With Saliva Versus Nasopharyngeal Swabs : A Systematic Review and Meta-analysis

8/10 醫學檢驗科 黃俊凱

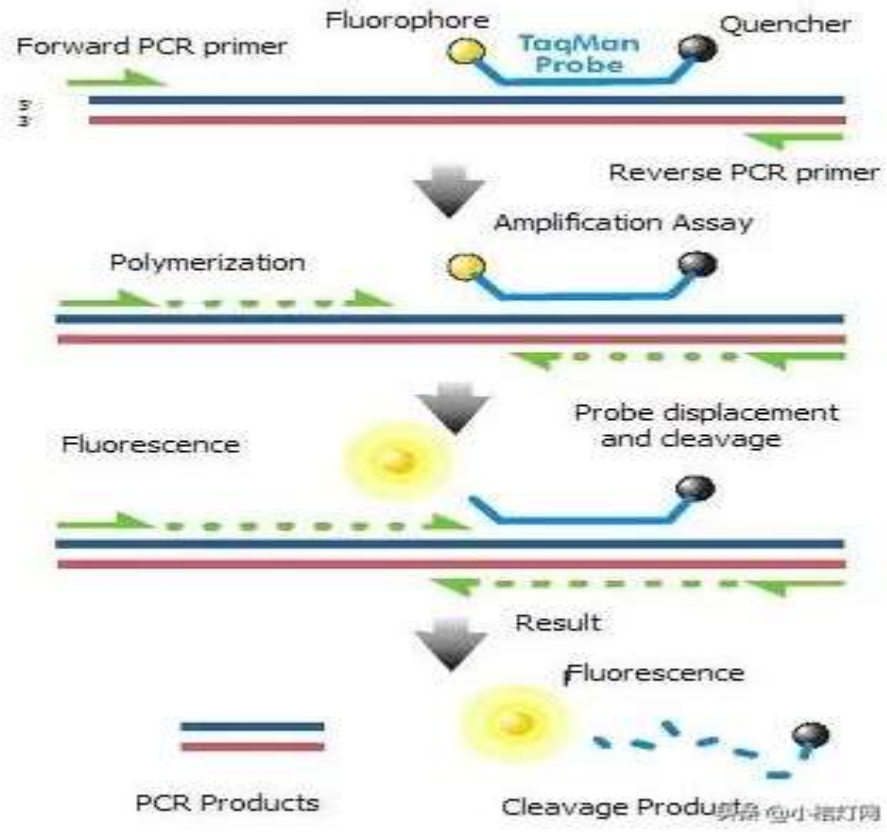
檢驗科同仁請掃QR Code報到

Outlier

- Covid 19 核酸檢驗介紹
- 認識實證
- 形成PICO
- 文章評讀
- 問題討論

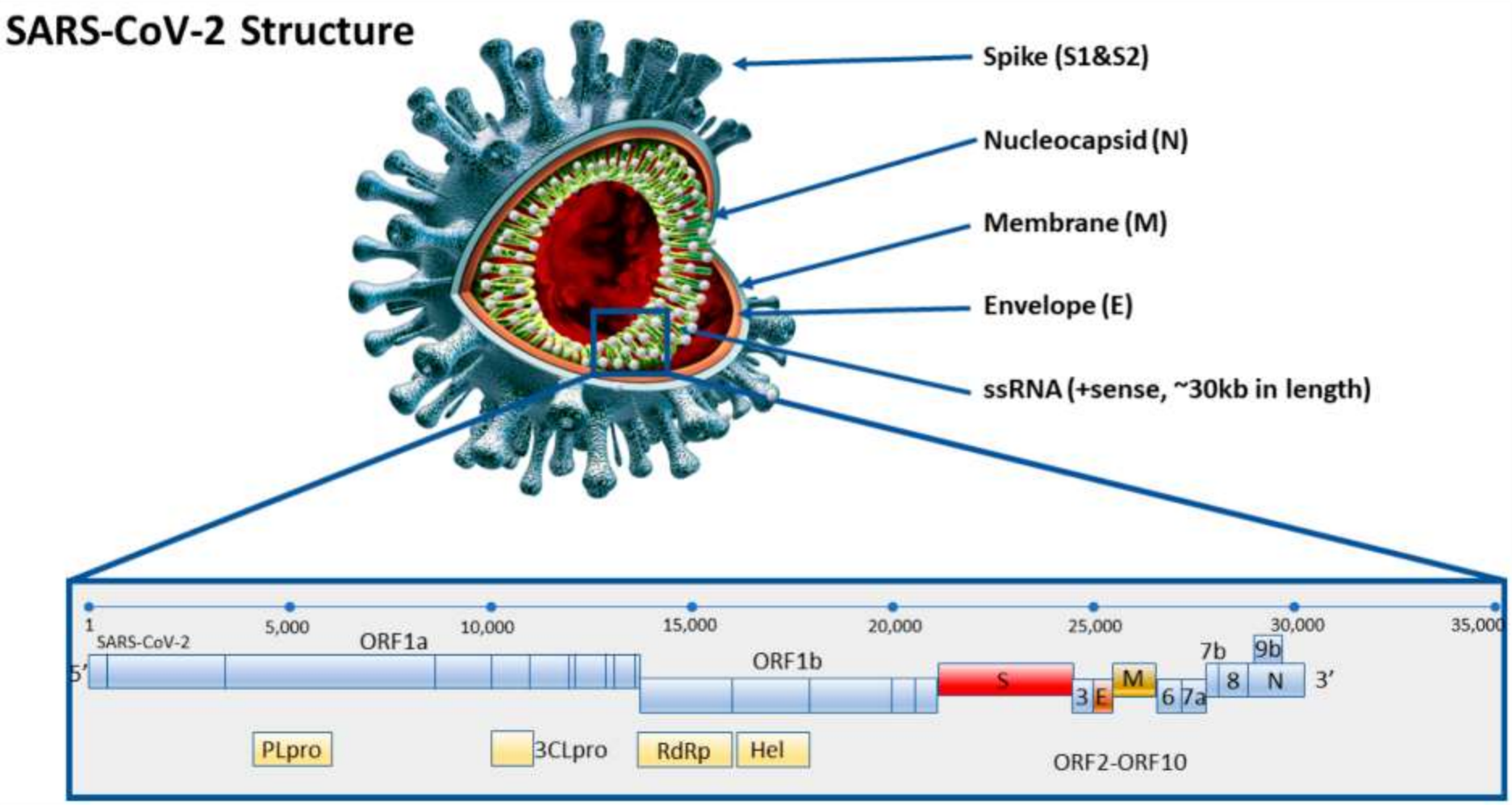
COVID核酸檢驗介紹

Real-time PCR(qPCR)



透過人工合成的TaqMan probe (oligonucleotid)，在oligonucleotid兩端分別標定上不同螢光物質，而這兩螢光物質彼此間距離太近時會遮蔽掉彼此的螢光，因此無法偵測到螢光，但是當DNA進行複製時，oligonucleotid會被切割水解，讓兩個螢光物質分開，因此能偵測到螢光，螢光越強代表PCR產物越多。

Figure 1. Real Time PCR COVID-19 genetic tests detecting ORF1ab, spike (S), envelope (E), or nucleocapsid (N) gene sequences of SARS-CoV-2 coronavirus (own interpretation, based on [8]).



Target gene fragment

檢測產品	Target gene
Xpert Xpress SARS-CoV-2	E / N2
Accula	E
QIAstat-Dx	Orf1ab / E
BioFire FilmArray	S / M
COVID-19 Go-Strips	ORF1ab / S
WizDx™ COVID-19 CrystalMix PCR kit	RdRP / E
Microchip RT-PCR COVID-19 Detection System	N1/N2
ARIES SARS-CoV-2	ORF1ab /N1/N3
iPonatic移動分子診斷系統	ORF1ab/N
2019新型冠狀病毒核酸檢測試劑盒（卡式螢光PCR法）	ORF1ab/N
Hologic SARS-CoV-2	兩個ORF1ab
ID now SARS-CoV-2	RdRP
Cobas 4800	E / RdRP
Liat	N / ORF1ab

認識實證

認識實證醫學

- 我們都處在資訊爆炸的時代，甚至無法讀完送達我們面前的所有科學文獻及其他資訊，而這些僅佔新研究資訊的一小部份：每天大約有 50 個新試驗及 2000 個新研究文章出版！
- 即使我們有時間讀完其中一些，也很難分辨哪些資料在臨床診療上最有用，同時很難在需要的時候，即時回想起最新醫療進展。但是，我們每天都會面臨一些臨床問題，為了確立最佳病患照護決策，我們必須一一解答這些問題，而這就是實證醫學的由來。
- **關於實證醫學五步驟，我至少應該知道哪些？**
- 實證醫學教育包括四個基本步驟：提問、搜尋、評讀及應用證據。

實證醫學中心

科部介紹

更新日期：2020/02/24

源起

文/ 陳杰峰主任

實證醫學(Evidence-Based Medicine) 的前身，是源自於臨床流行病學（ clinical epidemiology），1992 年後，因緣際會，因為internet 的普及，電腦運算快速，使統計更便捷，知識更新更即時，因此，讓實證醫學的實現成為可能。 發展至今，實證醫學的重點，主要有四大範疇：

1. 增進醫療決策技能 medical decision making technique
2. 改善醫療資訊擷取技能 accessing medical information
3. 嚴格評估醫療資訊及其臨床應用 assessing the validity of medical information
4. 促進專家間之合作，以作隨機對照試驗（RCT randomised controlled trials）的研究

而整個實證醫學的推行，有3大環節，完備的知識，先進的硬體設備，有理想的臨床工作者，缺一不可，本院於半年前，由於院長體認到此實證醫學潮流的重要性，及實際的需求，遂指示成立推動小組，籌建實證醫學中心，以萬芳醫院作實證醫學發展的基地，而以學校作為知識庫的泉源，以期最後能發展成醫學電子資料中心（ IDC internet data center）。

wanfang.gov.tw/p9_medical_detail.aspx?cu=172

實證5步驟

步驟1
- 形成可回答臨床問題

步驟2
- 搜尋最佳證據

步驟3
- 嚴格評讀

步驟4
- 運用結果

步驟5
- 評估成效與改善

形成PICO

步驟１：系統性文獻回顧探討的問題為何？

Question：一個問句簡潔有力表達臨床特定問題			
P	Patient/Problem	誰是病人：性別、年齡、種族、懷孕、肝腎功能、病史…. 何種疾病或症狀	COVID 19 感染
I	Intervention	關注的(實驗組)： 治療：方式、劑量、頻率…. 診斷工具 暴露因子	以Saliva-based檢體執行 COVID 19 RT-PCR檢驗
C	Comparison	對照的 治療：ex. Placebo 診斷工具： ex. Gold standard 暴露因子	以Nasopharyngeal Swabs執行 COVID 19 RT-PCR檢驗
O	Outcomes	臨床關注、對病患有意義可測量的結果	COVID 19 RT-PCR sensivitys

文章評讀

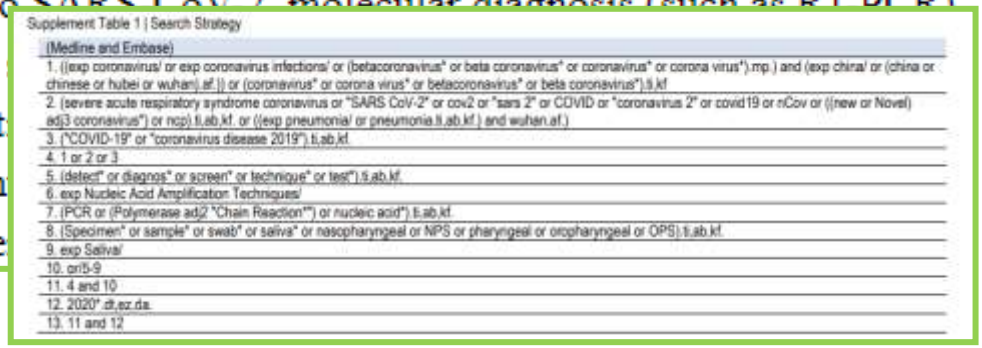
步驟 2：系統性文獻回顧的品質如何？(FAITH)

F - 研究是否找到 (Find) 所有的相關證據？

良好的文獻搜尋至少應包括二個主要的資料庫 (如：Medline, Cochrane 考科藍實證醫學資料庫, EMBASE 等)，並且加上文獻引用檢索(參考文獻中相關研究、Web of Science, Scopus 或 Google Scholar)、試驗登錄資料等。文獻搜尋應不只限於英文，並且應同時使用MeSH字串及一般檢索詞彙(text words)。

在文章的方法(Methods)章節，可以找到詳細搜尋策略的說明，包括使用的名詞。

Data Sources and Searches We searched Medline and Embase from 1 January to 1 November 2020. We used a comprehensive search strategy (Table 1 of Supplement 1) with a combination of medical subject headings and free text containing concepts related to SARS-CoV-2, molecular diagnosis (such as RT-PCR) and respiratory specimens (such as nasopharyngeal
We additionally searched medRxiv and bioRxiv unt
analytic code to screen for preprint manuscripts con
"saliva" in titles and abstracts before reviewer scree



Supplement Table 1 | Search Strategy

(Medline and Embase)
1. ((exp coronavirus/ or exp coronavirus infections/ or (betacoronavirus* or beta coronavirus* or coronavirus* or corona virus*).mp.) and (exp china/ or (china or chinese or hubei or wuhan).af.)) or (coronavirus* or corona virus* or betacoronavirus* or beta coronavirus*).ti,kf.
2. (severe acute respiratory syndrome coronavirus or "SARS CoV-2" or cov2 or "sars 2" or COVID or "coronavirus 2" or covid19 or nCov or ((new or Novel) adj3 coronavirus*) or ncp).ti,ab,kf. or ((exp pneumonia/ or pneumonia.ti,ab,kf.) and wuhan.af.)
3. ("COVID-19" or "coronavirus disease 2019").ti,ab,kf.
4. 1 or 2 or 3
5. (detect* or diagnos* or screen* or technique* or test*).ti,ab,kf.
6. exp Nucleic Acid Amplification Techniques/
7. (PCR or (Polymerase adj2 "Chain Reaction*") or nucleic acid*).ti,ab,kf.
8. (Specimen* or sample* or swab* or saliva* or nasopharyngeal or NPS or pharyngeal or oropharyngeal or OPS).ti,ab,kf.
9. exp Saliva/
10. or/5-9
11. 4 and 10
12. 2020*.dt,ez,da.
13. 11 and 12

評讀結果： ☑是 ☐否 ☐不清楚

步驟 2：系統性文獻回顧的品質如何？(FAITH)

F - 研究是否找到 (Find) 所有的相關證據？

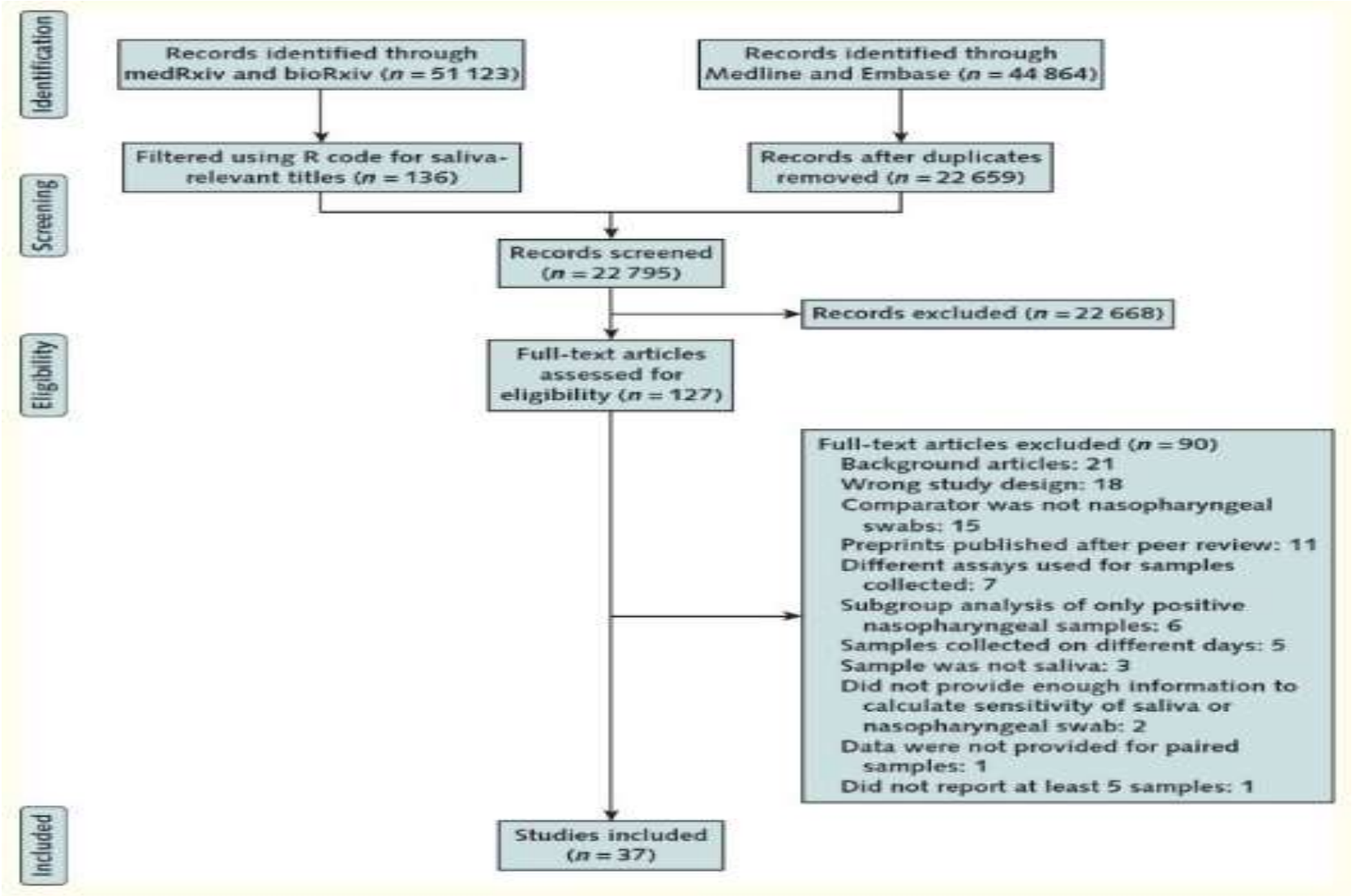
結果(Results) 章節中可以找到本篇系統性文獻回顧評估的摘要及全文文獻數目、文獻納入與排除的數量及原因。資料可能會以圖表或PRISMA的流程圖呈現。

Results Go to:

Systematic Review and Meta-analysis

Characteristics of Included Studies We identified 22 795 records for screening. After title and abstract screening, 127 studies entered full-text assessment. Overall, 37 studies (24–55-56–60) were included (Appendix Figure), comprising 7169 participants with 7332 paired saliva samples and nasopharyngeal swabs. Summary characteristics of included studies are reported in Table 1 and individual study characteristics in Tables 6 and 7 of Supplement 1. Of the 37 studies, 6 (16%) were at high or unclear risk of bias or applicability in 4 or more domains, 25 (68%) were at high or unclear risk of selection bias, and 32 (87%) were at high or unclear risk of bias due to blinding during sample analysis (Figure 1 of Supplement 1).

PRISMA 流程圖



評讀結果： ☑ 是 ☐否 ☐不清楚

步驟 2：系統性文獻回顧的品質如何？(FAITH)

A - 文獻是否經過嚴格評讀 (Appraisal)？

應根據不同臨床問題的文章類型，選擇適合的評讀工具，並說明每篇研究的品質(如針對治療型的臨床問題，選用隨機分配、盲法、及完整追蹤的研究類型)。

方法章節，可以找到所使用的文獻品質評讀標準的描述

結果章節則會列出每篇研究品質的評讀結果。

Risk of bias and applicability concerns among included studies were assessed using an adapted QUADAS-2 (Quality Assessment of Diagnostic Accuracy Studies 2) (11) tool. The tool assessed the following domains: patient selection, performance of the index test, performance of the reference test, and flow and timing (**Table 3** of **Supplement 1**). Two reviewers (M.L.B. and S.P.) independently assessed studies, and disagreement was resolved through consensus.

評讀結果： ☑是 □否 □不清楚

並說明每篇研究的品質(如針對治療型的臨床問題，選用隨機分配、盲法、及完整追蹤的研究類型)

Supplement Table 6 | Characteristics of Included Studies

Study	Peer Reviewed (Yes, No)	City and Country	Study Population	Time Period of Study	Setting (Inpatient, Outpatient)	Study Design	Symptoms (Symptomatic, Asymptomatic)
Azzi, et al. (5)	Yes	Varese, Italy	Both persons presenting for SARS-CoV-2 testing and persons with confirmed SARS-CoV-2 (results not stratified)	04/2020 - 05/2020	Both inpatient and outpatient (results not stratified)	Cohort	Both symptomatic and asymptomatic (results not stratified)
Chen, et al. (6)	Yes	Hong Kong, China	Persons with confirmed SARS-CoV-2	NR	Inpatient (non-specified)	Cohort	Symptomatic
Leung, et al. (7)	Yes	Hong Kong, China	Persons with confirmed SARS-CoV-2 (and negative controls)	02/2020 - 03/2020	Inpatient (non-specified setting)	Case-control (unmatched)	Symptomatic
McCormick-Baw, et al. (8)	Yes	Dallas, USA	Both persons presenting for SARS-CoV-2 testing and persons with confirmed SARS-CoV-2 (results not stratified)	NR	Inpatient (non-ICU only: hospitalized or emergency room)	Cohort	Symptomatic
Rao, et al. (9)	Yes	Kuala Lumpur, Malaysia	Persons with confirmed SARS-CoV-2	NR	Both inpatient and outpatient (results not stratified)	Cohort	Asymptomatic
Landry, et al. (10)	Yes	New Haven, USA	Persons presenting for SARS-CoV-2 testing	04/2020	Outpatient	Cohort	Symptomatic
Villar, et al. (11)	Yes	Rio de Janeiro, Brazil	Persons presenting for SARS-CoV-2 testing	NR	Outpatient	Cohort	Both symptomatic and asymptomatic (stratified results)
Akgun Dogan, et al. (12)	No	Istanbul, Turkey	Persons presenting for SARS-CoV-2 testing	NR	Inpatient (non-ICU only: hospitalized or emergency room)	Cohort	Symptomatic
Becker, et al. (13)	No	California, USA	Persons with confirmed SARS-CoV-2 Persons presenting for SARS-CoV-2 testing	03/2020 - 04/2020	Outpatient	Cohort	Symptomatic
Byrne, et al. (14)	Yes	Liverpool, UK	Persons presenting for SARS-CoV-2 testing	04/2020 - 06/2020	Both inpatient and outpatient (results not stratified)	Cohort	Symptomatic

並說明每篇研究的品質(如針對治療型的臨床問題，選用隨機分配、盲法、及完整追蹤的研究類型)

Supplement Table 7 | Patients' Characteristics for Included Studies

Study	N Participants Included	N Samples Tested	Age in Years (mean/median)	Male:Female	Symptom Severity
Azzi, et al. (5)	122	113	Mean: 53.5 (SD 19.8)	40:82	Mild or moderate or severe
Chen, et al. (6)	58	58	Median: 38 (IQR 31 – 52)	28:30	NR
Leung, et al. (7)	62	95	Mean: 42 (SD 17.1)	26:36	NR
McCormick-Baw, et al. (8)	156	155	Mean: 47.8	90:66	NR
Rao, et al. (9)	217	217	Median: 27 (IQR 18-36)	217:0	NR
Landry, et al. (10)	124	124	NR	NR	NR
Villar, et al. (11)	13	13	NR	NR	NR
Akgun Dogan, et al. (12)	200	200	Mean: 54.9 (SD 16.1)	106:94	Mild or moderate or severe
Becker, et al. (13)	111	109	NR	NR	NR
Byrne, et al. (14)	110	110	NR	49:61	NR
Griesemer, et al. (15)	463	463	NR	248:216	NR
Hanson, et al. (16)	368	354	Mean: 35 (range 18-75)	195:173	NR
Iwasaki, et al. (17)	76	76	Median: 69 (range 30-97)	NR	Mild and moderate
Jamal, et al. (18)	53	91	Median: 63 (range 27-106)	32:21	Mild or moderate or severe
Miller, et al. (19)	91	91	NR	NR	NR
Pasomsub, et al. (20)	200	200	Median: 36 (IQR 28-48)	69:131	NR
Ranoa, et al. (21)	100	99	NR	NR	NR
Wyllie, et al. (22)	142	97	NR	21:41	Asymptomatic, severe or critical
Bhattacharya, et al. (23)	74	74	NR	NR	Mild
Goldfarb, et al. (24)	50	38	Median: 25.1 (IQR 13.6-35.9)	22:28	NR
Ku, et al. (25)	42	42	NR	40:2	NR
Nacher, et al. (26)	776	776	Mean: 40 (SD 16.8)	NR	Mild
Sahajpal, et al. (27)	240	240	NR	NR	NR
Teo, et al. (28)	200	337	NR	NR	Mild or moderate or severe
Yee, et al. (29)	300	300	NR	NR	NR
Yokota, et al. (30)	42	42	Median: 73 (range 27-93)	25:17	NR
Yokota, et al. (31)	161	161	Median: 44.9 (IQR 29.8-66.4)	NR	NR
Barat, et al. (32)	449	459	Median: 42 (range 21-88)	184:265	NR
Aita, et al. (33)	49	43	Median: 60 (range 25-94)	33:16	NR
Altawalah, et al. (34)	891	891	NR	NR	NR
Binder, et al. (35)	19	19	Median: 50 (range 29-91)	NR	NR
Caulley, et al. (36)	272	272	NR	NR	Mild
Kojima, et al. (37)	45	45	Median: 42 (IQR 31-52)	NR	NR
Procop, et al. (38)	216	216	Mean: 44 (range 18-82)	NR	NR
Senok, et al. (39)	401	401	Mean: 35 (SD 9.5)	329:72	NR
Uwamino, et al. (40)	NR	196	NR	NR	NR

並說明每篇研究的品質(如針對治療型的臨床問題，選用隨機分配、盲法、及完整追蹤的研究類型)

Supplement Table 8 | Information on Laboratory Methods

	Index Test					Reference Test				
Study	Saliva Sampling Method	Instructed by HCW	Diagnostic Testing Method	Gene Target	Ct-value	Swab type	Collected by HCW	Diagnostic Testing Method	Gene Target	Ct-value
Azzi, et al. (5)	Drooling technique	Yes	Lab based RT-PCR	5'UTR region	NR	NPS	Yes	Lab based RT-PCR	Rdp, E, and N	NR
Chen, et al. (6)	Early-morning posterior oropharyngeal saliva spitting technique	Yes	Point of care RT-PCR (Xpert Xpress)	E and N2	NR	NPS	Yes	Point of care RT-PCR (Xpert Xpress)	E and N2	NR
Leung, et al. (7)	Early-morning posterior oropharyngeal saliva spitting technique	Yes	Lab based RT-PCR	E; positive samples tested for RdRp	NR	NPS	Yes	Lab based RT-PCR	E; positive samples tested for RdRp	NR
McCormick-Baw, et al. (8)	General spitting technique	Yes	Point of care RT-PCR (Xpert Xpress)	E and N2	NR	NPS	Yes	Point of care RT-PCR (Xpert Xpress)	E and N2	NR
Rao, et al. (9)	Early-morning posterior oropharyngeal saliva spitting technique	Yes	Lab based RT-PCR	E and RdRp	Ct < 38.	NPS	Yes	Lab based RT-PCR	E and RdRp	Ct < 38.
Landry, et al. (10)	General spitting technique	Yes	Lab based RT-PCR	N1 and N2	NR	NPS	Yes	Lab based RT-PCR	N1 and N2	NR
Villar, et al. (11)	Using a swabbing device	Yes	Lab based RT-PCR	N1 and N2	NR	NPS	NR	Lab based RT-PCR	N1 and N2	NR
Akgun Dogan, et al. (12)	Drooling technique	Yes	Lab based RT-PCR	ORF1ab and N	Ct ≤29	NPS	Yes	Lab based RT-PCR	ORF1ab and N	Ct ≤ 29
Becker, et al. (13)	General spitting technique	Yes	Lab based RT-PCR	ORF1ab	NR	NPS	Yes	Lab based RT-PCR	ORF1ab	NR
Byrne, et al. (14)	General spitting technique	Yes	Lab based RT-PCR	ORF1ab	Ct < 40	Nasal throat[1]	Yes	Lab based RT-PCR	ORF1ab	Ct < 40
Griesemer, et al. (15)	General spitting technique	Yes	Lab based RT-PCR	N1	Ct < 45	NPS	Yes	Lab based RT-PCR	N1	Ct < 45
Hanson, et al. (16)	General spitting technique	Yes	Transcription Mediated Amplification	NR	NA	NPS	Yes	Transcription Mediated Amplification	NR	NA
Iwasaki, et al. (17)	General spitting technique	Yes	Lab based RT-PCR	N2	NR	NPS	Yes	Lab based RT-PCR	N2	NR
Jamal, et al. (18)	General spitting technique	Yes	Lab based RT-PCR	RdRp, E and N	NR	NPS	Yes	Lab based RT-PCR	RdRp, E and N	NR

Supplement Table 2 | Fields Extracted from Included Studies

Field	Variables Extracted
Study Characteristics	
Study Identifiers	Study ID, Title, Type of Publication (Peer Reviewed or Pre-Peer Review)
Study Design	Type of Study (Cohort selection cross-sectional accuracy study or Case-control selection cross-sectional accuracy study), Language, Study Location (Country and City), Time Period of Study (Month and Year),
Index and Reference Tests Used	Sampling Setting (Done/Instructed by Healthcare Professional or Self-Collected), Sample Collection Method, Media Added to Samples, Diagnostic Test Used (Lab based RT-PCR, Point of Care RT-PCR, Digital PCR, LAMP or Transcription Mediated Amplification) Type of Diagnostic Test (Commercial Lab-Based, Commercial Point-of-Care, In-House), Company Name and Machine (For Commercial Lab-Based Tests), Threshold for Positive RT-PCR, SARS-CoV-2 Gene Target, Sample Collection Period
Study Entry Criteria	Inclusion and Exclusion Criteria
Patient Characteristics	
Clinical Characteristics of Population	SARS-CoV-2 diagnosis (Persons with Confirmed SARS-CoV-2 and Negative Controls, Persons with Confirmed SARS-CoV-2, and/or Suspected Cases), Cohort Symptoms (Symptomatic and/or Asymptomatic), Clinical Setting (Inpatient and/or Outpatient), Disease Severity (Mild, Moderate and/or Severe), Time Since Symptom Onset
Patients and Samples Included	Total Patients Enrolled, Total Patients Included, Total Samples Included, Number of Samples Tested, Number Positive on Viral Culture, Number Positive on Any Test (Non-Viral Culture), Number Negative on Both Tests, Number Positive on Index Test, Number Positive on Reference Test, Number Asymptomatic
Stratification by Disease Severity	Definition of Disease Severity. For Asymptomatic, Mild, Moderate and Severe Included Patients: Number Positive on Viral Culture, Number Positive on Any Test (Non-Viral Culture), Number Negative on Both Tests, Number Positive on Index Test, Number Positive on Reference Test
Stratification by Time Since Disease Onset	Definition of Time Since Symptom Onset. For First Week, Second Week, and Third Week Included Patients: Number Positive on Viral Culture, Number Positive on Any Test (Non-Viral Culture), Number Negative on Both Tests, Number Positive on Index Test, Number Positive on Reference Test
Sex	Number Male, Number Female
Age	Age Distribution (Young Children (0-4), Children (5-17), Adults (18-64), Elderly (65+)), Mean or Median (Including SD, IQR or Range)

Abbreviations: RT-PCR: reverse transcription polymerase chain reaction, LAMP: Loop-mediated isothermal amplification, SARS-CoV-2: severe acute respiratory syndrome coronavirus 2

步驟 2：系統性文獻回顧的品質如何？(FAITH)

I - 是否只納入 (Included) 具良好效度的文章？

僅進行文獻判讀是不足夠，系統性文獻回顧只納入至少要有一項研究結果是極小偏誤的試驗。

在文章的方法章節，可以找到文章評估的方式，以及是由誰完成評估的

Data Extraction and Quality Assessment Two reviewers (M.L.B. and S.P.) independently extracted 25% of the data using a standardized form (fields are shown in Table 2 of Supplement 1); findings were checked for agreement. Concordance was high; thus, a single reviewer extracted the remaining data, and the other reviewer verified extractions. Extracted information included study design, location, enrollment dates, included population (persons presenting for SARS-CoV-2 testing or persons with confirmed SARS-CoV-2 infection), study setting (inpatient or outpatient), presence of symptoms when sampling was done, demographic information (age and sex), laboratory methods (analytic method used, primer, transport media, and cycle threshold values), and sampling method for saliva collection. We extracted the number of persons testing positive via nasopharyngeal swabs, saliva sampling, or on either sample. To complete missing data, we contacted 25 authors, of whom 18 (72%) replied.

步驟 2：系統性文獻回顧的品質如何？(FAITH)

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Study Identifiers	Study ID, Title, Type of Publication (Peer Reviewed or Pre-Peer Review)
Study Design	Type of Study (Cohort selection cross-sectional accuracy study or Case-control selection cross-sectional accuracy study), Language, Study Location (Country and City), Time Period of Study (Month and Year),
Index and Reference Tests Used	Sampling Setting (Done/Instructed by Healthcare Professional or Self-Collected), Sample Collection Method, Media Added to Samples, Diagnostic Test Used (Lab based RT-PCR, Point of Care RT-PCR, Digital PCR, LAMP or Transcription Mediated Amplification) Type of Diagnostic Test (Commercial Lab-Based, Commercial Point-of-Care, In-House), Company Name and Machine (For Commercial Lab-Based Tests), Threshold for Positive RT-PCR, SARS-CoV-2 Gene Target, Sample Collection Period
Study Entry Criteria	Inclusion and Exclusion Criteria
Patient Characteristics	
Clinical Characteristics of Population	SARS-CoV-2 diagnosis (Persons with Confirmed SARS-CoV-2 and Negative Controls, Persons with Confirmed SARS-CoV-2, and/or Suspected Cases), Cohort Symptoms (Symptomatic and/or Asymptomatic), Clinical Setting (Inpatient and/or Outpatient), Disease Severity (Mild, Moderate and/or Severe), Time Since Symptom Onset
Patients and Samples Included	Total Patients Enrolled, Total Patients Included, Total Samples Included, Number of Samples Tested, Number Positive on Viral Culture, Number Positive on Any Test (Non-Viral Culture), Number Negative on Both Tests, Number Positive on Index Test, Number Positive on Reference Test, Number Asymptomatic
Stratification by Disease Severity	Definition of Disease Severity. For Asymptomatic, Mild, Moderate and Severe Included Patients: Number Positive on Viral Culture, Number Positive on Any Test (Non-Viral Culture), Number Negative on Both Tests, Number Positive on Index Test, Number Positive on Reference Test
Stratification by Time Since Disease Onset	Definition of Time Since Symptom Onset. For First Week, Second Week, and Third Week Included Patients: Number Positive on Viral Culture, Number Positive on Any Test (Non-Viral Culture), Number Negative on Both Tests, Number Positive on Index Test, Number Positive on Reference Test
Sex	Number Male, Number Female
Age	Age Distribution (Young Children (0-4), Children (5-17), Adults (18-64), Elderly (65+)), Mean or Median (Including SD, IQR or Range)

Abbreviations: RT-PCR: reverse transcription polymerase chain reaction, LAMP: Loop-mediated isothermal amplification, SARS-CoV-2: severe acute respiratory syndrome coronavirus 2

QUADAS-2 量表

- QUADAS(Quality Assessment of Diagnostic Accuracy Studies) 工具是當前最為推薦的診斷準確性試驗品質評價工具，也是Cochrane協作網的診斷試驗系統評價方法學組採用的工具。隨著實踐的不斷深入，QUADAS研發小組對其進行了修訂，於2011年推出修訂版QUADAS-2。

- QUADAS-2工具主要由4個部分組成: 病例的選擇，待評價試驗，金標準，病例流程和進展情況。所有組成部分在偏倚風險方面都會被評估，前3部分也會在臨床適用性方面被評估。在偏倚風險判斷上納入了標誌性的問題，這些研究設計方面的標識性問題與偏倚潛在性有關，旨在幫助評價者判斷偏倚風險; 但臨床適用性的判斷未納入標誌性問題。

- QUADAS-2工具的4個組成部分都要進行偏倚風險評價。根據每部分納入的相關標誌性問題的回答“是”、“否”或“不確定”，可對應將偏倚風險等級判定為“低”、“高”或“不確定”。

- 若一個範圍內所有標誌性問題答案均為“是”，那麼可以被評定為低偏倚風險; 若所有資訊化問題答案有一個為“否”，那麼偏倚風險判定為“高”。“不確定”分級指的是文獻中沒有提供詳細的內容以致評價者難以做出判斷，此類只有在報導的資料不充足的情況下才可以使用。

Supplement Table 3 | QUADAS-2 Adapted Quality Assessment Criteria

Criteria Number	Question
Patient Selection	
A. Risk of Bias	
1	Was a consecutive or random sample of patients enrolled (Yes / No / Unclear)
2	Was a case-control design avoided? (Yes / No / Unclear)
3	Did the study avoid inappropriate exclusions (based on exclusion criteria) (Yes / No / Unclear)
4	Could the selection of patients have introduced bias? (Low / High / Unclear)

標誌性問題1: 是否納入了連續或隨機的病例?
一個理想的研究應該連續或隨機納入帶有疑似疾病的符合要求的患者，以避免潛在偏倚發生。

標誌性問題2: 是否避免了病例 - 對照類研究設計?
其實就是納入患者必須是有診斷不明確的，如果你採用的是病例對照設計類型，診斷都是明確的，那肯定是不行的。

標誌性問題3: 研究是否避免了不恰當的排除?
在納入的病例中，若診斷不明確的病例占20% ~ 30%及以上就可以評價為 “是”；如果都能較明確診斷，也就是沒有包含他們診斷不明確的病例，就應評為 “ 否”；當納入的病例中，診斷不明確的所占比例少於20%，就認為是 “ 不清楚” 。

15	Did >=90% patients receive paired samples? (i.e., did >=90% people who could be included receive both saliva/pharyngeal tests) (Yes / No / Unclear)
16	Did patients receive the same reference standard? (i.e., different sampling technique oro- vs naso and/or different analytical method) (Yes / No / Unclear)
17	Could the patient flow have introduced bias? (Low / High / Unclear)

Notes: Answers highlighted in green indicate those that would improve quality; answers highlighted in red indicate those that would reduce quality

Supplement Table 3 | QUADAS-2 Adapted Quality Assessment Criteria

Criteria Number	Question
Patient Selection	
A. Risk of Bias	
1	Was a consecutive or random sample of patients enrolled (Yes / No / Unclear)
2	Was a case-control design avoided? (Yes / No / Unclear)
3	Did the study avoid inappropriate exclusions (based on exclusion criteria) (Yes / No / Unclear)
4	Could the selection of patients have introduced bias? (Low / High / Unclear)
B. Concerns Regarding Applicability	
5	Is there concern that the included patients do not match the review question? (Low / High / Unclear)
Index Tests	
A. Risk of Bias	
6	Were the index test results interpreted without knowledge of the results of the reference standard? (Yes / No / Unclear)
7	If a threshold was used, was it pre-specified? (Yes / No / Unclear)
8	If interpretation of test was subjective (for e.g., color changes or line changes - only needed for LAMP), was agreement between readers described? (Yes / No / Unclear)
9	Could the conduct or interpretation of the index test have introduced bias (Low / High / Unclear)
15	Did >=90% patients receive paired samples? (i.e., did >=90% people who could be included receive both saliva/pharyngeal tests) (Yes / No / Unclear)
16	Did patients receive the same reference standard? (i.e., different sampling technique oro- vs naso and/or different analytical method) (Yes / No / Unclear)
17	Could the patient flow have introduced bias? (Low / High / Unclear)

Notes: Answers highlighted in green indicate those that would improve quality; answers highlighted in red indicate those that would reduce quality

標誌性問題1: 待評價試驗的結果判讀是否是在不知曉金標準試驗結果的情況下進行的?
判定待評價試驗結果應該遵守盲法，因為金標準的資訊可能會影響待評價試驗的解釋

標志性問題2: 若使用了閾值，那麼它是否是事先確定的?
如果使用的閾值是在評判前確定的，就判定為“是”，相反即為“否”，資訊不足以判斷即為“不清楚”。

Supplement Table 3 | QUADAS-2 Adapted Quality Assessment Criteria

Criteria Number	Question
Patient Selection	
A. Risk of Bias	
1	Was a consecutive or random sample of patients enrolled (Yes / No / Unclear)
2	Was a case-control design avoided? (Yes / No / Unclear)
3	Did the study avoid inappropriate exclusions (based on exclusion criteria) (Yes / No / Unclear)

標誌性問題1: 金標準是否可以正確地區分目標疾病狀態?
其實就是你選擇的金標準準確性夠不夠

標志性問題2: 金標準結果判讀是否使用了盲法?
若金標準結果的判讀是在不瞭解待評價試驗結果下進行的即評價為“是”，相反則為“否”，難以判斷即認為“不清楚”。

B. Concerns Regarding Applicability	
10	Is there concern that the index test, its conduct, or interpretation differ from the review question (Low / High / Unclear)
Reference Tests	
A. Risk of Bias	
11	Is the reference standard likely to correctly classify the target condition? (Yes / No / Unclear)
12	Were the reference standard results interpreted without knowledge of the results of the index test? (Yes / No / Unclear)
13	Could the reference standard, its conduct, or its interpretation have introduced bias? (Low / High / Unclear)
B. Concerns Regarding Applicability	
14	Is there concern that the target condition as defined by the reference standard does not match the review question? (Low / High / Unclear)
Flow and Timing	
A. Risk of Bias	
15	Did >=90% patients receive paired samples? (i.e., did >=90% people who could be included receive both saliva/pharyngeal tests) (Yes / No / Unclear)
16	Did patients receive the same reference standard? (i.e., different sampling technique oro- vs naso and/or different analytical method) (Yes / No / Unclear)
17	Could the patient flow have introduced bias? (Low / High / Unclear)

Notes: Answers highlighted in green indicate those that would improve quality; answers highlighted in red indicate those that would reduce quality

Supplement Table 3 | QUADAS-2 Adapted Quality Assessment Criteria

Criteria Number	Question
Patient Selection	
A. Risk of Bias	
1	Was a consecutive or random sample of patients enrolled (Yes / No / Unclear)
2	Was a case-control design avoided? (Yes / No / Unclear)
3	Did the study avoid inappropriate exclusions (based on exclusion criteria) (Yes / No / Unclear)

標誌性問題1: 待評價試驗和金標準之間是否有恰當的時間間隔?
在相同時間對同一患者進行待評價試驗和金標準得到結果是最理想的。對於慢性疾病可能影響不大，但是對於急性疾病，短期內可能發生變化，影響結果判斷。

標志性問題2 ~ 3: 所有的患者是否只接受了一個相同的金標準?
若可以清晰地判斷所有的患者均通過了金標準驗證其疾病狀態，那麼就判定為“是”，相反則為“否”，若研究未報告該資訊則評價為“不清楚”。

標志性問題4: 是否所有的病例都納入了分析?
判斷標準是所有病例都納入研究及評價為“是”;有病例遺漏為“否”;未說明無法判斷即為“不確定”。

Flow and Timing	
A. Risk of Bias	
15	Did >=90% patients receive paired samples? (i.e., did >=90% people who could be included receive both saliva/pharyngeal tests) (Yes / No / Unclear)
16	Did patients receive the same reference standard? (i.e., different sampling technique oro- vs naso and/or different analytical method) (Yes / No / Unclear)
17	Could the patient flow have introduced bias? (Low / High / Unclear)

Notes: Answers highlighted in green indicate those that would improve quality; answers highlighted in red indicate those that would reduce quality

Supplement Table 3 | QUADAS-2 Adapted Quality Assessment Criteria

臨床適用性評價

域1病例選擇: 相關納入的病患和背景與評價問題匹配情況

域2待評價試驗: 待評價試驗的實施和解釋與評價問題的匹配情況評價。

域3金標準: 金標準的適用性評價。

4	Could the selection of patients have introduced bias? (Low / High / Unclear)
B. Concerns Regarding Applicability	
5	Is there concern that the included patients do not match the review question? (Low / High / Unclear)
Index Tests	
A. Risk of Bias	
6	Were the index test results interpreted without knowledge of the results of the reference standard? (Yes / No / Unclear)
7	If a threshold was used, was it pre-specified? (Yes / No / Unclear)
8	If interpretation of test was subjective (for e.g., color changes or line changes - only needed for LAMP), was agreement between readers described? (Yes / No / Unclear)
9	Could the conduct or interpretation of the index test have introduced bias (Low / High / Unclear)
B. Concerns Regarding Applicability	
10	Is there concern that the index test, its conduct, or interpretation differ from the review question (Low / High / Unclear)
Reference Tests	
A. Risk of Bias	
11	Is the reference standard likely to correctly classify the target condition? (Yes / No / Unclear)
12	Were the reference standard results interpreted without knowledge of the results of the index test? (Yes / No / Unclear)
13	Could the reference standard, its conduct, or its interpretation have introduced bias? (Low / High / Unclear)
B. Concerns Regarding Applicability	
14	Is there concern that the target condition as defined by the reference standard does not match the review question? (Low / High / Unclear)
Flow and Timing	
A. Risk of Bias	
15	Did >=90% patients receive paired samples? (i.e., did >=90% people who could be included receive both saliva/pharyngeal tests) (Yes / No / Unclear)
16	Did patients receive the same reference standard? (i.e., different sampling technique oro- vs naso and/or different analytical method) (Yes / No / Unclear)
17	Could the patient flow have introduced bias? (Low / High / Unclear)

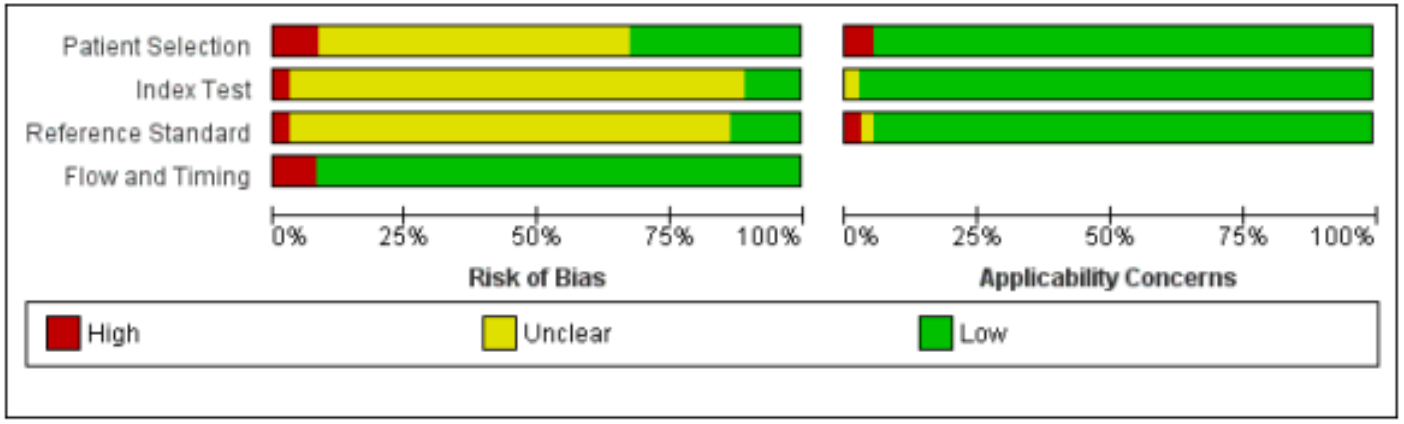
Notes: Answers highlighted in green indicate those that would improve quality; answers highlighted in red indicate those that would reduce quality

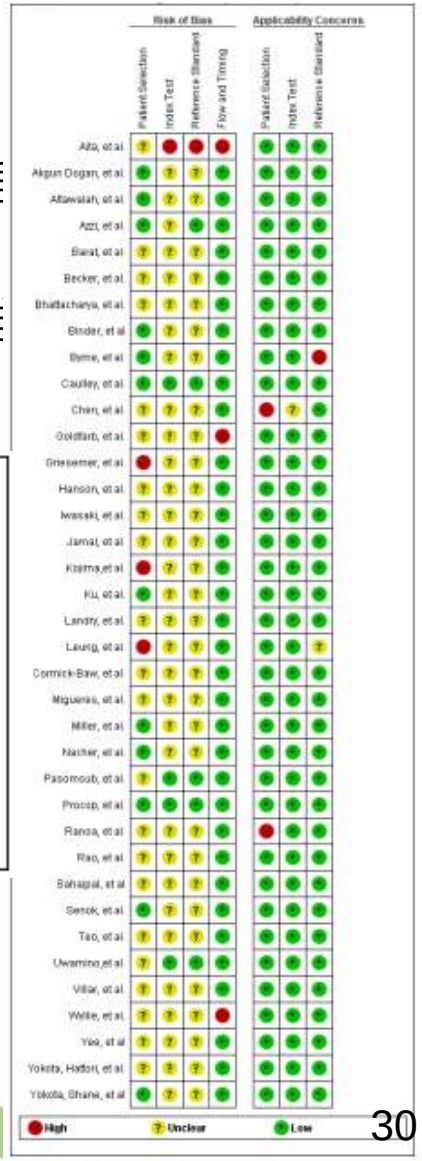
步驟 2：系統性文獻回顧的品質如何？(FAITH)

I - 是否只納入 (Included) 具良好效度的文章？

僅進行文獻判讀是不足夠，系統性文獻回顧只納入至少要有
究結果是極小偏誤的試驗。

在文章的方法章節，可以找到文章評估的方式，以及是由誰
估的，





評讀結果： ☑是 ☐否 ☐不清楚

步驟 2：系統性文獻回顧的品質如何？(FAITH)

T - 作者是否以表格和圖表「總結」(Total up) 試驗結果？

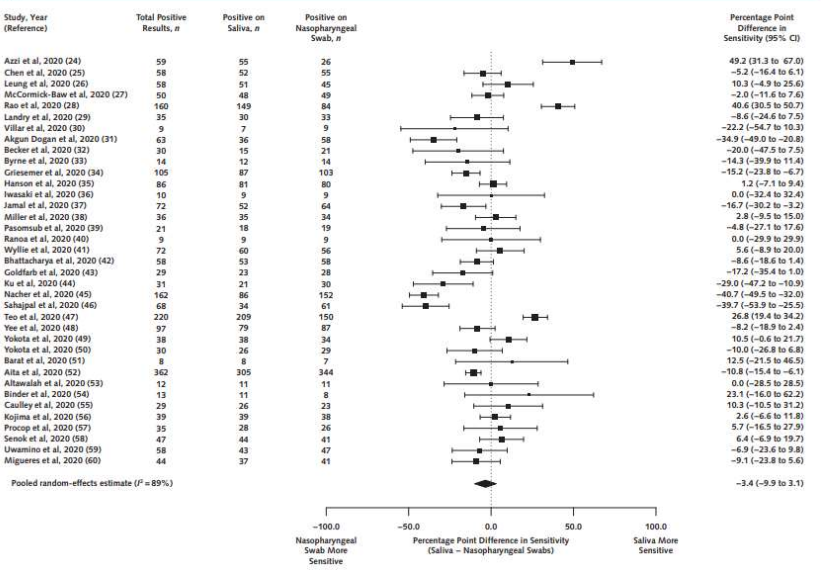
應該用至少1個摘要表格呈現所納入的試驗結果。若結果相近，可針對結果進行統合分析(meta-analysis)，並以「森林圖」(forest plot)呈現研究結果，最好再加上異質性分析。

在文章的結果章節，可以找到摘要的圖表，以及作者對系統性文獻回顧結果的解釋。

Supplement Table 11 | Difference in Sensitivity for SARS-CoV-2 Between Nasopharyngeal Swabs and Saliva, Stratified by Population Sampled

Study	N Paired Samples Tested	N Positive on Nasopharyngeal swab	N Positive on Saliva	N Positive on Any Sample (Reference)	Sensitivity Saliva (95% CI)	Difference in Sensitivity (95% CI) [Saliva-Nasopharyngeal swab]
People Presenting for SARS-CoV-2 Testing (N=22)						
Landry, et al. (10)	124	33	30	35	85.7% (69.7% to 95.2%)	-8.6% (-24.6% to 7.3%)
Villar, et al. (11)	13	9	7	9	77.8% (40% to 97.2%)	-22.2% (-54.7% to 11.7%)
Akgun Dogan, et al. (12)	200	58	36	63	57.1% (44% to 69.5%)	-34.9% (-49% to -18.4%)
Becker, et al. (13)	85	15	11	23	47.8% (26.8% to 69.4%)	-17.4% (-49.8% to 19.7%)
Byrne, et al. (14)	110	14	12	14	85.7% (57.2% to 98.2%)	-14.3% (-39.9% to 9.6%)
Griesemer, et al. (15)	463	103	87	105	82.9% (74.3% to 89.5%)	-15.2% (-23.8% to -7.3%)
Hanson, et al. (16)	354	80	81	86	94.2% (87% to 98.1%)	1.2% (-7.1% to 9.5%)
Pasomsub, et al. (20)	200	19	18	21	85.7% (63.7% to 97%)	-4.8% (-27.1% to 17.8%)
Ranoa, et al. (21)	99	9	9	9	100% (66.4% to 100%)	0% (-29.9% to 29.9%)
Bhattacharya, et al. (23)	74	58	53	58	91.4% (81% to 97.1%)	-8.6% (-18.6% to -0.7%)
Nacher, et al. (26)	776	152	86	162	53.1% (45.1% to 61%)	-40.7% (-49.5% to -30.9%
Sahajpal, et al. (27)	240	61	34	68	50% (37.6% to 62.4%)	-39.7% (-53.9% to -22.5%)
Teo, et al. (28)	190	50	95	98	96.9% (91.3% to 99.4%)	45.9% (34% to 56.2%)
Yee, et al. (29)	70	62	57	70	81.4% (70.3% to 89.7%)	-7.1% (-20% to 5.9%)
Barat, et al. (32)	451	29	26	30	86.7% (69.3% to 96.2%)	-10% (-26.8% to 6.1%)
Altawalah, et al. (34)	891	344	305	362	84.3% (80.1% to 87.9%)	-10.8% (-15.4% to -6.2%)
Caulley, et al. (36)	272	8	11	13	84.6% (54.6% to 98.1%)	23.1% (-16% to 54.6%)
Procop, et al. (38)	216	38	39	39	100% (91% to 100%)	2.6% (-6.6% to 13.2%)
Senok, et al. (39)	401	26	28	35	80% (63.1% to 91.6%)	5.7% (-16.5% to 27.2%)
Yokota, et al. (31)	161	41	44	47	93.6% (82.5% to 98.7%)	6.4% (-6.9% to 19.9%)
Uwamino, et al. (40)	114	2	2	2	100% (15.8% to 100%)	0% (-65.8% to 65.8%)
Migueres, et al. (41)	95	32	29	32	90.6% (75% to 98%)	-9.4% (-24.2% to 3%)
Pooled estimate (95% CI); I^2	5599	1243	1100	1381	85.4% (78.1% to 90.6%); I^2 = 89%	-7.9% (16.7% to 0.8%); I^2 = 89%
Persons with Confirmed SARS-CoV-2 Infection (N=17)						
Chen, et al. (6)	58	55	52	58	89.7% (78.8% to 96.1%)	-5.2% (-16.4% to 5.7%)
Leung, et al. (7)	95	45	51	58	87.9% (76.7% to 95%)	10.3% (-4.9% to 25.1%)
Rao, et al. (9)	217	84	149	160	93.1% (88% to 96.5%)	40.6% (30.5% to 49.6%)
Becker, et al. (13)	24	6	4	7	57.1% (18.4% to 90.1%)	-28.6% (-66.4% to 24.4%)
Iwasaki, et al. (17)	10	9	9	10	90% (55.5% to 99.7%)	0% (-32.4% to 32.4%)
Jamal, et al. (18)	91	64	52	72	72.2% (60.4% to 82.1%)	-16.7% (-30.2% to -2.4%)
Miller, et al. (19)	91	34	35	36	97.2% (85.5% to 99.9%)	2.8% (-9.5% to 15.7%)
Wyllie, et al. (22)	97	56	60	72	83.3% (72.7% to 91.1%)	5.6% (-8.9% to 19.7%)
Ku, et al. (25)	42	30	21	31	67.7% (48.6% to 83.3%)	-29% (-47.2% to -9%)
Teo, et al. (28)	147	100	114	122	93.4% (87.5% to 97.1%)	11.5% (2.7% to 20.2%)
Yee, et al. (29)	27	25	22	27	81.5% (61.9% to 93.7%)	-11.1% (-30.7% to 9%)

Figure. Forest plot of all included studies in the primary analysis estimating the difference in sensitivity between saliva and nasopharyngeal swabs.



評讀結果： ☑是 ☐否 ☐不清楚

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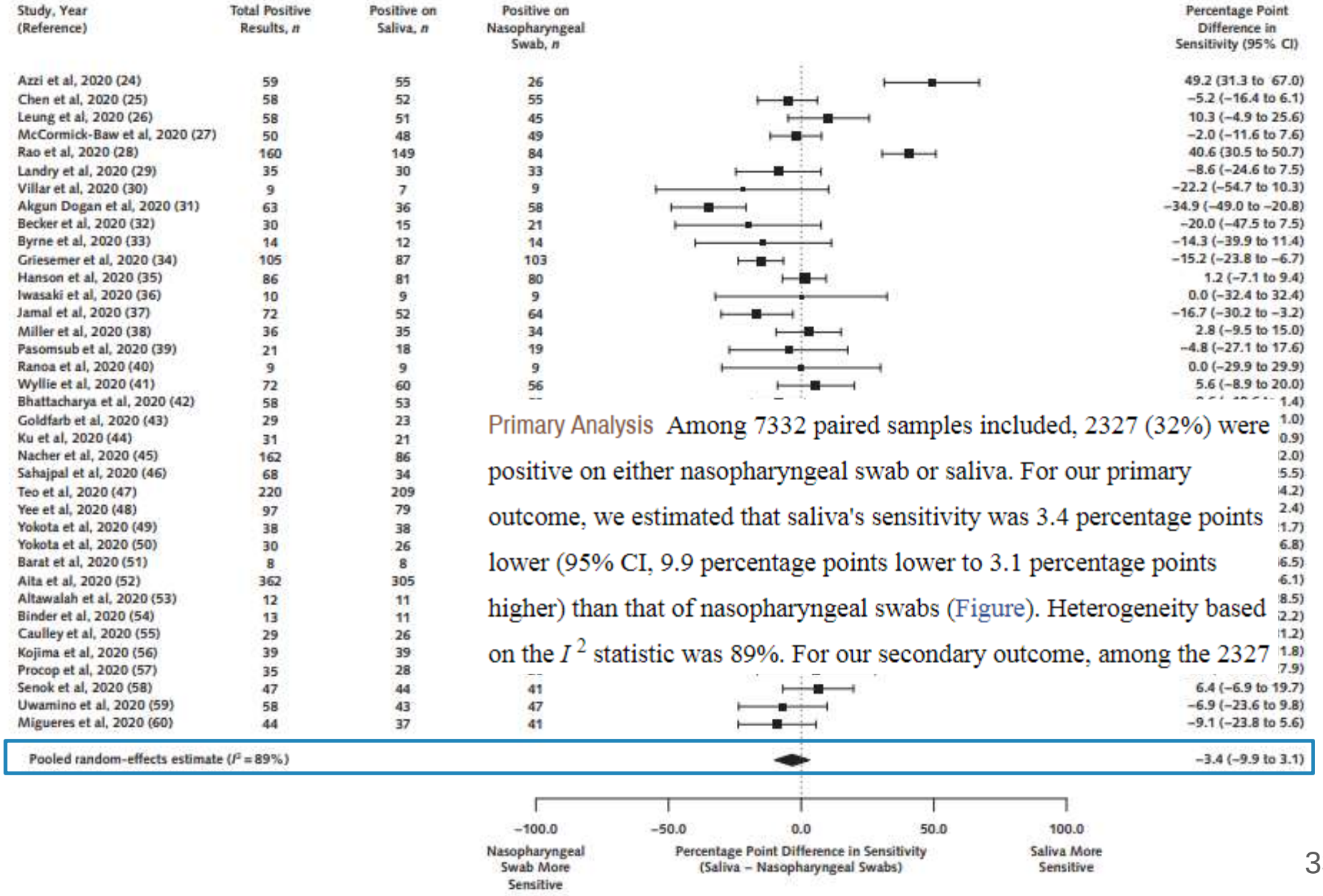
Altawalah, et al. (34)	891	344	305	362	84.3% (80.1% to 87.9%)	-10.8% (-15.4% to -6.2%)
Caulley, et al. (36)	272	8	11	13	84.6% (54.6% to 98.1%)	23.1% (-16% to 54.6%)
Procop, et al. (38)	216	38	39	39	100% (91% to 100%)	2.6% (-6.6% to 13.2%)
Senok, et al. (39)	401	26	28	35	80% (63.1% to 91.6%)	5.7% (-16.5% to 27.2%)
Yokota, et al. (31)	161	41	44	47	93.6% (82.5% to 98.7%)	6.4% (-6.9% to 19.9%)
Uwamino, et al. (40)	114	2	2	2	100% (15.8% to 100%)	0% (-65.8% to 65.8%)
Migueres, et al. (41)	95	32	29	32	90.6% (75% to 98%)	-9.4% (-24.2% to 3%)
Pooled estimate (95% CI); I^2	5599	1243	1100	1381	85.4% (78.1% to 90.6%); I^2 = 89%	-7.9% (16.7% to 0.8%); I^2 = 89%
Persons with Confirmed SARS-CoV-2 Infection (N=17)						
Chen, et al. (6)	58	55	52	58	89.7% (78.8% to 96.1%)	-5.2% (-16.4% to 5.7%)
Leung, et al. (7)	95	45	51	58	87.9% (76.7% to 95%)	10.3% (-4.9% to 25.1%)
Rao, et al. (9)	217	84	149	160	93.1% (88% to 96.5%)	40.6% (30.5% to 49.6%)
Becker, et al. (13)	24	6	4	7	57.1% (18.4% to 90.1%)	-28.6% (-66.4% to 24.4%)
Iwasaki, et al. (17)	10	9	9	10	90% (55.5% to 99.7%)	0% (-32.4% to 32.4%)
Jamal, et al. (18)	91	64	52	72	72.2% (60.4% to 82.1%)	-16.7% (-30.2% to -2.4%)
Miller, et al. (19)	91	34	35	36	97.2% (85.5% to 99.9%)	2.8% (-9.5% to 15.7%)
Wyllie, et al. (22)	97	56	60	72	83.3% (72.7% to 91.1%)	5.6% (-8.9% to 19.7%)
Ku, et al. (25)	42	30	21	31	67.7% (48.6% to 83.3%)	-29% (-47.2% to -9%)
Teo, et al. (28)	147	100	114	122	93.4% (87.5% to 97.1%)	11.5% (2.7% to 20.2%)
Yee, et al. (29)	27	25	22	27	81.5% (61.9% to 93.7%)	-11.1% (-30.7% to 9%)

Figure. Forest plot of all included studies in the primary analysis estimating the difference in sensitivity between saliva and nasopharyngeal swabs.



Primary Analysis Among 7332 paired samples included, 2327 (32%) were positive on either nasopharyngeal swab or saliva. For our primary outcome, we estimated that saliva's sensitivity was 3.4 percentage points lower (95% CI, 9.9 percentage points lower to 3.1 percentage points higher) than that of nasopharyngeal swabs (Figure). Heterogeneity based on the I^2 statistic was 89%. For our secondary outcome, among the 2327

步驟 2：系統性文獻回顧的品質如何？(FAITH)

H - 試驗的結果是否相近 - 異質性 (Heterogeneity)?

在理想情況下，各個試驗的結果應相近或具同質性，若具有異質性，作者應評估差異是否顯著(卡方檢定)。根據每篇個別研究中不同的PICO及研究方法，探討造成異質性的原因。

在文章的結果章節，可以找到研究結果是否具異質性，及造成異質性可能的原因探討。森林圖中可以找到異質性的卡方檢定結果。

Table 2. Summary Table of Pooled Estimates on Difference in Sensitivity for SARS-CoV-2 Between Nasopharyngeal Swabs and Saliva, Stratified by Population Characteristics

Population Characteristic	Studies, *n*	Paired Samples Tested, *n*	Positive Results on Nasopharyngeal Swab, *n*	Positive Results on Saliva, *n*	Positive Results on Any Sample (Reference), *n*	Saliva Sensitivity		Difference in Sensitivity (Saliva - Nasopharyngeal)	
						Estimate (95% CI), %	I^2, %	Estimate (95% CI), *percentage points*	I^2, %
Population sampled*									
Persons with confirmed SARS-CoV-2 infection	17	1158	637	701	808	87.3 (81.3 to 91.6)	74	1.5 (−7.3 to 10.3)	78
Persons p SARS-C								7.9 (−16.7 to 0.8)	89
Symptoms									
Symptomatic								−4.9 (−10.2 to 0.4)	75
Asymptomatic	8	800	226	317	357	85.8 (69.6 to 94.1)	83	−1.6 (−37.4 to 34.1)	96
Setting‡									
Outpatient	20	4429	899	862	1039	87.9 (81.5 to 92.2)	82	−4.3 (−11.8 to 3.2)	79
Inpatient	14	1917	865	784	950	85.3 (77.3 to 90.9)	85	−6.6 (−14.7 to 1.4)	79
Age group§									
Adults (≥18 y)	24	3843	983	1104	1243	90.4 (86.1 to 93.5)	76	3.1 (−5.1 to 11.3)	86
Pediatric (<18 y): only 1 study, not pooled									
Yee et al, 2020 (48)	1	43	38	34	43‖	79.1 (64.4 to 88.7)	–	−9.3 (−26.1 to 7.5)	–

SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2.
* Three studies did not report information stratified by population being sampled.
† Ten studies did not report information stratified by symptoms.
‡ Six studies did not report information stratified by setting.
§ Thirteen studies did not report information by age group.
‖ This study did not report information on dual negatives stratified by age.

以人群、症狀做異質性分析

Table 3. Summary Table of Pooled Estimates on Difference in Sensitivity for SARS-CoV-2 Between Nasopharyngeal Swabs and Saliva, Stratified by Study Characteristics

Study Characteristic	Studies, *n*	Paired Samples Tested, *n*	Positive Results on Nasopharyngeal Swab, *n*	Positive Results on Saliva, *n*	Positive Results on Any Sample (Reference), *n*	Saliva Sensitivity		Difference in Sensitivity (Saliva - Nasopharyngeal)	
						Estimate (95% CI), %	I^2, %	Estimate (95% CI), %	I^2, %
Used transport media*									
Yes	18	3380	1066	1036	1232	88.0 (80.2 to 93)	89	−2.8 (−11.6 to 6.1)	86
No	18	3878	859	838	1037	85.4 (79.3 to 89.9)	80	−3.7 (−14.8 to 7.3)	90
Saliva collection method†									
Drooling technique	5	882	133	137	173	87.9 (69.9 to 95.8)	77	0.6 (−38.4 to 39.6)	90
Early-morning posterior o te	3	370	184	252	276	91.3 (87.4 to 94.1)	0	15.4 (−42.9 to 73.8)	93
Ger tec Sali Pos									
spitting technique									
Laboratory method‡									
RT-PCR	34	6765	1799	1746	2133	85.9 (80.9 to 89.8)	87	−3.6 (−10.7 to 3.6)	89
Other molecular method‡	3	567	184	181	194	93.3 (88.8 to 96.1)	0	−1.4 (−9.1 to 6.3)	8
Study design									
Cohort	34	7192	1915	1850	2240	86.8 (81.9 to 90.5)	87	−4.2 (−11 to 2.6)	89
Case–control: only 2 studies, not pooled									
Leung et al, 2020 (26)	1	95	45	51	58	87.9 (76.7 to 95)	–	10.3 (−4.9 to 25.1)	–
Kojima et al, 2020 (56)	1	45	23	26	29	89.7 (72.6 to 97.8)	–	10.3 (−10.5 to 30.4)	–
Quality assessment									
Scored ≥4 points across 7 domains	31	6902	1783	1724	2093	86.5 (81.1 to 90.5)	89	−4.1 (−11.7 to 3.5)	91
Scored <4 points across 7 domains	6	430	200	203	234	86.8 (81.8 to 90.5)	0	−0.1 (−11.4 to 11.2)	44

RT-PCR = reverse transcriptase polymerase chain reaction; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2.
* One study did not report whether transport medium was used.
† Two studies did not report method of saliva collection.
‡ Two studies used point-of-care polymerase chain reaction system (Xpert Xpress [Cepheid]), and 1 used transcription-mediated amplification.

以檢體收集、研究設計做異質性分析

評讀結果： ☑是 □否 □不清楚

systematic review 異質性-
文獻結果是否合併，適當與否？

- 主要原因在於，並不是所有的系統性回顧 (systematic review)都適合把結果合併成一個值，變成統合分析 (meta-analysis)，例如研究彼此間研究設計差異太大、異質性 (heterogeneity)太大時。

- 通常可以從文章尋找方法 (Methods)中統計分析 (statistical analysis)的描述部分判斷合理性。常用來闡述研究間異質性的統計方法如下：

- I^2值：通常介於0-100%，數字越大異質性越大，可分為低 (25%)、中 (50%)、高 (75%)異質性，但事實上 I^2 值低，不代表研究間異質性低，也有可能是檢定力不足。

異質性探討

Table 2. Summary Table of Pooled Estimates on Difference in Sensitivity for SARS-CoV-2 Between Nasopharyngeal Swabs and Saliva, Stratified by Population Characteristics

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Population sampled*									
Persons with confirmed SARS-CoV-2 infection	17	1158	637	701	808	87.3 (81.3 to 91.6)	74	1.5 (−7.3 to 10.3)	78
Persons presenting for SARS-CoV-2 testing	22	5599	1243	1100	1381	85.4 (78.1 to 90.6)	89	−7.9 (−16.7 to 0.8)	89
Symptoms at the time of sampling†									
Symptomatic	24	3605	1292	1221	1437	87.0 (81.6 to 90.9)	82	−4.9 (−10.2 to 0.4)	75
Asymptomatic	8	800	226	317	357	85.8 (69.6 to 94.1)	83	−1.6 (−37.4 to 34.1)	96
Setting‡									
Outpatient	20	4429	899	862	1039	87.9 (81.5 to 92.2)	82	−4.3 (−11.8 to 3.2)	79
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Early-morning posterior oropharyngeal spitting technique	3	370	184	252	276	91.3 (87.4 to 94.1)	0	15.4 (−42.9 to 73.8)	93
General spitting technique	20	4223	960	827	1064	84.7 (77.4 to 90)	87	−8.1 (−15.3 to −0.9)	80
Saliva collection device	3	101	39	41	46	89.1 (76.4 to 95.4)	0	1.6 (−44.5 to 47.6)	47
Posterior pharyngeal spitting technique	4	1486	562	574	652	91.5 (72.7 to 97.7)	94	−1.8 (−38.8 to 35.1)	97
Laboratory method‡									
RT-PCR	34	6765	1799	1746	2133	85.9 (80.9 to 89.8)	87	−3.6 (−10.7 to 3.6)	89
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RT-PCR = reverse transcriptase polymerase chain reaction; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2.
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‡ Two studies used point-of-care polymerase chain reaction system (Xpert Xpress [Cepheid]), and 1 used transcription-mediated amplification.

Cost vs identified

以 1% 的流行率計算，我們的分析表明，用鼻咽拭子檢測 SARS-CoV-2 感染的額外成本（8093 美元，每10萬人）

Table 4. The Incremental Cost per Additional SARS-CoV-2 Infection Identified via Nasopharyngeal Versus Saliva Sampling at Varying Levels of SARS-CoV-2 Prevalence in Persons Presenting for Testing*

Prevalence of SARS-CoV-2 in Sampled Population, %	Additional SARS-CoV-2 Infections Identified (Nasopharyngeal − Saliva) per 100 000 Persons Sampled (95% UI), *n*	Incremental Cost per Additional SARS-CoV-2 Infection Identified (Nasopharyngeal − Saliva), $
0.01	0.8 (−0.1 to 1.7)	809 277
0.1	7.9 (−0.5 to 16.6)	80 928
1	78.6 (−5.2 to 166.0)	8093
10	786.0 (−51.8 to 1659.9)	809

SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2; UI = uncertainty interval.

* The difference in cost per 100 000 persons sampled (nasopharyngeal – saliva) is $636 105 (95% UI, $467 427 to $831 770). The probability that saliva is dominant (i.e., cheaper and more sensitive) is 3.9%. Estimates and uncertainty ranges are derived from sampling 1000 times from probabilistic distributions of cost and sensitivity parameters. The difference in sensitivity between nasopharyngeal swabs and saliva sampling was derived from meta-analysis of persons with undiagnosed SARS-CoV-2 infection presenting for testing (saliva sensitivity is 7.9 percentage points lower [95% CI, 14.7 percentage points lower to 0.8 percentage point higher] than nasopharyngeal swab sensitivity)—i.e., the point estimate indicates that saliva is *less* sensitive.

結果為何？

- 針對37篇研究、 7169 名參與者的綜合評估，現這些樣本對 SARS-CoV-2 檢測的敏感性沒有統計學上的顯著差異。
- 但分析研究顯示隨機吐痰、口水收集方式，敏感性明顯低於鼻咽拭子。
- 在無症狀人群和門診患者（提示病情較輕）中，唾液敏感性與鼻咽拭子敏感性沒有顯著差異。
- 但是各分組研究結果均有非常高的異質性(>75%)。
- 若以1%流行率計算，我們的分析表明，用鼻咽拭子檢測額外的 SARS-CoV-2 感染的額外成本（8093 美元）可用於收集 3900 多個唾液樣本。

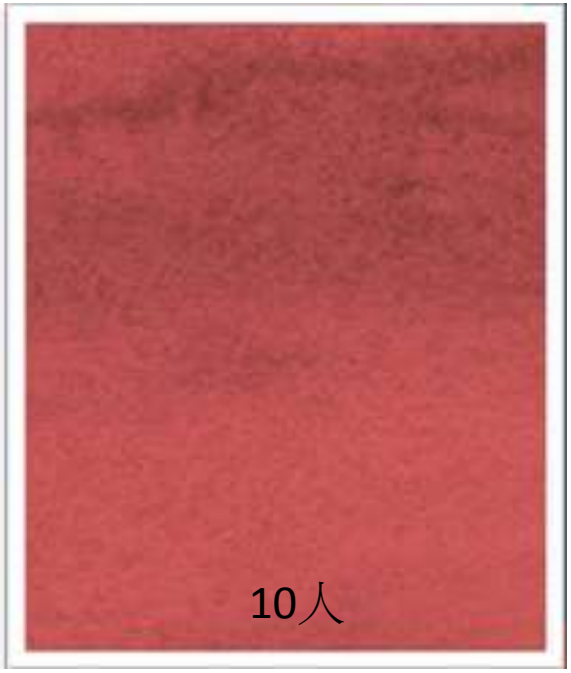
問題討論

討論：COVID 19 RT-PCR檢驗是否可接受口水檢體

同意 (綠牌)

需要更多文獻支持 (黃牌)

不同意 (紅牌)



投票網址： https://rate.cx/LhoAl7 QR code：

第一線的醫護人員、防疫人員，
辛苦了，謝謝您們。

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