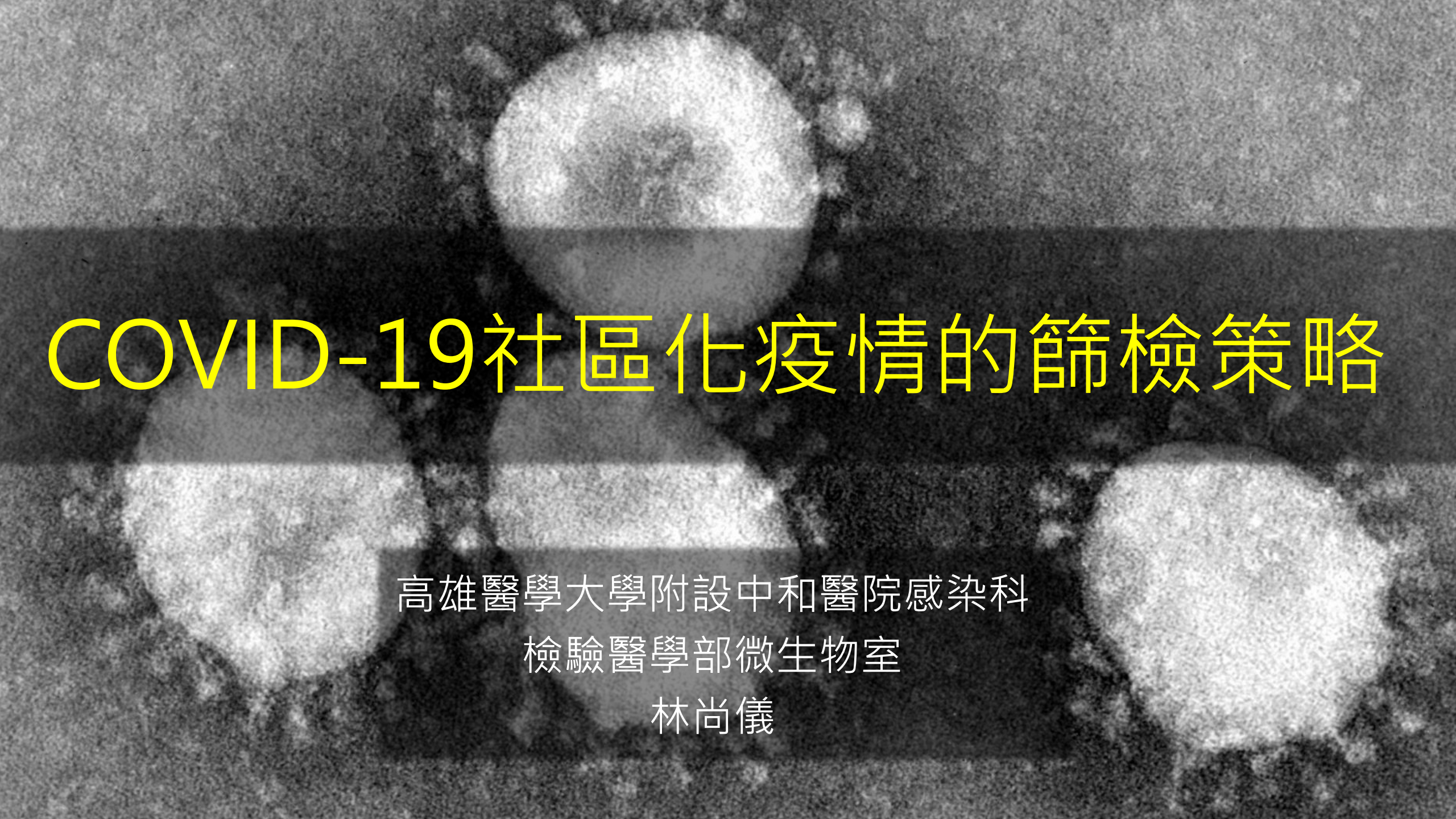


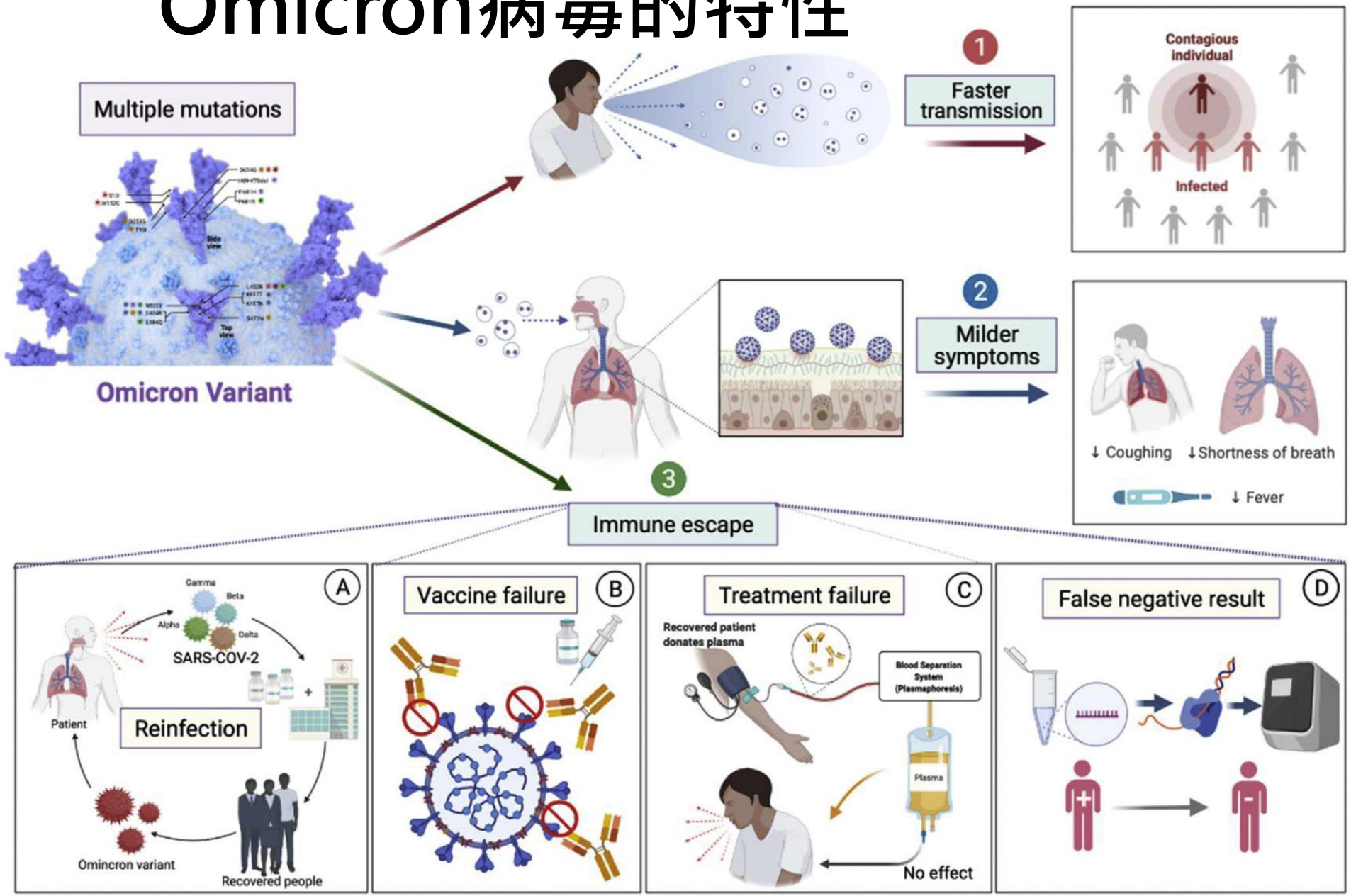
COVID-19社區化疫情的篩檢策略

高雄醫學大學附設中和醫院感染科
檢驗醫學部微生物室
林尚儀

演講大綱

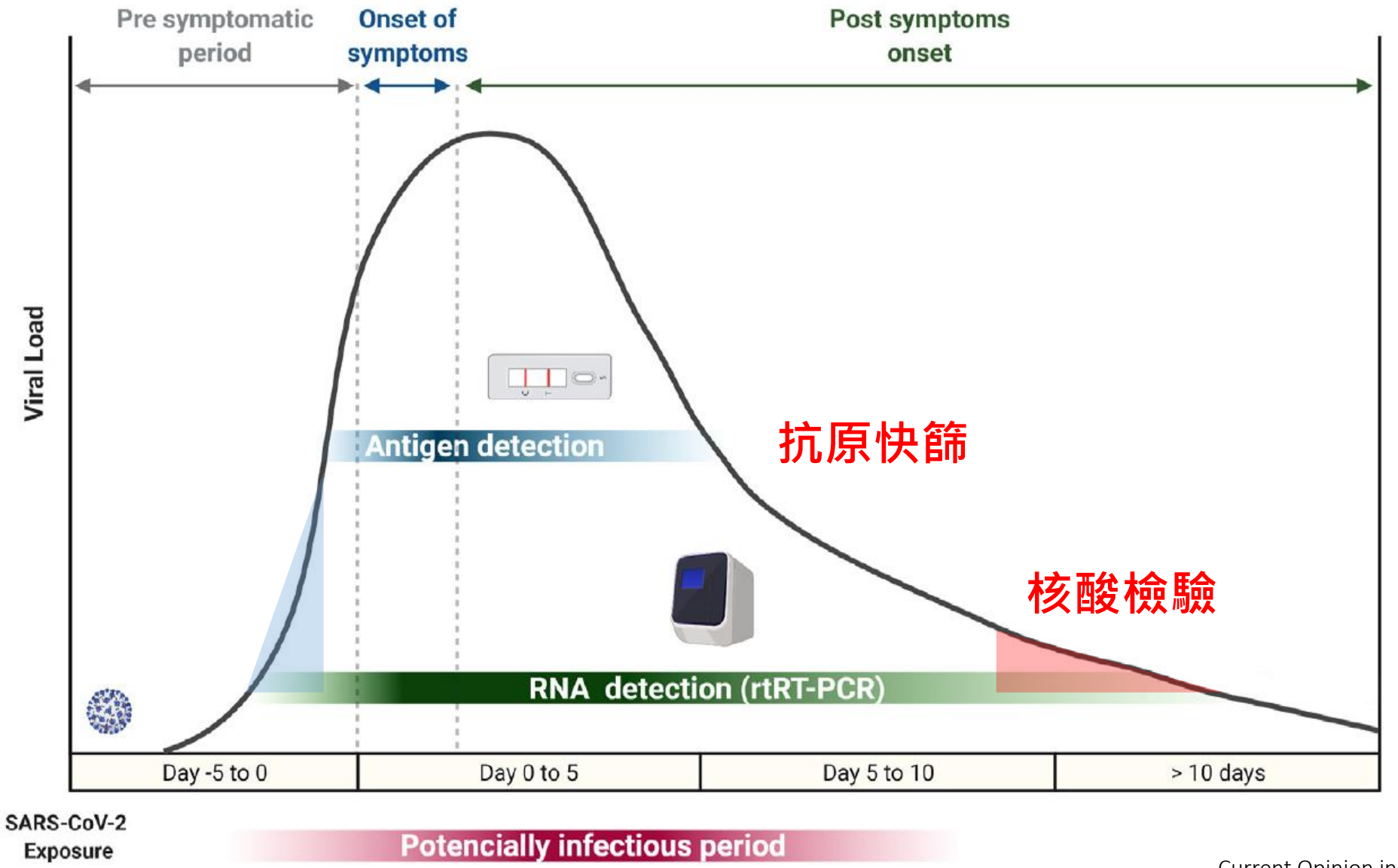
- 新冠檢驗工具簡介
  - 核酸檢測及抗原快篩
- 檢驗結果的判讀
  - 有症狀(前測機率高)及無症狀患者(前測機率低)的篩檢
- 篩檢策略考量
- 高風險及易感受族群的篩檢策略
  - 密切接觸者、養護中心及醫療機構

Omicron病毒的特性



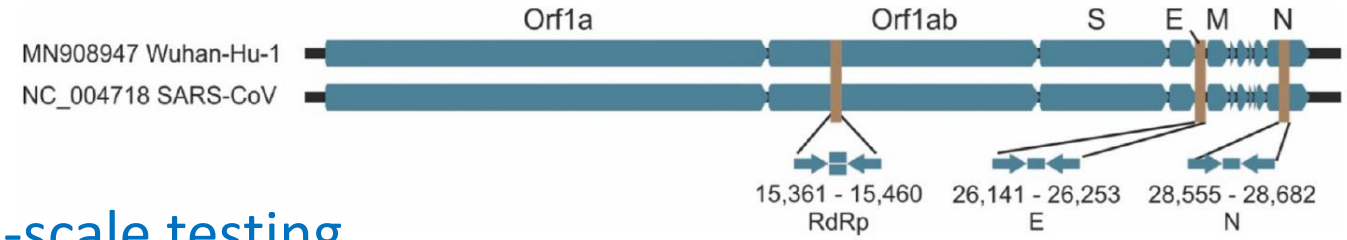
Wenxia Shao, et al. J Microbiol Immunol Infect. 2022

COVID-19 檢測工具的使用時機



Current Opinion in Pharmacology 2022, 62:152–158

核酸檢驗



- Gold standard method
  - the standard for population-scale testing
  - Based on measuring the amplification of *RdRP*, *E*, *N* or *S* gene fragments
  - Sensitivity 80-90% and specificity ~99%
- Disadvantage
  - typically conducted in large, centralized laboratories, efficient sample collection is critical to minimize reporting delays
  - false-negative rate across different specimens and time periods
  - Occasional false positive results may occur due to technical errors and reagent contamination

1. Corman, V. M. et al. Eur. Surveill. 2020. 2. Liu, R. et al..Clin. Chim. Acta 2020. 3. Wikramaratna, P., et al. Euro Surveill. 2020 4. M. Yüce, et al. Biosensors and Bioelectronics 2021

Flow Chart for COVID-19 Diagnostic through RT-PCR

Symptoms:

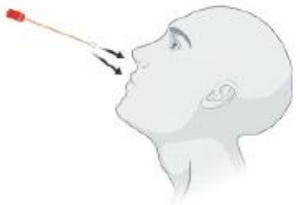
Cough

Fever

Difficulty breathing

Pneumonia (severe cases)

1 Nasopharyngeal or Oropharyngeal swab

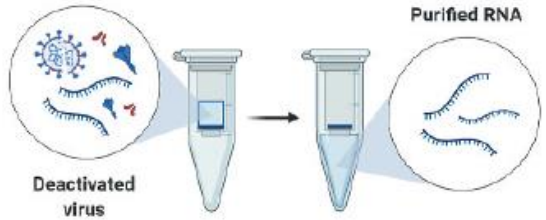


2 Sample Handling

The collected sample should be immediatedly inactivated and proceed to RNA extraction.

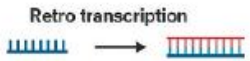
3 RNA extraction and purification

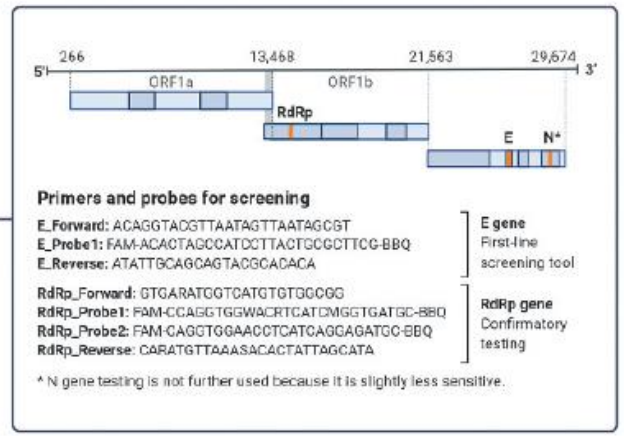
Purified RNA is extracted from deactivated virus.



4 RT-qPCR

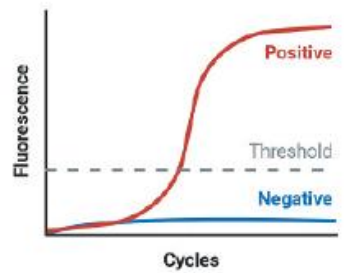
Purified RNA is reverse transcribed to cDNA and amplified by qPCR.

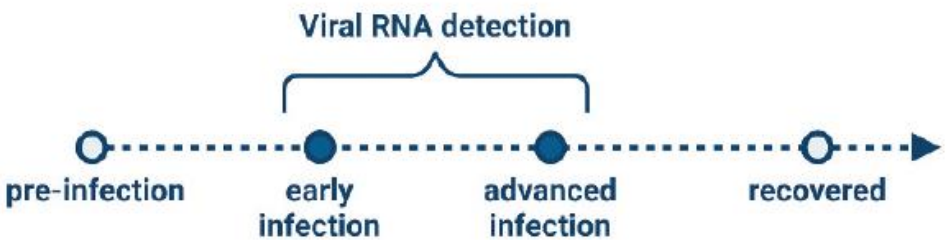




5 Test results real-time

Positive SARS-CoV-2 patients cross the threshold line within 40.00 cycles (< 40.00 Ct).





L. BENEVIDES LIMA, et al. Expert Rev Mol Diagn. 2022

高通量機台

快速反應機台

Xpert

ID NOW

Liat

CT value(cycle threshold)與病毒量的關係

- WHO: Ct values as a surrogate for the level of viral load

The Depiction of Viral load and infectivity basis on the RT PCR Ct (Cycle threshold) values.

Inversely Proportional relationship of Ct values and Viral load.

Lower the Ct values = Higher the viral load

Higher the Ct values = Lower the viral load

Score	Viral load
17-24	High Viral load
24-35	Moderate Viral load
≥ 36	Non-diagnostic result

Ali A. Rabaan, et al. Diagnostics 2021
Rao, S.N, et al. Infect. Dis. Ther. 2020

CT value(cycle threshold)的迷思

- CT值跟嚴重度有關嗎?
  - 低CT值與嚴重的臨床表現相關？
    - ex, CT value of 14 vs 35
- CT值能預測感染力嗎?
  - 一般而言，高CT值表示病毒量較低(ex, 大於35)
    - ex, CT value of 35 比較不會傳染嗎?
  - 病人最常問:
    - CT值還驗得到，怎麼辦...
    - 錯誤的聯想:不必遵守防疫措施，因為我CT值很高...

Rao SN, et al. Infectious diseases and therapy 2020
https://www.idsociety.org/globalassets/idsa/public-health/covid-19/idsa-amp-statement.pdf

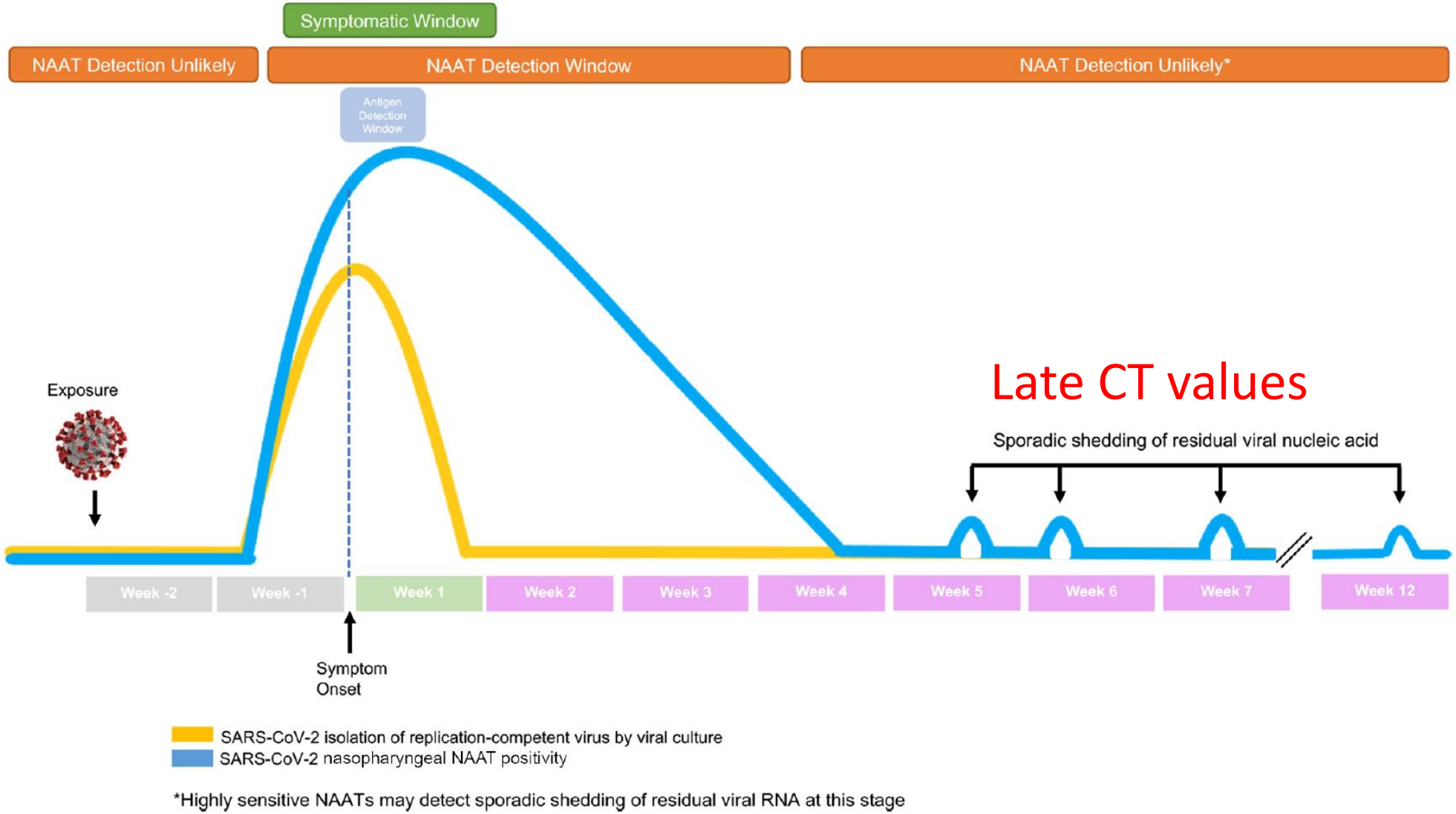
影響CT值的因子

IDSA Infectious Diseases Society of America

AMP Association for Molecular Pathology

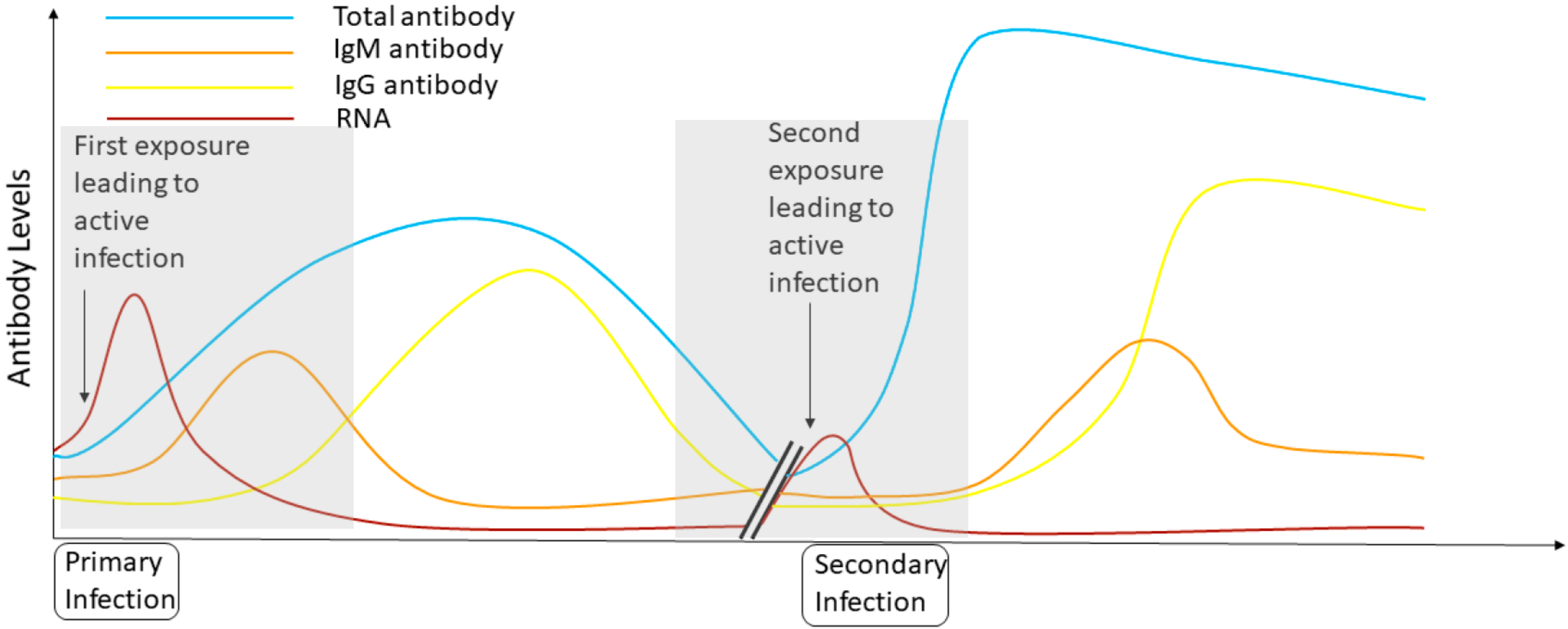
Patient factors	Specimen factors	Test factors
Presence or absence of symptoms	Adequacy of specimen collection	Volume of sample subjected to testing
Severity of symptoms	Reproducibility of the specimen collection method	Gene target
Time from symptom onset	Specimen type (e.g., nasal swab, saliva, BAL)	PCR primer and probe design, which may be variably affected by emerging viral variants
Immune status	Dilution of the sample in transport medium or other liquid	Nucleic acid extraction efficiency (note, not all tests include a nucleic acid purification and extraction step to remove potential PCR inhibitors in the specimen)
Age	Specimen transport and storage conditions	Gene target amplification efficiency
		PCR instrument parameters and settings

新冠病毒量的變化及核酸檢測的關係



Stephanie L. Mitchell and Michael J. Loeffelholz, J Clin Microbiol. 2022

初次感染及再感染的抗體及核酸檢測的關係



Emmanuel Thomas, et al. Virus 2021

新冠再感染、復發及核酸復陽定義

-歐洲臨床微生物學和傳染病學會共識

Variable	Confirmed reinfection	Clinical reinfection	Epidemiological reinfection	Relapse/ reactivation	Repositivity
Clinical symptoms	Characteristic clinical symptoms[a]	Characteristic clinical symptoms[a]	Asymptomatic/ symptomatic	Characteristic clinical symptoms[a]	Asymptomatic
PCR	Positive	Positive	Positive	Positive	Positive
Viral culture (should one be performed)	Positive	Positive	Positive	Positive	Negative
Time frame from original infection	>90 days[b]			<90 days	<90 days
Isolation measures	Recommended	Recommended	Recommended	Should be considered	Not recommended
Additional findings	Viral RNA sequencing from both episodes show different strains	Epidemiological risk factor (known exposure or outbreak setting), no other cause	Epidemiological risk factor (known exposure or outbreak setting)	No new exposure, area of low community spread	—

[a] Clinical manifestations characteristic of coronavirus disease 2019 (COVID-19).
[b] Could be considered in the event of under 90 days if recovery proven by two consecutive negative PCR tests and current known COVID-19 exposure.

Dafna Yahav, et al. Clinical Microbiology and Infection 2021

台灣疾病管制署定義 Publish Time 2022/7/1

一、已解除隔離治療之COVID-19確診個案，除症狀惡化等特殊情況外，建議於發病日或採檢日3個月內無需再進行SARS-CoV-2檢驗。惟如於發病日或採檢日**1至3個月內**症狀惡化，且SARS-CoV-2 **RT-PCR檢驗陽性且Ct值<27或抗原/核酸快篩陽性**：

(一)醫師可進行法定傳染病通報，並先比照確定病例處理。
(二)後續由衛生福利部疾病管制署(以下稱疾管署)各區管制中心研判是否為新的確定病例並啟動相關防疫措施。

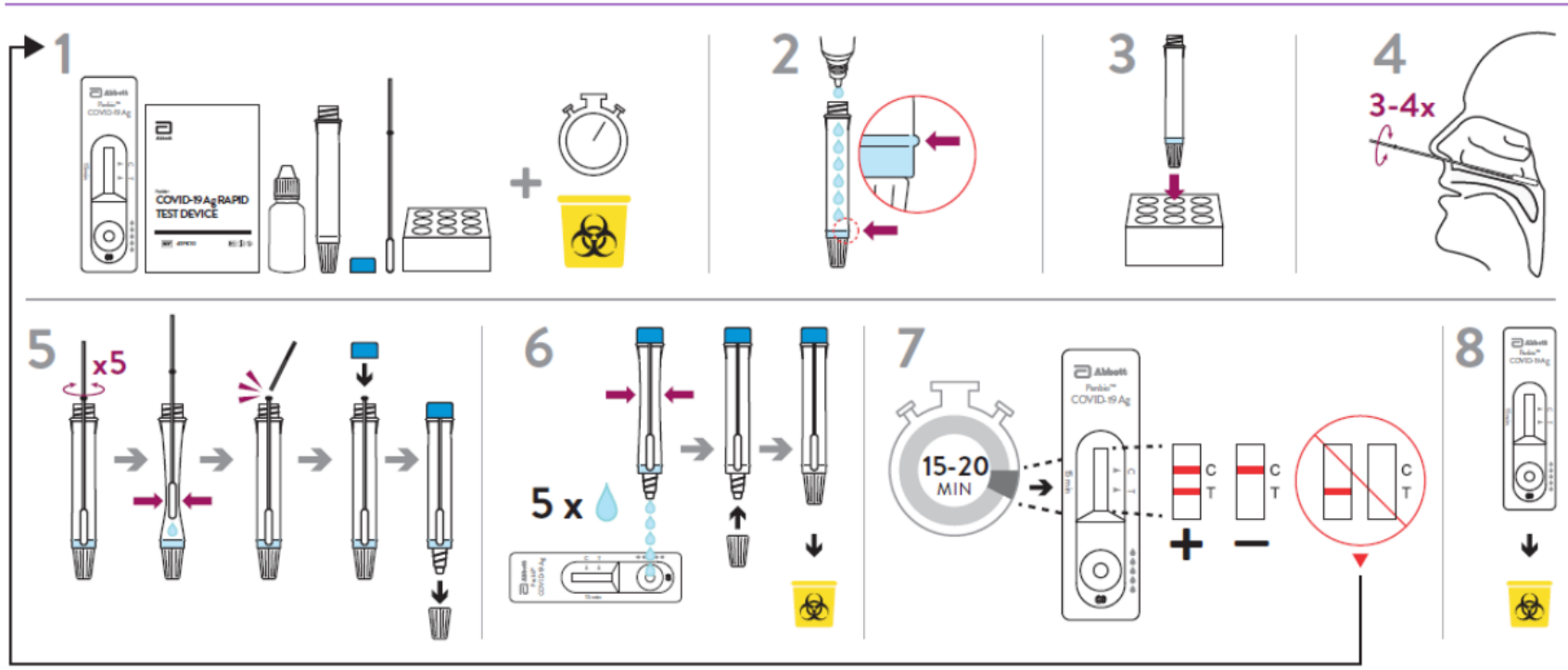
二、已解除隔離治療之確診個案，於發病日或採檢日間隔**至少3個月後**再次SARS-CoV-2 RT-PCR檢驗陽性且**Ct值< 30或抗原/核酸快篩檢驗**陽性：
(一)經醫師評估可能為重複感染個案後，應進行法定傳染病通報。
(二)依確定病例處理原則，啟動相關防疫措施及醫療處置。

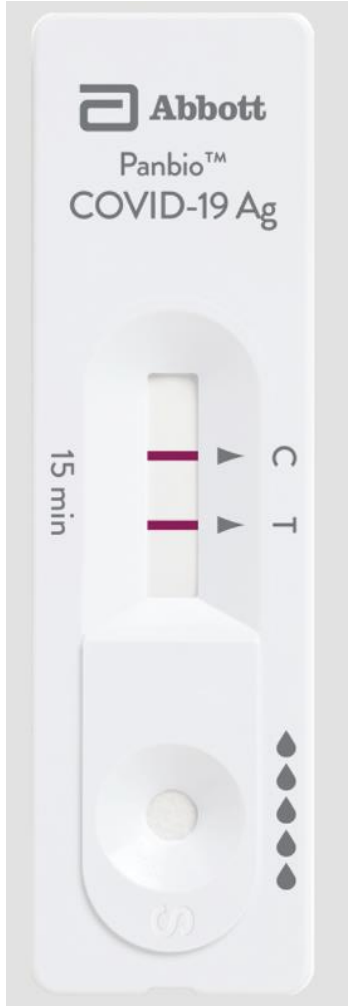
指揮中心指出，重複感染個案之PCR陽性檢體，應送疾管署檢驗及疫苗研製中心進行**基因定序**，以利持續進行SARS-CoV-2變異株監測，並適時調整因應作為。

快速抗原檢測工具

對於疑似患者的快速篩檢工具

- 操作簡易(有居家試劑)、快速





症狀發生時篩檢 抗原快篩的表現都不錯

	Sample type	Time of sample collection*	Result reading	Sensitivity, specificity†	Comments
Abbott BinaxNOW, USA	Nasal swab	0–7 days	Visual, 15 min	97%, 99%	WHO Emergency Use Listing; US FDA Emergency Use Authorization; app for results; influenza A and B tests available
Abbott Panbio, USA	Nasal swab, nasopharyngeal swab	0–7 days	Visual, 15–20min	93%, 99%	WHO Emergency Use Listing; US FDA Emergency Use Authorization pending
Access Bio CareStart, USA	Nasal swab, nasopharyngeal swab	0–5 days	Visual, 15–20min	88%, 100%	US FDA Emergency Use Authorization
BD Veritor, USA	Nasal swab	0–5 days	Instrument, 30 min	84%, 100%	US FDA Emergency Use Authorization
LumiraDx, UK	Nasal swab	0–12 days	Instrument, 12 min	98%, 97%	US FDA Emergency Use Authorization
Quidel Sofia SARS Antigen Fluorescent Immunoassay, USA	Nasal swab, nasopharyngeal swab	0–5 days	Instrument, 20 min	97%, 100%	US FDA Emergency Use Authorization; does not differentiate between SARS-CoV and SARS-CoV-2
Quidel Sofia Flu and SARS Antigen Fluorescent Immunoassay, USA	Nasal swab, nasopharyngeal swab	0–5 days	Instrument, 20 min	95%, 100%	US FDA Emergency Use Authorization
SD Biosensor, South Korea	Nasal swab, nasopharyngeal swab	Not stated	Visual, 15–30min	97%, 100%	WHO Emergency Use Listing

Data from the Foundation for Innovative New Diagnostics.[2] SARS-CoV=severe acute respiratory syndrome coronavirus. FDA=Food and Drug Administration. *Days after symptom onset. †Data from manufacturers.

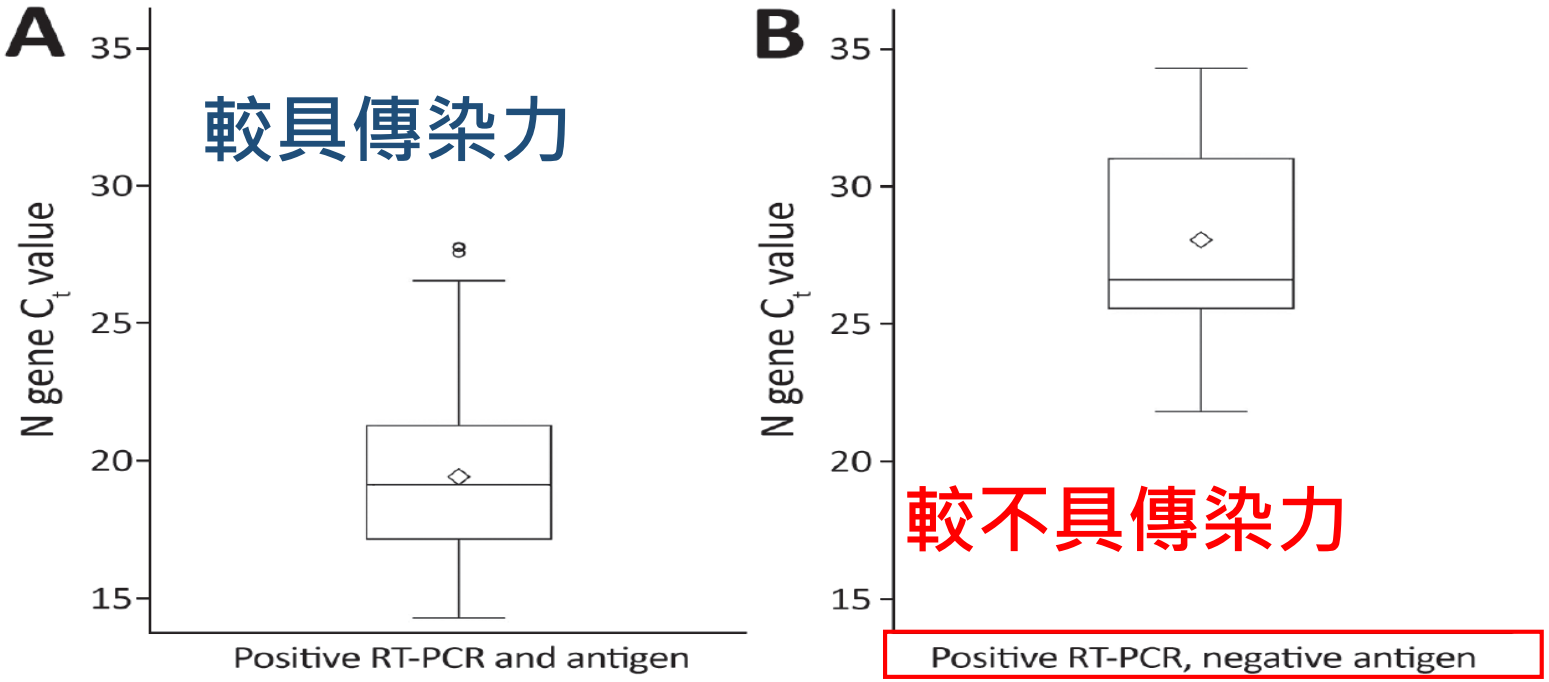
Rosanna W Peeling,et al. Lancet Infect Dis 2021

抗原快篩、PCR及病毒培養的關係

Table 1. Positive predictive value of the BinaxNOW COVID-19 Antigen Card Test and RT-PCR relative to viral culture, Winnebago County, Wisconsin, USA, November–December 2020*

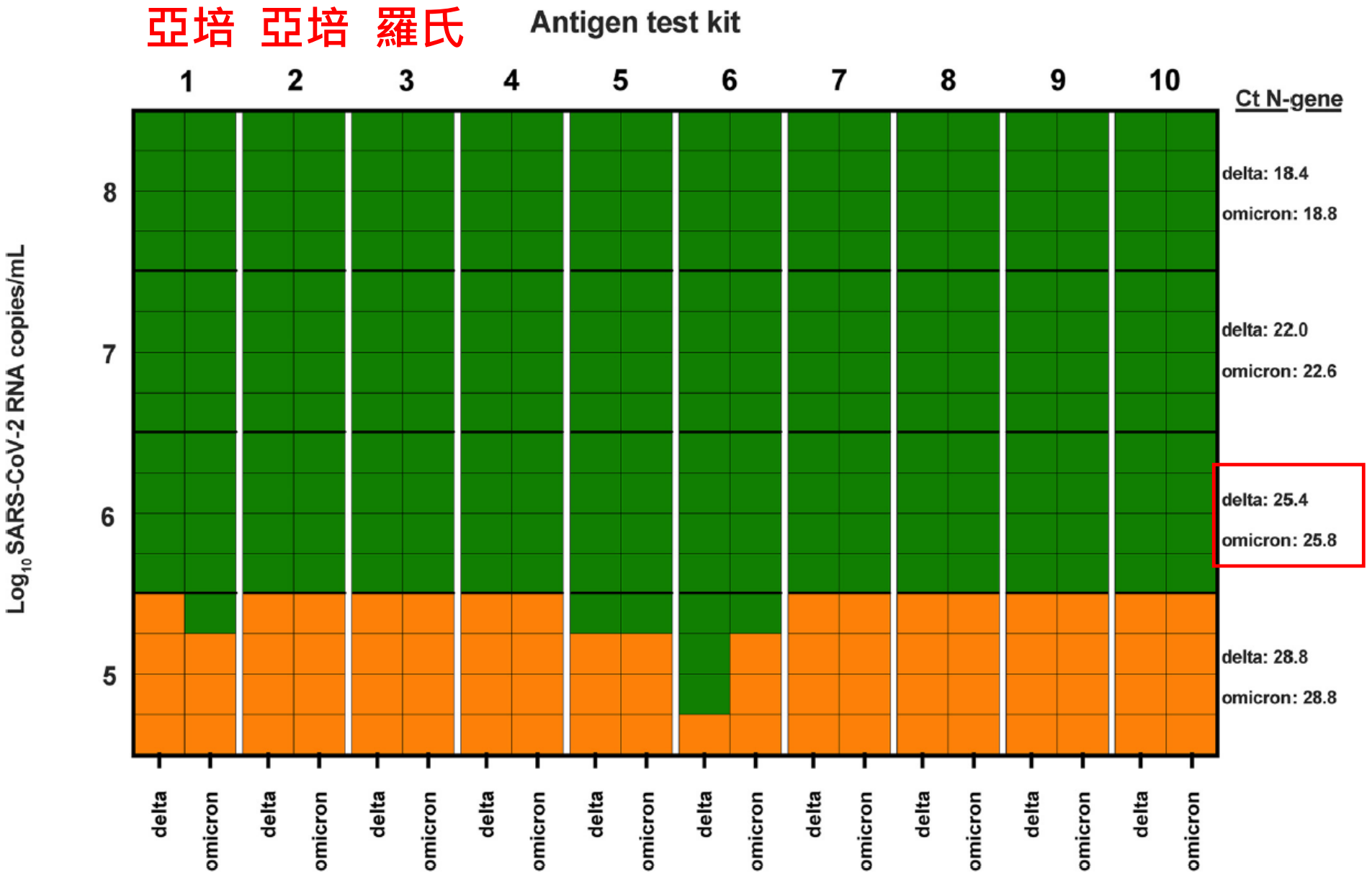
SARS-CoV-2 diagnostic test result	No. culture positive	No. culture negative	Total	Positive predictive value, %
BinaxNOW positive	191	78	269	71.0
RT-PCR positive	200	134	334	59.9

*BinaxNOW, https://www.abbott.com. RT-PCR, reverse transcription PCR; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.



Emerging Infectious Diseases • www.cdc.gov/eid • Vol. 28, No. 3, March 2022

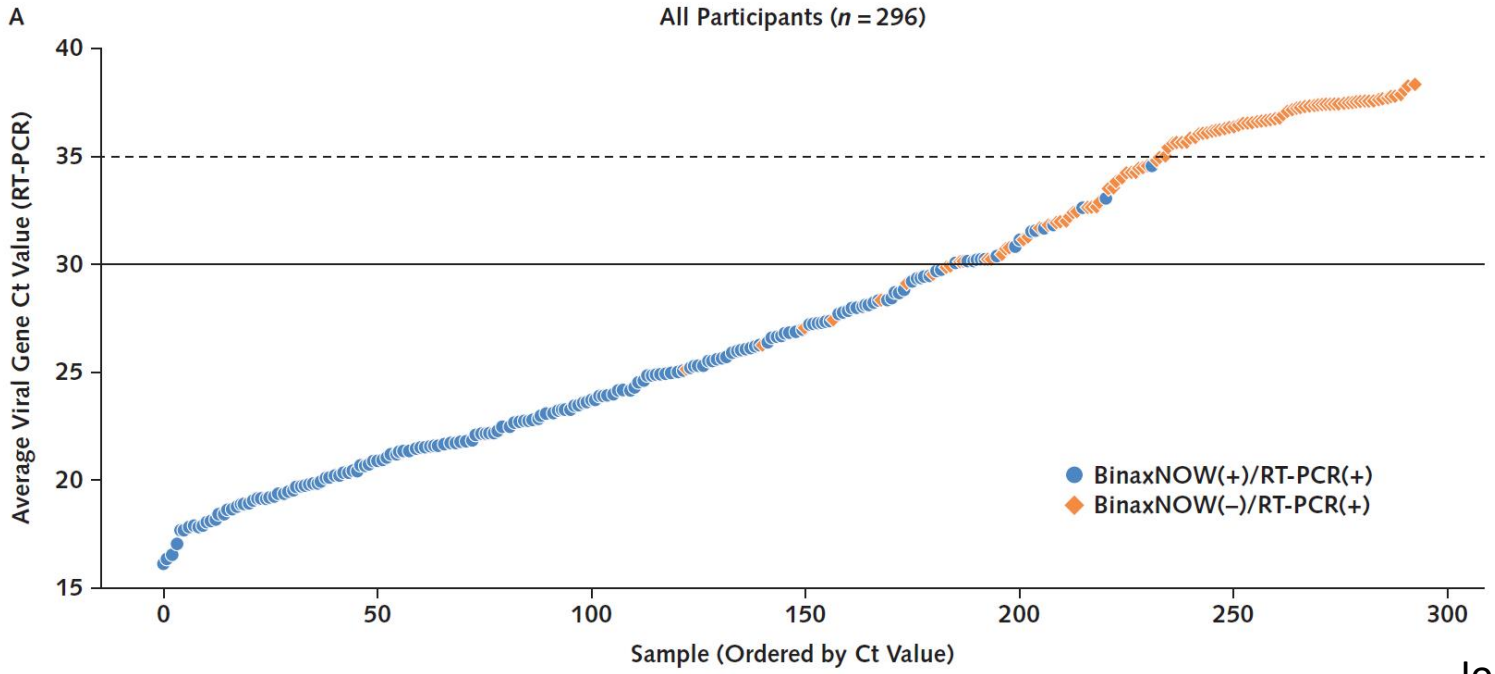
市面上抗原快篩的表現



Joshua Deerain, et al. J Clin Microbiol 2022

Omicron大流行- 快篩仍準確

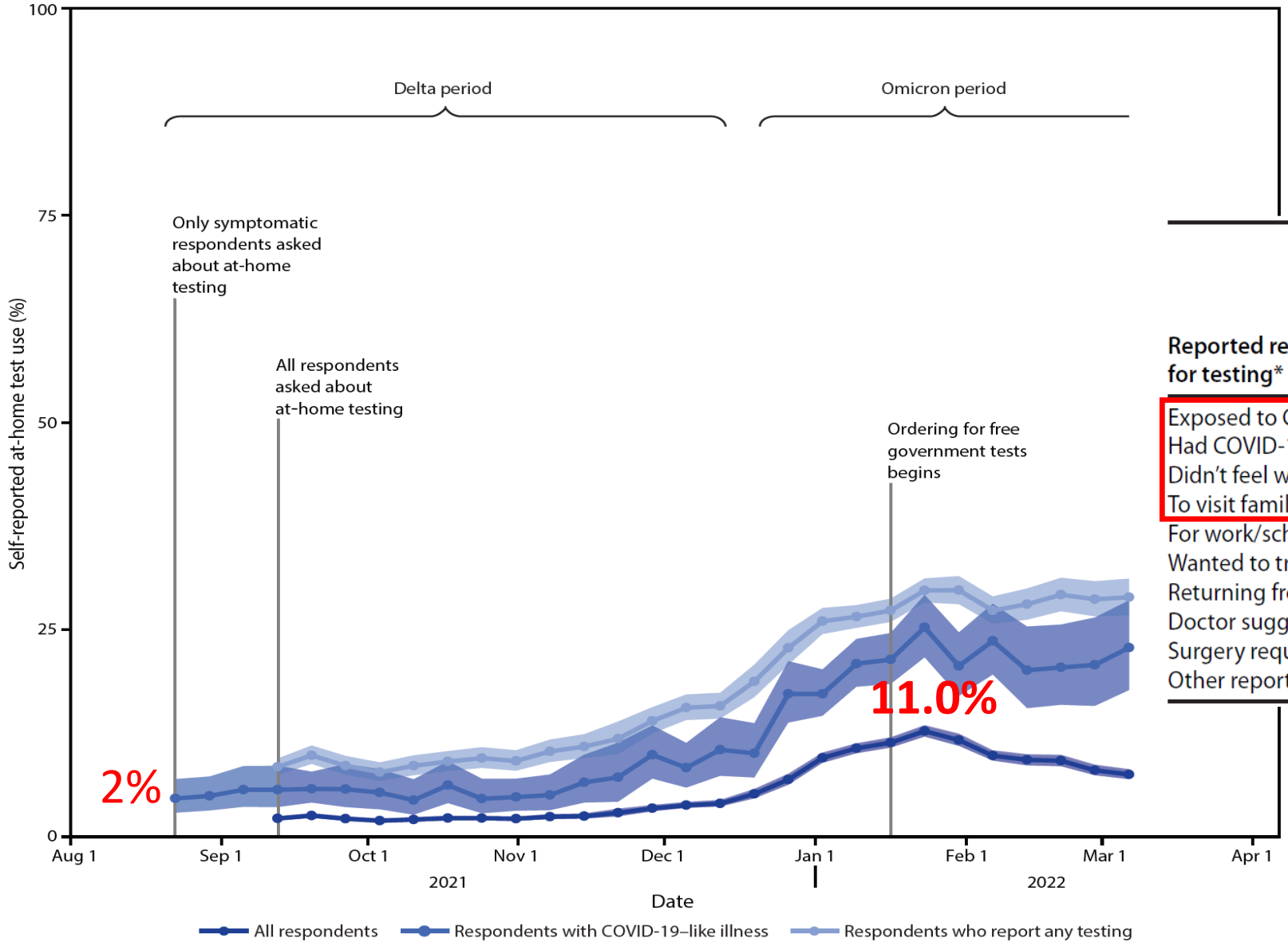
- 美國加州舊金山 (n=731):
- 95.2% and 82.1% of persons who tested positive on RT-PCR with Ct values below 30 and below 35, respectively



John Schrom, et al. Ann Intern Med 2022

家用快篩大量使用-美國

FIGURE. Proportion* of adults aged ≥18 years who reported at-home rapid COVID-19 antigen test use during the preceding 30 days — United States, August 23, 2021–March 12, 2022†,§



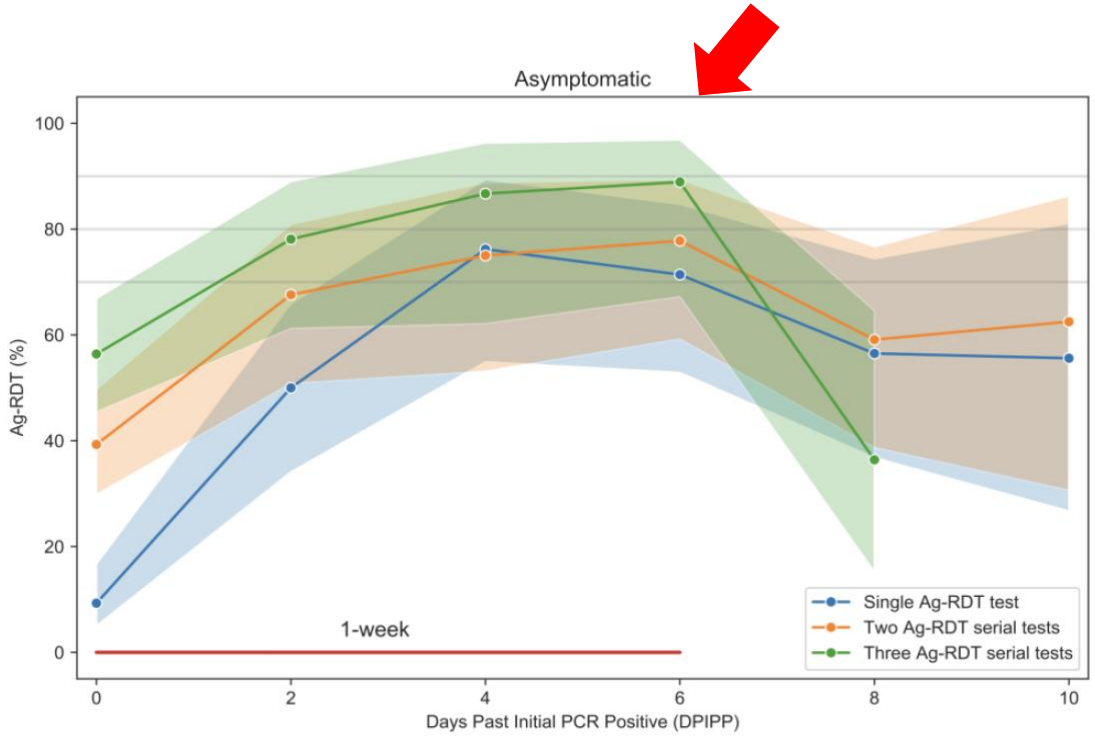
Reported reason for testing*	% Reporting (95% CI) Among those using at-home rapid COVID-19 antigen test (n = 18,578†)	Among those using other COVID-19 test (n = 80,851†)
Exposed to COVID-19	39.4 (38.5–40.3)	19.4 (19.0–19.7)
Had COVID-19 symptoms	28.9 (28.1–29.7)	16.7 (16.3–17.0)
Didn't feel well	28.6 (27.8–29.4)	7.0 (6.7–7.2)
To visit family	17.0 (16.4–17.7)	5.5 (5.3–5.7)
For work/school	10.6 (10.1–11.3)	17.4 (17.0–17.7)
Wanted to travel	9.2 (8.7–9.8)	23.2 (22.8–23.6)
Returning from travel	8.8 (8.3–9.3)	7.8 (7.5–8.0)
Doctor suggested	3.7 (3.4–4.2)	8.4 (8.2–8.7)
Surgery required testing	2.0 (1.7–2.3)	6.4 (6.2–6.6)
Other reported reason	10.3 (9.8–10.9)	13.0 (12.7–13.3)

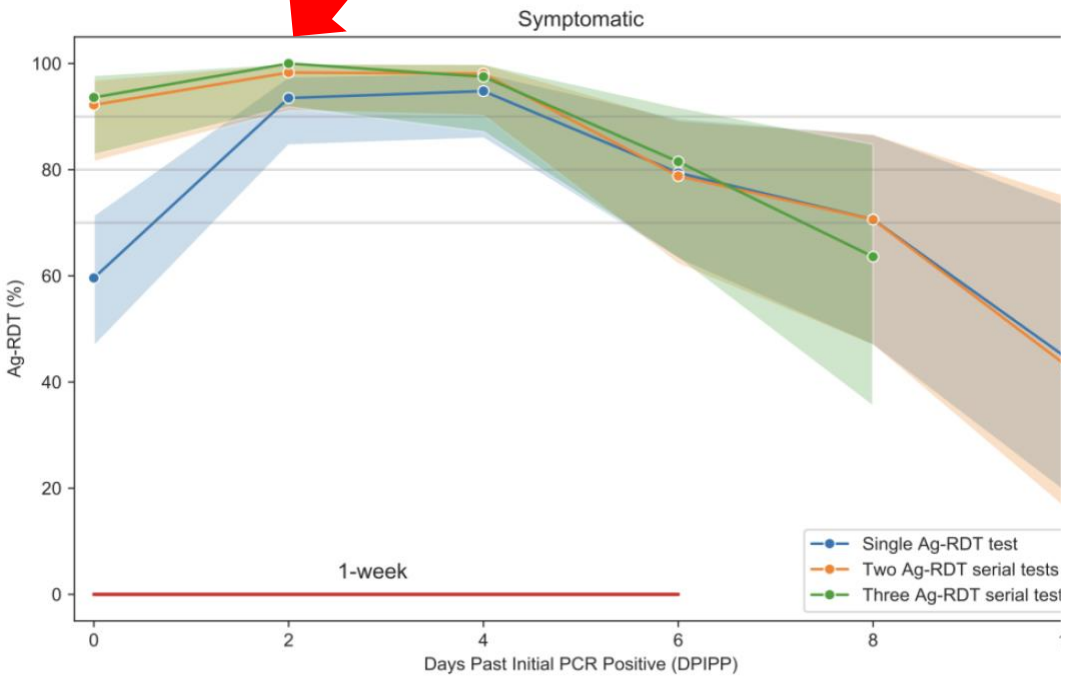
Benjamin Rader, et al. MMWR / April 1, 2022

家用快篩的表現

比較單獨使用、連續使用兩次及三次的表現:

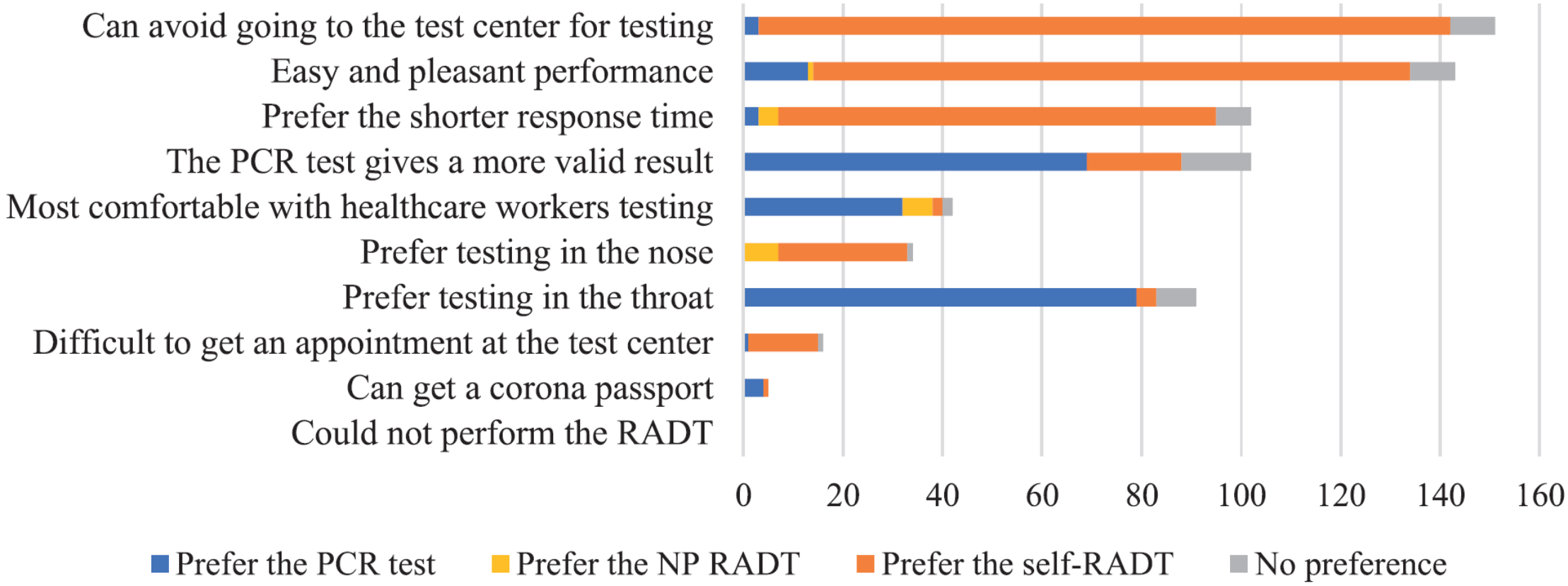
- 無症狀患者的平均敏感性:
  34.2%, 55.6% and 68.8%
- 有症狀患者的平均敏感性:
- 59.6%, 93.4% and 94.3%





medRxiv. 2022 Aug 6:2022.08.05.22278466

家用快篩-使用者的接受度(滿意度)調查

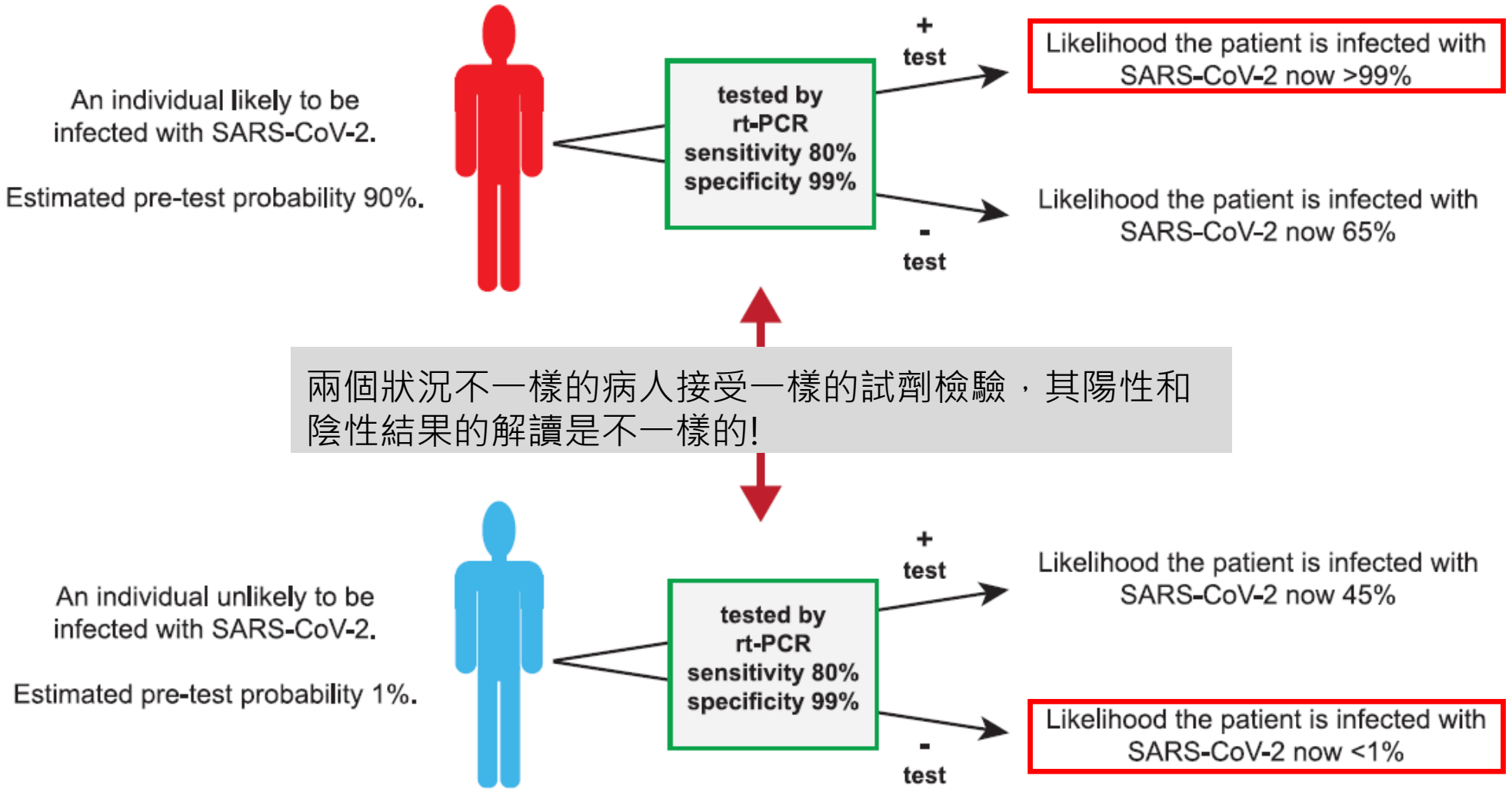


Ida Johanne B. Møller, et al. Int J Infect Dis. 2022

核酸及抗原檢測的比較

	原理	優點	缺點
核酸檢測	偵測病毒的核酸片段(黃金準則)	• 高敏感性及特異性的檢驗方法 • 再感染或復發的評估工具	• 技術門檻高 • 需要特定的設備及實驗室要求 • 檢驗時間較久
抗原檢測	偵測病毒抗原	• 快速提供結果 • 便宜 • 不一定需要專門的技術人員執行	• 敏感性較核酸檢驗差 • 檢驗品質不易掌握(尤其家用快篩)

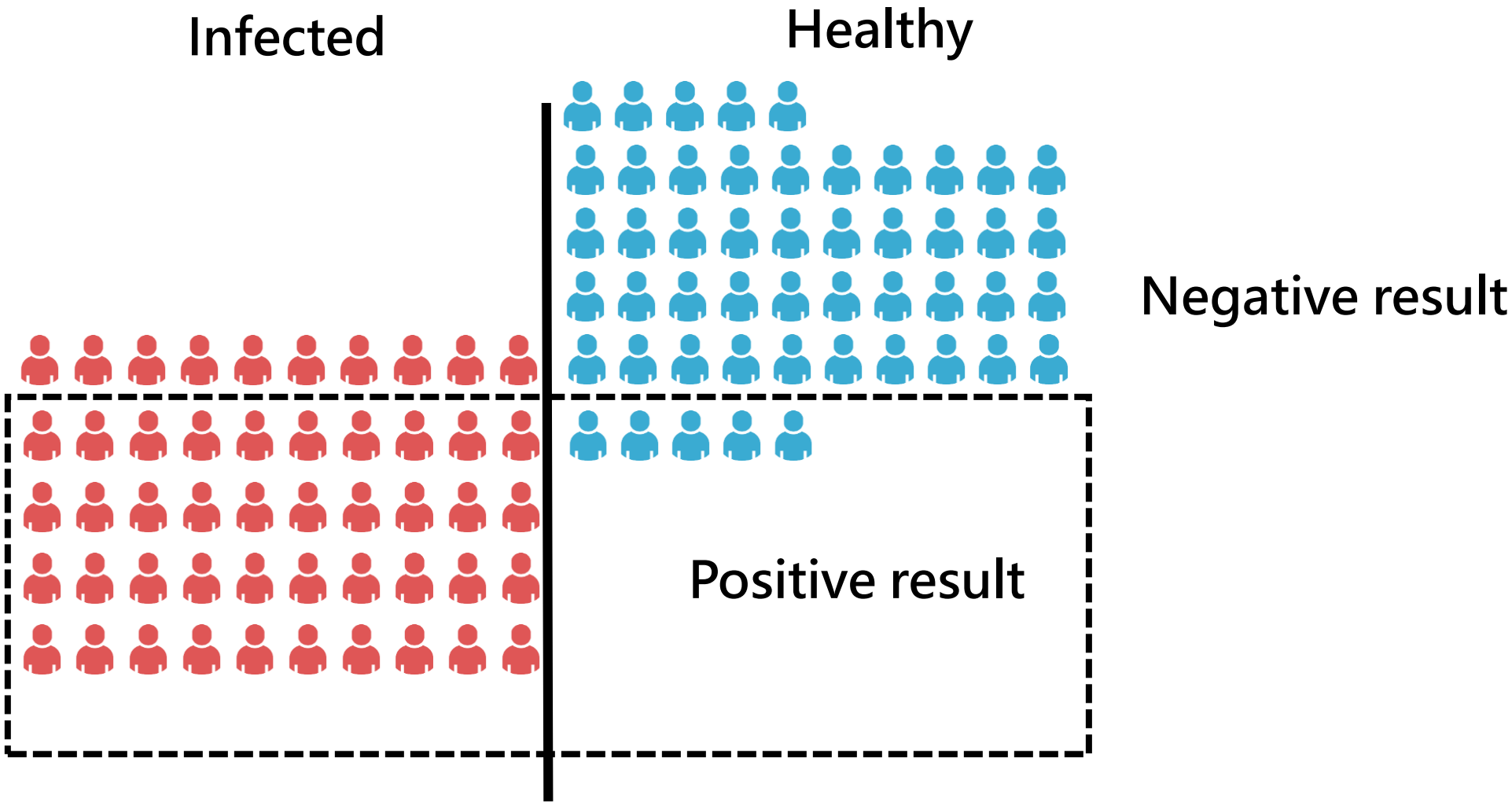
前測機率影響結果判讀



Edward C. Stites and Craig B. Wilen. Med (N Y) 2020

Disease prevalence= 50%

Diagnostic assay sensitivity 80%, specificity：90%



Disease prevalence= 50%

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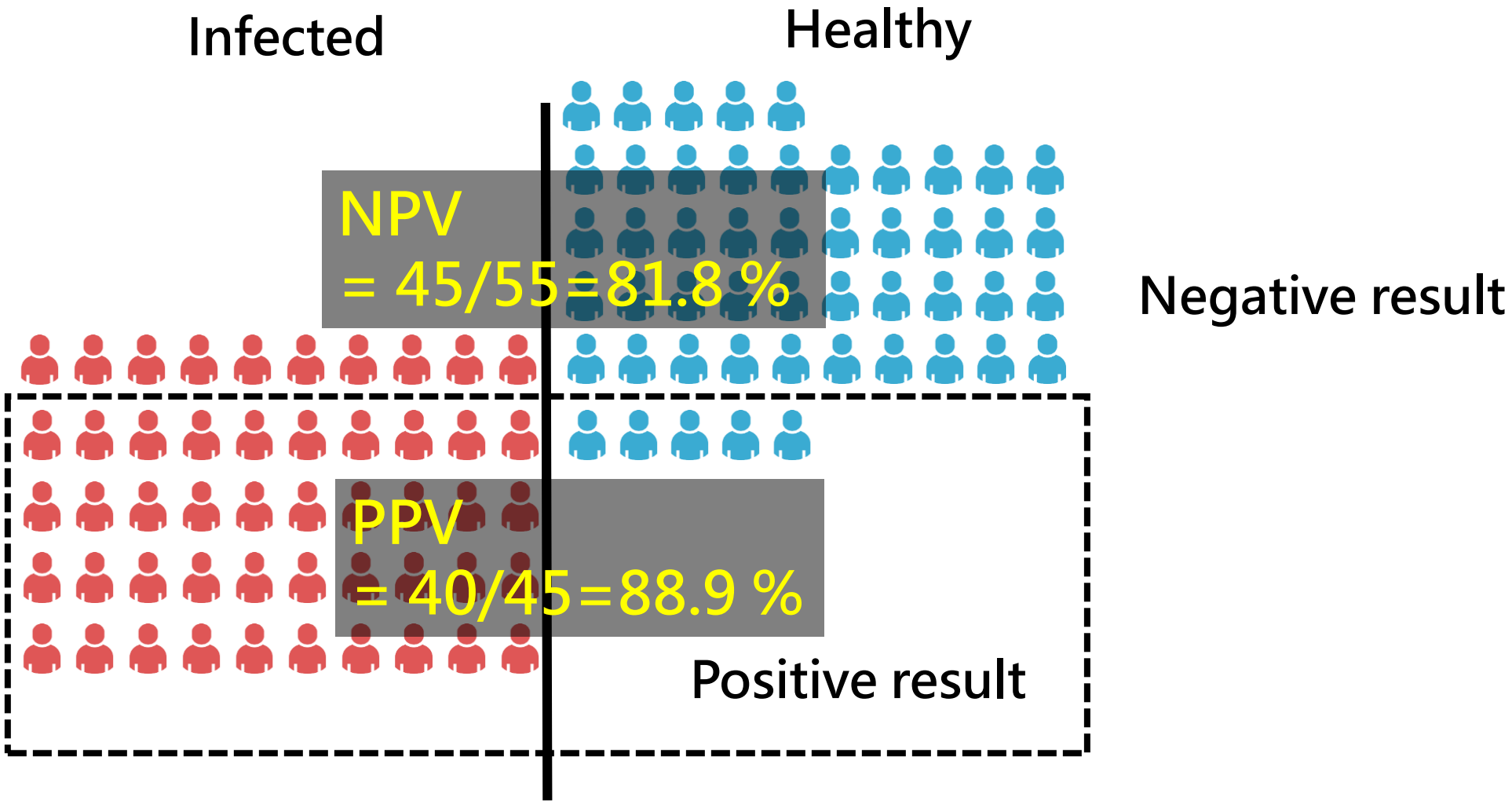
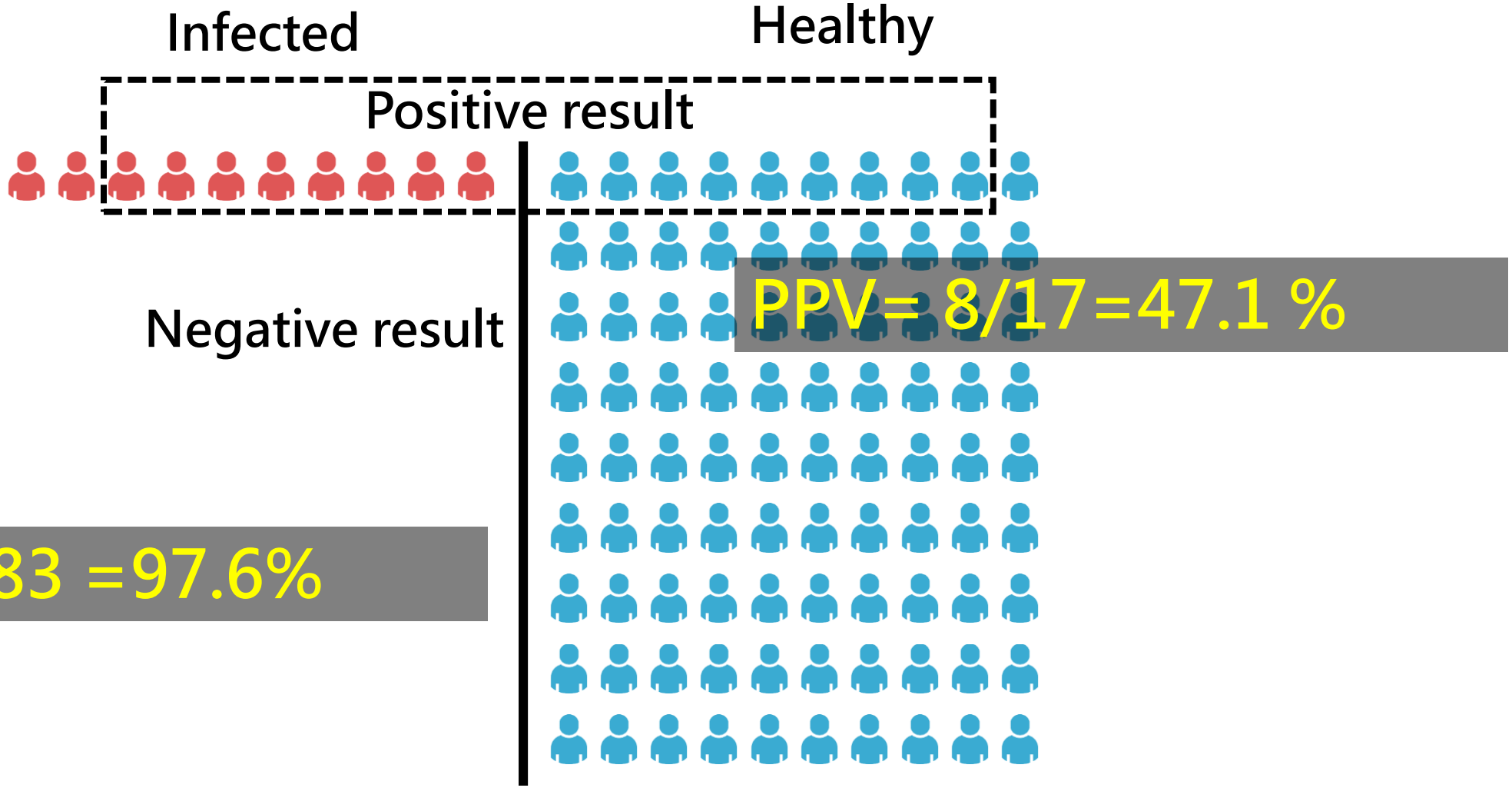


Disease prevalence= 10%

Diagnostic assay sensitivity 80%, specificity：90%



COVID-19最常見的症狀 (前測機率高)

- **喉嚨痛 - 58%**
- **頭痛 - 49%**
- **鼻塞 - 40%**
- **乾咳 - 40%**
- **流鼻涕 - 40%**
- 咳嗽有痰 - 37%
- 聲音嘶啞 - 35%
- 打噴嚏 - 32%

疲勞 - 27%
肌肉痠痛 - 25%
頭暈目眩 - 18%
頸部痠痛 - 15%
眼睛酸痛 - 14%
味覺改變 - 13%
胸痛 - 13%
發燒 - 13%
發冷或顫抖 - 12%
呼吸急促 - 11%
耳痛 - 11%
嗅覺喪失 - 10%

Zoe study and the React-1 study

無症狀的人員篩檢 (前測機率低)

- **Asymptomatic testing** for SARS-CoV-2 needs clear goals and protocols
- Select asymptomatic patients
  - Close contact with index case
  - individuals at risk for severe disease

    (eg, long-term care facilities, cancer patients, unvaccinated population…)
  - **hospitalized patients** at locations where prevalence is high
- Screening program
  - depends on population prevalence of infection, the different tests, different people's willingness to accept personal inconvenience…

1. Infectious Diseases Society of America Guidelines on the Diagnosis of COVID-19, updated December 23, 2020
2. CDC Guidance for Expanded Screening Testing to Reduce Silent Spread of SARS-CoV-2. https://www.cdc.gov/coronavirus/2019-ncov/php/testing/expanded-screening-testing.html
3. European Society for Blood and Marrow Transplantation. COVID-19 anbd BMT. https://www.ebmt.org/covid-19-and-bmt

篩檢策略考量的四大因素

- **社區新冠的盛行率**
  - prevalence in the overall population, prevalence among vaccinated people, or probability of severe outcomes
- **社區新冠變異株的盛行率**
  - Transmissibility, virulence, effectiveness of available diagnostics, vaccines or therapeutics, effectiveness of established public health measures
- **群突發outbreaks多寡**
  - break chains of transmission and prevent the infection from spreading further
- **易感受族群**
  - such as long-term care and acute care facilities

https://www.canada.ca/en/public-health/services/diseases/coronavirus-disease-covid-19/testing-screening-contact-tracing/testing-vaccinated-populations.html

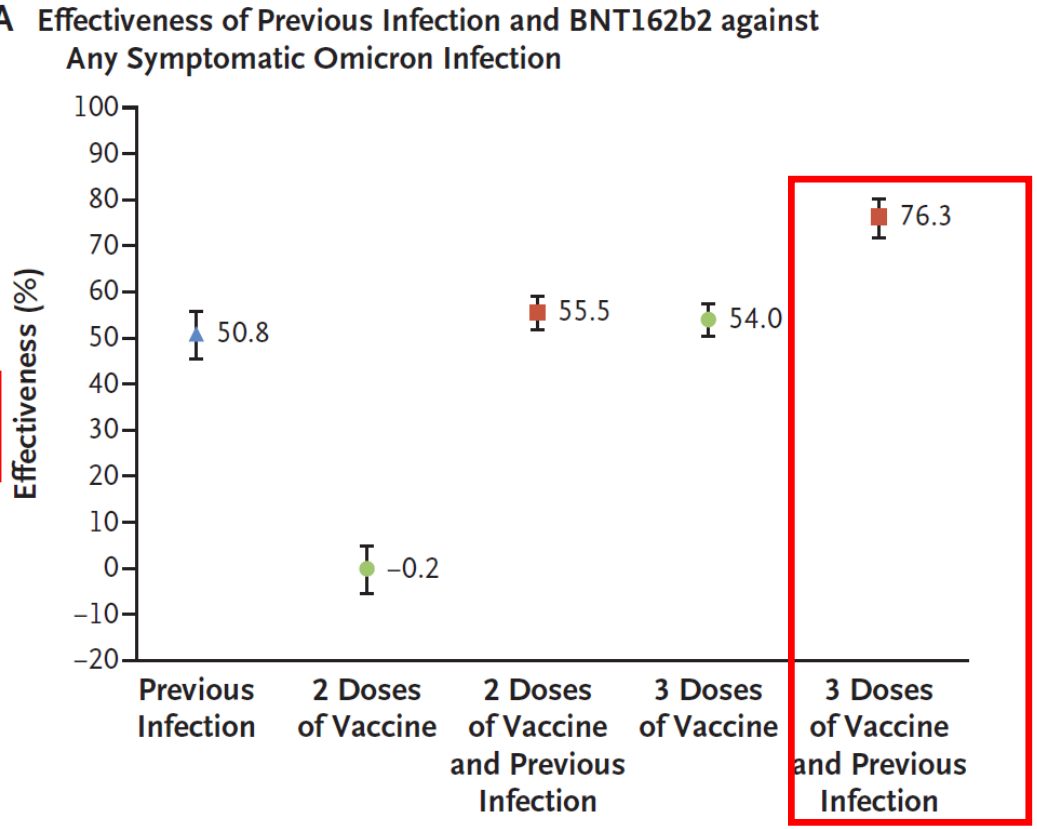
疫苗普及率及COVID-19盛行率關係

- 疫苗注射及過去感染會降低**有症狀**的COVID-19發生

Table 2. Association Between Omicron or Delta Symptomatic SARS-CoV-2 Infection and Prior mRNA COVID-19 Vaccination Among Adults 18 Years or Older Tested in the Increasing Community Access to Testing Platform, December 10, 2021, to January 1, 2022

Vaccine type evaluated	SARS-CoV-2 variant	Total test-positive cases	Total test-negative controls	OR (95% CI)		Q value[b]
				Crude	Adjusted[a]	
3 Doses vs unvaccinated[c]						
Any 3 doses of mRNA vaccine[d]	Delta	5723	27 308	0.063 (0.058-0.069)	0.065 (0.059-0.071)	<.001
	Omicron	5853	27 308	0.34 (0.32-0.36)	0.33 (0.31-0.35)	
3 Doses of BNT-162b2[e]	Delta	5508	19 239	0.076 (0.069-0.084)	0.077 (0.070-0.086)	<.001
	Omicron	4906	19 239	0.36 (0.34-0.39)	0.35 (0.32-0.38)	
3 Doses of mRNA-1273[f]	Delta	5216	15 395	0.045 (0.038-0.052)	0.045 (0.038-0.053)	<.001
	Omicron	4143	15 395	0.28 (0.26-0.31)	0.28 (0.26-0.31)	

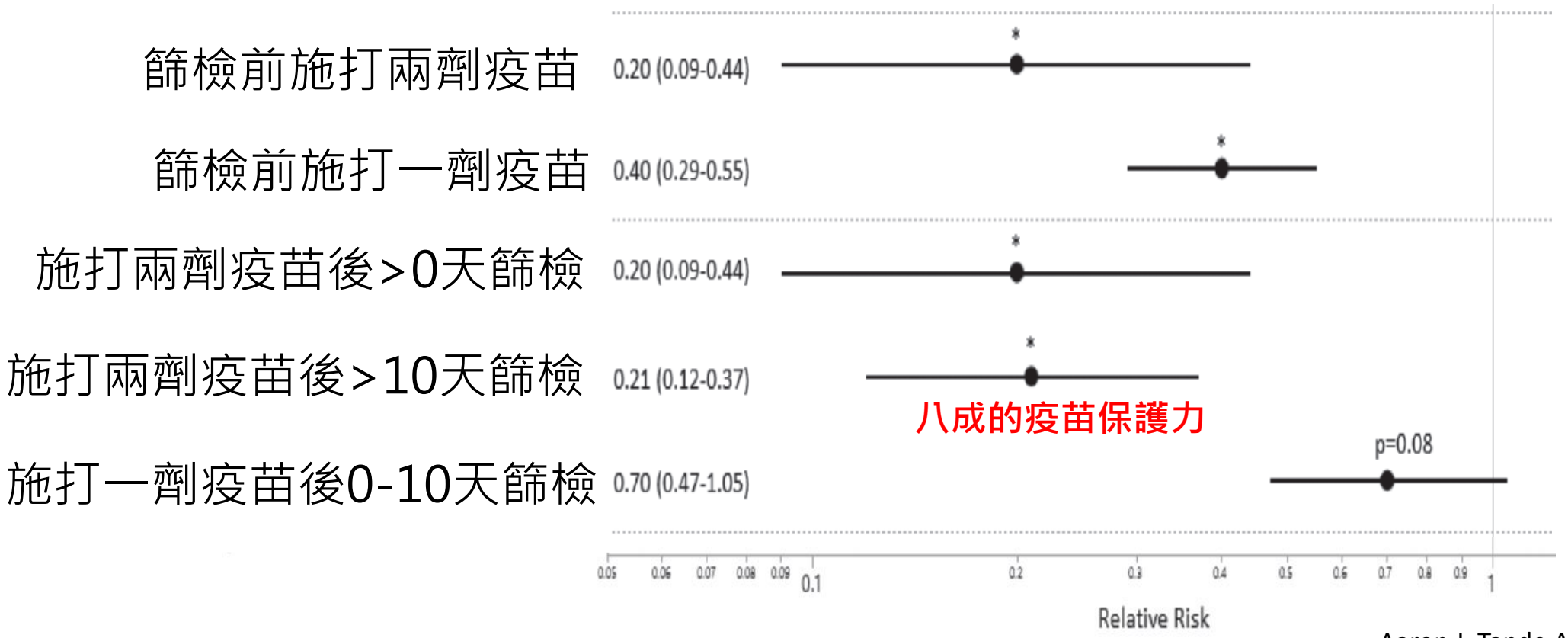
Accorsi EK, et al. JAMA. 2022



Altarawneh HN, et al. N Engl J Med. 2022

疫苗普及率及COVID-19盛行率關係

- 疫苗注射會降低**無症狀**COVID-19發生



Aaron J. Tande AJ, et al. Clin Infect Dis 2022

Prior Omicron infection protects against BA.4 and BA.5 variants

- **Natural immunity**
  - Prior infected with pre-Omicron variant
    - prevented reinfection with BA.4 or BA.5 with an effectiveness of 28.3%
  - Prior infection with Omicron
    - **79.7%** effective at preventing BA.4 and BA.5 reinfection
- **Time between infections**
  - natural immunity against SARS-CoV-2 wanes over time

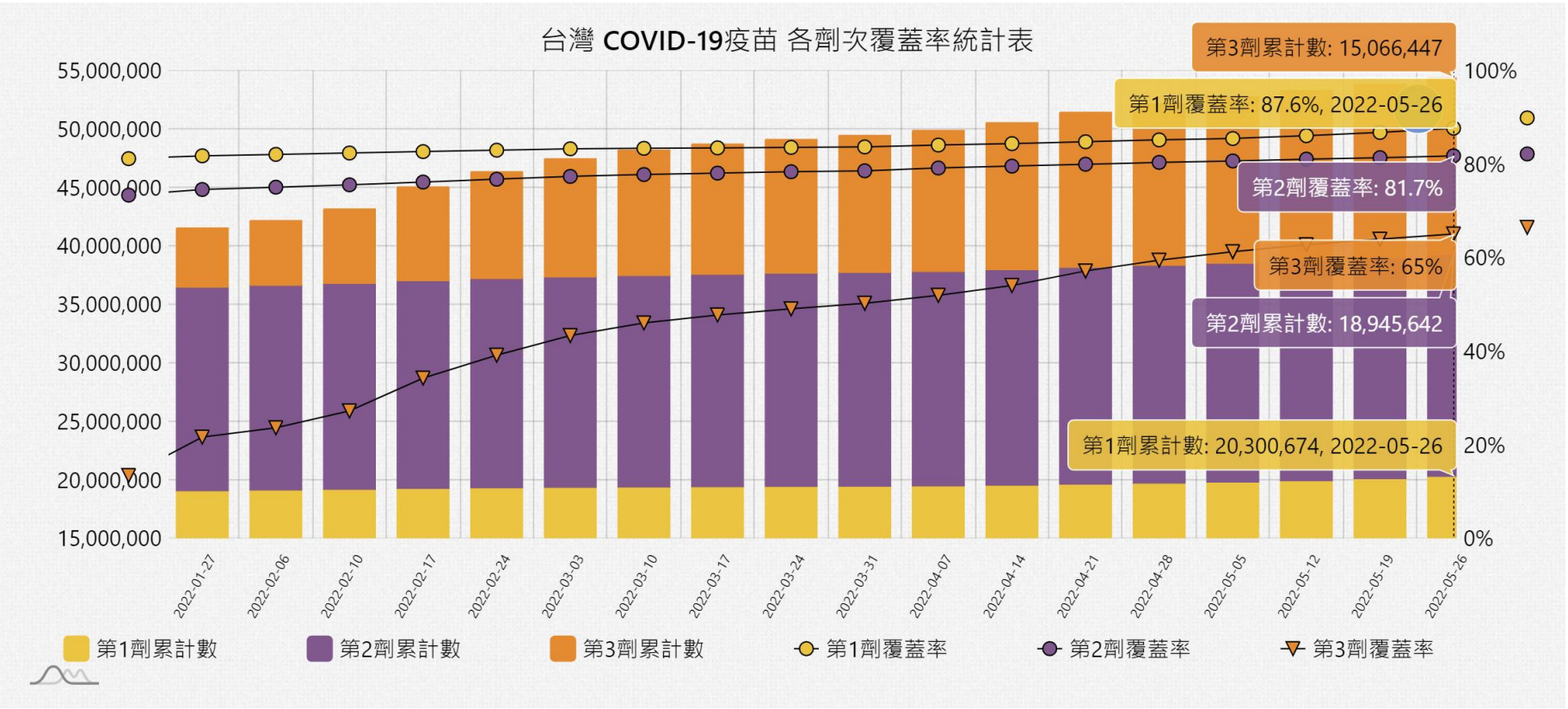
https://doi.org/10.1101/2022.07.27.22277602
https://doi.org/10.1101/2022.07.11.22277448

Nature NEWS 21 July 2022

每個人對SARS-CoV2的免疫力都不一樣:
宿主、疫苗廠牌、注射時間、過去感染病史...

圖片來源 / pixabay

台灣疫苗覆蓋率與感染人數



https://covid-19.nchc.org.tw/dt_002 csse_covid_19_daily_reports_vaccine_city2.php accessed on 2 Sep 2022

密切接触者的檢驗-荷蘭經驗

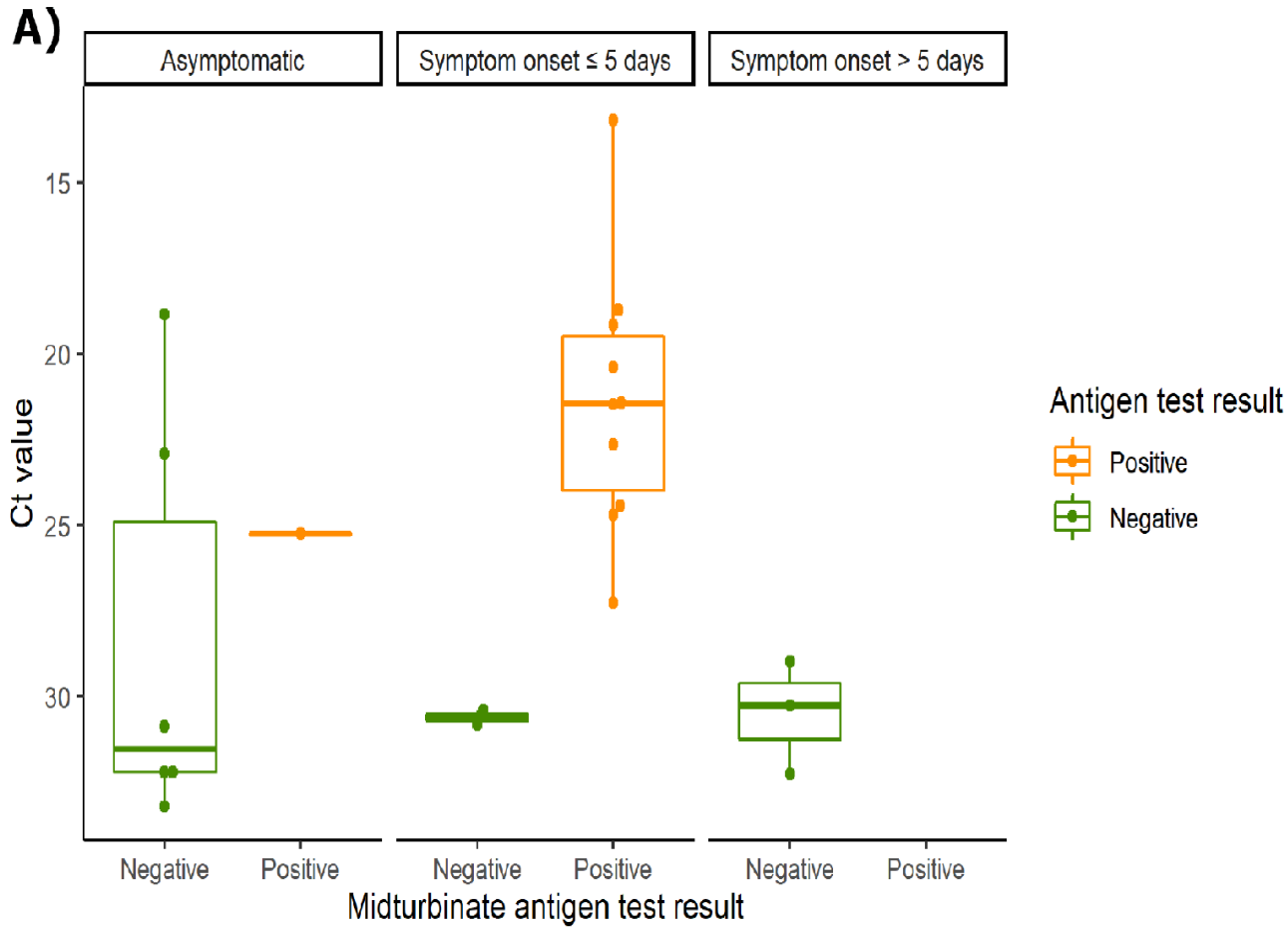
Table 1 | Diagnostic accuracy variables of two rapid antigen tests. Values are percentages (95% confidence interval) unless stated otherwise

Analysis	No	Prevalence* (%)	Sensitivity	Specificity	PPV	NPV
Veritor System (Beckton Dickinson)						
Primary analysis	2678	8.7	63.9 (57.4 to 70.1)	99.6 (99.3 to 99.8)	94.3 (89.5 to 97.4)	96.7 (95.9 to 97.3)
Secondary (stratified) analysis:						
Infectiousness viral load cut-off†	2677‡	5.7	90.1 (84.2 to 94.4)	99.2 (98.8 to 99.5)	87.3 (81.0 to 92.0)	99.4 (99.0 to 99.7)
Symptoms present at sampling§:						
Yes	219	17.4	84.2 (68.7 to 94.0)	99.4 (97.0 to 100)	97.0 (84.2 to 99.9)	96.8 (93.1 to 98.8)
No	2317	7.7	58.7 (51.1 to 66.0)	99.6 (99.3 to 99.8)	92.9 (86.5 to 96.9)	96.6 (95.8 to 97.4)
Interval (days) between sampling and last contact with index case¶:						
<5	379	14.8	69.6 (55.9 to 81.2)	99.7 (98.3 to 100)	97.5 (86.8 to 99.9)	95.0 (92.1 to 97.1)
5	1303	6.5	62.4 (51.2 to 72.6)	99.9 (99.5 to 100)	98.1 (90.1 to 100)	97.4 (96.4 to 98.2)
>5	511	9.0	56.5 (41.1 to 71.1)	99.1 (97.8 to 99.8)	86.7 (69.3 to 96.2)	95.8 (93.7 to 97.4)
Biosensor (Roche Diagnostics)						
Primary analysis	1596	8.3	62.9 (54.0 to 71.1)	99.5 (98.9 to 99.8)	91.2 (83.4 to 96.1)	96.7 (95.7 to 97.6)
Secondary (stratified) analysis:						
Infectiousness viral load cut-off†	1596	5.7	86.8 (78.1 to 93.0)	99.2 (98.6 to 99.6)	86.8 (78.1 to 93.0)	99.2 (98.6 to 99.6)
Symptoms present at sampling§:						
Yes	158	19.0	73.3 (54.1 to 87.7)	98.4 (94.5 to 99.8)	91.7 (73.0 to 99.0)	94.0 (88.6 to 97.4)
No	1414	7.1	59.4 (49.2 to 69.1)	99.5 (99.0 to 99.8)	90.9 (81.3 to 96.6)	97.0 (95.9 to 97.8)
Interval (days) between sampling and last contact with index case¶:						
<5	153	13.1	75.0 (50.9 to 91.3)	99.2 (95.9 to 100)	93.8 (69.8 to 99.8)	96.4 (91.7 to 98.8)
5	1095	7.8	61.2 (50.0 to 71.6)	99.5 (98.9 to 99.8)	91.2 (80.7 to 97.1)	96.8 (95.6 to 97.8)
>5	205	6.3	69.2 (38.6 to 90.9)	99.5 (97.1 to 100)	90.0 (55.5 to 99.7)	97.9 (94.8 to 99.4)

Ewoud Schuit, et al. BMJ 2021

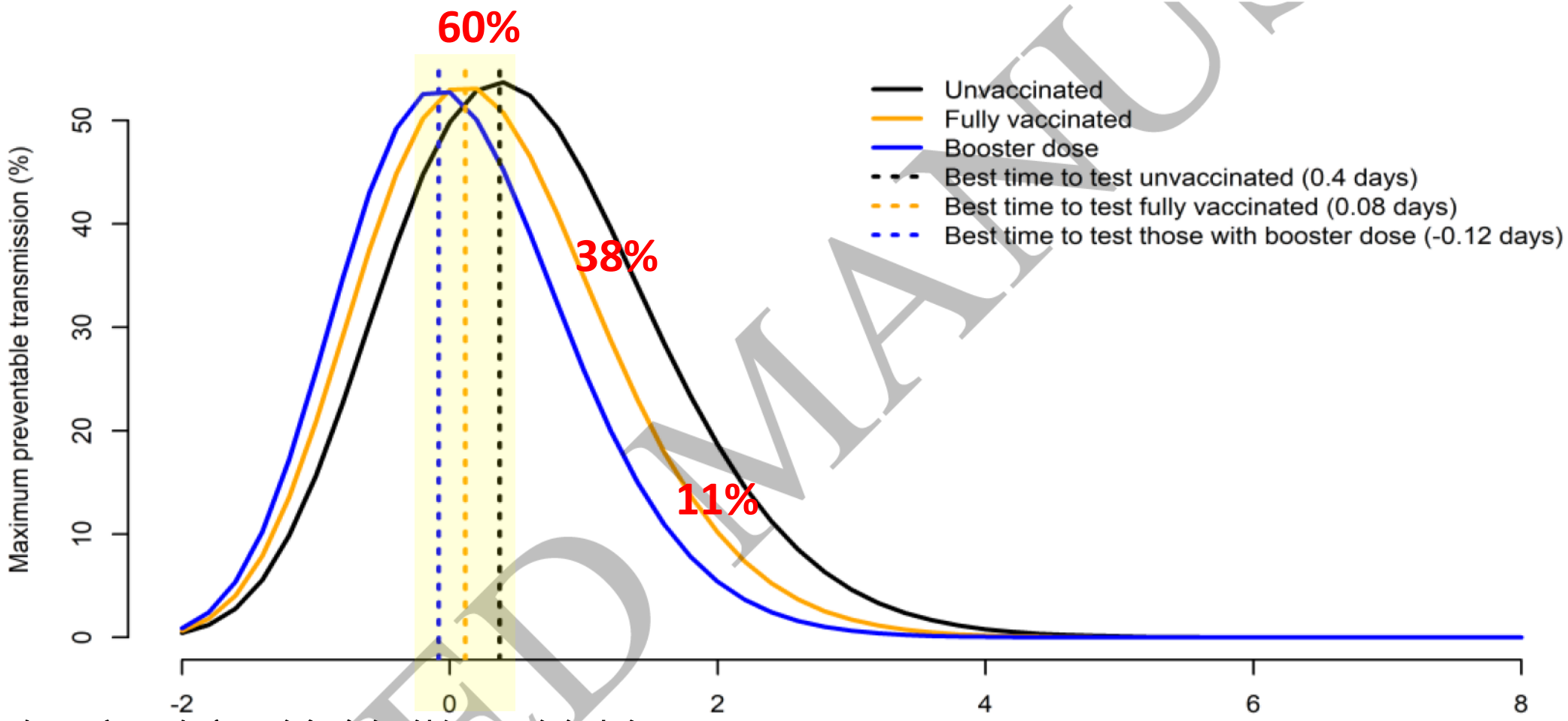
密切接觸者的檢驗- 美國經驗

- 抗原快篩可能會低估感染者
- 密切接觸者
  - 35位有症狀者(<5 天)
    - PPV:83.3% NPV:95.7%
  - 64位無症狀者或>5天才有症狀者
    - PPV:18.2%
- 解決之道:
- **連續2-3天檢測**



ML. Robinson, et al. J Clin Microbiol 2022

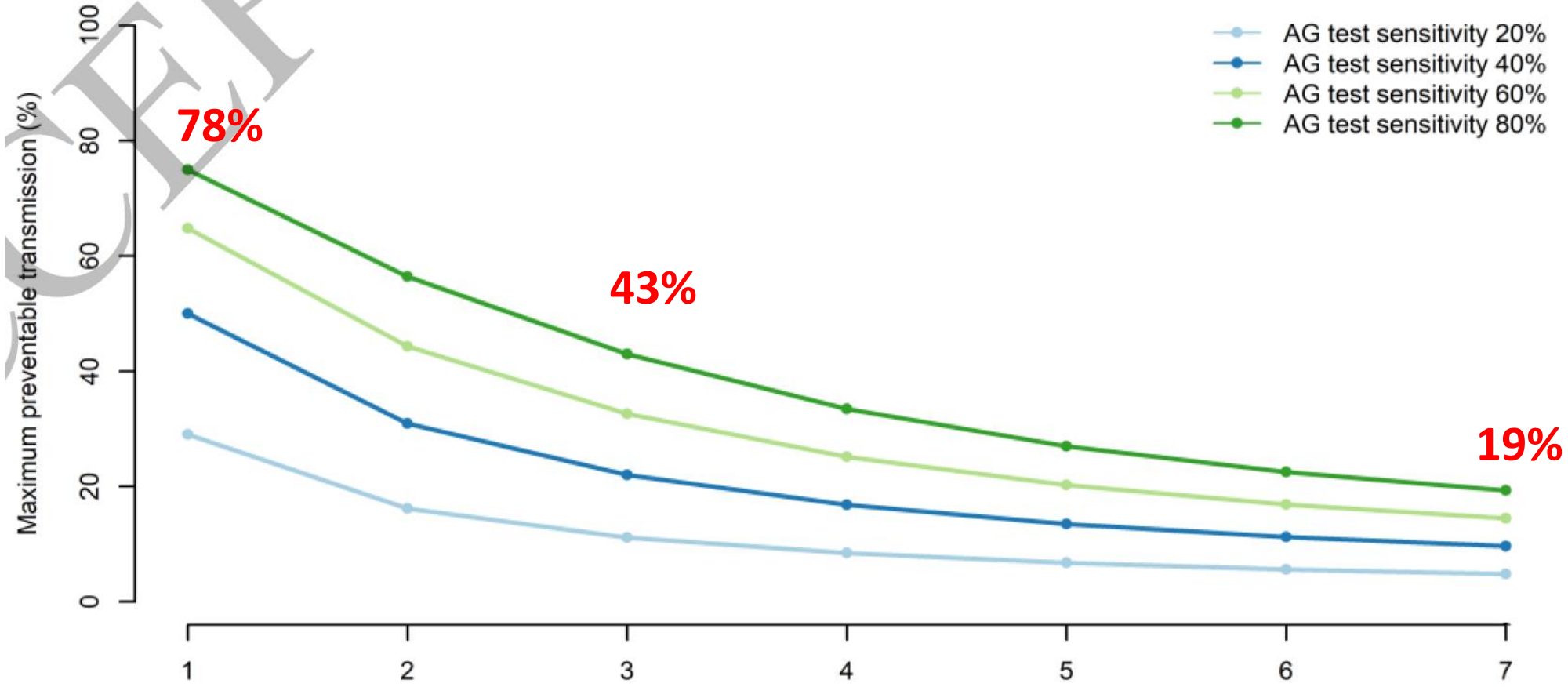
安養院的篩檢策略
case-initiated testing screening testing



指標個案確認後第幾天篩檢

Zipfel CM, et al. Clin Infect Dis. 2022

安養院的篩檢策略
screening testing



篩檢的周期性

Zipfel CM, et al. Clin Infect Dis. 2022

醫療機構無症狀個案篩檢建議

- 無症狀住院病人全面篩檢(或反覆篩檢)的考量
  - 社區盛行率、患者狀況及疫苗施打率等等
- 手術前無症狀患者篩檢
  - 是否麻醉、是否產生氣霧
- 指標個案接觸者的篩檢策略
- 訪客及照顧者的篩檢考量
- 高風險單位週期性篩檢
  - 不須考量疫苗施打狀況

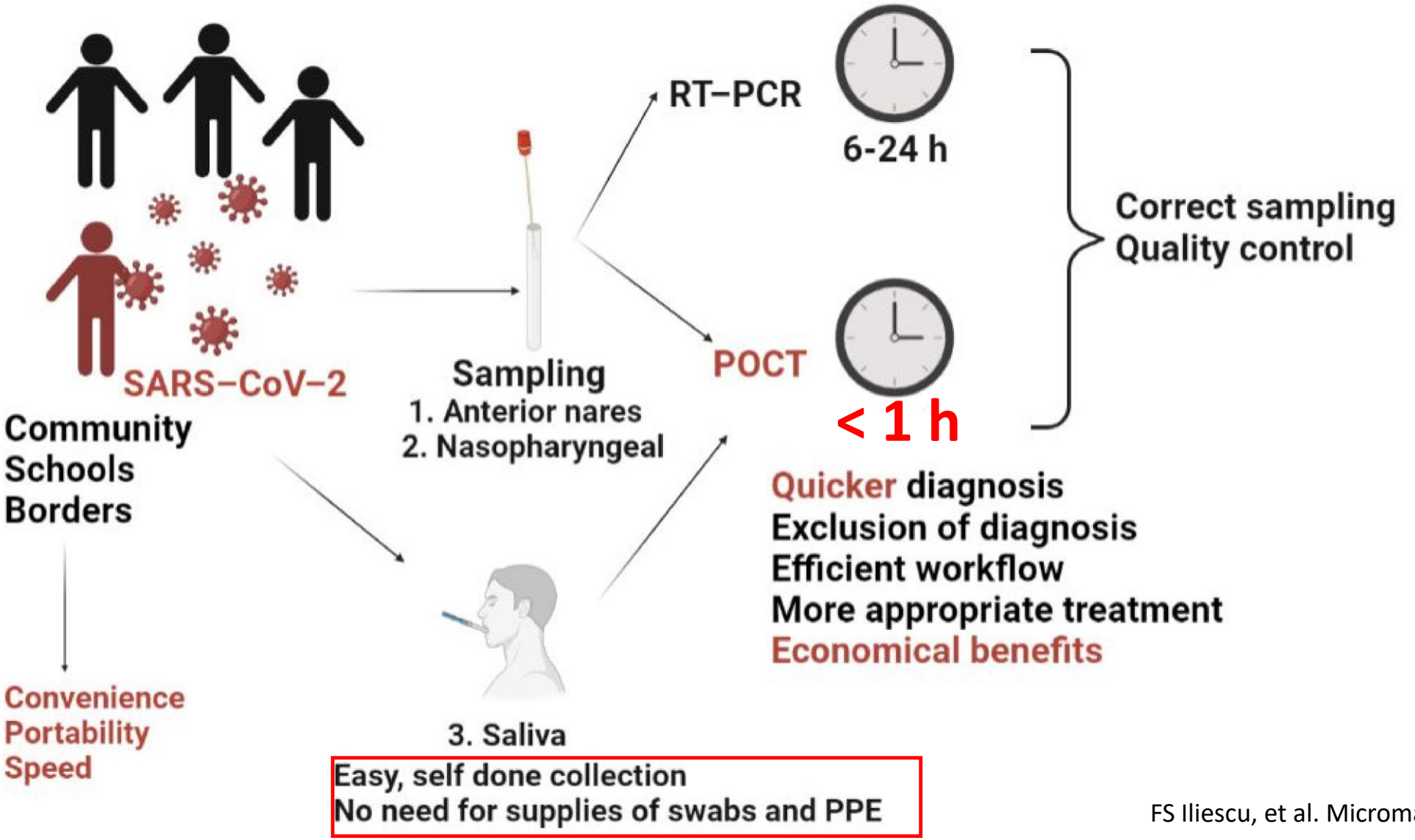
(建議閱讀全文)

目前台灣的政策 (自111年9月1日起)

- 考量疫情及檢驗量能
- 調整醫療照顧相關篩檢對象之檢驗方式為家用快篩，酌予**修正為核酸檢驗或抗原快篩(含家用快篩)方式併行**
- 住院病人或陪病者除入院篩檢外，增加定期**每周執行兩次篩檢措施**
- 醫療照護人員到職及定期篩檢以**家用快篩**進行

摘自嚴重特殊傳染性肺炎中央流行疫情指揮中心　函 111.8.25

定點照護檢驗(POCT)用於診斷新冠感染的優勢

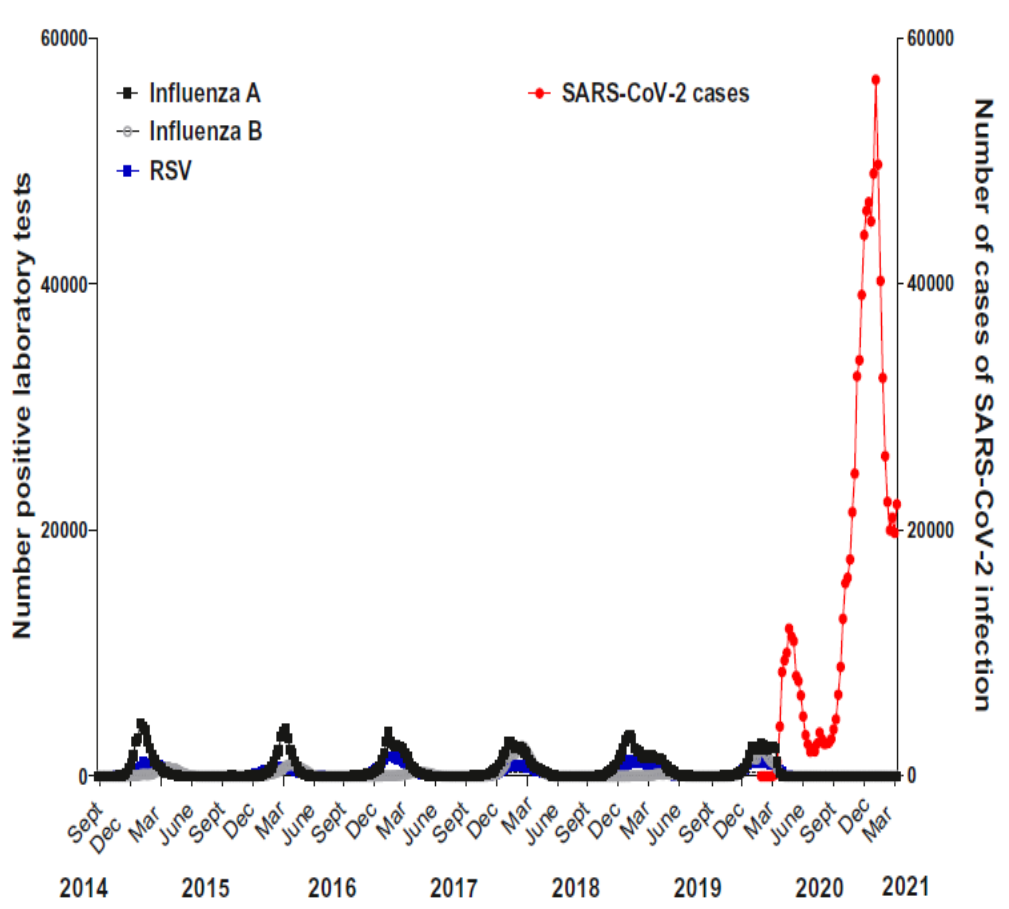


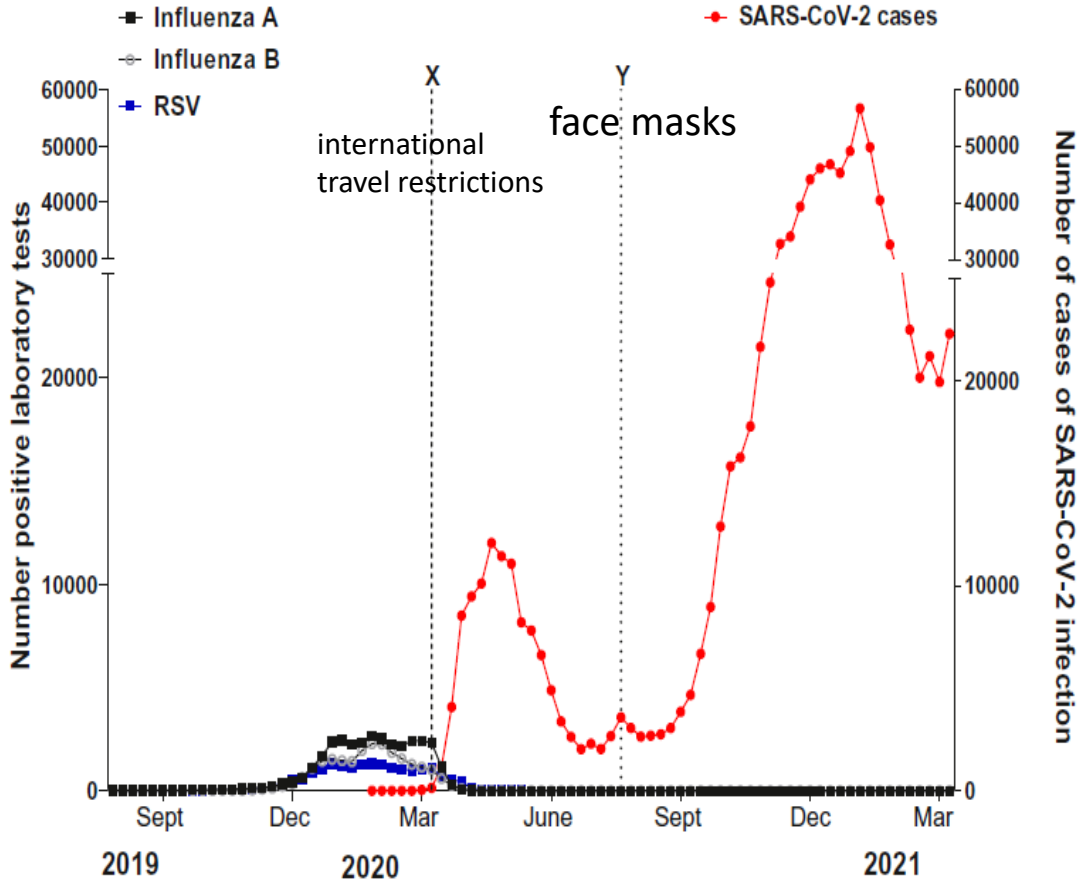
FS Iliescu, et al. Micromachines 2021

秋冬挑戰

https://www.medpagetoday.com/infectiousdisease/covid19/89495

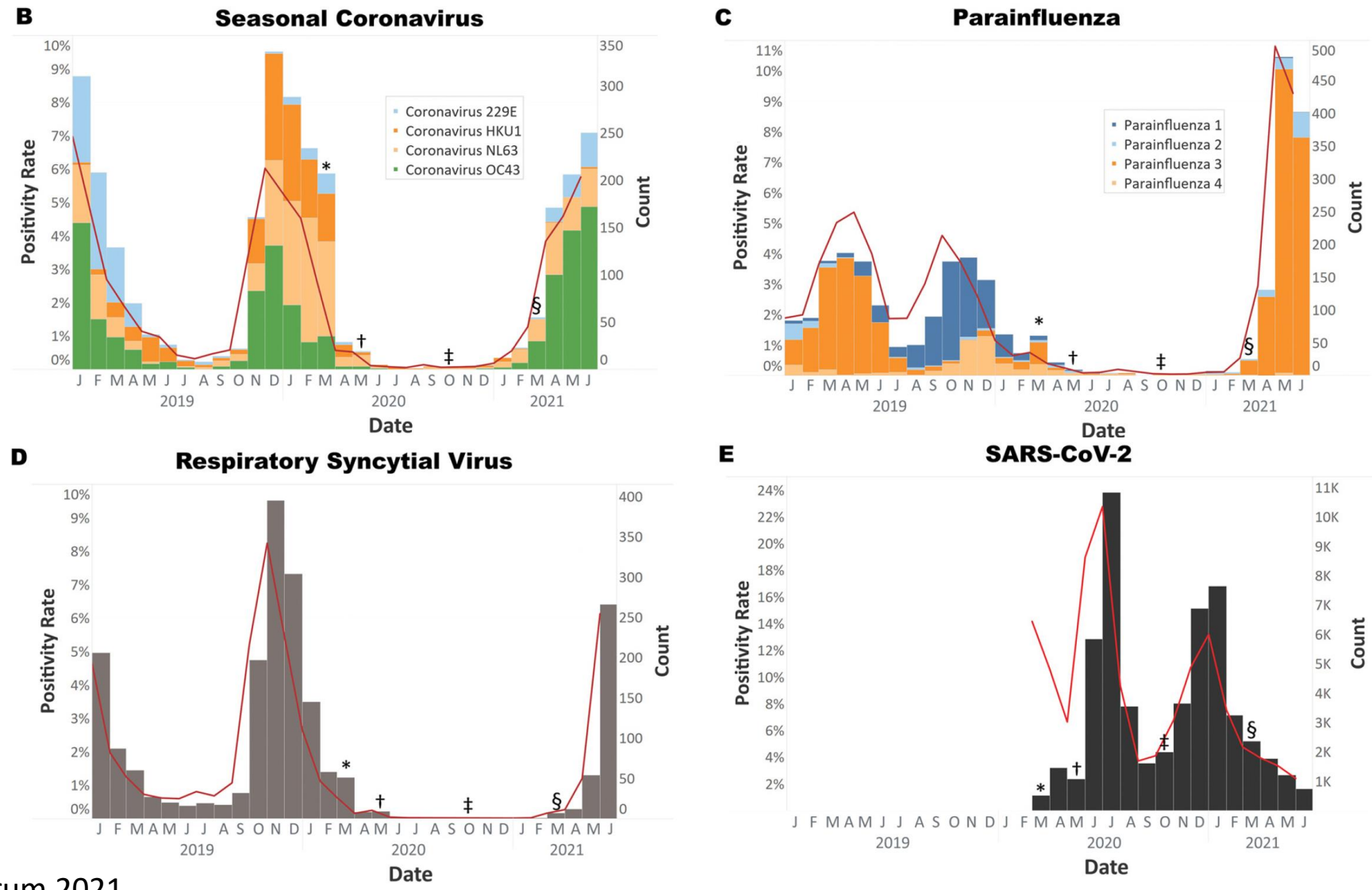
流感病毒及呼吸道融合病毒盛行率在新冠大流行前後的變化





Groves HE, et al. The Lancet Regional Health 2021

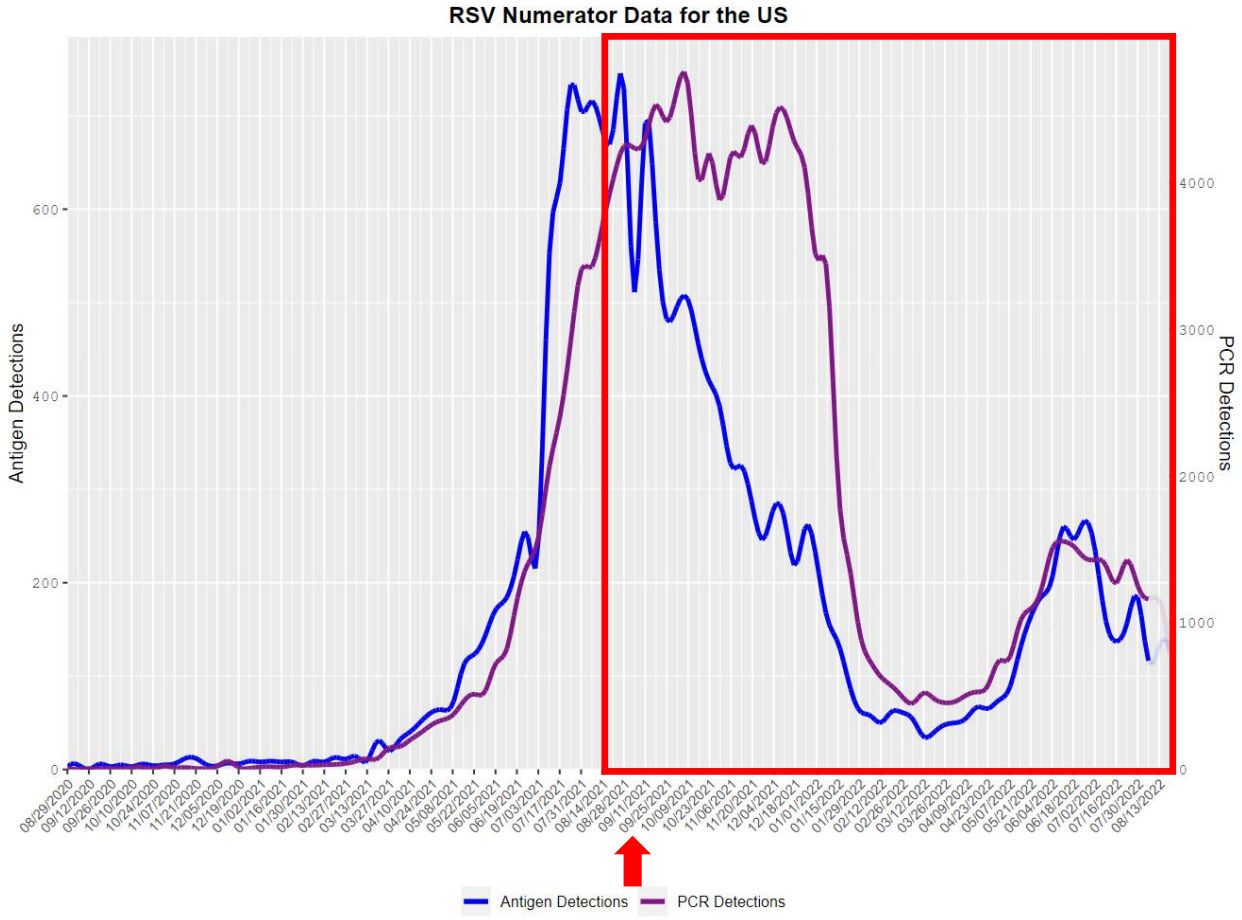
季節呼吸道病毒因為COVID-19防疫措施鬆綁而再度流行

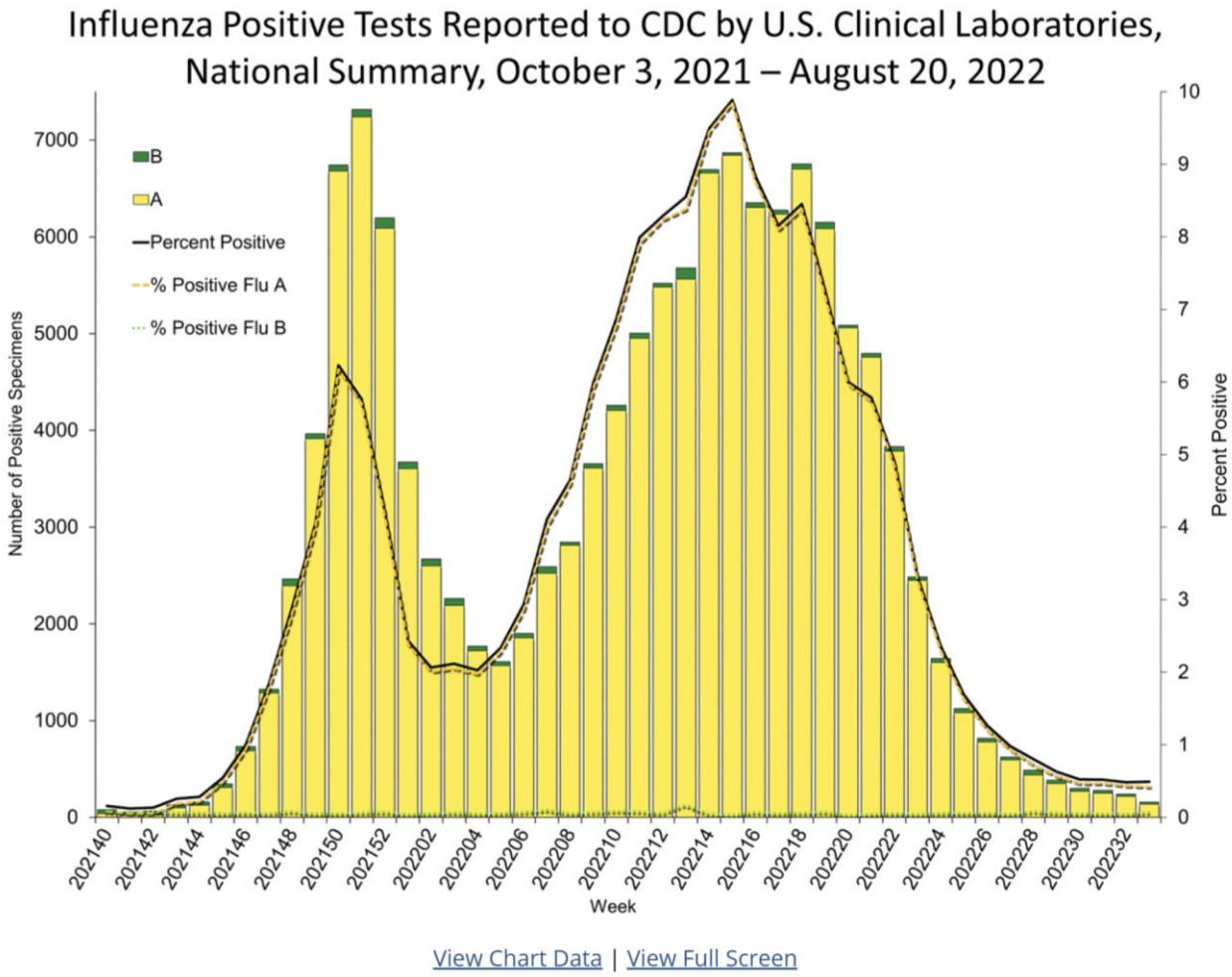


Parsa Hodjat, et al. Microbiol Spectrum 2021

美國CDC呼吸道病毒監測

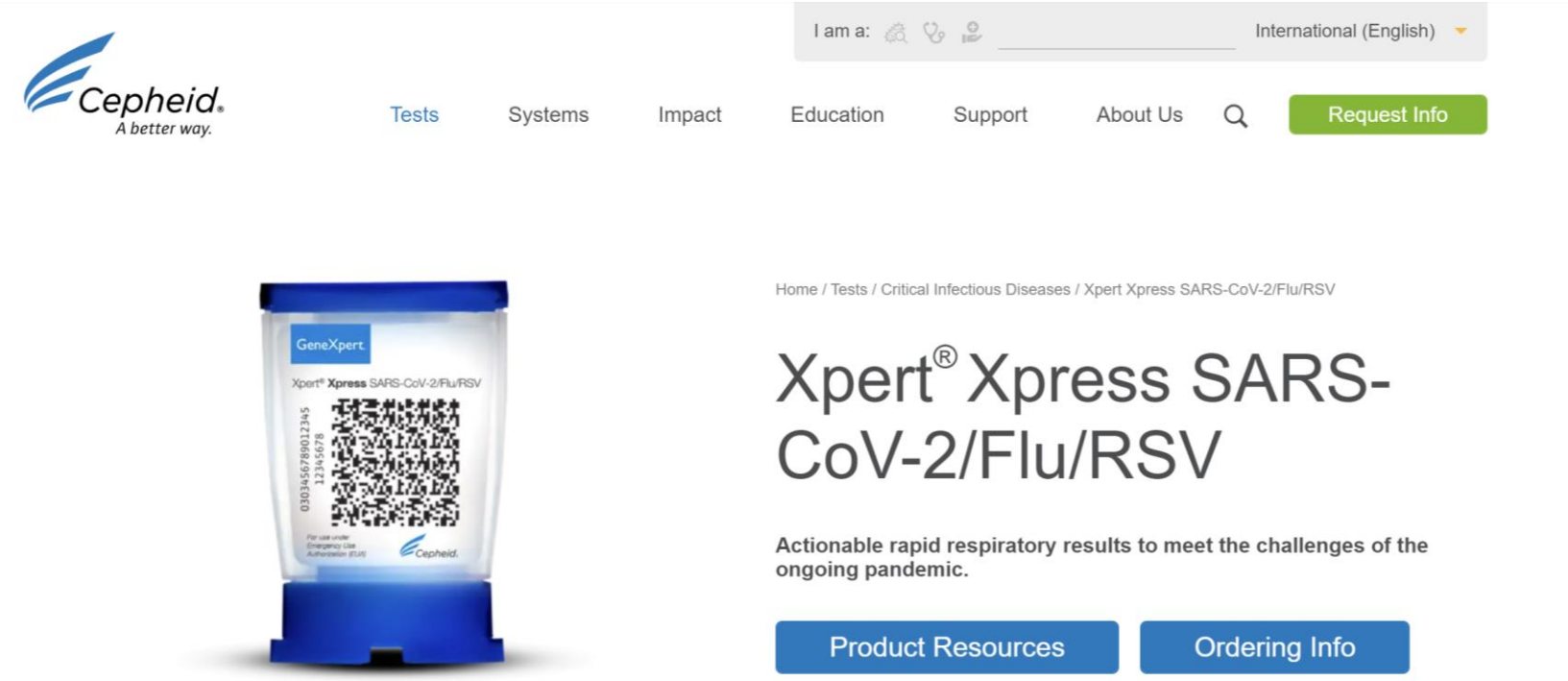
Detections





多種呼吸道病毒檢測
-類似的症狀，不一樣的病毒不一樣的治療

cobas ® SARS-CoV-2 & Influenza A/B test



結語

- 新冠流行時，適當且足夠的檢驗量能很重要
  - 核酸檢驗:
    - 準確性高，需謹慎的判讀CT值結果
  - 抗原快篩
    - 對於高度懷疑的患者能提供快速且準確的檢驗結果
    - 重複檢驗能提升準確率
  - 有症狀時進行篩檢時最好，小心評估及擬定無症狀篩檢策略
    - 綜合檢驗前評估與檢驗後結果才能做出正確的判斷
    - 易感受及高風險族群的篩檢效益
- 其他呼吸道病毒再度流行的可能性