



COVID-19 in Children

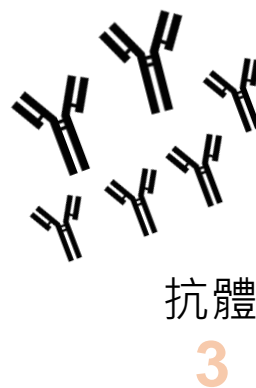
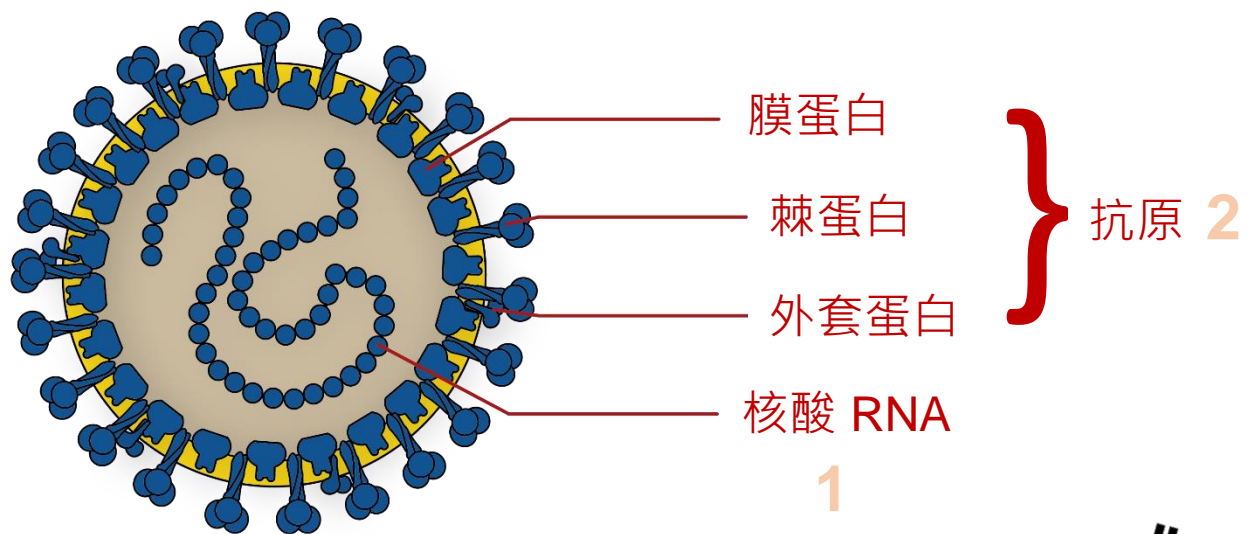
兒童急診的考量

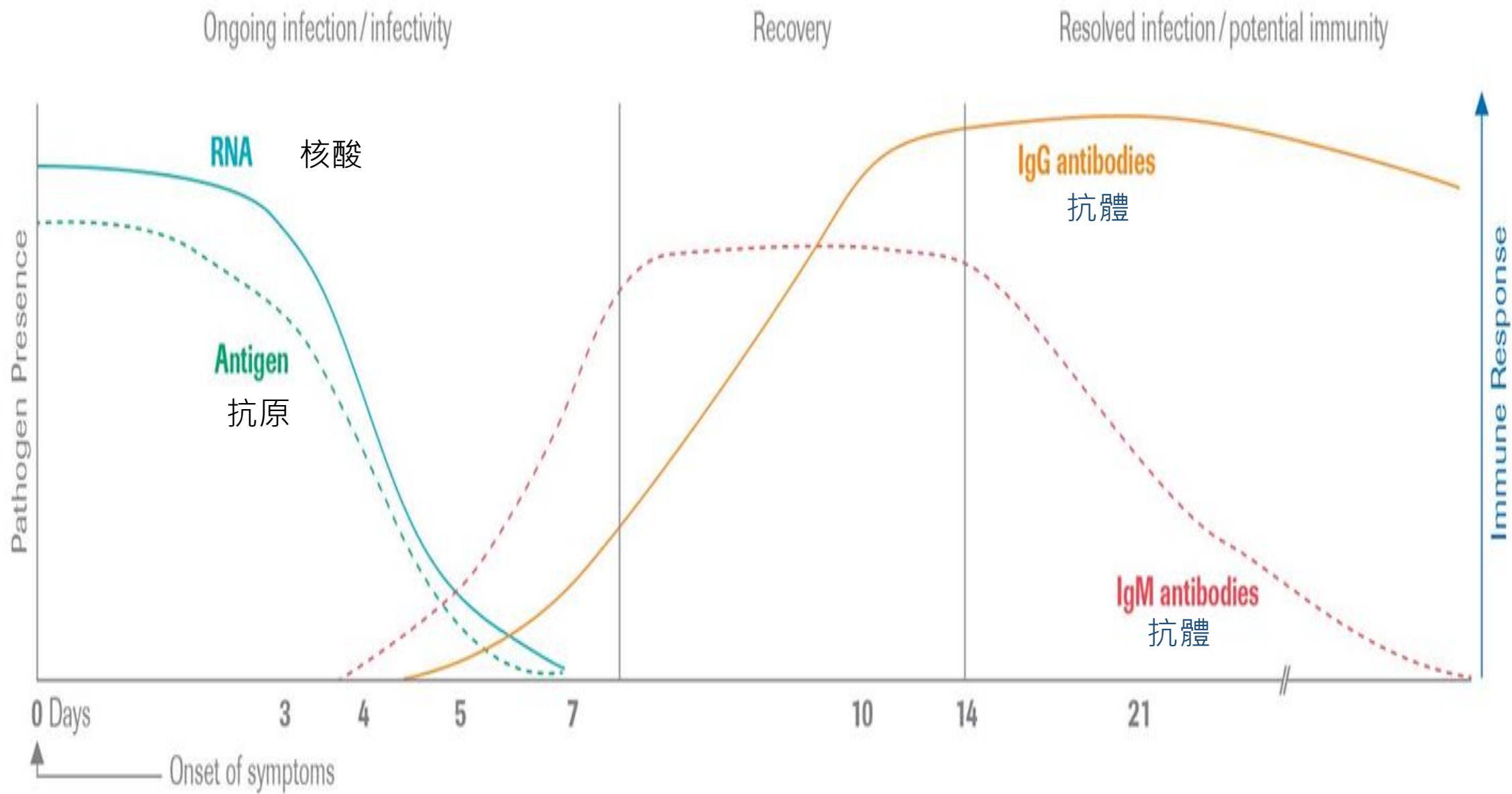
李建璋 MD, ScD

台灣兒童急診醫學會理事長
臺大急診醫學科教授
臺大醫院智慧醫療中心 副主任

檢驗標的：核酸、抗原、抗體

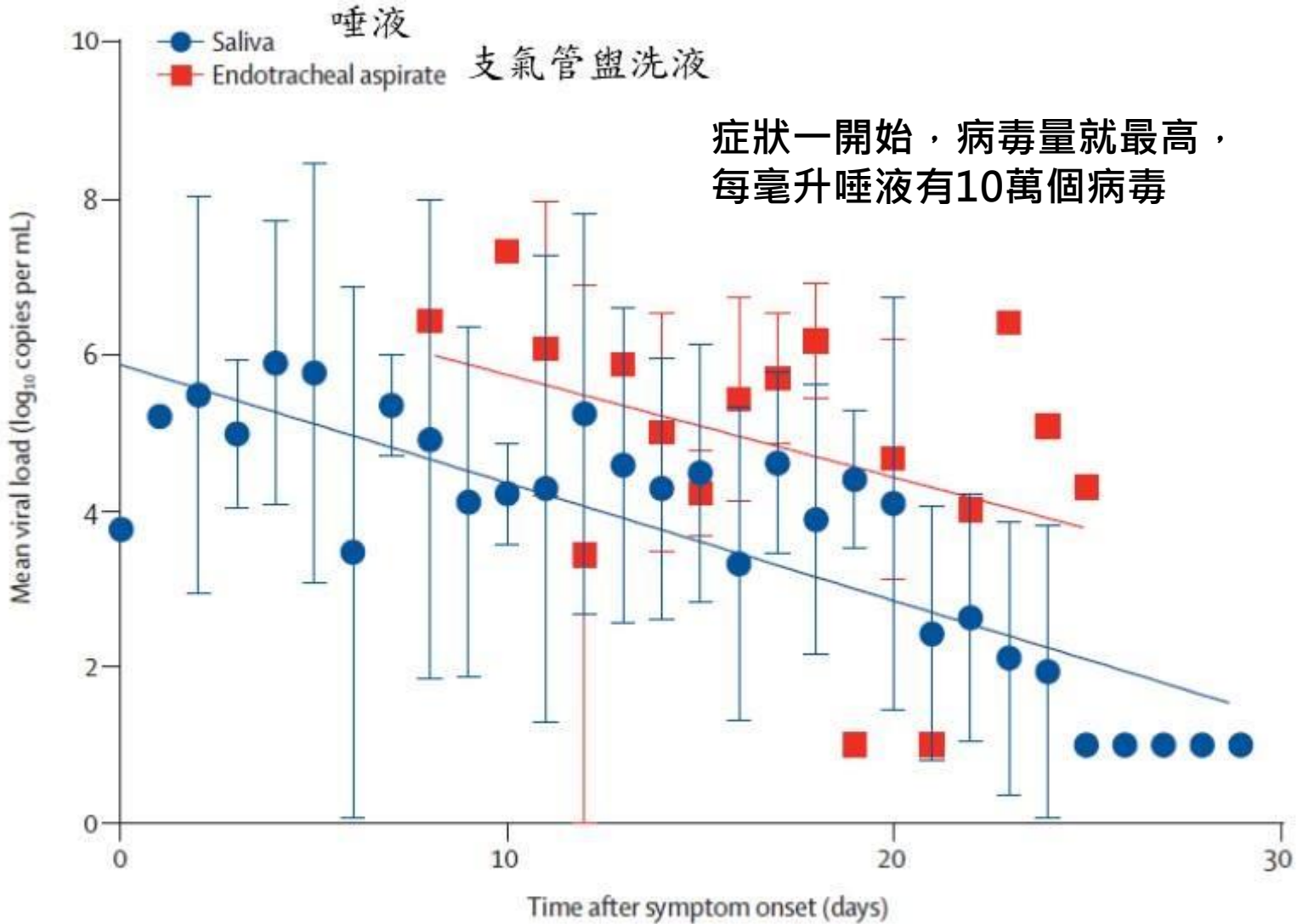






症狀開始病毒量最高，
第20天還有1/3測出病毒

病毒量



從症狀起算天數

Yuan et al. *Lancet Infect Dis* 2020

檢驗科技：PCR、RIDT、
Immunoassay



檢驗科技



高通量核酸檢驗



床旁一體化核酸檢驗



定性抗原快篩



定量抗原抗體檢驗

快篩準確度: 七成五

Test by Abbott

Albert	43	54
Berger	106	124
Bulilete	100	140
Drevinek	148	223
Fenollar	154	204
Gremmels - Aruba	51	63
Gremmels - NL	101	139
Linares	44	60
Schwob	105	122



Random effects model

Heterogeneity: $I^2=68\%$, $\tau^2=0.0970$, $p<0.01$

Test by Roche/SDB

Berger	170	191
Cerutti	77	109
Chaimayo	59	60
Igloi	158	186
Khairat	55	80
Krüger	36	47
Krüttgen	53	75
Lindner	31	39
Nalumansi	63	90
Schwob	104	112



Random effects model

Heterogeneity: $I^2=88\%$, $\tau^2=0.5186$, $p<0.01$

Overall

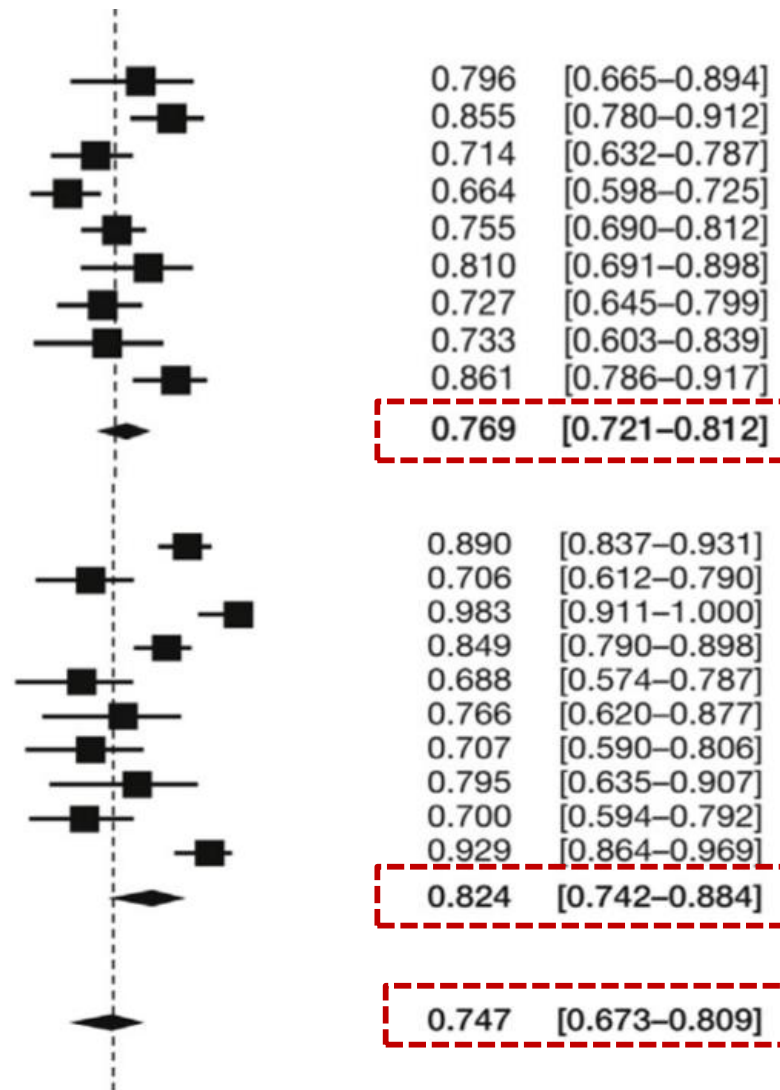
Random effects model

Heterogeneity: $I^2=93\%$, $\tau^2=0.7550$, $p<0.01$
Residual heterogeneity: $I^2=77\%$, $p<0.01$

1129

989

2589



迷思一：食藥署或廠商的說明書快篩敏感度高達93%到100%？

- 食藥署的測試是標準樣本，比較快篩和PCR的“一致率” Agreement
- 送交食藥署的報告是選取病例-對照設計，選抗原量高的和抗原量低的去會高估快篩正確率。
- 真實世界是連續樣本，抗原濃度有高、有低，要連續樣本的測試結果才是真實世界的正確率。

“病例-对照”和“連續樣本”測試檢驗試劑準確度的差異



病例

病例-对照設計高估真實世界快篩正確率

对照

流感抗原快篩 末日條款

- 流感抗原快篩的低敏感度造成誤診、甚至病人死亡
- FDA 在 2017 將流感的快速抗原檢驗試劑由 Class I 改列為 Class II
 - 每年檢測，當前流行病毒株的敏感度 > 80%
- 不符合新標只能銷售至 2018 年 1 月 12 日
- **台灣COVID快篩應該比照辦理**

床旁一體化核酸檢驗(快速分子檢驗)

- 集核酸萃取、擴增、與病原辨識於一機
- 檢驗時間20-45分鐘
- Roche 機器提供 SARS-CoV2 單一測試
- bioFire FilmArray 機器可以檢驗22個病毒和細菌，適合重症兒童使用



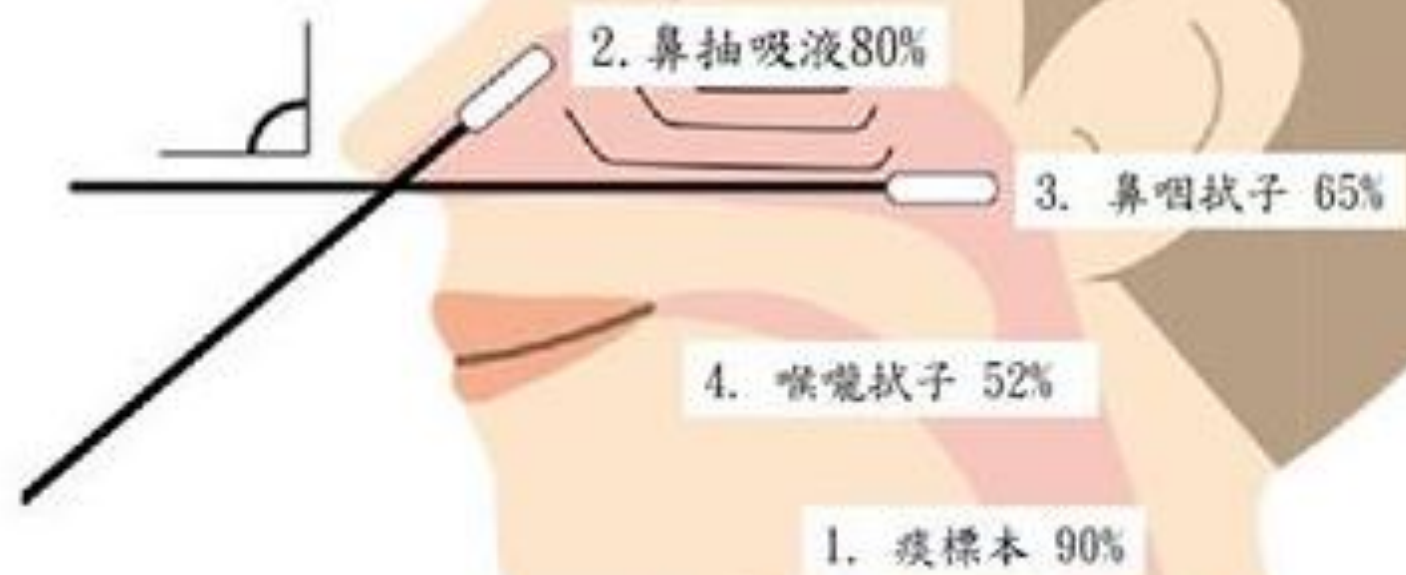
迷思二：快速分子檢驗準確性不如大機器？

- 快速分子檢驗靈敏度 95-99% 與常規高通量機器一致
- 快速分子診段的障礙是費用與通量
- 嚴重案例，盡量使用快速分子診斷

檢驗檢體：口咽、鼻咽、口水



流感不同檢體病毒培養陽性率





Chien-Chang Lee

3月15日 · 地球

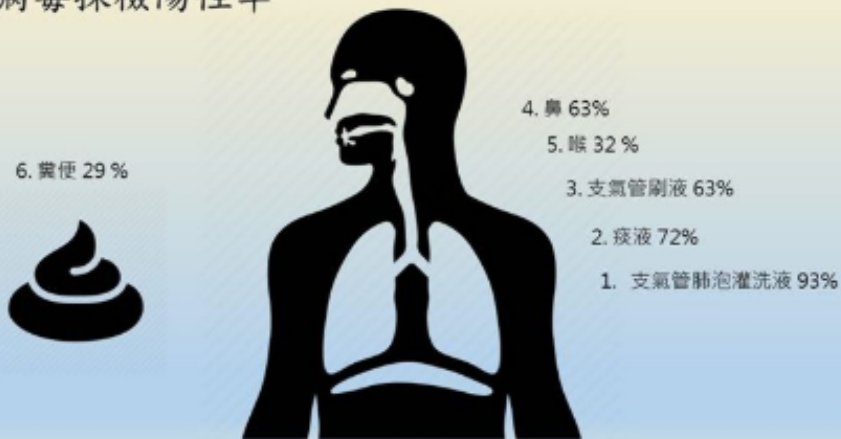


麥擱挖喉嚨了

冠狀病毒從飛沫傳染，所以直覺上，病毒量應該由口咽、支氣管、肺泡依次減少，喉嚨拭子是最合理的採樣部位，可是挖喉嚨會引發咳嗽反應、製造飛沫，使採樣的醫護暴露於感染的危險，大家一直有疑慮。鼻咽或鼻腔的採檢病患可以閉口，比較不會製造飛沫，相對是比較安全，但是沒有數據佐證之下，為了採檢品質，挖喉嚨一直是官版的標準程序。

四天前在JAMA刊出的研究數據解答大家的疑惑，研究者報告不同呼吸道樣本的冠狀病毒採檢陽性率，喉頭只有32%，遠低於其他呼吸道檢體，欲往深處走，陽性率就愈高，依次是支氣管、痰、肺泡，到了肺泡可以高達93%陽性率。由於冠狀病毒是和ACE2受體結合進入人體細胞，ACE2的分布也是在支氣管、肺泡多，口咽上皮少。樣本陽性率的分布和ACE2的分布似乎吻合。…… [更多](#)

新冠病毒採檢陽性率



“那叫病患咳痰就好了，也不用穿兔子裝在那邊採！準確率又高！我要去建議醫院了！QQ”



Chih-Hung Wang、Jeanetta Hsu和其他405人

34則留言 96次分享

Clinical Microbiology and Infection
Official Publication of the European Society of Clinical Microbiology and Infectious Diseases

26-Apr-2018

CLM-18-13581

Expectorated saliva as a diagnostic specimen for testing respiratory virus by a point-of-care molecular assay: a diagnostic accuracy study

To, Kelvin; Yip, Cyril; Lai, Cherie; Wong, Carlos; Ho, Deborah; Pang, Polly; Ng, Anthony; Leung, Kit-Hang; Poon, Rosana; Chan, Kwok-Hung ; Cheng, Vincent; Hung, Ivan; Yuen, Kwok Yung

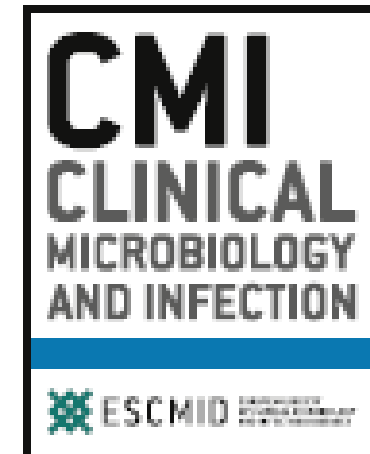
Dear Dr. Lee,

Thank you for agreeing to review this submission, which is now available to you.

To access the manuscript without the need to login to the website, please click on the following link:

https://mc.manuscriptcentral.com/cmi?URL_MASK=f2350c23334c4d4585a53159225b2221

香港院士
袁國勇教授





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HEALTH AND SCIENCE

Coronavirus saliva tests could be as accurate as or better than nasal swabs, Yale researchers say

PUBLISHED WED, APR 22 2020•4:06 PM EDT | UPDATED FRI, APR 24 2020•1:33 PM EDT



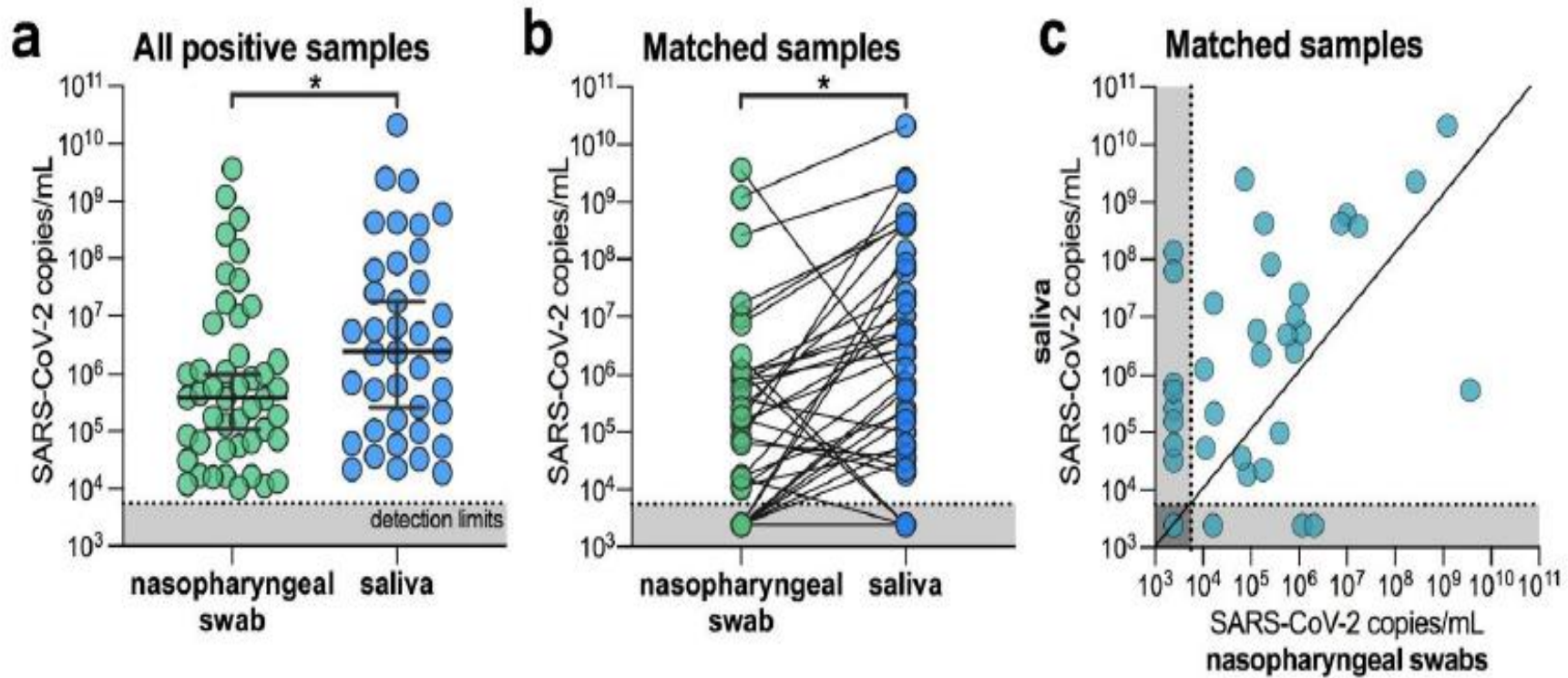
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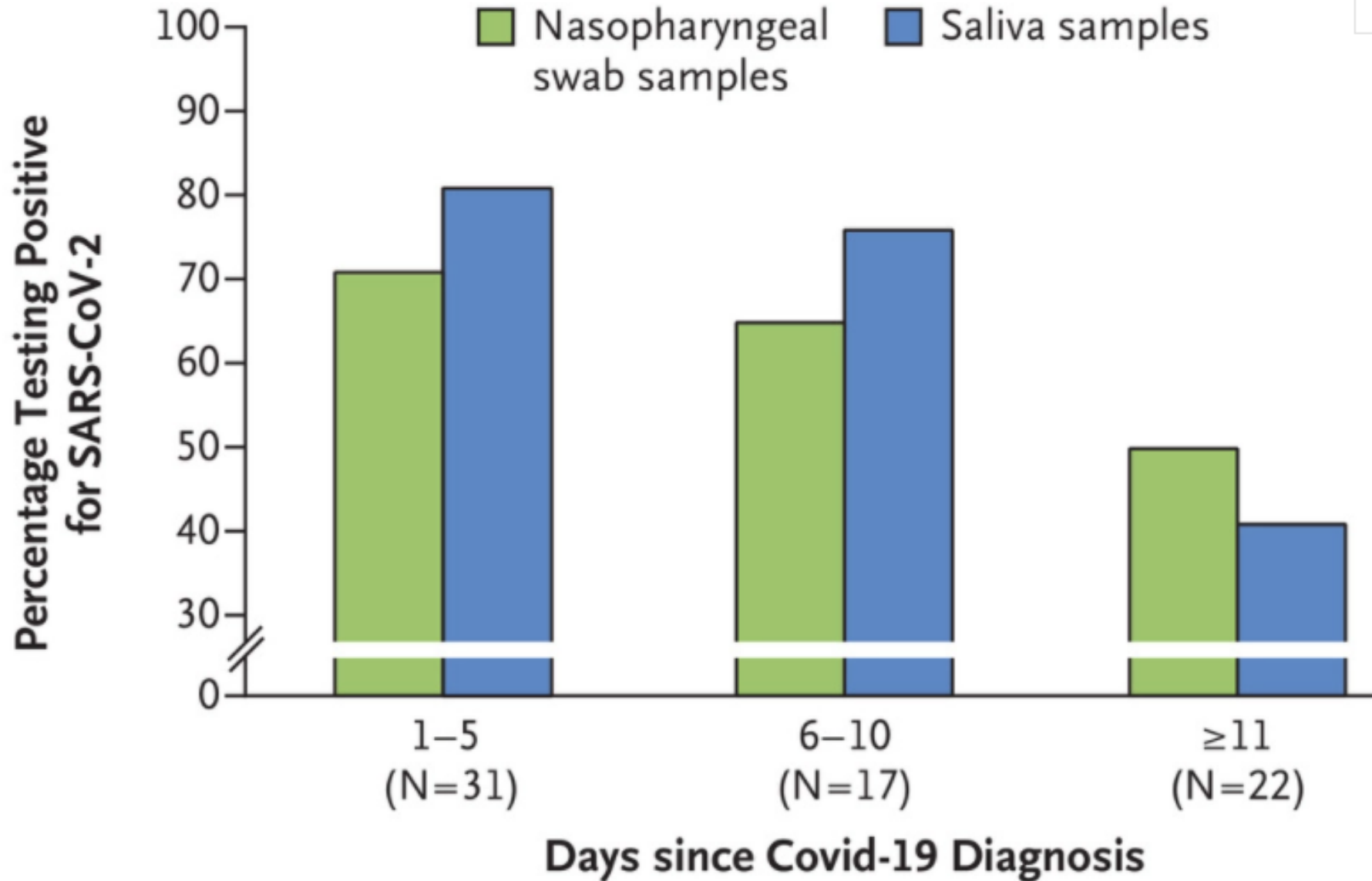
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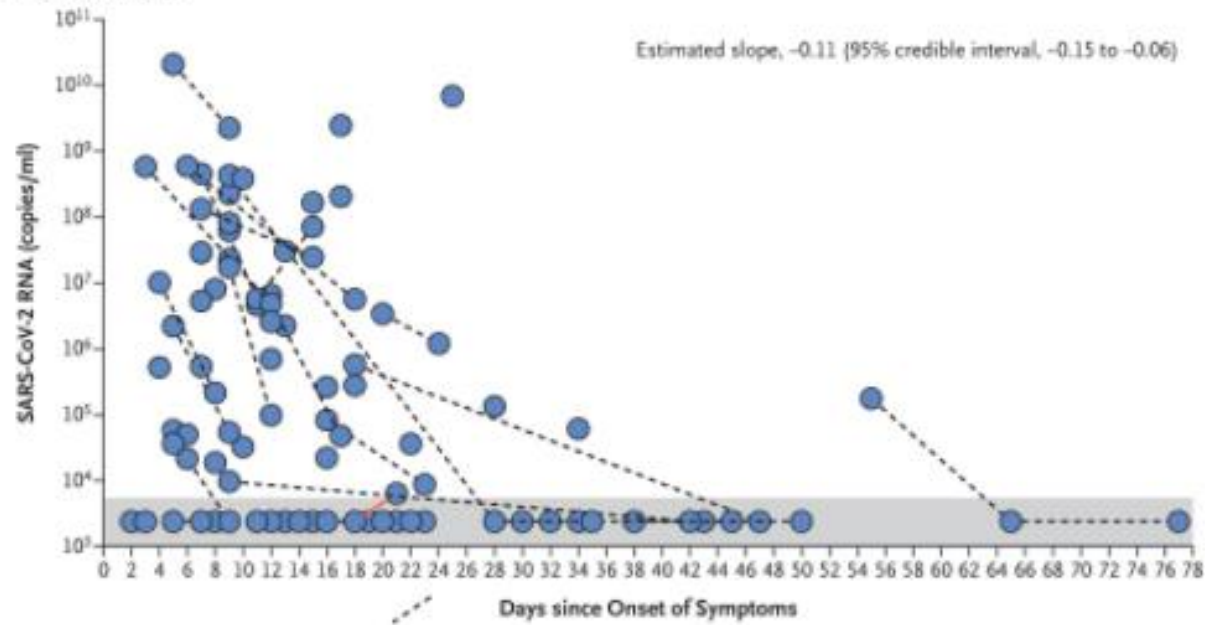


Department of Epidemiology of Microbial Diseases, Yale School of Public Health, New Haven, CT 06510, USA

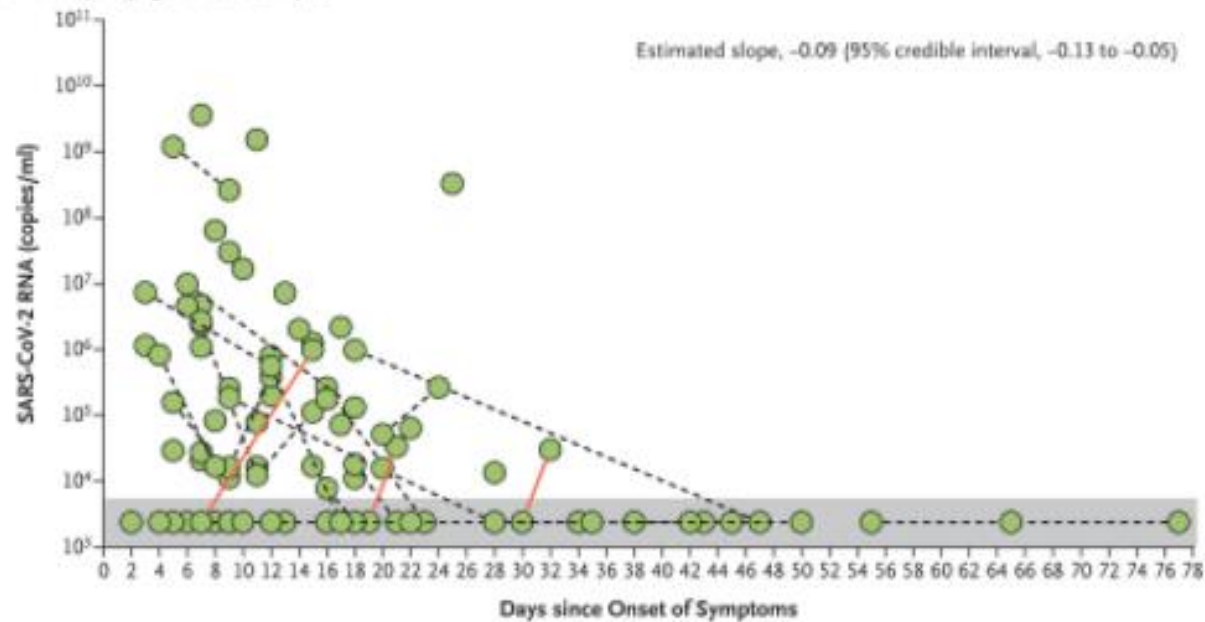
B Positivity for SARS-CoV-2



C Saliva Samples



D Nasopharyngeal Swab Samples



The NEW ENGLAND
JOURNAL of MEDICINE

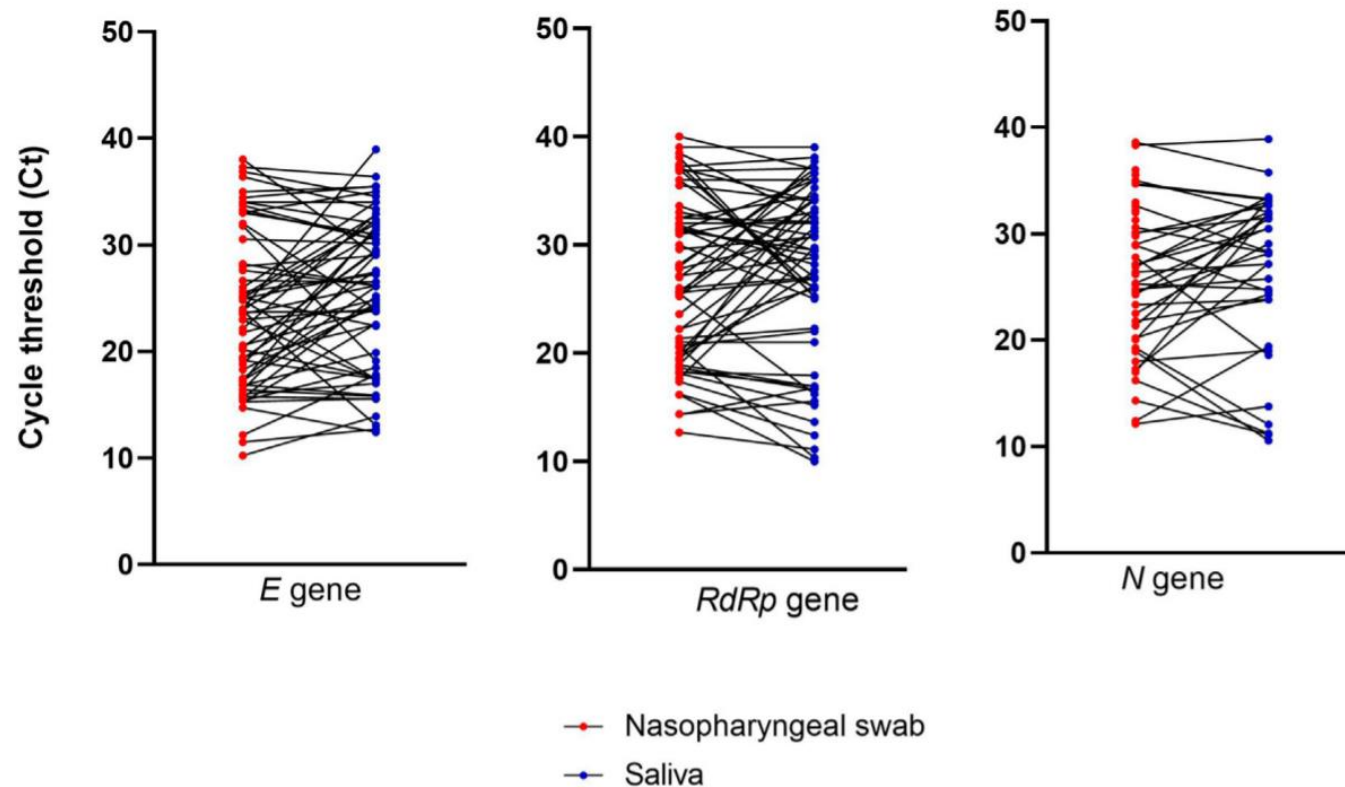
Saliva for molecular detection of SARS-CoV-2 in school-age children

Hanan Al Suwaidi ^{1,†}, Abiola Senok ^{1,*†}, Rupa Varghese ², Zulfa Deesi ²,
Hamda Khansaheb ³, Sabeel Pokasirakath ², Bino Chacko ², Ibrahim Abufara ²,
Tom Loney ¹, Alawi Alsheikh-Ali ¹

¹) College of Medicine, Mohammed Bin Rashid University of Medicine and Health Sciences, Dubai, United Arab Emirates

²) Microbiology and Infection Control Unit, Pathology and Genetics Department, Latifa Women and Children Hospital, Dubai Health Authority, Dubai, United Arab Emirates

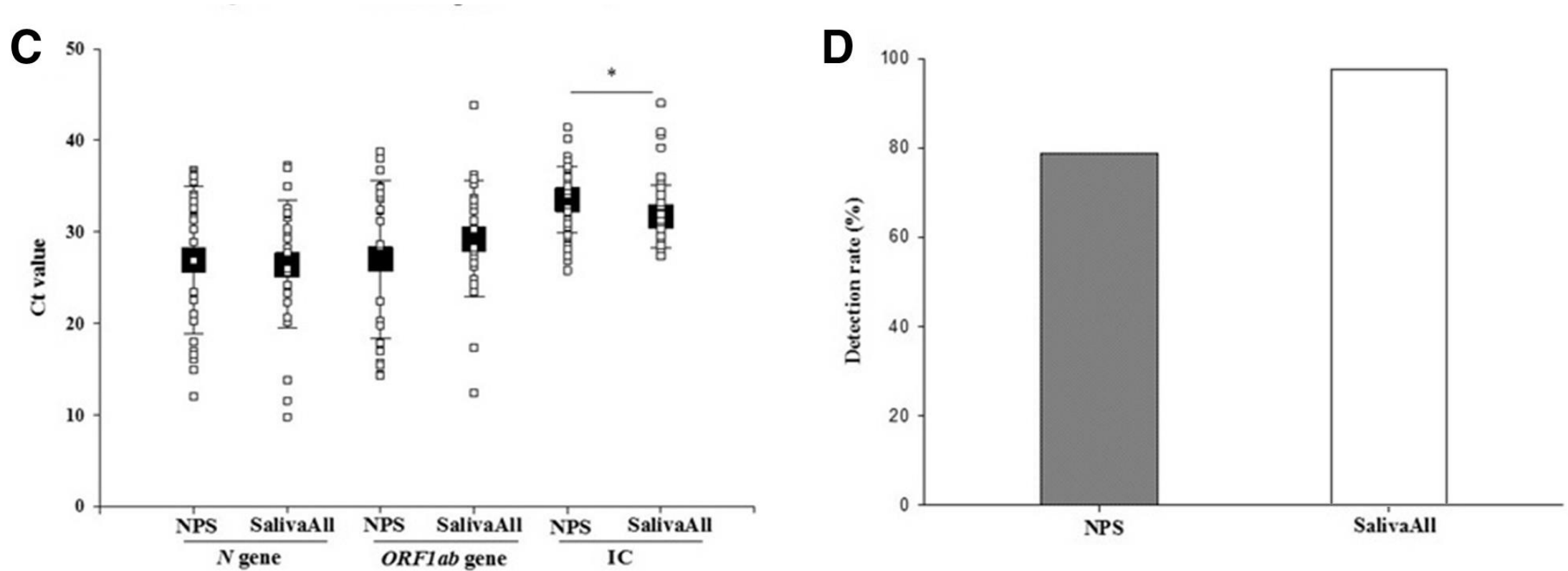
³) Education and Research Department, Dubai Health Authority, Dubai, United Arab Emirates



Saliva Homogenization before PCR greatly enhance sensitivity



Saliva can be more effective than nasopharyngeal swabs for COVID-19 testing





最佳的篩檢檢體

唾液也有高
濃度病毒

The background is a vibrant blue with a wavy, textured pattern. On the right side, there is a dark blue silhouette of a child's head in profile, facing left. On the left side, there is a stylized anatomical structure, possibly representing a lung or a part of the respiratory system, rendered in lighter blue and white tones. A small, bright pink, starburst-like shape is located within the anatomical structure.

Biomarkers in Children

Diagnosis

Table 2: Comparison of laboratory data between the three groups

Items	COVID-19 alone (n=35)	Non-COVID-19 (n=33)	Coinfection (n=4)	Adjusted P Value
WBC($\times 10^9/L$)	5.37 (4.67-8.1)	6.94 (5.72-8.87)	8.76 (6.34-13.7)	0.147
N %	40.9 (30-48.5)	54.8 (41.4-67.5)	34.4 (29.1-45.2)	0.003,0.003*,1.000**
L%	45.3 (39.2-56.6)	33.2 (22.7-42.5)	52.1 (42.9-61.1)	0.002,0.003*,1.000**
NC ($\times 10^9/L$)	2.25 (1.43-3.53)	3.33 (2.8-5.18)	2.78 (2.66-4.6)	0.018,0.014*,1.000**
LC ($\times 10^9/L$)	2.68 (1.99-4.01)	2.26 (1.67-2.92)	5.19 (2.84-7.16)	0.027,0.043*,0.273**
Hb (g/L)	128 (124-142)	130 (119-137)	119 (112-144)	0.457
PLT ($\times 10^9/L$)	271.5 (234-328)	255 (219-314)	281(202.8-531.8)	0.204
hs-CRP (mg/L)	5.5 (1.1-9)	9.1 (7.4-9.5)	12.3 (3.2-26.2)	0.007,0.007*,0.429**
PCT (ng/mL)	0.05(0.029-0.076)	0.103(0.053-0.21)	0.144(0.109-2.26)	0.000,0.000*,0.010**

*COVID-19 alone Vs Non-COVID-19; **COVID-19 alone Vs Coinfection

Diagnosis

Table 3: Independent differential diagnostic indicators for COVID-19 alone

Items	P Value	B	Exp(B)	95%CI
NC	0.082	-0.466	0.628	0.371-1.061

Table 5: Differentiating characteristics of PCT for COVID-19 alone

Items	Cut-off Value	Sensitivity	Specificity	PPV	NPV
PCT	0.1 ng/mL	65.9%	78.6%	82.9%	59.5%

Table 4: Performance of differential diagnostic indicators for COVID-19 alone

Items	AUC	SE	P Value	95%CI
Model	0.834	0.047	0.000	0.741-0.926
PCT	0.809	0.051	0.000	0.710-0.909

Diagnosis

IL-6

Table 1 Characteristic of included studies.

Characteristics	Zhang et al. ⁴	Yu et al. ⁵	Du et al. ⁶	Sun et al. ⁷	Su et al. ⁸	Zeng et al. ⁹
Location	China	China	China	China	China	China
Number of cases	3	82	14	8	9	1
Age	6–9 years	3 days - 16 years	6.20 (median)	2 mo - 15 years	11 mo - 9 years	2 weeks (neonates)
Males, %	100	62.2	42.9	75	33.3	100
Major clinical feature	Mild	Mild	Mild-intermediate	Mild	Asymptomatic - mild	Mild
IL-6	67% ↔	82.86% ↔	92.85% ↔	75% ↔	100% ↔	↔

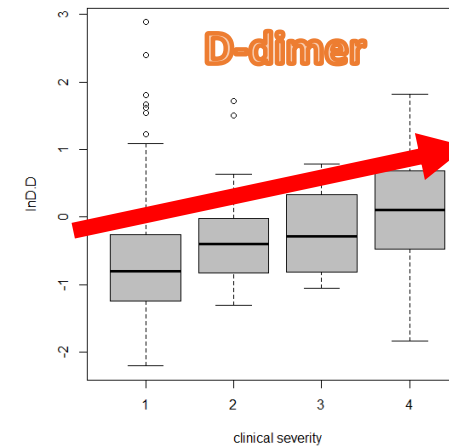
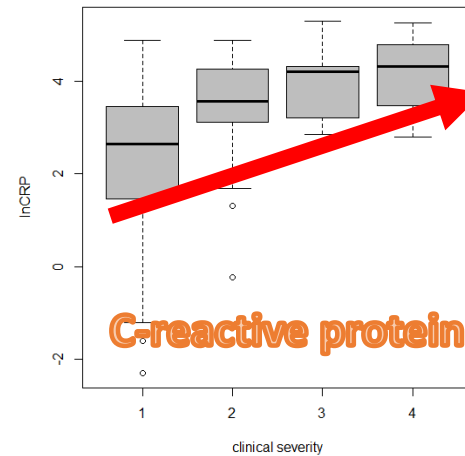
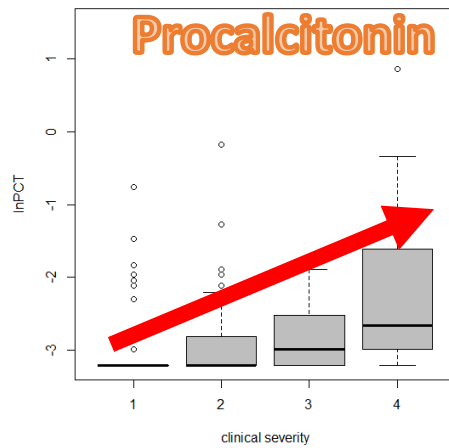
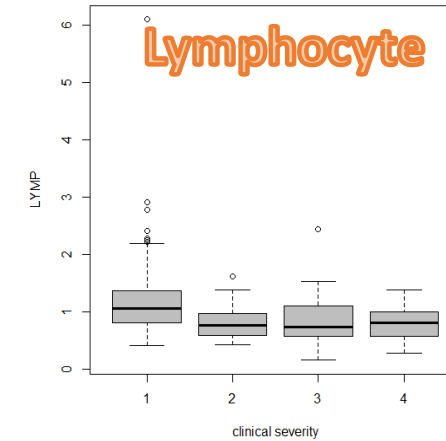
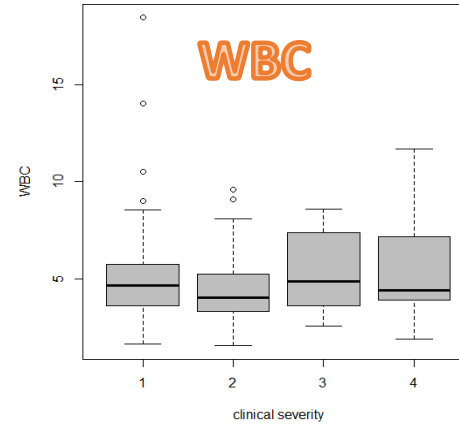
↔ value within the normal reference range.

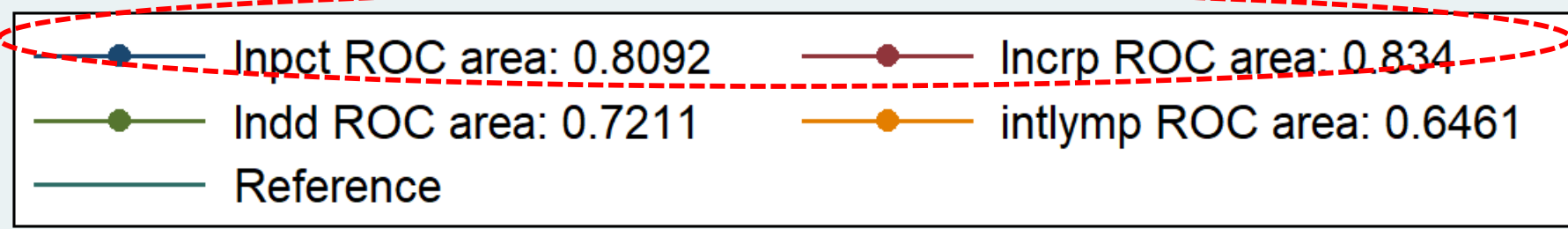
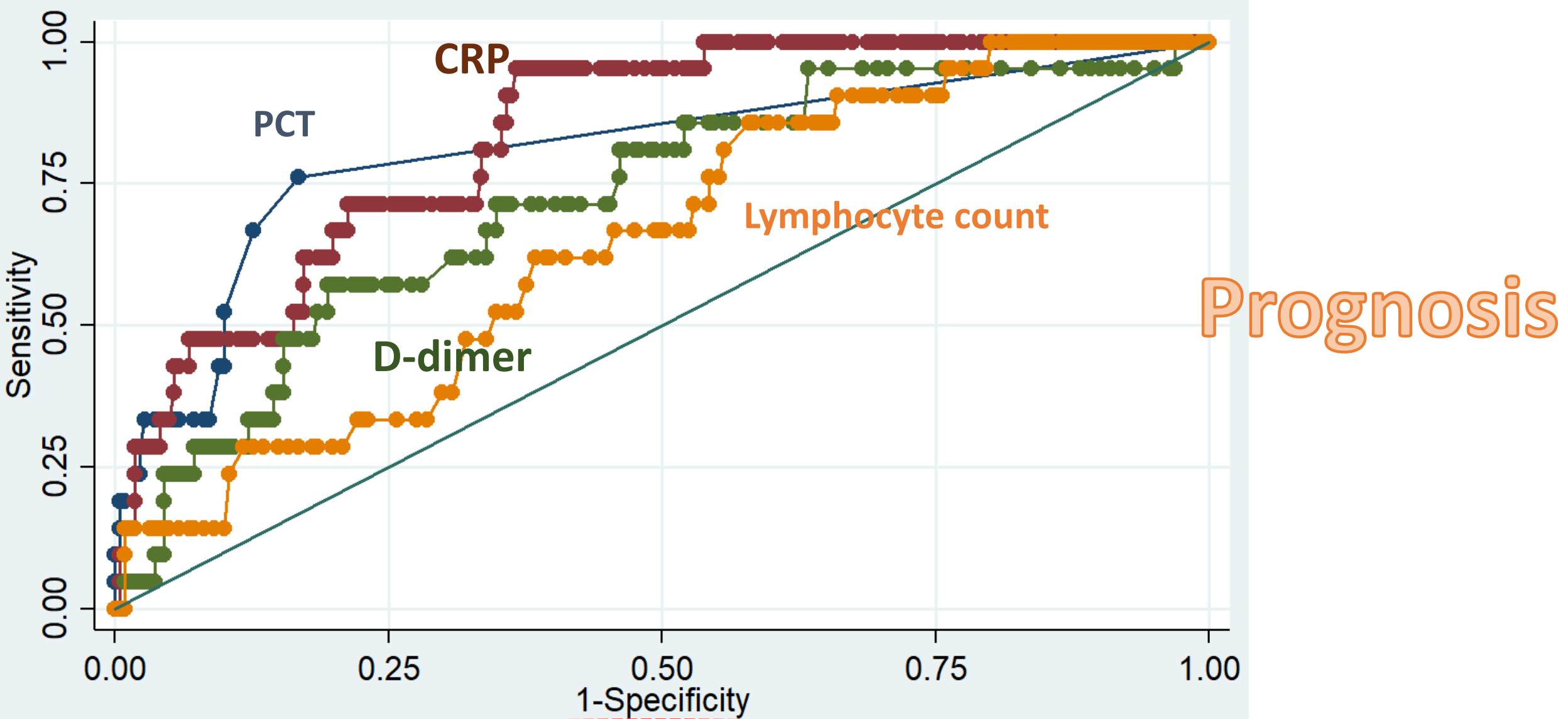
- In contrast to previous belief, most children with COVID-19 do not have elevated IL-6

Prognosis

In a cohort of 252 patients with COVID-19, we evaluated the correlation of biomarkers and clinical Severity. Severity classified by

1. Mild COVID-19
2. Moderate COVID-19
3. Severe COVID-19
4. Death





Compare Severe and Non-severe Pediatric Patients

Table 5 Laboratory and radiological characteristics of the COVID-19 groups

Studied variables	COVID-19 groups		Test f sig.	P value
	Group I N = 295	Group II N = 103		
CRP (0–5.00 mg/L)				
Mean ± SD	76.58 ± 56.88	78.44 ± 43.53	2.15	0.03*
Median (Range)	77 (0–270)	98 (0–148)		
ESR (0–10 mm/hr.)				
Mean ± SD	32.52 ± 13.08	27.82 ± 13.11	3.15	0.002*
Median (Range)	35 (15–55)	25 (15–50)		
Ferritin (7–140 ng/ml)				
Mean ± SD	453.99 ± 405.27	438.41 ± 218.50	3.72	< 0.001**
Median (Range)	300 (95–4000)	480 (90–700)		
D-dimer (< 0.5 µg/ml)				
Mean ± SD	0.881 ± 0.591	1.196 ± 0.849	2.09	0.04*
Median (Range)	1.4 (1.7–3.3)	1 (1.7–5)		

Summary of biomarker findings

- Suggested useful markers in COVID-19
 - PCT, CRP, d-dimer, Ferritin, IL-6
- In mild to moderate pediatric patients
 - CRP, PCT, and IL-6 usually low
- In severe patients
 - CRP, PCT, d-dimer elevated, Ferritin decreased
 - Elevated PCT also indicated co-infection
- The cutoff of PCT should be set as 0.1 ng/L

An abstract graphic with a blue color palette. The background consists of wavy, layered lines in various shades of blue. On the right side, there is a dark blue silhouette of a human head in profile, facing left. In the center-left area, there is a stylized representation of a virus or cell, depicted as a pink, spiky sphere. The overall composition suggests themes of healthcare, technology, and human biology.

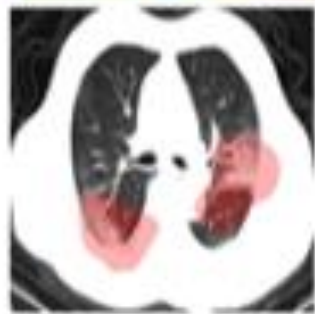
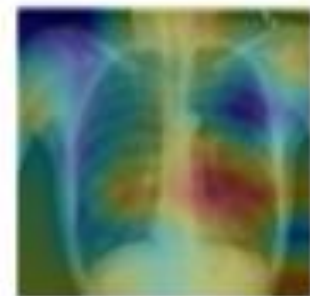
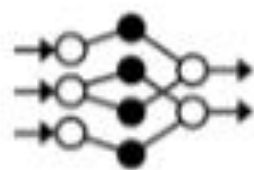
Application of Intelligent healthcare

AI Interpretation of COVID-19 Chest X ray Detection, Description, Prognostication

台大智慧醫療中心
李建璋



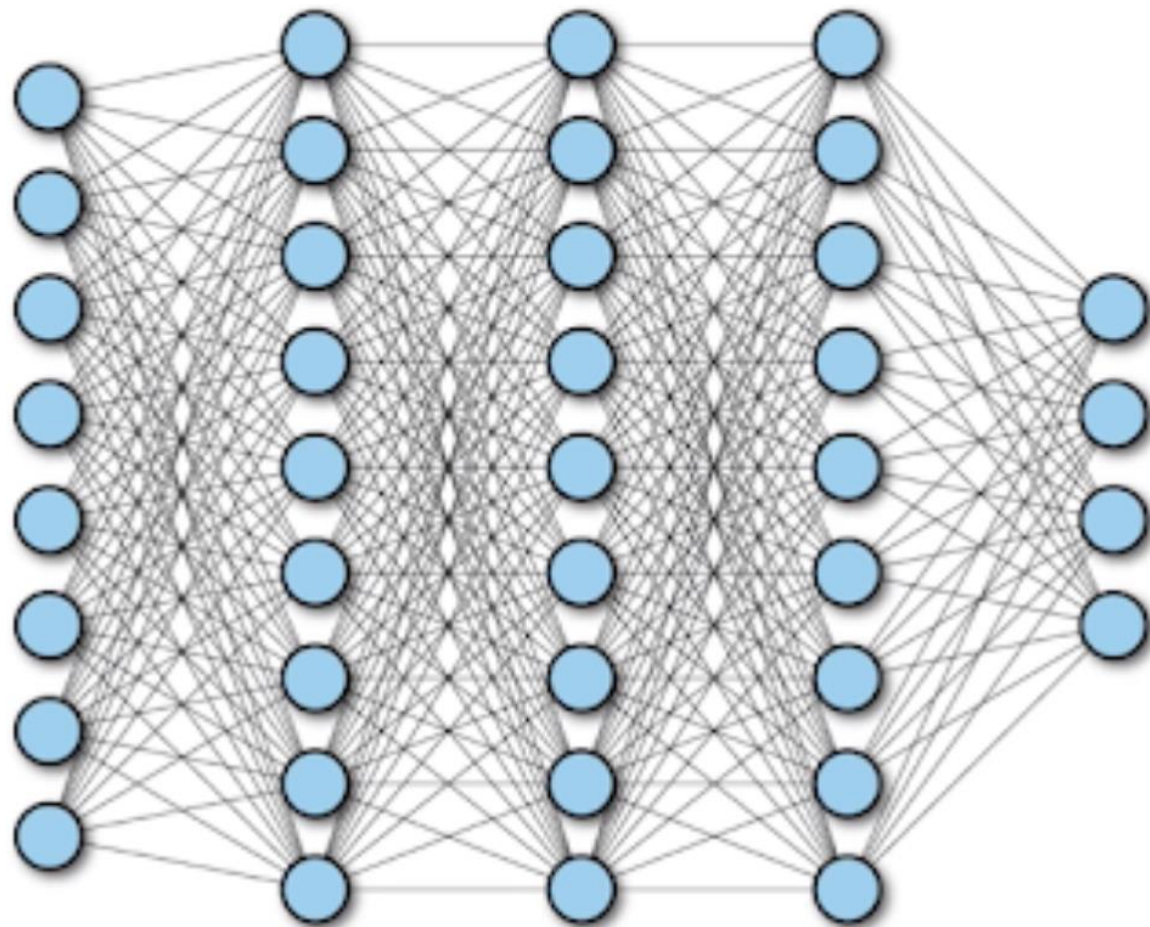
醫師上傳影像



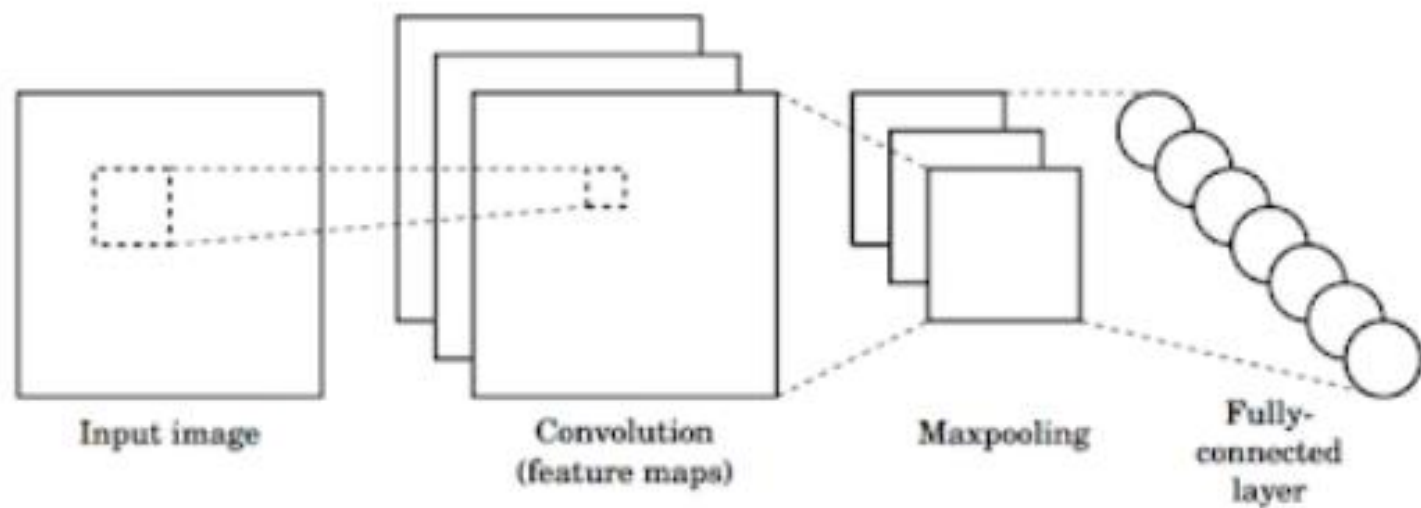
輸出報告

COVID-Net
COVID-NetCT推論


Deep Neural Network




CNNs for Classification



1. **Convolution:** Apply filters to generate feature maps.
2. **Non-linearity:** Often ReLU.
3. **Pooling:** Downsampling operation on each feature map.

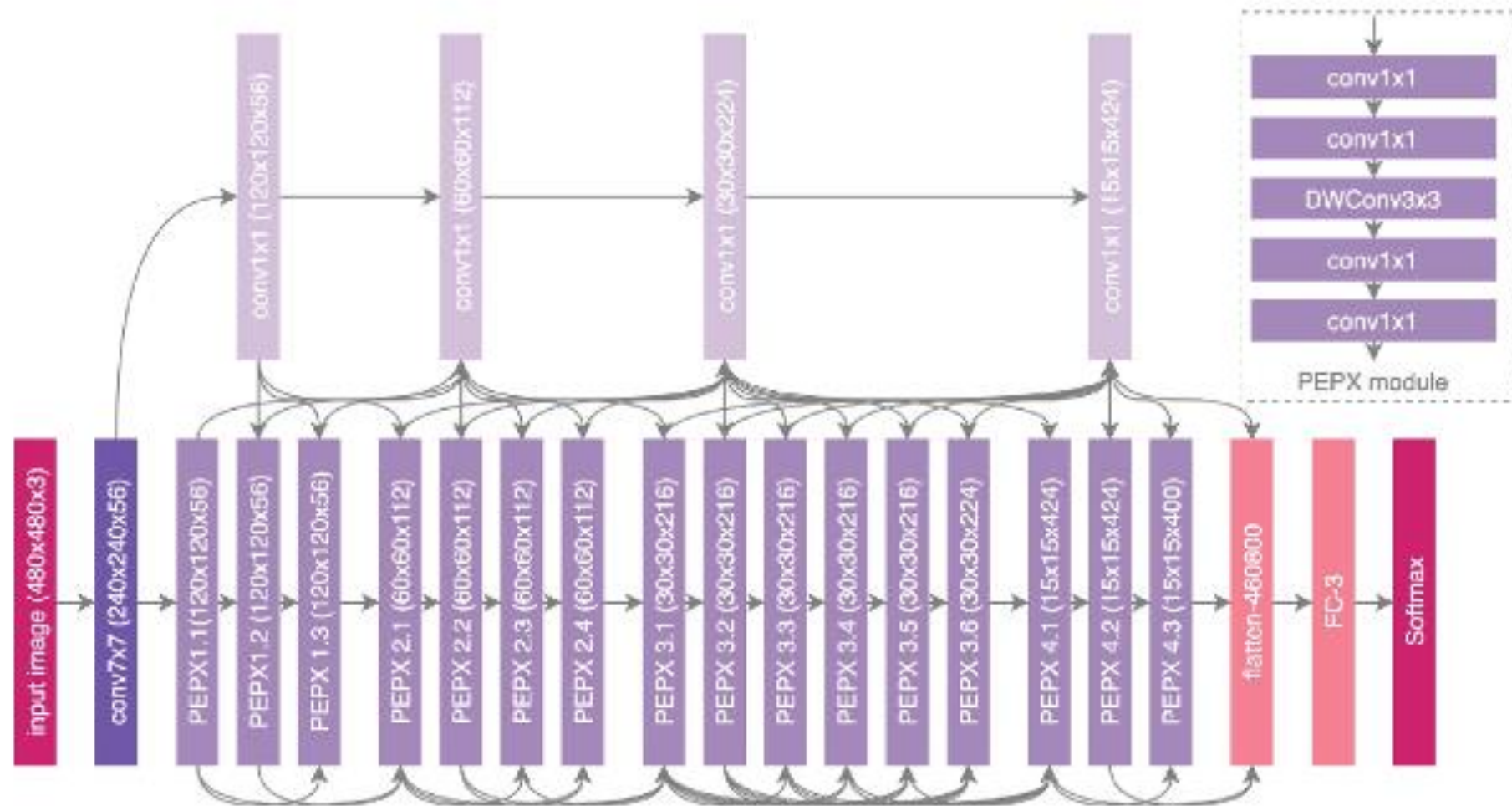
 `tf.keras.layers.Conv2D`

 `tf.keras.activations.*`

 `tf.keras.layers.MaxPool2D`

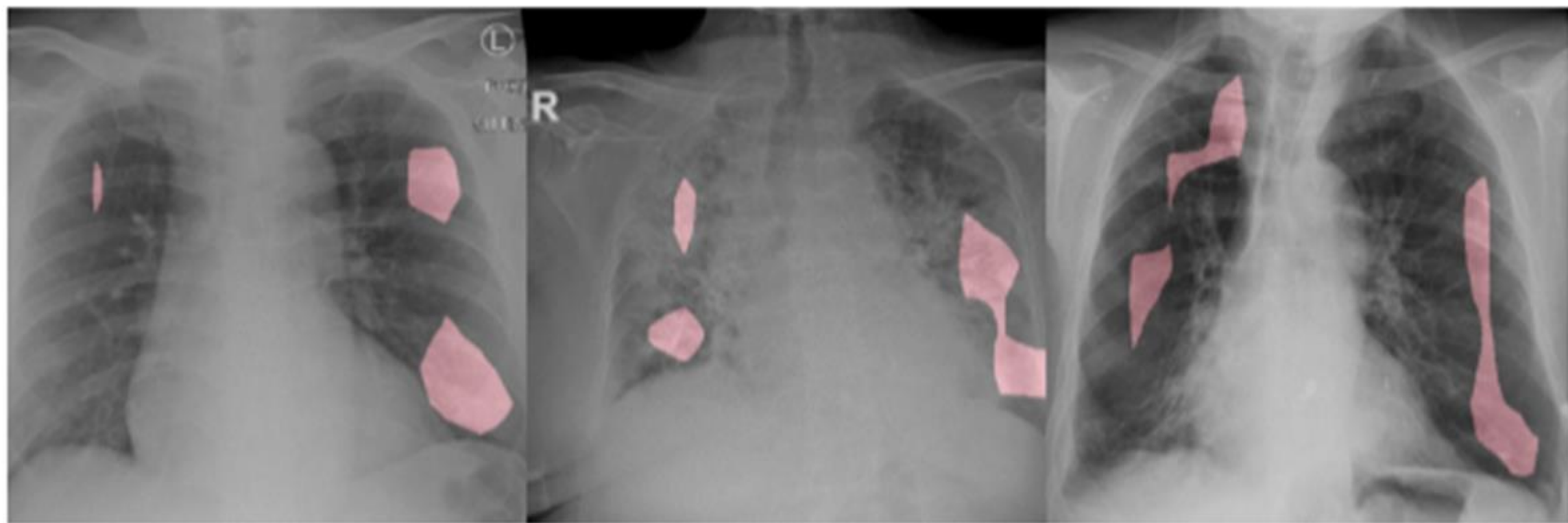
Train model with image data.
Learn weights of filters in convolutional layers.

COVID-Net



預期輸出的受感染熱區影像呈現如下

COVID-Net

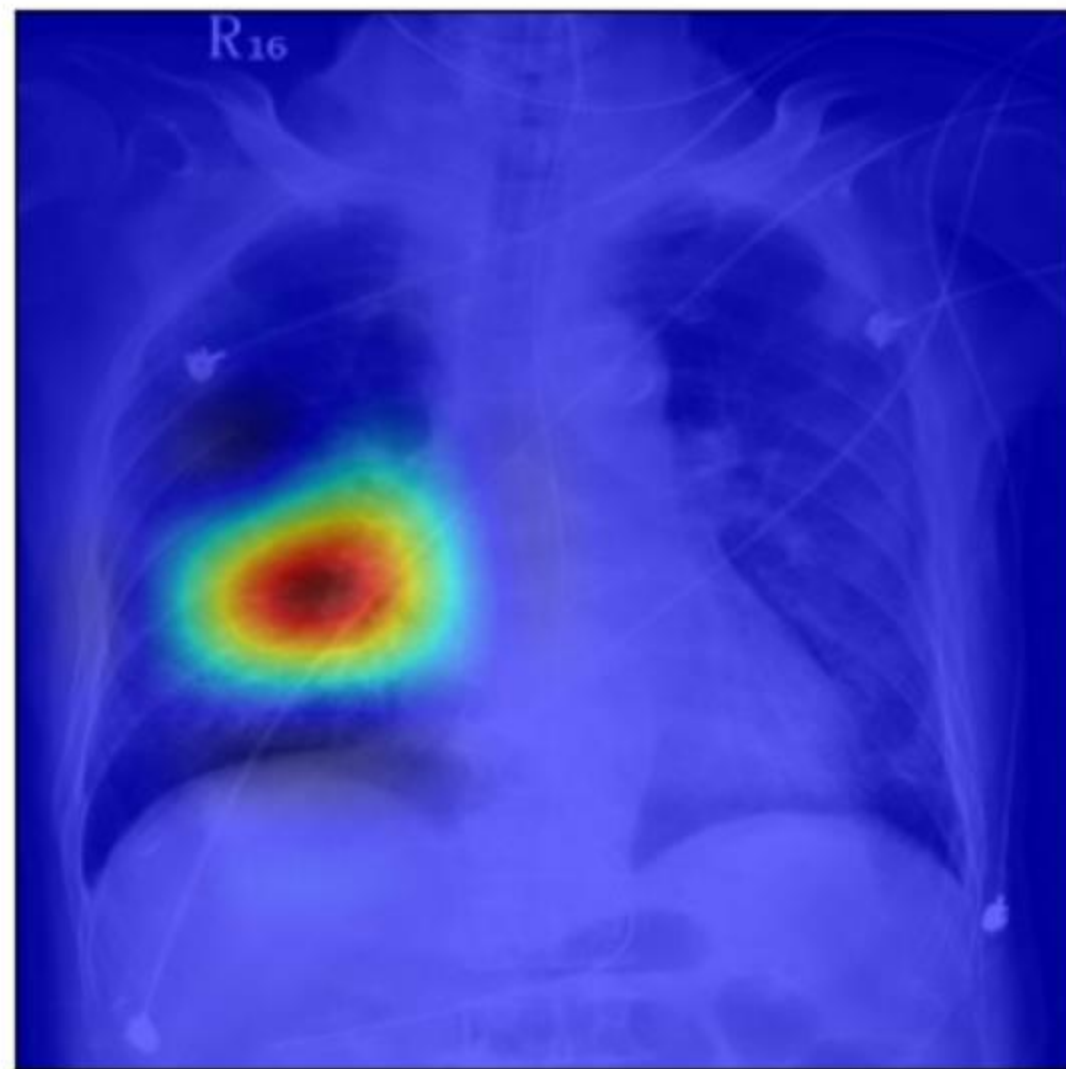


ARDS Probability: 0.843

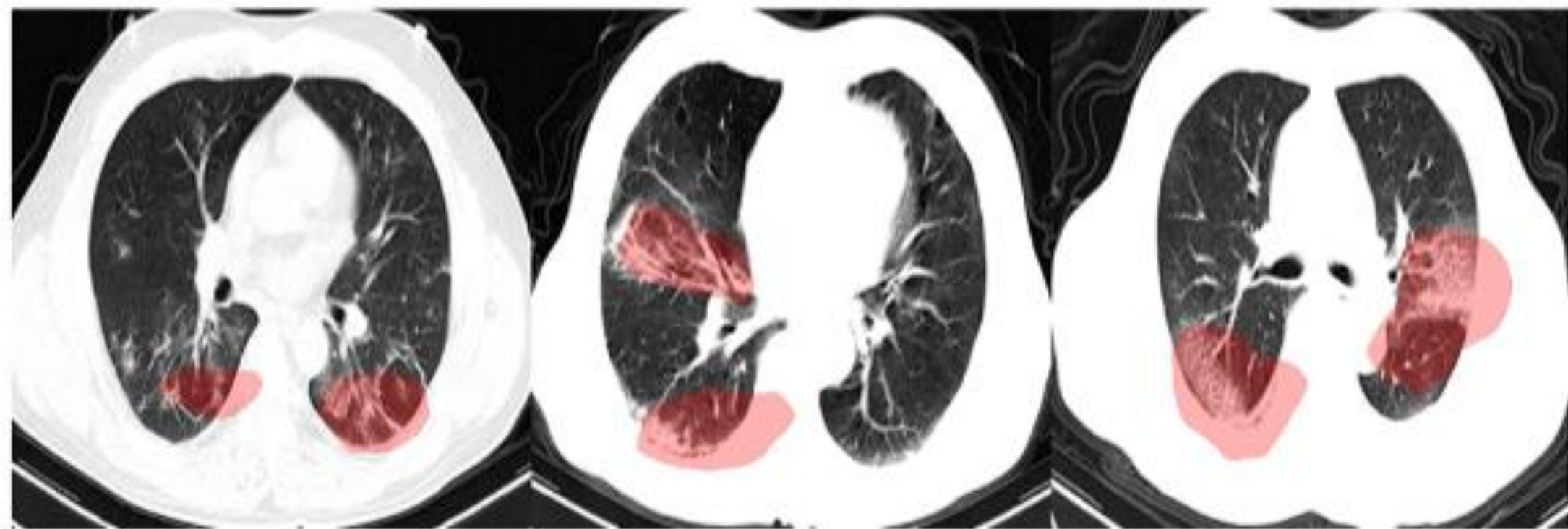
Chest X-Ray



Grad-CAM



COVID-NetCT



Use Scenario

- Rapid progressing cases, while waiting for PCR results
- Prognostication of chest image
- Highly suspected patients with initial negative PCR results
- Serial lung severity monitoring

Take home message

- Antigen test is only suitable for outdoor mass screening use, the suboptimal accuracy does not meet the clinical diagnosis standard
- Saliva has same or even higher concentration of viral load in the first 10 days
- Comparative study showed comparable saliva test accuracy to NP in school-aged children
- Homogenization of saliva before PCR may further increase sensitivity
- Rapid POC molecular test is as accurate as conventional PCR, the multiplex nature of FilmArray can help diagnose co-infections early
- In mild to moderate pediatric patients, CRP, PCT, and IL-6 usually low; in severe patients, CRP, PCT, d-dimer elevated, Ferritin decreased. Elevated PCT also indicated co-infection
- AI image interpretation can be used in rapid progressing cases, while waiting for PCR or Highly suspected patients with initial negative PCR results results



Thank you