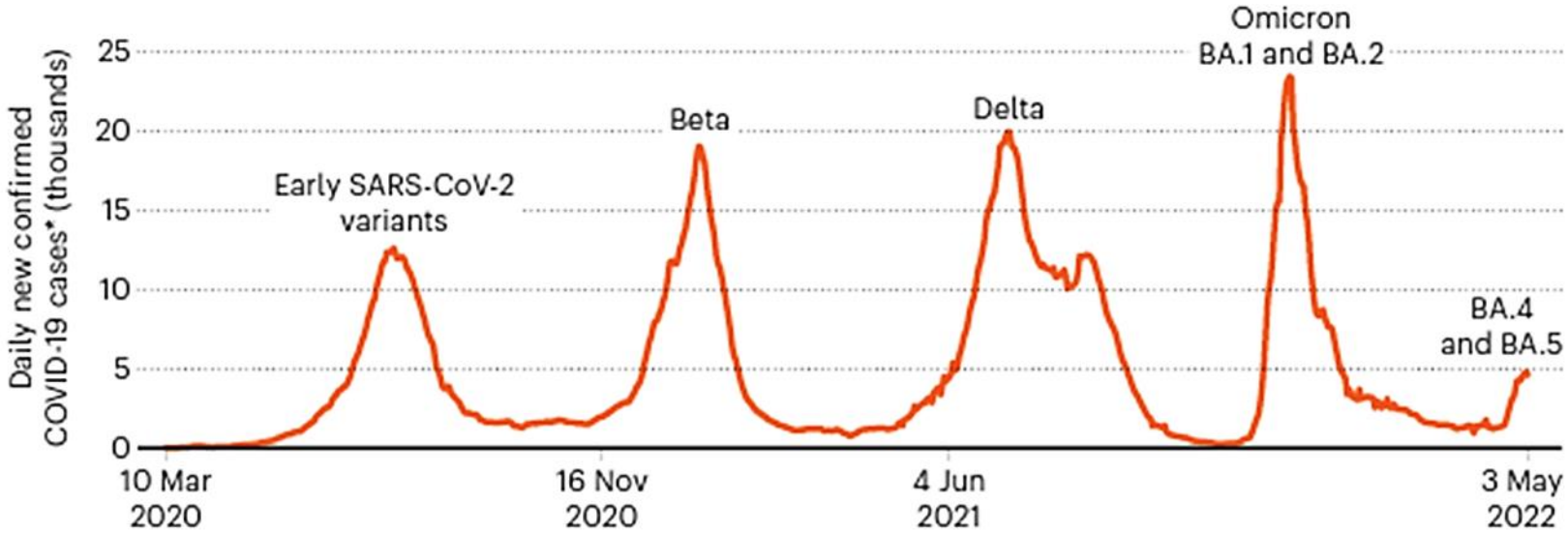
兒童感染COVID-19後腦炎與MIS-C的發展可能及後續治療

黃高彬 M.D., Ph.D., Prof.

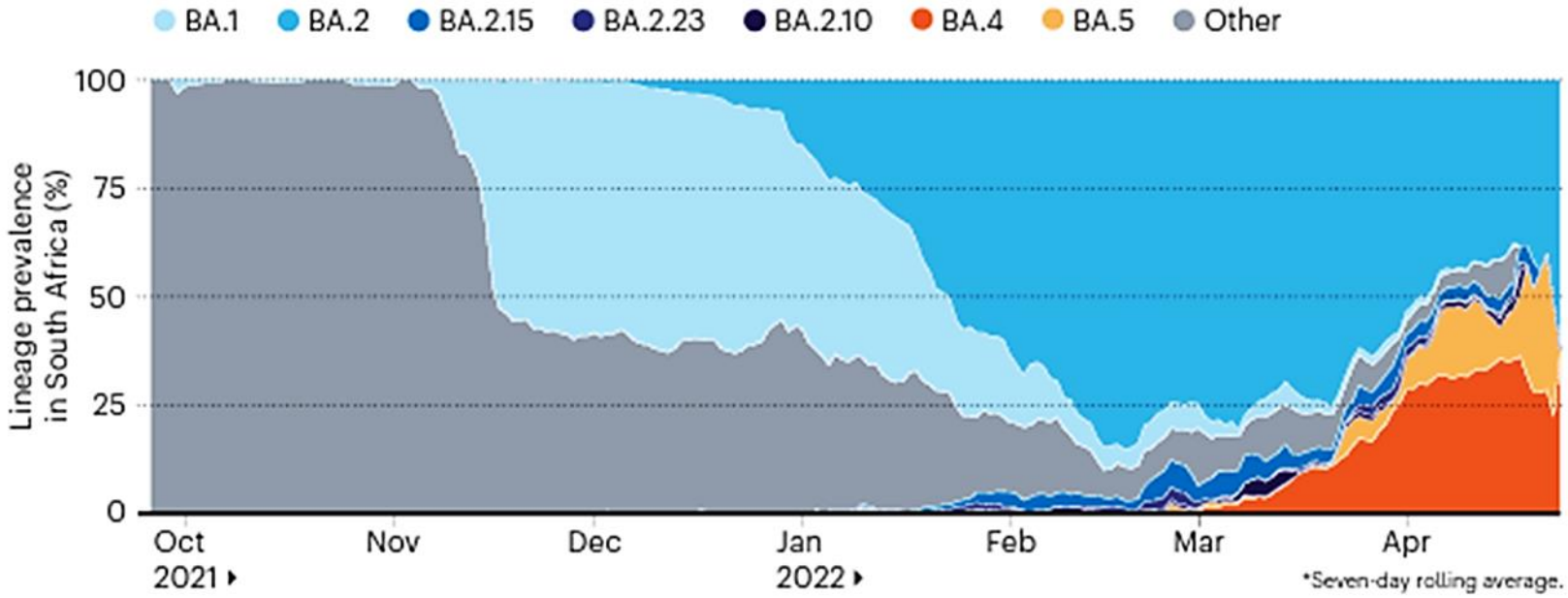
中國醫藥大學附設醫院　副院長
衛福部傳染病醫療網　中區指揮官

OMICRON'S NEW IDENTITIES

Cases of COVID-19 are rising again in South Africa, after the emergence of Omicron variants called BA.4 and BA.5.

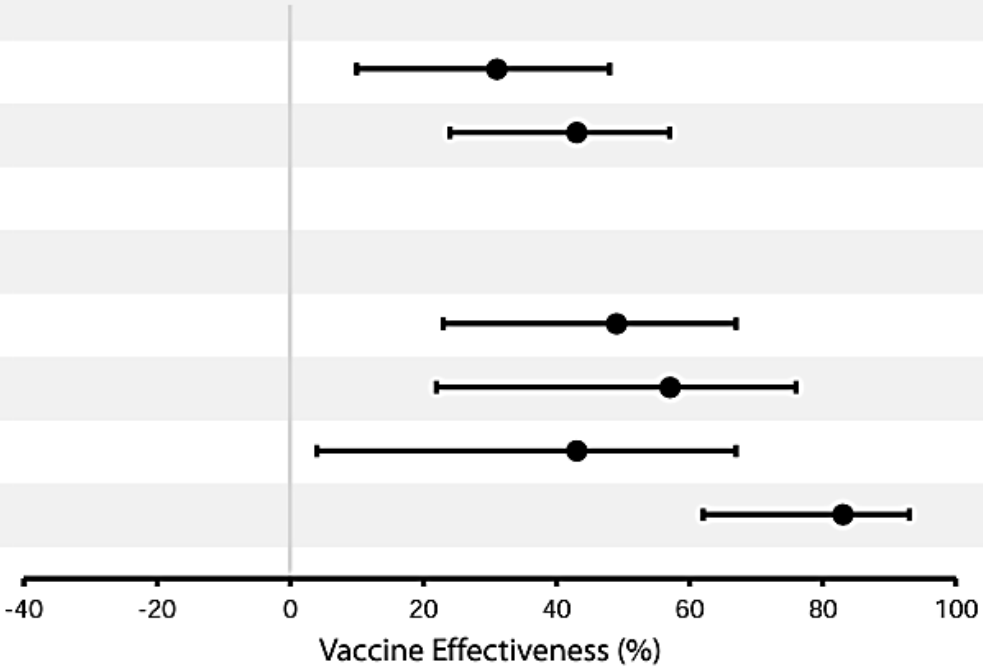


BA.4 and BA.5 spread faster than previous Omicron variants and are accounting for a growing proportion of COVID-19 cases in South Africa.



PROTECT: VE against SARS-CoV-2 infection by age group during Omicron variant predominance, Dec 2021-Apr 2022

	Person-days	SARS-CoV-2 positive	Adjusted VE % (95% CI)
5 - 11 years			
2 doses (≥14 days)	60,290	212	31 (10-48)
2 doses (14-59 days)	26,411	156	43 (24-57)
12 - 17 years			
2 doses (≥14 days)	14,501	59	49 (23-67)
2 doses (14-59 days)	785	20	57 (22-76)
2 doses (≥60 days)	13,716	39	43 (4-67)
3 doses (≥7 days)*	8,340	8	83 (62-93)



* Median time from vaccination to test was 95 days

CDC preliminary unpublished. Based on methods in: Fowlkes AL, Yoon SK, Lutrick K, et al. Effectiveness of 2-Dose BNT162b2 (Pfizer BioNTech) mRNA Vaccine in Preventing SARS-CoV-2 Infection Among Children Aged 5-11 Years and Adolescents Aged 12-15 Years — PROTECT Cohort, July 2021-February 2022. MMWR Morb Mortal Wkly Rep 2022;71:422-428. DOI: http://dx.doi.org/10.15585/mmwr.mm7111e1

Neurologic Involvement in COVID-19

- Encephalopathy
- Meningoencephalitis
- Acute disseminated encephalomyclitis
- Seizure
- Stroke
- Guillain-Barre' syndrome

Mechanisms

- Direct viral infection of nervous system
- Inflammatory injury mediated by cytokines release

兒童 COVID-19 後腦病變

- 急性腦炎
- 腦幹腦炎
- 腦脊髓炎

臨床表徵(I)

1. 意識或行為改變、精神混亂、肌躍型抽搐、抽搐、肢體麻痺、非自主性眼球動作（眼球往上看、眼球固定偏向一側、眼球亂轉、眼球震顫、鬥雞眼）、顱神經功能異常、囟門膨出、運動失調等。

2. 上運動神經元症狀 (如Babinski sign，垂足[foot plantar flexion])，錐體外症候群(像extrapyramidal symptoms, EPS的表現)，角弓反張，肌張力不全(dystonia)等。

臨床表徵(II)

3. 若是抽搐發作，需與兒童單純性熱性痙攣(常見年齡6個月至5歲)鑑別診斷，其中若是focal seizures，抽搐發作時間較長，反覆抽搐發作，發作後30分鐘意識沒有恢復，且GCS ≤ 12，需特別小心。
4. 詳細記錄抽筋型態(全身與局部)與重點式神經學檢查(GCS+REM-BR: Respiratory pattern, Eye response (pupil size), Motor (decerebrate /decorticate posture, foot plantar flexion, Babinski sign), Brainstem Reflex: light reflex and corneal reflex)。

重症前驅症狀

- 體溫大於41度、意識不佳(GCS ≤ 12)、持續昏睡、持續頭痛、持續嘔吐、肌躍型抽搐、抽搐、步態不穩。

- 出現任何非兒童單純性熱性痙攣可解釋的腦病變(如下點所示病徵)與重症前驅症狀時，建議應住院或立即轉診至新冠病毒重症責任醫院。

腦病變之照護

- 考慮會診兒童神經科，可視臨床需要進行腦部與脊髓的影像檢查(如電腦斷層，磁振造影)，或採集腦脊髓液送驗檢查。
- 可安裝心電圖監視器、監測心臟肌肉酵素（MB型肌酸磷酸激酶、肌鈣蛋白troponin I）、BNP或NT-proBNP、及血糖、進行心臟超音波檢查。
- 監測血壓。如出現血壓升高、需過度換氣治療、昏迷指數低於9分或快速降低中，應住進加護病房。
- 有些個案，血液動力學變化可能極為快速，需注意。

相關的危險因子

(一) 臨床表現

1. 昏迷指數(Glasgow Coma Scale, GCS)
2. 抽搐發作 (Seizures): focal seizure, repetitive seizure without consciousness recovery, status epilepticus)
3. 腦幹症狀(Brainstem signs): cranial nerve abnormalities
4. 高燒(High fever)

(二) 實驗室與影像學檢查

1. Ferritin, IL-6, D-dimer
2. Brain CT: impending herniation (suspected brainstem involvement)

診　斷

- 臨床表徵
- 新冠感染病史
- 檢驗：
  - Ferritin, IL-6, LDH, DIC profile (D-dimer)
- 監測：
  - BP, HR, SpO2, Sugar, Troponin I, BNP or NT-proBNP

新冠病毒腦炎之治療

- 抗病毒藥物:需跟家屬說明清楚得到同意後，給予靜脈注射瑞德西偉(Remdesivir) 5天。
- 抗發炎：考慮給予靜脈注射免疫球蛋白與IL-6 antagonist (Tocilizumab)，適應症如下:
  - 兒童新冠急性腦病變免疫球蛋白使用適應症：

    A. 急性腦病變、急性無力性輕癱麻痺、自主神經失調、急性心肺衰竭、敗血症候群。

    B. 急性腦病變有抽搐症狀者，須合併意識不佳(GCS ≤ 12)，並排除兒童單純性熱性痙攣，才符合使用條件。

    C. 劑量: 1 gm/kg 靜脈滴注12小時X 2天。

Multisystem inflammatory syndrome in Children (MIS-C)

- 2020年4月，英國發現，8個病例
  - incomplete Kawasaki disease (KD)
  - toxic shock syndrome
- 接著：歐洲、加拿大、美國和南非報告
- 亞洲國家少見

流 行 病 學

- 發生率：< 1%，2/10萬
- 好發年齡：≥ 5歲到青春期 (中位數8~11歲)
- 種族：黑人、西班牙裔人
- 常見的共病：肥胖、氣喘病
- 距COVID-19感染：3到4週 (小於6週)

病理生理學(推測)

- 免疫調節不良 (immune dysregulation)
  - Kawasaki disease
  - Macrophage activation syndrome
  - Cytokine release syndrome
- SARS-CoV-2病毒的免疫反應
  - 宿主的因素

SARS-CoV-2病毒和血清學變化

- 血清學陽性，PCR陰性：60%
- 血清學陽性，PCR陽性：34%
- 血清學陰性，PCR陰性：5%

心肌傷害的機轉

1. 全身性炎症反應
2. 急性病毒性心肌炎
3. 缺氧
4. 壓力導致心肌病變
5. 冠狀動脈缺血

案例病理報告

- Myocarditis
- Pericarditis
- Endocarditis
- 切片：炎症細胞浸潤
- 嚴重肺部侵犯

臨 床 表 徵

- Fever
- Gastrointestinal symptoms
- Cardiorespiratory symptoms
- Neurocognitive symptoms

臨 床 症 狀

1. Fever
2. G-I symptoms
3. Rash
4. Conjunctivitis
5. Mucous membrane involvement
6. Neurocognitive symptoms
7. Respiratory symptoms
8. Sore throat
9. Myalgia
10. Swollen hands/feet
11. Lymphadenopathy

Figure 5. Conjunctival injection.

Clin. Pract. 2021, 11, 363–373. https://doi.org/10.3390/clinpract11020051

Figure 6. Periorbital edema and hyperemia of skin.

Clin. Pract. 2021, 11, 363–373. https://doi.org/10.3390/clinpract11020051

Figure 4. Cracking and hyperemia of lips.

Clin. Pract. 2021, 11, 363–373. https://doi.org/10.3390/clinpract11020051

January 13, 2021, Public Health , Disease Guide

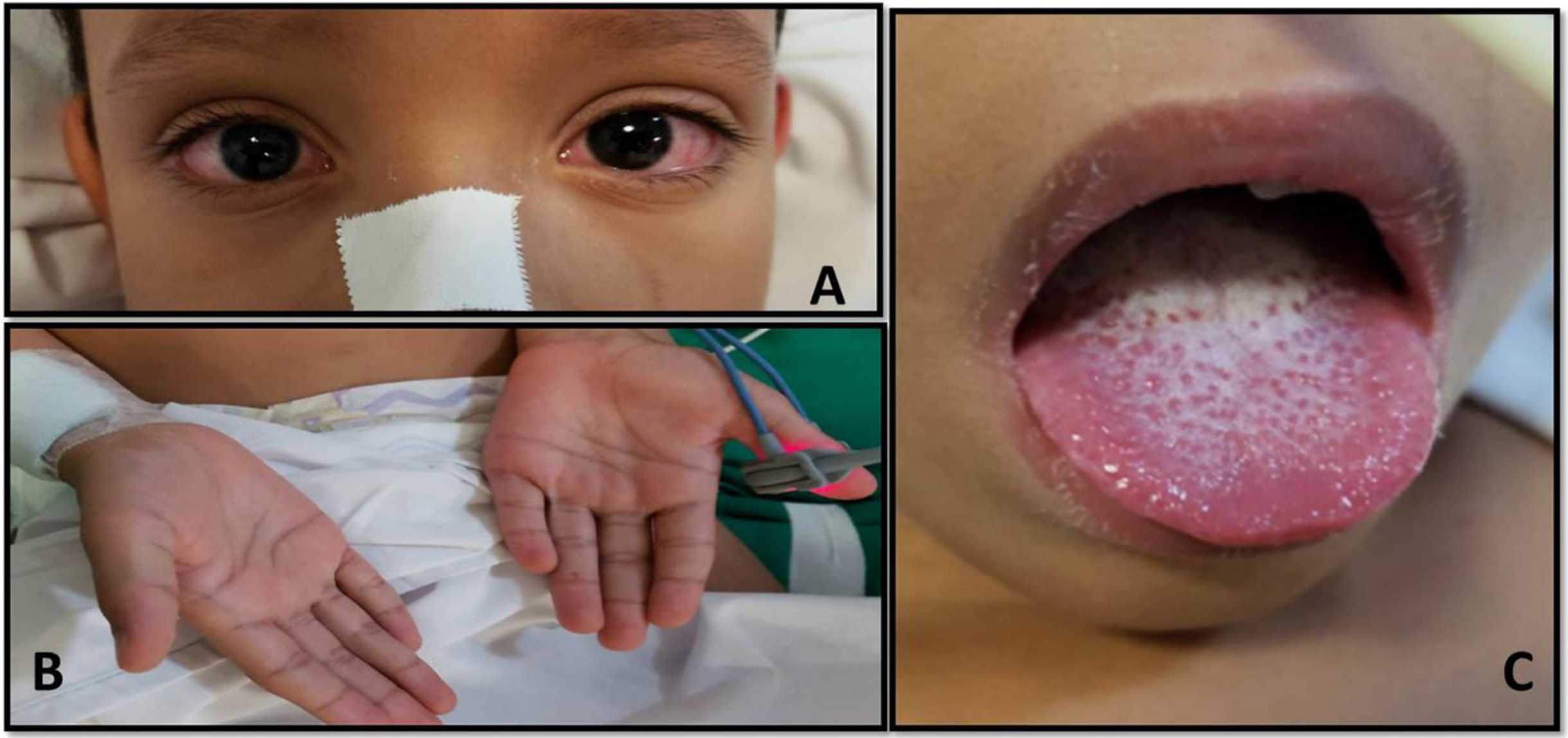


FIGURE 1 | **(A)** Presence of bilateral, nonexudative conjunctival hyperemia. **(B)** Maculopapular lesions in the palmoplantar region. **(C)** Presence of mucosal changes with peeling lip and raspberry tongue.

January 13, 2021, Public Health , Disease Guide

實驗室檢查(I)

- Abnormal blood cell counts
  - Lymphocytopenia
  - Neutrophilia
  - Mild anemia
  - Thrombocytopenia
- Elevated inflammatory markers
  - C-reactive protein (CRP)
  - Erythrocyte sedimentation rate (ESR)
  - D-dimer
  - Fibrinogen
  - Ferritin
  - Procalcitonin
  - Interleukin-6 (IL-6)

實驗室檢查(II)

- Elevated cardiac markers:
  - Troponin
  - BNP or N-terminal pro-BNP
- Hypoalbuminemia
- Mildly elevated liver enzymes
- Elevated lactate dehydrogenase (LDH)
- Hypertriglyceridemia

心臟超音波 (echocardiography)

- Depressed LV function
- Coronary artery abnormalities : dilation, aneurysm
- Mitral regurgitation
- Pericardial effusion

Other Imaging Findings

- Chest radiograph
- Computed tomography (CT) of chest
- Abdominal imaging (ultrasound, CT)
  - Free fluid, ascites, bowel and mesenteric inflammation (ileitis), adenitis

Table 1
MIS-C diagnostic criteria.

Criteria	CDC [3]	WHO [66]	RCPCH [67]
Age	<21 years	<19 years	All children (age not defined)
Fever	≥38C for ≥24 h or subjective fever lasting ≥ 24 h	Fever ≥ 3 days	Persistent fever ≥ 38.5C
Clinical	Evidence of clinically severe illness requiring hospitalization, with multisystem organ involvement (≥2 of the following: cardiac, renal, respiratory, hematologic, GI, dermatologic, or neurologic)	At least 2 of the following: 1) Rash, conjunctivitis, mucocutaneous inflammation 2) Hypotension or shock 3) Cardiac involvement* 4) Coagulopathy 5) Acute GI symptoms	Single or multiorgan dysfunction and additional features**
Inflammation	At least one of the following: elevated CRP, ESR, fibrinogen, procalcitonin, D-dimer, ferritin, lactic acid dehydrogenase, IL-6, elevated neutrophils, reduced lymphocytes, low albumin	Elevated CRP, ESR, procalcitonin	Neutrophilia, elevated CRP, and lymphopenia
SARS-CoV-2	Positive for current or recent SARS-CoV-2 infection by RT-PCR, serology, or antigen test, or COVID-19 exposure within the 4 weeks prior to symptom onset	Positive for current or recent SARS-CoV-2 infection by RT-PCR, serology, or antigen test, or likely COVID-19 exposure	Positive or negative RT-PCR
Exclusion	No alternative diagnosis	No obvious microbial cause	Exclusion of other infections

CDC, Centers for Disease Control and Prevention; WHO, World Health Organization; RCPCH, Royal College of Paediatric and Child Health; GI, gastrointestinal; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; IL-6, interleukin-6; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; RT-PCR, reverse transcription polymerase chain reaction; NT-proBNP, N-terminal pro-brain natriuretic peptide.

* Cardiac involvement defined by the WHO MIS-C case definition: features of myocardial dysfunction, pericarditis, valvulitis, or coronary abnormalities (including echocardiogram findings or elevated troponin/NT-proBNP).

** Additional features for the RCPCH definition: abdominal pain, confusion, conjunctivitis, cough, diarrhea, headache, lymphadenopathy, mucous membrane changes, neck swelling, rash, respiratory symptoms, sore throat, swollen hands and feet, syncope, vomiting.

American Journal of Emergency Medicine 49 (2021) 148–152

Table 2

Distinctions between MIS-C and Kawasaki disease [35]

MIS-C	Kawasaki disease
- More commonly affects older children and adolescents (>7 years)	- More commonly affects younger children and infants (<5 years)
- GI symptoms very common	- GI symptoms not common
- Myocardial dysfunction and shock more common	- Myocardial dysfunction and shock less common
- Inflammatory markers [CRP (12–22 times normal values), ferritin (1–3 times normal values), D-dimer (10–20 times normal values)] more significantly elevated	- Inflammatory markers (CRP, ferritin, D-dimer) not very elevated
- Absolute lymphocyte count and platelet counts are low	- Leukocytosis and thrombocytosis are common

MIS-C, Multisystem Inflammatory Syndrome in Children; GI, gastrointestinal; CRP, C reactive protein.

American Journal of Emergency Medicine 49 (2021) 148–152

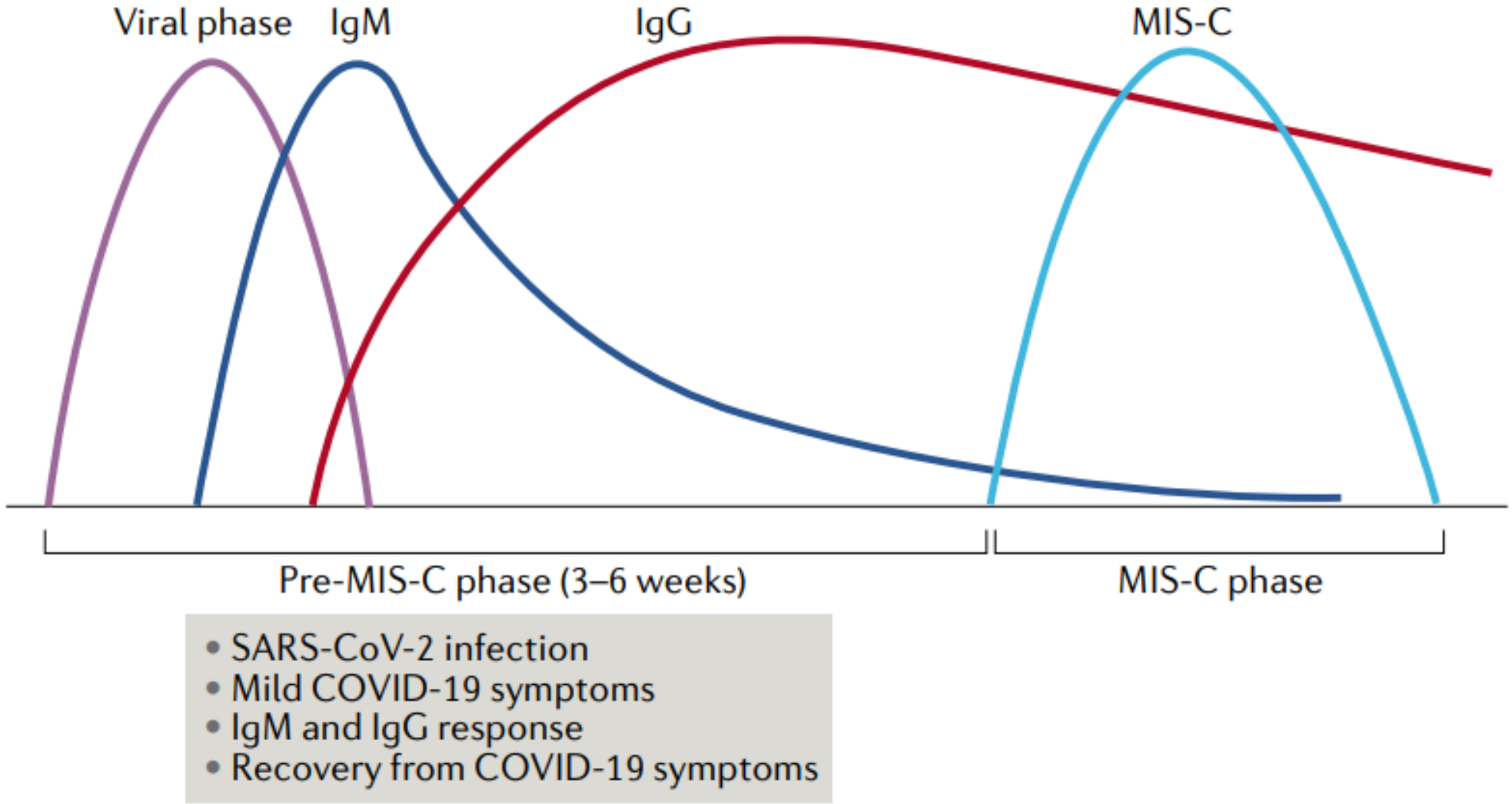


Fig. 1 | **The temporal relationship between SARS-CoV-2 infection and development of MIS-C.** Evidence suggests that a relationship exists between the timing of severe

Nature Reviews Rheumatology
volume 17, pages731–748 (2021)

Multisystem inflammatory syndrome after COVID-19

- 2020 年 4 月於英國首先報告於兒童發生多重器官發炎症候群
  - ✓與Kawasaki Disease (KD), toxic shock syndrome (TSS) and macrophage activation syndrome (MAS)/secondary hemophagocytic lymphohistiocytosis (具有類似表現
- 美國與英國陸續報告亦有成人發生類似症狀
- 相較於兒童個案，成人個案
  - ✓更高比例先有呼吸道症狀
  - ✓更高比例心臟受影響或有血栓
  - ✓死亡率可能更高

Multisystem inflammatory syndrome after COVID-19

- 2020 年 4 月於英國首先報告於兒童發生多重器官發炎症候群
  - ✓與Kawasaki Disease (KD), toxic shock syndrome (TSS) and macrophage activation syndrome (MAS)/secondary hemophagocytic lymphohistiocytosis (具有類似表現
- 美國與英國陸續報告亦有成人發生類似症狀
- 相較於兒童個案，成人個案
  - ✓更高比例先有呼吸道症狀
  - ✓更高比例心臟受影響或有血栓
  - ✓死亡率可能更高

Case Series of Multisystem Inflammatory Syndrome in Adults Associated with SARS-CoV-2 Infection—UnitedKingdom and United States, March—August 2020

- 27 patients from reports to CDC (aged 21-50 years, 7 male, 9 female)and active literature search on August 20, 2020 (aged 20-50 years)
- All had Cardiovascular, gastrointestinal, dermatologic, and neurologic symptoms
  - ✓hypotension or shock, cardiac dysfunction, arterial or venous thrombosis or thromboembolism, or acute liver injury
  - ✓absence of severe respiratory illness
  - ✓laboratory evidence of severe inflammation (e.g., elevated CRP, ferritin, D dimer, interleukin 6)
  - ✓concurrently received positive test results for SARS CoV 2 recent infection
- 30% adults had negative PCR and positive SARS-CoV-2 antibody test results
- MIS-A developed approximately 2-5 weeks after typical COVID-19 symptoms
  - ✓Some patients reported no preceding respiratory symptoms
- Survival rate 29%

Clinical Characteristics of Multisystem Inflammatory Syndrome in Adults: A Systematic Review

- Of 221 patients with MIS-A, the median age was 21 years (interquartile range, 19-34)
- 70% were men. 36% were non Hispanic Black
- 58% had no underlying comorbidity. 68% noted a previous symptomatic COVID-19 like
- illness (median, 28 [IQR,20-36] days previously)
- 96% fever, 60% hypotension, 54% cardiac dysfunction, 52% shortness of breath, 52% diarrhea
- The median organ systems involved was 5 (IQR, 4-6)
- Median hospital stay was 8 (IQR, 5-12) days; 57% were admitted to the ICU; 47% required respiratory support, and 7% died
- 90% had elevated markers of coagulopathy and/or inflammation
- 72% positive SARS-CoV-2 serologic finding

JAMA Netw Open. 2021;4(9):e2126456.

Treatment, prevention and unknown

- No evidence based recommendations for treatment of MIS-A
  - ✓ Possible options include steroids, IVIG, Anakinra (IL-1 receptor antagonist) and supportive care treatments
- CDC recommends COVID-19 vaccination as the best protection from MIS-A
- The true incidence and the pathophysiology of MIS-A is not known
  - ✓ Likely due to antibody mediated process or dysregulated immune response

COVID-19 Real time learning network by CDC and IDSA
https://www.idsociety.org/covid-19-real-time-learning-network/

美國疾病控制及預防中心(CDC)的MIS-A病例定義

年齡≥21歲且住院≥24小時或因疾病而死亡，並符合以下臨床和實驗室標準的患者。病人應無其他更可能解釋病程的疾病診斷(例如細菌性敗血症、慢性疾病惡化)。

臨床標準

住院前24小時或更長時間或住院前三天內有主觀發燒或客觀發燒記錄（≥38.0度），並且在住院前或住院前三天內至少符合以下臨床標準中的三項。至少一項必須是主要臨床標準。

主要臨床標準

嚴重心臟疾病：

包括心肌炎、心包炎、冠狀動脈擴張/冠狀動脈瘤或新發的左右心室功能障礙(LVEF<50%)、2或3度房室傳導阻滯或室性心動過速。

(註：僅心臟驟停則不符合此標準)

皮疹

非化膿性結膜炎

次要臨床標準

新發的神經系統病徵和症狀
包括過去無認知障礙病史患者的腦病變、癲癇、腦膜炎病徵或周圍神經病變(包括格林巴利症候群)

不能歸因於藥物治療(例如鎮靜、透析)的休克或低血壓

腹痛、嘔吐或腹瀉

血小板減少
(血小板計數低於150,000/微升)

實驗室標準

同時具有發炎和新冠病毒感染的實驗室證據：

- 以下至少兩項指數升高：CRP, Ferritin, IL-6, ESR, procalcitonin
- SARS-CoV-2 RT-PCR、血清學或抗原檢測陽性

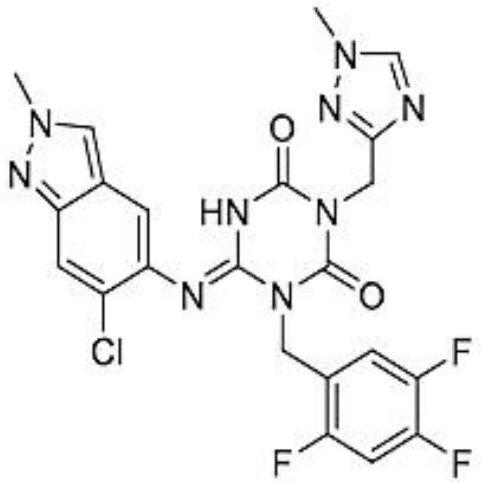
資料來源：美國CDC官網 (https://www.cdc.gov/mis/mis-a/hcp.html)

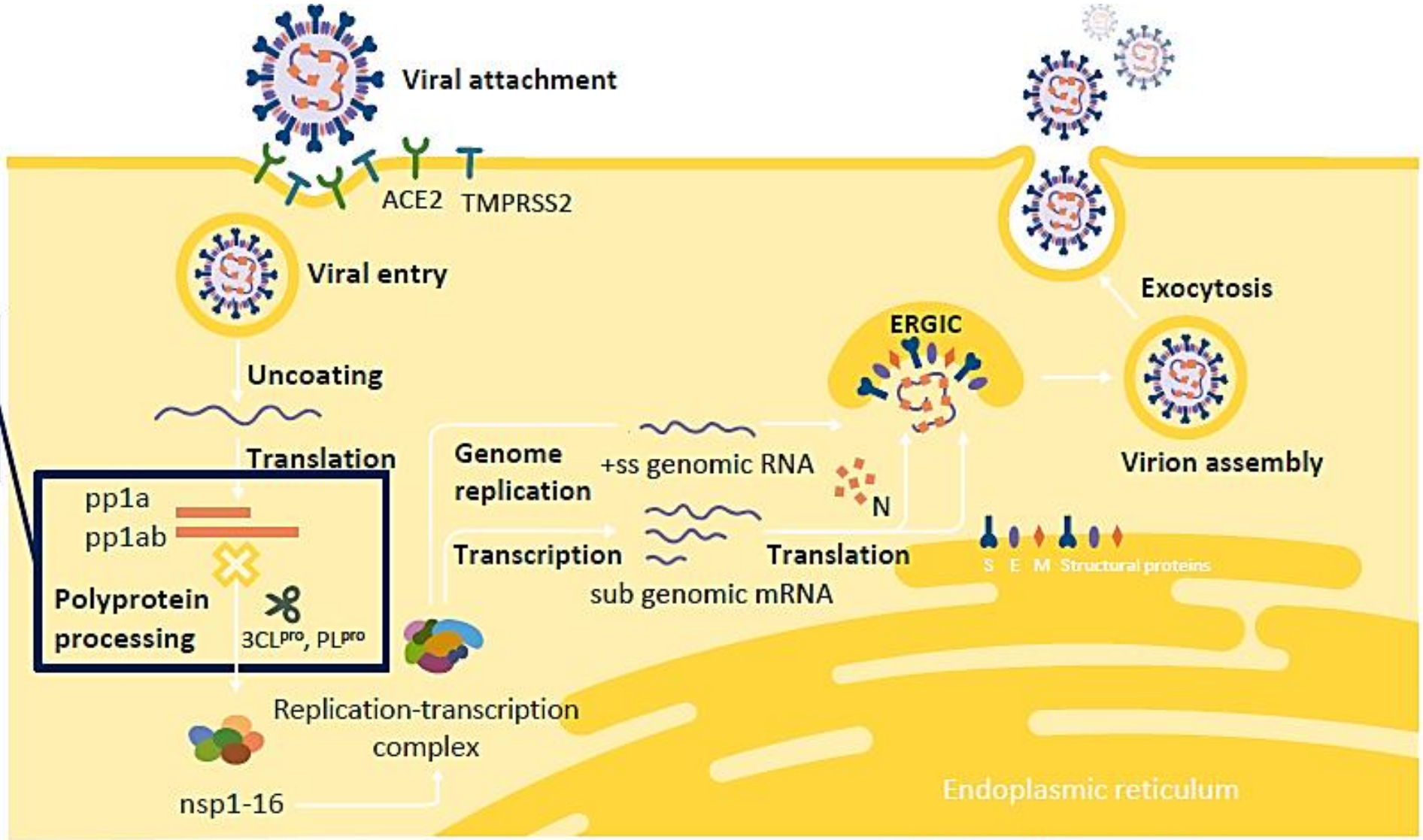
2022/06/21

中央流行疫情指揮中心

Novel orally bioavailable 3CLpro inhibitor, S-217622

3CL^{pro} inhibitor
S-217622

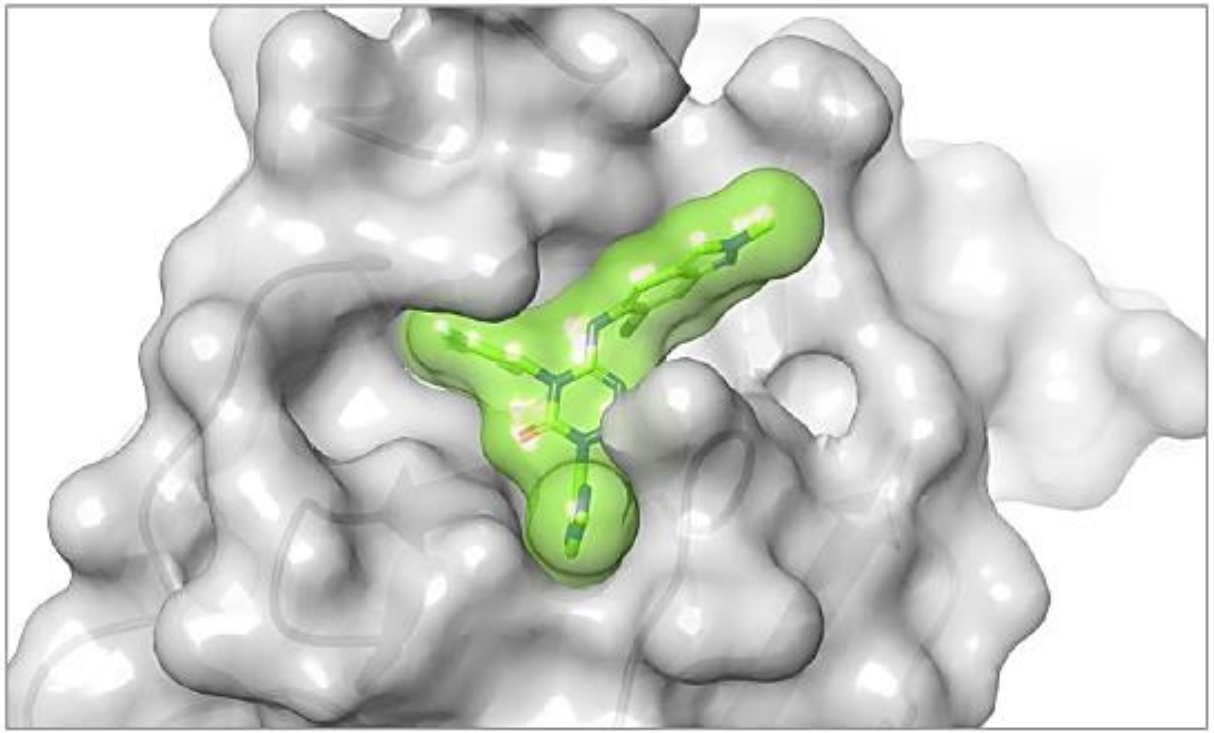




Unoh, Y et al. J. Med. Chem. 2022

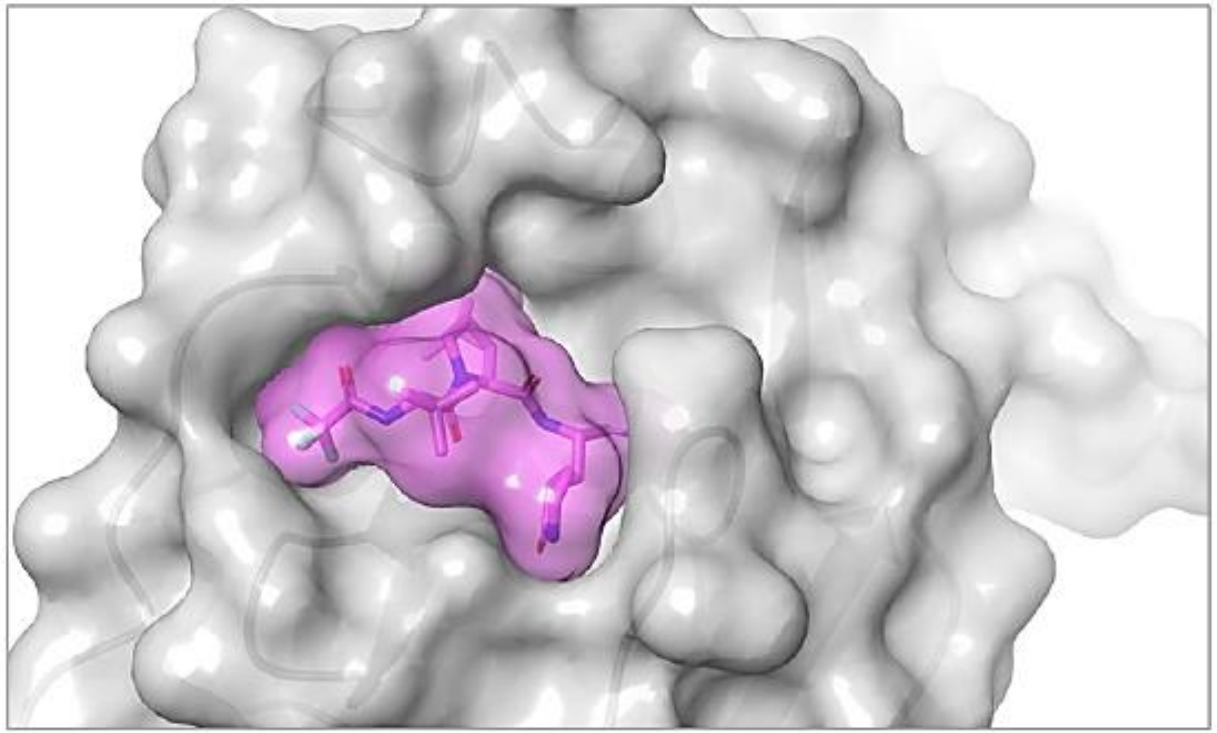
Structural differences of protease inhibitors:
Binding sites in complex with the SARS CoV 2 3CL protease

S-217622



S-217622, a newly synthesized small molecule with high bioavailability (not requiring PK booster), binds to cysteine residues in the active site noncovalently

Paxlovid (nirmatrelvir)



Nirmatrelvir, structurally mimicking the peptide cleaved by the protease, covalently binds to cysteine residues in the active site

Virology: Activity against SARS-CoV-2 Variants

In vitro assay using VeroE6T cells

SARS-CoV-2 variant	EC_{50} (μM)	Major mutation site	
		Spike-protein	3CL-protease
Conventional strain (WK-521)	0.37	-	-
Alpha variant (QHN001/QHN002/QK002)	0.31/0.46/0.33	N501Y, D614G	-
Beta variant (TY8-612)	0.40	K417N, E484K, N501Y, D614G	K90R*
Gamma variant (TY7-501/TY7-503)	0.50/0.43	K417T, E484K, N501Y, D614G	-
Delta variant (TY11-927)	0.41	L452R, T478K, D614G	-
Omicron variant (BA.1/BA.1.1/BA.2)	0.29/0.36/0.52	K417N, N440K, G446S, S477N, T478K, E484A, Q493K, G496S, Q498R, N501Y, Y505H	BA.1: P132Y BA1.1/BA.2: P132H*

Antiviral activity retained across various strains, including the current globally problematic omicron variant

* Inhibitory assessment using K90R and P132H enzyme confirmed no effect on drug efficacy

Dose regimen in clinical study vs target concentration

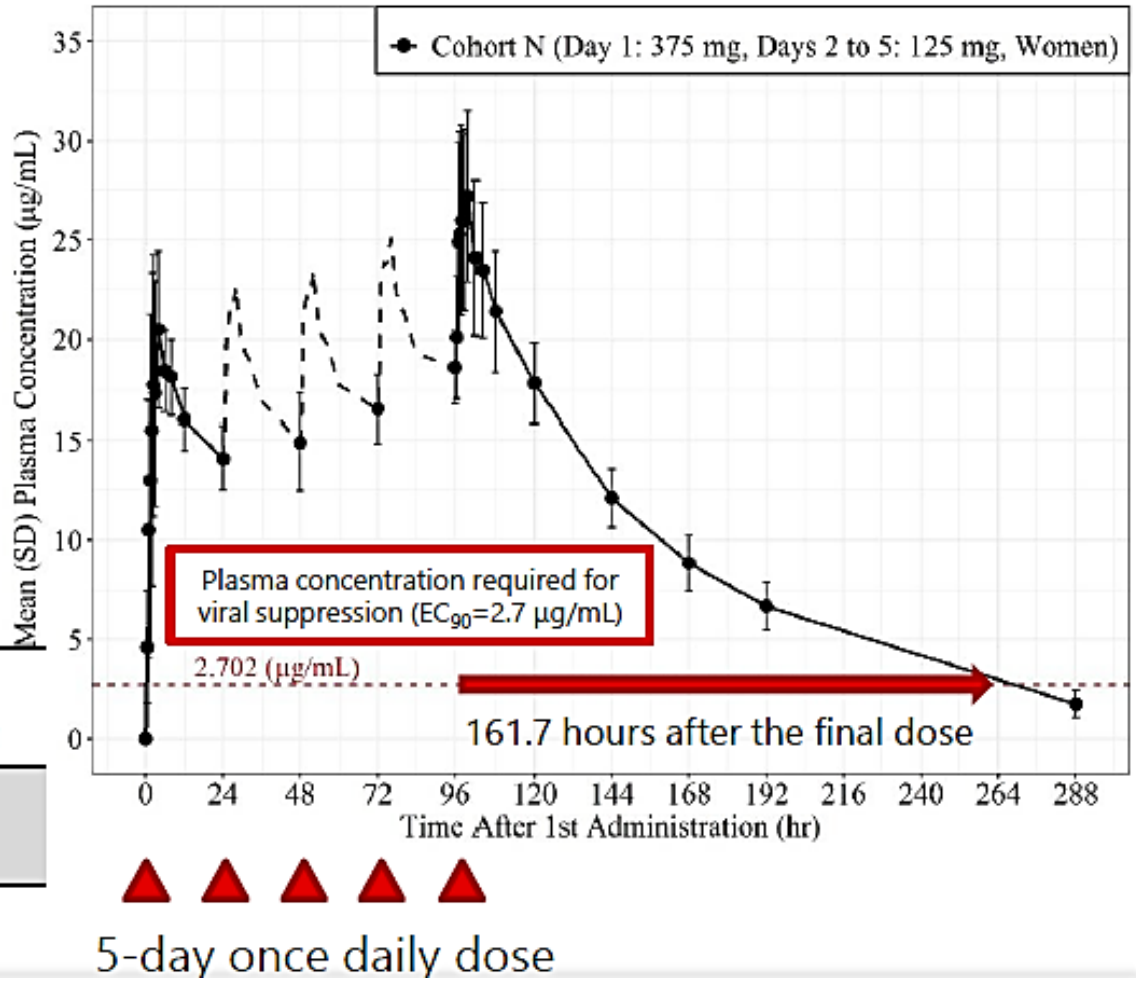
Dose and Administration

5-day once daily oral dose, loading dose (3 tablets) at Day 1 followed by 4-day maintenance doses (1 tablet)

- High dose: 750 mg (Day 1 loading), 250 mg (Day 2-5)
- Low dose: 375 mg (Day 1 loading), 125 mg (Day 2-5)

S-217622 has a long half-life of 51.4 hours.
The S-217622 concentration above its EC_{90} of 2.702 µg/mL* (accounted for plasma protein binding) can be maintained around 161.7 hours after the final dose (on Day 5).

*EC_{90} using human airway epithelial cells (MucilAir®)

SARS-CoV-2 variant	EC_{90} using MucilAir®	Plasma Protein binding	EC_{90} account for plasma protein binding
Delta strain (TY11-927)	0.117 µmol/L (0.0623 µg/mL)	97.7% @50 µg/mL	**2.702 µg/mL**

Plasma exposure of S-217622 in humans