

COVID-19 情報

ワクチンもモノクローナル抗体も無効

薬のチェック108号
Web資料

2023/6/23

薬のチェック編集委員会

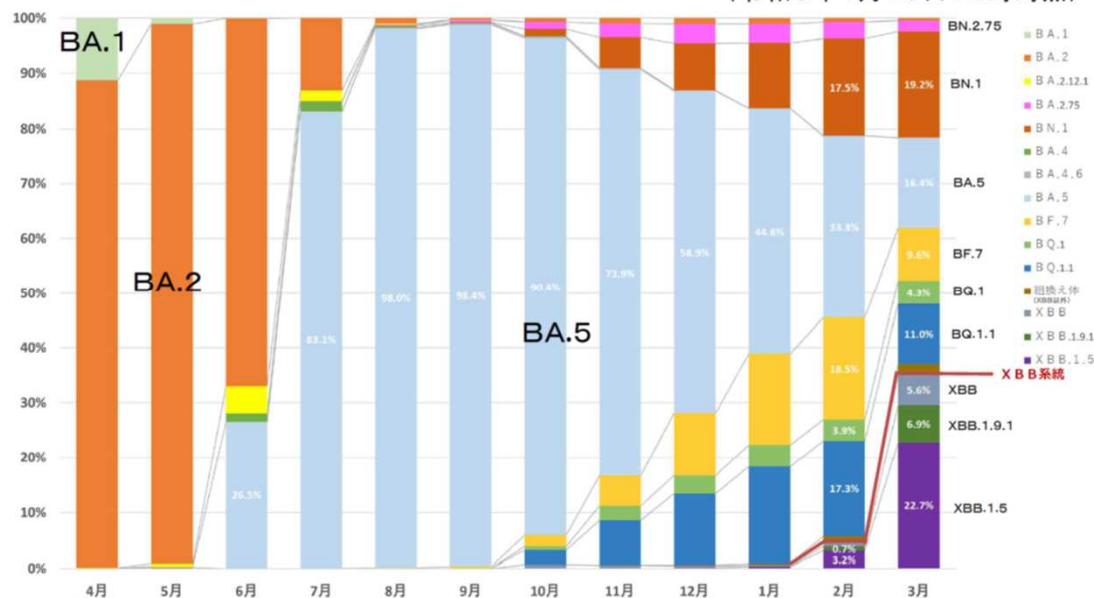
オミクロンXBB亜系株の推移：日本でも、3月で約50%に

https://www.bousai.metro.tokyo.lg.jp/res/projects/default_project/page/001/027/736/20230413_05.pdf

東京都の公表データ

ゲノム解析結果の推移（月別）

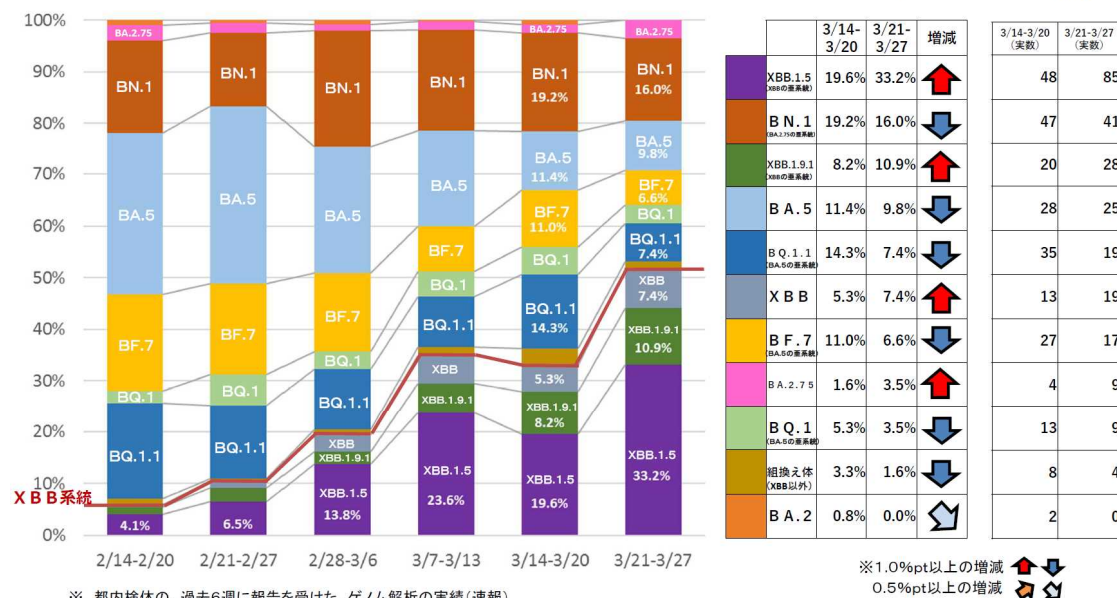
（令和5年4月13日12時時点）



※ 都内検体の、過去1年間に報告を受けた、ゲノム解析の実績
 ※ 追加の報告により、更新する可能性あり
 ※ BA.2とBA.2.12.1とBA.2.75とBN.1は別々に計上。BA.4とBA.4.6は別々に計上。BA.5とBF.7とBQ.1とBQ.1.1は別々に計上。XBB.1.5とXBB.1.9.1は別々に計上（XBBはXBB.1.5とXBB.1.9.1以外のXBB系統）。組換え体（XBB以外）はXBBとXBB.1.5とXBB.1.9.1を除く。

ゲノム解析結果の推移（週別）

（令和5年4月13日12時時点）



※ 都内検体の、過去6週に報告を受けた、ゲノム解析の実績（速報）
 ※ 追加の報告により、更新する可能性あり
 ※ BA.2とBA.2.12.1とBA.2.75とBN.1は別々に計上。BA.4とBA.4.6は別々に計上。BA.5とBF.7とBQ.1とBQ.1.1は別々に計上。XBB.1.5とXBB.1.9.1は別々に計上（XBBはXBB.1.5とXBB.1.9.1以外のXBB系統）。組換え体（XBB以外）はXBBとXBB.1.5とXBB.1.9.1を除く。

※ 1.0%pt以上の増減 ↑ ↓
 0.5%pt以上の増減 ↗ ↘

変異株

厚生科学審議会感染症部会での最終確認

国立感染症研究所によれば

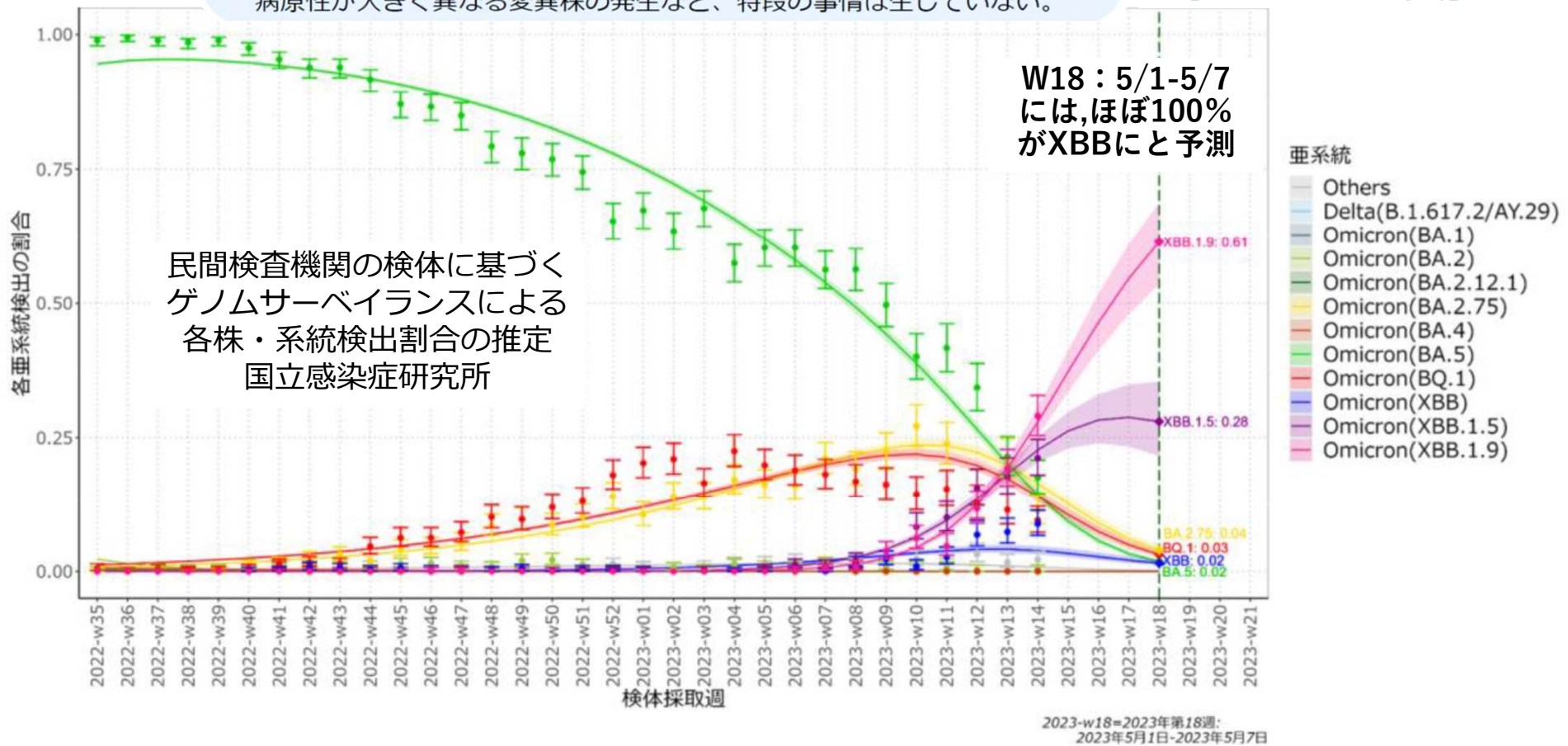
- 世界では、オミクロン株が支配的な状況が継続。
- 国内では、オミクロン株の亜系統であるXBB.1.5系統、XBB.1.9系統が占める割合が上昇と推計。

病原性が大きく異なる変異株の発生など、特段の事情は生じていない。

参考資料

新型コロナウイルス感染症（COVID-19）の
感染症法上の位置づけの変更について

<https://www.mhlw.go.jp/content/001091819.pdf>



SARS-CoV-2 sequences by variant,
The share of analyzed sequences in the preceding two weeks t

COVID-19 Data Explorer - Our World in Data

<https://ourworldindata.org/explorers/coronavirus-data-explorer?facet=none&country=JPN~GBR~USA&Interval=7-day+rolling+average&Relative+to+Population=true&Color+by+test+positivity=false&Metric=Variants>

Alpha Beta Gamma Delta Omicron (BA.2) Omicron (BA.1) Omicron (BA.5) Omicron (BA.4) Omicron (BA.2.12.1)
Omicron (BA.2.75) Omicron (BQ.1) Omicron (XBB) Omicron (XBB.1.5) Omicron (XBB.1.16) Recombinant Others

2023/6/5

英国



オミクロン
XBB亜株
合計

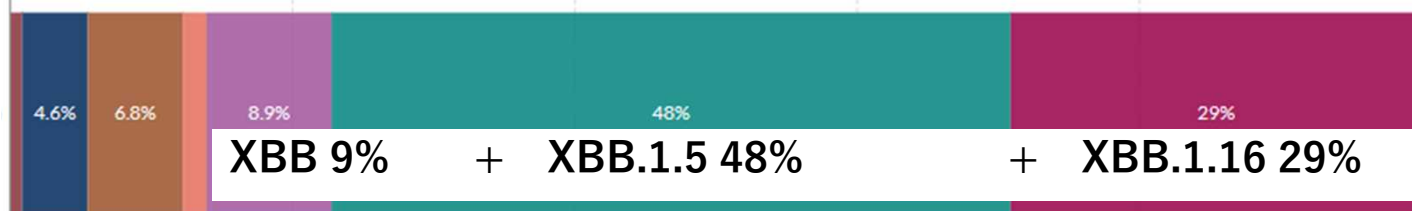
98%

米国



98%

日本



XBB 9% + XBB.1.5 48% + XBB.1.16 29% = 86%

= 86%

Source: GISAID, via CoVariants.org

Note: This share may not reflect the complete breakdown of cases, since only a fraction of all cases are sequenced. Recently-discovered or actively-monitored variants may be overrepresented, as suspected cases of these variants are likely to be sequenced preferentially or faster than other cases.

CC BY

▶ May 11, 2020

○ Jun 5, 2023

Omicron variant BQ.1.1: nirmatrelvir + ritonavir retains activity, monoclonal antibodies do not**Omicron変異株BQ1.1.に:nirmarelvir+ritonavirは効力維持、Mabは全滅**

The Sars-CoV-2 circulating in France as of December 2022 is the BQ.1.1 sublineage of Omicron variant BA.5 (1). To what degree does this affect the possible benefits of treatment with Sars-CoV-2-specific monoclonal antibodies or the combination of *nirmatrelvir + ritonavir* (Paxlovid[®])? A few studies have provided some answers to this question.

In vitro: monoclonal antibodies have no or barely any activity. A Japanese team tested several drugs in vitro for their neutralising activity against the BQ.1.1 sublineage of Omicron variant BA.5 (2).

Among the monoclonal antibodies targeting the spike protein of Sars-CoV-2, and known to have marked in-vitro neutralising activity against an ancestral strain of this virus, several had no or barely any effect on this sublineage: the combinations of *tixagevimab + cilgavimab* (Evusheld[®]) and *casirivimab + imdevimab* (Ronapreve[®]), and *sotrovimab* (Xevudy[®]) (2). They are therefore likely to have greatly reduced clinical efficacy against infections with sublineage BQ.1.1.

In contrast, *nirmatrelvir*, which inhibits a protease essential for viral replication, through a mechanism unrelated to the spike protein mutations that characterise Sars-CoV-2 variants, appeared to have a similar level of in-vitro activity against this sublineage as against an ancestral strain (2,3).

Retrospective studies using health databases: nirmatrelvir + ritonavir probably still useful when the Omicron variant is dominant. Two teams published the results of epidemiological studies on the use of the *nirmatrelvir + ritonavir* combination in the US in 2022, when Omicron was the dominant variant (4,5).

パキロビッドの有効性は、オミクロン株流行時の米国における2つの観察研究で指摘されている。

- ・モノクローナル抗体は、XBB、BQ1.1.には完全に無効：全滅
- ・抗ウイルス剤のニルマトレルビル（パキロビッド）は効力を維持
- ・ただし、レムデシビル、モルヌピラビル（ラゲブリオ[®]）は無効化

Low neutralization of SARS-CoV-2 Omicron BA.2.75.2, BQ.1.1 and XBB.1 by parental mRNA vaccine or a BA.5 bivalent booster

Received: 31 October 2022

Chaitanya Kurhade^{1,7}, Jing Zou^{1,7}, Hongjie Xia¹, Mingru Liu², Hope C. Chang², Ping Ren^{1,2}, Xuping Xie^{1,7} & Pei-Yong Shi^{1,3,4,5,6}

二価ワクチンも、起源ウイルスに対する中和抗体を作るのみ。変異株には効かない

③ SARS-CoV-2既感染で、起源2~4回後+BA5二価

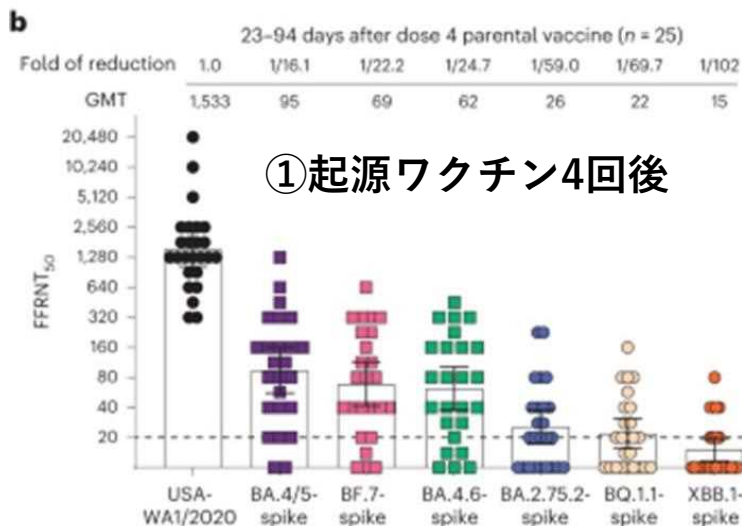
Abstract

The newly emerged severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) Omicron sublineages, including the BA.2-derived BA.2.75.2 and the BA.5-derived BQ.1.1 and XBB.1, have accumulated additional spike mutations that may affect vaccine effectiveness. Here we report neutralizing activities of three human serum panels collected from individuals 23–94 days after dose 4 of a parental mRNA vaccine; 14–32 days after a BA.5 bivalent booster from individuals with 2–4 previous doses of parental mRNA vaccine; or 14–32 days after a BA.5 bivalent booster from individuals with previous SARS-CoV-2 infection and 2–4 doses of parental mRNA vaccine. The results showed that a BA.5 bivalent booster elicited a high neutralizing titer against BA.4/5 measured at 14–32 days after boost; however, the BA.5 bivalent booster did not produce robust neutralization against the newly emerged BA.2.75.2, BQ.1.1 or XBB.1. Previous infection substantially enhanced the magnitude and breadth of BA.5 bivalent booster-elicited neutralization. Our data support a vaccine update strategy that future boosters should match newly emerged circulating SARS-CoV-2 variants.

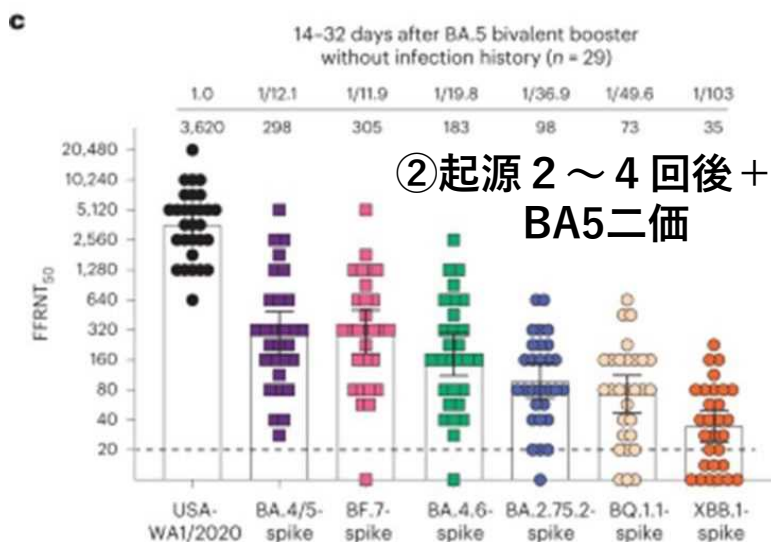
- ①起源ワクチン4回後
- ②起源2~4回後+BA5二価
- ③起源2~4回後+BA5二価 (SARS-CoV-2既感染)

を比較：

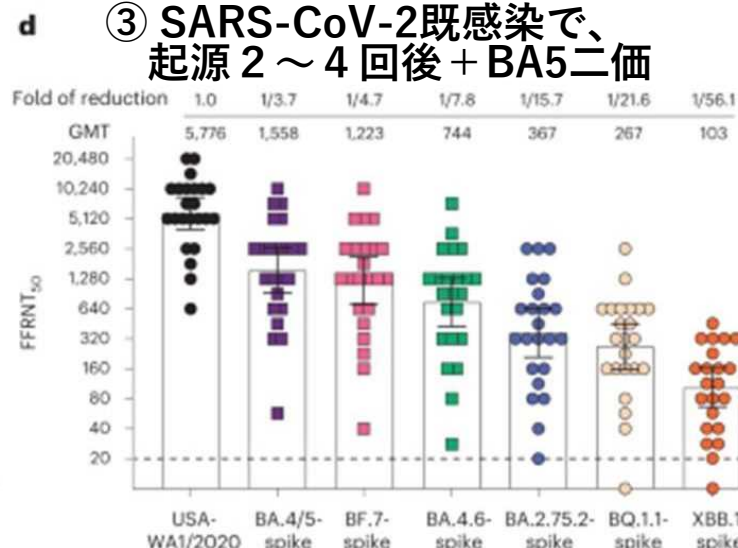
- ・ BA.5 二価Vaxは、新しいBQ.1.1、XBB.1 に対して中和抗体を作らず。
- ・ 変異が新しいほど、産生少ない。
- ・ 既感染者は未感染より産生多い。



①起源ワクチン4回後



②起源2~4回後+BA5二価



9) Kurhade C, Zou J, Xia H et al <https://pubmed.ncbi.nlm.nih.gov/36473500/>
 Low neutralization of SARS-CoV-2 Omicron BA.2.75.2, BQ.1.1 and XBB.1 by parental mRNA vaccine or a BA.5 bivalent booster.
 Nat Med. 2023 Feb;29(2):344-347. doi: 10.1038/s41591-022-02162-x. PMID: 36473500

10) Wang Q, Iketani S, Li Z et al. <https://pubmed.ncbi.nlm.nih.gov/36580913/>

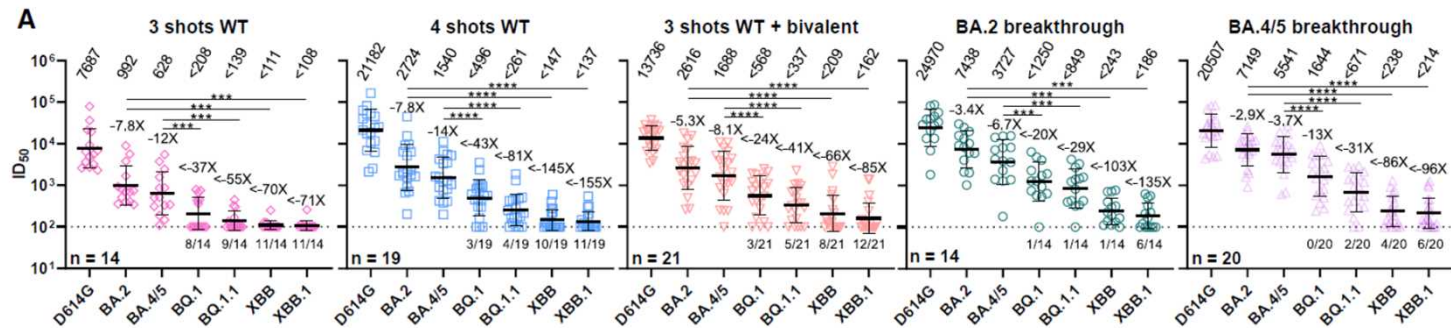
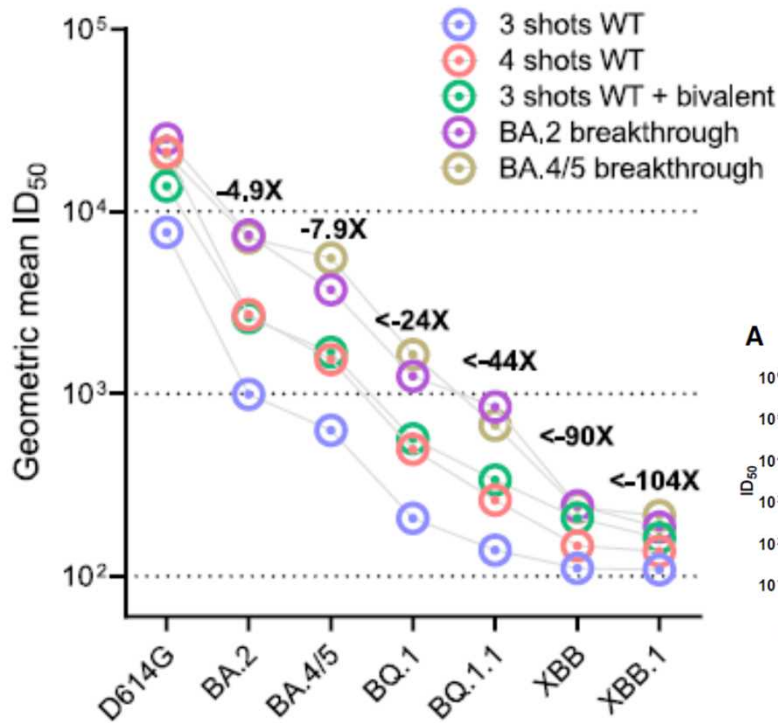
Alarming antibody evasion properties of rising SARS-CoV-2 BQ and XBB subvariants.

Cell. 2023 Jan 19;186(2):279-286.e8. doi: 10.1016/j.cell.2022.12.018. Epub 2022 Dec 14. PMID: 36580913

ハイライト

- ・ BQ.1、BQ.1.1、XBB、XBB.1 は、最強の耐性変異株である。
- ・ 二価ブースターを含めてワクチンによる中和抗体価は著しく低い。
- ・ モノクローナル抗体はすべて変異株に無効となった。
- ・ これら変異株のACE2受容体への親和性は起源ウイルスと同程度。

Neutralization by sera from 5 cohorts

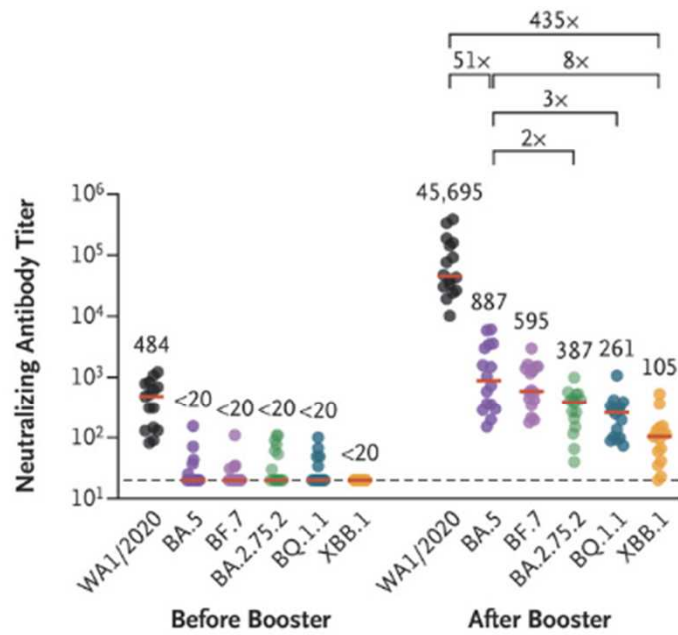


Substantial Neutralization Escape by SARSCoV-2 Omicron Variants BQ.1.1 and XBB.1

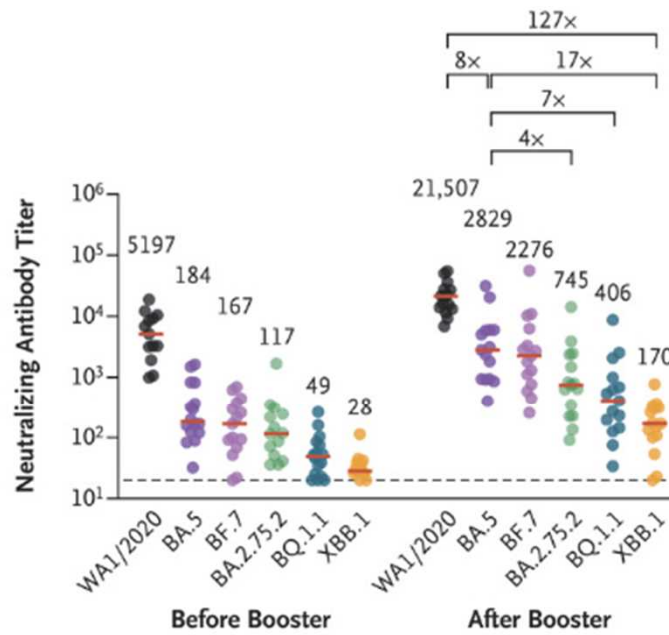
11) Miller J et al NEJM 2023 Feb 16;388(7):662-664. <https://pubmed.ncbi.nlm.nih.gov/36652339/>

doi: 10.1056/NEJMc2214314. Epub 2023 Jan 18. PMID: 36652339

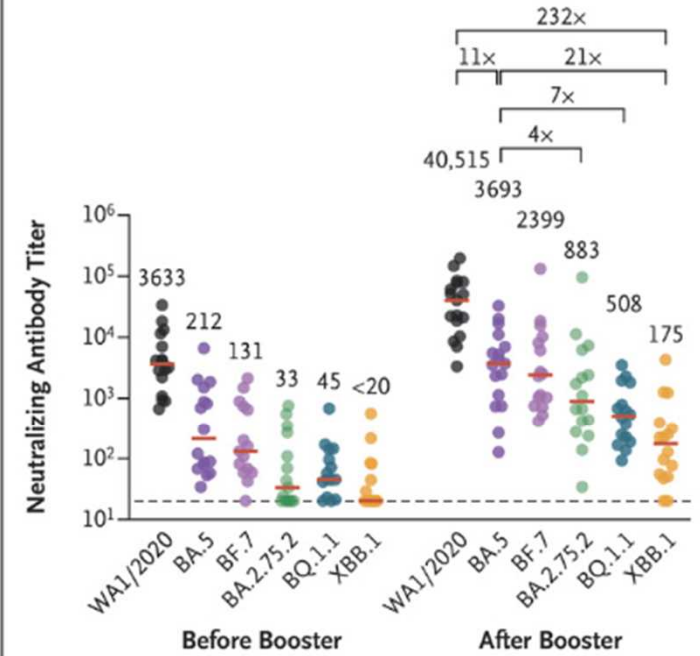
B Neutralizing Antibody Titers before and after Receipt of Monovalent mRNA Booster (2021)



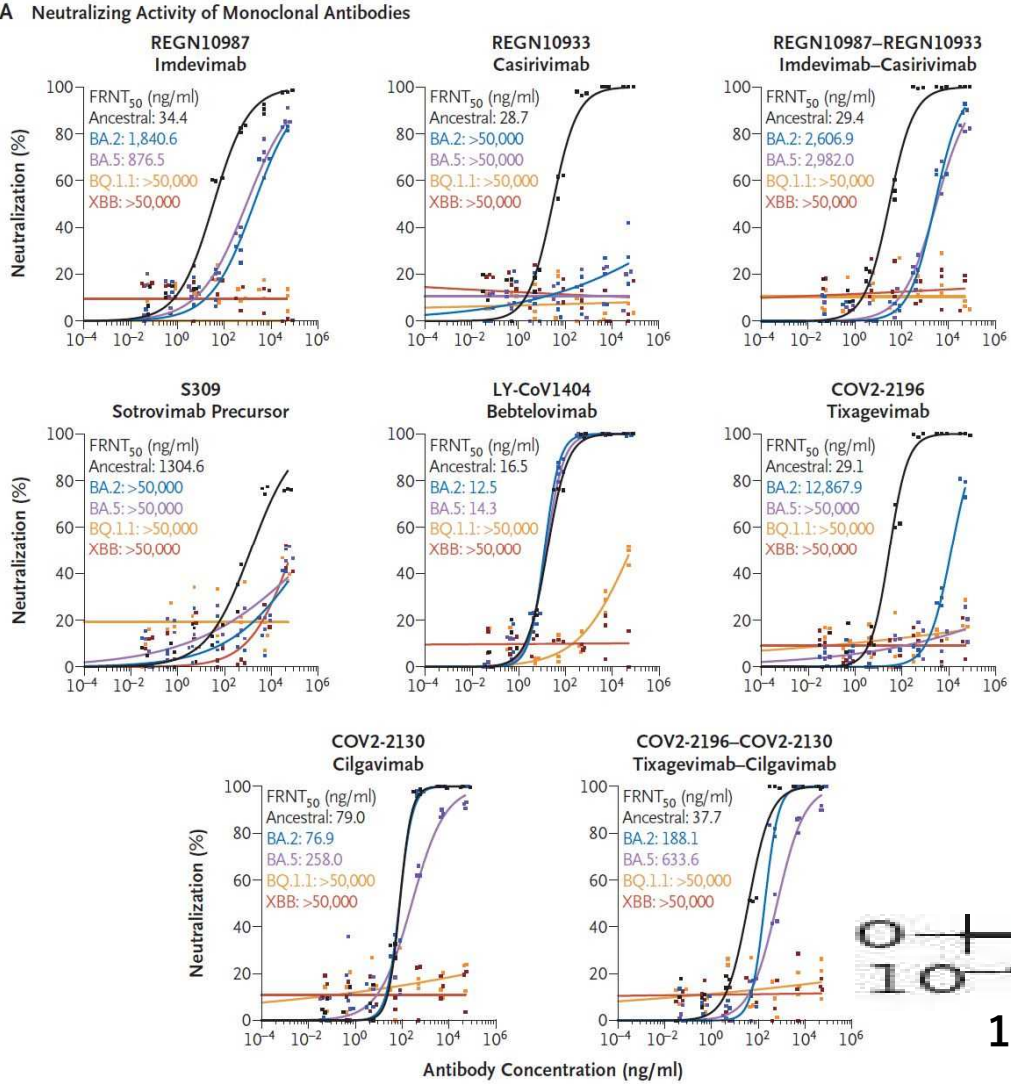
C Neutralizing Antibody Titers before and after Receipt of Monovalent mRNA Booster (2022)



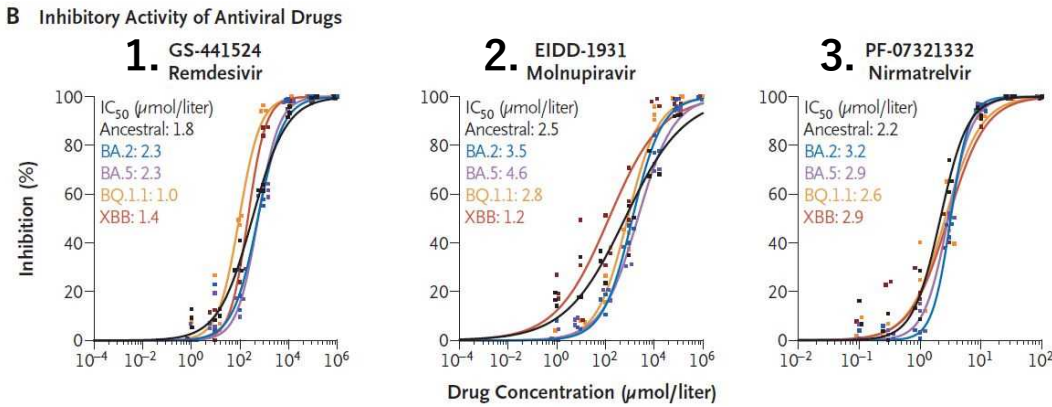
D Neutralizing Antibody Titers before and after Receipt of Bivalent mRNA Booster (2022)



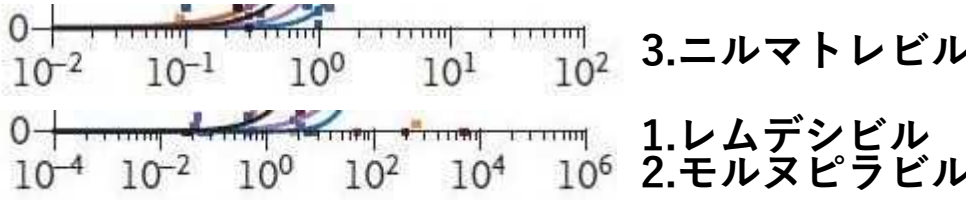
SARS-CoV-2各種変異株、とくにBQ, XBB などに対するモノクローナル抗体と抗ウイルス剤の阻害効果



12) Imai M et al. Efficacy of Antiviral Agents against Omicron Subvariants BQ.1.1 and XBB <https://pubmed.ncbi.nlm.nih.gov/36476720/>
 NEJM 2023 Jan 5;388(1):89-91. doi: 10.1056/NEJMc2214302.

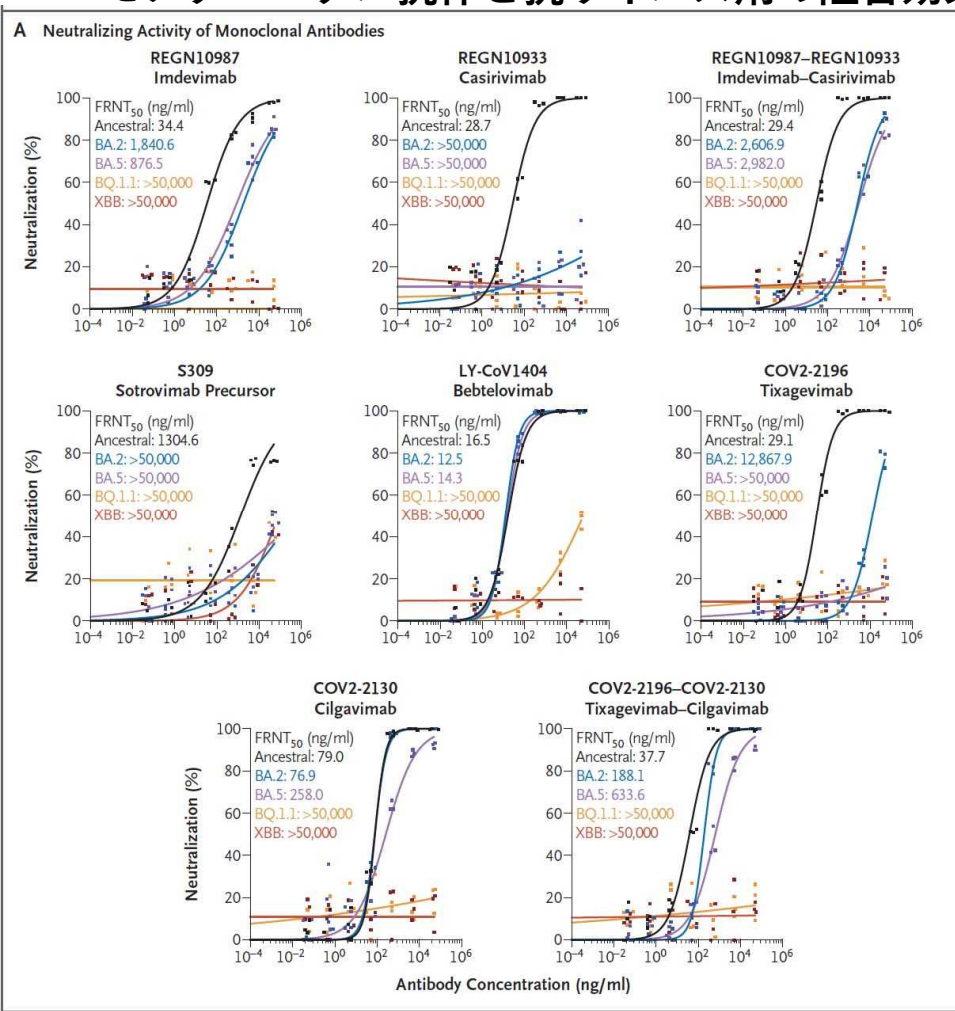


横軸のスケールが全く異なることに注意



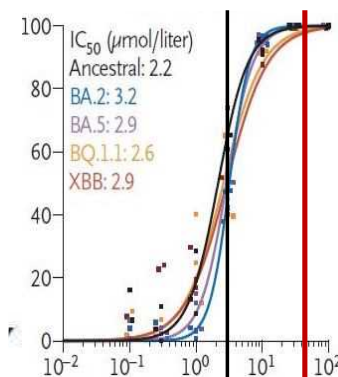
1.と2.の横軸スケールを3.ニルマトレルビルの横軸に合わせると

SARS-CoV-2各種変異株、とくにBAQなどに対する モノクローナル抗体と抗ウイルス剤の阻害効果



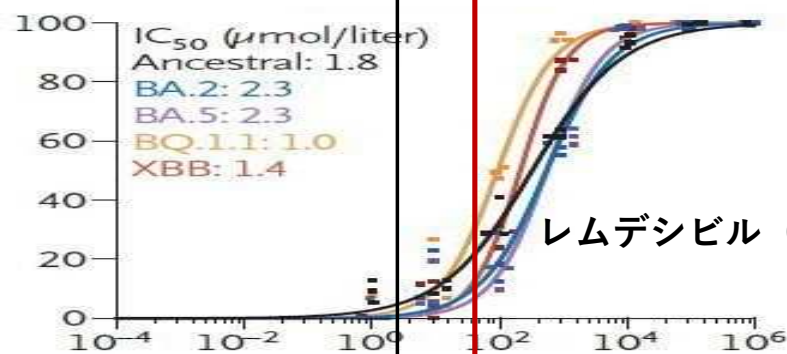
ニルマトレルビル (パキロビッド)

3剤の
濃度の
スケールを
揃えると

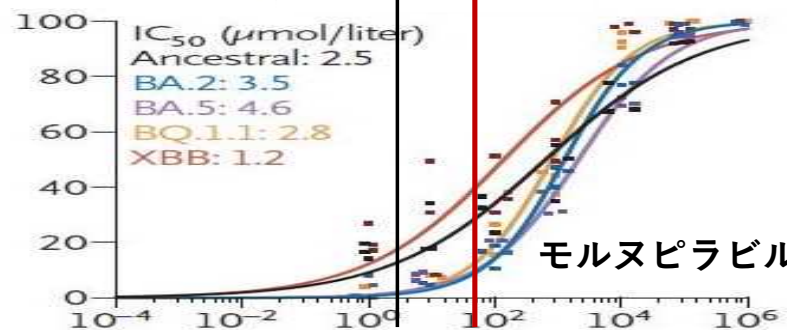


実質、有効なのは
ニルマトレルビル
(パキロビッド)
のみ

Inhibition (%)



レムデシビル (ベクルリー)



モルヌピラビル (ラゲブリオ)

モルヌピラビルでCOVID-19患者の入院・死亡減らず と報じている。

16) Butler CC, et al. Molnupiravir plus usual care versus usual care alone as early treatment for adults with COVID-19 at increased risk of adverse outcomes (PANORAMIC): an open-label, platform-adaptive randomised controlled trial. Lancet. 2022 Dec 22. Online ahead of print.

<https://pubmed.ncbi.nlm.nih.gov/36566761/>

要旨（翻訳とまとめ：薬のチェック）

ワクチン接種済みの高リスクのCOVID-19患者に、通常ケアにモルヌピラビルを追加して入院と死亡が減少するかどうかを確認するために、英国で多施設、非遮蔽、ランダム化比較試験が実施された。対象者を通常ケア群と、通常ケア＋モルヌピラビル群（モルヌピラビル上乘せ群）に、ほぼ1：1にランダムに割り付けられた。

解析対象の99%は少なくとも1回はワクチンを接種し、93%は3回以上接種していた。ほぼ1：1にランダムに割り付けられ、発症から28日以内の全入院または死亡主要評価項目とした。解析対象者数と結果は以下のとおり。

モルヌピラビル上乘せ群（平均55.7歳）；105人/12,529人（0.84%）

通常ケア群（平均56.5歳）：98人/12,525人（0.76%）

補正オッズ比1.06、95%信頼区間0.81-1.41）であった。

重篤な有害事象は、モルヌピラビル上乘せ群50人/12,774人（0.39%）

通常ケア群45人/12,934人（0.35%）

で、モルヌピラビルに関連すると判断されたものはなかった。

モルヌピラビル元論文 <https://pubmed.ncbi.nlm.nih.gov/36566761/>

16) Butler CC, et al. Molnupiravir plus usual care versus usual care alone as early treatment for adults with COVID-19 at increased risk of adverse outcomes (PANORAMIC): an open-label, platform-adaptive randomised controlled trial. Lancet. 2022 Dec 22. Online ahead of print.

Background: The safety, effectiveness, and cost-effectiveness of molnupiravir, an oral antiviral medication for SARS-CoV-2, has not been established in vaccinated patients in the community at increased risk of morbidity and mortality from COVID-19. We aimed to establish whether the addition of molnupiravir to usual care reduced hospital admissions and deaths associated with COVID-19 in this population.

Methods: PANORAMIC was a UK-based, national, multicentre, open-label, multigroup, prospective, platform adaptive randomised controlled trial. Eligible participants were aged 50 years or older-or aged 18 years or older with relevant comorbidities-and had been unwell with confirmed COVID-19 for 5 days or fewer in the community. Participants were randomly assigned (1:1) to receive 800 mg molnupiravir twice daily for 5 days plus usual care or usual care only. A secure, web-based system (Spinnaker) was used for randomisation, which was stratified by age (<50 years vs ≥50 years) and vaccination status (yes vs no). COVID-19 outcomes were tracked via a self-completed online daily diary for 28 days after randomisation. The primary outcome was all-cause hospitalisation or death within 28 days of randomisation, which was analysed using Bayesian models in all eligible participants who were randomly assigned. This trial is registered with ISRCTN, number 30448031.

Findings: Between Dec 8, 2021, and April 27, 2022, 26 411 participants were randomly assigned, 12 821 to molnupiravir plus usual care, 12 962 to usual care alone, and 628 to other treatment groups (which will be reported separately). 12 529 participants from the molnupiravir plus usual care group, and 12 525 from the usual care group were included in the primary analysis population. The mean age of the population was 56.6 years (SD 12.6), and 24 290 (94%) of 25 708 participants had had at least three doses of a SARS-CoV-2 vaccine. Hospitalisations or deaths were recorded in 105 (1%) of 12 529 participants in the molnupiravir plus usual care group versus 98 (1%) of 12 525 in the usual care group (adjusted odds ratio 1.06 [95% Bayesian credible interval 0.81-1.41]; probability of superiority 0.33). There was no evidence of treatment interaction between subgroups. Serious adverse events were recorded for 50 (0.4%) of 12 774 participants in the molnupiravir plus usual care group and for 45 (0.3%) of 12 934 in the usual care group. None of these events were judged to be related to molnupiravir.

Interpretation: Molnupiravir did not reduce the frequency of COVID-19-associated hospitalisations or death among high-risk vaccinated adults in the community.

Funding: UK National Institute for Health and Care Research.

	Molnupiravir plus usual care	Usual care	Estimated treatment effect (95% BCI)	Estimated benefit (95% BCI)	Probability of superiority
Primary outcomes					
Hospitalisations	103	96
Deaths	3	5
Hospitalisation or death	105/12 529 (1%)	98/12 525 (1%)	1.06 (0.81-1.41)*	..	0.33*

Paxlovid Associated with Decreased Hospitalization Rate Among Adults with COVID-19 — United States, April–September 2022

19) Shah MM, Joyce B, Plumb ID et al. <https://pubmed.ncbi.nlm.nih.gov/36454693/>
MMWR Morb Mortal Wkly Rep. 2022 Dec 2;71(48):1531-1537. doi: 10.15585/mmwr.mm7148e2.PMID: 36454693

2022年4月1日から8月31日までの間に18歳以上で、COVID-19と診断された人が1,713,120人いた。このうち、699,848人(40.9%)が選択基準を満たした。診断後5日以内に198,927人にパキロビッドが使用され、500,921人には使用されなかった。

TABLE 1. Characteristics of persons eligible for Paxlovid (nirmatrelvir-ritonavir) by prescription receipt within 5 days after COVID-19 diagnosis — Cosmos,* United States, April–September 2022

Characteristic	No. (column %)		Standardized mean difference
	Paxlovid prescribed (n = 198,927)	Paxlovid not prescribed (n = 500,921)	
Age group, yrs			
18–35	20,543 (10.3)	113,716 (22.7)	–0.34
36–49	36,077 (18.1)	107,373 (21.4)	–0.08
50–64	66,929 (33.7)	147,274 (29.4)	0.09
≥65	75,378 (37.9)	132,558 (26.5)	0.25
Sex			
Female	122,921 (61.8)	316,677 (63.2)	–0.03
Male	75,984 (38.2)	184,184 (36.8)	0.03

19) Shah MM et al. MMWR Morb Mortal Wkly Rep. 2022;;71(48):1531-1537. <https://pubmed.ncbi.nlm.nih.gov/36454693/>

まとめ

既知の知見：パキロビッドは、軽度から中等度の入院していないCOVID-19の成人患者のうち重篤化リスクが高い場合に推奨されている抗ウイルス剤である。

本調査の追加知見：米国でCOVID-19と診断された成人（既感染者やワクチン既接種者含む）で、パキロビッドが、診断後5日以内に処方された人は、処方されなかった人より、診断後30日以内の入院率が51%低かった。

公衆衛生上の意味：パキロビッドは、特に高齢者や複数の基礎疾患を持つCOVID-19重症化リスクの高いグループで禁忌がない場合には、ワクチン接種に関係なく提供すべきである。

TABLE 2. Adjusted hazard ratios for COVID-19-associated hospitalization based on Paxlovid prescription receipt (exposure) — Cosmos,* United States, April–September 2022

Characteristic	Adjusted HR (95% CI) [†]	No. of participants	No. hospitalized	Events per 100,000 person-days		
				Overall	Exposed [§]	Unexposed [§]
Total	0.49 (0.46–0.53)	693,084	5,229	25.31	15.88	29.05
COVID-19 vaccination status [¶]						
Vaccinated (≥3 mRNA doses)	0.50 (0.45–0.55)	310,196	2,126	22.98	14.30	27.87
Vaccinated (2 mRNA doses)	0.50 (0.42–0.58)	149,498	1,086	24.37	16.37	26.92
Unvaccinated	0.50 (0.43–0.59)	170,789	1,477	29.05	19.60	31.08
UHC**						
0	0.89 (0.58–1.36)	52,592	106	6.73	6.51	6.83
1	0.57 (0.45–0.71)	200,116	503	8.40	6.46	9.03
≥2	0.47 (0.44–0.51)	440,376	4,620	35.29	20.56	41.57
Previous infection ^{††}						
No	0.48 (0.44–0.51)	589,147	4,715	26.86	16.12	31.53
Yes	0.76 (0.60–0.98)	103,937	514	16.56	13.54	17.20
Immunocompromised ^{§§}						
No	0.49 (0.45–0.53)	628,706	3,770	20.09	12.61	23.03
Yes	0.50 (0.44–0.58)	64,378	1,459	77.01	45.99	90.49

19) Shah MM et al. MMWR Morb Mortal Wkly Rep. 2022;71(48):1531-1537. <https://pubmed.ncbi.nlm.nih.gov/36454693/>

TABLE 2. Adjusted hazard ratios for COVID-19–associated hospitalization based on Paxlovid prescription receipt (exposure) — Cosmos,* United States, April–September 2022

Characteristic	Adjusted HR (95% CI) [†]	No. of participants	No. hospitalized	Events per 100,000 person-days		
				Overall	Exposed [§]	Unexposed [§]
Total	0.49 (0.46–0.53)	693,084	5,229	25.31	15.88	29.05
Age group, yrs						
18–49	0.59 (0.48–0.71)	275,930	886	10.73	6.99	11.68
50–64	0.40 (0.34–0.48)	211,940	1,032	16.30	7.90	20.10
≥65	0.53 (0.48–0.58)	205,214	3,311	54.56	29.72	68.80
By age group, yrs						
18–49						
Vaccinated (≥3 mRNA doses)	0.75 (0.53–1.06)	84,054	178	7.07	6.10	7.46
Vaccinated (2 mRNA doses)	0.53 (0.35–0.82)	70,159	198	9.43	6.20	10.16
Unvaccinated	0.54 (0.39–0.76)	97,637	417	14.29	9.09	15.13
1 UHC 合併症 1つだけ	0.91 (0.58–1.44)	109,620	157	4.78	4.11	4.91
≥2 UHC	0.54 (0.43–0.67)	166,310	729	14.67	8.35	16.54
50–64						
Vaccinated (≥3 mRNA doses)	0.41 (0.30–0.55)	98,699	284	9.61	5.28	12.11
Vaccinated (2 mRNA doses)	0.46 (0.33–0.63)	47,111	265	18.84	10.96	21.89
Unvaccinated	0.38 (0.27–0.53)	45,154	355	26.39	12.43	30.35
No UHC 合併症なし	1.11 (0.46–2.68)	32,519	25	2.56	2.87	2.46
1 UHC	0.30 (0.17–0.55)	53,493	109	6.80	2.45	8.72
≥2 UHC	0.40 (0.33–0.48)	125,928	898	23.91	11.04	30.26
≥65						
Vaccinated (≥3 mRNA doses)	0.51 (0.46–0.57)	127,443	1,664	44.02	24.51	57.35
Vaccinated (2 mRNA doses)	0.53 (0.43–0.65)	32,228	623	65.58	36.83	78.59
Unvaccinated	0.58 (0.47–0.72)	27,998	705	85.92	52.75	96.15
No UHC	0.84 (0.51–1.36)	20,073	81	13.50	10.34	15.49
1 UHC 合併症なし	0.63 (0.47–0.85)	37,003	237	21.47	13.66	26.77
≥2 UHC	0.51 (0.47–0.56)	148,138	2,993	68.58	37.33	85.48

Abbreviations: HR = hazard ratio; UHC = underlying health condition.

ただし、50歳未満で合併症が1つだけ、50歳以上でも合併症がない人に対しては無効であった。

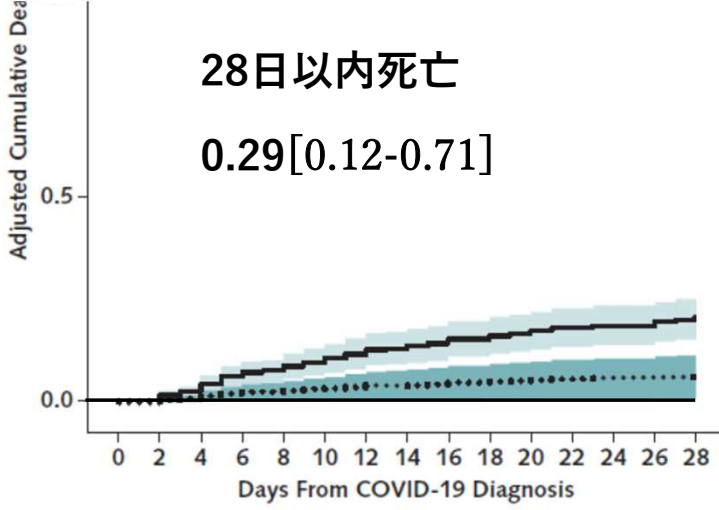
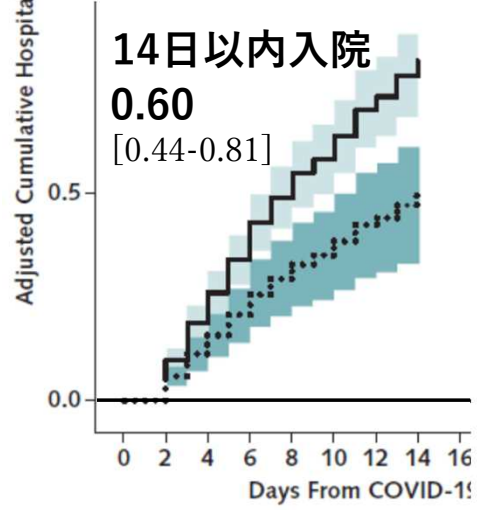
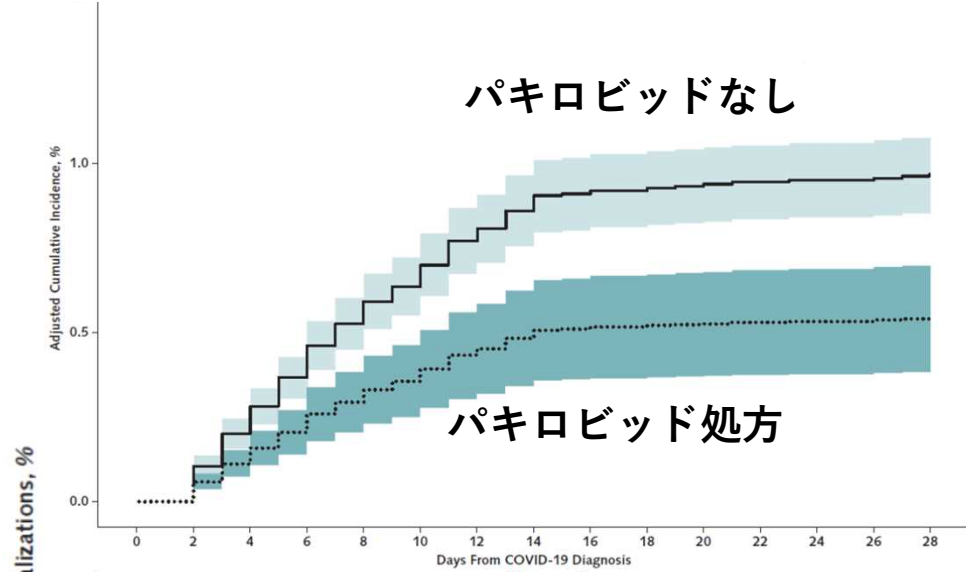
主アウトカム：14日以内入院または28日以内死亡

20) Dryden-Peterson S et al. <https://pubmed.ncbi.nlm.nih.gov/36508742/>
 2023;176(1):77-84. doi: 10.7326/M22-2141.

Annals of Internal Medicine

ORIGINAL RESEARCH

Nirmatrelvir Plus Ritonavir for Early COVID-19 in a Large U.S. Health System
 A Population-Based Cohort Study



調査方法：

2022年1月1日から7月17日のオミクロン流行時に、マサチューセッツ州とニューハンプシャー州で150万人の患者にケアを提供する大規模な医療システムにおいて調査を実施した。50歳以上でCOVID-19に感染し、パキロビッドに禁忌でない入院していない成人44,551人(90.3%がワクチンを3回以上接種)を対象とした。

結果：

研究期間中、12,541人(28%)にパキロビッドが処方され、32,010人(72%)には処方されなかった。パキロビッド群は高齢で、合併症が多く、ワクチン接種を受けている人が多かった。

入院または死亡の複合アウトカムは、パキロビッド群69人(0.55%)、非パキロビッド群で310人(0.97%)であった(調整リスク比0.56 [95% CI、0.42～0.75])。

入院の調整リスク比：0.60[0.44-0.81]

死亡の調整リスク比：0.29[0.12-0.71]

であった。

Abstract

Since its emergence in 2019, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has caused hundreds of millions of cases and continues to circulate globally. To establish a novel SARS-CoV-2 human challenge model that enables controlled investigation of pathogenesis, correlates of protection and efficacy testing of forthcoming interventions, 36 volunteers aged 18-29 years without evidence of previous infection or vaccination were inoculated with 10 TCID₅₀ of a wild-type virus (SARS-CoV-2/human/GBR/484861/2020) intranasally in an open-label, non-randomized study (ClinicalTrials.gov identifier [NCT04865237](https://clinicaltrials.gov/ct2/show/study/NCT04865237); funder, UK Vaccine Taskforce).

After inoculation, participants were housed in a high-containment quarantine unit, with 24-hour close medical monitoring and full access to higher-level clinical care. The study's primary objective was to identify an inoculum dose that induced well-tolerated infection in more than 50% of participants, with secondary objectives to assess virus and symptom kinetics during infection. All pre-specified primary and secondary objectives were met.

Two participants were excluded from the per-protocol analysis owing to seroconversion between screening and inoculation, identified post hoc. Eighteen (~53%) participants became infected, with viral load (VL) rising steeply and peaking at ~5 days after inoculation.

Virus was first detected in the throat but rose to significantly higher levels in the nose, peaking at ~8.87 log₁₀ copies per milliliter (median, 95% confidence interval (8.41, 9.53)). Viable virus was recoverable from the nose up to ~10 days after inoculation, on average. There were no serious adverse events. Mild-to-moderate symptoms were reported by 16 (89%) infected participants, beginning 2-4 days after inoculation, whereas two (11%) participants remained asymptomatic (no reportable symptoms). Anosmia or dysosmia developed more slowly in 15 (83%) participants. No quantitative correlation was noted between VL and symptoms, with high VLs present even in asymptomatic infection.

All infected individuals developed serum spike-specific IgG and neutralizing antibodies. Results from lateral flow tests were strongly associated with viable virus, and modeling showed that twice-weekly rapid antigen tests could diagnose infection before 70-80% of viable virus had been generated.

Thus, with detailed characterization and safety analysis of this first SARS-CoV-2 human challenge study in young adults, viral kinetics over the course of primary infection with SARS-CoV-2 were established, with implications for public health recommendations and strategies to affect SARS-CoV-2 transmission. Future studies will identify the immune factors associated with protection in those participants who did not develop infection or symptoms and define the effect of prior immunity and viral variation on clinical outcome.

要旨 Killingley B et al. Nat Med. 2022 May;28(5):1031-41 <https://pubmed.ncbi.nlm.nih.gov/35361992/> doi: 10.1038/s41591-022-01780-9.

2019年の出現以来、重症急性呼吸器症候群コロナウイルス-2 (SARS-CoV-2) は数億人に発症させ、世界中に蔓延し続けている。病因研究や感染制御との関係、今後必要になる治療介入の効力試験を容易にすることを目的として SARS-CoV-2のヒト感染実験モデルを確立するために、感染歴やワクチン接種歴のない18~29歳のボランティア 36人に対して、野生型ウイルス (SARS-CoV-2/human/GBR/484861/2020) TCID₅₀ の10単位を非盲検非ランダム的に鼻腔内に接種した (ClinicalTrials.gov NCT04865237 ; 資金提供者、英国ワクチンタスクフォース)。

接種後、参加者は高度封じ込め隔離室に収容され、24時間の厳重な医学的監視が行われ、高度な臨床ケアを受けた。事前に設定した研究の主目的は、十分に忍容性のある感染を参加者の50%以上に誘発する接種量を特定することであり、副次目的は感染中のウイルス量と症状の変化 (動態) を評価することとした。

事前に指定された主目的と副次目的はすべて達成された。スクリーニング時と接種の間にセロコンバージョンを起こした2人はプロトコール適合解析 (perprotocol analysis) から除外した。34人中18人 (約53%) が感染し、ウイルス量 (VL) は急激に上昇し、接種後約5日でピークに達した。ウイルスは最初に喉で検出されたが、鼻で著しく高いレベルに上昇し、中央値で約 8.87 log₁₀ コピー/mLのピークに達した (95% 信頼区間 (8.41、9.53))。生きたウイルスは接種後平均10日間、鼻から回収できた。重篤な有害事象はなかった。

感染者18人中16人 (89%) が、接種後2~4日から軽度から中等度の症状を報告したが、2人 (11%) は無症状のままであった (症状の報告がなかった)。15人 (83%) に嗅覚脱失または嗅覚障害が起きたが遅くに発症した。ウイルス量と症状の間には相関関係は認められず、無症候性感染でもウイルス量は多かった。すべての感染者は、血清スパイクに特異的なIgG抗体と中和抗体が発現した。

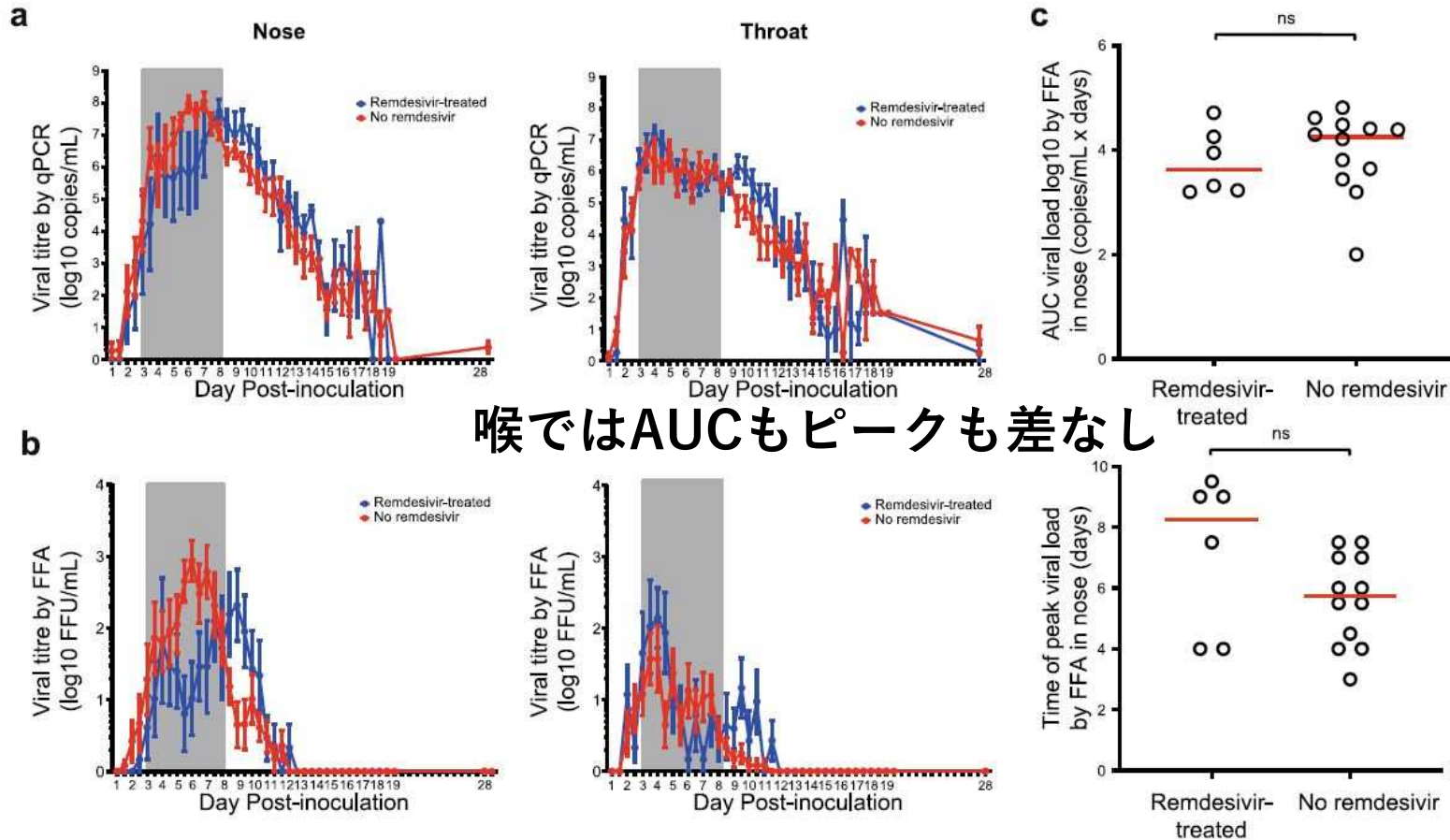
迅速抗原検査 (lateral flow test) の結果は生存ウイルスと強く関連しており、モデリングにより、週2回の迅速抗原検査により、生存ウイルスの70~80%が生成される前に感染を診断できることが示された。

したがって、若年成人を対象としたこの最初のSARS-CoV-2ヒト感染実験で得られた詳細な感染の特徴と安全性が分析されたことで、SARS-CoV-2の一次感染過程におけるウイルス量の変化 (動態) が確立されたので、SARS-CoV-2の感染に関わる公衆衛生上の推奨や戦略の考察に役立つと考える。

今後は、感染や症状を発症しなかった人における防御の免疫因子を特定し、臨床転帰に影響する事前の免疫状態やウイルスの違いの影響を明らかにするための研究を実施する予定である。

感染実験による詳細なウイルス量の比較 レムデシビルはウイルス量を減らさない

Killingley B et al. doi: 10.1038/s41591-022-01780-9.
<https://pubmed.ncbi.nlm.nih.gov/35361992/>



喉ではAUCもピークも差なし

鼻の
ウイルス濃度
AUCは差なし

レムデシビルで、
鼻のウイルス濃度
がピークに到達する
日が遅くなる

Extended Data Fig. 3 | Pre-emptive remdesivir treatment is associated with no statistically significant changes in VL following human SARS-CoV-2 challenge. Healthy adult volunteers were challenged intranasally with SARS-CoV-2. VL was measured twice-daily in nose and throat swab samples by (a) qPCR and (b) FFA from remdesivir-treated (blue) and untreated (red) participants (n=6 biologically independent subjects). Results are expressed as means +/- S.E.M. Grey shading indicates the average 5-day remdesivir treatment period. AUC of VL by FFA (c) and days to peak VL by FFA (d) were compared between remdesivir-treated and untreated groups using two-sided Mann-Whitney tests (ns=non-significant).

Early Remdesivir to Prevent Progression to Severe Covid-19 in Outpatients

Gottlieb RL et al. NEJM 2022; 386(4):305-15
<https://pubmed.ncbi.nlm.nih.gov/34937145/>

レムデシビルが軽症COVID-19の入院を防止したとする試験結果でも、ウイルスは変化なし。したがって重症化（入院）の減少はウイルス減少とは無関係→免疫抑制によるみかけの症状軽減（タミフル同様）のためかも

引用文献外DOI: 10.1056/NEJMoa2116846

* Baseline stratification factors were residence in a skilled nursing facility (yes or no), age (<60 years or ≥60 years), and country (United States or outside the United States). Covid-19 denotes coronavirus disease 2019, and NC not calculated.

† Of the eight patients who were adolescents, none had a Covid-19–related hospitalization or death from any cause by day 28.

‡ Data are shown for patients who underwent randomization, received at least one infusion of remdesivir or placebo, and met **eligibility criteria as defined** in protocol amendment 2 or later.

§ The analysis was conducted post hoc.

¶ The value is the least-squares mean. ??

|| On the FLU-PRO (Influenza Patient-Reported Outcome) Plus questionnaire, which was adapted for patients with Covid-19, alleviation of Covid-19 symptoms was defined as mild or absent symptoms.

** The value is the rate ratio.

Table 2. Efficacy Calculated with the Use of a Cox Proportional-Hazards Model with Baseline Stratification Factors as Covariates.*

End Point	Remdesivir (N = 279)	Placebo (N = 283)	Hazard Ratio (95% CI)	P Value
Primary efficacy end point				
Covid-19–related hospitalization or death from any cause by day 28 — no. (%)†	2 (0.7)	15 (5.3)	0.13 (0.03 to 0.59)	0.008
Secondary efficacy end points				
Covid-19–related hospitalization or death from any cause by day 14 — no. (%)	2 (0.7)	15 (5.3)	0.13 (0.03 to 0.59)	
Covid-19–related medically attended visit or death from any cause — no./total no. (%)‡				
Day 14	2/246 (0.8)	20/252 (7.9)	0.10 (0.02 to 0.43)	
Day 28	4/246 (1.6)	21/252 (8.3)	0.19 (0.07 to 0.56)	
Death from any cause by day 28 — no.	0	0	NC	
Hospitalization for any cause by day 28 — no. (%)§	5 (1.8)	18 (6.4)	0.28 (0.10 to 0.75)	
Time-weighted average change in nasopharyngeal SARS-CoV-2 viral load from baseline to day 7 — log ₁₀ copies/ml	-1.24	-1.14	0.07 (-0.10 to 0.24)¶	
D7のウイルス変化量：有意差なし				
Alleviated baseline Covid-19 symptoms, according to FLU-PRO Plus questionnaire — no./total no. (%) 				
Questionnaire completed before infusion on day 1	23/66 (34.8)	15/60 (25.0)	1.41 (0.73 to 2.69)**	
Questionnaire completed on day 1, either before or after infusion — no./total no. (%)§	61/169 (36.1)	33/165 (20.0)	1.92 (1.26 to 2.94)**	