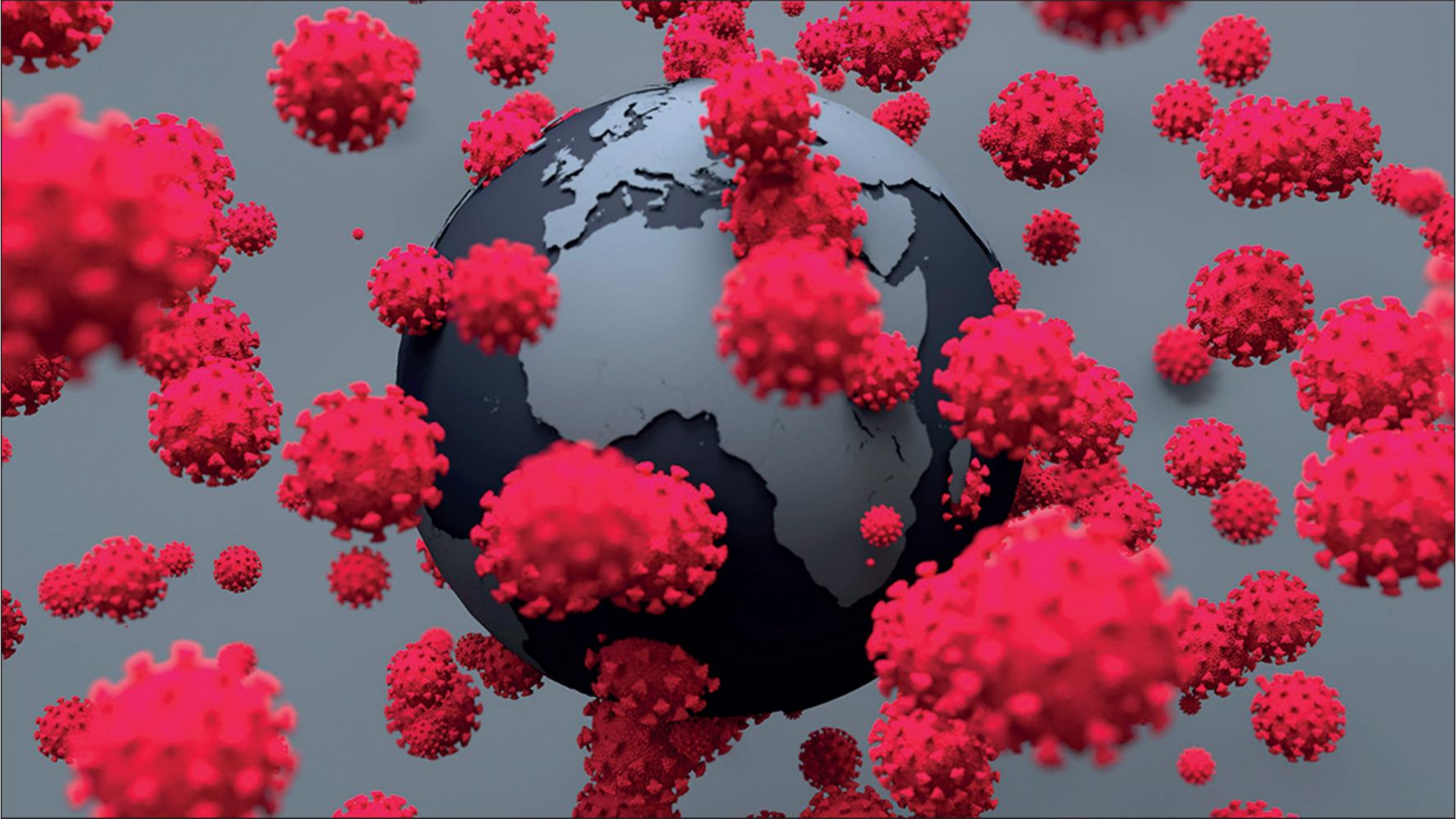
Antivirale middelen

tegen COVID-19

Marc Van Ranst
UZ/KU Leuven



TIMELINE OF THE VARIANTS OF CORONAVIRUS

Sources: WHO, National Collaborating Centre for Infectious Diseases, Centers for Disease Control and Prevention

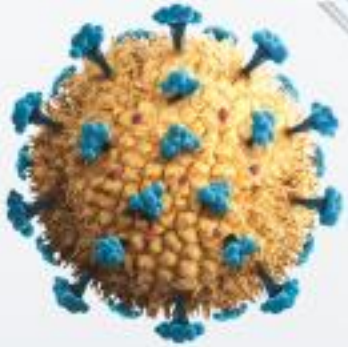
* There are indications that Omicron was already spreading in western Europe before being identified in southern Africa. The RIVM health institute said it found Omicron in samples dating from November 19 and 23.

1 ALPHA B.1.1.7

TYPE OF VARIANT: **Variant of concern**
EARLIEST DOCUMENTED ON: **September 2020**
EARLIEST DOCUMENTED IN: **United Kingdom**
SPIKE MUTATIONS: **11** 50% more transmissible than earlier strains

2 BETA B.1.351

TYPE OF VARIANT: **Variant of concern**
EARLIEST DOCUMENTED ON: **May 2020**
EARLIEST DOCUMENTED IN: **South Africa**
SPIKE MUTATIONS: **10**



3 GAMMA B.1.1.248

TYPE OF VARIANT: **Variant of concern**
EARLIEST DOCUMENTED ON: **November 2020**
EARLIEST DOCUMENTED IN: **Brazil**
SPIKE MUTATIONS: **12**

4 DELTA B.1.617.2

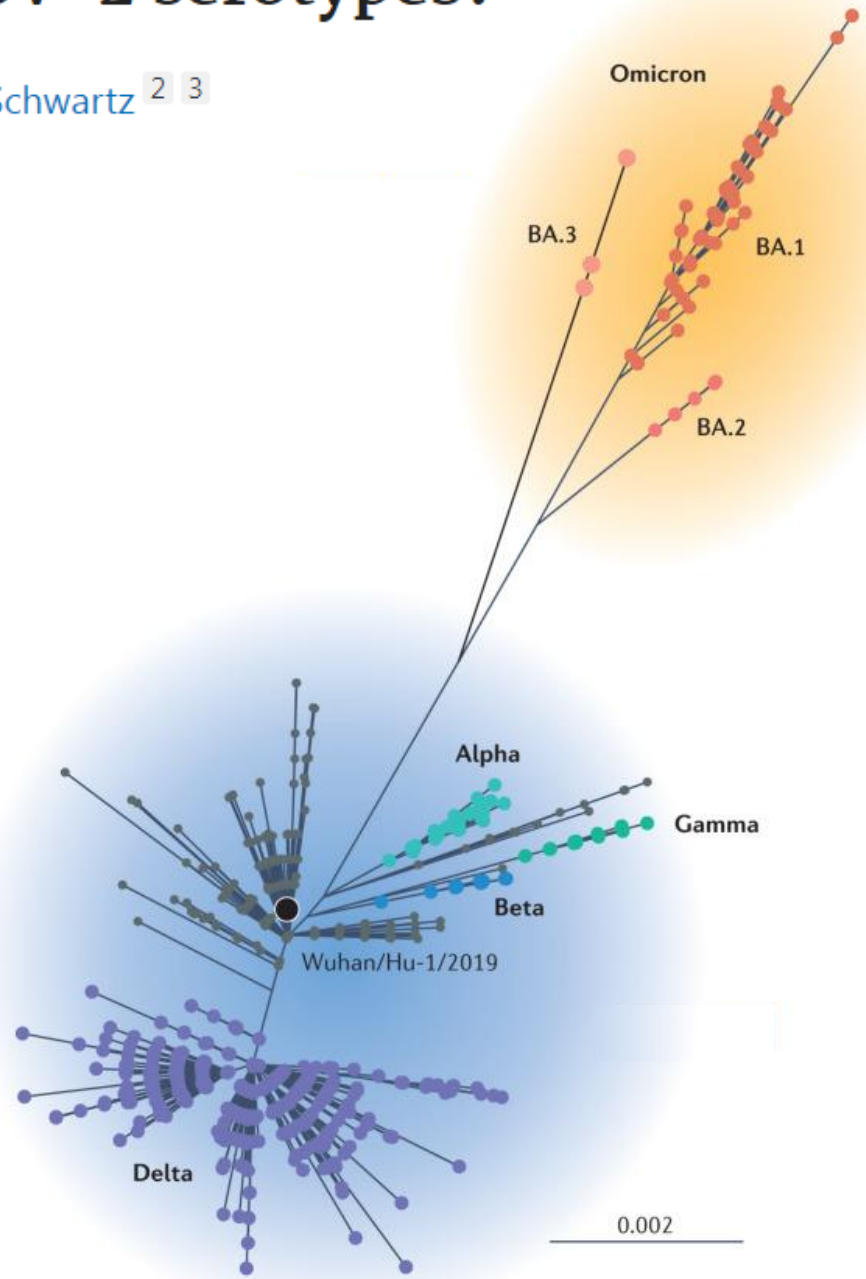
TYPE OF VARIANT: **Variant of concern**
EARLIEST DOCUMENTED ON: **October 2020**
EARLIEST DOCUMENTED IN: **India**
SPIKE MUTATIONS: **10** 60% more transmissible than the Alpha variant

5 OMICRON* B.1.1.5.29

TYPE OF VARIANT: **Variant of concern**
EARLIEST DOCUMENTED ON: **November 24, 2021**
EARLIEST DOCUMENTED IN: **Multiple countries**
South Africa first reported the case*
SPIKE MUTATIONS: **32**

Towards SARS-CoV-2 serotypes?

Etienne Simon-Loriere [1], Olivier Schwartz [2 3]



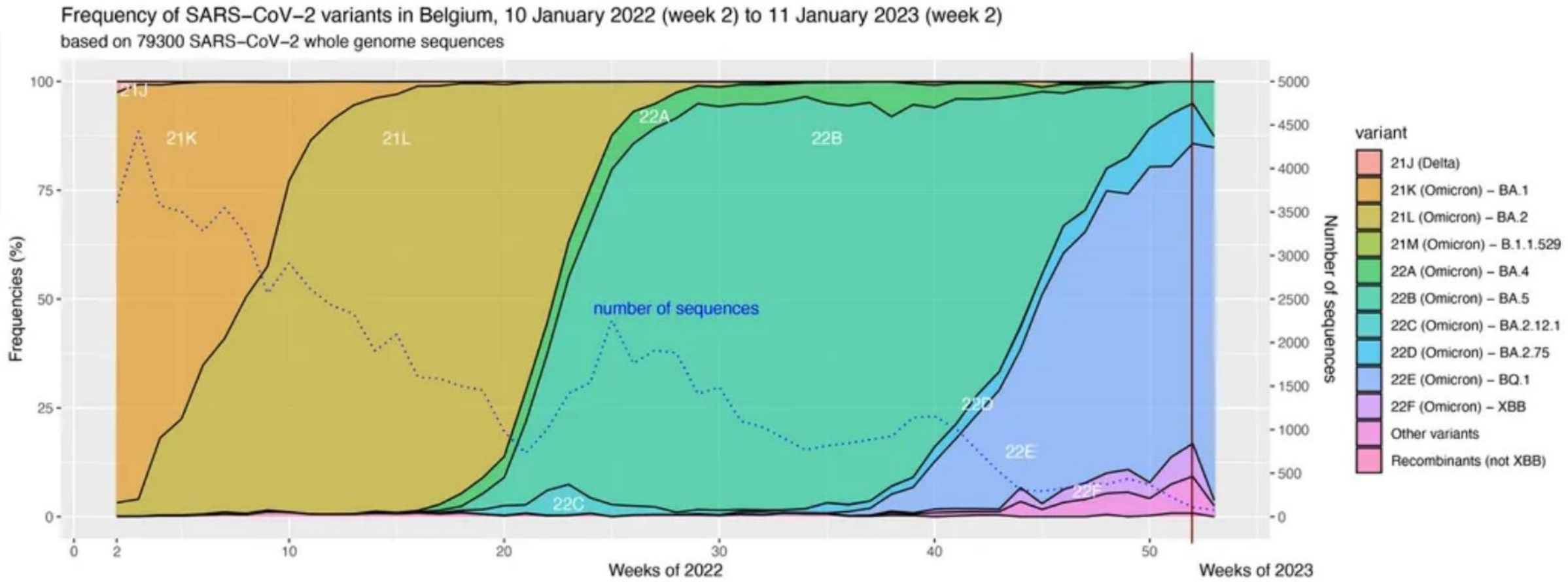
Serotype 2

Serotype 1

Nat Rev Microbiol . 2022 Apr;20(4):187-188. doi: 10.1038/s41579-022-00708

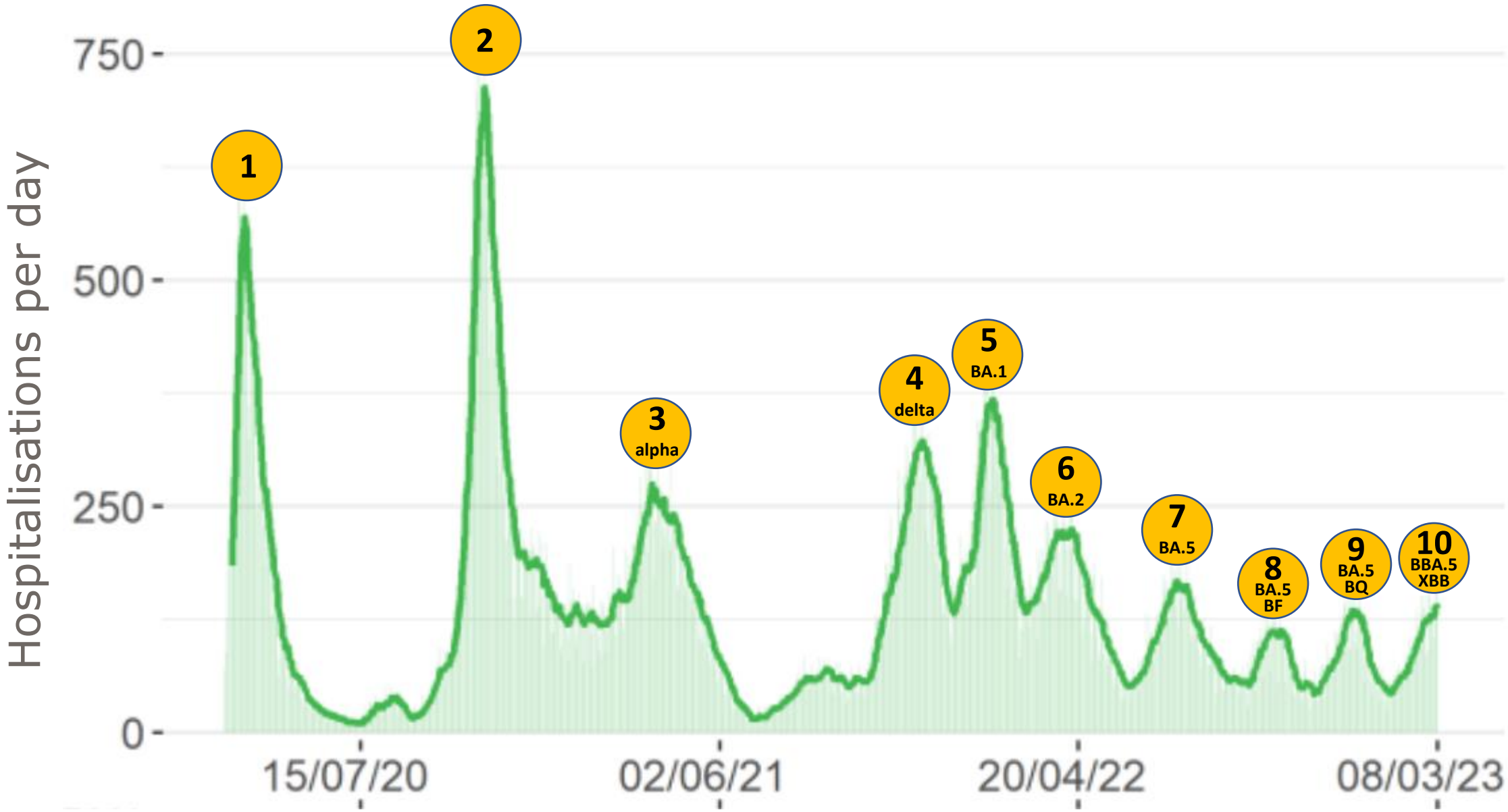
KU LEUVEN sciensano

National Coronavirus Reference Laboratory

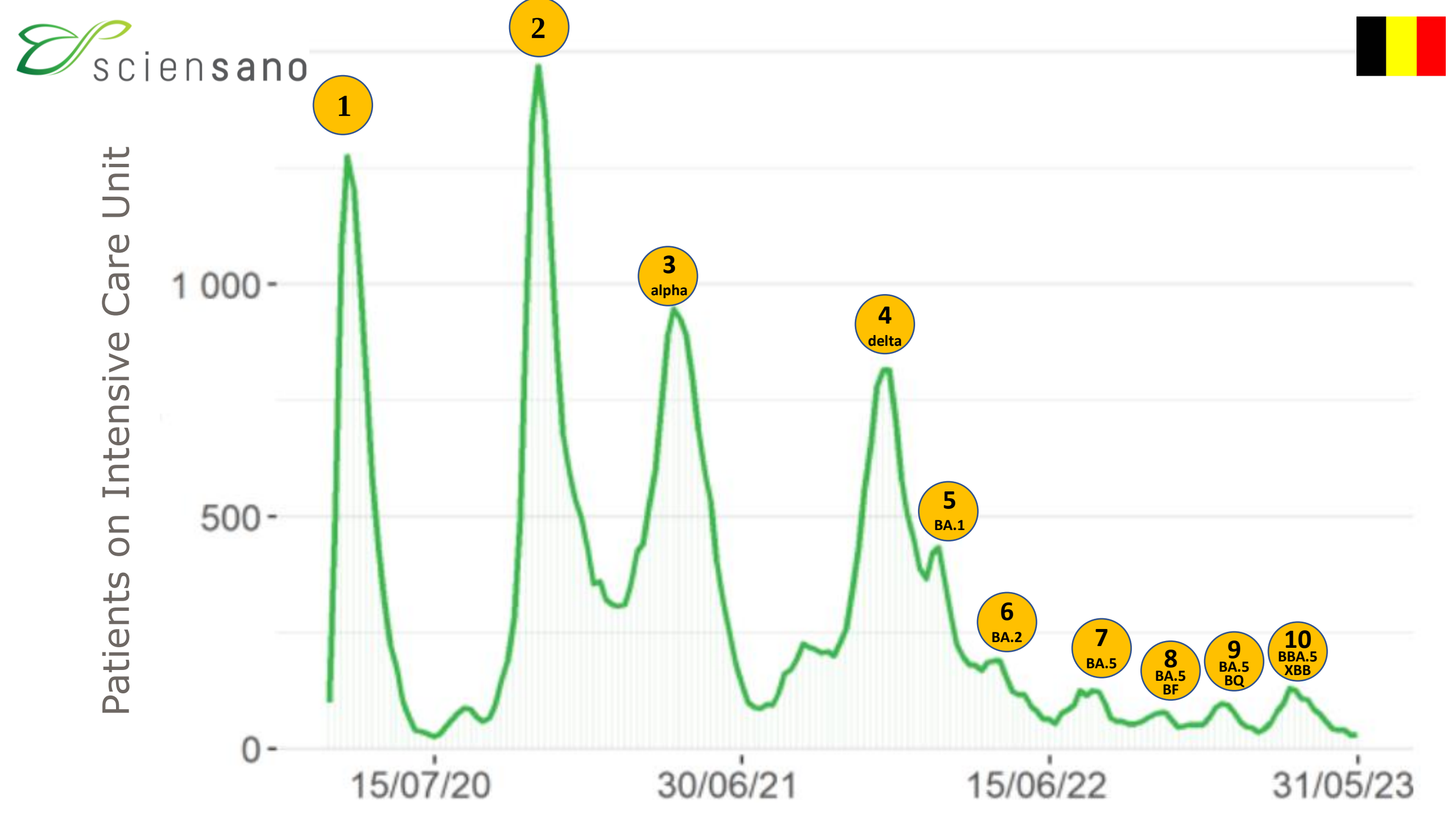


https://www.uzleuven.be/nl/laboratoriumgeneeskunde/genomic-surveillance-sars-cov-2-belgium

sciensano


Hospitalisations per day
750
500
250
0
1
2
3
alpha
4
delta
5
BA.1
6
BA.2
7
BA.5
8
BA.5
BF
9
BA.5
BQ
10
BBA.5
XBB
15/07/20
02/06/21
20/04/22
08/03/23

sciensano


Patients on Intensive Care Unit
1 000
500
0
15/07/20
30/06/21
15/06/22
31/05/23
1
2
3
alpha
4
delta
5
BA.1
6
BA.2
7
BA.5
8
BA.5
BF
9
BA.5
BQ
10
BBA.5
XBB

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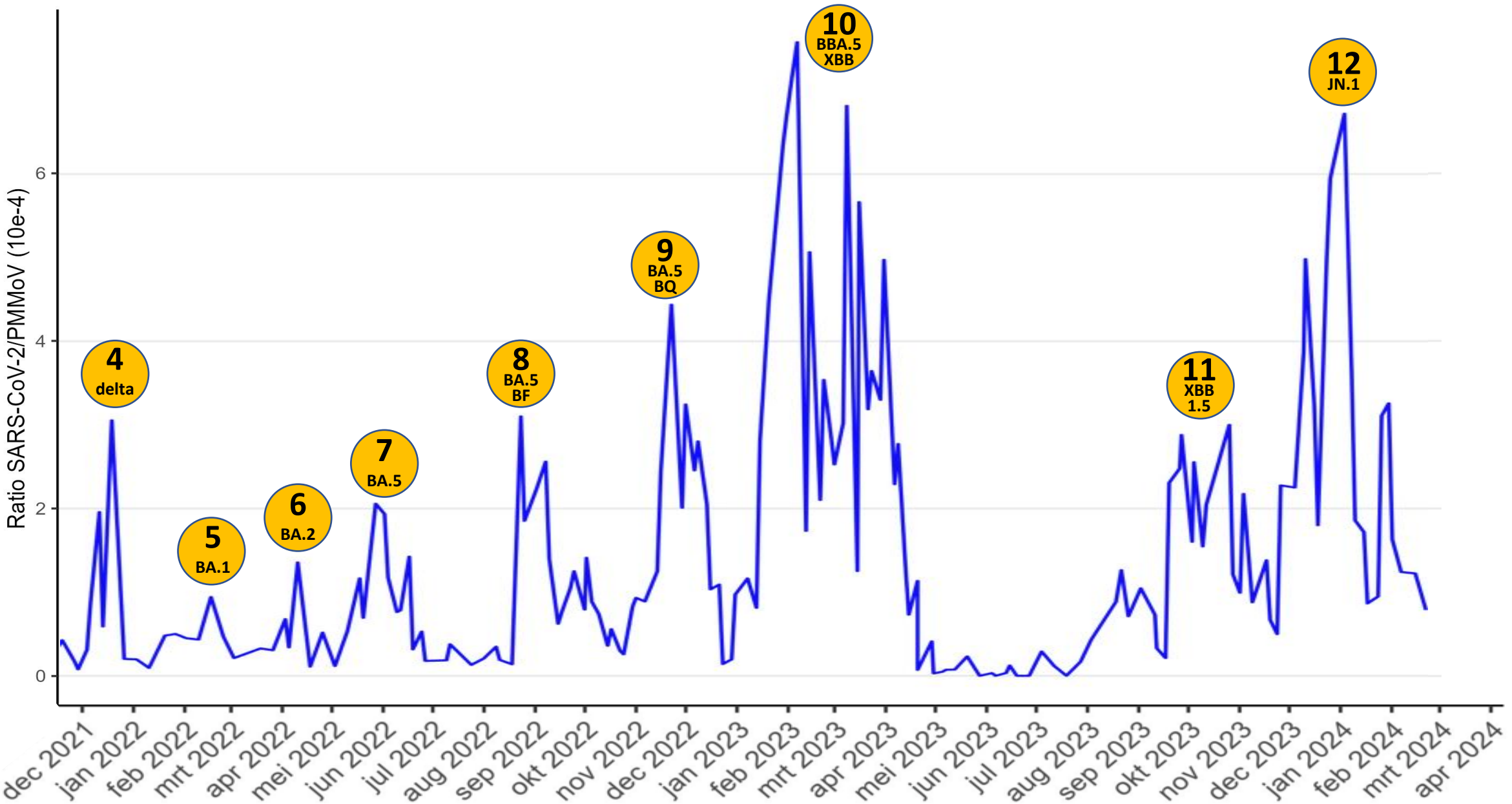

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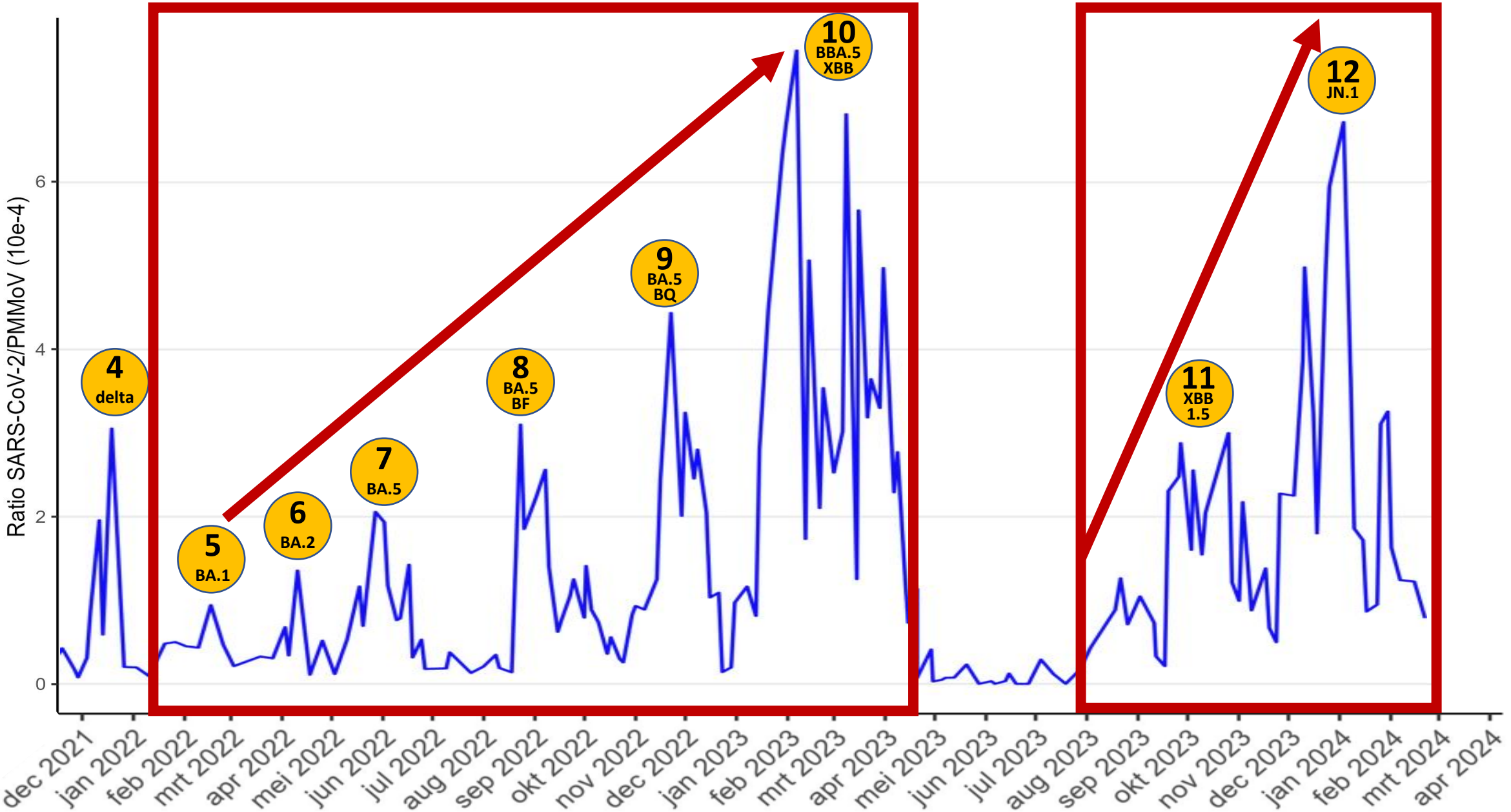
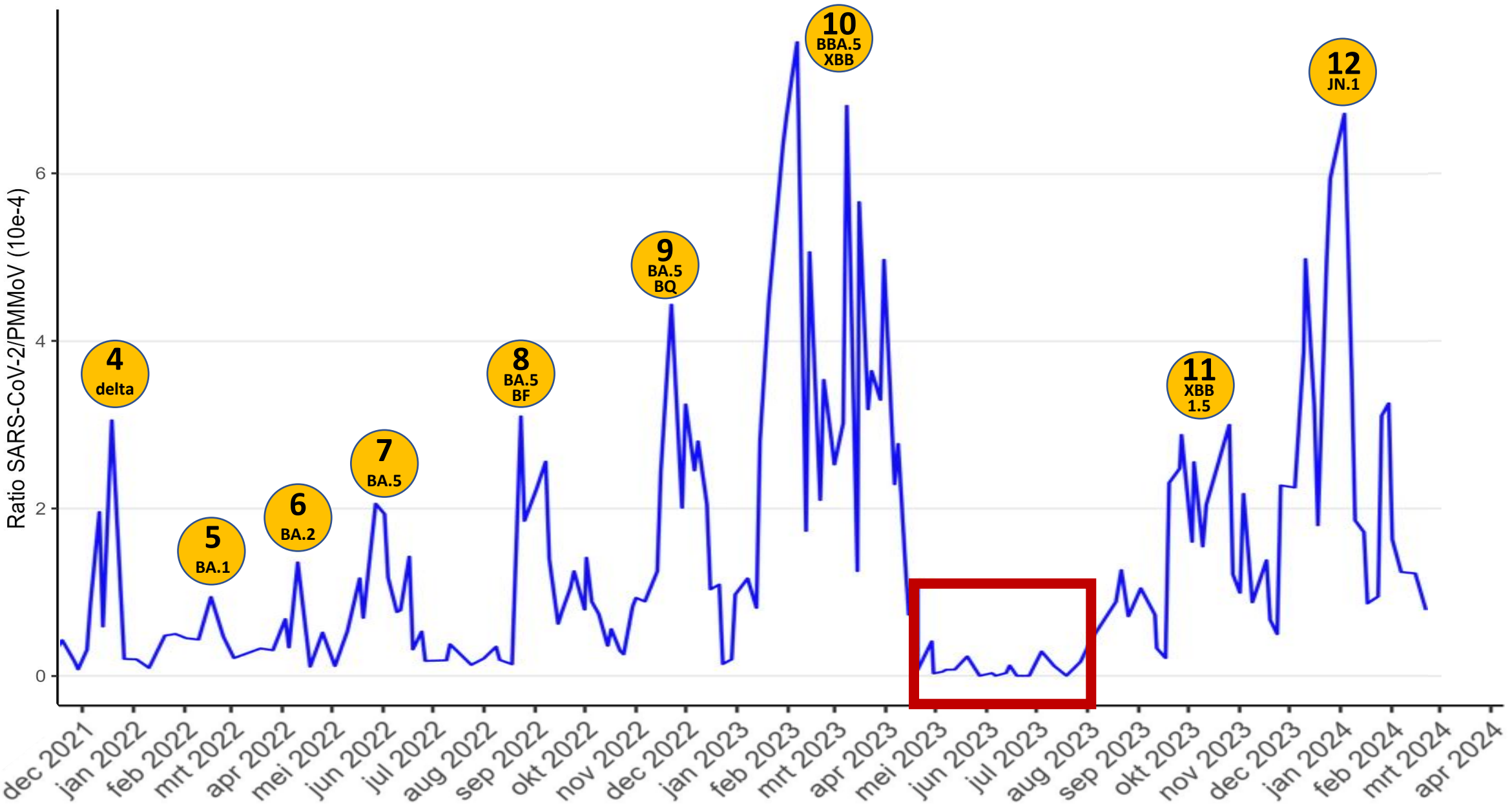
National Coronavirus Reference Laboratory

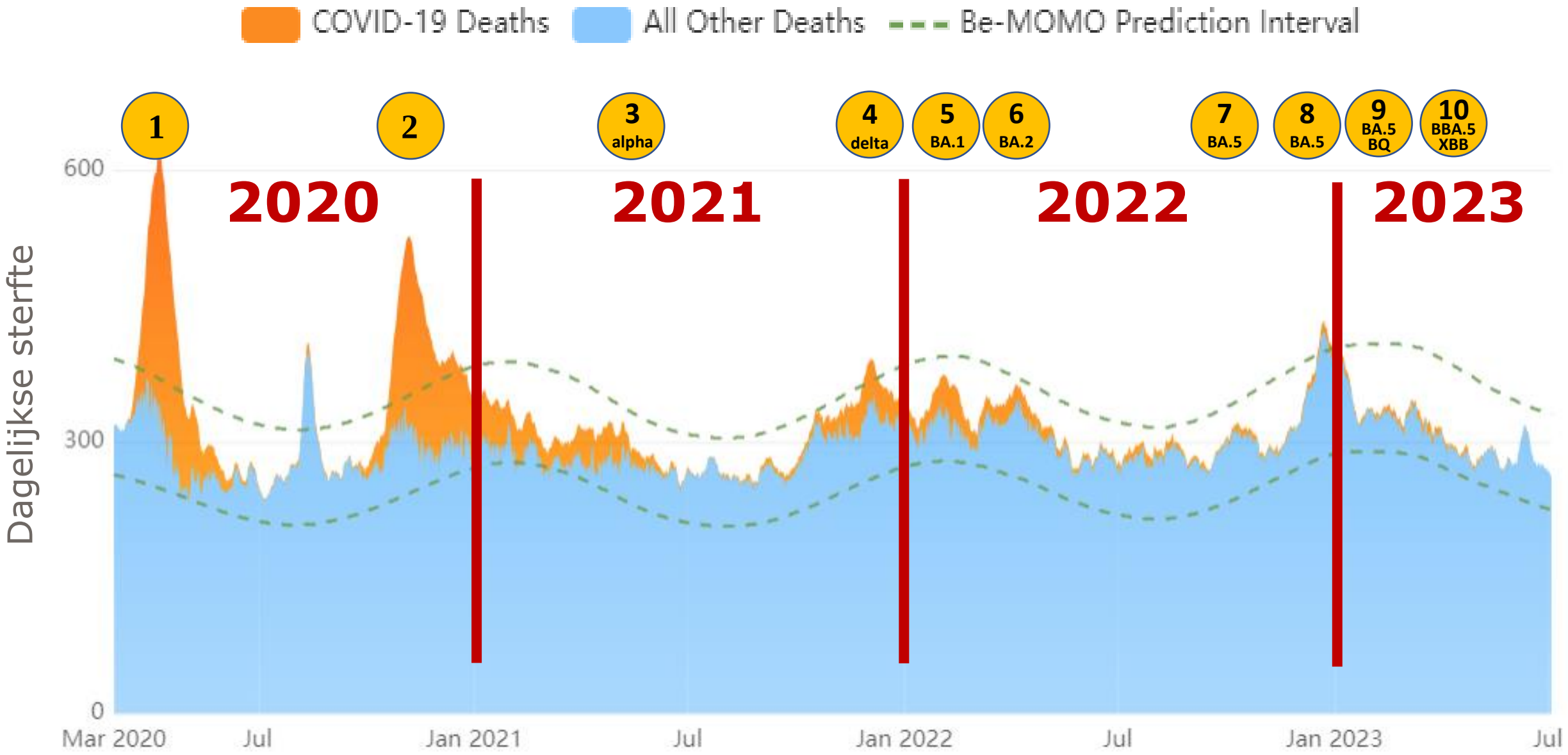


KU LEUVEN

National Coronavirus Reference Laboratory



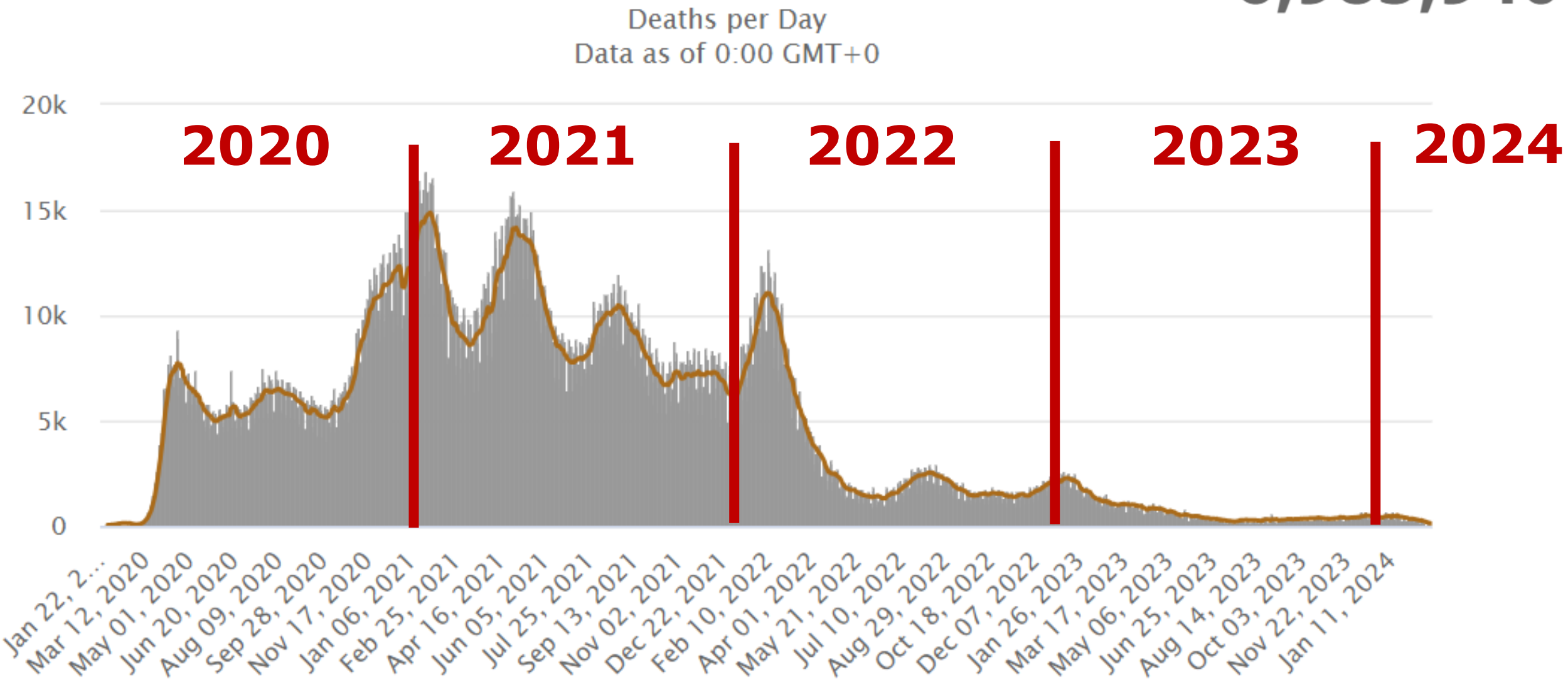
sciensano


COVID-19 Deaths
All Other Deaths
Be-MOMO Prediction Interval
1
2
3 alpha
4 delta
5 BA.1
6 BA.2
7 BA.5
8 BA.5
9 BA.5 BQ
10 BBA.5 XBB
2020
2021
2022
2023
Dagelijkse sterfte
600
300
0
Mar 2020
Jul
Jan 2021
Jul
Jan 2022
Jul
Jan 2023
Jul

worldometer

Deaths:

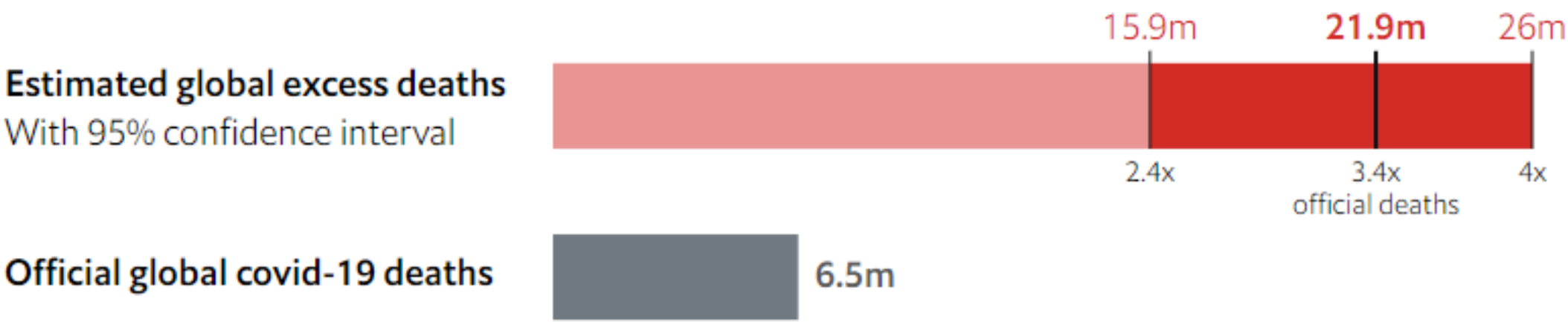
6,985,940



The Economist

The pandemic's true death toll

Our daily estimate of excess deaths around the world



www.economist.com/graphic-detail/coronavirus-excess-deaths-estimates (accessed 12 sep 2022)

Antivirale middelen

03/07/2020 (EMA conditional marketing authorisation)

03/07/2020 (EMA conditional marketing authorisation)

20/06/2023 (marketing authorisation application withdrawn)

03/07/2020 (EMA conditional marketing authorisation)

Veklury®
remdesivir 100 MG FOR INJECTION

GILEAD

20/06/2023 (marketing authorisation application withdrawn)

Lagevrio®
molnupiravir

MERCK

27/01/2022 (EMA conditional marketing authorisation)

Paxlovid®
(nirmatrelvir 150 mg tablets | ritonavir 100 mg tablets)

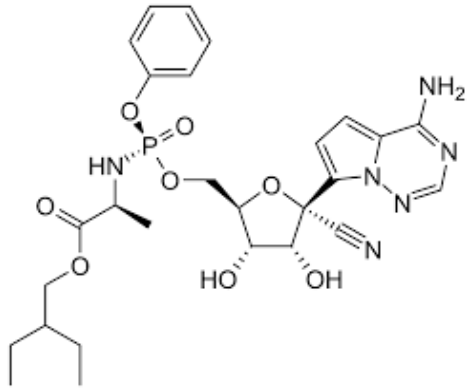
Pfizer

03/07/2020 (EMA conditional marketing authorisation)

Veklury®
remdesivir 100 MG FOR INJECTION

GILEAD

Polymerase inhibitor



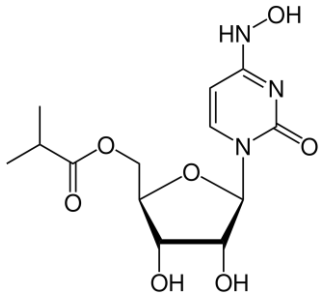
$C_{27}H_{35}N_6O_8P$

20/06/2023 (marketing authorisation application withdrawn)

Lagevrio®
molnupiravir

MERCK

Polymerase inhibitor



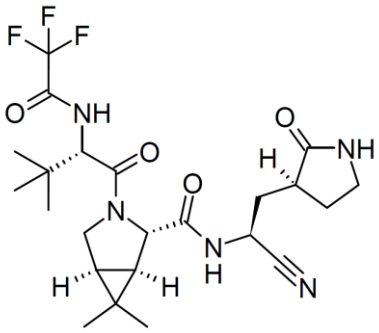
$C_{13}H_{19}N_3O_7$

27/01/2022 (EMA conditional marketing authorisation)

Paxlovid®
(nirmatrelvir 150 mg tablets | ritonavir 100 mg tablets)

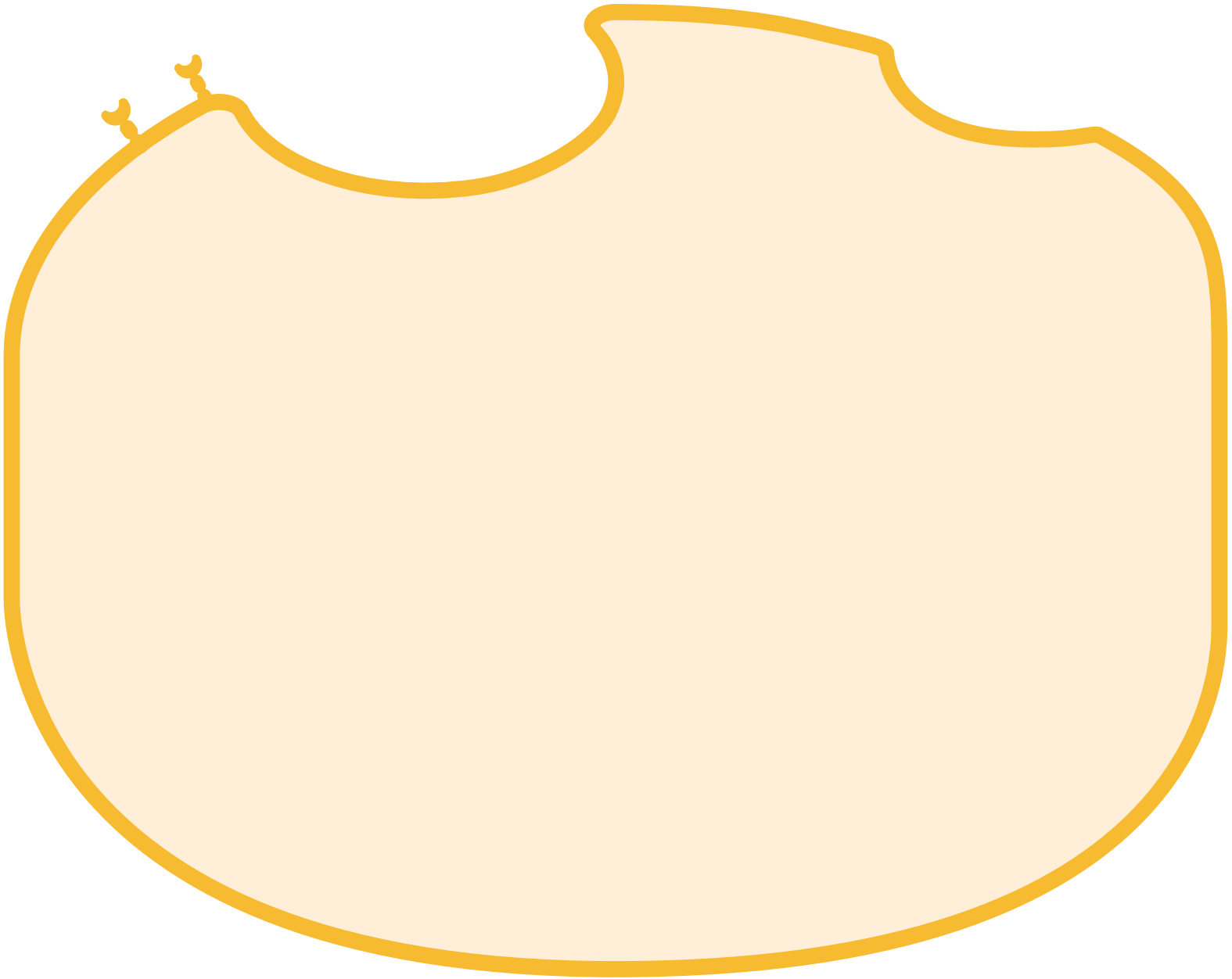
Pfizer

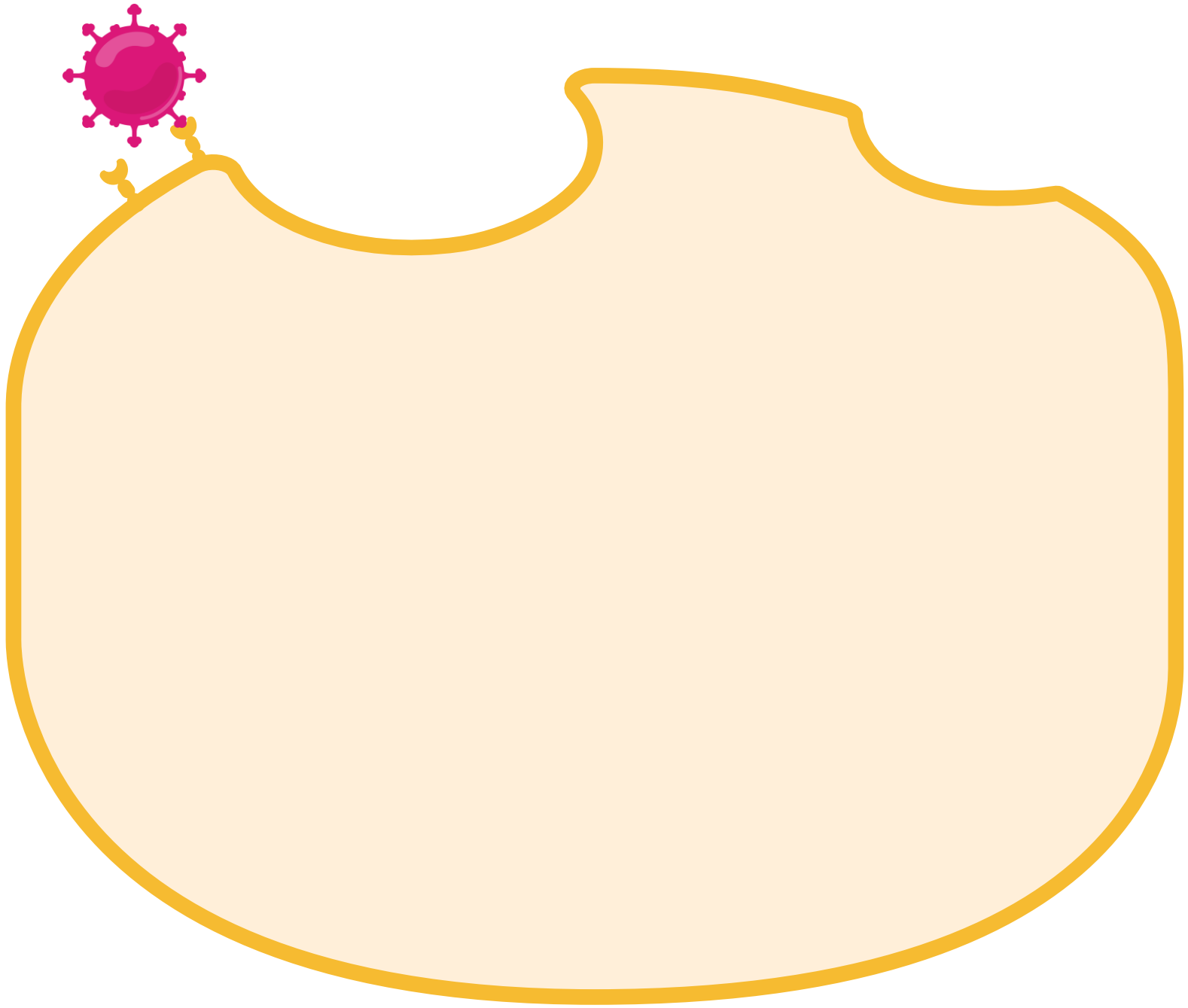
Protease inhibitor

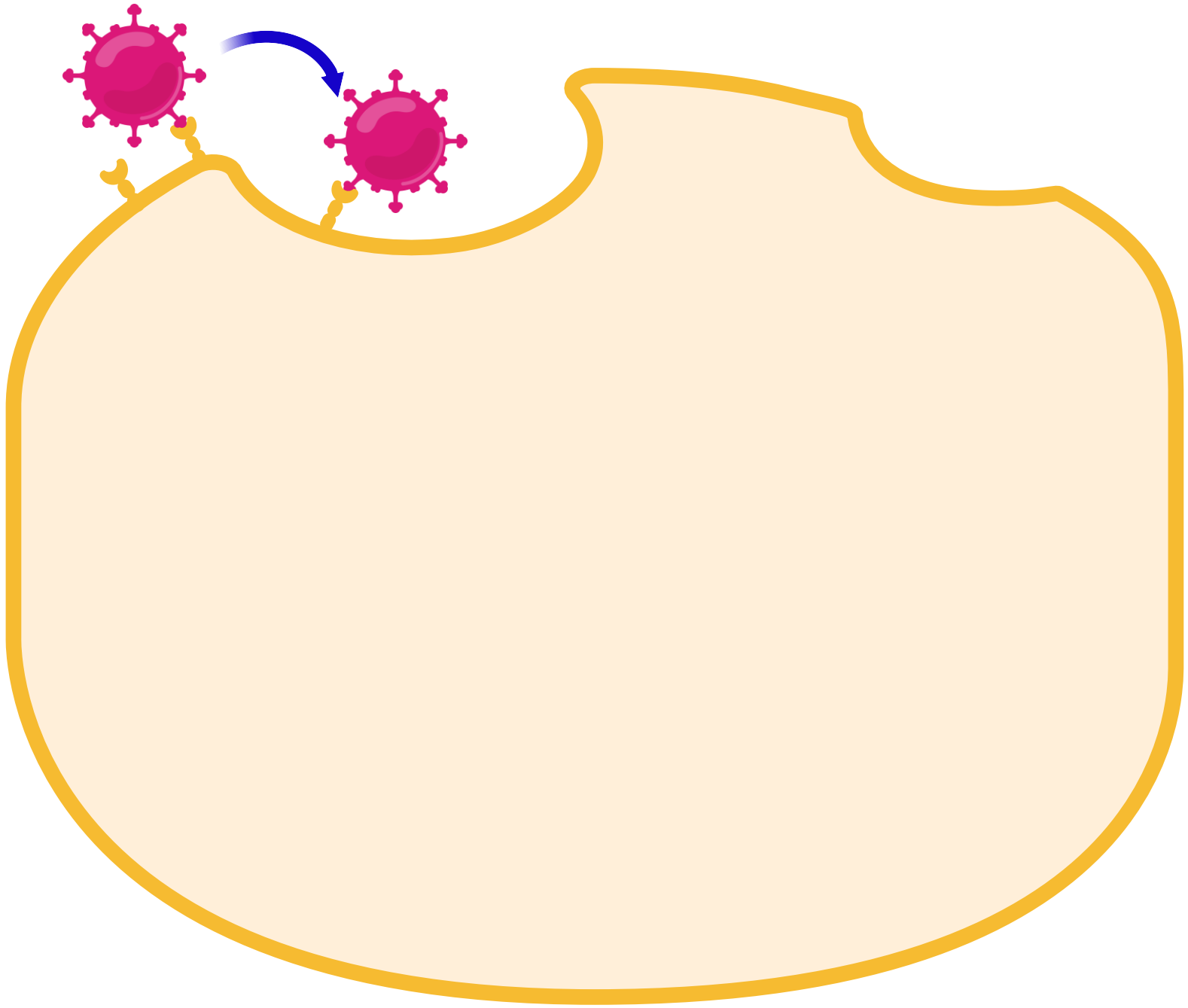


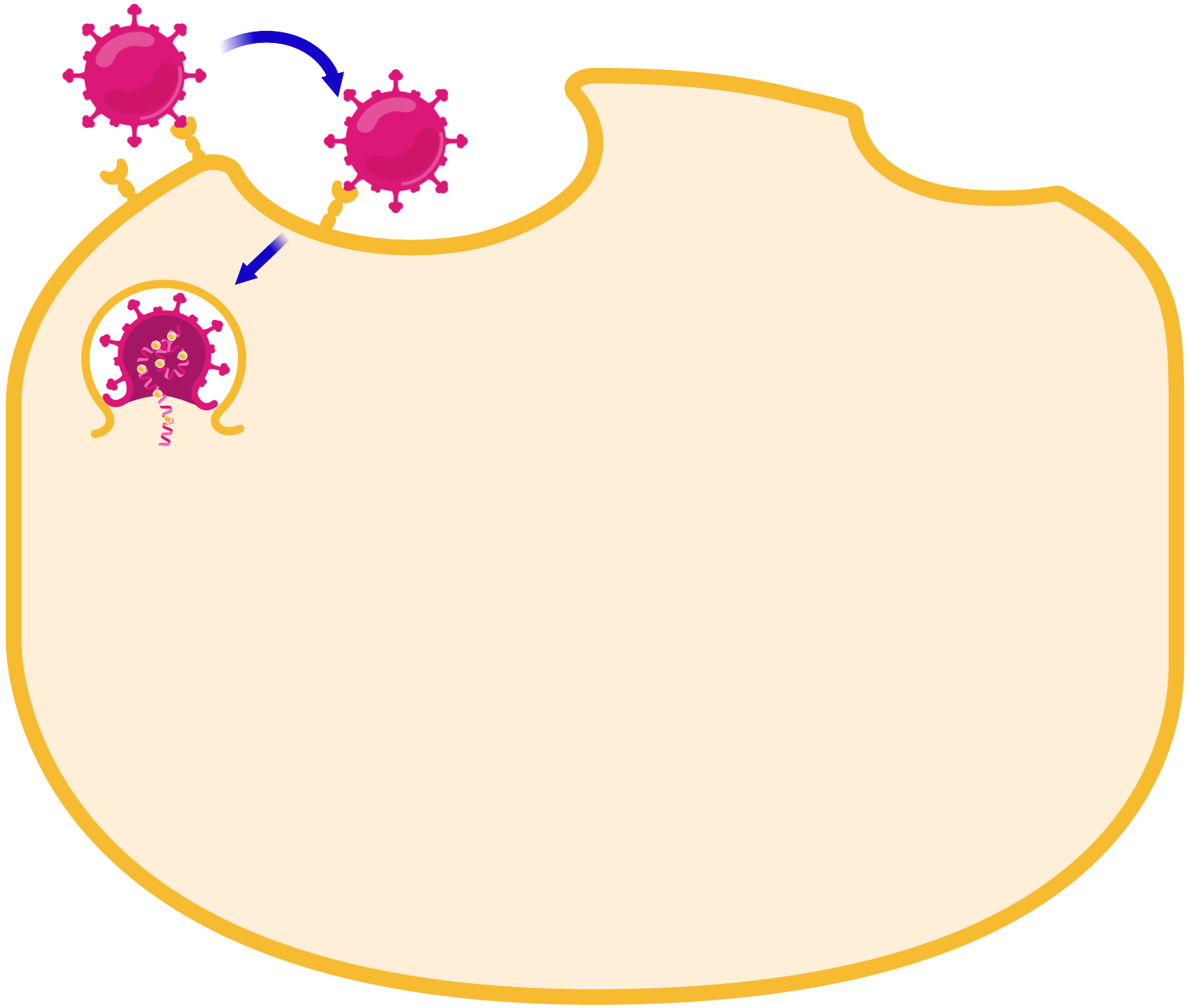
$C_{23}H_{32}F_3N_5O_4$

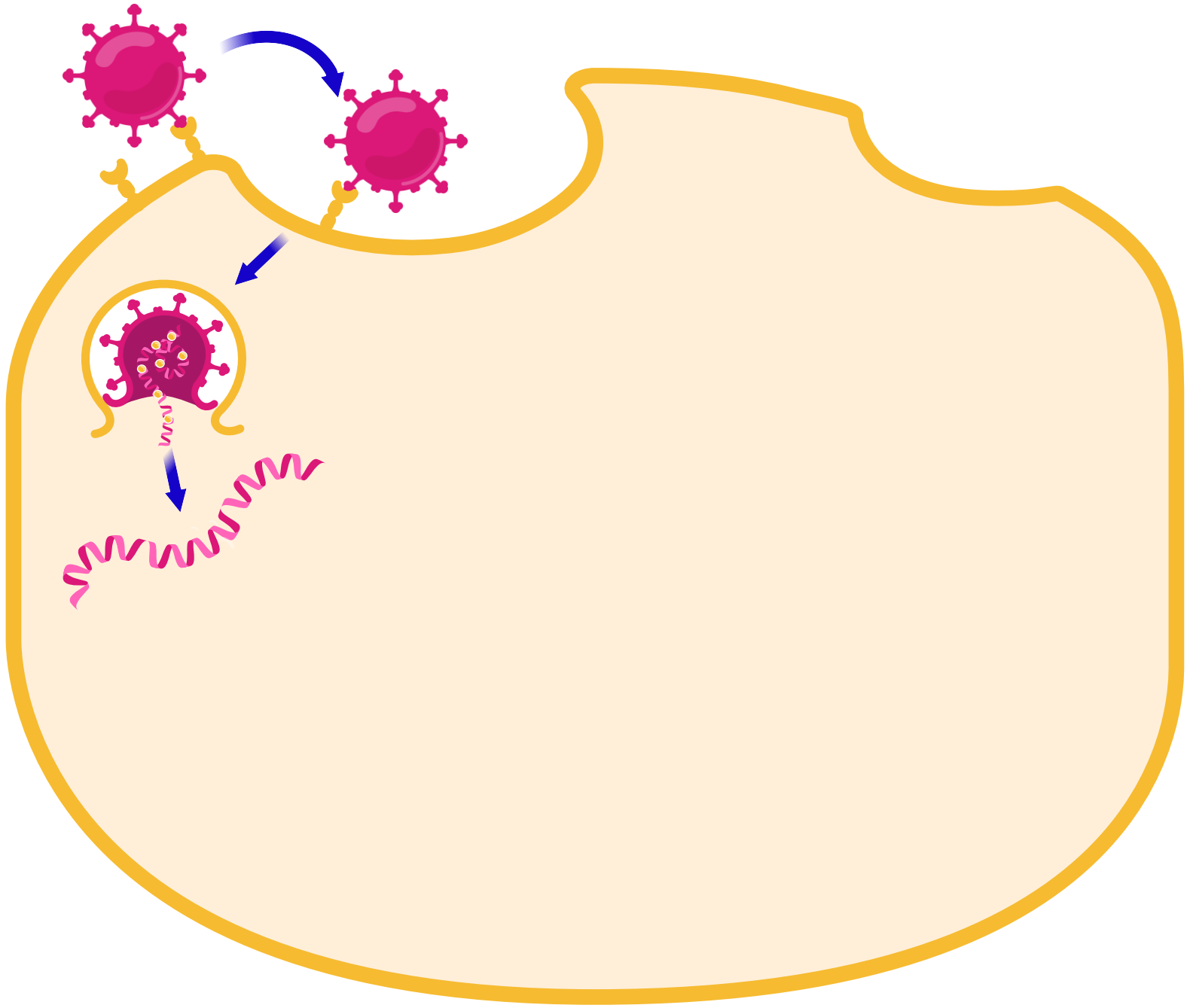
aangrijpingspunten voor antivirale middelen

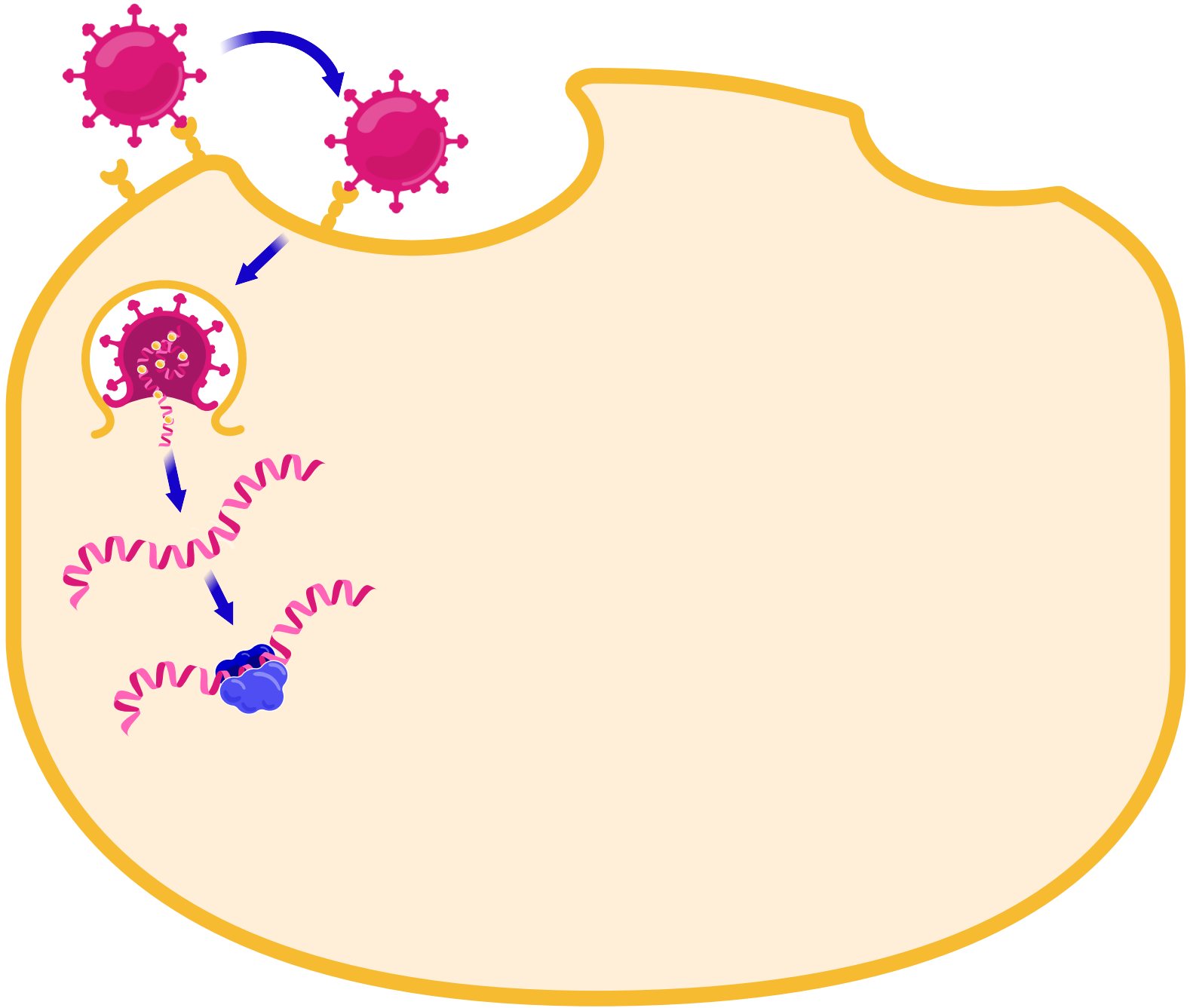


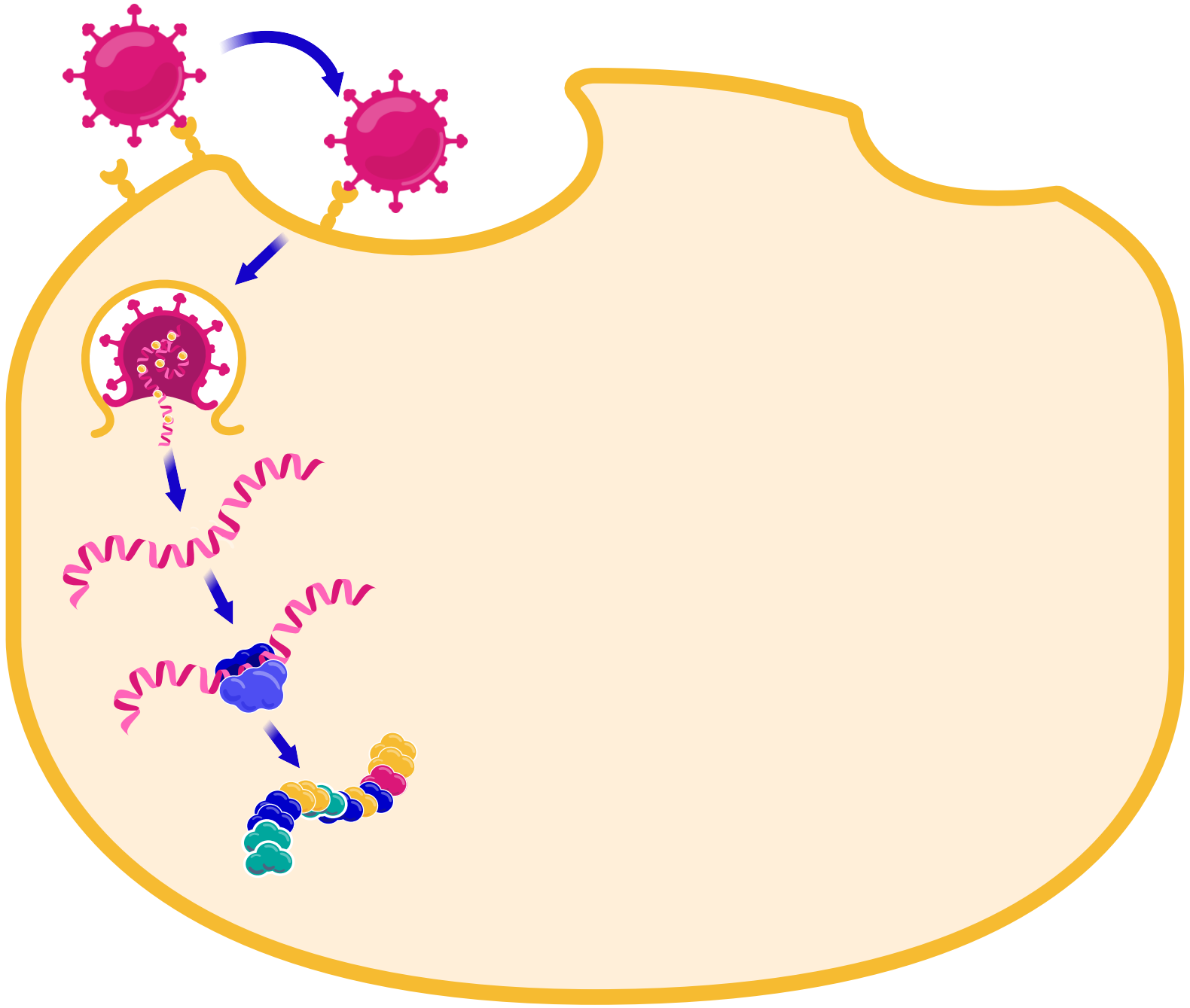


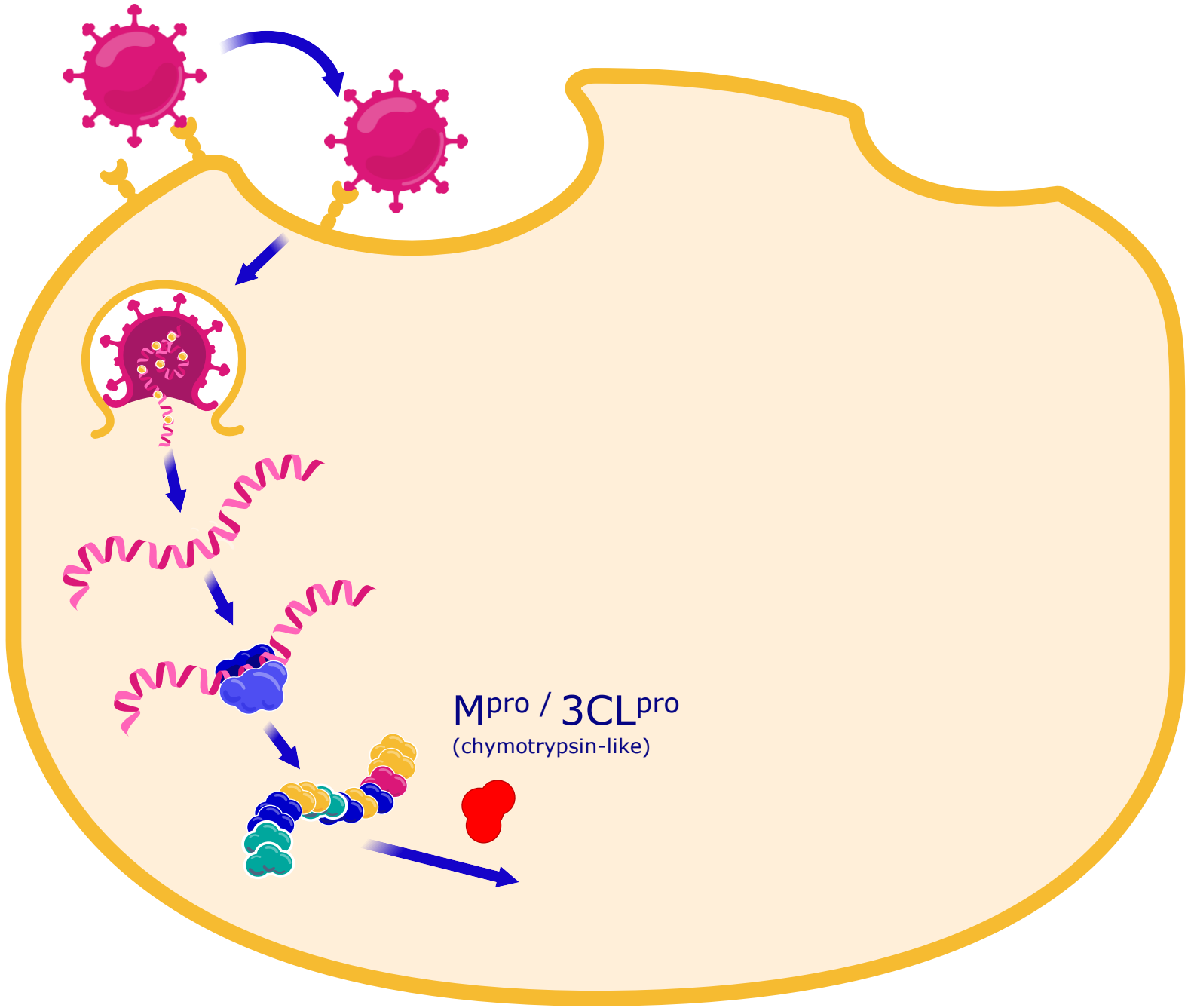


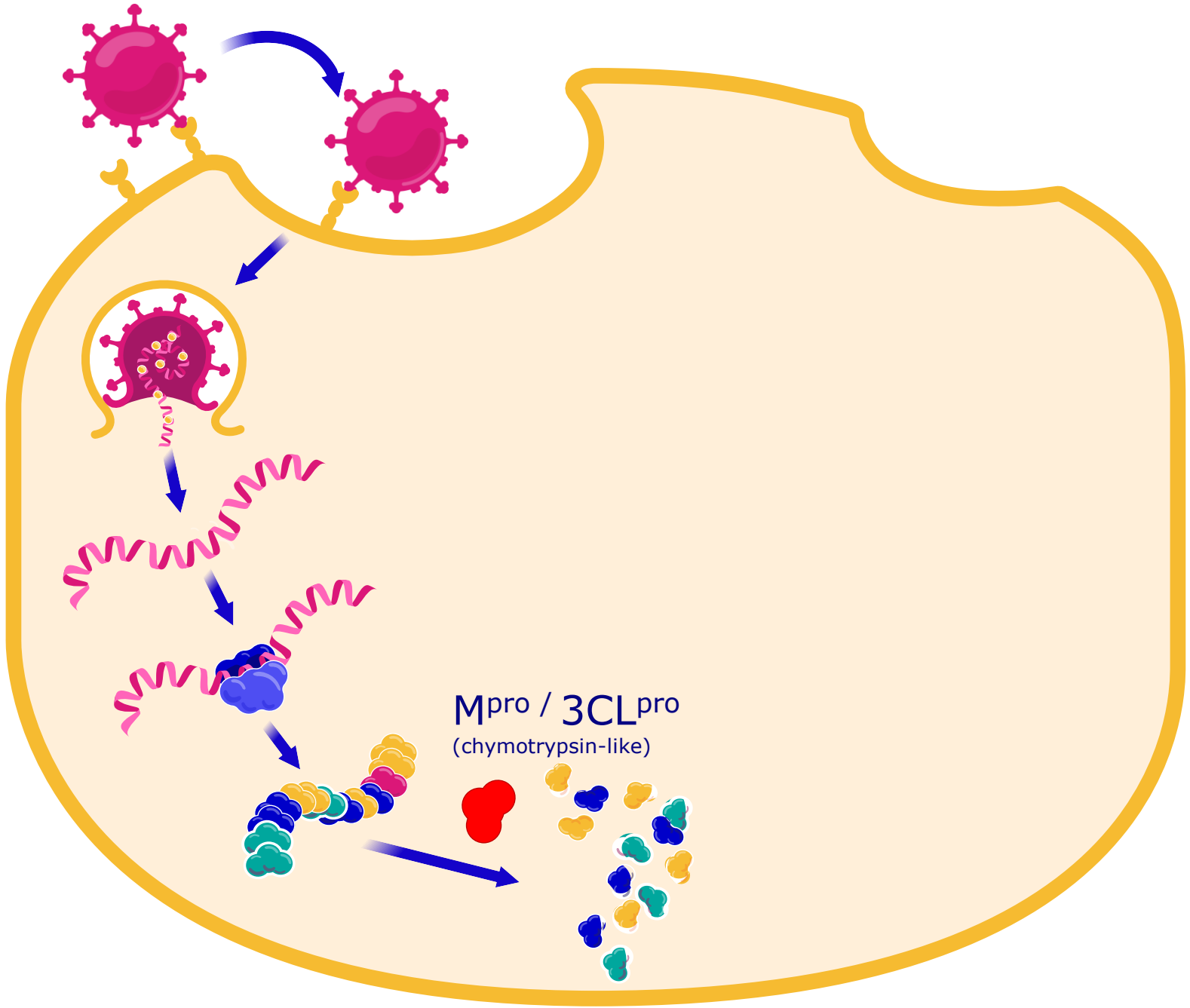


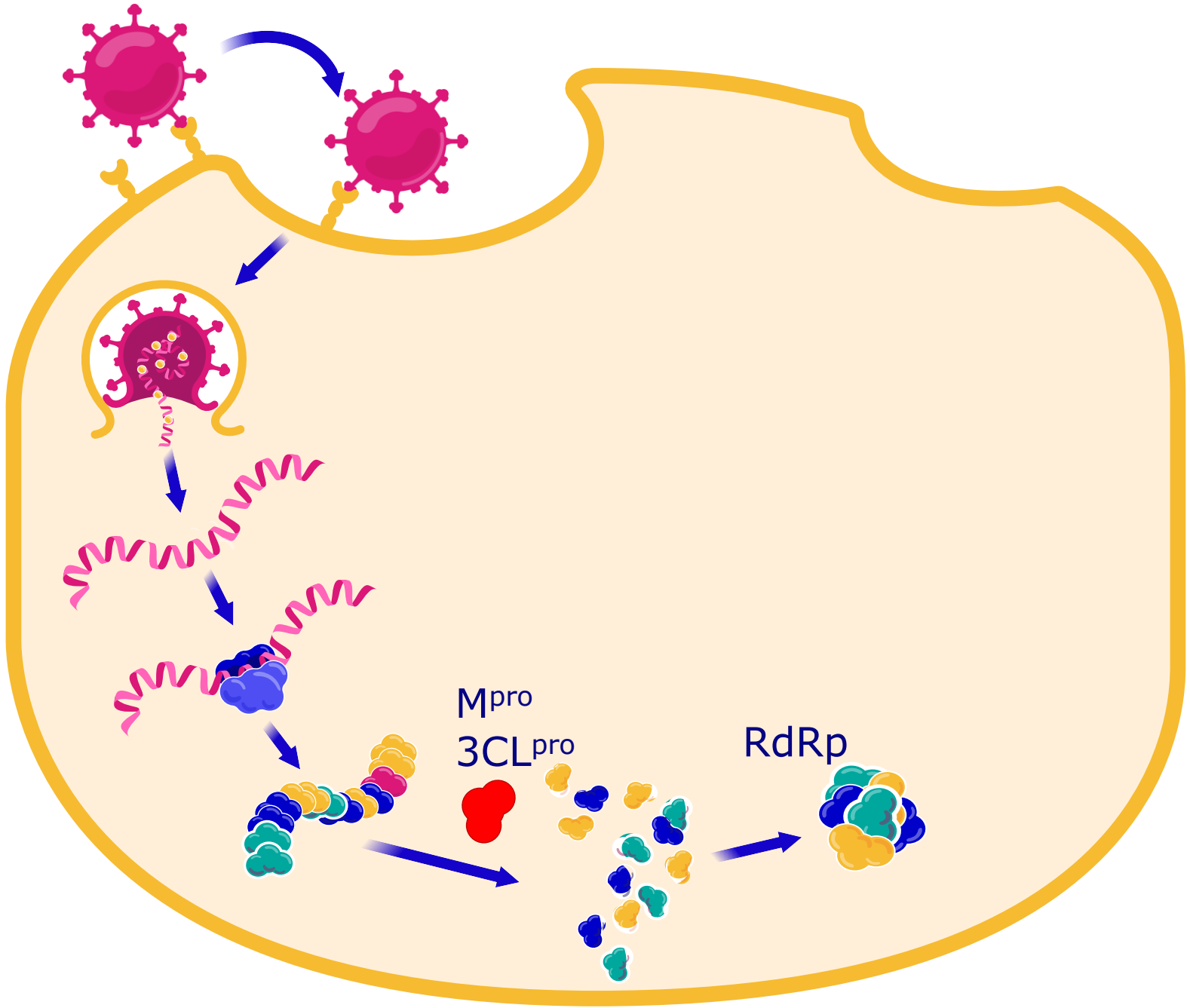


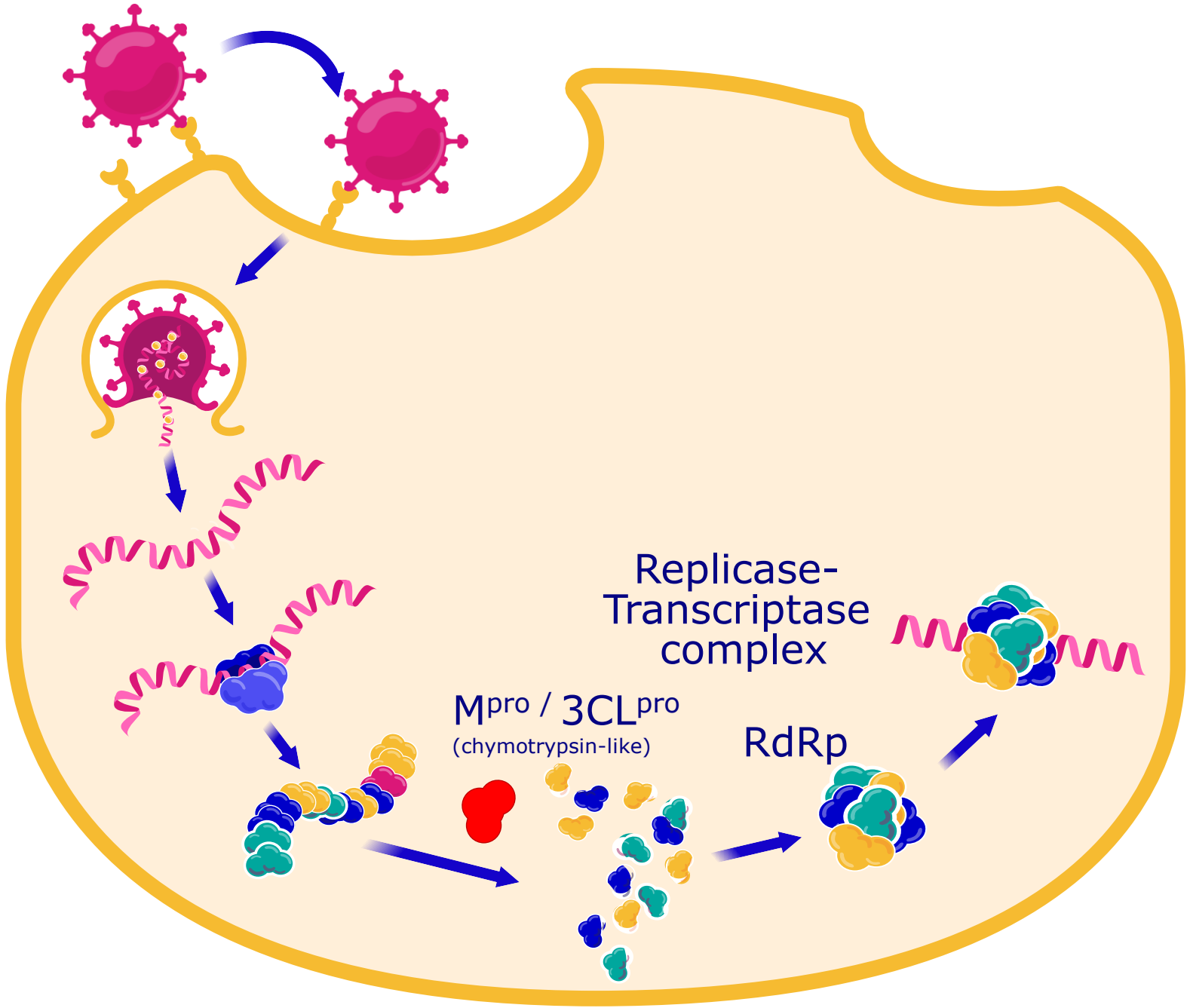


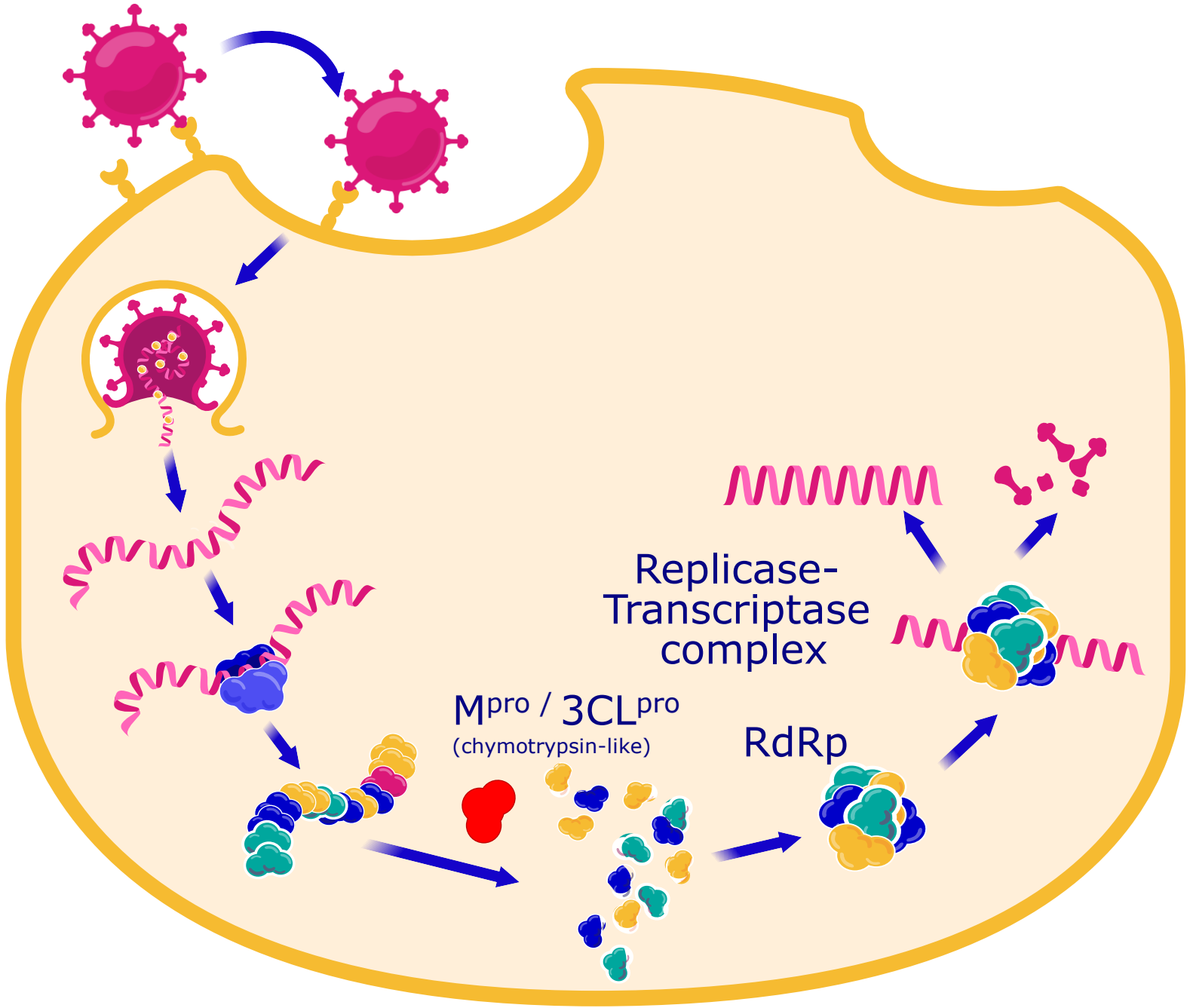


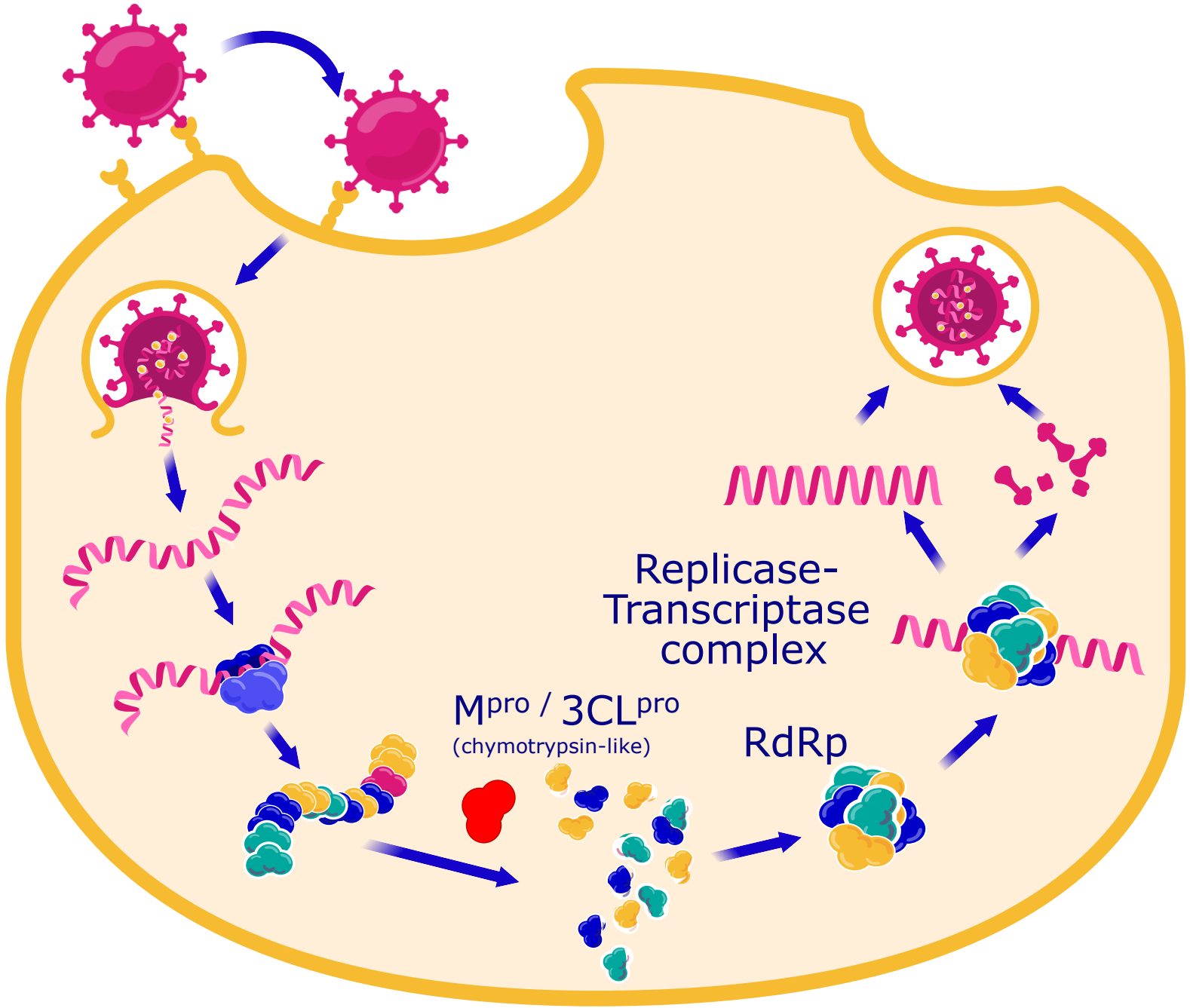

Mpro / 3CLpro
(chymotrypsin-like)

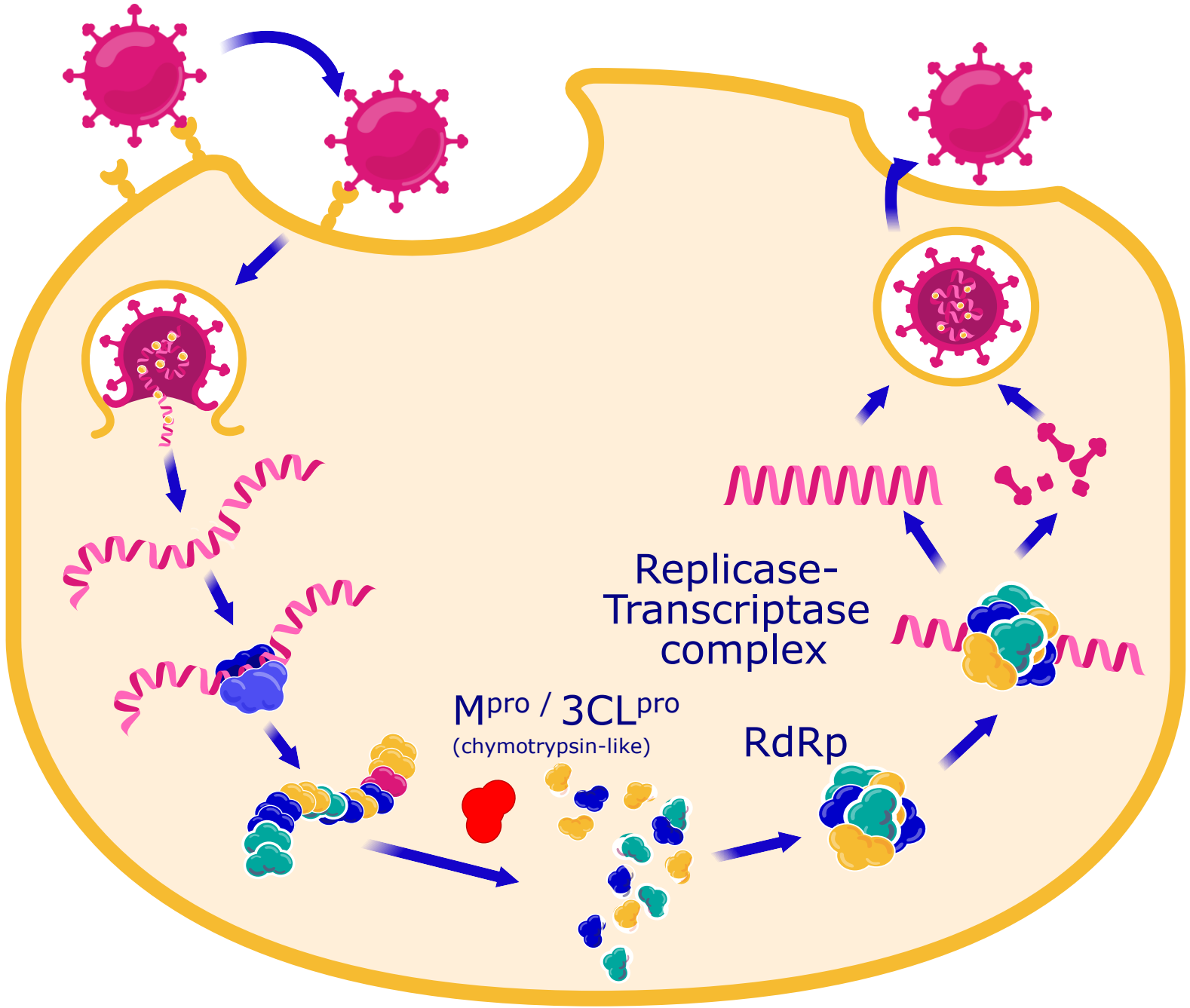

Mpro / 3CLpro
(chymotrypsin-like)

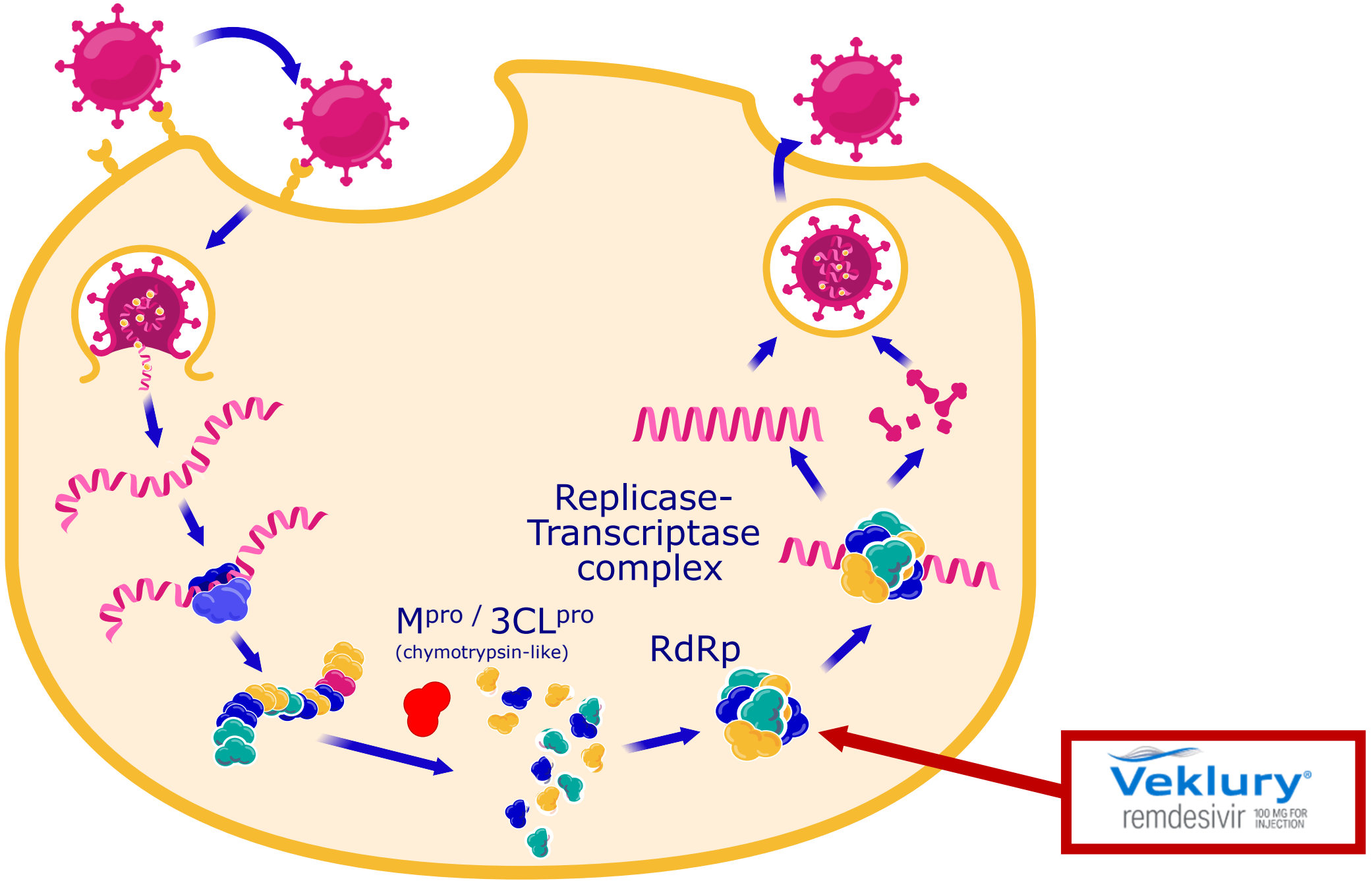

M^pro
3CL^pro
RdRp

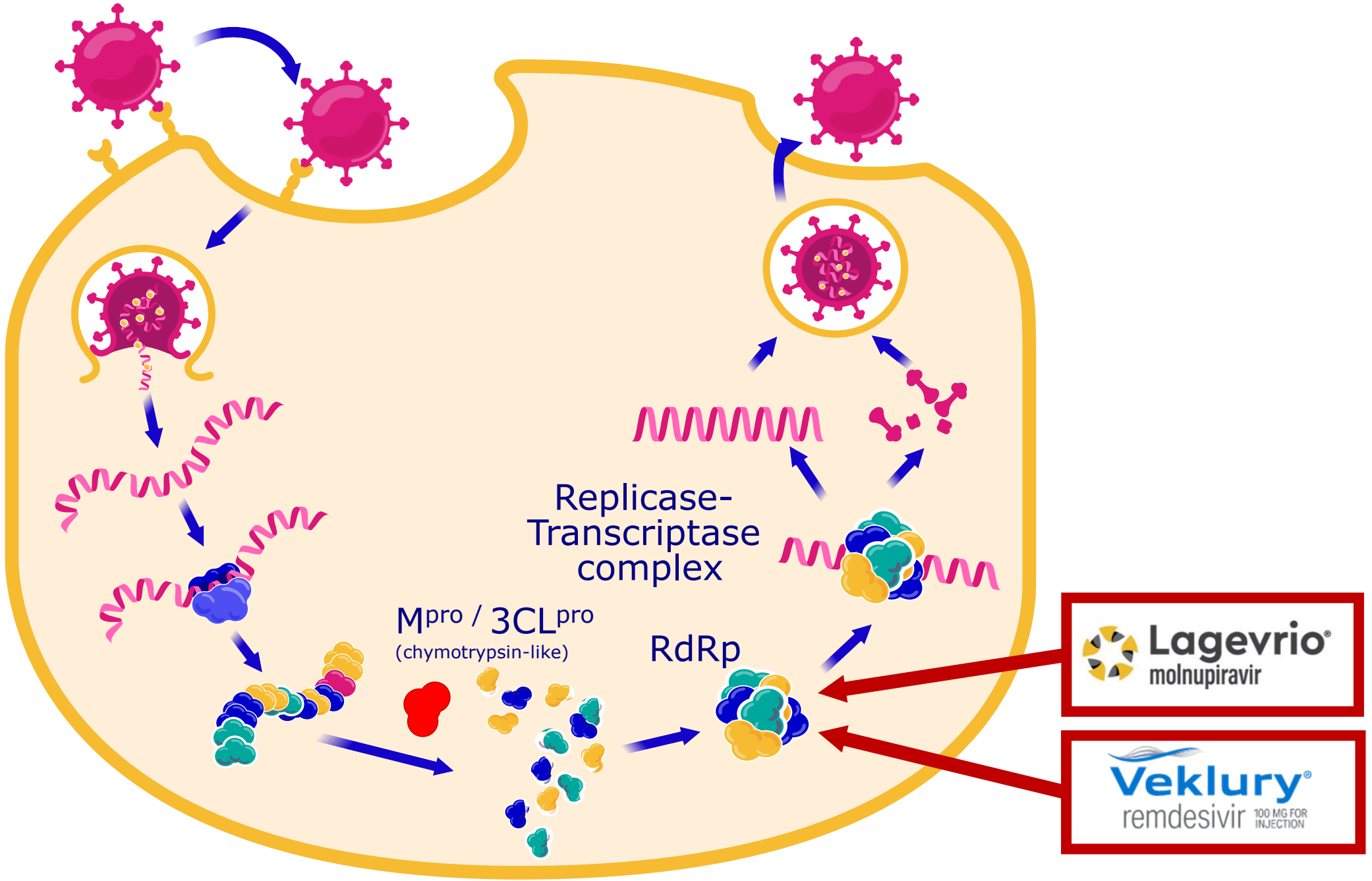

Replicase-
Transcriptase
complex
M^pro / 3CL^pro
(chymotrypsin-like)
RdRp

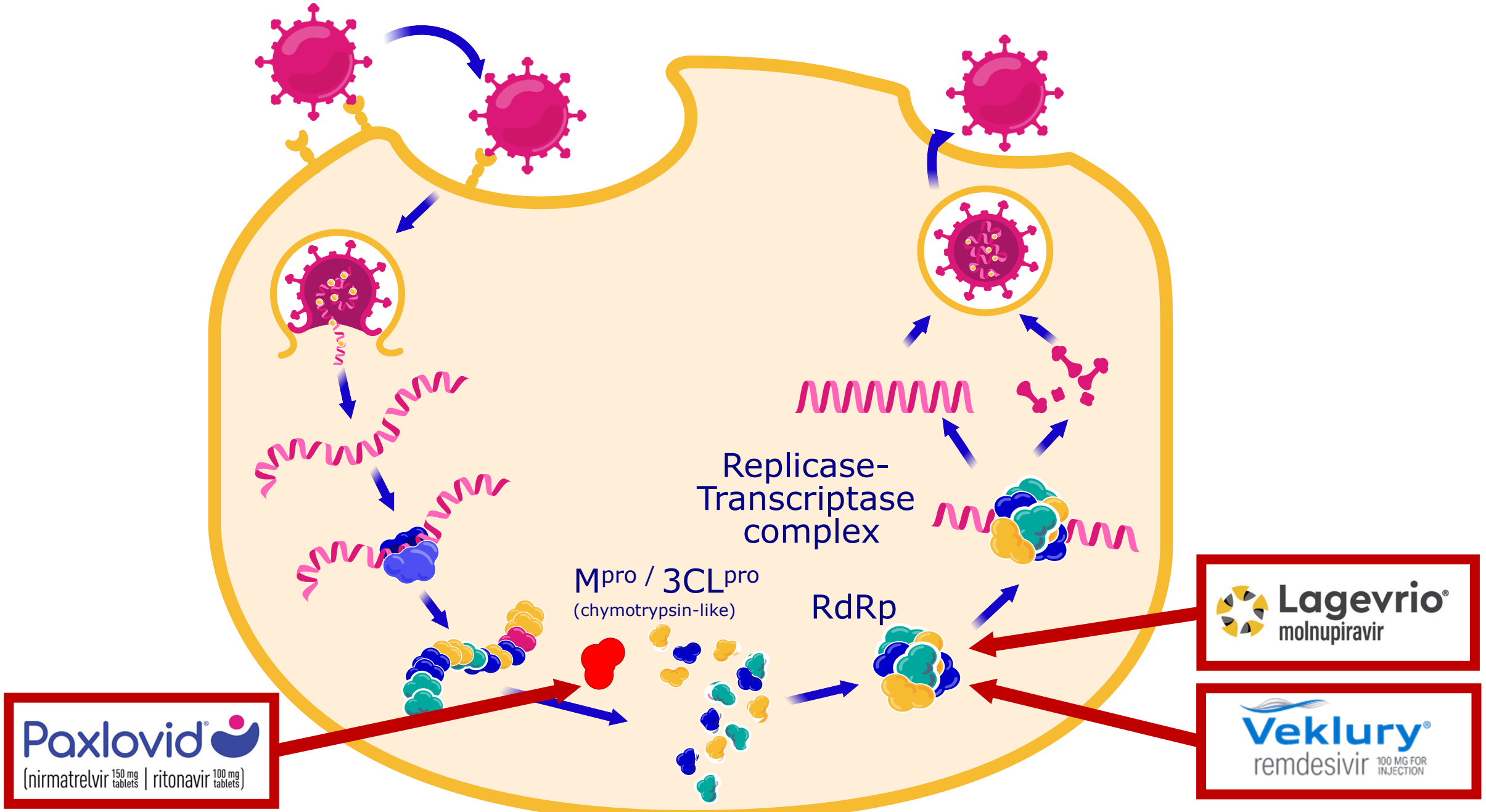

Replicase-
Transcriptase
complex
Mpro / 3CLpro
(chymotrypsin-like)
RdRp


Replicase-
Transcriptase
complex
Mpro / 3CLpro
(chymotrypsin-like)
RdRp


Replicase-
Transcriptase
complex
Mpro / 3CLpro
(chymotrypsin-like)
RdRp


Replicase-
Transcriptase
complex
Mpro / 3CLpro
(chymotrypsin-like)
RdRp
Veklury®
remdesivir 100 MG FOR INJECTION


Replicase-
Transcriptase
complex
Mpro / 3CLpro
(chymotrypsin-like)
RdRp
Lagevrio®
molnupiravir
Veklury®
remdesivir 100 MG FOR INJECTION


Replicase-
Transcriptase
complex
Mpro / 3CLpro
(chymotrypsin-like)
RdRp
Paxlovid
(nirmatrelvir 150 mg tablets | ritonavir 100 mg tablets)
Lagevrio
molnupiravir
Veklury
remdesivir 100 MG FOR INJECTION

Toediening, indicaties en beschikbaarheid

Veklury® remdesivir 100 MG FOR INJECTION

IV

Lagevrio® molnupiravir

Oraal

Paxlovid® (nirmatrelvir 150 mg tablets | ritonavir 100 mg tablets)

Oraal

IV

Volwassen of adolescente (≥12 jaar en >40 kg) COVID-19-patiënten met pneumonie en zuurstofnood.

Oraal

Volwassen COVID-19-patiënten die geen zuurstofnood hebben maar risico hebben op een ernstig klinisch verloop.

Oraal

Volwassen COVID-19-patiënten die geen zuurstofnood hebben maar risico hebben op een ernstig klinisch verloop.

488 Euro/100 mg

IV

Volwassen of adolescente (≥12 jaar en >40 kg) COVID-19-patiënten met pneumonie en zuurstofnood.

Beschikbaar in ziekenhuis

Oraal

Volwassen COVID-19-patiënten die geen zuurstofnood hebben maar risico hebben op een ernstig klinisch verloop.

gecontroleerd gebruik bij uitbraken in woonzorgcentra

Niet meer beschikbaar (sinds 20/6/2023)

976 Euro/5 dagen

Oraal

Volwassen COVID-19-patiënten die geen zuurstofnood hebben maar risico hebben op een ernstig klinisch verloop.

Gecontroleerde distributie

Beschikbaar bij apotheek (sinds 1/11/23)

BCFi
BELGISCH CENTRUM VOOR
FARMACOTHERAPEUTISCHE INFORMATIE

1/11/2023

nirmatrelvir + ritonavir (Paxlovid® ▼)

Het antivirale geneesmiddel **nirmatrelvir+ritonavir** (Paxlovid ® ▼, hoofdstuk 11.4.7.) wordt sinds 01/11/2023 terugbetaald in categorie b! **bij bepaalde volwassenen met COVID-19 in de ambulante zorg**. Het gaat om volwassenen die een verhoogd risico lopen op progressie naar ernstige COVID-19 (zie verder onder "rechthebbenden"*) en voldoen aan de volgende criteria: (1) er zijn symptomen die kunnen wijzen op een COVID-19-infectie, en dit sinds minder dan 5 dagen, (2) de diagnose van COVID-19 (PCR-test of antigeentest) is bevestigd, (3) er is geen zuurstofnood **én** (4) de persoon wordt niet behandeld met geneesmiddelen waarvan volgens de SKP gelijktijdige behandeling met Paxlovid® is gecontra-indiceerd (het gaat om een aantal CYP3A4-substraten waaronder amiodaron, carbamazepine, oxycodon, rivaroxaban,... en CYP3A4-inductoren waaronder carbamazepine, rifampicine, Sint-Jans-kruid,... zie SKP > rubriek "Contra-indicaties").

* De "rechthebbenden" zijn: (1) personen ≥ 65 jaar met minstens 1 van de gespecificeerde co-morbiditeiten, (2) personen met ernstige immuunstoornissen en (3) personen met COPD of hartfalen. Voor details: zie de terugbetalingsvoorwaarden: klik op symbool b! ter hoogte van de specialiteit Paxlovid® in het Repertorium.

Paxlovid® mag worden voorgeschreven door alle artsen en is beschikbaar via de officina-apotheken.

https://www.bcfi.be/nl/articles/query?number=F50N11I#nir

BIJLAGE A: Model van het formulier voor aanvraag

Formulier voor aanvraag tot vergoeding van de farmaceutische specialiteit op basis van nirmatrelvir+ritonavir ingeschreven in § 12330000 van hoofdstuk IV van de lijst gevoegd bij het K.B. van 1 februari 2018 voor de behandeling van volwassen rechthebbenden met COVID-19 veroorzaakt door het SARS-CoV-2 virus, met een verhoogd risico op het ontwikkelen van een ernstige COVID-19.

I - Identificatie van de rechthebbende:

|_|_|_|_|_|_|_|_|_|_|_|_|_|_|_|_|_|_|_|_|_| (naam)

|_|_|_|_|_|_|_|_|_|_|_|_|_|_|_|_|_|_|_|_|_| (voornaam)

|_|_|_|_|_|_|_|_|_|_|_|_|_|_|_|_|_|_|_|_|_| (aansluitingsnummer)

II - Elementen te bevestigen door de arts verantwoordelijk voor de behandeling:

Ik, ondergetekende arts verantwoordelijk voor de behandeling, verklaar dat de hierboven vermelde rechthebbende aan COVID-19 veroorzaakt door het SARS-CoV-2 virus, met een verhoogd risico op het ontwikkelen van een ernstige COVID-19 lijdt, en tegelijk voldoet aan alle voorwaarden gesteld in § 12330000 van hoofdstuk IV van de lijst gevoegd bij het K.B. van 1 februari 2018:

Rechthebbende met symptomen die mogelijk gecorreleerd zijn met een COVID-19 infectie sinds minder dan 5 dagen, gediagnosticeerd met COVID-19 op basis van een moleculaire test (RT-PCR) of antigeentest en geen zuurstofnood omwille van een SpO2 > of = 94% en niet behandeld met geneesmiddelen met contra-indicaties voor simultaan gebruik met nirmatrelvir+ritonavir, zoals opgenomen in de SPK (geneesmiddelen die voor de klaring in hoge mate afhankelijk zijn van CYP3A en waarbij verhoogde concentraties gepaard gaan met ernstige en/of levensbedreigende reacties of geneesmiddelen die krachtige CYP3A-inductoren zijn, waarbij significant verlaagde nirmatrelvir+ritonavir-plasmaconcentraties gepaard kunnen gaan met mogelijk verlies van de virologische respons en met mogelijke resistentie)

Het betreft:

☐ Een rechthebbende met een leeftijd >= 65 jaar met aanwezigheid van minstens een van volgende co-morbiditeiten

- ☐ BMI>= 30mg/kg
- ☐ Diabetes mellitus
- ☐ Chronisch nierlijden met GFR > 29 ml/min/1,73m²
- ☐ Chronisch neurologische pathologie
- ☐ Chronisch leverlijden of cirrose

Of

☐ Een rechthebbende met ernstige immuunstoornis omwille van de aanwezigheid van minstens een van onderliggende morbiditeiten:

- ☐ Hematologische maligniteit
- ☐ Soliede tumor die behandeld wordt met een cytotoxische behandeling
- ☐ Orgaantransplantatie of stamceltransplantatie
- ☐ B-cel reducerende behandeling gedurende het voorafgaande jaar
- ☐ Primaire immuundeficiëntie
- ☐ HIV-infectie met CD4 <200/mm³ en/of een detecteerbare virale lading
- ☐ CAR-T cel behandeling
- ☐ Behandeling met immunosuppressiva
- ☐ Langdurige behandeling met hoge dosis corticosteroïden (>20mg prednisolone of equivalent per dag) of methotrexaat (meer dan 20mg per week)
- ☐ Hemodialyse of peritoneale dialyse

Of

☐ Een rechthebbende met :

- ☐ hartfalen of
- ☐ COPD

Op grond hiervan bevestig ik dat voor deze rechthebbende de vergoeding van een behandeling met een specialiteit ingeschreven in § 12330000 van hoofdstuk IV van de lijst gevoegd bij het K.B. van 1 februari 2018 noodzakelijk is voor een periode van 5 dagen, zoals bepaald in punt d van §123300000, overeenkomend met 1 vergoedbare verpakking.

Ik verbind mij ertoe om het bewijsmateriaal waaruit blijkt dat de rechthebbende zich in de verklaarde toestand bevindt, ter beschikking te houden van de adviserend arts.

III. Identificatie van de arts:

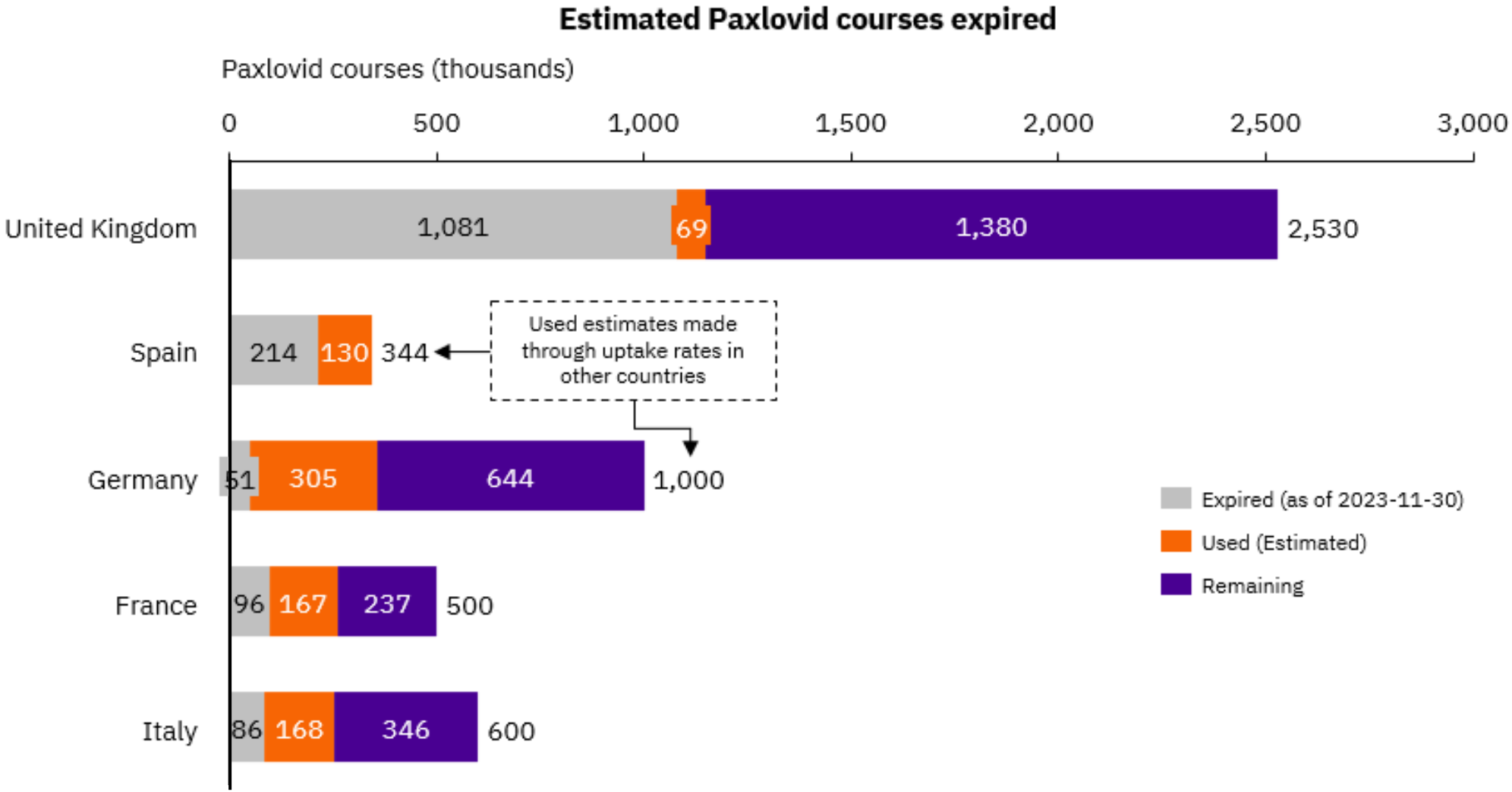
|_|_|_|_|_|_|_|_|_|_|_|_|_|_|_|_|_|_|_|_|_| (naam)

|_|_|_|_|_|_|_|_|_|_|_|_|_|_|_|_|_|_|_|_|_| (voornaam)

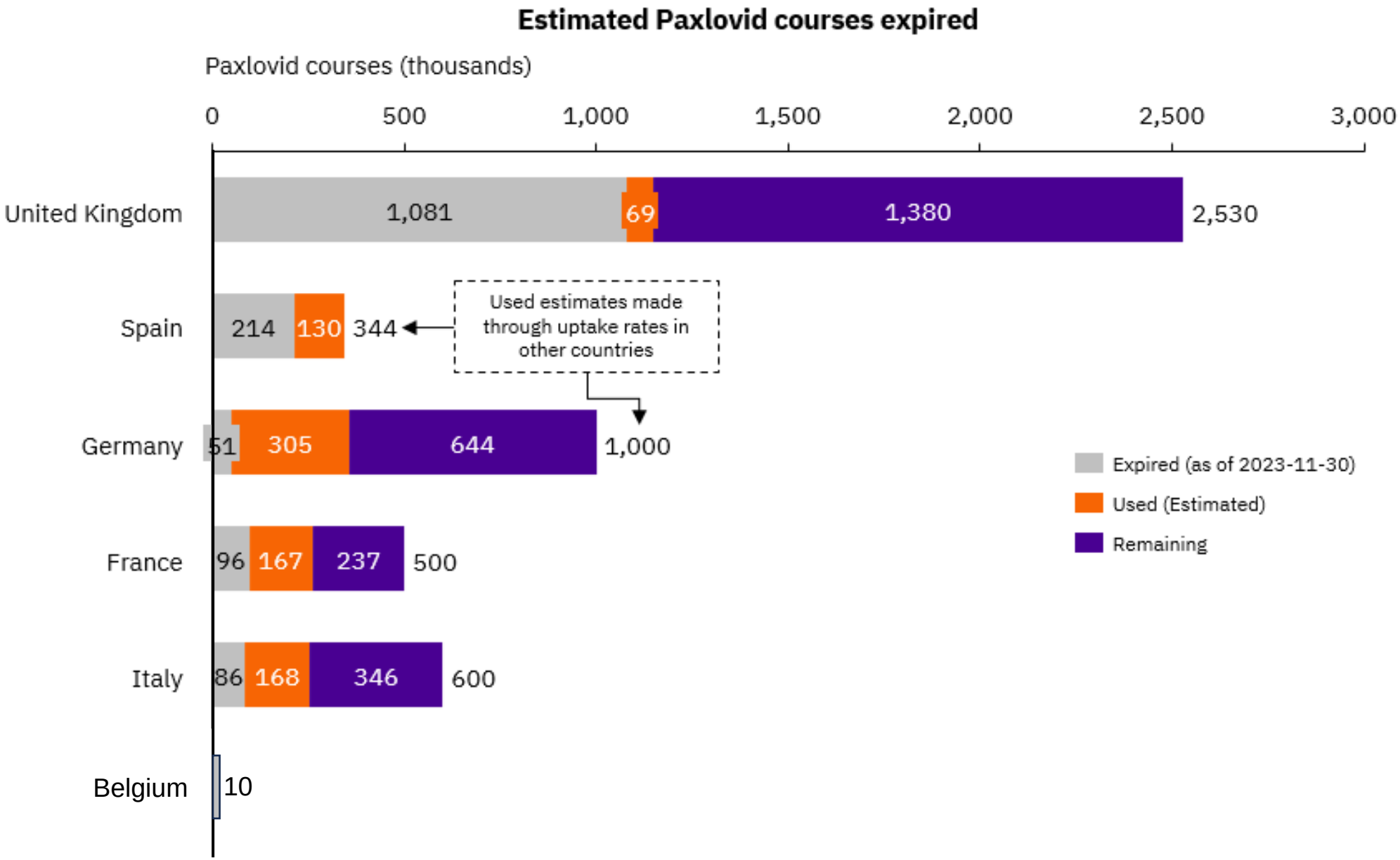
|1| - |_|_|_|_|_| - |_|_| - |_|_|_| (RIZIV n°)

|_|_| / |_|_| / |_|_|_|_| (datum)

(stempel) ..... (handtekening van de arts)



https://www.airfinity.com/articles/stockpiles-worth-usd1-1-billion-of-covid-19-antiviral-pill-paxlovid-have



https://www.airfinity.com/articles/stockpiles-worth-usd1-1-billion-of-covid-19-antiviral-pill-paxlovid-have

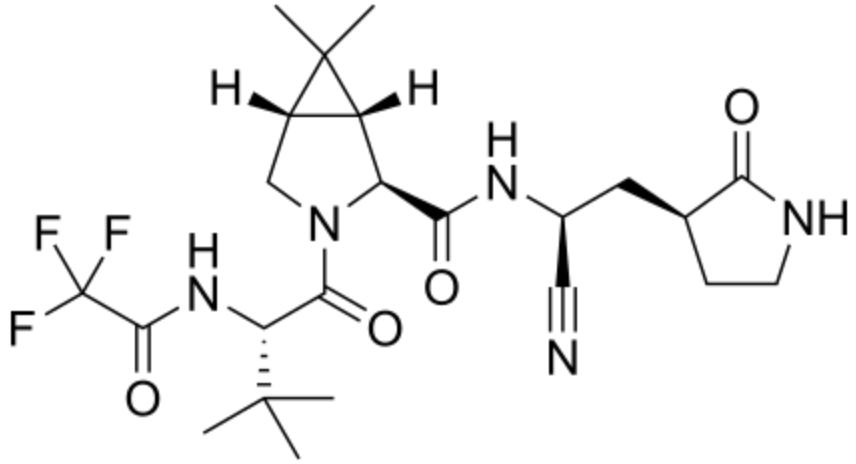
https://healthpolicy-watch.news/pfizers-paxlovid-goes-generic-in-95-countries-too-little-too-late-critics-say/


Uit wat bestaat
Paxlovid?

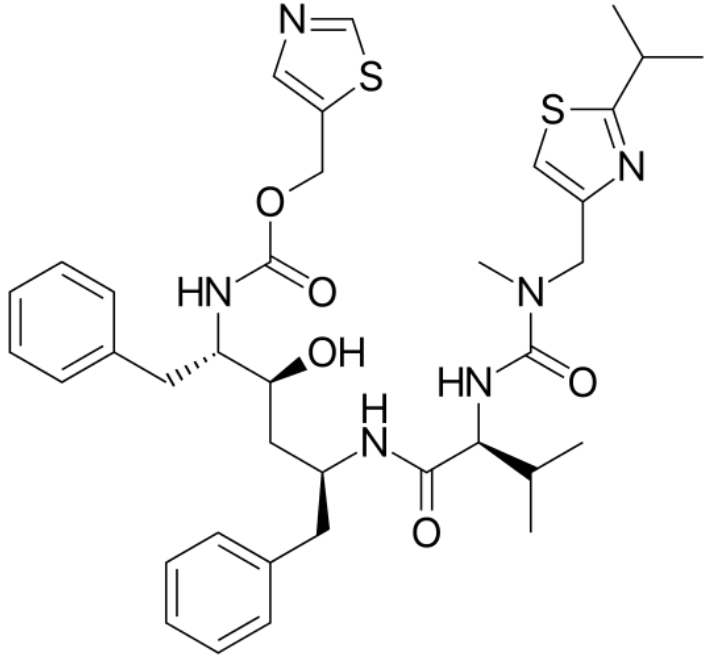

Pfizer
PAXLOVID™
150 mg + 100 mg
film-coated tablets
PF-07321332 and ritonavir
Oral use.
30 film-coated tablets
(20 PF-07321332 tablets and 10 ritonavir tablets)

PAXLOVID™

nirmatrelvir 150 mg tablets
PF-07321332



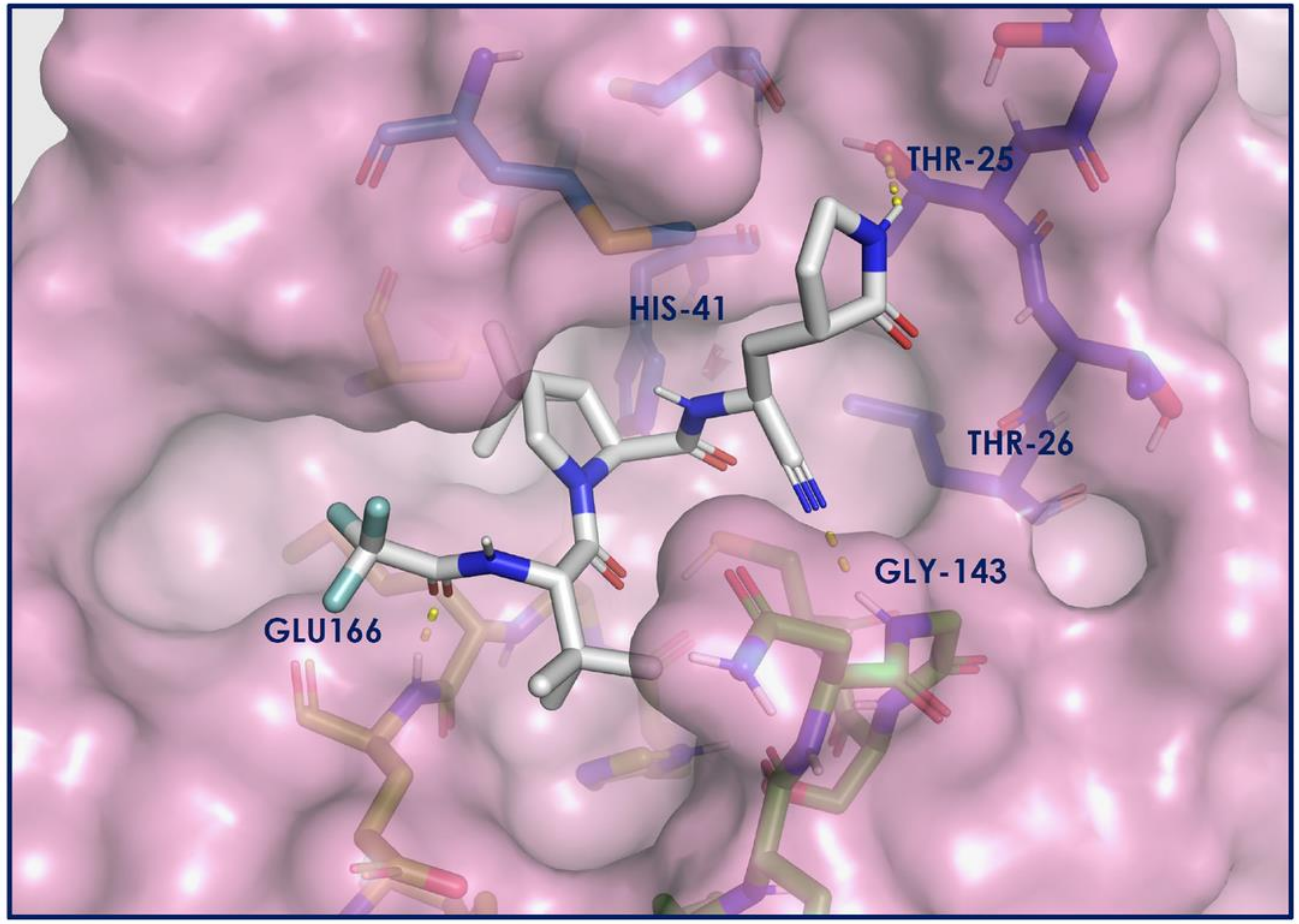
ritonavir 100 mg tablets



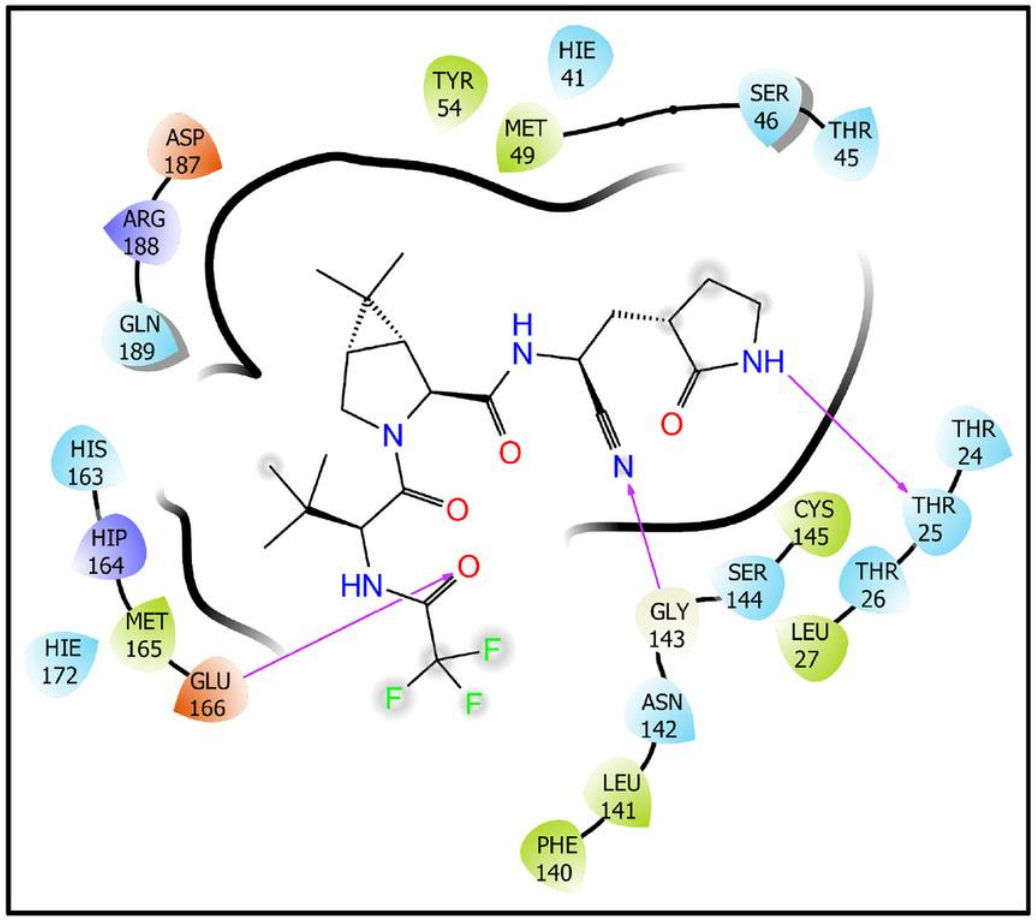
STRUCTURAL CHEMISTRY

Fragment-based design of SARS-CoV-2 Mpro inhibitors

Divya M. Teli, Bansari Patel & Mahesh T. Chhabria



Nirmatrelvir (Pfizer)



Structural Chemistry volume 33, pages2155–2168 (2022)

CYP3A4: Cytochrome P450 3A4

Drugs metabolized by CYP3A4

Fentanyl	Diazepam	Amlodipine
Buprenorphine	Midazolam	Rivaroxaban
Oxycodone	Alprazolam	Dabigatran
Methadone	Metoprolol	Apixaban
Nirmatrelvir	Losartan	Tacrolimus

CYP3A4 inhibitors

- Amiodarone
- Cimetidine
- Conazoles
- Diltiazem
- Verapamil
- Erythromycin
- Clarithromycin
- Fluoxetine
- Isoniazide
- **Ritonavir**
- Grapefruit
- Black pepper
- Goldenseal
- Inflammation

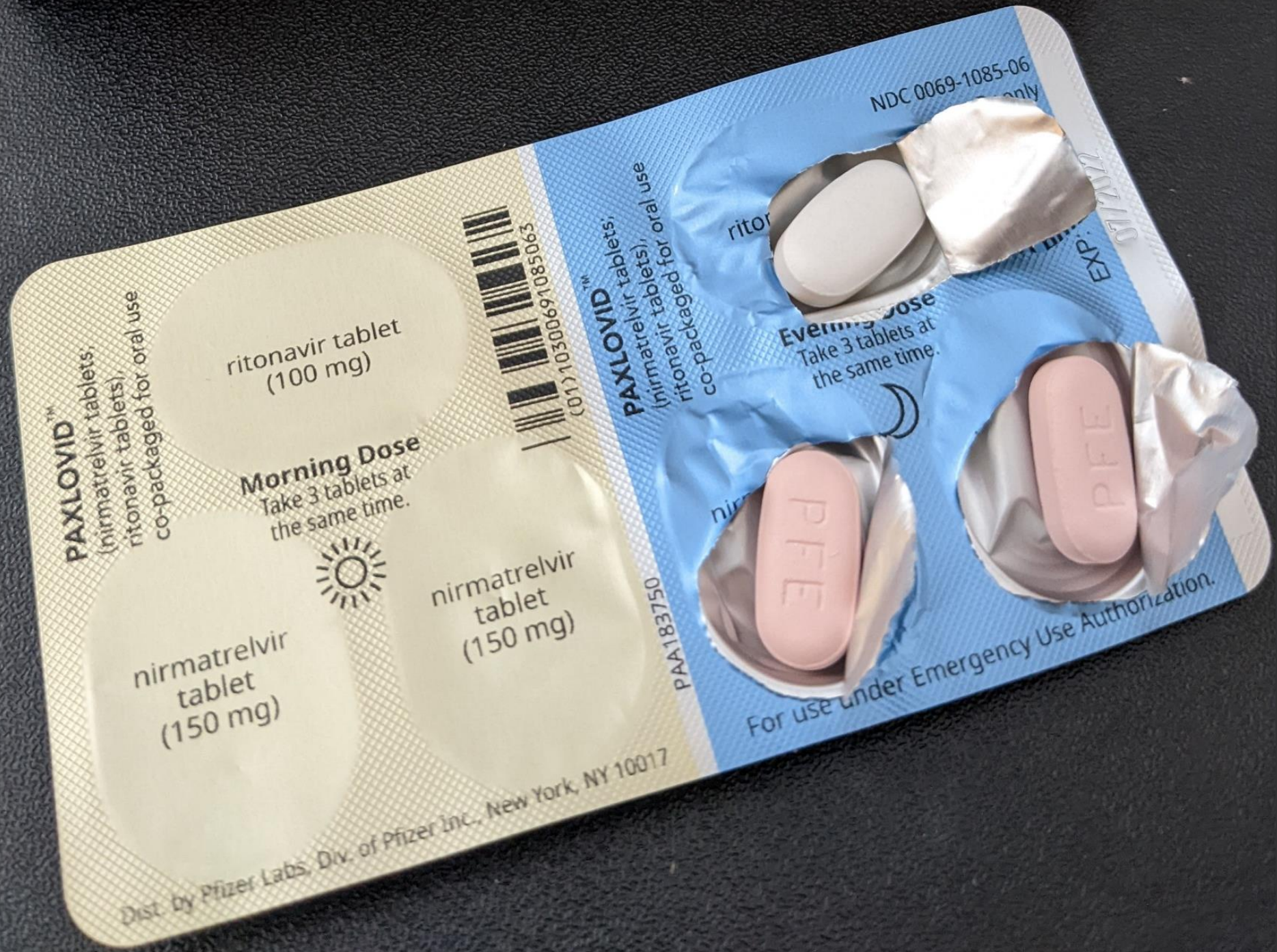
CYP3A4 inducers

- Butalbital
- Dexamethasone
- St. John's Wort

Sint-Janskruid

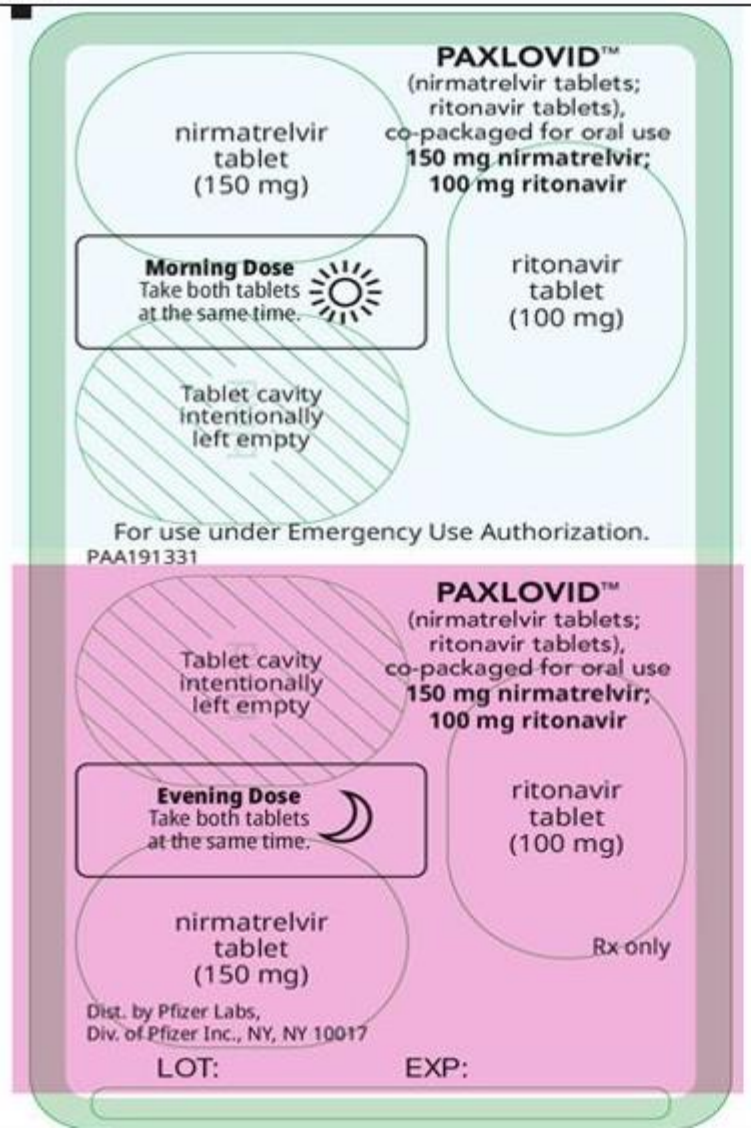

Dosering van
Paxlovid


PAXLOVID™
(nirmatrelvir tablets;
ritonavir tablets),
co-packaged for oral use
300 mg nirmatrelvir;
100 mg ritonavir
NDC 0069-1085-06
nirmatrelvir
tablet
(150 mg)
ritonavir
tablet
(100 mg)
Morning Dose
Take 3 tablets
at the same time.
For use under Emergency
Use Authorization.
14732501
Evening Dose
Take 3 tablets
at the same time.
Rx only


PAXLOVID™
(nirmatrelvir tablets;
ritonavir tablets),
co-packaged for oral use
ritonavir tablet
(100 mg)
Morning Dose
Take 3 tablets at
the same time.
nirmatrelvir
tablet
(150 mg)
nirmatrelvir
tablet
(150 mg)
(01)10300691085063
Dist. by Pfizer Labs, Div. of Pfizer Inc., New York, NY 10017
PAXLOVID™
(nirmatrelvir tablets;
ritonavir tablets),
co-packaged for oral use
PAA183750
NDC 0069-1085-06
EXP:
Take 3 tablets at
the same time.
PFE
PFE
For use under Emergency Use Authorization.

Dosisaanpassing bij minder goede nierfunctie

Blister Label



PAXLOVID™
(nirmatrelvir tablets; ritonavir tablets) co-packaged for oral use
150 mg nirmatrelvir; 100 mg ritonavir
Morning Dose
Take both tablets at the same time.
ritonavir tablet (100 mg)
nirmatrelvir tablet (150 mg)
Tablet cavity intentionally left empty
Evening Dose
Take both tablets at the same time.
ritonavir tablet (100 mg)
nirmatrelvir tablet (150 mg)
Tablet cavity intentionally left empty

Contra-indicaties voor Paxlovid

Do not take PAXLOVID if:

- You are allergic to nirmatrelvir, ritonavir, or any of the ingredients in PAXLOVID
- You are taking any of the following medicines:
  - alfuzosin
  - amiodarone
  - apalutamide
  - carbamazepine
  - colchicine
  - dihydroergotamine
  - dronedarone
  - eletriptan
  - eplerenone
  - ergotamine
  - finerenone
  - flecainide
  - flibanserin
  - ivabradine
  - lomitapide
  - lovastatin
  - lumacaftor/ivacaftor
  - lurasidone
  - methylergonovine
  - midazolam (oral)
  - naloxegol
  - phenobarbital
  - phenytoin
  - pimozide
  - primidone
  - propafenone
  - quinidine
  - ranolazine
  - rifampin
  - St. John's Wort (*hypericum perforatum*)
  - sildenafil (Revatio®) for pulmonary arterial hypertension
  - silodosin
  - simvastatin
  - tolvaptan
  - triazolam
  - ubrogepant
  - voclosporin

https://www.paxlovid.com/how-to-take

Interactieszoeker

Zoek naar interacties op namen van werkzame stoffen of op trefwoorden

De vermelde geneesmiddelen zijn een leidraad en worden niet beschouwd als een volledige lijst van alle mogelijke geneesmiddelen die een wisselwerking kunnen hebben met PAXLOVID. De zorgverlener dient de juiste referenties te raadplegen voor uitgebreide informatie. Neem voor vragen of aanvullende informatie contact op met de lokale vertegenwoordiger op 0800/58 037.

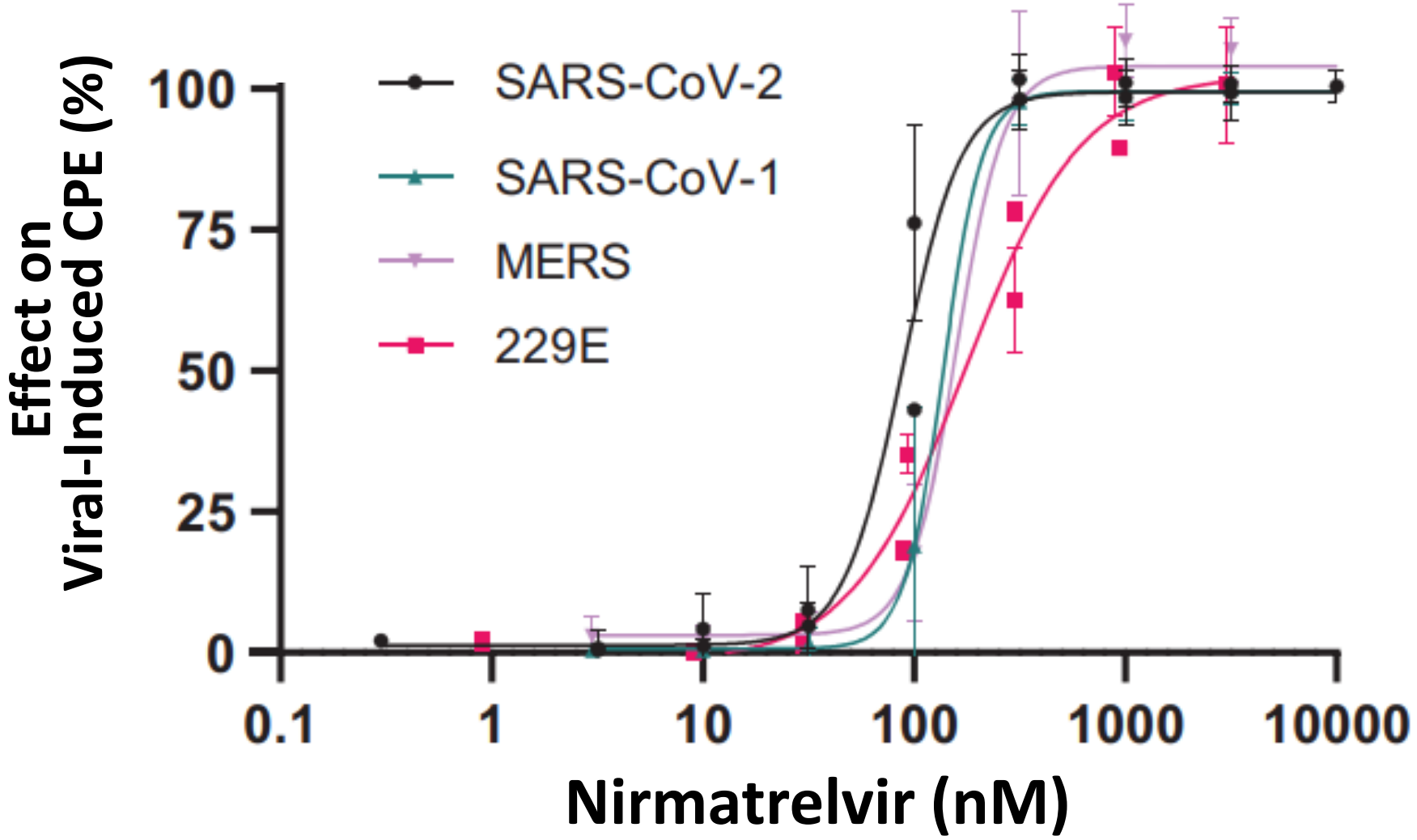
Type something

https://www.paxlovideducation.be/nl/geneesmiddeleninteractieszoeker

Hoe goed werkt Paxlovid tegen SARS-CoV-2?

An oral SARS-CoV-2 M^{pro} inhibitor clinical candidate for the treatment of COVID-19

Owen D.R. et al.



Owen et al., Science 374, 1586–1593 (2021) 24 December 2021
https://www.science.org/doi/pdf/10.1126/science.abl4784

The NEW ENGLAND JOURNAL of MEDICINE

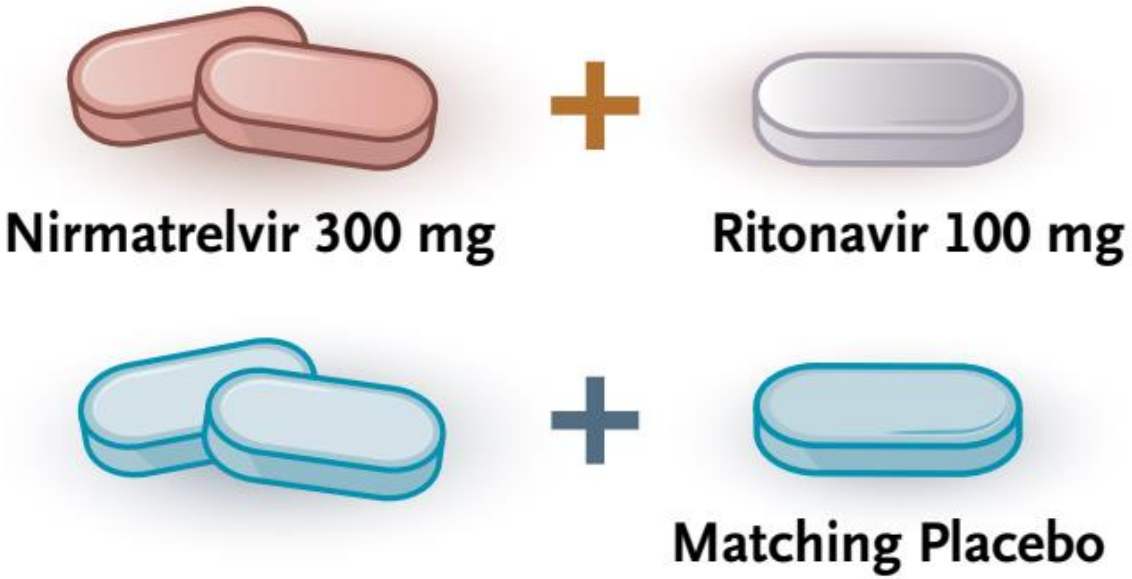
Oral Nirmatrelvir for High-Risk, Nonhospitalized Adults with Covid-19

Hammond J. et al.

CLINICAL TRIAL

Design: An international, phase 2–3, double-blind, randomized, controlled trial assessed the efficacy and safety of the antiviral agent nirmatrelvir plus ritonavir (a pharmacokinetic enhancer) in preventing disease progression in unvaccinated adults with mild-to-moderate Covid-19 who were at high risk for progression to severe Covid-19.

Intervention: 2246 adults with confirmed SARS-CoV-2 infection were randomly assigned to receive nirmatrelvir (300 mg) plus ritonavir (100 mg) or matching placebo every 12 hours for 5 days, beginning within 5 days after the onset of Covid-19 symptoms. The primary outcome of the final analysis involving 1379 patients was the incidence of Covid-19–related hospitalization or death from any cause by day 28 in patients receiving treatment within 3 days after symptom onset.

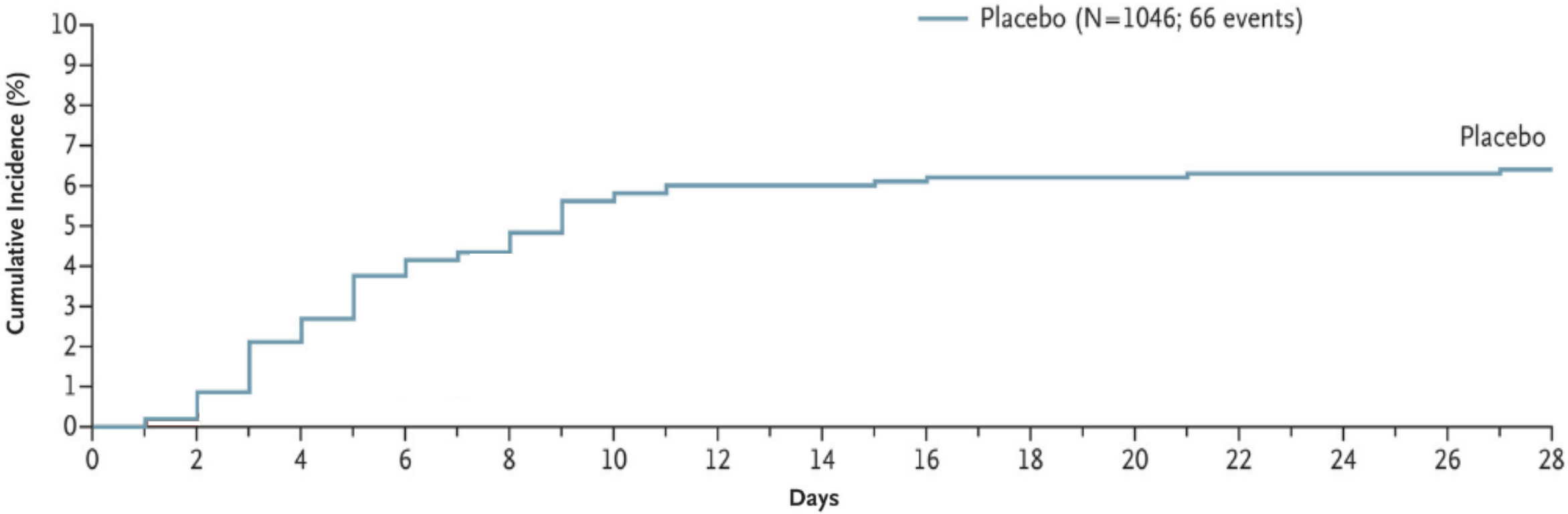


April 14, 2022 N Engl J Med 2022; 386:1397-1408
DOI: 10.1056/NEJMoa2118542

The NEW ENGLAND JOURNAL of MEDICINE

Oral Nirmatrelvir for High-Risk, Nonhospitalized Adults with Covid-19

Hammond J. et al.



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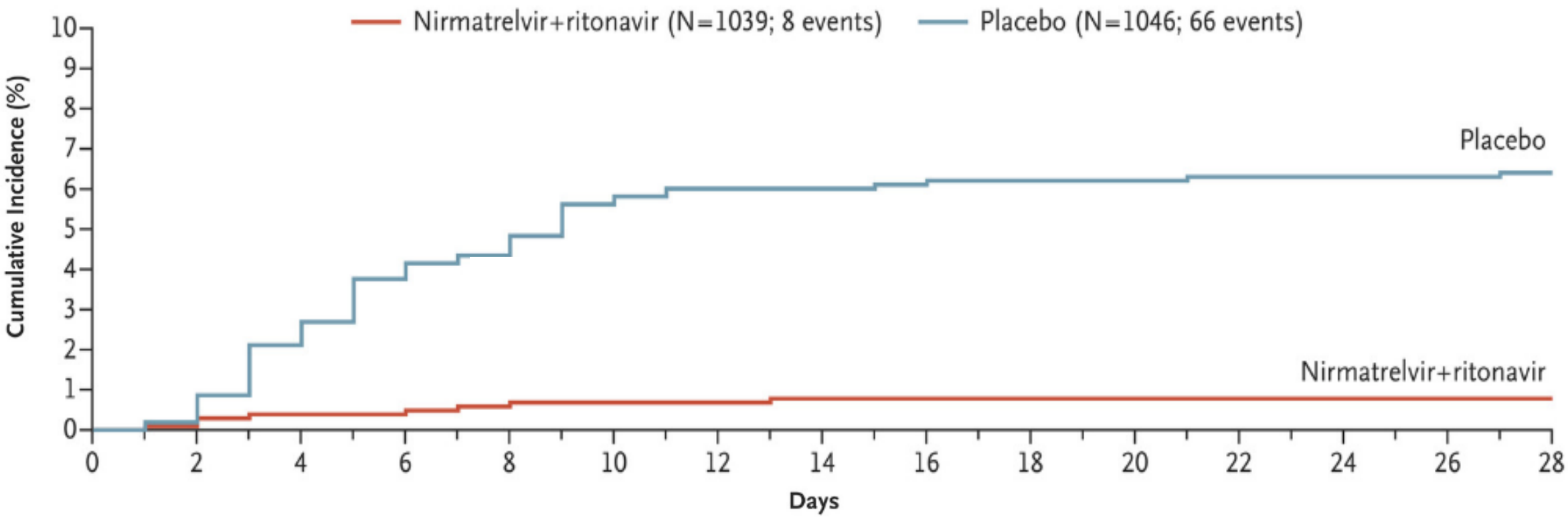


April 14, 2022 N Engl J Med 2022; 386:1397-1408
DOI: 10.1056/NEJMoa2118542

The NEW ENGLAND JOURNAL of MEDICINE

Oral Nirmatrelvir for High-Risk, Nonhospitalized Adults with Covid-19

Hammond J. et al.

Treated ≤3 Days after Onset of Symptoms through Day 28 (modified intention-to-treat population)

	Nirmatrelvir Group N = 697	Placebo Group N = 682
Total number of patients with event	5	44
Covid-19–related hospitalization	5	44
Death from any cause	0	9
Estimated percentage with event (95% CI)	0.72 (0.30–1.73)	6.53 (4.90–8.68)
Difference ±SE from placebo — percentage points	−5.81±1.01	
Relative risk reduction	88.9%	

April 14, 2022 N Engl J Med 2022; 386:1397-1408
DOI: 10.1056/NEJMoa2118542

JOURNAL OF MEDICAL VIROLOGY

Nirmatrelvir–ritonavir compared with other antiviral drugs for the treatment of COVID-19 patients: A systematic review and meta-analysis

Tian et al.

We conducted a meta-analysis to estimate the effects of nirmatrelvir–ritonavir compared with other antiviral drugs for the treatment of COVID-19 patients and safety outcomes.

Twelve studies were included, including 30 588 COVID-19 patients, of whom 13 402 received nirmatrelvir–ritonavir.

The meta-analysis results showed that the nirmatrelvir–ritonavir group had a lower proportion of patients than the control group in terms of long-term mortality (odds ratio [OR] = 0.29, 95% confidence interval [CI]: 0.13–0.66), hospitalization (OR = 0.44, 95% CI: 0.37–0.53, short term; OR = 0.52, 95% CI: 0.36–0.77, long term), and disease progression (OR = 0.56, 95% CI: 0.38–0.83, short term; OR = 0.60, 95% CI: 0.48–0.74, long term), and nirmatrelvir ritonavir showed little difference in safety compared to the control group.

Nirmatrelvir–ritonavir can reduce the mortality and hospitalization of COVID-19 patients compared with other antiviral drugs. Further large-scale studies remain to validate these findings.

13 april 2023 https://onlinelibrary.wiley.com/doi/10.1002/jmv.28732

JOURNAL OF
MEDICAL VIROLOGY

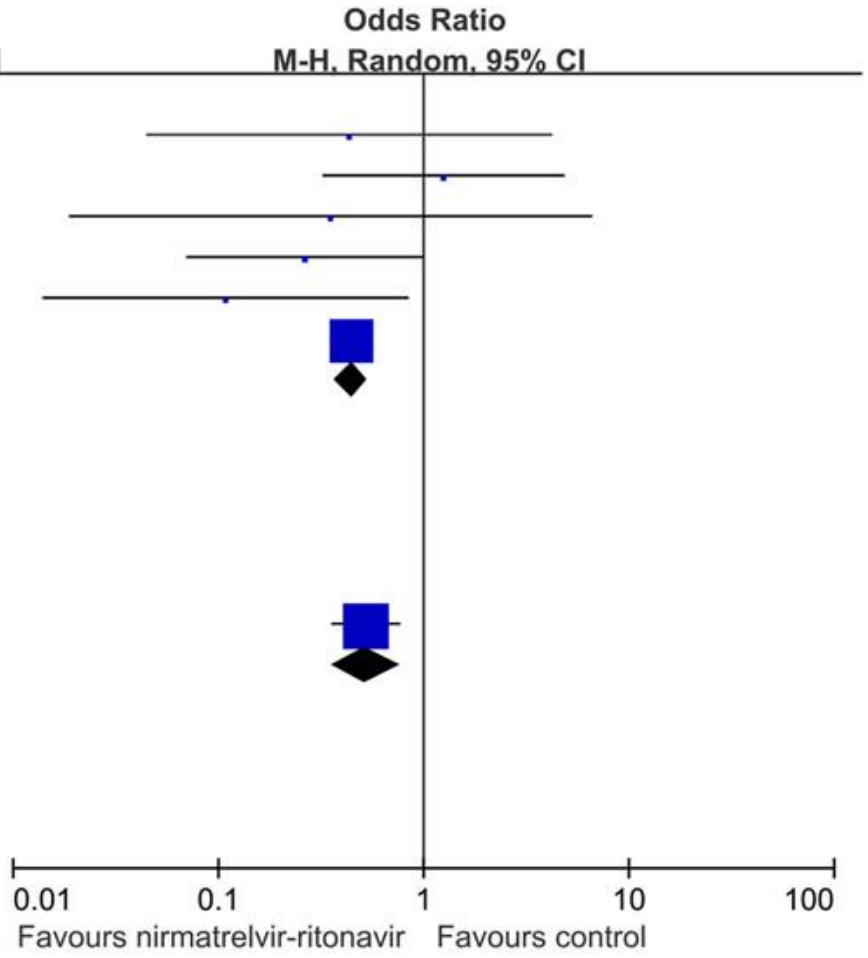
Nirmatrelvir–ritonavir compared with other antiviral drugs for the treatment of COVID-19 patients: A systematic review and meta-analysis

Tian et al.

Hospitalisation

Study or Subgroup	Nirmatrelvir-ritonavir Events	Total	Control Events	Total	Weight	Odds Ratio M-H, Random, 95% CI
1.2.1 short-term						
Gentile, et al. 2022	1	111	3	146	0.6%	0.43 [0.04, 4.22]
Hedvat, et al. 2022	4	28	6	51	1.7%	1.25 [0.32, 4.86]
Martin-Blondel, et al. 2022	0	60	4	195	0.4%	0.35 [0.02, 6.63]
Qian, et al. 2022	4	307	5	105	1.7%	0.26 [0.07, 1.00]
Tiseo, et al. 2023	1	252	11	310	0.7%	0.11 [0.01, 0.84]
Yip, et al. 2022	172	4921	437	5808	94.9%	0.45 [0.37, 0.53]
Subtotal (95% CI)		**5679**		**6615**	**100.0%**	**0.44 [0.37, 0.53]**
Total events	182		466			
Heterogeneity: Tau² = 0.00; Chi² = 4.66, df = 5 (P = 0.46); I² = 0%						
Test for overall effect: Z = 9.05 (P < 0.00001)						
1.2.2 long-term						
Wong, et al. 2022b	41	5542	70	4983	100.0%	0.52 [0.36, 0.77]
Subtotal (95% CI)		**5542**		**4983**	**100.0%**	**0.52 [0.36, 0.77]**
Total events	41		70			
Heterogeneity: Not applicable						
Test for overall effect: Z = 3.28 (P = 0.001)						

Test for subgroup differences: Chi² = 0.57, df = 1 (P = 0.45), I² = 0%



13 april 2023 https://onlinelibrary.wiley.com/doi/10.1002/jmv.28732

JOURNAL OF
MEDICAL VIROLOGY

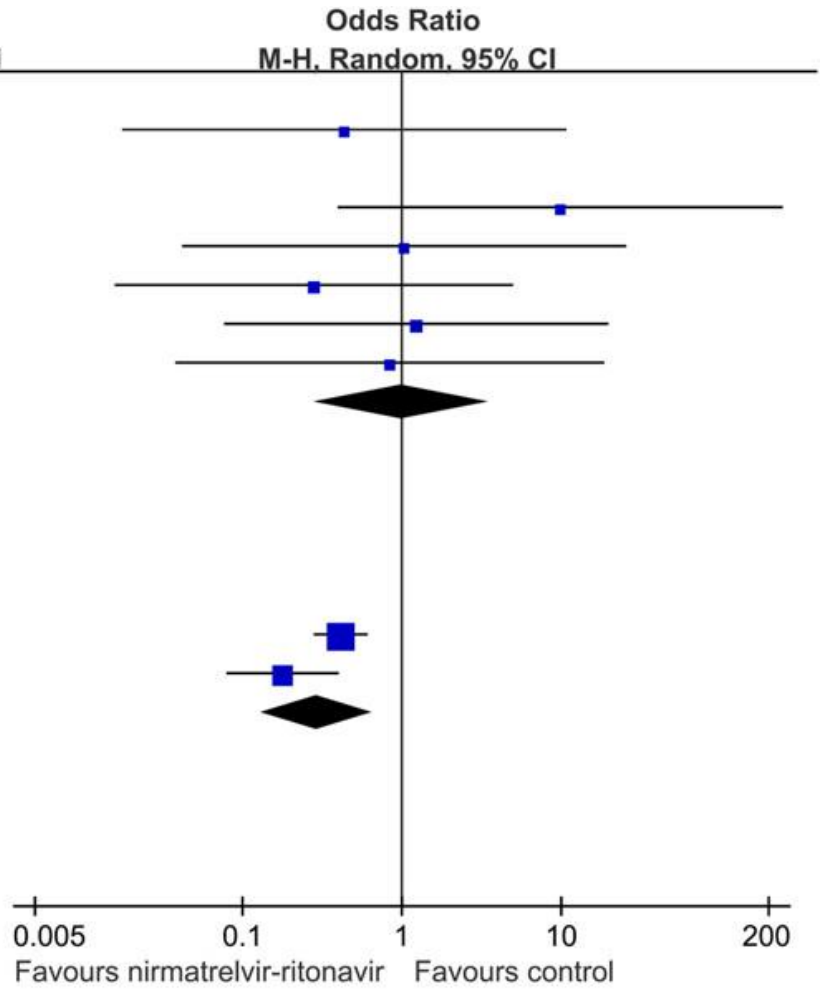
Nirmatrelvir–ritonavir compared with other antiviral drugs for the treatment of COVID-19 patients: A systematic review and meta-analysis

Tian et al.

Mortality

Study or Subgroup	Nirmatrelvir-ritonavir Events	Total	Control Events	Total	Weight	Odds Ratio M-H, Random, 95% CI
1.1.1 short-term						
Gentile, et al. 2022	0	111	1	146	15.0%	0.43 [0.02, 10.78]
Hedvat, et al. 2022	0	28	0	51		Not estimable
Martin-Blondel, et al. 2022	1	60	0	195	15.0%	9.86 [0.40, 245.17]
Qian, et al. 2022	1	307	0	105	15.0%	1.03 [0.04, 25.54]
Razonable, et al. 2022	0	774	6	2833	18.7%	0.28 [0.02, 4.99]
Tiseo, et al. 2023	1	252	1	310	20.1%	1.23 [0.08, 19.78]
Vora, et al. 2023	0	12	2	54	16.1%	0.84 [0.04, 18.62]
Subtotal (95% CI)		**1544**		**3694**	**100.0%**	**1.00 [0.29, 3.47]**
Total events	3		10			
Heterogeneity: Tau² = 0.00; Chi² = 3.01, df = 5 (P = 0.70); I² = 0%						
Test for overall effect: Z = 0.00 (P = 1.00)						
1.1.2 long-term						
Wong, et al. 2022a	32	924	150	1880	59.4%	0.41 [0.28, 0.61]
Wong, et al. 2022b	7	5542	35	4983	40.6%	0.18 [0.08, 0.40]
Subtotal (95% CI)		**6466**		**6863**	**100.0%**	**0.29 [0.13, 0.66]**
Total events	39		185			
Heterogeneity: Tau² = 0.25; Chi² = 3.34, df = 1 (P = 0.07); I² = 70%						
Test for overall effect: Z = 2.97 (P = 0.003)						

Test for subgroup differences: Chi² = 2.61, df = 1 (P = 0.11), I² = 61.6%



13 april 2023 https://onlinelibrary.wiley.com/doi/10.1002/jmv.28732

Werkt Paxlovid beter dan molnupiravir?

THE LANCET
Infectious Diseases

Antiviral efficacy of molnupiravir versus ritonavir-boosted nirmatrelvir in patients with early symptomatic COVID-19 (PLATCOV): an open-label, phase 2, randomised, controlled, adaptive trial

William H K Schilling et al.

Between June 6, 2022, and Feb 23, 2023, **209 patients in Thailand** were enrolled and concurrently randomly assigned to molnupiravir (n=65), ritonavir-boosted nirmatrelvir (n=59), or no study drug (n=85). 129 (62%) of the patients were female and 80 (38%) were male. Relative to the no study drug group, the rates of viral clearance were 37% (95% credible interval 16–65) faster with molnupiravir and 84% (54–119) faster with ritonavir-boosted nirmatrelvir. **In the non-inferiority comparison, viral clearance was 25% (10–38) slower with molnupiravir than ritonavir-boosted nirmatrelvir.** Molnupiravir was removed from the study platform when it reached the prespecified inferiority margin of 10% compared with ritonavir-boosted nirmatrelvir. Median estimated viral clearance half-lives were 8·5 h (IQR 6·7–10·1) with ritonavir-boosted nirmatrelvir, 11·6 h (8·6–15·4) with molnupiravir, and 15·5 h (11·9–21·2) with no study drug. **Viral rebound occurred more frequently following nirmatrelvir (six [10%] of 58) compared with the no study drug** (one [1%] of 84; p=0·018) or the molnupiravir (one [2%] of 65; p=0·051) groups. **Persistent infections following molnupiravir had more viral mutations (three of nine patients had an increased number of single nucleotide polymorphisms in samples collected at 7 or more days compared with those at baseline) than after nirmatrelvir (zero of three) or no study drug (zero of 19)**. There were no adverse events of grade 3 or worse, or serious adverse events in any of the reported treatment groups.

THE LANCET
Infectious Diseases

Antiviral efficacy of molnupiravir versus ritonavir-boosted nirmatrelvir in patients with early symptomatic COVID-19 (PLATCOV): an open-label, phase 2, randomised, controlled, adaptive trial

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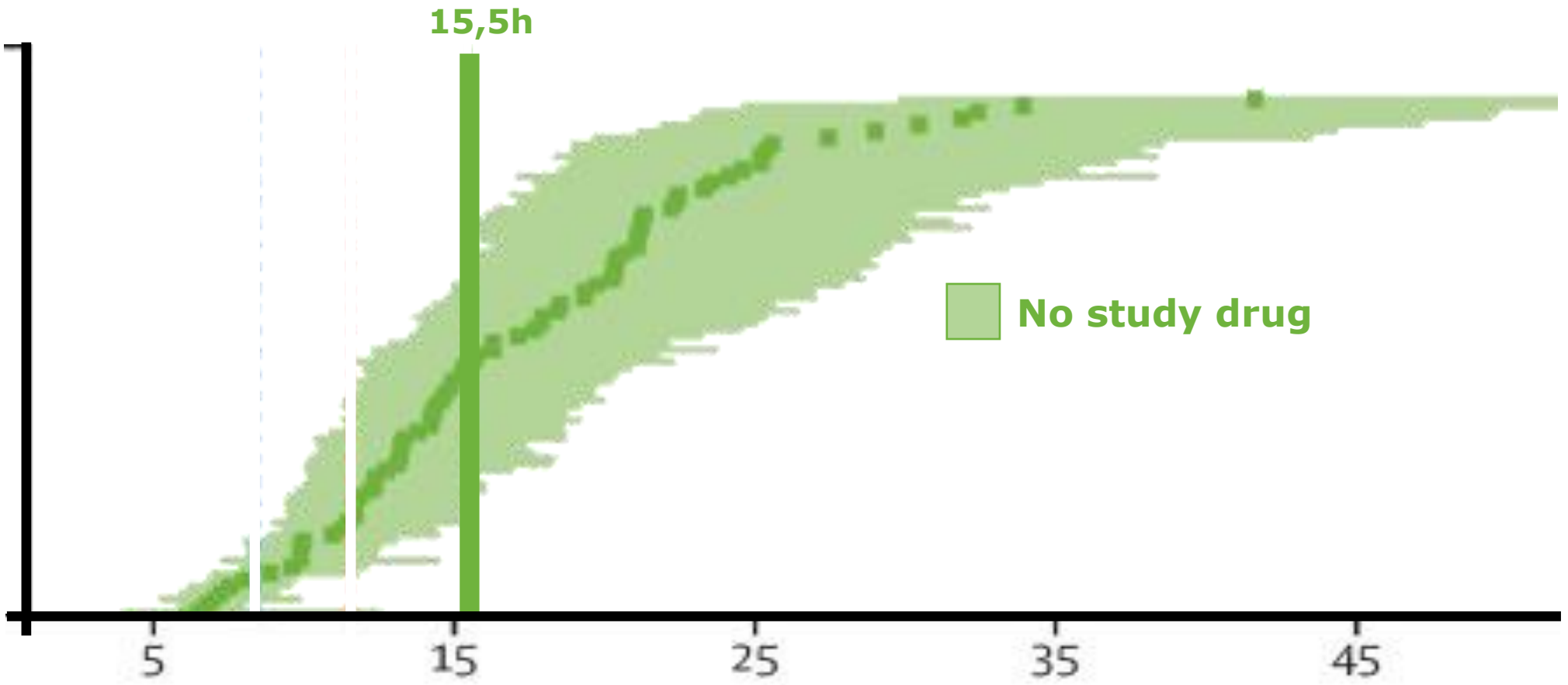

THE LANCET
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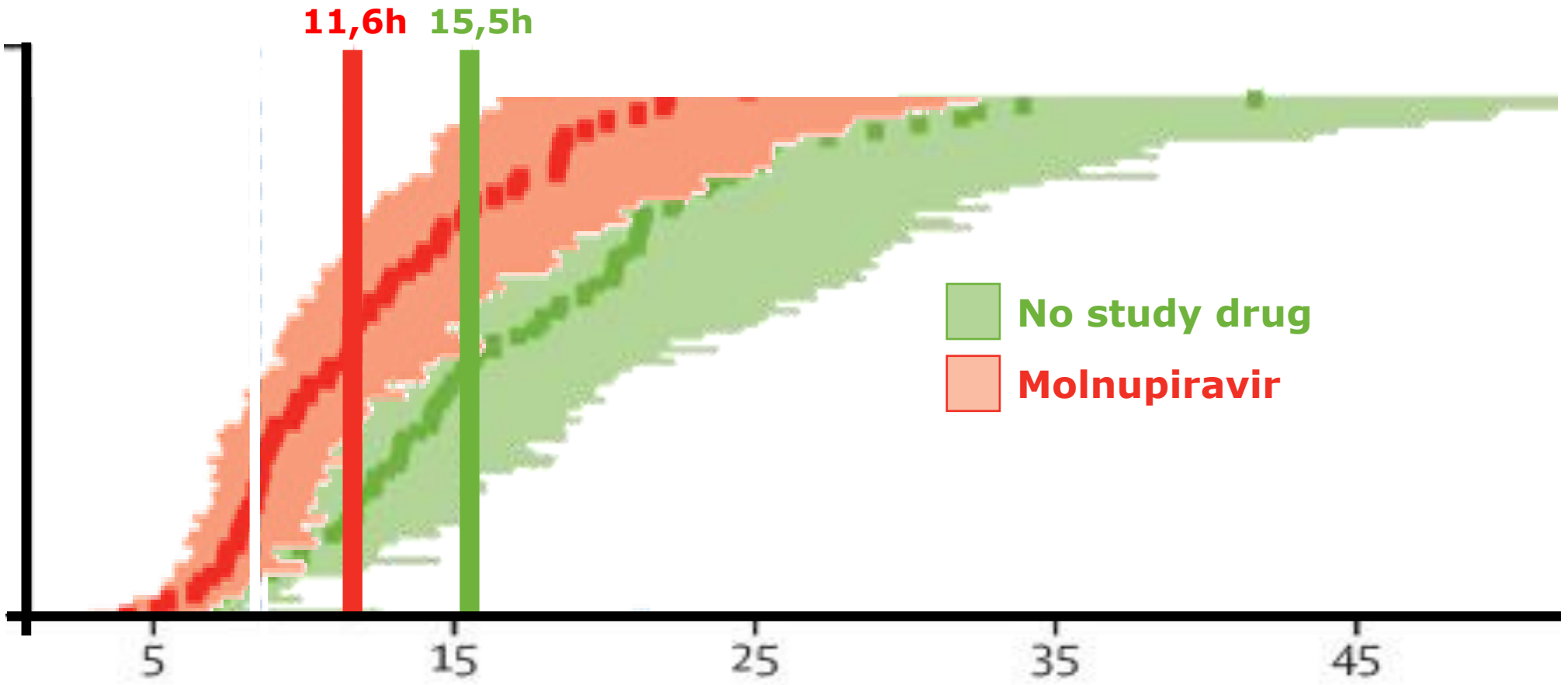
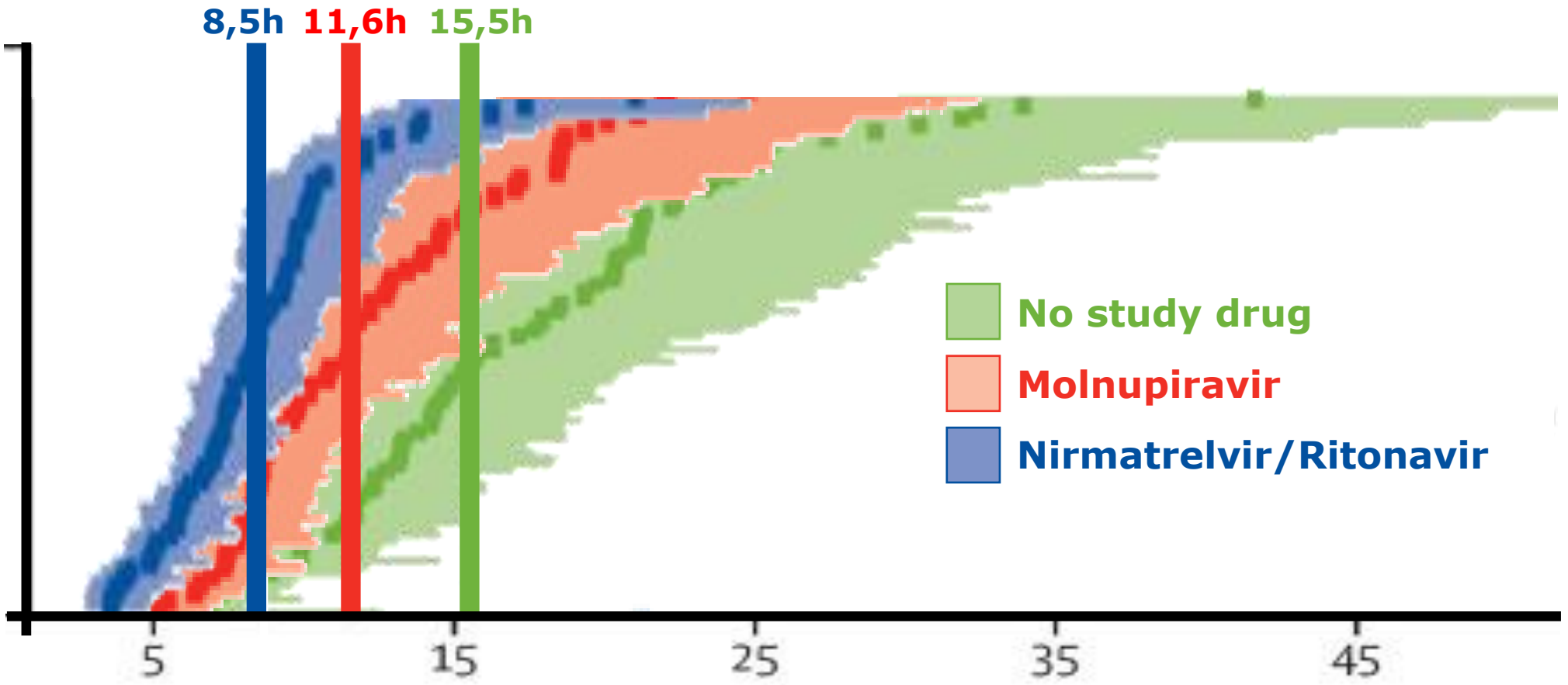


THE LANCET
Infectious Diseases

Antiviral efficacy of molnupiravir versus ritonavir-boosted nirmatrelvir in patients with early symptomatic COVID-19 (PLATCOV): an open-label, phase 2, randomised, controlled, adaptive trial

William H K Schilling et al.



THE LANCET Regional Health Europe

Real-life comparison of mortality in patients with SARS-CoV-2 infection at risk for clinical progression treated with molnupiravir or nirmatrelvir plus ritonavir during the Omicron era in Italy: a nationwide, cohort study

Carlo Torti et al.

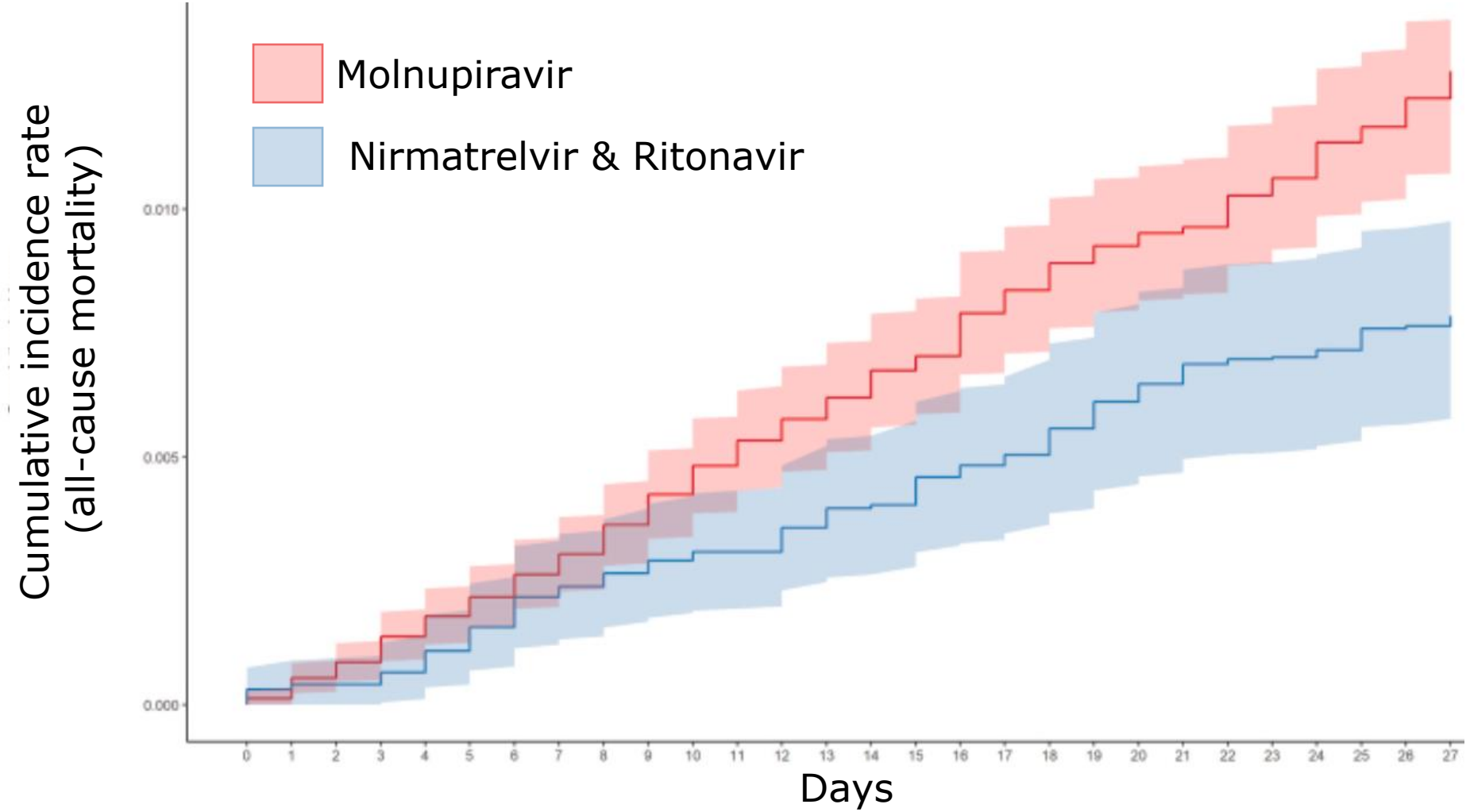
17,977 patients treated with molnupiravir and 11,576 patients with nirmatrelvir plus ritonavir were included in the analysis. Most patients (25,617/29,553 = 86.7%) received a full vaccine course including the booster dose. A higher crude incidence rate of all-cause mortality was found among molnupiravir users (51.83 per 100,000 person-days), compared to nirmatrelvir plus ritonavir users (22.29 per 100,000 person-days). However, molnupiravir-treated patients were older than those treated with nirmatrelvir plus ritonavir and differences between the two populations were found as far as types of co-morbidities were concerned. For this reason, we compared the weight-adjusted cumulative incidences using the Aalen estimator and found that the adjusted cumulative incidence rates were 1.23% (95% CI 1.07%-1.38%) for molnupiravir-treated and 0.78% (95% CI 0.58%-0.98%) for nirmatrelvir plus ritonavir-treated patients (adjusted log rank p = 0.0002). Moreover, the weight-adjusted mixed-effect Cox model including Italian regions and NHS centers as random effects and treatment as the only covariate confirmed a significant reduced risk of death in patients treated with nirmatrelvir plus ritonavir. Lastly, a significant reduction in the risk of death associated with nirmatrelvir plus ritonavir was confirmed in patient subgroups, such as in females, fully vaccinated patients, those treated within day 2 since symptom onset and patients without (haemato)-oncological diseases.

Lancet Reg Health Eur . 2023 Jul 14:31:100684. doi: 10.1016/j.lanepe.2023.100684

THE LANCET *Regional Health*
Europe

Real-life comparison of mortality in patients with SARS-CoV-2 infection at risk for clinical progression treated with molnupiravir or nirmatrelvir plus ritonavir during the Omicron era in Italy: a nationwide, cohort study

Carlo Torti et al.



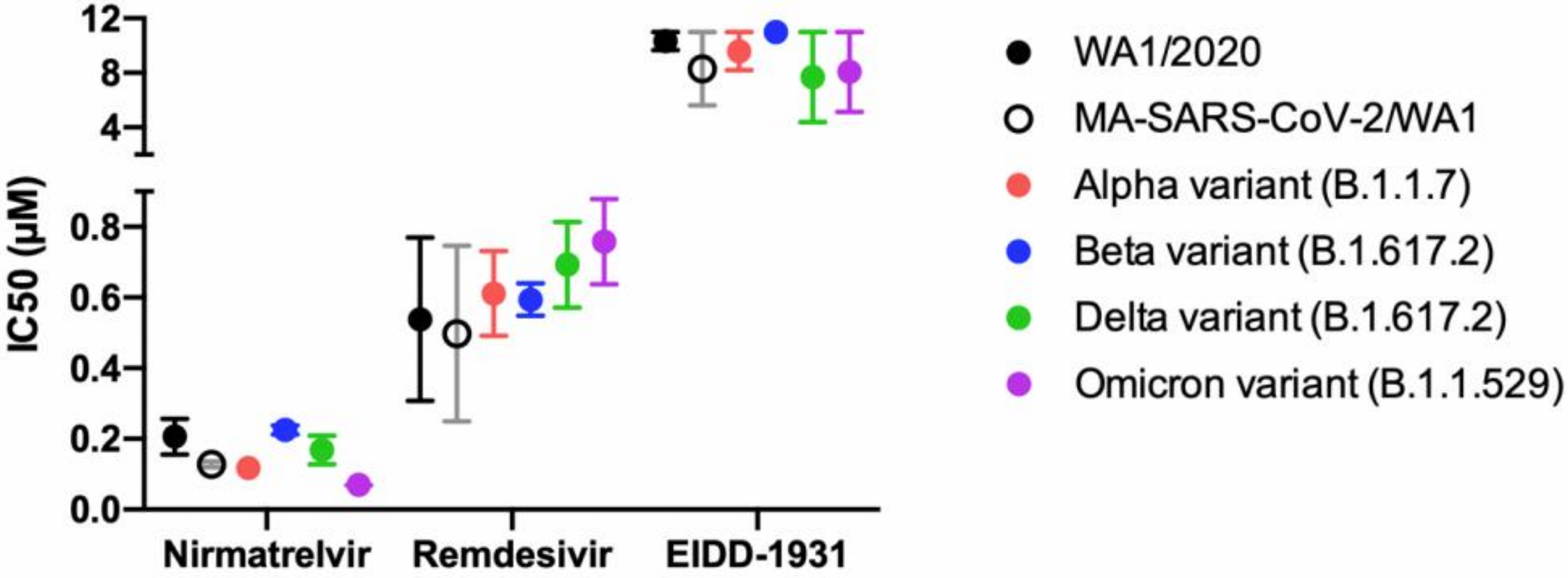
Lancet Reg Health Eur . 2023 Jul 14:31:100684. doi: 10.1016/j.lanepe.2023.100684

Activiteit van Paxlovid tegen varianten?

ANTIVIRAL RESEARCH

Remdesivir, Molnupiravir and Nirmatrelvir remain active against SARS-CoV-2 Omicron and other variants of concern

Laura Vangeel, Winston Chiu, Steven De Jonghe, Piet Maes, Bram Slechten, Joren Raymenants, Emmanuel André, Pieter Leyssen, Johan Neyts, Dirk Jochmans



Antiviral Res . 2022 Feb;198:105252; Epub 2022 Jan 24
doi: 10.1016/j.antiviral.2022.105252

Nevenwerkingen van Paxlovid

Possible side effects of PAXLOVID are:

- **Allergic Reactions.** Allergic reactions, including severe allergic reactions (known as 'anaphylaxis'), can happen in people taking PAXLOVID, even after only 1 dose. Stop taking PAXLOVID and call your healthcare provider right away if you get any of the following symptoms of an allergic reaction:
  - hives
  - trouble swallowing or breathing
  - swelling of the mouth, lips, or face
  - throat tightness
  - hoarseness
  - skin rash
- **Liver Problems.** Tell your healthcare provider right away if you have any of these signs and symptoms of liver problems: loss of appetite, yellowing of your skin and the whites of your eyes (jaundice), dark-colored urine, pale-colored stools and itchy skin, or stomach area (abdominal) pain
- **Resistance to HIV Medicines.** If you have untreated HIV infection, PAXLOVID may lead to some HIV medicines not working as well in the future
- **Other possible side effects include:**
  - altered sense of taste
  - diarrhea
  - high blood pressure
  - muscle aches
  - abdominal pain
  - nausea
  - feeling generally unwell

https://www.paxlovid.com/how-to-take

The NEW ENGLAND JOURNAL of MEDICINE

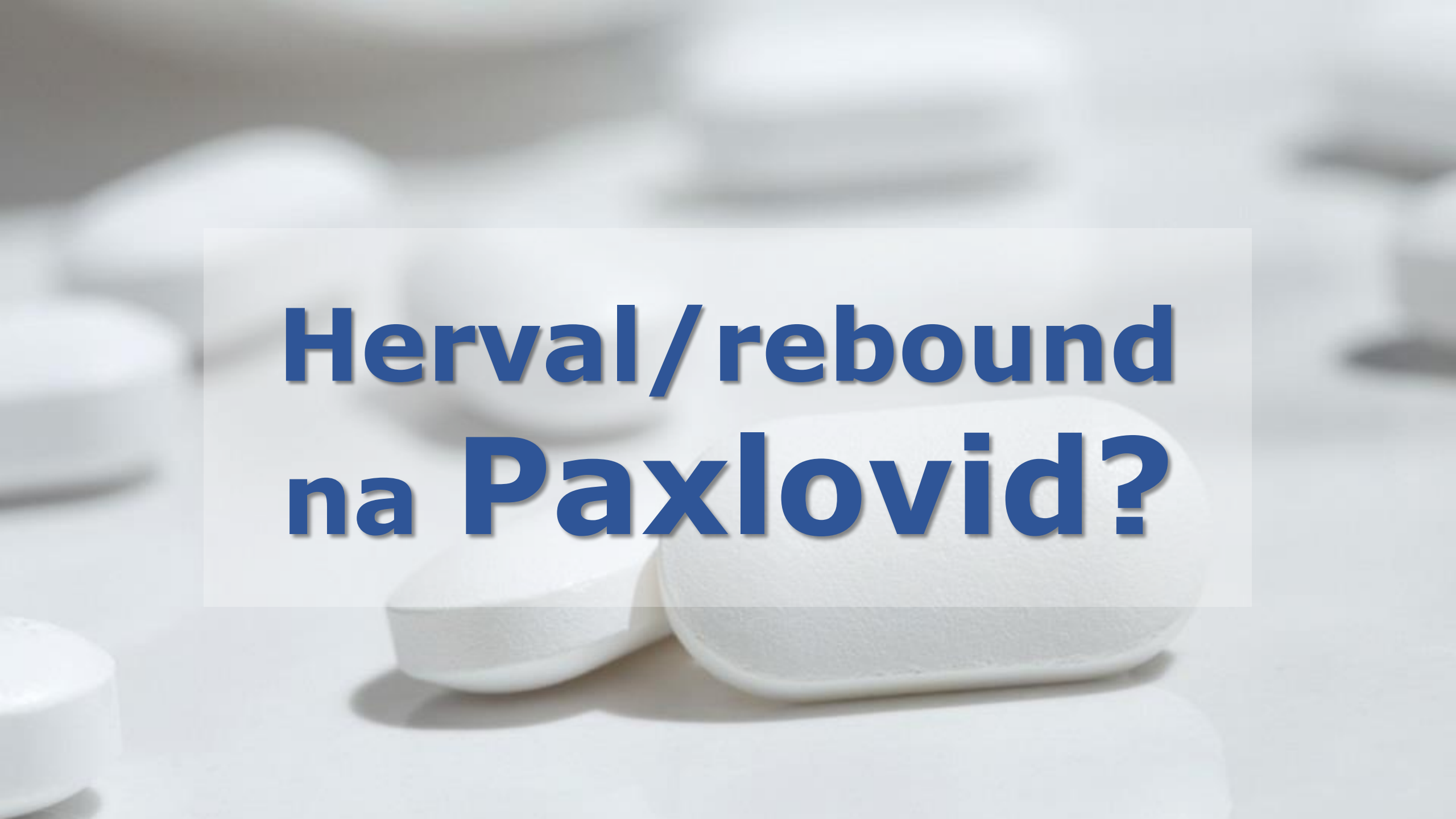
Oral Nirmatrelvir for High-Risk, Nonhospitalized Adults with Covid-19

Hammond J. et al.

Adverse Events during Treatment Period (safety-analysis population)

	Nirmatrelvir Group N=1109	Placebo Group N=1115
No. of adverse events	476	525
Patients with any adverse event — no. (%)	251 (22.6)	266 (23.9)
Serious adverse event	18 (1.6)	74 (6.6)
Maximum grade 3 or 4 adverse event	45 (4.1)	93 (8.3)
Maximum grade 5 adverse event	0	13 (1.2)
Discontinued drug or placebo because of adverse event	23 (2.1)	47 (4.2)
Had dose reduction or temporary discontinuation owing to adverse event	4 (0.4)	4 (0.4)

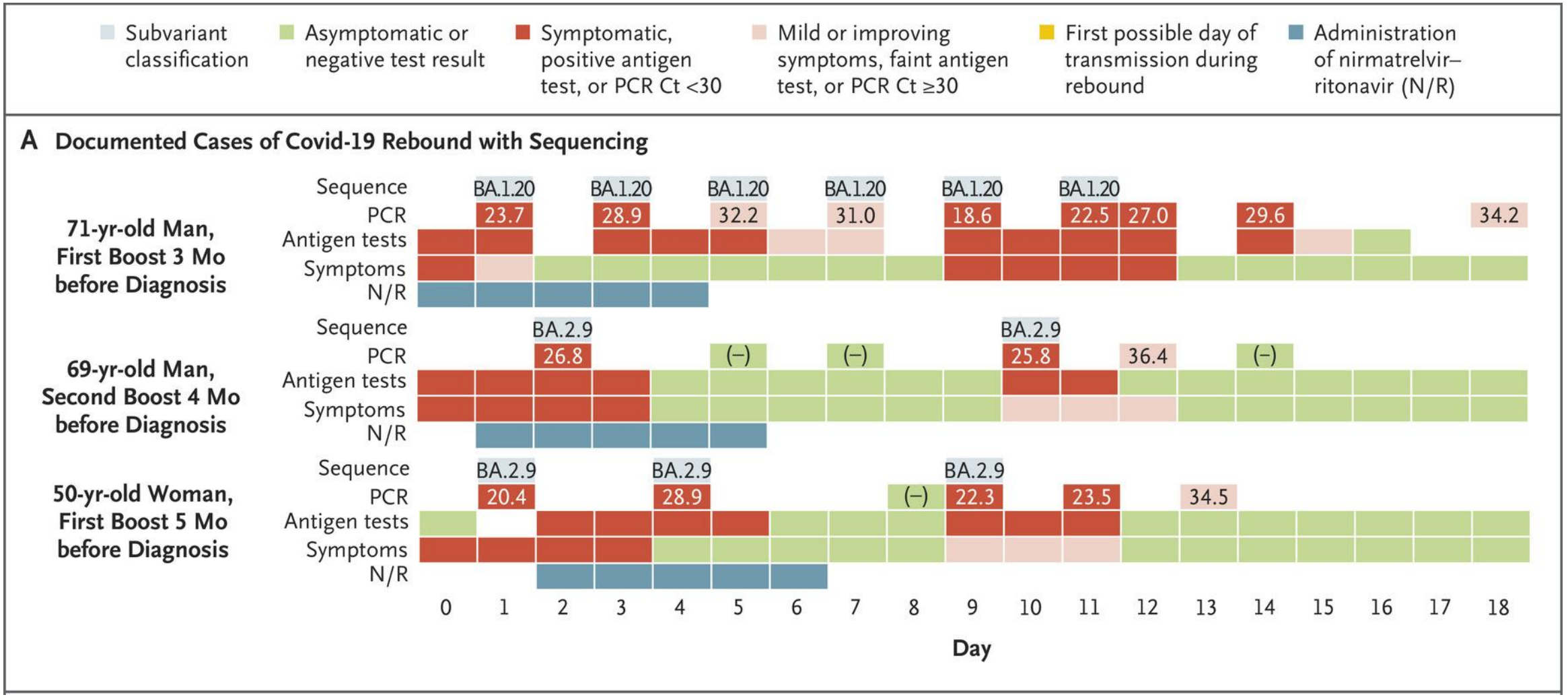
022; 386:1397-1408
DOI: 10.1056/NEJMoa2118542


Herval/rebound
na Paxlovid?

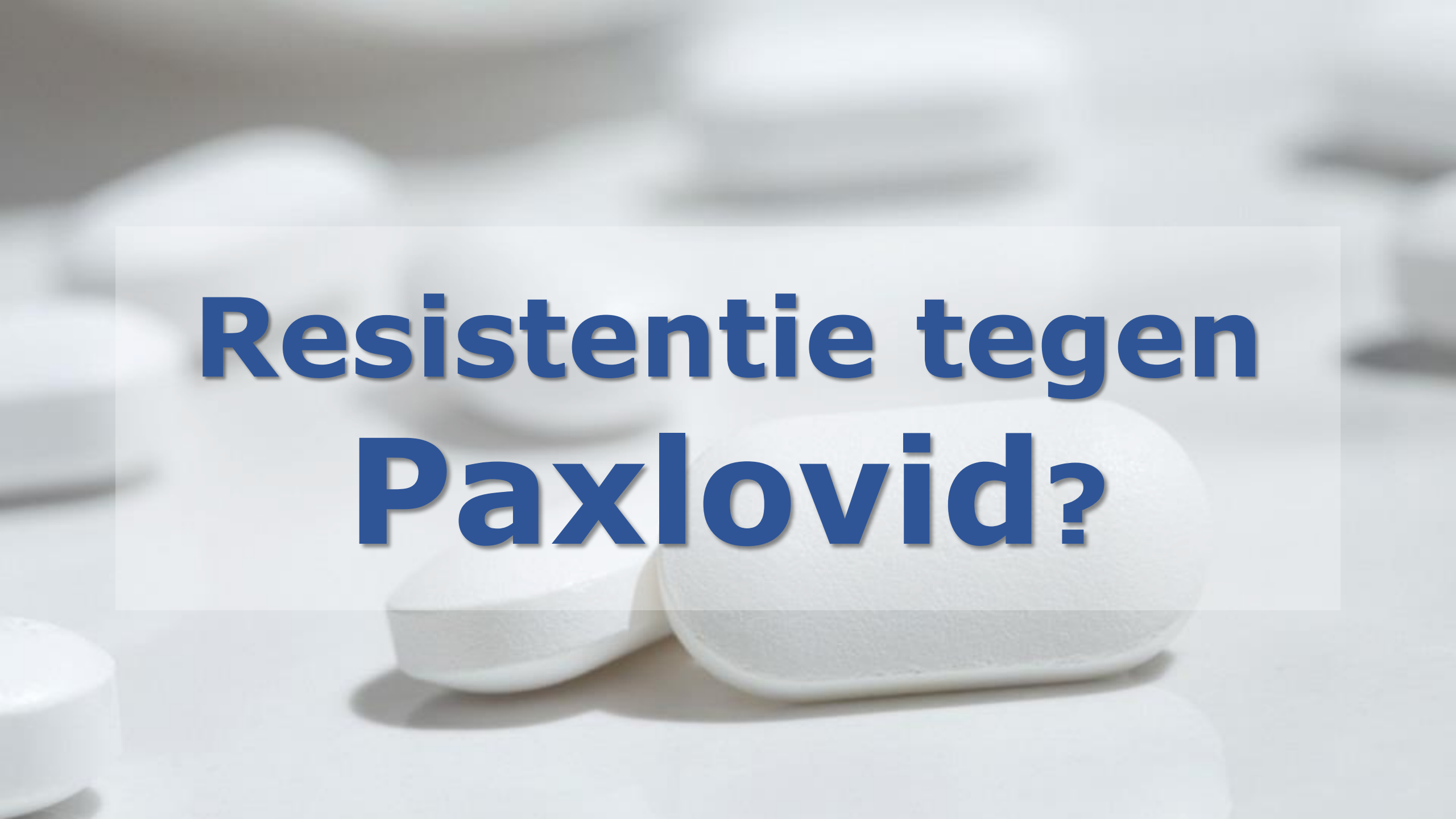
The NEW ENGLAND JOURNAL of MEDICINE

Rebound of SARS-CoV-2 Infection after Nirmatrelvir–Ritonavir Treatment

Charness M.E. et al.



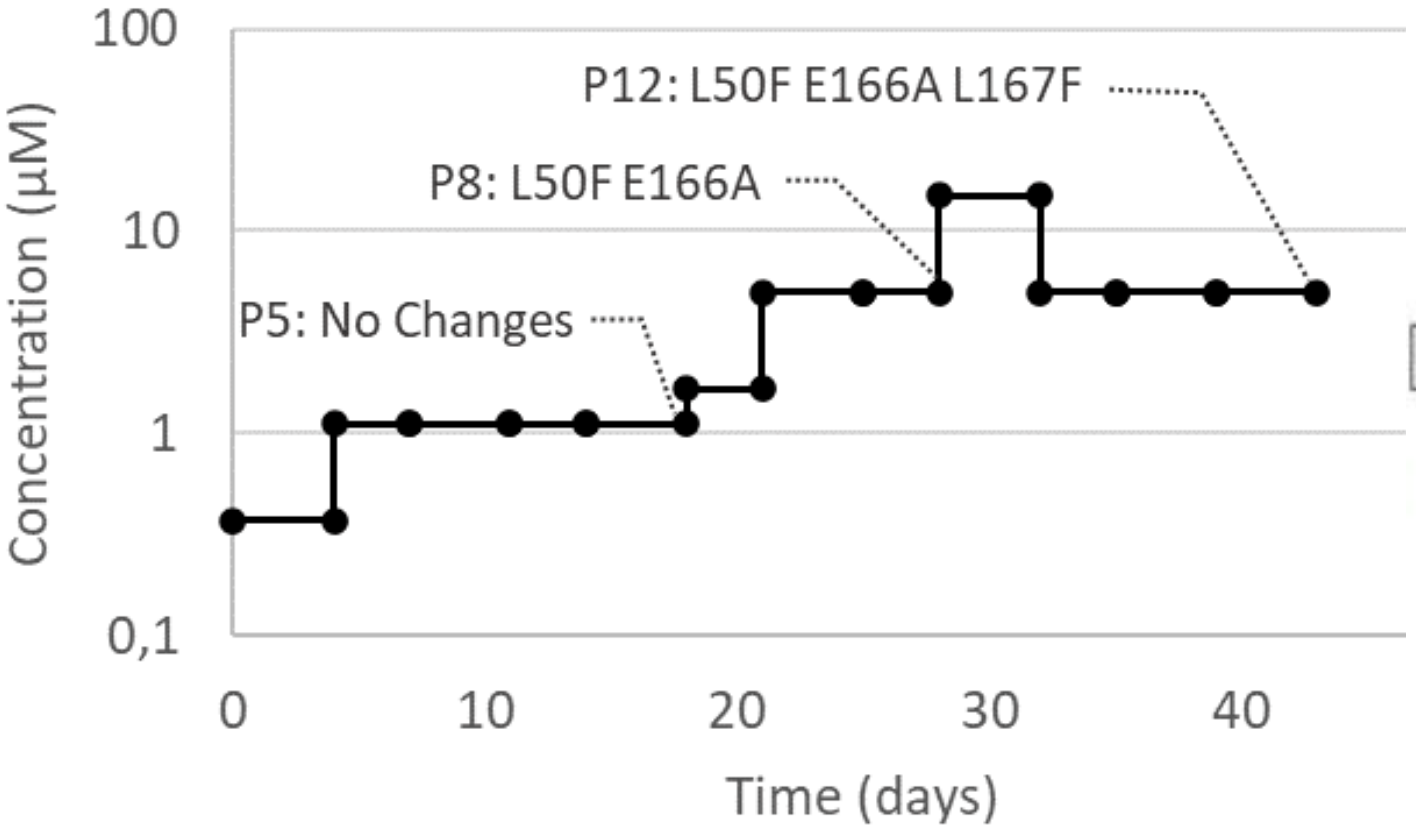
N Engl J Med 2022; 387:1045-1047

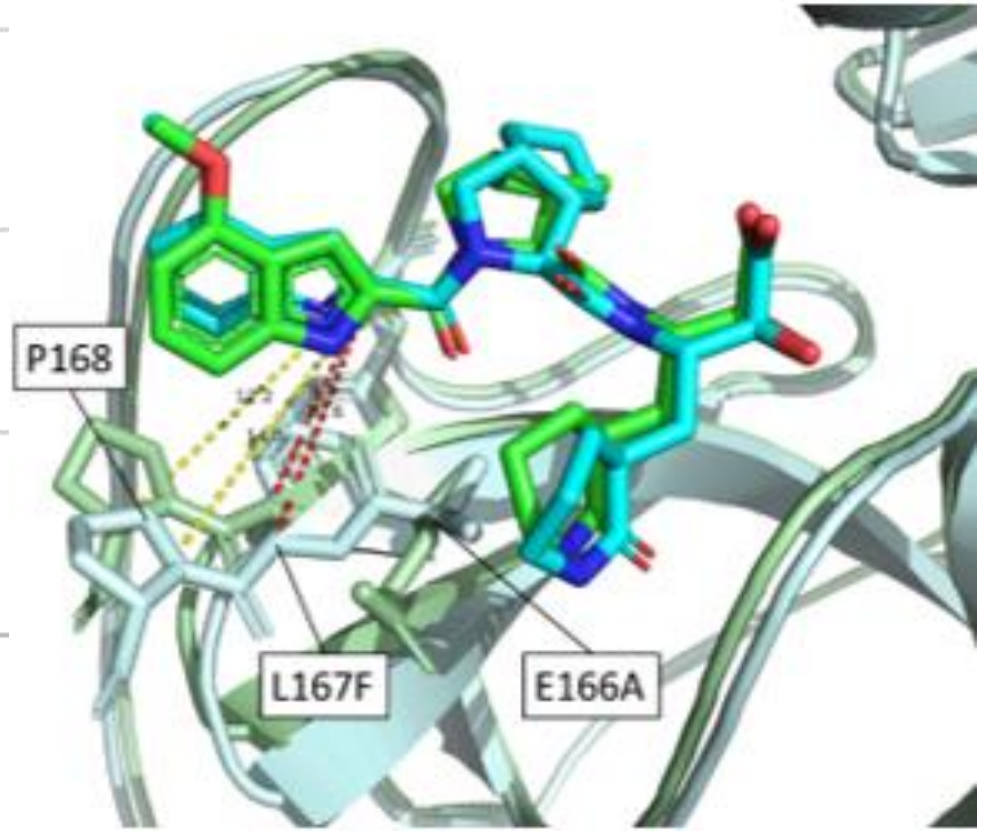

Resistentie tegen
Paxlovid?

mBio
AN OPEN ACCESS JOURNAL PUBLISHED BY
THE AMERICAN SOCIETY FOR MICROBIOLOGY

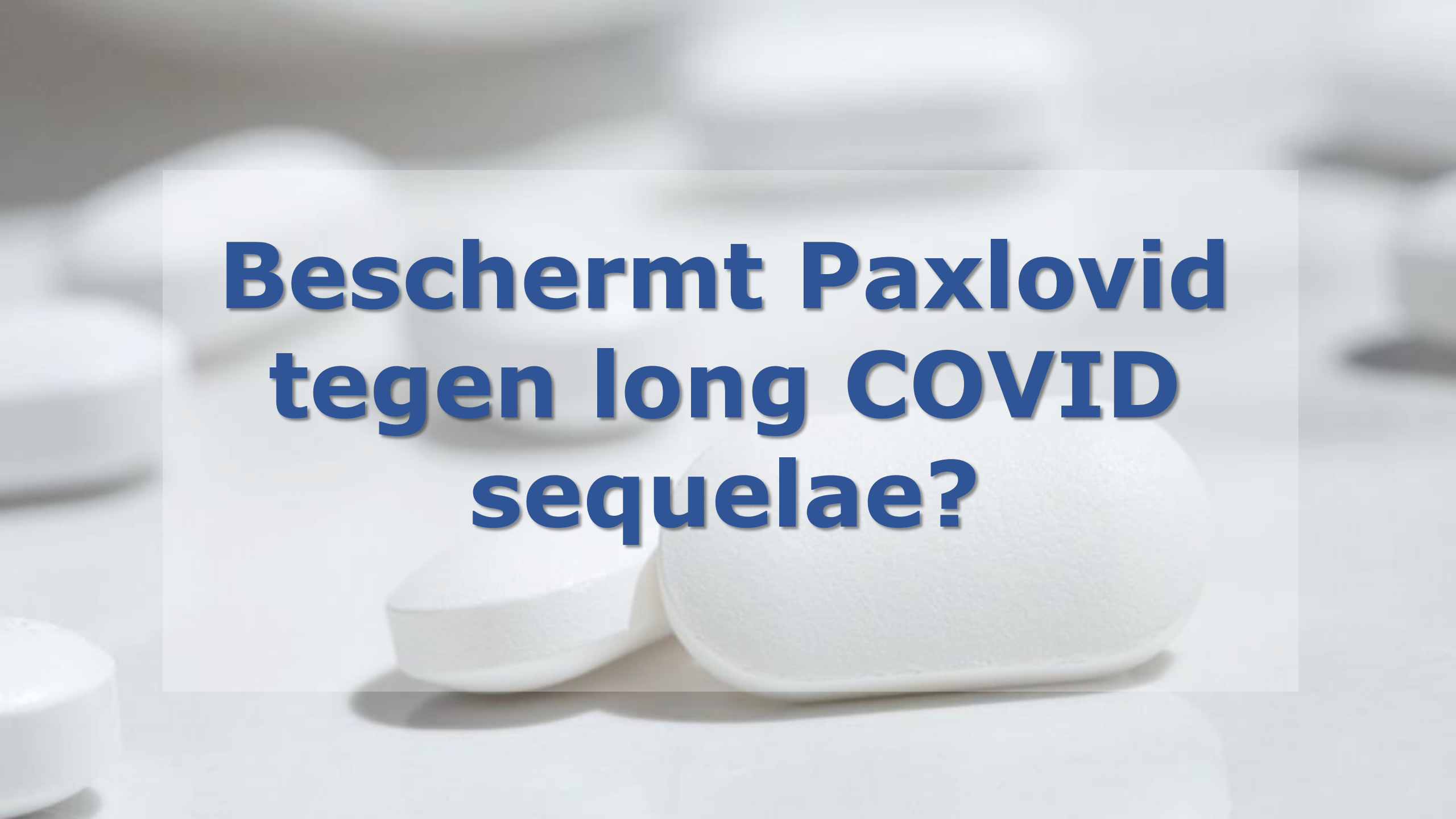
The Substitutions L50F, E166A, and L167F in SARS-CoV-2 3CLpro Are Selected by a Protease Inhibitor *In Vitro* and Confer Resistance To Nirmatrelvir

Jochmans Dirk, et al.





mBio 2023 Jan 10
doi: 10.1128/mbio.02815-22



Beschermt Paxlovid tegen long COVID sequelae?

medRxiv
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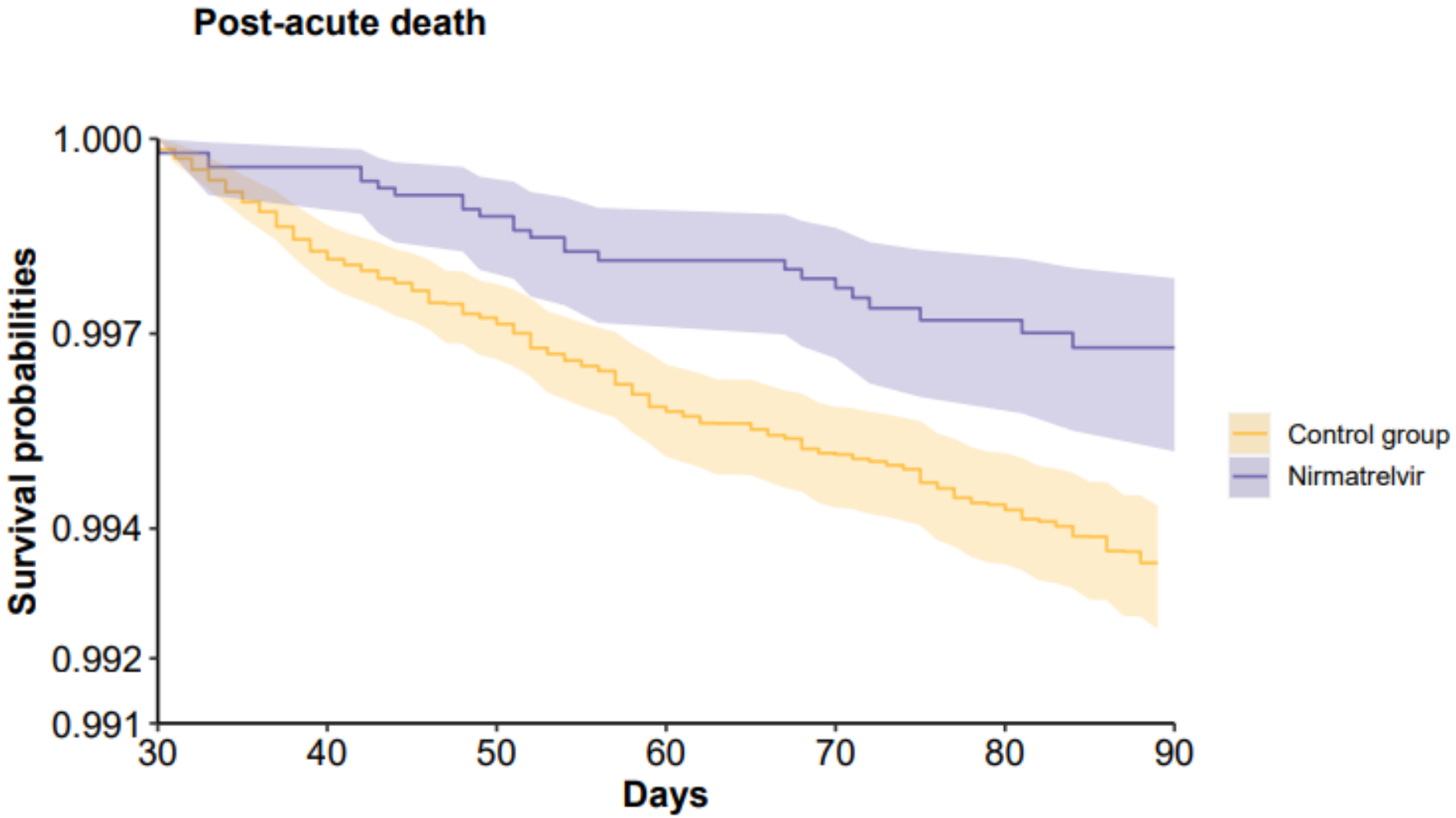
Nirmatrelvir and the risk of post-acute sequelae of COVID-19

Xie Y. et al.



5 november 2022
doi: https://doi.org/10.1101/2022.11.03.22281783

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Nirmatrelvir and the risk of post-acute sequelae of COVID-19

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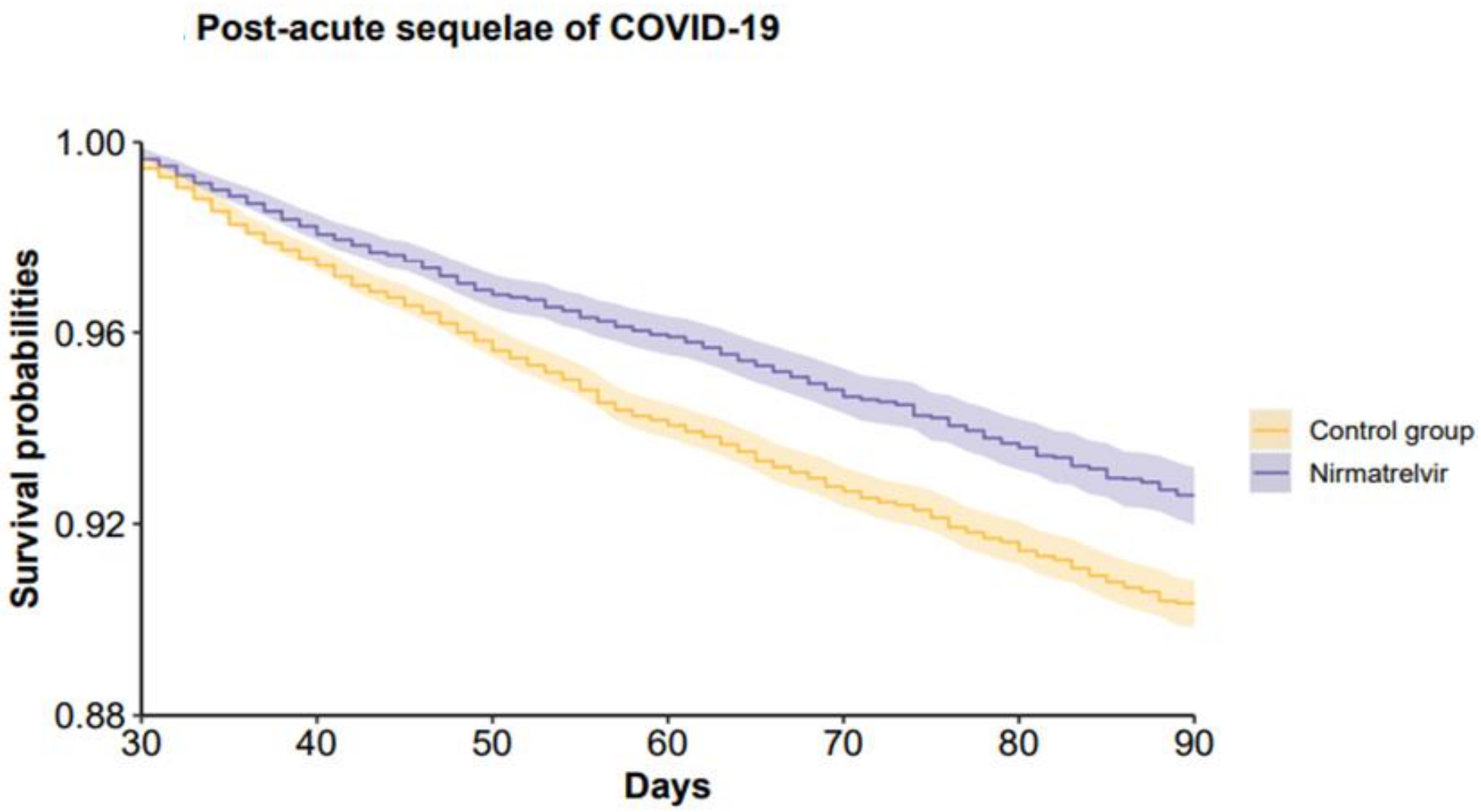
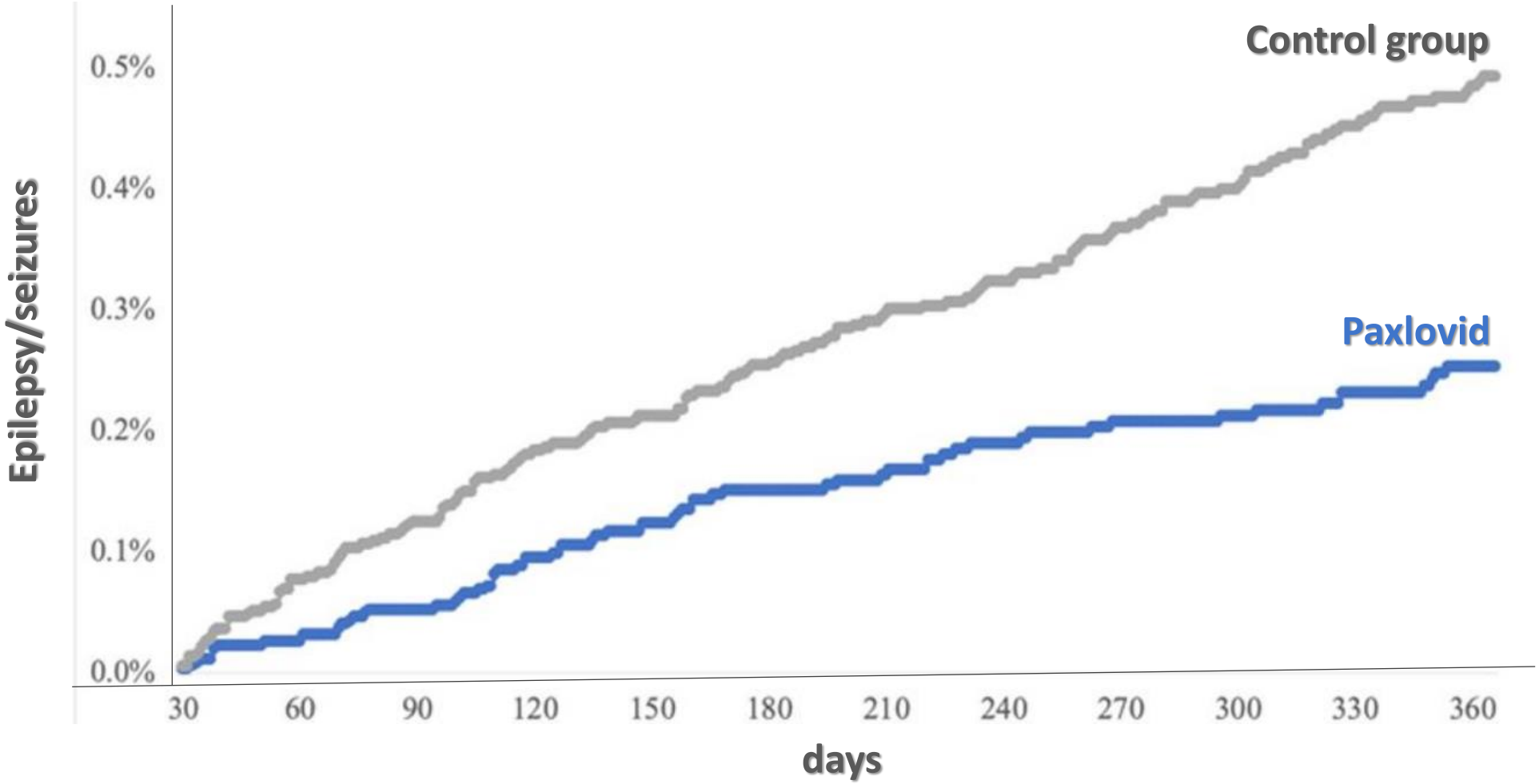


5 november 2022
doi: https://doi.org/10.1101/2022.11.03.22281783

JOURNAL OF INFECTION

The effect of nirmatrelvir plus ritonavir on the long-term risk of epilepsy and seizure following COVID-19: A retrospective cohort study including 91,528 patients

Liu T.-H. et al.



J Infect. 2023 Jan 14
doi: 10.1016/j.jinf.2023.01.014

Besluit

NATIONAL GEOGRAPHIC

PUBLISHED NOVEMBER 5, 2021

How the rise of antivirals may change the course of the pandemic

Making them isn't easy. But new pills to treat COVID-19 are now showing promise at curbing illness and saving lives.

Antiviral pills cascade down the channels of a packaging plant in Khimki, Russia, May 18, 2020.