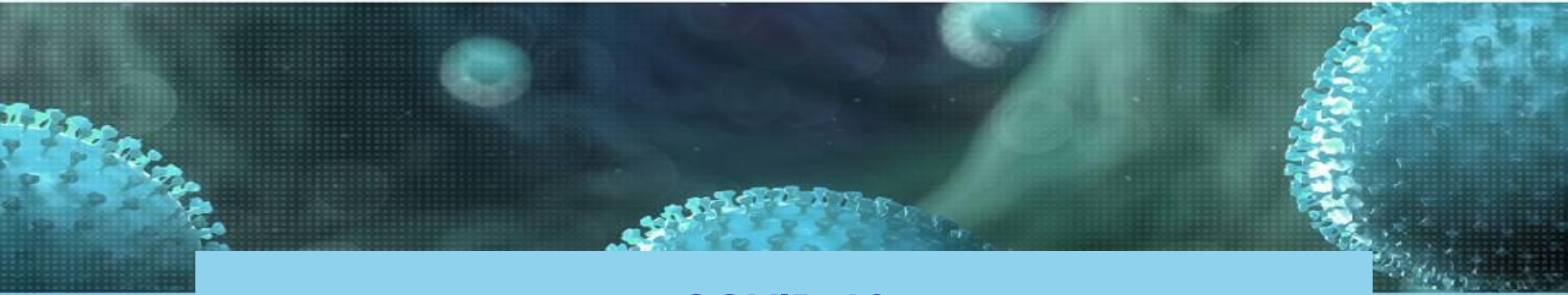
Erasmus MC

Viroscience lab

WHERE SKILLS MEET TO STUDY & PROTECT



COVID-19

Jeroen van Kampen
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Afdeling Viroscience, Erasmus MC
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Casus 1

40 jarige vrouw

- Blanco VG
- 1 maand geleden SARS-CoV-2 vaccinatie (Pfizer)
- 3 maanden geleden beeld passend bij milde COVID-19. Geen diagnostiek gedaan.
- Nu klachten die kunnen passen bij post-COVID (“long COVID”)

Vraag: 3 maanden geleden COVID-19 doorgemaakt?

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Vraag: 3 maanden geleden COVID-19 doorgemaakt?

Kan deze vraag beantwoord worden met diagnostiek? Zo ja, welke?

COVID-19 vaccins goedgekeurd door WHO

- AstraZeneca/Oxford vaccine
- Johnson and Johnson
- Moderna
- Pfizer/BionTech
- Sinopharm
- Sinovac
- COVAXIN
- Covovax
- Nuvaxovid
- CanSino

https://www.who.int/emergencies/diseases/novel-coronavirus-2019/covid-19-vaccines/advice

Wat voor soort vaccins zijn dit (mRNA, vector etc)?

- AstraZeneca/Oxford vaccine
- Johnson and Johnson
- Moderna
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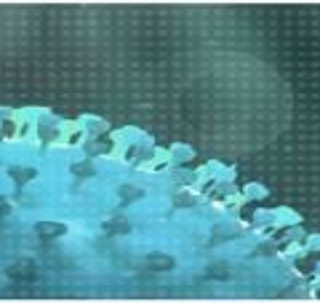
Wat voor soort vaccins zijn dit (mRNA, vector etc)?

- AstraZeneca/Oxford vaccine = ADV **vector** expressing SARS-CoV-2 spike
- Johnson and Johnson = ADV **vector** expressing SARS-CoV-2 spike
- Moderna = modified **mRNA** SARS-CoV-2 spike
- Pfizer/BionTech = modified **mRNA** SARS-CoV-2 spike
- Sinopharm = inactivated **whole virus** SARS-CoV-2
- Sinovac = inactivated **whole virus** SARS-CoV-2
- COVAXIN = inactivated **whole virus** SARS-CoV-2
- Covovax = adjuvanted **recombinant spike protein** nanoparticle vaccine
- Nuvaxovid = adjuvanted **recombinant spike protein** nanoparticle vaccine
- CanSino = ADV **vector** expressing SARS-CoV-2 spike

https://www.who.int/emergencies/diseases/novel-coronavirus-2019/covid-19-vaccines/advice



Detectie antistoffen tegen SARS-CoV-2

	LIAISON® SARS-CoV-2 TrimericS IgG (spike)	WANTAI SARS-CoV-2 IgM ELISA (spike)	WANTAI SARS-CoV-2 Ig total ELISA (spike)	ARCHITECT SARS-CoV-2 IgG (nucleocapsid)
Natuurlijke infectie				
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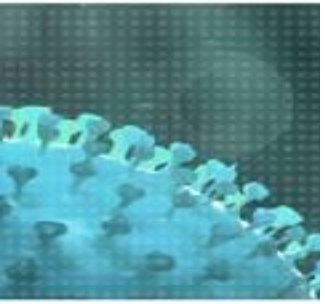

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Nuvaxovid	ja	ja	ja	**Nee**
CanSino	ja	ja	ja	**Nee**

Casus 2

- 65 jarige man
- Blanco VG
- Opgenomen ivm COVID-19 (PCR bewezen) in november 2020
- tracheostoma
- Al 25 dagen opgenomen
- Laatste week klinische verbetering, maar nog wel klachten
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Vraag: Mag patient uit isolatie?

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Is hier een rol voor diagnostiek?

infectivity

nature COMMUNICATIONS

ARTICLE

https://doi.org/10.1038/s41467-020-20568-4 OPEN

Duration and key determinants of infectious virus shedding in hospitalized patients with coronavirus disease-2019 (COVID-19)

Jeroen J. A. van Kampen[1✉], David A. M. C. van de Vijver[1], Pieter L. A. Fraaij[1,2], Bart L. Haagmans[1], Mart M. Lamers[1], Nisreen Okba[1], Johannes P. C. van den Akker[3], Henrik Endeman[3], Diederik A. M. P. J. Gommers[3], Jan J. Cornelissen[4], Rogier A. S. Hoek[5,6], Menno M. van der Eerden[5], Dennis A. Hesselink[6,7], Herold J. Metselaar[6,8], Annelies Verbon[9], Jurriaan E. M. de Steenwinkel[9], Georgina I. Aron[1], Eric C. M. van Gorp[1], Sander van Boheemen[1], Jolanda C. Voermans[1], Charles A. B. Boucher[1], Richard Molenkamp[1], Marion P. G. Koopmans[1,10], Corine Geurtsvankessel[1,10] & Annemiek A. van der Eijk[1,10]

Key Questions

1. What is the **duration** of infectious virus shedding from respiratory tract in hospitalized patients with **severe** COVID-19?

2. **Which factors determine** shedding of infectious virus:

- Duration of symptoms?
- Viral RNA load?
- Presence of serum neutralizing antibodies?
- Immune status?

Methods

March and beginning of April 2020:

- Virus cultures on respiratory samples from hospitalized COVID-19 patients
- Vero cells (clone 118), max 7 days culture, confirmation of CPE with immunofluorescence

For patients with at least one virus culture result:

- SARS-CoV-2 RNA loads (Wolfel et al.)
- Serum neutralizing antibody titers (Okba et al.)
- Duration of symptoms, severity of disease and immunocompromised status.

Multivariate analysis:

- Assess factors associated with shedding infectious virus: **duration of symptoms, immunocompromised status, viral RNA loads, presence serum neutralizing antibodies**
- Generalized estimating equations to account for repeated measurements obtained from the same patient during hospitalization.

Immunocompromised score

Table 1. Criteria used to categorize the level of immune compromise

Level of immune suppression	Reason for immune compromise (acquired condition/iatrogenic/drug-induced)
Severe	Allogeneic HSCT (<12 months)
	GVHD after allogeneic HSCT
	HIV-positive with $CD4^+$ T-cell count <200 cells/μl
	Induction chemotherapy for paediatric leukaemia
	Chemotherapy with >7 days neutropenia
	SOT patients
	Lung transplant (always)
	<6 months and induction Rx
	>1 year SOT and rejection (<3 months)
	Use of immunomodulating biologicals
	Daily corticosteroid dosage (based on prednisone) of >30 mg (adults) or >2 mg/kg (infants) for longer than 14 days
Non-severe (mild/moderate)	Maintenance chemotherapy for haematological malignancies
	Chemotherapy for solid tumours
	Autologous HSCT
	1 year after SOT and no rejection
	HIV-positive with or without HAART, with undetectable viral load and $CD4^+$ T-cell count >200 cells/μl
	Methotrexate use for autoimmune disease
	Daily corticosteroid dosage (based on prednisone) of ≤30 mg (adults) or ≤2 mg/kg (infants) for ≤14 days
	Other possible immune deficiencies (that is, untreated autoimmune disease, DM, etc.)

Fraaij et al., Antiviral Therapy, 2015

Characteristics patients

Table 1 Patient characteristics.

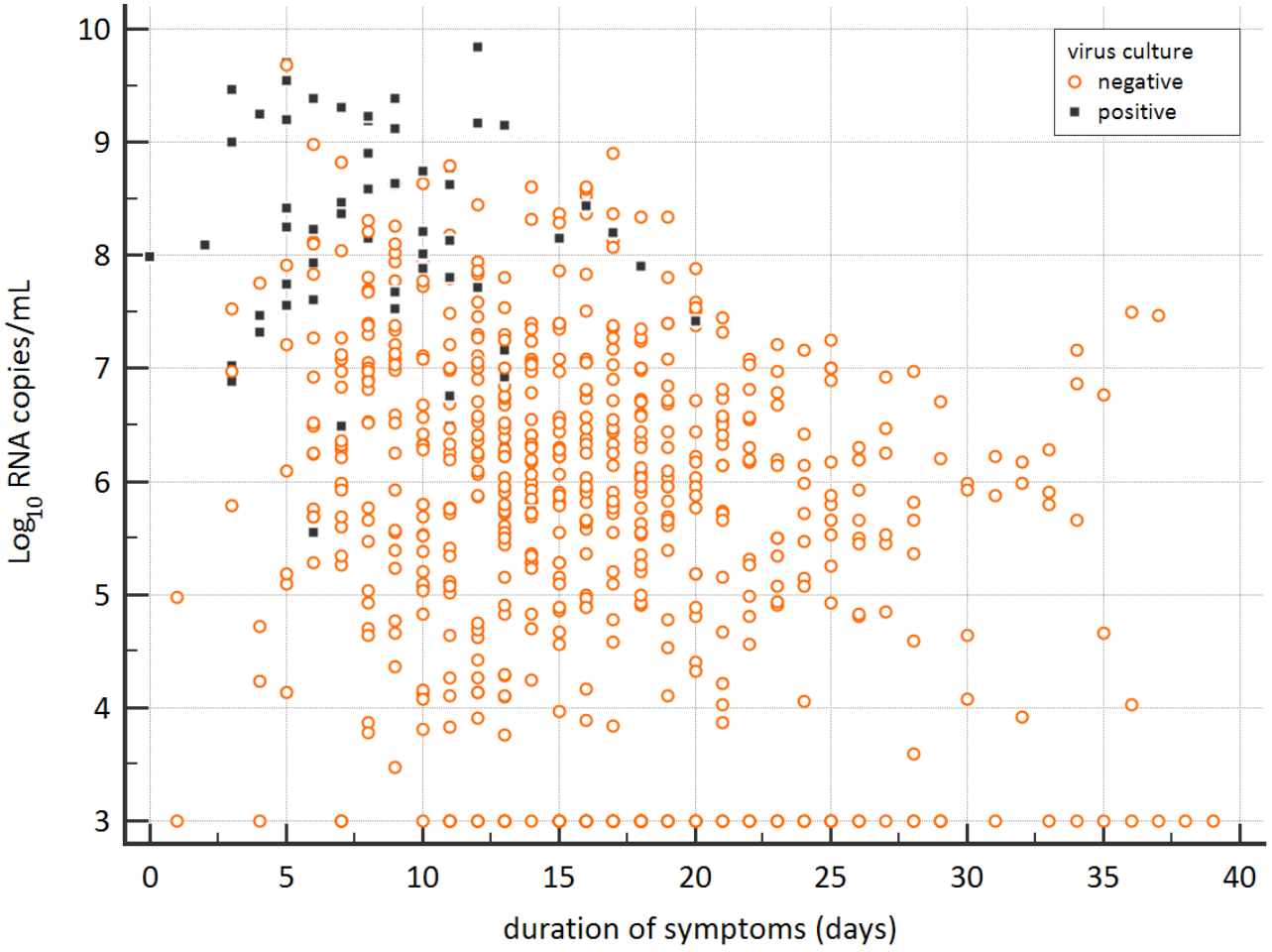
Characteristic	All	Intensive care	Ward	*p* value (ICU vs ward)
Number[a]	129	89 (69.0%)	40 (31.0%)	
Male	86 (66.7%)	65 (73.0%)	21 (52.5%)	0.04
Age (median—IQR)	65 (57–72)	66 (57–72)	63 (57–74)	0.90
Immunocompromised[b]				
Moderate	19 (14.7%)	10 (11.2%)	9 (22.5%)	0.04
Severe	11 (8.5%)	5 (5.6%)	6 (15.0%)	
Clinical parameters				
Mechanical ventilation	81 (62.8%)	81 (91.0%)	0	
Supplemental oxygen	43 (33.3%)	8 (9.0%)	35 (87.5%)	
Died	14 (10.9%)	11 (12.3%)	3 (7.5%)	
Duration of illness[c]				
Median (IQR)	18 (13–21)	18 (13–22)	15 (12–18)	0.009
Tests per patient, total (mean per person)				
Culture	690 (5.3)	601 (6.8)	89 (2.2)	
PRNT	112 (0.9)	82 (0.9)	30 (0.8)	
PCR	688 (5.3)	599 (6.7)	89 (2.2)	

[a]Disease severity classification according to NIH criteria (https://www.covid19treatmentguidelines.nih.gov/overview/management-of-covid-19/): 81/129 (62.5%) critical disease, 43/129 (33.3%) severe disease, 5/129 (3.9%) moderate disease.

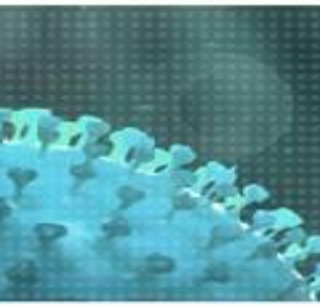
[b]Immunocompromised level was scored as described previously[25]. Patients with severe immunosuppression ($n = 11$): Lung transplantation, or other solid organ transplantation and treatment for rejection within the last 3 months ($n = 3$); Underlying disease treated with daily corticosteroid dosages (based on prednisone) >30 mg for >14 days and/or immunomodulating biologicals ($n = 4$); Allogeneic hematopoietic stem cell transplantation within the last 12 months, or allogeneic hematopoietic stem cell transplantation with with graft-versus-host-disease treated with immunosuppressive drugs, or acute leukemia ($n = 4$). Patients with nonsevere immunosuppression ($n = 19$): Untreated auto-immune disease or underlying disease treated with immunosuppressive drugs (excluding treatment with daily corticosteroid dosages (based on prednisone) >30 mg for >14 days and/or treatment with immunomodulating biologicals) ($n = 10$); At least 1 year after solid organ transplantation (excluding lung transplantation) and no rejection ($n = 3$); Hematological malignancies (excluding acute leukemia and leukemia treated with induction therapy or chemotherapy resulting in neutropenia for >7 days) ($n = 4$); Other nonsevere immunodeficiencies ($n = 2$).

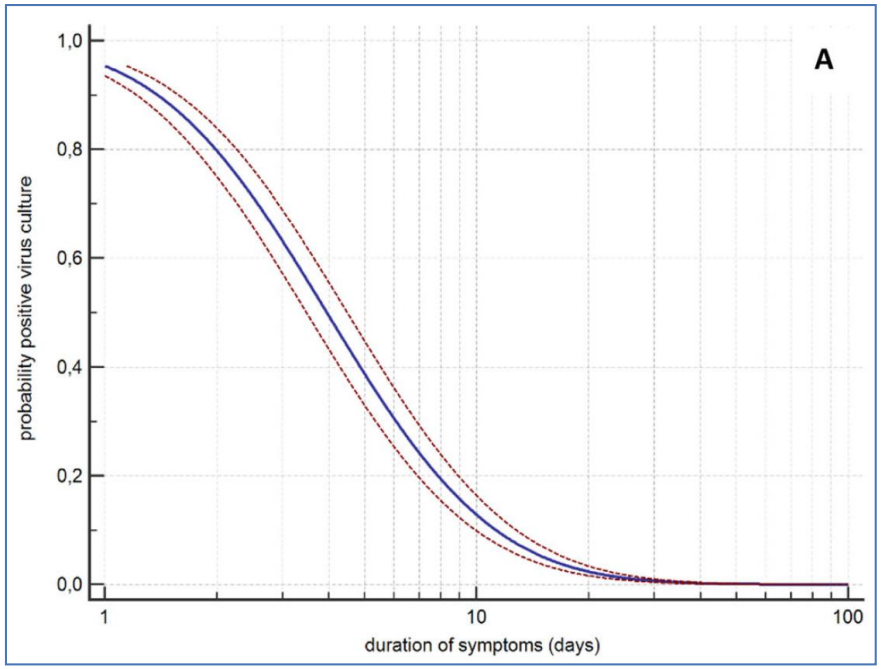
[c]As of April 17th 2020. PRNT = plaque-reduction neutralization titer. Respiratory tract samples for virus culture and PCR were obtained from the lower respiratory tract (sputum) on the intensive care unit (538/690 samples, 78%) and from the upper respiratory tract (swabs) on the intensive care unit as well as on the medium care unit (152/690 samples, 22%). A total of 127 out of the 690 respiratory tract samples that were submitted for virus culture (18.4%) were obtained from immunocompromised patients. For categorical variables a two-sided Chi-square test was used and for continuous variables a two-sided student's *t*-test was used. No adjustments were made for multiple comparisons.

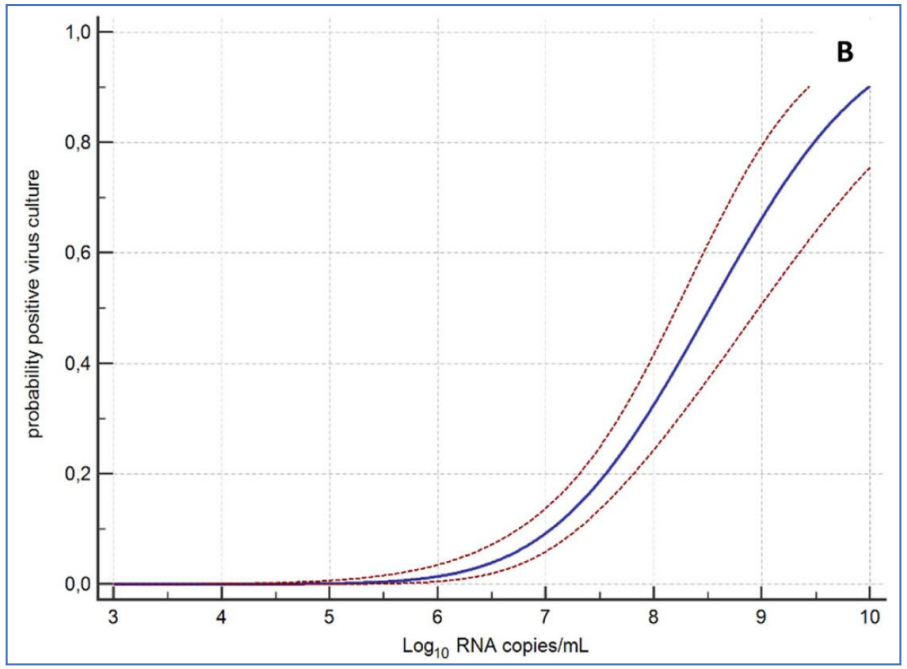
Duration of infectious virus shedding

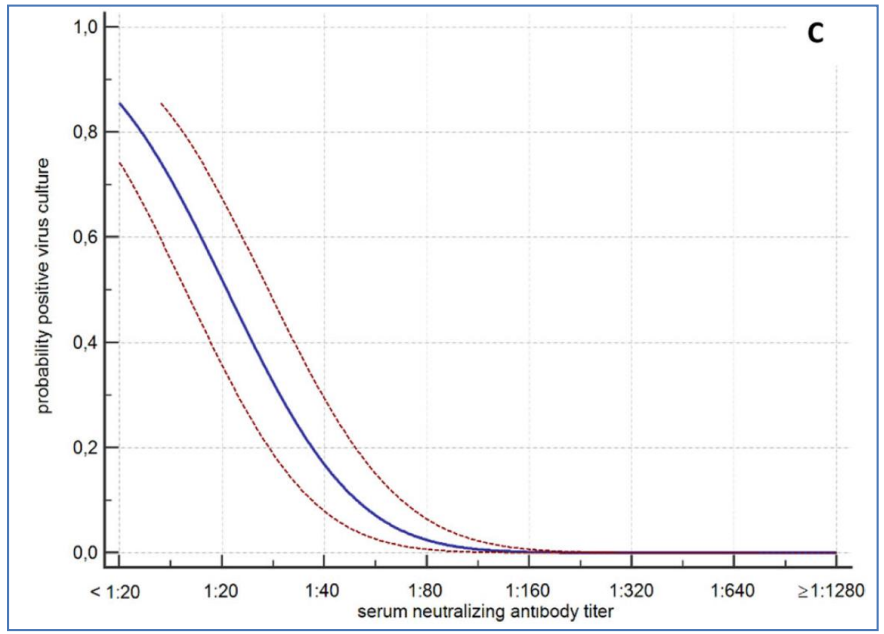


- 23/129 patients positive
- 62/690 samples positive
- Median duration shedding: 8 days
- IQR: 5 – 11 days
- Range: 0 -20 days

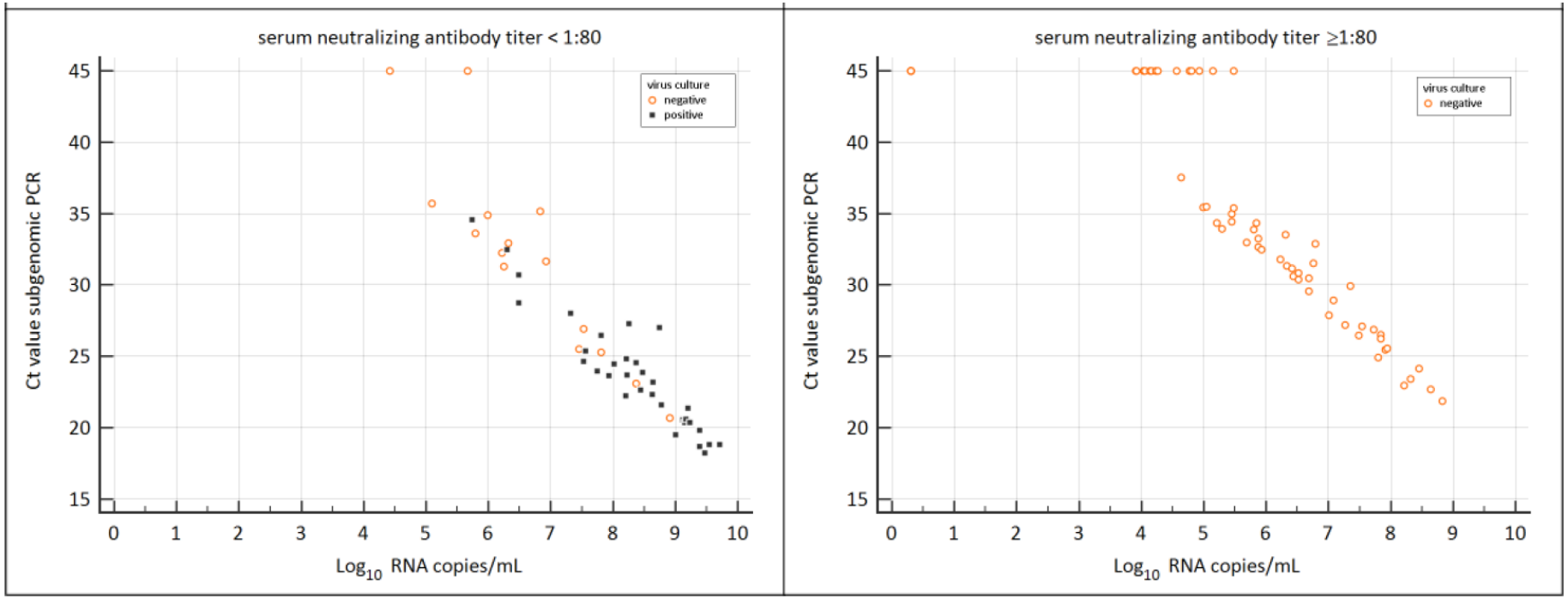



A
probability positive virus culture
1,0
0,8
0,6
0,4
0,2
0,0
1
10
100
duration of symptoms (days)


B
probability positive virus culture
1,0
0,8
0,6
0,4
0,2
0,0
3
4
5
6
7
8
9
10
Log10 RNA copies/mL


C
probability positive virus culture
1,0
0,8
0,6
0,4
0,2
0,0
< 1:20
1:20
1:40
1:80
1:160
1:320
1:640
≥1:1280
serum neutralizing antibody titer

The importance of neutralizing antibodies in COVID-19



The importance of neutralizing antibodies in COVID-19

Table 3 Univariate and multivariate analysis of key determinants for infectious virus shedding.

Variable	Positive virus culture ($n = 33$)	Negative virus culture ($n = 79$)	Univariate odds ratio (95% CI)	Multivariate odds ratio (95% CI)
Viral RNA load				
$>10^7$ RNA copies/mL	29 (87.9%)	22 (27.8%)	18.8 (5.5–64.2), $p < 0.001$	14.7 (3.7–58.1), $p < 0.001$
Duration of symptoms				
<7 days	20 (60.6%)	17 (21.5%)	5.6 (1.7–18.1), $p = 0.004$	2.1 (0.4–11.7), $p = 0.31$
Serum neutralizing antibody titer				
1:20 or higher	6 (18.2%)	75 (94.9%)	0.01 (0.003–0.05), $p < 0.001$	0.01 (0.002–0.08), $p < 0.001$
Immunocompromised				
Yes	10 (30.3%)	10 (12.7%)	3.00 (0.8–11.0), $p = 0.098$	2.0 (0.7–5.3), $p = 0.22$

Results of the univariate and multivariate generalized estimating equation analysis. The analyses were limited to the samples for which a viral RNA load and a serum neutralizing antibody titer were available from samples taken at the same day.

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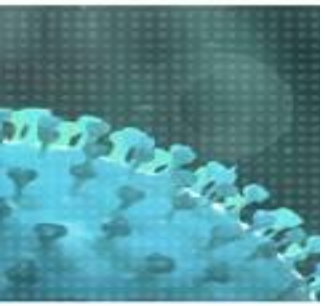
Is hier een rol voor diagnostiek? JA



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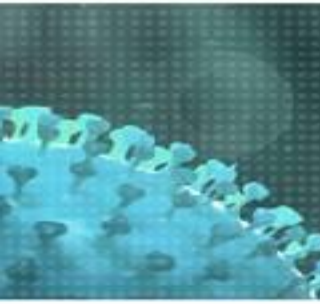
Niet meer besmettelijk na COVID-19 infectie

Federatie Medisch Specialisten

III. <u>Overwegingen om patiënt vrij te verklaren van COVID-19 bij een nog beademde en/of tracheostoma patiënt:</u>

- Minstens 21 dagen** na eerste ziektedag **EN** ten minste 24 uur klinisch hersteld (ter beoordeling klinisch team) **EN** 2 maal negatieve PCR test van (diep) luchtweg materiaal met minstens 24 uur tussen de 2 afnames OF
- Op basis van lokale kennis en het volgen van CT waarden in meerdere (diepe) luchtwegmonsters van een patiënt, kan men **na** 21dagen met aanhoudende hoge CT waarden (bijv. >90ste percentiel***) overwegen de isolatie te beëindigen, mits klinisch herstellende OF
- Bij positieve serologie (bij <u>primo</u> infectie) kan men **na** 21 dagen** overwegen de isolatie te beëindigen mits klinisch herstellende.

Erasmus MC Ervaring



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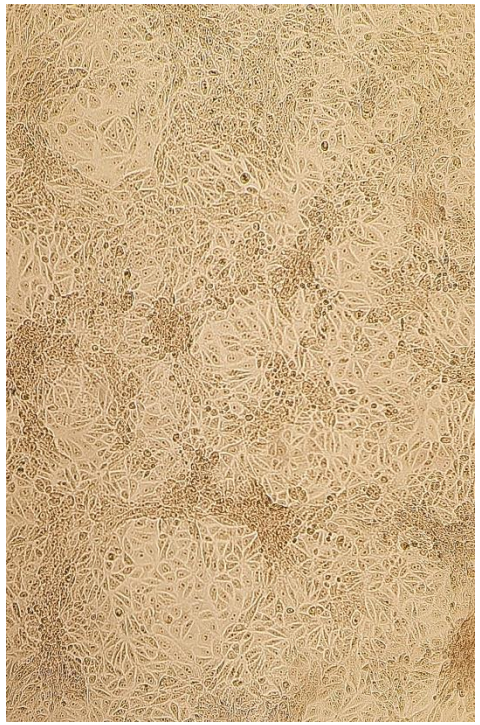
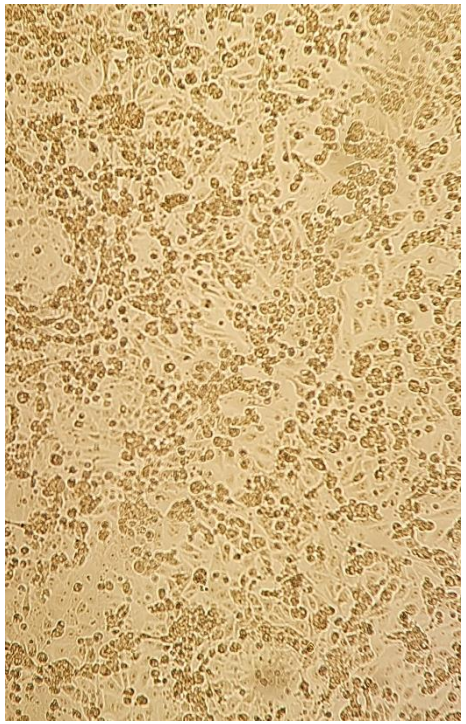
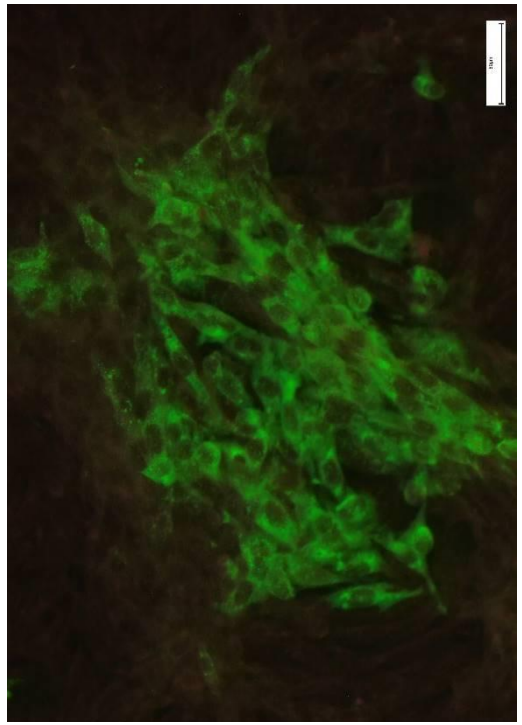
Waarom is viruskweek geen criterium?

Erasmus MC

Virus culture - (g)old standard virology

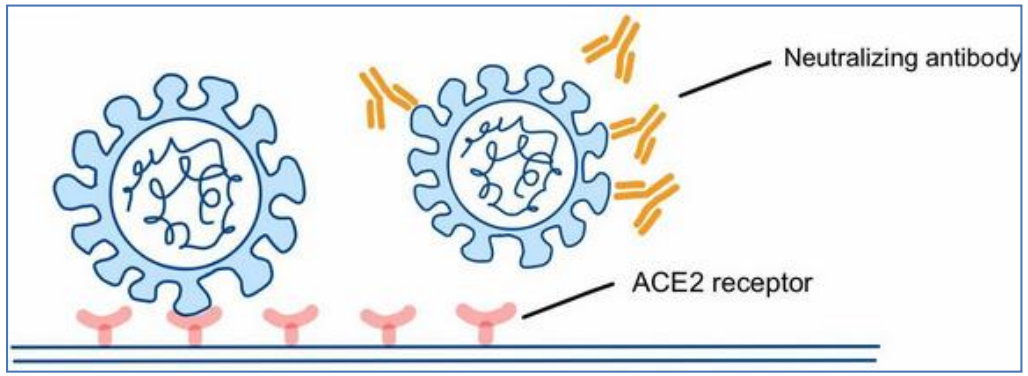


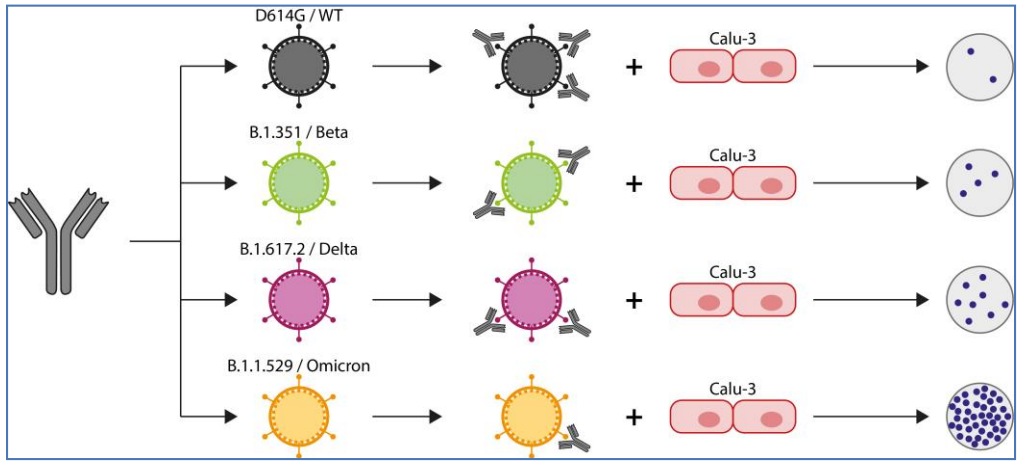


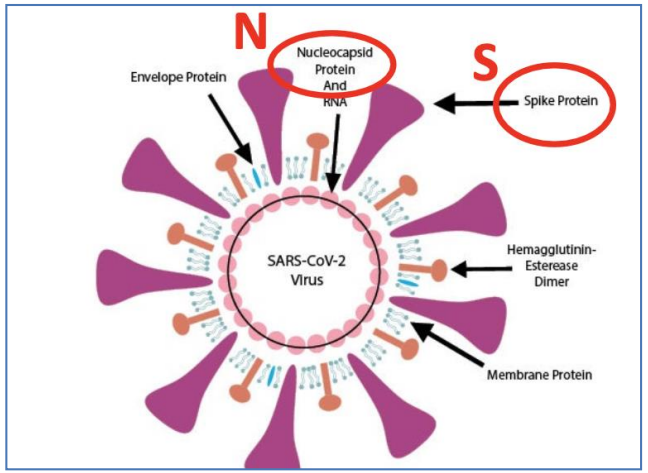


- Detects infectious / replication-competent virus
- Laborious
- Biosafety issue
- Long turn-around-time
- Many viruses can not be cultured

Plaque reduction neutralization test
(g)old standard virology



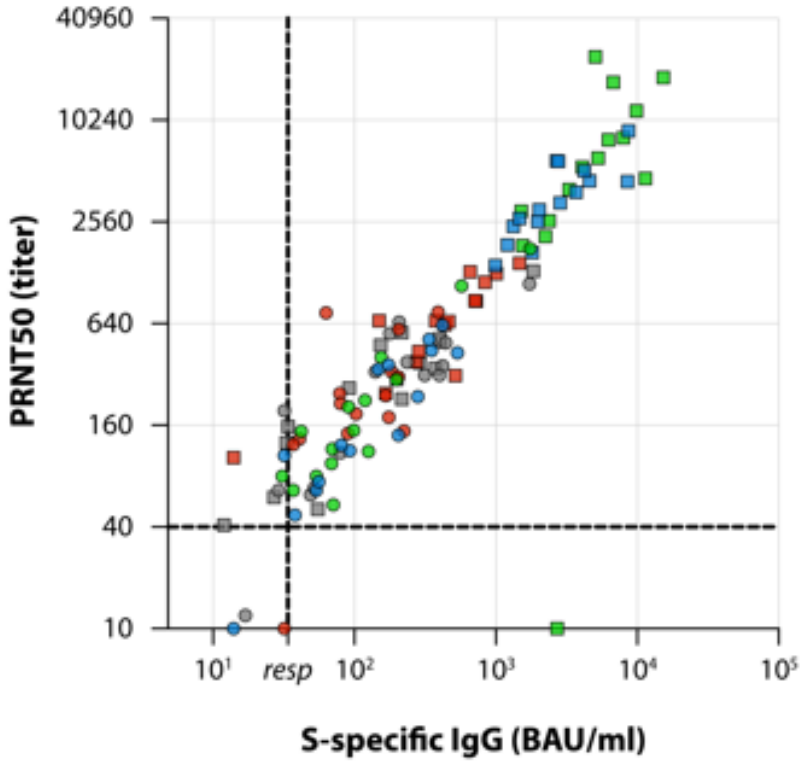




- Detects functional (neutralizing) antibodies
- Virus culture based technique → same disadvantages as virus culture

SARS-CoV-2 serology

Wild type virus



Liaison Trimeric S

Courtesy of Corine GeurtsvanKessel

Casus 2 - aangepast

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- tracheostoma
- Al 25 dagen opgenomen
- Laatste week klinische verbetering, maar nog wel klachten
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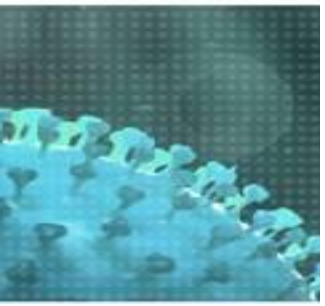
Vraag: Mag patient uit isolatie?

Is hier een rol voor diagnostiek? Zo ja, welke?



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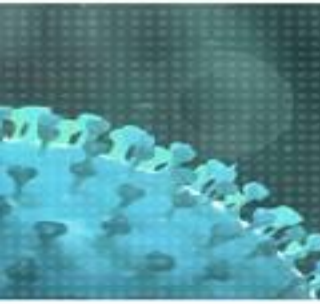
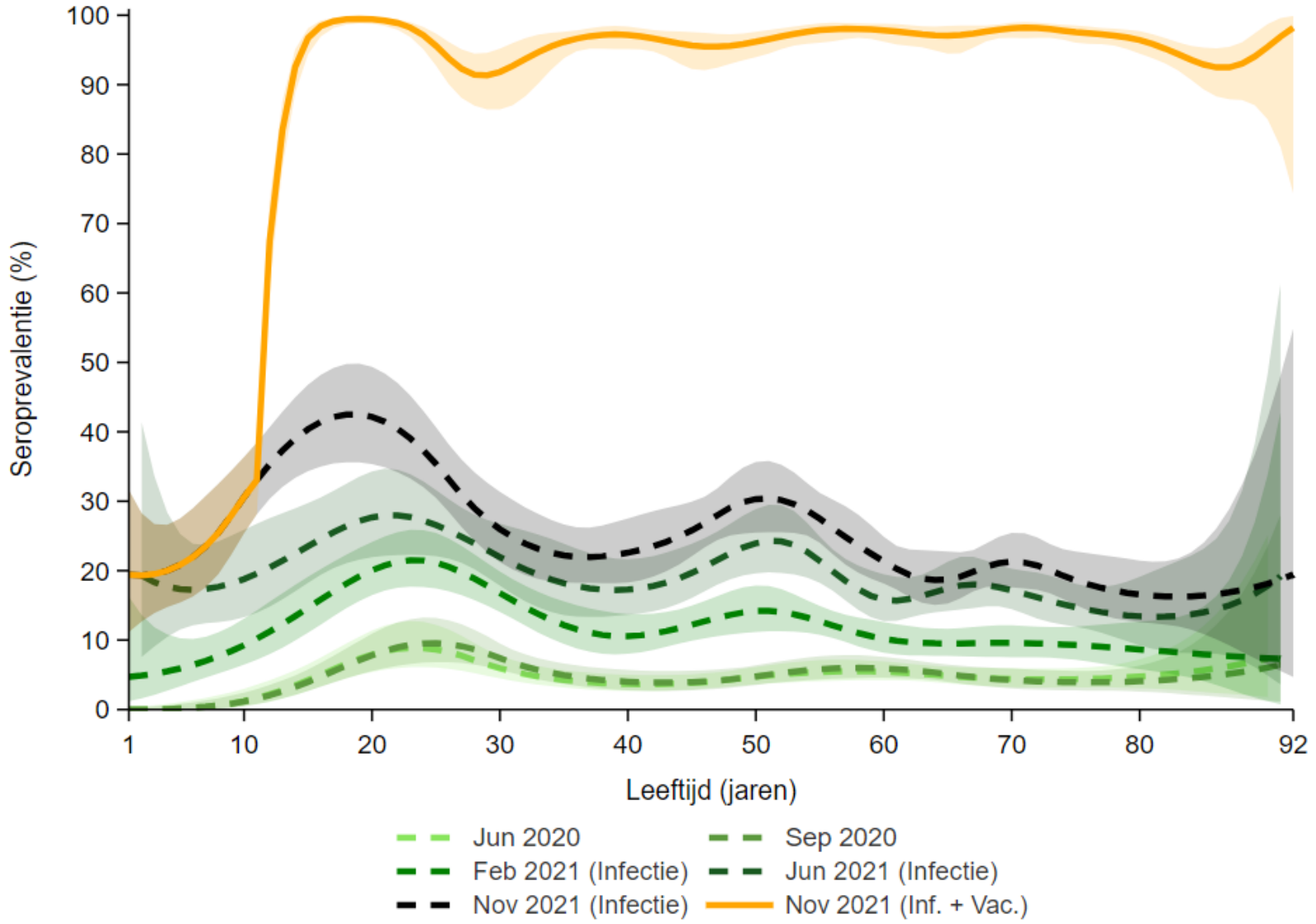
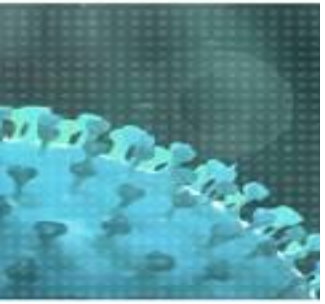
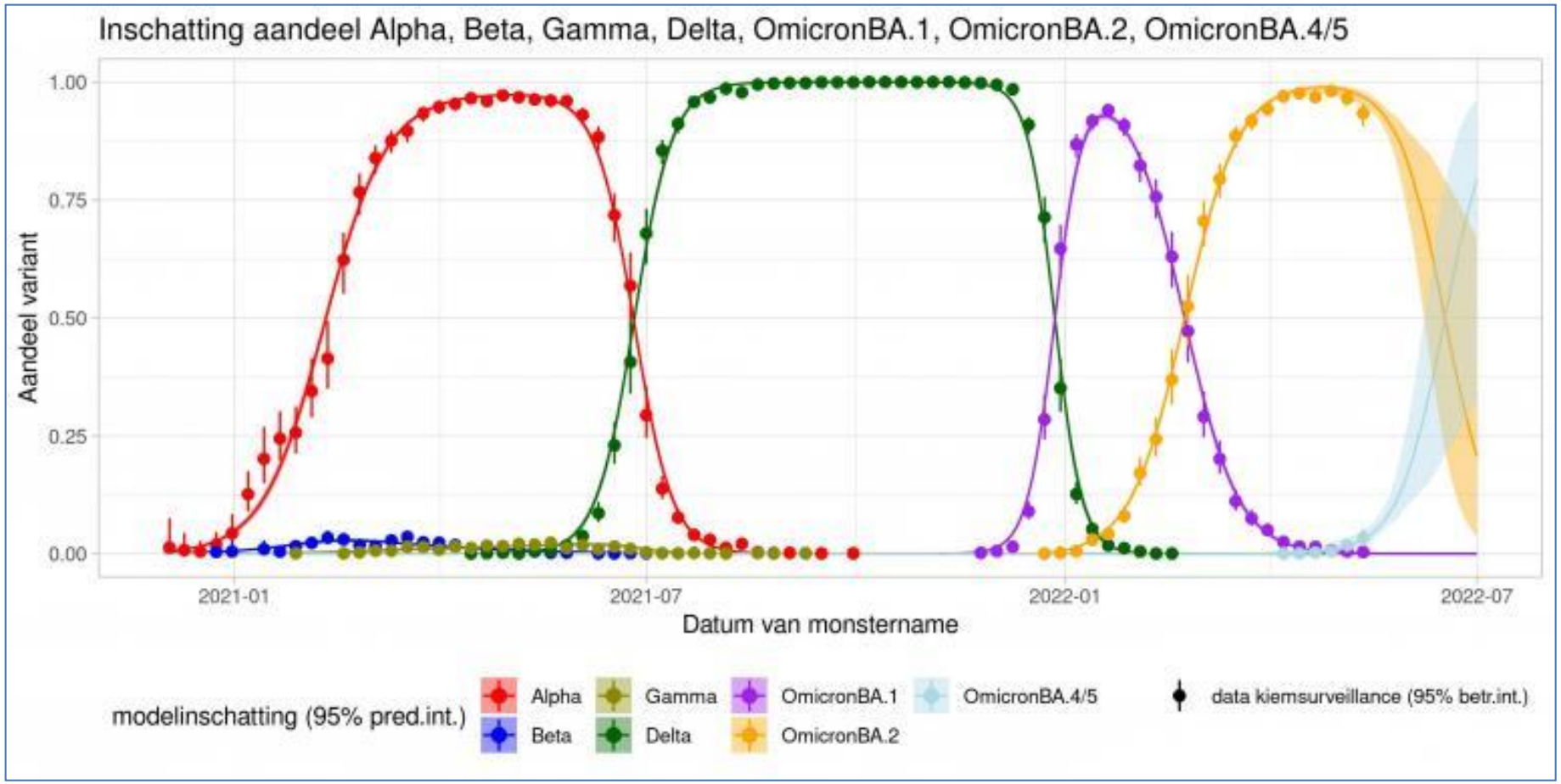
Erasmus MC Ervaring



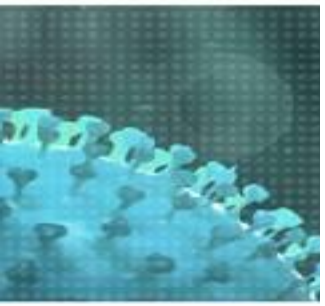


https://www.rivm.nl/pienter-corona-onderzoek/resultaten



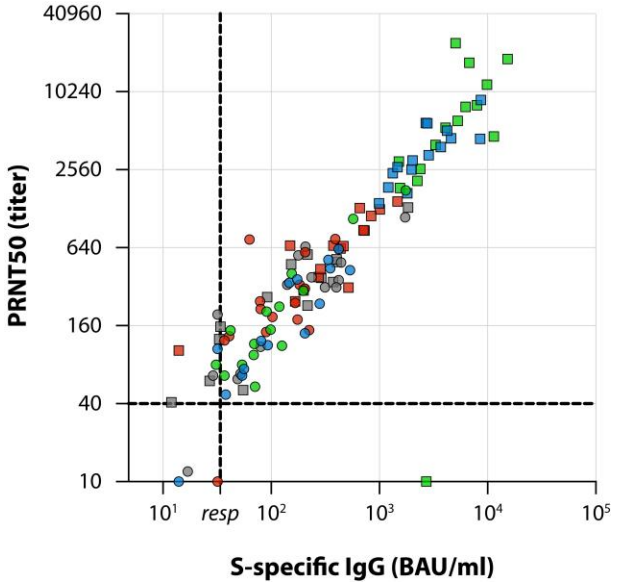


https://www.rivm.nl/coronavirus-covid-19/virus/varianten



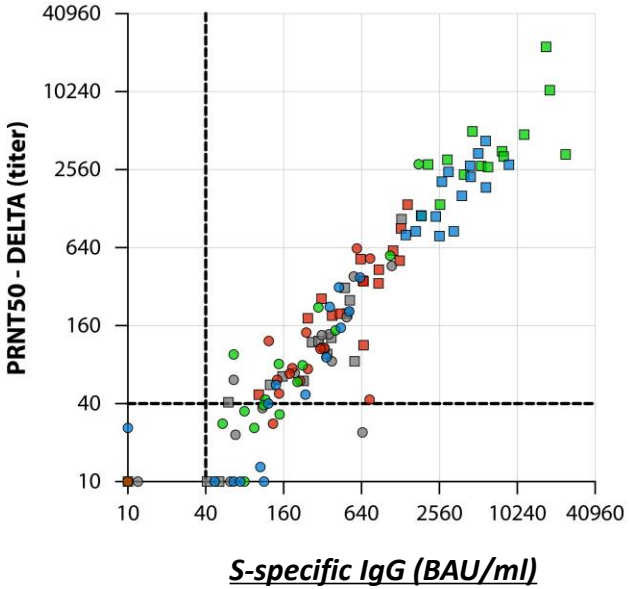
SARS-CoV-2 serology

Wild type virus



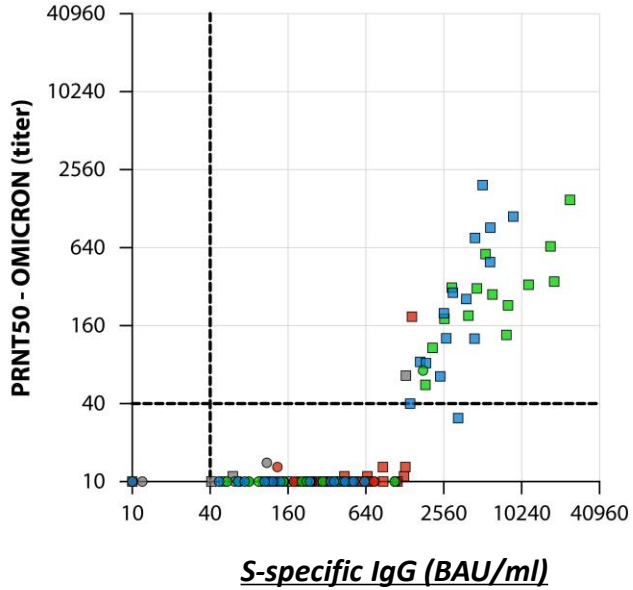
Liaison Trimeric S

Delta



Liaison Trimeric S

Omicron



Liaison Trimeric S

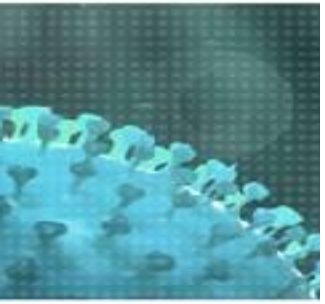
Courtesy of Corine GeurtsvanKessel

Casus 2 - aangepast

- 65 jarige man
- Blanco VG
- Opgenomen ivm COVID-19 (PCR bewezen) in **januari 2022**
- tracheostoma
- Al 25 dagen opgenomen
- Laatste week klinische verbetering, maar nog wel klachten
- PCR SARS-CoV-2 is nog steeds positief

Vraag: Mag patient uit isolatie?

Is hier een rol voor diagnostiek? JA, maar serologie interpretatie heeft pitfalls



https://swab.nl/nl/covid-19

Contact Over de Stichting Inschrijven A-teams Switch to English Zoeken

SWAB 25 JAAR Stichting Werkgroep Antibioticabeleid

Home Onderwerpen Agenda Nieuws

Onderwerpen

- COVID-19/SARS-CoV-2
- Antimicrobial Stewardship
- SWAB adviezen over actuele antibioticabeleid vraagstukken
- Richtlijnen SWAB
- SWAB-ID
- Surveillance Antibioticagebruik
- Surveillance Antibioticaresistentie
- NethMap
- Educatie & nascholing
- Werkgroepen SWAB
- SWAB Symposium
- Meer over de SWAB
- Journalisten & media
- Informatie voor het publiek

Home → Medicamenteuze behandeling voo...

Delen via:

Medicamenteuze behandeling voor patiënten met COVID-19 (infectie met SARS-CoV-2)

Direct naar:

Erasmus MC

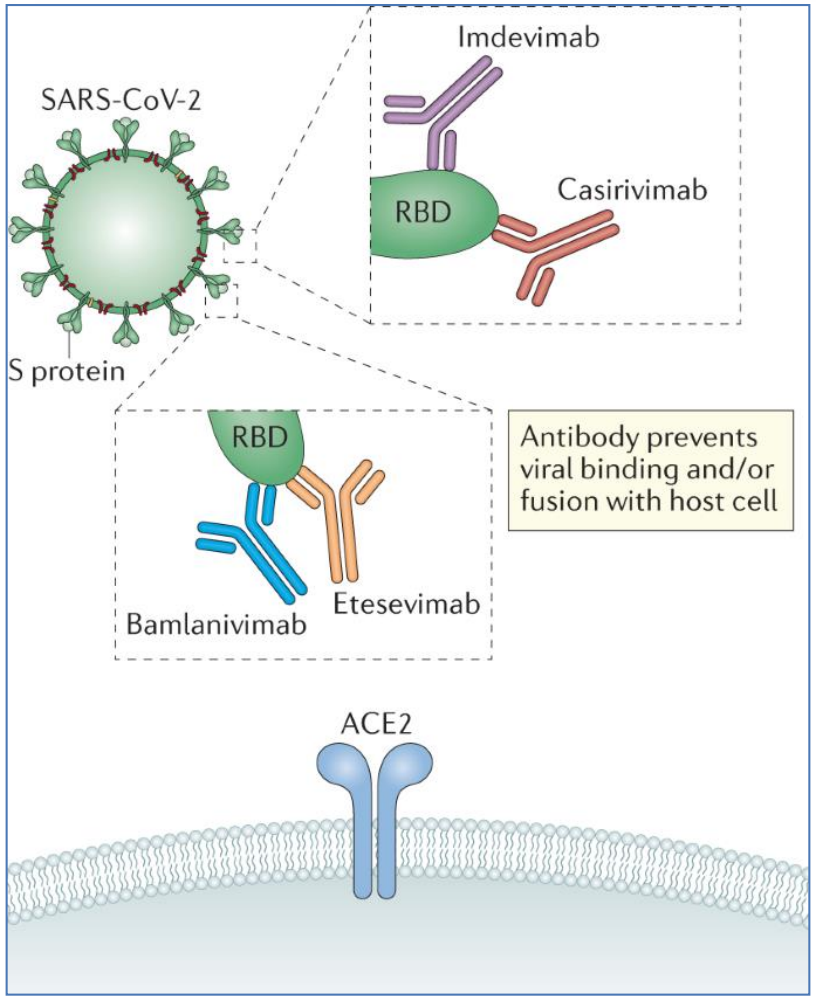
Casus 3

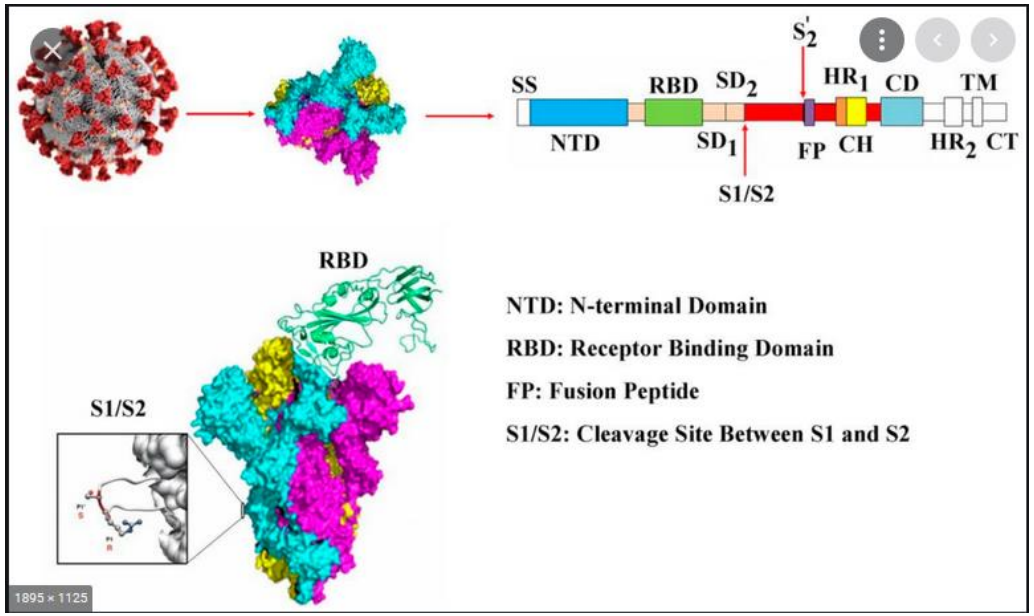
- 67 jarige man, opname ivm COVID-19
- 3 dagen klachten

Vraag: komt deze patient in aanmerking voor behandeling met Ronapreve?

Is hier een rol voor diagnostiek? Zo ja, welke?

therapeutic / antiviral antibodies





THE RECOVERY TRAILS

REGEN-COV for COVID-19

Casirivimab and imdevimab in patients admitted to hospital with COVID-19 (RECOVERY): a randomised, controlled, open-label, platform trial

Running title: REGEN-COV for COVID-19

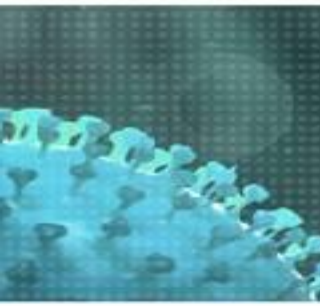
RECOVERY Collaborative Group*

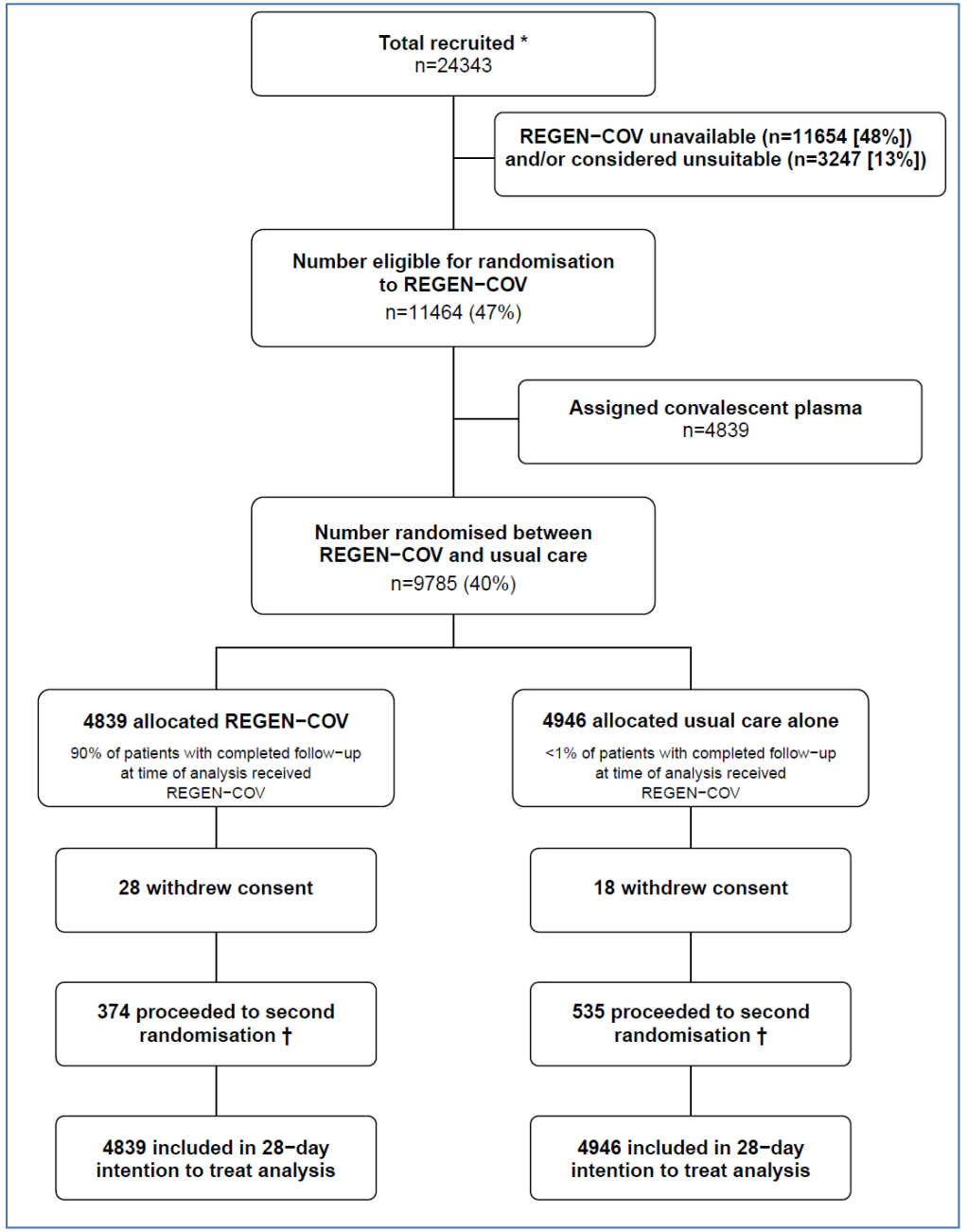
RECOVERY TRIAL

- 177 hospitals in the UK

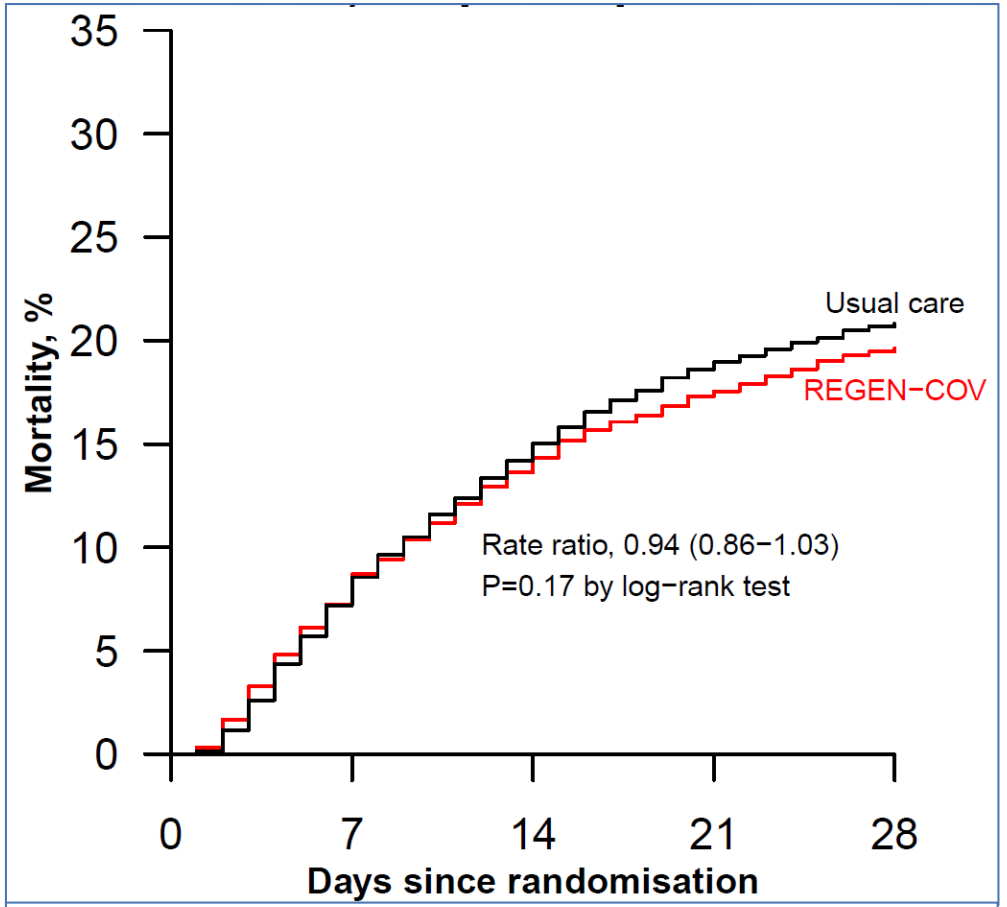
- “Pragmatic” trials: not many exclusion criteria, bias?

> Patients admitted to hospital were eligible for the study if they had clinically suspected or laboratory confirmed SARS-CoV-2 infection and no medical history that might, in the opinion of the attending clinician, put the patient at significant risk if they were to participate in the trial. Patients who had received intravenous immunoglobulin treatment during the current admission and children weighing <40 kg or aged <12 years were not eligible for randomisation to REGEN-COV. Pregnant or breastfeeding women were eligible for inclusion. Written informed consent was obtained from all patients, or a legal representative if patients were too unwell or unable to provide consent.




Total recruited *
n=24343
REGEN-COV unavailable (n=11654 [48%]) and/or considered unsuitable (n=3247 [13%])
Number eligible for randomisation to REGEN-COV
n=11464 (47%)
Assigned convalescent plasma
n=4839
Number randomised between REGEN-COV and usual care
n=9785 (40%)
4839 allocated REGEN-COV
90% of patients with completed follow-up at time of analysis received REGEN-COV
4946 allocated usual care alone
<1% of patients with completed follow-up at time of analysis received REGEN-COV
28 withdrew consent
18 withdrew consent
374 proceeded to second randomisation †
535 proceeded to second randomisation †
4839 included in 28-day intention to treat analysis
4946 included in 28-day intention to treat analysis

No effect on survival…..



No. at risk					
REGEN−COV	4839	4388	4112	3952	3848
Usual Care	4946	4504	4182	3980	3888

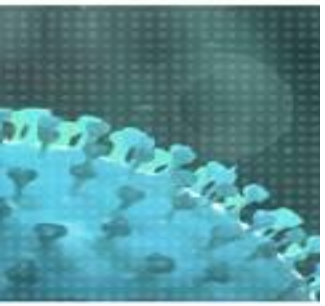
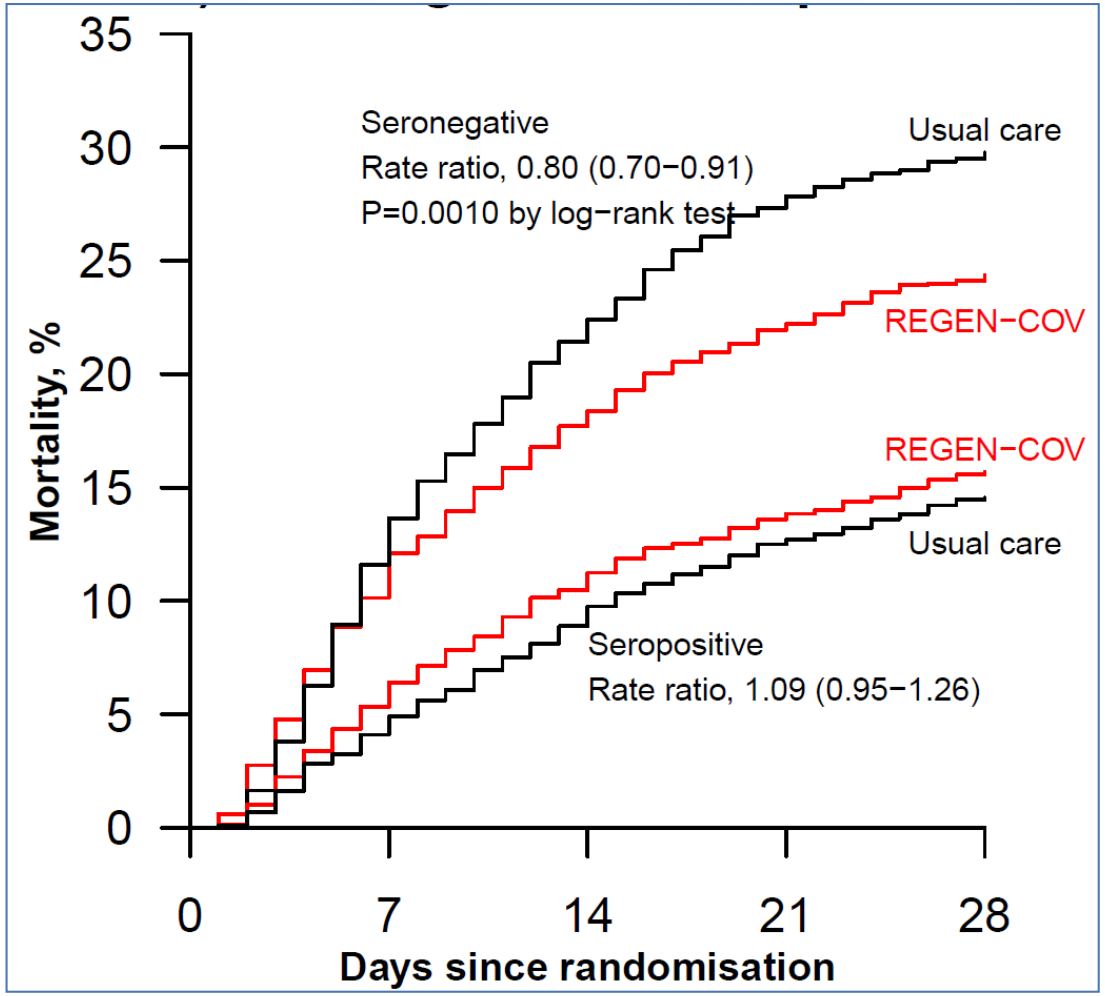


Table 1: Baseline characteristics (seronegative and all participants) by treatment allocation

	Seronegative patients		All patients	
	REGEN-COV (n=1633)	Usual Care (n=1520)	REGEN-COV (n=4839)	Usual Care (n=4946)
Age, years	63.2 (15.5)	64.0 (15.2)	61.9 (14.6)	61.9 (14.4)
<70*	1054 (65)	943 (62)	3389 (70)	3454 (70)
70 to 79	348 (21)	344 (23)	936 (19)	962 (19)
≥80	231 (14)	233 (15)	514 (11)	530 (11)
Sex				
Men	995 (61)	879 (58)	3033 (63)	3095 (63)
Women†	638 (39)	641 (42)	1806 (37)	1851 (37)
Ethnicity				
White	1324 (81)	1250 (82)	3768 (78)	3810 (77)
Black, Asian, and minority ethnic	147 (9)	136 (9)	588 (12)	696 (14)
Unknown	162 (10)	134 (9)	483 (10)	440 (9)
Number of days since symptom onset	7 (4-10)	7 (5-9)	9 (6-12)	9 (6-12)
Number of days since admission to hospital	1 (1-2)	1 (1-3)	2 (1-3)	2 (1-3)
Respiratory support received				
No oxygen received	182 (11)	148 (10)	332 (7)	309 (6)
Simple oxygen	1085 (66)	995 (65)	2980 (62)	3016 (61)
Non-invasive ventilation	332 (20)	341 (22)	1244 (26)	1317 (27)
Invasive mechanical ventilation	34 (2)	36 (2)	283 (6)	304 (6)
Previous diseases				
Diabetes	403 (25)	407 (27)	1240 (26)	1337 (27)
Heart disease	407 (25)	398 (26)	1038 (21)	1061 (21)
Chronic lung disease	455 (28)	458 (30)	1085 (22)	1159 (23)
Tuberculosis	7 (<1)	5 (<1)	18 (<1)	16 (<1)
HIV	7 (<1)	4 (<1)	24 (<1)	22 (<1)
Severe liver disease‡	28 (2)	17 (1)	69 (1)	70 (1)
Severe kidney impairment§	114 (7)	114 (8)	266 (5)	242 (5)
Any of the above	935 (57)	913 (60)	2557 (53)	2662 (54)
SARS-CoV-2 PCR test result				
Positive	1580 (97)	1470 (97)	4680 (97)	4791 (97)
Negative	17 (1)	16 (1)	38 (1)	53 (1)
[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
Patient SARS-CoV-2 antibody test result				
Positive	0	0	2636 (54)	2636 (53)
Negative	1633 (100)	1520 (100)	1633 (34)	1520 (31)
Missing	0	0	570 (12)	790 (16)
[illegible]				
Yes	1481 (91)	1399 (92)	4530 (94)	4639 (94)
No	152 (9)	118 (8)	308 (6)	299 (6)
Not recorded	0	3 (<1)	1 (<1)	8 (<1)
Other randomised treatments				
Azithromycin	38 (2)	43 (3)	124 (3)	124 (3)
Colchicine	364 (22)	350 (23)	1085 (22)	1139 (23)
Aspirin	405 (25)	372 (24)	1339 (28)	1389 (28)

Data are mean (SD), n (%), or median (IQR). *Includes 11 children (<18 years). † Includes 25 pregnant women. ‡ Defined as requiring ongoing specialist care. § Defined as estimated glomerular filtration rate <30 mL/min per 1·73 m²

Seronegative patients!

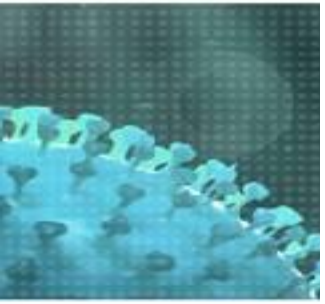


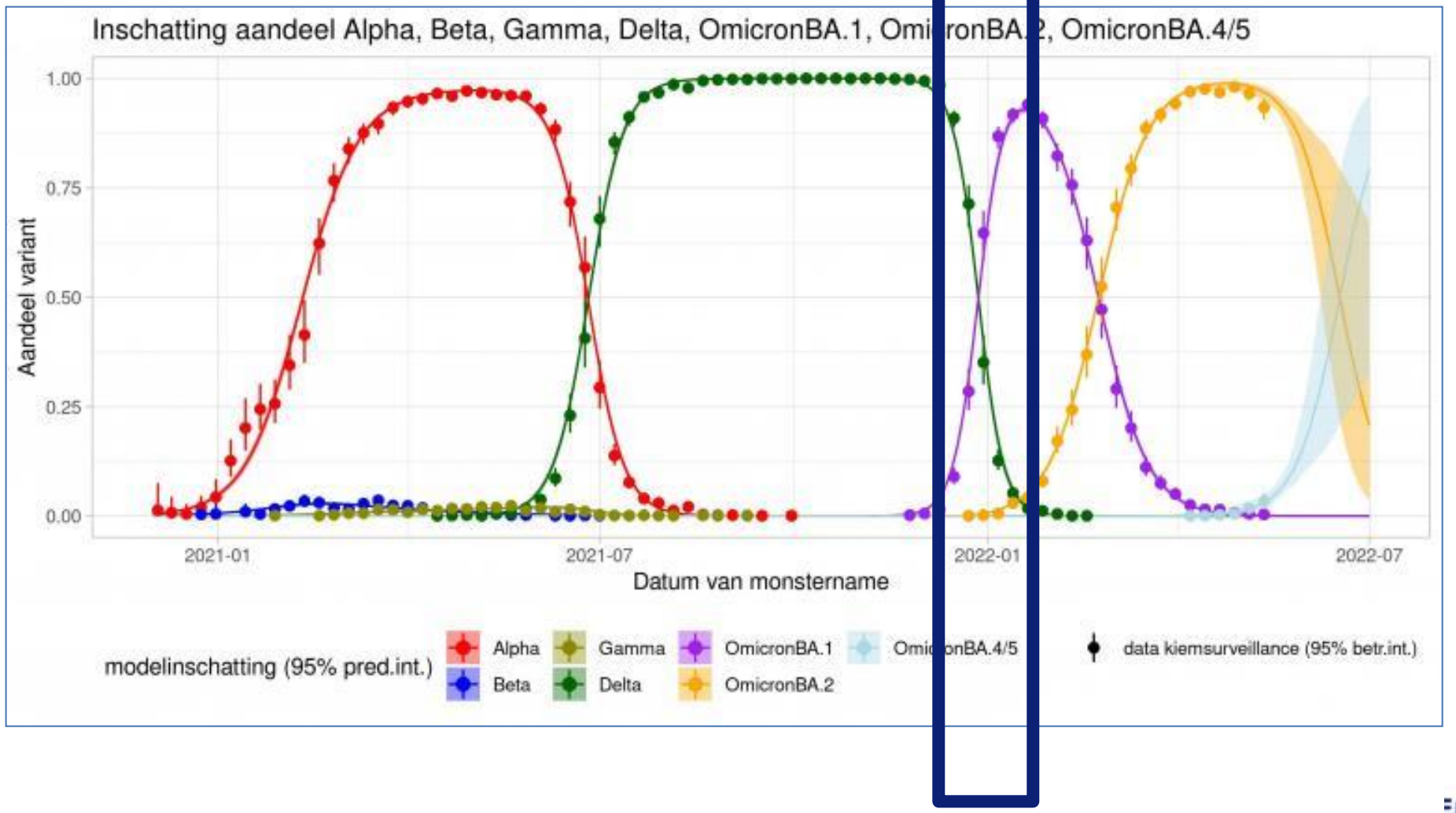
Casus 3

- 67 jarige man, opname ivm COVID-19
- 3 dagen klachten
- **Geen antistoffen tegen SARS-CoV-2 aantoonbaar bij opname**

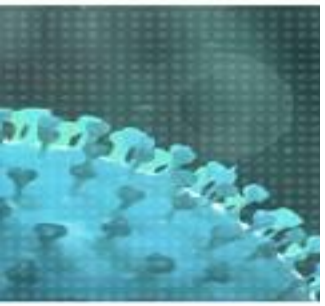
Vraag: komt deze patient in aanmerking voor behandeling met Ronapreve?

Nog meer diagnostiek nodig? Zo ja, welke?





https://www.rivm.nl/coronavirus-covid-19/virus/varianten



Article

Omicron escapes the majority of existing SARS-CoV-2 neutralizing antibodies

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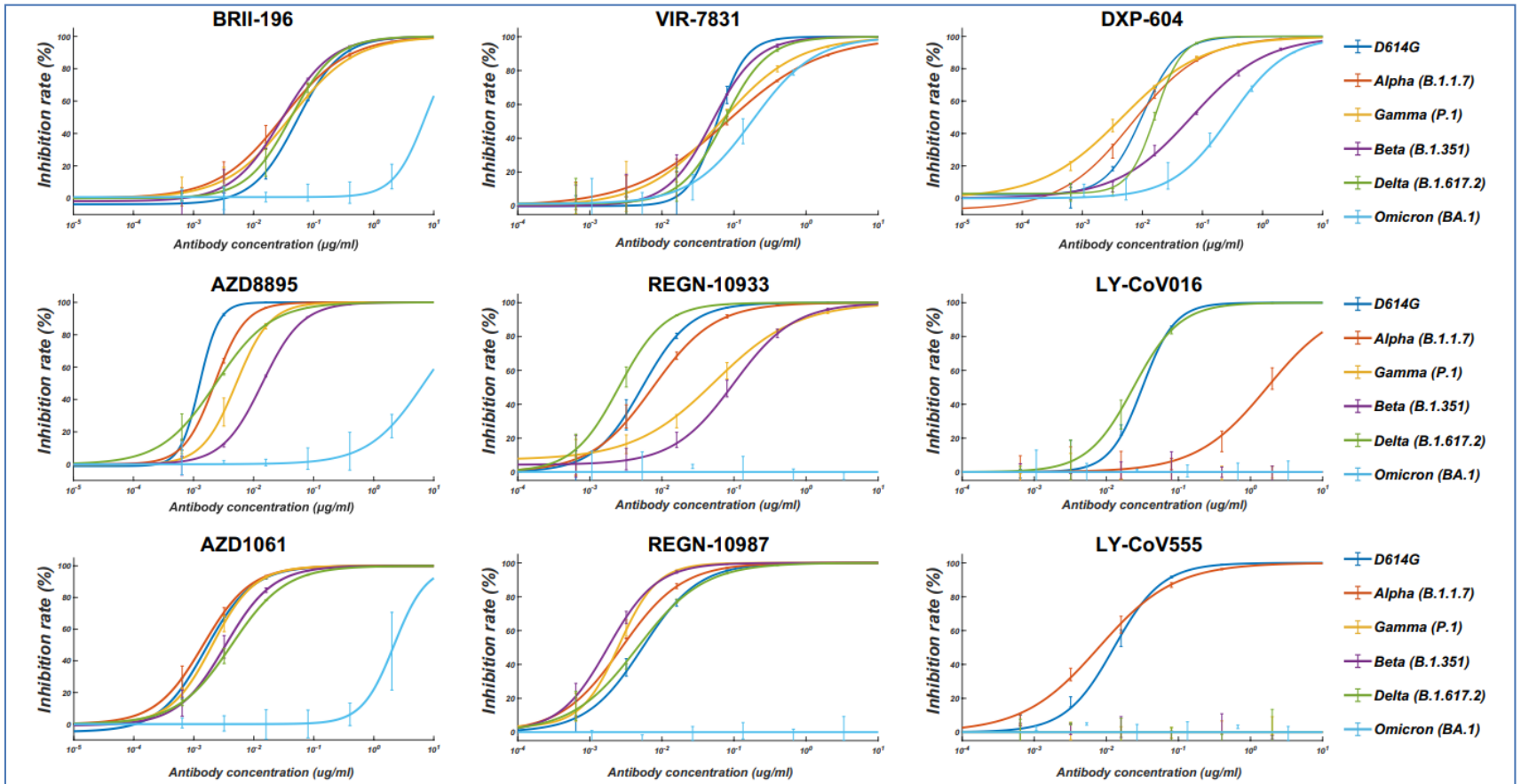
Yunlong Cao[1,2,11✉], Jing Wang[1,3,11], Fanchong Jian[1,4,11], Tianhe Xiao[1,5,11], Weiliang Song[1,3,11], Ayijiang Yisimayi[1,3,11], Weijin Huang[6,11], Qianqian Li[6], Peng Wang[1], Ran An[1], Jing Wang[1], Yao Wang[1], Xiao Niu[1,4], Sijie Yang[1,7], Hui Liang[1], Haiyan Sun[1], Tao Li[6], Yuanling Yu[6], Qianqian Cui[8], Shuo Liu[6], Xiaodong Yang[8], Shuo Du[3], Zhiying Zhang[3], Xiaohua Hao[9], Fei Shao[1], Ronghua Jin[9], Xiangxi Wang[10✉], Junyu Xiao[2,3✉], Youchun Wang[6✉] & Xiaoliang Sunney X

Nature | Vol 602 | 24 February 2022 |



Extended Data Fig. 9 | Pseudovirus neutralization of neutralizing-antibody-based drugs against SARS-CoV-2 variants of concern. Pseudovirus (VSV-based) assays were performed using Huh-7 cells. Data are collected from three biological replicates and represented as mean ± s.d.

Erasmus MC

Casus 3

- 67 jarige man, opname ivm COVID-19
- 3 dagen klachten
- **Geen antistoffen tegen SARS-CoV-2 aantoonbaar bij opname**
- **Uitslag variant PCR: K417N + S371L + S373P = Omicron BA1**

Vraag: komt deze patient in aanmerking voor behandeling met Ronapreve?

Antwoord: NEE

Vragen?