KLINIKEN SÜDOSTBAYERN

Klinische Infektiologie






Gemeinsam im Verbund

Ein Jahr COVID-19 Update und Fokus auf Impfung

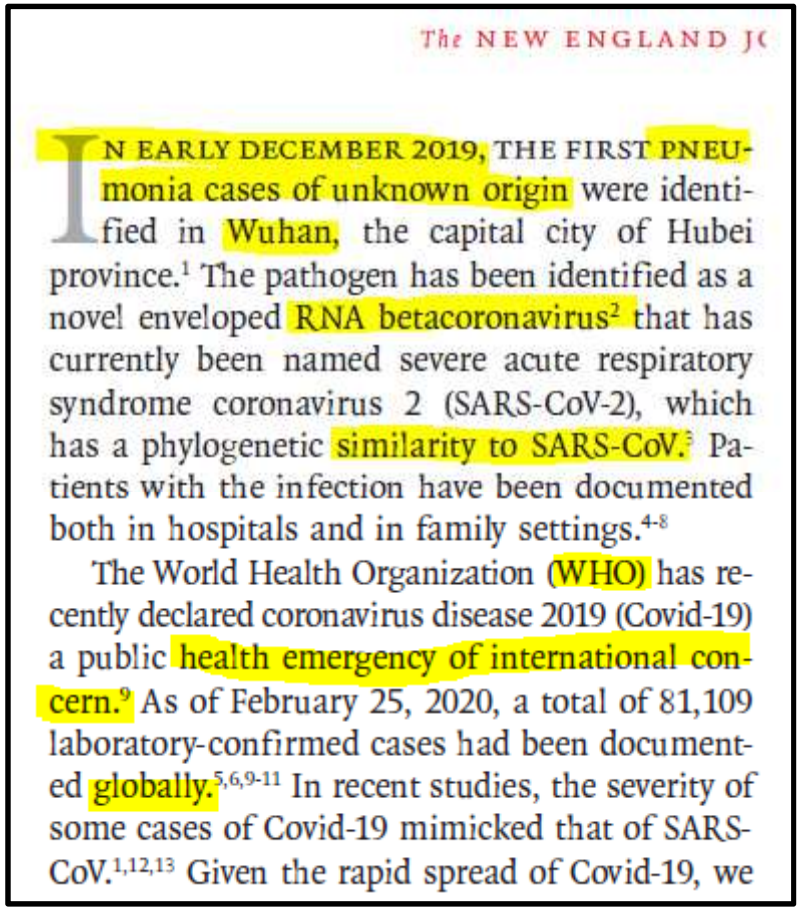
20.01.2021 – Zoom-meeting

B. Vogel, T. Glück, H. Bruckmayer

Themen am 20.01.2021

- B. Vogel: Update zu Virologie und Epidemiologie
  - aktuelle Zahlen
  - virologische Grundlagen
  - Virusvarianten
  - Clinical specials
- T. Glück: Impfungen und Immunität
  - Impfen – welche Optionen?
  - die verschiedenen Impfstoffe und aktueller Zulassungsstatus
  - Nebenwirkungen
  - Immunität: Schutz vor Infektion oder nur vor Erkrankung?
  - Reinfektion
- H. Bruckmayer: Von der Theorie zur Praxis
  - das Impfzentrum in Altenmarkt:
  - Organisation, Priorisierung, Ablauf
  - Ausblick auf weitere Entwicklungen

Was bisher geschah….



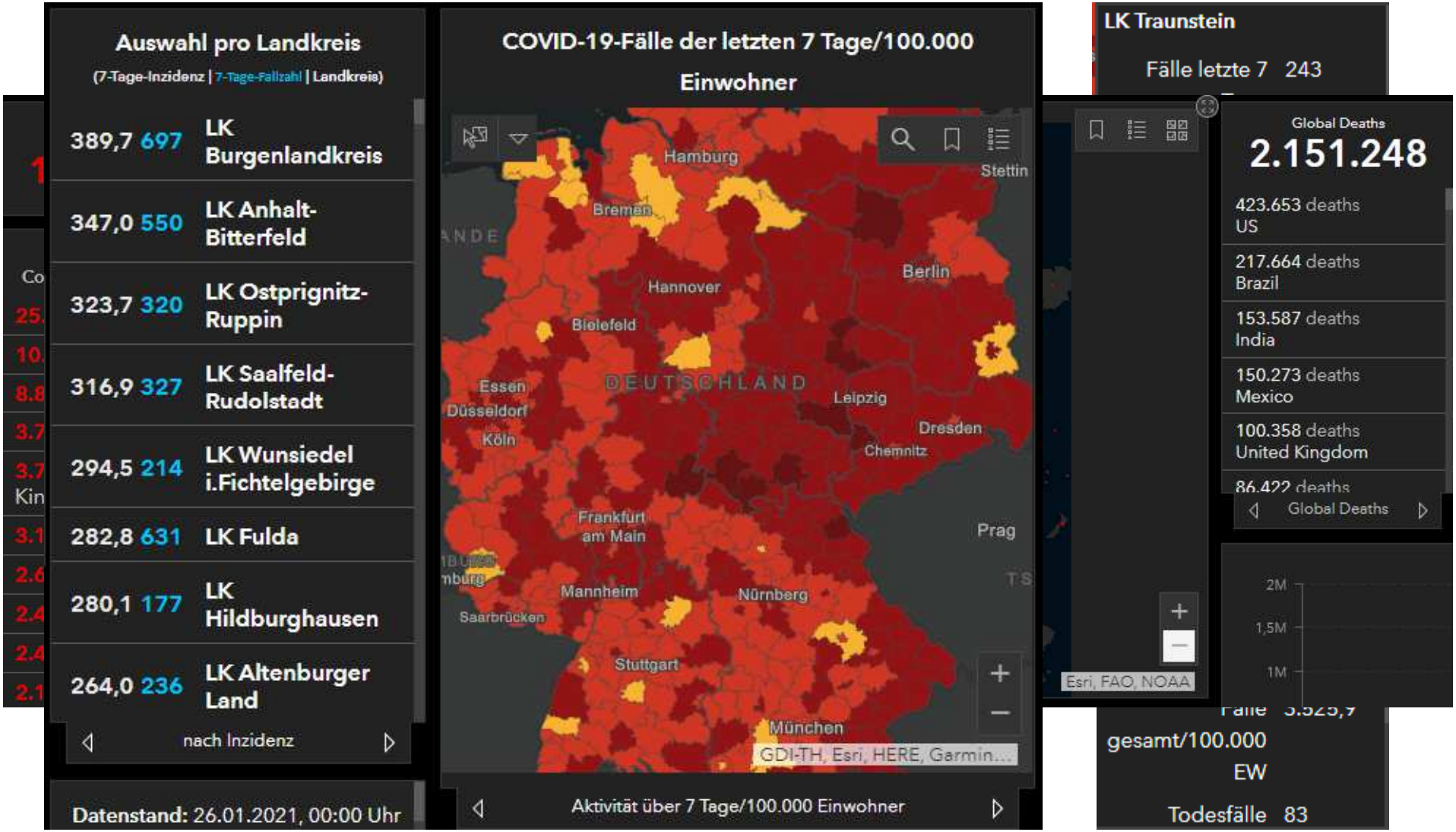
The NEW ENGLAND JC

IN EARLY DECEMBER 2019, THE FIRST PNEUmonia cases of unknown origin were identified in Wuhan, the capital city of Hubei province.[1] The pathogen has been identified as a novel enveloped RNA betacoronavirus[2] that has currently been named severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), which has a phylogenetic similarity to SARS-CoV.[3] Patients with the infection have been documented both in hospitals and in family settings.[4-8]

The World Health Organization (WHO) has recently declared coronavirus disease 2019 (Covid-19) a public health emergency of international concern.[9] As of February 25, 2020, a total of 81,109 laboratory-confirmed cases had been documented globally.[5,6,9-11] In recent studies, the severity of some cases of Covid-19 mimicked that of SARS-CoV.[1,12,13] Given the rapid spread of Covid-19, we

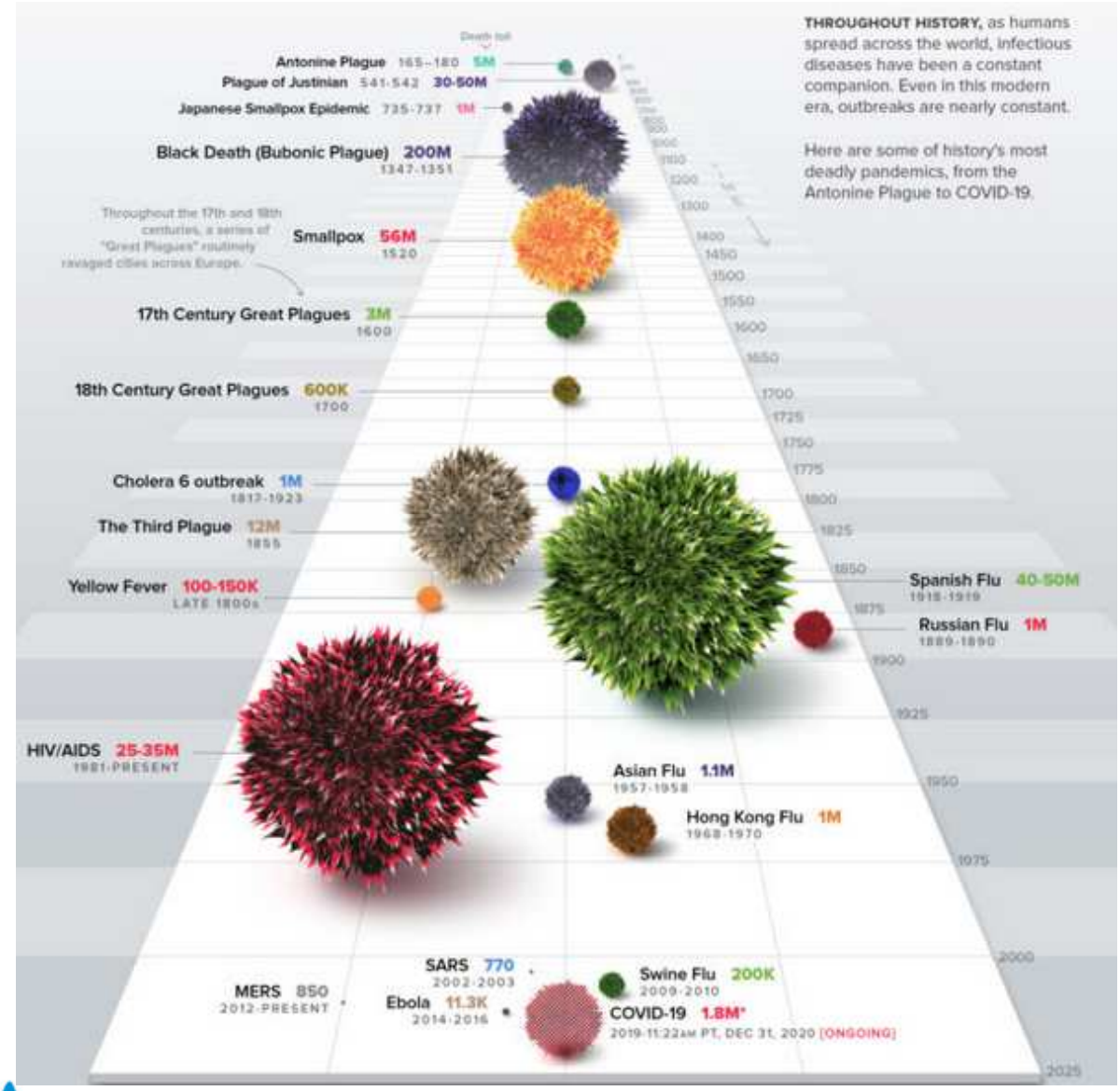
Guan, W. et al: Clinical Characteristics of Coronavirus Disease 2019 in China, NJJM 2020-03

Zur Lage der Nation



https://gisanddata.maps.arcgis.com/apps/opsdashboard/index.html#/bda7594740fd40299423467b48e9ecf6

history of pandemics



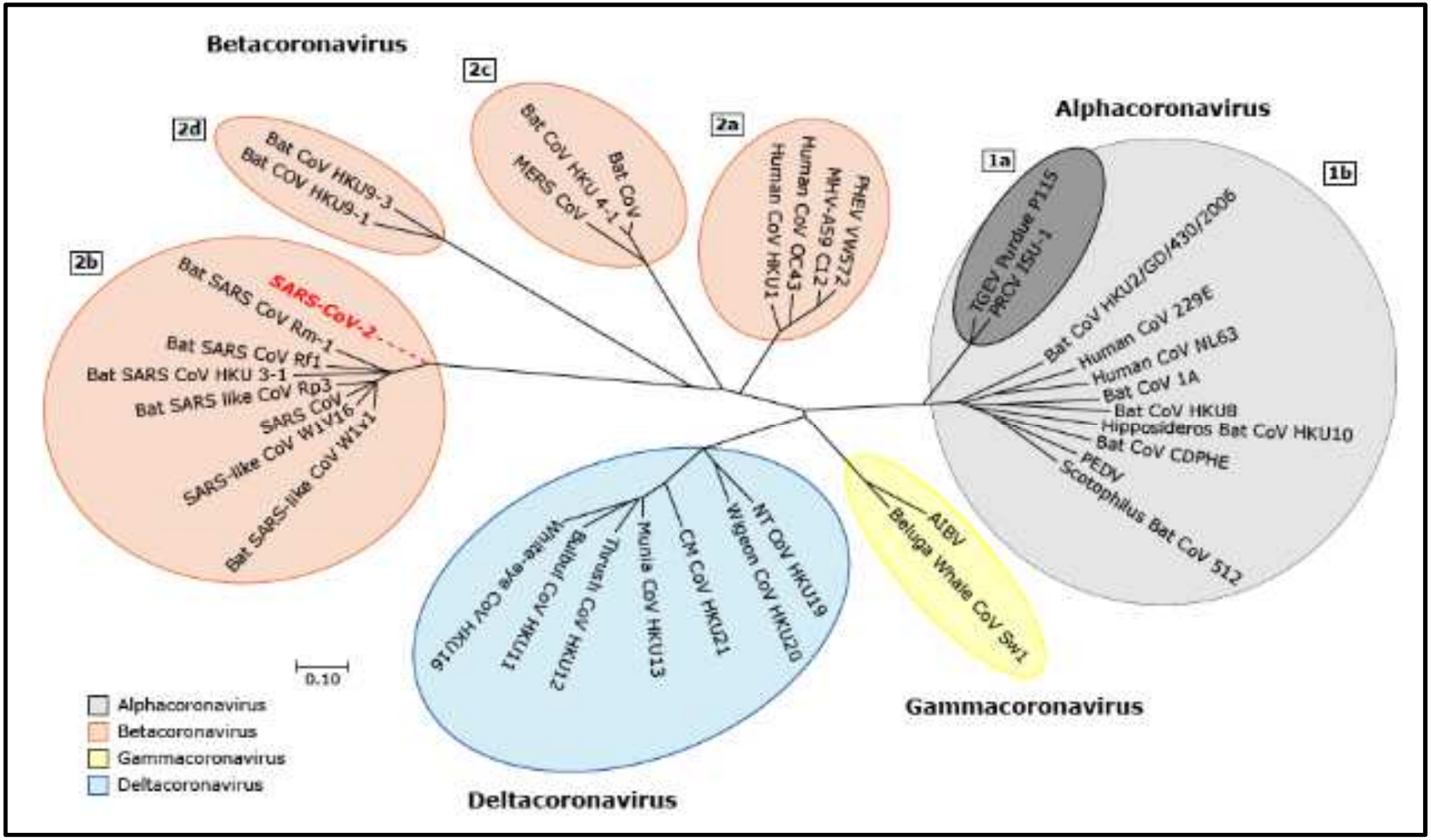
https://www.visualcapitalist.com/history-of-pandemics-deadliest/

Coronaviren – common cold

1) Die respiratorische Multiplex-Analyse lieferte folgende Ergebnisse:Bocavirus: negativCoronavirus NL63: negativCoronavirus 229E: negativCoronavirus OC43: negativCoronavirus HKU1: negativAdenovirus: negativRhinovirus: negativHum. Metapneumovirus: negativParainfluenzavirus 1: negativParainfluenzavirus 2: negativParainfluenzavirus 3: negativParainfluenzavirus 4: negativRespiratory Syncytial V: negativInfluenza A Virus: negativInfluenza B Virus: negativChlamydia pneumoniae: negativLegionella pneumophila: negativMycoplasma pneumoniae: negativSomit konnte keiner der Erreger in dem untersuchten Probenmaterialnachgewiesen werden.Die oben aufgeführten Coronaviren stellen n i c h t dasCOVID-19 assoziierte SARS-CoV-2 dar.
2) Chlamydia pneumoniae-DNA n i c h t nachgewiesen.

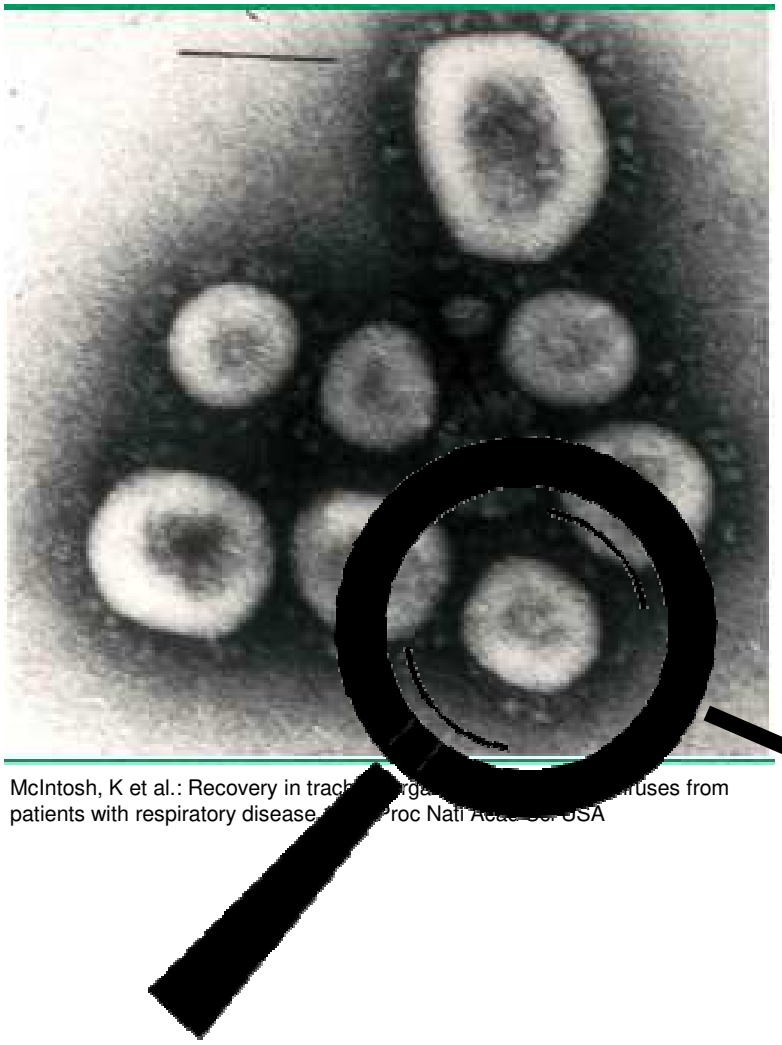
-**1960** Entdeckung von **HCoV-229E** und **HCoV-OC43**
-1970/1980: ursächlich für 5-10% aller Erkältungen bei Erwachsenen, bis zu 1/3 verantwortlich für saisonale Ausbrüche von Infektionen des oberen Respirationstraktes, bei kleinen Kindern auch unterer Respirationstrakt (2-8% aller hospitalisierten CAPs); häufiges „Kopathogen“ mit unklarer Rolle
-2002 SARS (jetzt: SARS-CoV-1)
-**2004/2005**: Entdeckung **HCoV-NL63** und **HCoV-HKU1**
-2012: MERS
-2019: SARS-CoV-2

Coronaviren-Phylogenetik



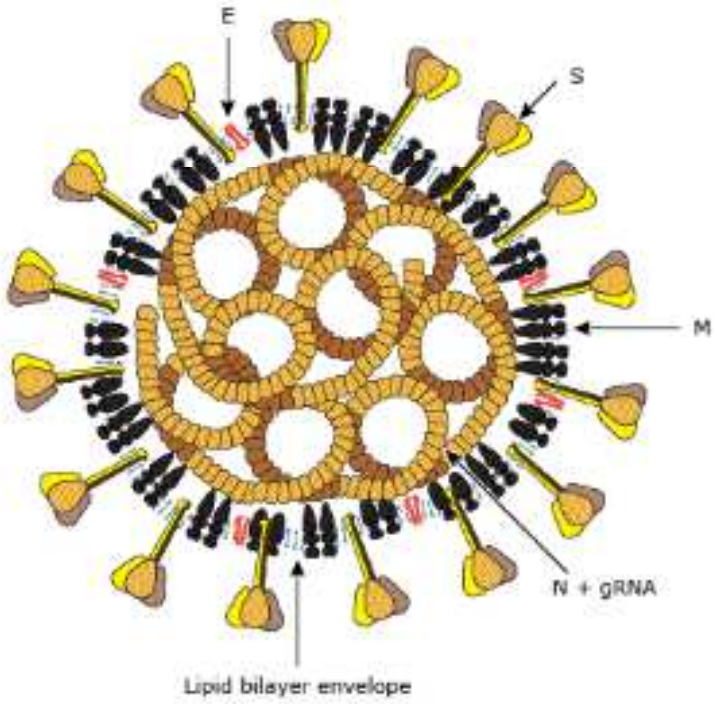
Shereen MA et al.: Covid-19 Infection: Origin, Transmission and Characteristics of Human Coronaviruses: J Adv Res 2020

Coronaviren-Oberflächenproteine



McIntosh, K et al.: Recovery in trach[illegible] uses from patients with respiratory disease. Proc Natl Acad Sci USA

S spike protein, M membrane protein,
E envelope protein N nucleocapsid protein



Masters PS et al.: Coronaviridae. 2013, Fields Virology

Coronaviren-Replikation

Yuang H et al.: Structural and functional properties of SARS-CoV-2 spike protein: potential antivirus drug development for COVID-19. 2020-08 Acta Pharmacologica Sinica

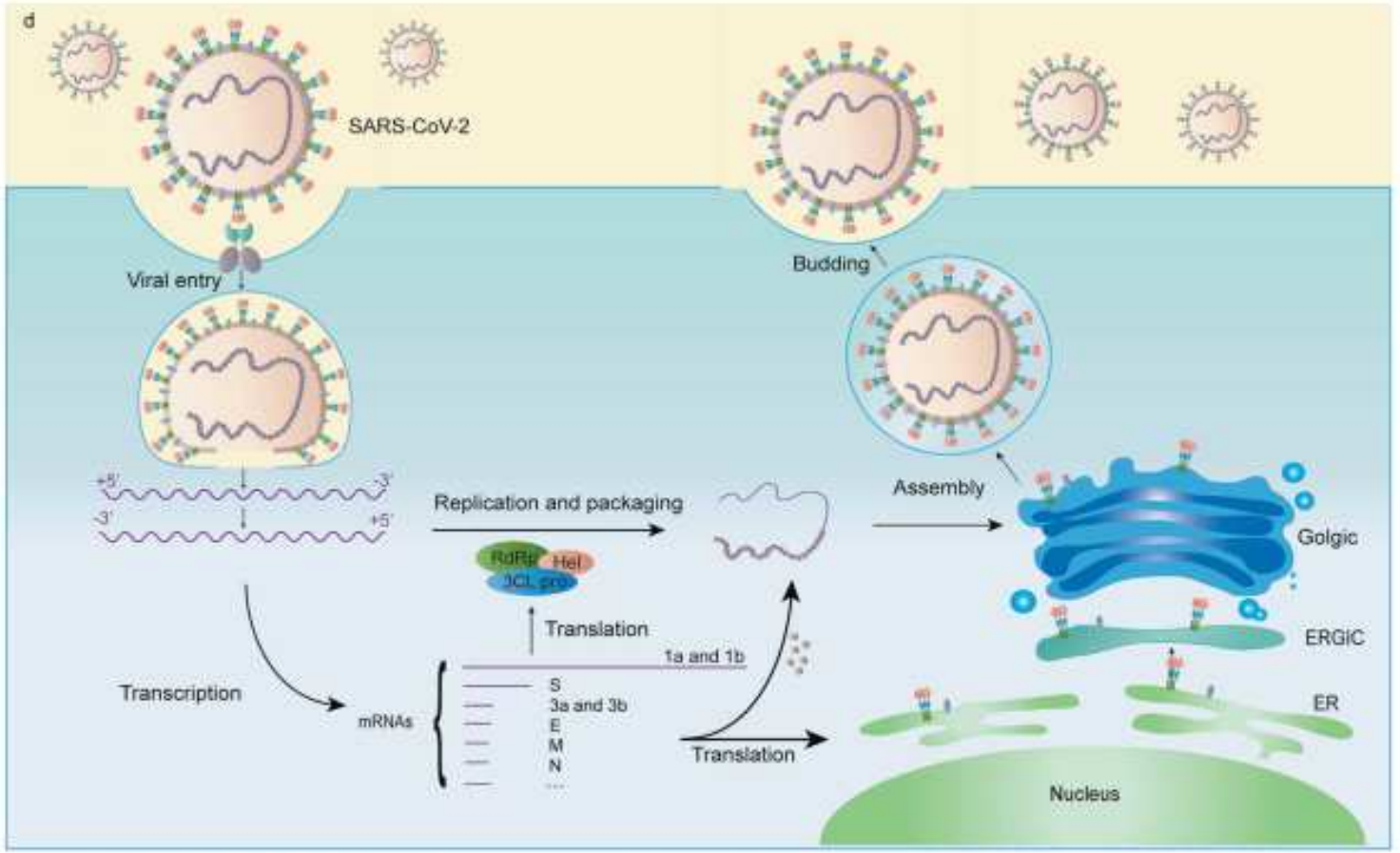


Fig. 1 Schematic of the SARS-CoV-2 S protein. a The schematic structure of the S protein. **b** The S protein binds to the receptor ACE2. **c** The binding and virus–cell fusion process mediated by the S protein. **d** The life cycle of SARS-CoV-2 in host cells.

Bleiben wir noch kurz auf der Zellebene…

- Diagnostik:
  - ✓PCR – Und nach Impfung?
  - ✓Antigentest – Und nach Impfung?
  - ✓Antikörper – Und nach Impfung?
- Mutationen

SARS-CoV-2: NAAT

Goldstandard: **Real-time-PCR**

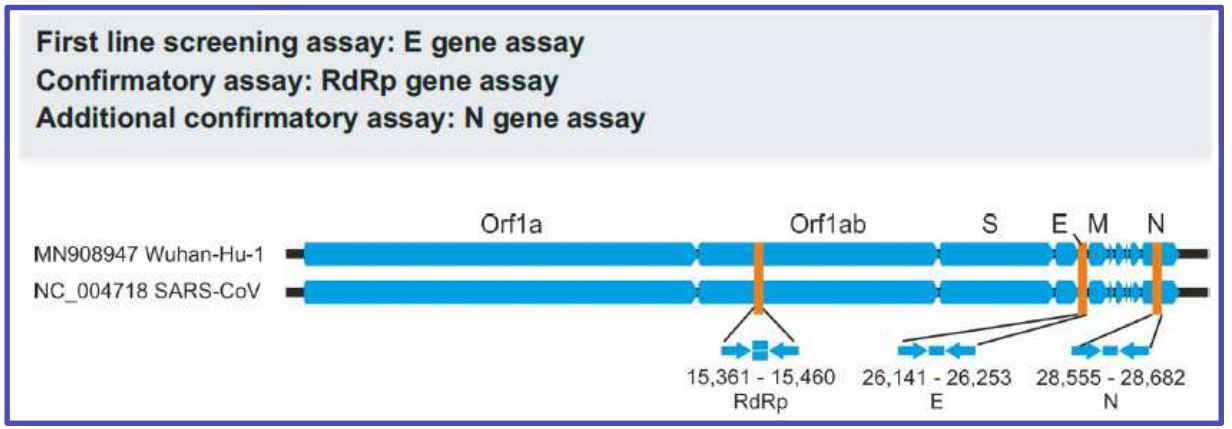
Verschiedene Zielsequenzen (Basenpaarfragmente, z.B. E-Gen mit 76BP, RdRp-Gen100BP)

-> unterschiedliche Testsysteme,
unterschiedliche internationale Empfehlungen:

China: ORF1ab + N-Gen
CDC: Ziele im N-Gen
Institut Pasteur: zwei Sequenzen im RdRP
***Charité Berlin*:** dreistufig (E-Gen + N-Gen + RdRP)

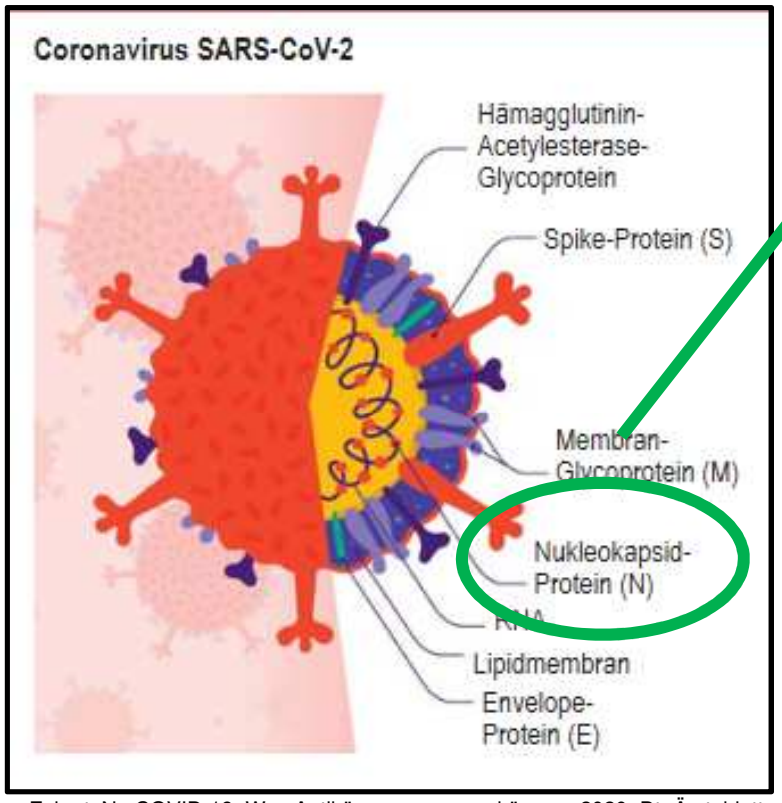
Seegene Assay Synlab TS

Methode	Ergebnis
INFEKTIOLOGIE ALLGEMEIN	
SARS-CoV-2 PCR (Seegene Assay)	positiv ▲
CT-Werte: S gene 32.95, RdRP gene 36.99, N gene 34.95	



Corman, V. et al: Diagnostic detection of Wuhan coronavirus 2019 by real-time RT-PCR. 2020/01 Berlin

SARS-CoV-2: Antigentest



Eckert, N.: COVID-19: Was Antikörper aussagen können. 2020, Dt. Ärzteblatt

-frühe Expression in der Infektionsphase
-hohe Expression während der Infektion
-stabile Domäne

TABLE 2. Results of the N protein of SARS-CoV assay for sera from patients with SARS in the serological test-positive group

Days after onset of symptoms	No. of patients with positive sera/total no. of patients with SARS (%)
1–5	78/84 (92.9)
6–10	44/63 (69.8)
11–15	12/33 (36.4)
16–20	4/19 (16.7)
21–115	0/220 (0)

Biao, D et al: Monoclonal Antibody-Based Antigen Capture Enzyme-Linked Immunsorbent Assay Reveals High Sensitivity of the Nucleocapsid Protein in Acute-Phase Sera of SARS Patients. 2004 Clin and Diag. Lab.Immunology

Aber: „es ist alles im Fluss“

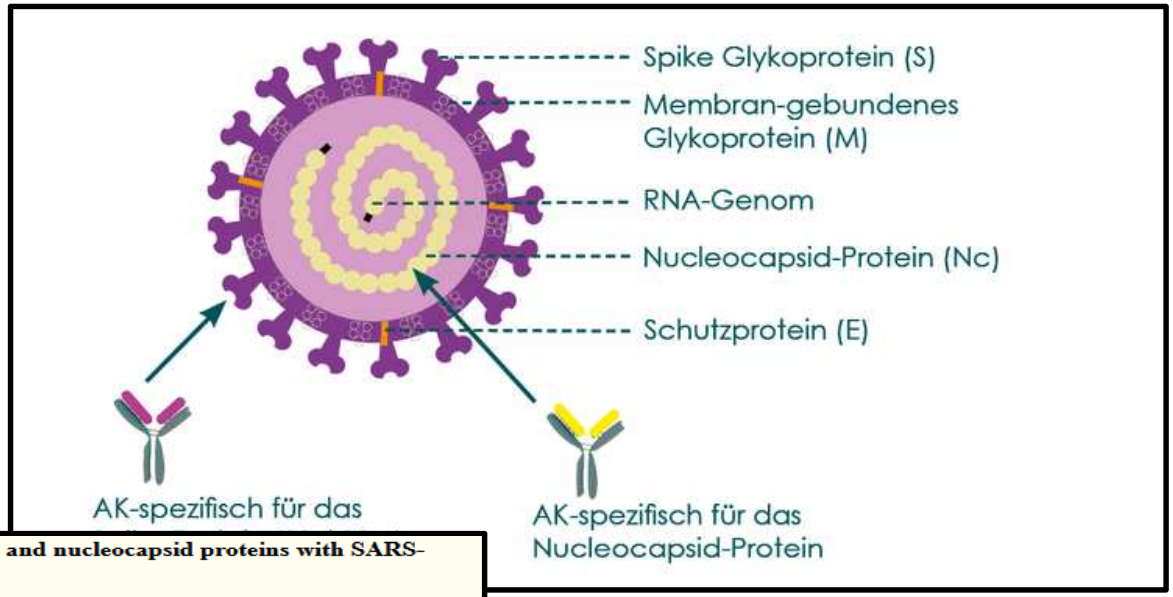
A novel rapid detection for SARS-CoV-2 spike 1 antigens using human angiotensin converting enzyme 2 (ACE2)

Jong-Hwan Lee [a], Minsuk Choi [a], Yujin Jung [a], Sung Kyun Lee [a], Chang-Seop Lee [b,c], Jung Kim [a], Jongwoo Kim [a], Nam Hoon Kim [a], Bum-Tae Kim [a], Hong Gi Kim [a,*]

[a] Center for Convergent Research of Emerging Virus Infection, Korea Research Institute of Chemical Technology, Daejeon, 34114, Republic of Korea
[b] Department of Internal Medicine, Jeonbuk National University Medical School, Jeonju, Jeollabuk-do, 54986, Republic of Korea
[c] Biomedical Research Institute of Jeonbuk National University Hospital, Jeonju, Jeollabuk-do, 54907, Republic of Korea

SARS-CoV-2: Antikörper-Tests I

- 4 Strukturproteine
-16 Nicht-Strukturproteine



https://www.imd-berlin.de/spezielle-kompetenzen/covid-19.html

Percentage amino acid identity of coronavirus spike and nucleocapsid proteins with SARS-CoV-2 proteins*

Virus type	*Virus*	*Nucleocapsid*	*S*	*S1*	*S2*	*S1^A*	*RBD*
Betacoronavirus	SARS-CoV	90	77	66	90	52	73
	MERS-CoV	49	33	24	43	ND	ND
	HCoV-OC43	34	33	25	42	ND	ND
	HCoV-HKU1	34	32	25	40	ND	ND
Alphacoronavirus	HCoV-229E	28	30	24	35	ND	ND
	HCoV-NL63	29	28	21	36	ND	ND

*SARS-CoV-2, HCoV-OC43, MERS-CoV, HCoV-HKU1, HCoV-NL63, SARS-CoV, HCoV-229E (GenBank accession nos. NC_045512.2, NC_006213.1, NC_019843.3, NC_006577.2, NC_005831.2, NC_004718.3, and NC_002645.1). Protein sequences were aligned by using ClustalW (https://www.genome.jp/tools-bin/clustalw). RBD, receptor-binding domain; ND, not done; S, spike; S1, N-terminal subunit of the spike protein; S2, C-terminal subunit of the spike protein; S1^A, domain A of the spike S1 subunit; SARS-CoV, severe acute respiratory syndrome coronavirus; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

Okba NMA et al.: SARS-CoV-2 specific antibody responses in COVID-19 patients. 2020-06 Emerg Infect Dis

SARS-CoV-2: Antikörper-Tests II

Country of development	USA
Type of Serological Test	RDT
Authors/Company	ChemBio
Description	This test detects IgM and IgG antibodies to the nucleocapsid (N) protein of SARS-CoV-2. Sensitivity and specificity values were not released.
Sensitivity	
Specificity	
Phase of development	Approved for EUA by the FDA
Propo	
Date	

Country of development	USA
Type of Serological Test	ELISA
Authors/Company	Mount Sinai Laboratory COVID-19 ELISA IgG Antibody Test
Description	This test detects, qualitatively, IgG present in the serum of patients. The ELISA based method uses a 1:50 dilution of human serum that is flowed over a plate coated with the spike protein receptor binding domain (RBD). Sensitivity and specificity are not yet available.
Sensitivity	
Specificity	
Phase of development	Approved for E
Proposed release	April 15, 2020
Date	April 16, 2020

Country of development	South Korea
Type of Serological Test	RDT
Authors/Company	Sugentech Inc.
Description	The SGTi-flex COVID-19 IgG is a colloidal gold based lateral flow assay, specific for IgG to SARS-CoV2. The test strip is within a cassette, and the results can be read by eye within about 15 minutes. The assay detects IgG specific to the SARS-CoV-2 nucleocapsid and RBD of the spike protein. This test can use human serum, plasma, or whole blood samples. Sensitivity was determined from 185 positive clinical samples and stratified by time post symptom onset, and specificity from 234 negative clinical samples. The test was also validated by the NCI, with a sensitivity of 96.7%, and a specificity of 100%.
Sensitivity	41.2% (0-7 days), 91.7% (7-14 days), 98.6% (15+ days)
Specificity	99.15%
Phase of development	Received FDA EUA, CE mark, Korea MFDS Product license, and Brazil ANVISA certified
Proposed release	Current
Date	September 3, 2020

Country of development	US
Type of Serological Test	photonic ring immunoassay (PRI)
Authors/Company	Genalyte, Inc
Description	The Maverick SARS-CoV-2 Multi-Antigen Serology Panel v2 is a qualitative assay to detect IgG and IgM antibodies specific to SARS-CoV-2. The photonic ring immunoassay uses silicon photonics to multiplex several antigens on a small chip. This allows for simultaneous detection of a variety of antibodies to different viruses. This assay can detect antibodies to SARS-CoV-2 nucleocapsid, full length spike, S1, S2, and RBD subunits. It also detects antibodies to the spike protein of the common coronaviruses, 229E, OC43, and HKU1, and to the nucleoprotein of NL63. Further, it can detect antibodies to influenza A H1 and H3 proteins, the S1 subunit of MERS, and the nucleoprotein of SARS-CoV-1. However, the test only reports positivity/negativity for SARS-CoV-2. The test must be run on the Maverick platform, and a proprietary algorithm analyzes the signal to determine test results. This table depicts the sensitivity and specificity measures for SARS-CoV-2 only. Sensitivity was determined using 338 positive clinical samples, stratified by time post sympto onset. Specificity was determined from 862 negative samples.
Sensitivity	66.7% (0-7 days); 90.91% (8-14 days); 96.1% (15+ days)
Specificity	97.7%%
Phase of development	Received FDA EUA
Proposed release	Current
Date	October 8, 2020

Mutationen I

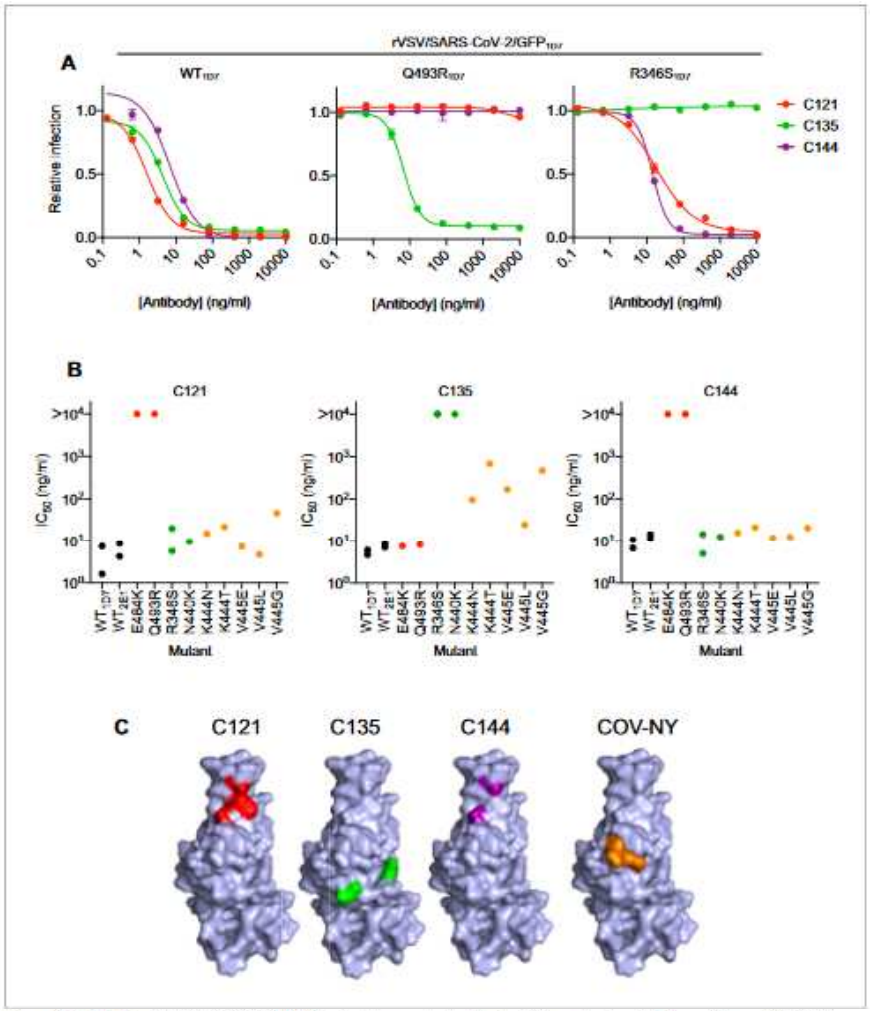


Figure 4. Neutralization of rVSV/SARS-CoV-2/GFP RBD mutants by monoclonal antibodies. (**A**) Examples of neutralization resistance of rVSV/SARS-CoV-2/GFP mutants that were isolated following passage in the presence of antibodies. 293T/ACE2cl.22 cells were inoculated with WT or mutant rVSV/SARS-CoV-2/GFP in the presence of increasing amount of each monoclonal antibody, and infection quantified by FACS 16 hr later. Mean and SD from two technical replicates, representative of two independent experiments. (**B**) Neutralization sensitivity/resistance of rVSV/SARS-CoV-2/GFP mutants isolated following replication in the presence of antibodies. Mean IC_{50} values were calculated for each virus-monoclonal antibody combination in two independent experiments. (**C**) Position of neutralization resistance-conferring substitutions. Structure of the RBD (from PDB 6M17 *Yan et al., 2020*) with positions that are occupied by amino acids where mutations were acquired during replication in the presence of each monoclonal antibody or COV-NY plasma indicated.

Weisblum, Y. et al.: Escape from neutralizing antibodies by SARS-CoV-2 spike protein variants. 2020-10 Elife

Mutationen II

2020-01/02: D614G Mutation breitet sich global aus und wird global zur dominierenden Stamm (entspricht bereits nicht mehr dem Ursprungsstamm aus Hubei): erhöhte Infektiosität

2020-08/09: Cluster 5 Variante in dänischen Nerzfarmen wird auf Menschen übertragen -> Kombination aus mehreren Mutationen, Besorgnis, dass eine verminderte Virusneutralisation resultieren könnte; bislang nur 12 Infizierte

2020-11: N501Y.V2 (auch B.1.351) in Südafrika -> keine phylogenetische Verwandtschaft zu den sonst bislang zirkulierenden Linien, verdrängt in verschiedenen Provinzen die bis dato vorherrschenden Stämme; erhöhte Übertragbarkeit wird postuliert, evtl. Ursache erhöhte Viruslast; vereinzelt auch in mind. vier anderen Ländern nachgewiesen

2020-12: VOC 202012/01 (auch B.1.1.7) im Südosten Englands -> keine phylogenetische Verwandtschaft zu den sonst im UK zirkulierenden Linien, erhöhte Übertragbarkeit, Hinweise für höhere Viruslasten; Zitat WHO „affects …PCR assays with an S gene target“, kein Effekt auf Antigentests; dominiert bereits Großraum London, Ende Dezember in 31 anderen Ländern ebenfalls nachgewiesen *(Anmerkung: COG-UK ist ein Genomsequenzierungskonsortium für SARS-CoV-2, es werden ca. 5-10% aller Positivproben in GB sequenziert)*

Back to the clinics….

-Risikostratifizierung
-Therapieoptionen
-Langzeitfolgen

Covid-19 - Risikostratifizierung

4C Mortality Score

The 4C Mortality Score is a risk stratification score that predicts in-hospital mortality for hospitalised COVID 19 patients, produced by the ISARIC 4C consortium. **It is intended for use by clinicians.**

It is designed to be easy-to-use, and require only parameters that are commonly available at hospital presentation.

It is based on a UK cohort of patients, and should not be adopted for routine clinical use in other settings until it has been appropriately validated.

For full details, see the paper introducing the score.

This page is an infographic that visualises risk, based on observed mortality among hospitalised adult COVID19 patients recruited into the ISARIC 4C study in the UK.

▸ How this calculation is done

Age (years):

18-49	50-59	60-69	70-79	⩾80
(+0)	(+2)	(+4)	(+6)	(+7)

Sex at birth:

Female	Male
(+0)	(+1)

Number of comorbidities:
▸ Definition

0	1	⩾2
(+0)	(+1)	(+2)

Respiratory rate (breaths/minutes):

<20	20-29	⩾30
(+0)	(+1)	(+2)

Peripheral oxygen saturation on room air (%):

<92	⩾92
(+2)	(+0)

Glasgow Coma Scale:

<15	15
(+2)	(+0)

Urea (mmol/L):

<7	7-14	>14
(+0)	(+1)	(+3)

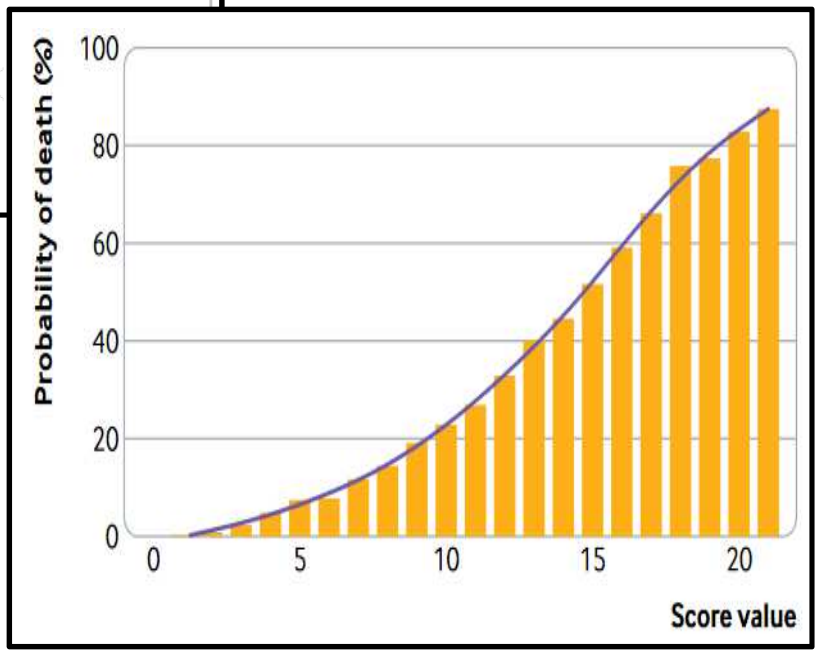
Use BUN (mg/dL)

CRP (mg/L):

<50	50-99	⩾100
(+0)	(+1)	(+2)

Knight, BM: Risk stratification of patients admitted to hospital with covid-19 using the ISARIC WHO Clinical Characterisation Protocol: development and validation of the 4C Mortality Score; 2020-09 BJM

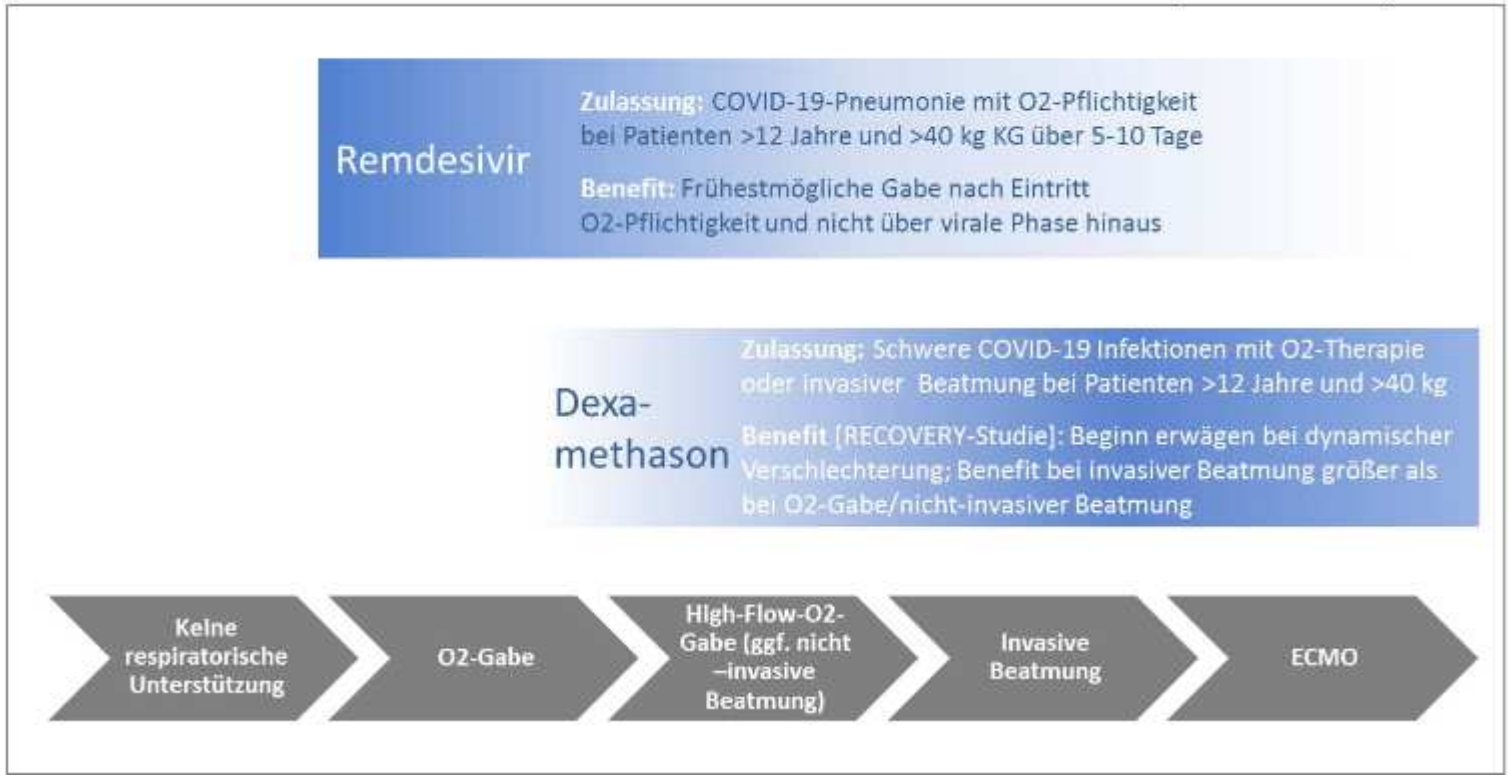
ISARIC-4C COVID-19 Mortality Risk Prediction Model



Covid-19 - Therapieoptionen

-Antikoagulation
-Remdesivir (virämische Frühphase)
-Dexamethason (immunologische Spätphase)

Grafik 1: Gabe von Remdesivir und Dexamethason in zeitlicher Relation zur Atmungsunterstützung



https://www.rki.de/DE/Content/Kommissionen/Stakob/Stellungnahmen/Stellungnahme-Covid-19_Therapie_Diagnose.pdf?__blob=publicationFile

Langzeitfolgen

-“Long-COVID“, „Post-COVID-Syndrom“, „long hauler“

Lenzen-Schulte, M.: Long COVID: Der lange Schatten von COVID-19. Dt. Ärzteblatt 2020-12

	Total (n=1733)	Seven-category scale			OR or β (95% CI)	
		Scale 3: not requiring supplemental oxygen (n=439)	Scale 4: requiring supplemental oxygen (n=1172)	Scale 5-6: requiring HFNC, NIV, or IMV (n=122)	Scale 4 vs 3	Scale 5-6 vs 3
Symptoms						
Any one of the following symptoms	1265/1655 (76%)	344/424 (81%)	820/1114 (74%)	101/117 (86%)	OR 0·70 (0·52 to 0·96)*	OR 2·42 (1·15 to 5·08)*
Fatigue/muscle weakness	1038/1655 (63%)	281/424 (66%)	662/1114 (59%)	95/117 (81%)	OR 0·74 (0·58 to 0·96)*	OR 2·69 (1·46 to 4·96)*
Sleep difficulties	437/1655 (26%)	116/424 (27%)	290/1114 (26%)	31/117 (26%)	OR 0·92 (0·71 to 1·21)	OR 1·15 (0·68 to 1·94)
Hair loss	359/1655 (22%)	93/424 (22%)	238/1114 (21%)	28/117 (24%)	OR 0·99 (0·74 to 1·31)	OR 1·17 (0·67 to 2·04)
Smell disorder	176/1655 (11%)	55/424 (13%)	107/1114 (10%)	14/117 (12%)	OR 0·69 (0·48 to 1·00)	OR 0·90 (0·43 to 1·87)
Palpitations	154/1655 (9%)	45/424 (11%)	96/1114 (9%)	13/117 (11%)	OR 0·86 (0·58 to 1·28)	OR 1·31 (0·61 to 2·80)
Joint pain	154/1655 (9%)	51/424 (12%)	86/1114 (8%)	17/117 (15%)	OR 0·56 (0·38 to 0·83)*	OR 0·74 (0·36 to 1·50)
Decreased appetite	138/1655 (8%)	42/424 (10%)	85/1114 (8%)	11/117 (9%)	OR 0·84 (0·56 to 1·27)	OR 1·56 (0·71 to 3·43)
Taste disorder	120/1655 (7%)	37/424 (9%)	75/1114 (7%)	8/117 (7%)	OR 0·84 (0·54 to 1·30)	OR 0·80 (0·32 to 2·02)
Dizziness	101/1655 (6%)	32/424 (8%)	60/1114 (5%)	9/117 (8%)	OR 0·77 (0·48 to 1·22)	OR 0·95 (0·39 to 2·31)
Diarrhoea or vomiting	80/1655 (5%)	27/424 (6%)	48/1114 (4%)	5/117 (4%)	OR 0·71 (0·42 to 1·22)	OR 0·39 (0·11 to 1·42)
Chest pain	75/1655 (5%)	19/424 (4%)	46/1114 (4%)	10/117 (9%)	OR 0·94 (0·52 to 1·67)	OR 2·55 (0·99 to 6·62)
Sore throat or difficult to swallow	69/1655 (4%)	20/424 (5%)	44/1114 (4%)	5/117 (4%)	OR 0·91 (0·50 to 1·65)	OR 1·21 (0·40 to 3·73)
Skin rash	47/1655 (3%)	16/424 (4%)	27/1114 (2%)	4/117 (3%)	OR 0·64 (0·32 to 1·26)	OR 0·71 (0·18 to 2·87)
Myalgia	39/1655 (2%)	11/424 (3%)	24/1114 (2%)	4/117 (3%)	OR 0·80 (0·38 to 1·69)	OR 1·72 (0·47 to 6·27)
Headache	33/1655 (2%)	10/424 (2%)	20/1114 (2%)	3/117 (3%)	OR 0·76 (0·35 to 1·69)	OR 1·53 (0·36 to 6·52)
Low grade fever	2/1655 (<1%)	1/424 (<1%)	1/1114 (<1%)	0	NA	NA

Huang,C: et al: 6-month consequences of COVID-19 in patients discharged from hospital: a cohort study. 2020-01 The Lancet