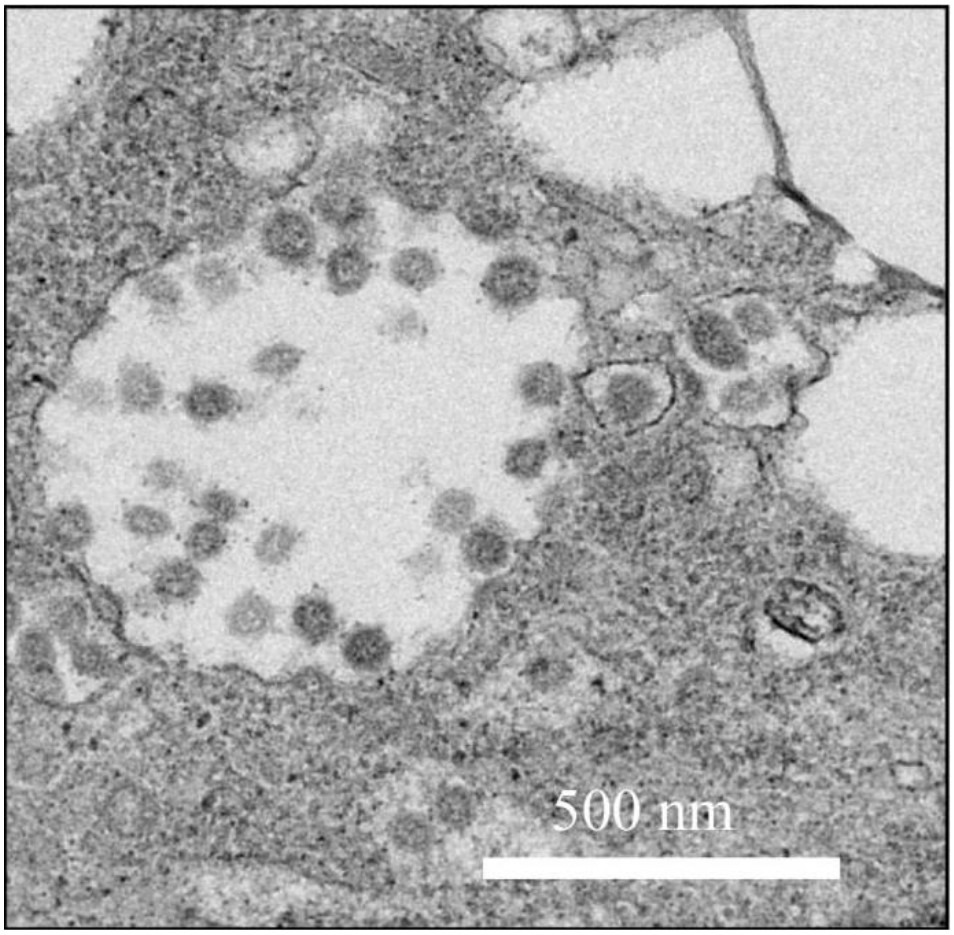
Coronavirus 2019
Erkrankung und Prävention

Dr. Christoph Wenisch - Klinik Favoriten

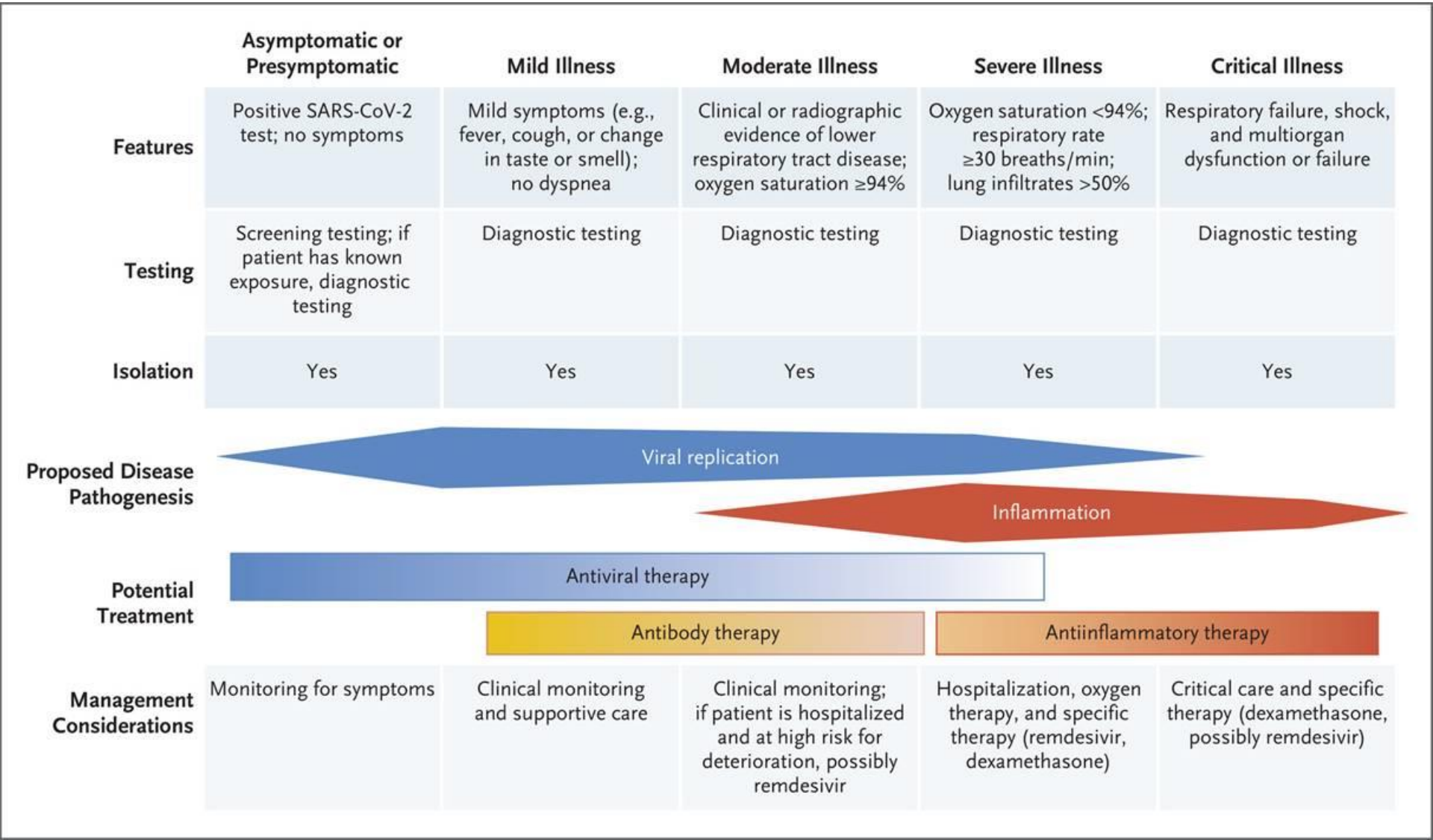
März 2021

SARSCov2 und COVID 19

- Klinik
- Prävention



Klinik


Asymptomatic or Presymptomatic
Mild Illness
Moderate Illness
Severe Illness
Critical Illness
Features
Positive SARS-CoV-2 test; no symptoms
Mild symptoms (e.g., fever, cough, or change in taste or smell); no dyspnea
Clinical or radiographic evidence of lower respiratory tract disease; oxygen saturation ≥94%
Oxygen saturation <94%; respiratory rate ≥30 breaths/min; lung infiltrates >50%
Respiratory failure, shock, and multiorgan dysfunction or failure
Testing
Screening testing; if patient has known exposure, diagnostic testing
Diagnostic testing
Diagnostic testing
Diagnostic testing
Diagnostic testing
Isolation
Yes
Yes
Yes
Yes
Yes
Proposed Disease Pathogenesis
Viral replication
Inflammation
Potential Treatment
Antiviral therapy
Antibody therapy
Antiinflammatory therapy
Management Considerations
Monitoring for symptoms
Clinical monitoring and supportive care
Clinical monitoring; if patient is hospitalized and at high risk for deterioration, possibly remdesivir
Hospitalization, oxygen therapy, and specific therapy (remdesivir, dexamethasone)
Critical care and specific therapy (dexamethasone, possibly remdesivir)

RESEARCH SUMMARY

Safety and Efficacy of the BNT162b2 mRNA Covid-19 Vaccine

F.P. Polack, et al. DOI: 10.1056/NEJMoa2034577

CLINICAL PROBLEM

Safe and effective vaccines to prevent severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection and Covid-19 are urgently needed. No vaccines that protect against betacoronaviruses are currently available, and mRNA-based vaccines have not been widely tested.

CLINICAL TRIAL

A randomized, double-blind study of an mRNA vaccine encoding the SARS-CoV-2 spike protein.

43,548 participants ≥16 years old were assigned to receive the vaccine or placebo by intramuscular injection on day 0 and day 21. Participants were followed for safety and for the development of symptomatic Covid-19 for a median of 2 months.

RESULTS

Safety:
Vaccine recipients had local reactions (pain, erythema, swelling) and systemic reactions (e.g., fever, headache, myalgias) at higher rates than placebo recipients, with more reactions following the second dose. Most were mild to moderate and resolved rapidly.

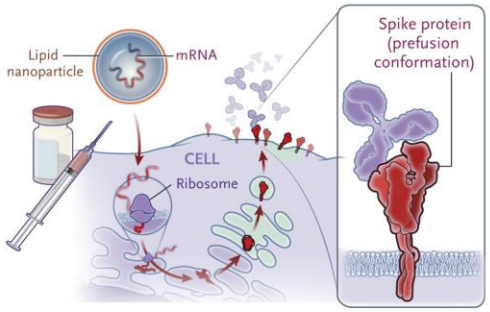
Efficacy:
The vaccine showed protection 7 days after the second dose; 95% efficacy was observed.

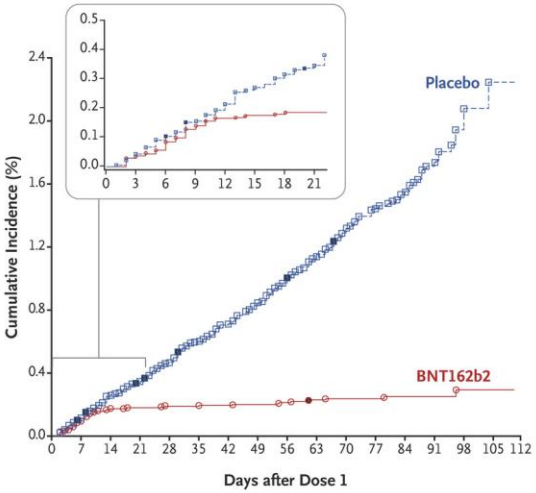
LIMITATIONS AND REMAINING QUESTIONS

Further study is required to understand the following:

- Safety and efficacy beyond 2 months and in groups not included in this trial (e.g., children, pregnant women, and immunocompromised persons).
- Whether the vaccine protects against asymptomatic infection and transmission to unvaccinated persons.
- How to deal with those who miss the second vaccine dose.

Links: Full article | Quick Take | Editorial





Vaccine efficacy of 95% (95% credible interval, 90.3 –97.6%)

CONCLUSIONS

Two doses of an mRNA-based vaccine were safe over a median of two months and provided 95% protection against symptomatic Covid-19 in persons 16 years of age or older.

RESEARCH SUMMARY

Efficacy and Safety of mRNA-1273 SARS-CoV-2 Vaccine

L.R. Baden, et al. DOI: 10.1056/NEJMoa2035389

CLINICAL PROBLEM

The Covid-19 pandemic continues and expands. Additional data regarding vaccines to prevent symptomatic severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection are needed. The mRNA-1273 vaccine is a lipid-encapsulated mRNA vaccine encoding the prefusion stabilized spike protein of SARS-CoV-2.

CLINICAL TRIAL

A randomized, double-blind trial to evaluate the efficacy and safety of mRNA-1273.

30,420 participants ≥18 years old were assigned to receive either the vaccine or placebo in two intramuscular injections 28 days apart. Participants were followed for safety and the development of laboratory-confirmed, symptomatic Covid-19 over a median of 2 months after the second dose.

RESULTS

Safety:
Vaccine recipients had higher rates of local reactions (e.g., pain, erythema, swelling) and systemic reactions (e.g., headache, fatigue, myalgia) than placebo recipients. Most reactions were mild to moderate and resolved over 1–3 days.

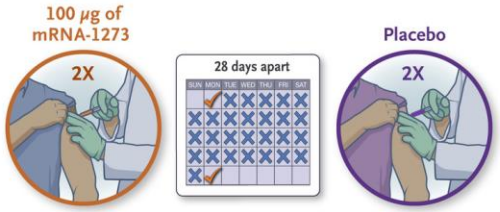
Efficacy:
The incidence of Covid-19 was lower among vaccine recipients than among placebo recipients as early as 14 days after the first dose. Protection in the vaccine group persisted for the period of follow-up.

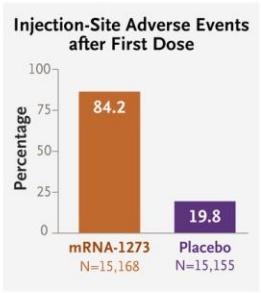
LIMITATIONS AND REMAINING QUESTIONS

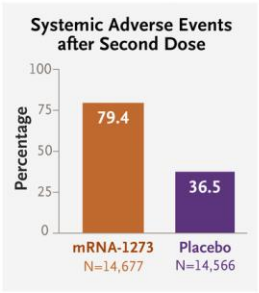
Further study is required to understand the following:

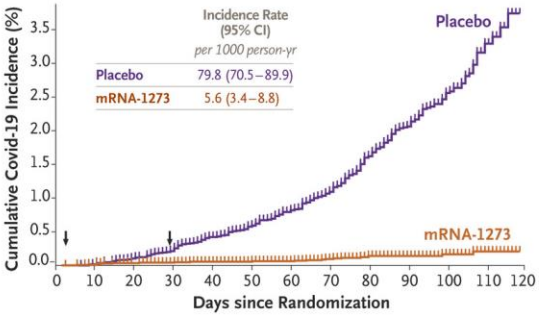
- Safety and efficacy over a longer period of time, in a larger population, and in pregnant women and children.
- Whether the vaccine protects against asymptomatic infection and transmission to unvaccinated persons.
- How to care for those who miss the second vaccine dose.

Links: Full article | NEJM Quick Take | Editorial









	mRNA-1273 Vaccine N=14,550	Placebo N=14,598
Symptomatic Covid-19	11	185
Severe Covid-19	0	30

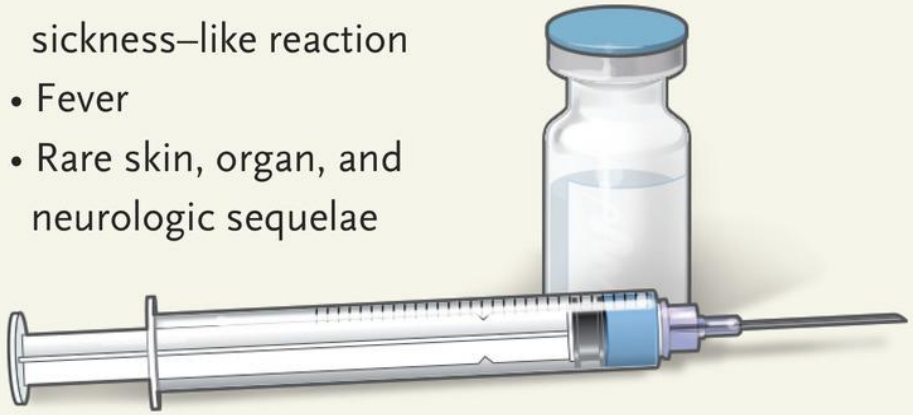
Vaccine efficacy of 94.1% (95% CI, 89.3–96.8%; P<0.001)

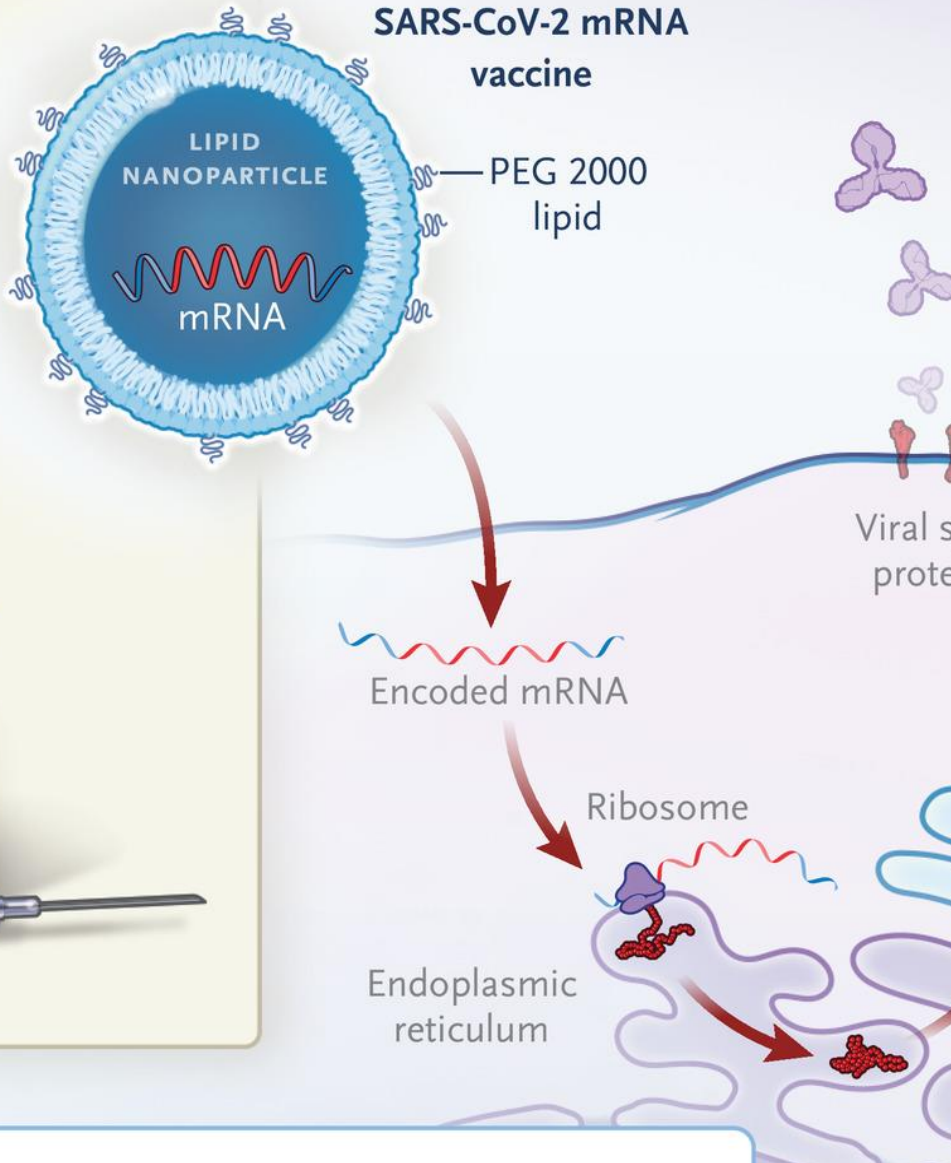
CONCLUSIONS

Two doses of a SARS-CoV-2 mRNA-based vaccine were safe and provided 94% efficacy against symptomatic Covid-19 in persons 18 or older.

Vaccine Reactions

- Immediate
  - IgE
  - Non-IgE
  - Nonimmune (vasovagal syncope)
- Delayed
  - Site reactions
  - Urticaria or benign exanthem
  - Serum sickness and serum sickness–like reaction
  - Fever
  - Rare skin, organ, and neurologic sequelae

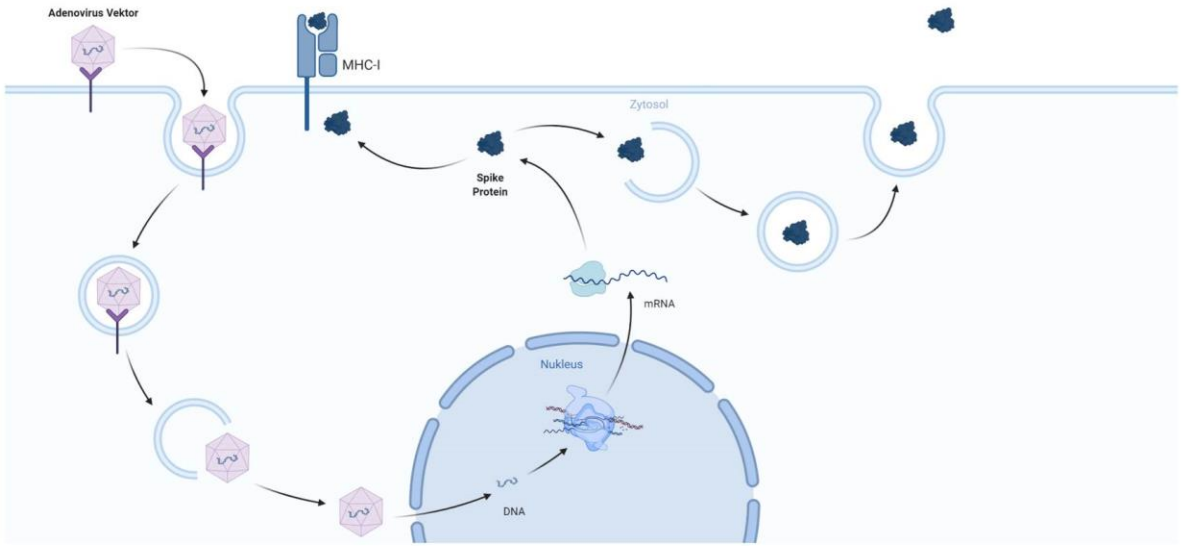




Vektor

Funktionsweise von AZD1222

- Adenovirus wirkt als Transportvehikel, um die Erbinformation des Spike Proteins in den Körper zu bringen
- Die Körperzelle produziert das Spike Protein in großen Mengen.



1. Ewer, K., et al., Chimpanzee adenoviral vectors as vaccines for outbreak pathogens. Human vaccines & immunotherapeutics, 2017. 13(12): p. 3020-3032.
2. Coughlan, L., Factors Which Contribute to the Immunogenicity of Non-replicating Adenoviral Vectored Vaccines. 2020. 11(909).

Safety and efficacy of the ChAdOx1 nCoV-19 vaccine (AZD1222) against SARS-CoV-2: an interim analysis of four randomised controlled trials in Brazil, South Africa, and the UK

	Total number of cases	ChAdOx1 nCoV-19		Control		Vaccine efficacy (CI*)
		n/N (%)	Incidence rate per 1000 person-years (person-days of follow-up)	n/N (%)	Incidence rate per 1000 person-years (person-days of follow-up)	
All LD/SD and SD/SD recipients	131	30/5807 (0·5%)	44·1 (248 299)	101/5829 (1·7%)	149·2 (247 228)	70·4% (54·8 to 80·6)†
COV002 (UK)	86	18/3744 (0·5%)	38·6 (170 369)	68/3804 (1·8%)	145·7 (170 448)	73·5% (55·5 to 84·2)
LD/SD recipients	33	3/1367 (0·2%)	14·9 (73 313)	30/1374 (2·2%)	150·2 (72 949)	90·0% (67·4 to 97·0)‡§
SD/SD recipients	53	15/2377 (0·6%)	56·4 (97 056)	38/2430 (1·6%)	142·4 (97 499)	60·3% (28·0 to 78·2)
COV003 (Brazil; all SD/SD)	45	12/2063 (0·6%)	56·2 (77 930)	33/2025 (1·6%)	157·0 (76 780)	64·2% (30·7 to 81·5)‡
All SD/SD recipients	98	27/4440 (0·6%)	56·4 (174 986)	71/4455 (1·6%)	148·8 (174 279)	62·1% (41·0 to 75·7)
Other non-primary symptomatic COVID-19 disease¶	18	7/5807 (0·1%)	10·3 (248 299)	11/5829 (0·2%)	16·3 (247 228)	36·4% (−63·8 to 75·3)‡
Any symptomatic COVID-19 disease	149	37/5807 (0·6%)	54·4 (248 299)	112/5829 (1·9%)	165·5 (247 228)	67·1% (52·3 to 77·3)
Asymptomatic or symptoms unknown (COV002)	69	29/3288 (0·9%)	69·8 (151 673)	40/3350 (1·2%)	96·0 (152 138)	27·3% (−17·2 to 54·9)
LD/SD recipients	24	7/1120 (0·6%)	41·4 (61 782)	17/1127 (1·5%)	100·6 (61 730)	58·9% (1·0 to 82·9)‡
SD/SD recipients	45	22/2168 (1·0%)	89·4 (89 891)	23/2223 (1·0%)	92·9 (90 408)	3·8% (−72·4 to 46·3)
Any NAAT-positive swab	221	68/5807 (1·2%)	100·0 (248 299)	153/5829 (2·6%)	226·0 (247 228)	55·7% (41·1 to 66·7)

Vaccine efficacy was calculated from the robust Poisson model. The primary efficacy population (LD/SD and SD/SD) includes randomly assigned participants who were seronegative at baseline and received LD/SD or SD/SD or were in a corresponding control group, and remained on study more than 14 days after their second dose without having had a previous virologically confirmed SARS-CoV-2 infection. In addition, for groups in COV002, only efficacy groups (ie, groups 4, 6, 9, and 10) are included. SARS-CoV-2=severe acute respiratory syndrome coronavirus 2. LD/SD=low-dose prime plus standard-dose boost. SD/SD=two standard-dose vaccines given. NAAT=nucleic acid amplification test. *CIs are 95% unless indicated otherwise. †95·8% CI used for primary analysis. ‡Vaccine efficacy calculated from a reduced robust Poisson model that was not adjusted for age. All other models included an adjustment for age. §p value for interaction term comparing LD/SD with SD/SD is p=0·010. ¶Other non-primary symptomatic COVID-19 disease includes cases who have symptoms other than the five main symptoms that are required for inclusion in the primary analysis (eg, a participant who has diarrhoea and malaise but no fever, cough, shortness of breath, anosmia, or ageusia).

Table 2: **Efficacy against SARS-CoV-2 more than 14 days after a second dose of ChAdOx1 nCoV-19 vaccine in the primary efficacy population**

retained editorial control. All other funders of the study aged 18–55 years (6542 [86·7%] of 7548 in the UK

Lancet 2021; 397: 99–111

Published Online December 8, 2020 https://doi.org/10.1016/S0140-6736(20)32661-1

5657	4765	3146	435	0	6297	5718	4836	3652	2452	0
(182)	(1164)	(2636)	(5322)	(5728)	(0)	(639)	(1424)	(2599)	(3760)	(6156)

ulative incidence of primary symptomatic, NAAT-positive COVID-19
mptomatic COVID-19 after two doses (left) or after first standard dose in participants se vaccines (right). Grey shaded areas show the exclusion period after each dose in from the analysis. Blue and red shaded areas show 95% CIs. LD/SD=low-dose prime plus ACWY=meningococcal group A, C, W, and Y conjugate vaccine. NAAT=nucleic acid wo standard-dose vaccines given.

$p_{interaction}$=0·019; table 3). When further restricted to those who received their vaccines more than 8 weeks apart, 33 cases were included in the SD/SD analysis and vaccine efficacy was 65·6% (24·5 to 84·4; $p_{interaction}$=0·082; table 3; appendix 1 pp 12–13). In the SD/SD cohorts in the UK and Brazil, vaccine efficacy was similar when analysed in subgroups according to time between

	Total number of cases	ChAdOx1 nCoV-19	Control	Vaccine efficacy (95% CI)	p value for interaction
COV002 (UK), age 18–55 years*	..	..	..	..	0·019
LD/SD recipients	33	3/1367 (0·2%)	30/1374 (2·2%)	90·0% (67·3 to 97·0)	..
SD/SD recipients	49	14/1879 (0·7%)	35/1922 (1·8%)	59·3% (25·1 to 77·9)	..
COV002 (UK), age 18–55 years with >8 weeks' interval between vaccine doses*	..	..	..	..	0·082
LD/SD recipients	33	3/1357 (0·2%)	30/1362 (2·2%)	90·0% (67·3 to 97·0)	..
SD/SD recipients	34	8/1407 (0·6%)	26/1512 (1·7%)	65·6% (24·5 to 84·4)	..
All SD/SD (UK and Brazil)†	..	..	..	..	0·557
<6 weeks' interval between vaccine doses	28	9/1702 (0·5%)	19/1698 (1·1%)	53·4% (−2·5 to 78·8)	..
≥6 weeks' interval between vaccine doses	70	18/2738 (0·7%)	52/2757 (1·9%)	65·4% (41·1 to 79·6)	..

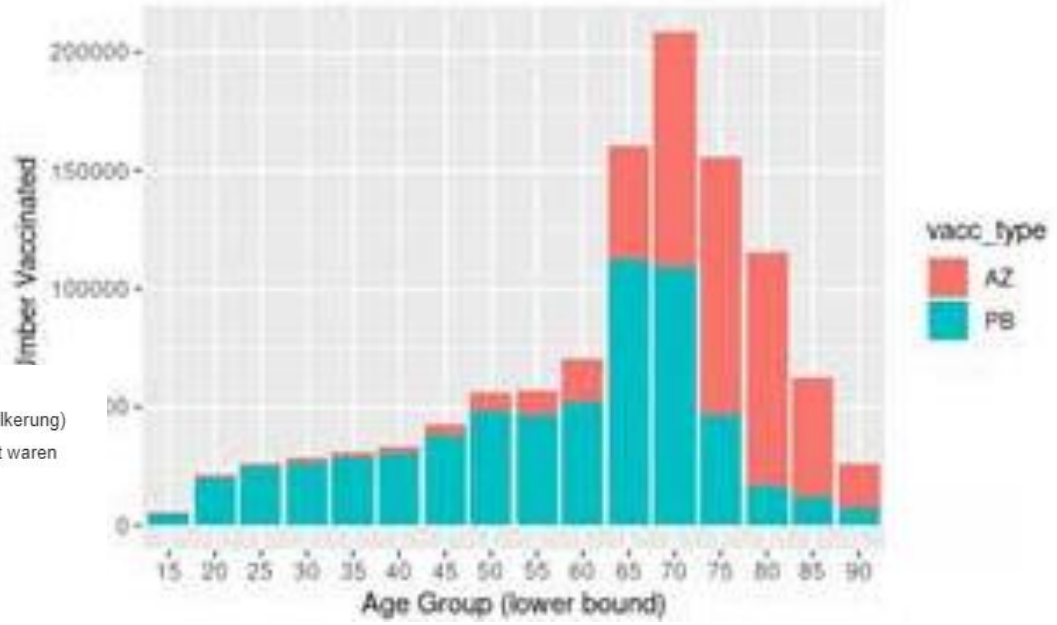
Cohorts are all subsets of the primary efficacy population. SARS-CoV-2=severe acute respiratory syndrome coronavirus 2. LD/SD=low-dose prime plus standard-dose boost. SD/SD=two standard-dose vaccines given. BMI=body-mass index. *Models adjusted for BMI (<30 *vs* ≥30 kg/m²), health-care worker status (yes *vs* no), and ethnicity (white *vs* non-white). †Model adjusted for BMI (<30 *vs* ≥30 kg/m²), health-care worker status (yes *vs* no), ethnicity (white *vs* non-white), age (<56 years *vs* ≥56 years), and study (COV002 *vs* COV003).

Table 3: **Subgroup comparisons of efficacy against SARS-CoV-2 more than 14 days after a second dose of ChAdOx1 nCoV-19 vaccine in the primary efficacy population**

Table 3: SARS-CoV-2 S-binding antibody levels by dose level and interval (seronegative at baseline)

Visit Window	Statistic	SDSD				LDSD			
		AZD1222				AZD1222			
		< 6 wks	6-8 wks	9-11 wks	≥ 12 wks	< 6 wks	6-8 wks	9-11 wks	≥ 12 wks
		N=677	N=239	N=169	N=235	N=3	-	N=126	N=168
Baseline	N	481	137	110	154	3	NA	30	35
	GMT	**60.51**	**58.02**	**48.79**	**52.98**	**50.92**	**NA**	**64.09**	**52.42**
	95% CI for GMT	(54.1, 67.7)	(46.3, 72.6)	(39.6, 60.1)	(44.4, 63.2)	(3.9, 669.2)	NA	(40.4, 101.6)	(37.7, 72.9)
	Min, Max	16.5, 71694.0	16.5, 7228.0	16.5, 4497.0	16.5, 827.0	16.5, 127.0	NA	16.5, 565.0	16.5, 304.0
Day 28 post the first dose	N	479	99	87	152	3	NA	30	35
	GMT	**8734.08**	**7295.54**	**7492.98**	**8618.17**	**7496.44**	**NA**	**4803.21**	**6750.27**
	95% CI for GMT	(7883.1, 9676.9)	(5857.4, 9086.7)	(5885.1, 9540.2)	(7195.4, 10322.3)	(1461.4, 38454.7)	NA	(3255.7, 7086.4)	(4184.6, 10889.0)
	Min, Max	16.5, 126108.0	426.0, 84533.0	46.0, 82133.0	93.0, 263135.0	3922.0, 14622.0	NA	268.0, 35010.0	51.0, 85889.0
Day 28 post the second dose	N	443	116	106	154	3	NA	29	35
	GMT	**22222.73**	**24363.10**	**34754.10**	**63181.59**	**22121.36**	**NA**	**36928.89**	**66274.91**
	95% CI for GMT	(20360.5, 24255.3)	(20088.5, 29547.3)	(30287.2, 39879.8)	(55180.1, 72343.4)	(8547.7, 57250.2)	NA	(24509.6, 55641.2)	(49546.6, 88651.1)
	Min, Max	101.0, 178580.0	40.0, 276501.0	3590.0, 579194.0	4612.0, 767654.0	14411.0, 30100.0	NA	3713.0, 559449.0	6456.0, 481664.0

AZ vs. PB



Übersicht der Studie

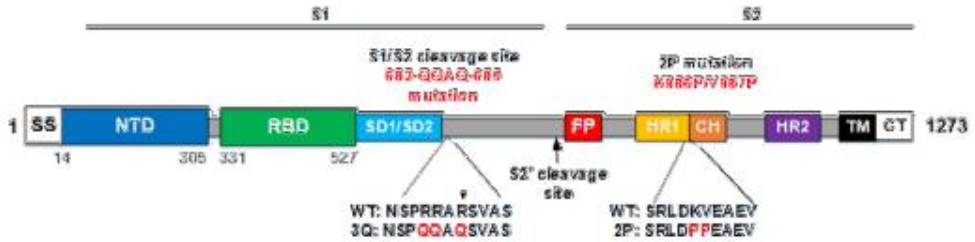
- Daten von 5,4 Millionen Menschen in Schottland wurden ausgewertet (~99 % der Bevölkerung)
- 1.137.775 (35 %) Personen wurden geimpft, wobei die meisten Impflinge ≥ 80 Jahre alt waren

age groups	vaccinated	unvaccinated	Uptake (% of total)
18-64	395,439 (34.8)	2,989,015 (91.4)	11.7
65-79	535,607 (47.1)	223,349 (6.8)	70.6
≥80	206,729 (18.2)	59,473 (1.8)	77.7

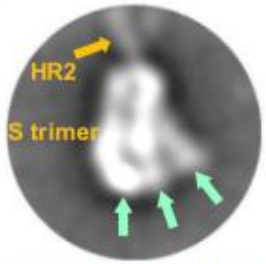
COVID19 Vaccine AstraZeneca		
Vaccination status	**events**	**Vaccine effect (95% CI)**
Unvaccinated (total)	7090	NA
Vaccinated		
7-13 days after 1st dose	108	70% (63 to 76)
14-20 days after 1st dose	60	74% (66 to 81)
21-27 days after 1st dose	18	84% (72 to 90)
28-34 days after 1st dose	2	94% (73 to 99)

BNT162b2		
Vaccination status	**events**	**Vaccine effect (95% CI)**
Unvaccinated (total)	6690	NA
Vaccinated		
7-13 days after 1st dose	104	38% (28 to 47)
14-20 days after 1st dose	60	60% (50 to 68)
21-27 days after 1st dose	34	72% (62 to 79)
28-34 days after 1st dose	18	85% (76 to 91)

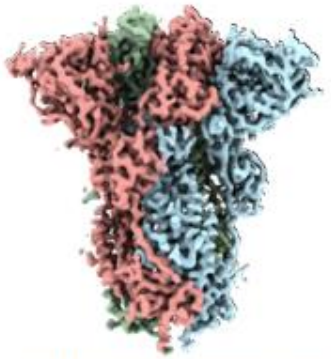
NVX-CoV2373: A full-length, prefusion stabilized SARS-CoV-2 spike (S) glycoprotein + Matrix-M™



SARS-CoV-2 Full Length Spike Protein

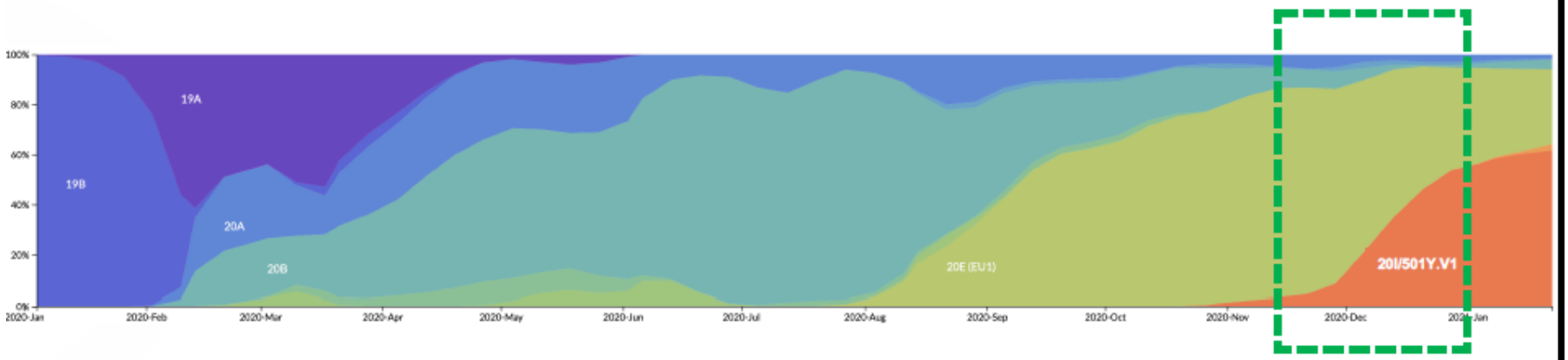


Transmission Electron Microscopy of CoV2373 Trimers
Tian et al., 2020



Cryo-EM map of trimers showing the spike in prefusion state
Bangaru et al., 2020

UK 501Y.V1 Mutant Strain Increased in Prevalence During Efficacy Collection Window



Efficacy Endpoint Accrual:
November 11 – January 1

Primary Endpoint Met in Interim Analysis

Severity	NVX-CoV2373 (n=7,016)	Placebo (n=7,033)
Total	**6**	**56**
Mild	*1*	*15*
Moderate	*5*	*40*
Severe	*0*	*1*
Vaccine Efficacy	**89.3%** (95% CI: 75.2, 95.4)	

- Preliminary PCR data show >50% of cases attributable to UK 501Y.V1 variant
- Final analysis to be conducted once at least 100 cases accrued

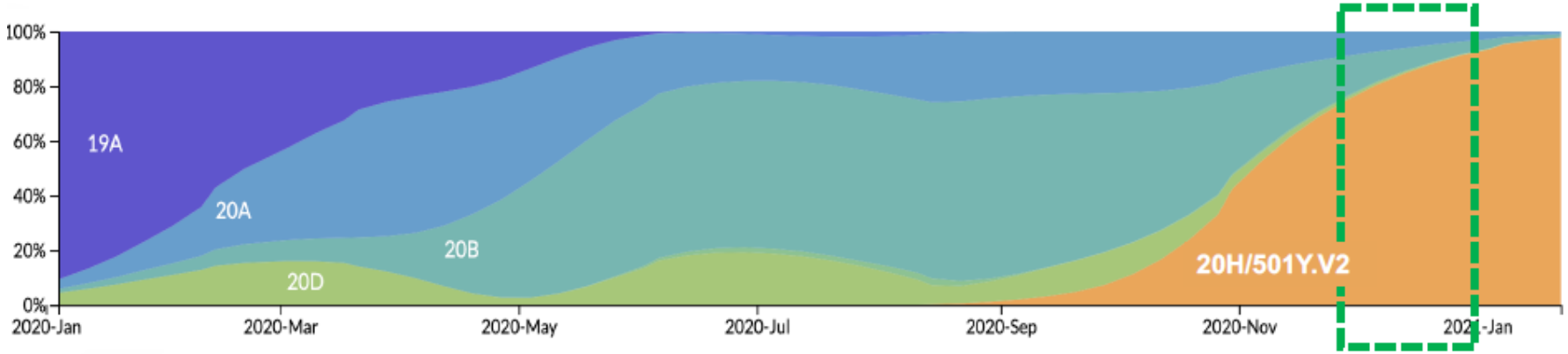
Primary Endpoint: PCR-confirmed mild, moderate, or severe COVID-19 illness occurring ≥7 days after second dose in baseline seronegative participants

Summary of PCR-Confirmed Mild, Moderate or Severe COVID-19 with Onset from 7 Days after the Second Vaccination by Variant Strain and Severity, Per-Protocol Efficacy Analysis Set

	SARS-CoV-2 rS (5 µg) + Matrix-M1 adjuvant (50 µg) (N=7016)				Placebo (N=7033)		
	Variant-UK	Non-Variant	No Sequence Data		Variant-UK	Non-Variant	No Sequence Data
PCR-Confirmed COVID-19 Symptomatic Mild, Moderate, Severe	4	1	1		28	23	5

Preliminary, post-hoc analysis based on PCR performed on strains from 56 of the 62 cases showed **96%** efficacy in the COVID-19 strain, **86%** efficacy in the variant strain.

South Africa 501Y.V2 Escape Mutant Dominant During Efficacy Collection Window



Efficacy Endpoint Accrual:
November 23 – December 30

Cross-Protection Demonstrated Against South Africa Escape Variant

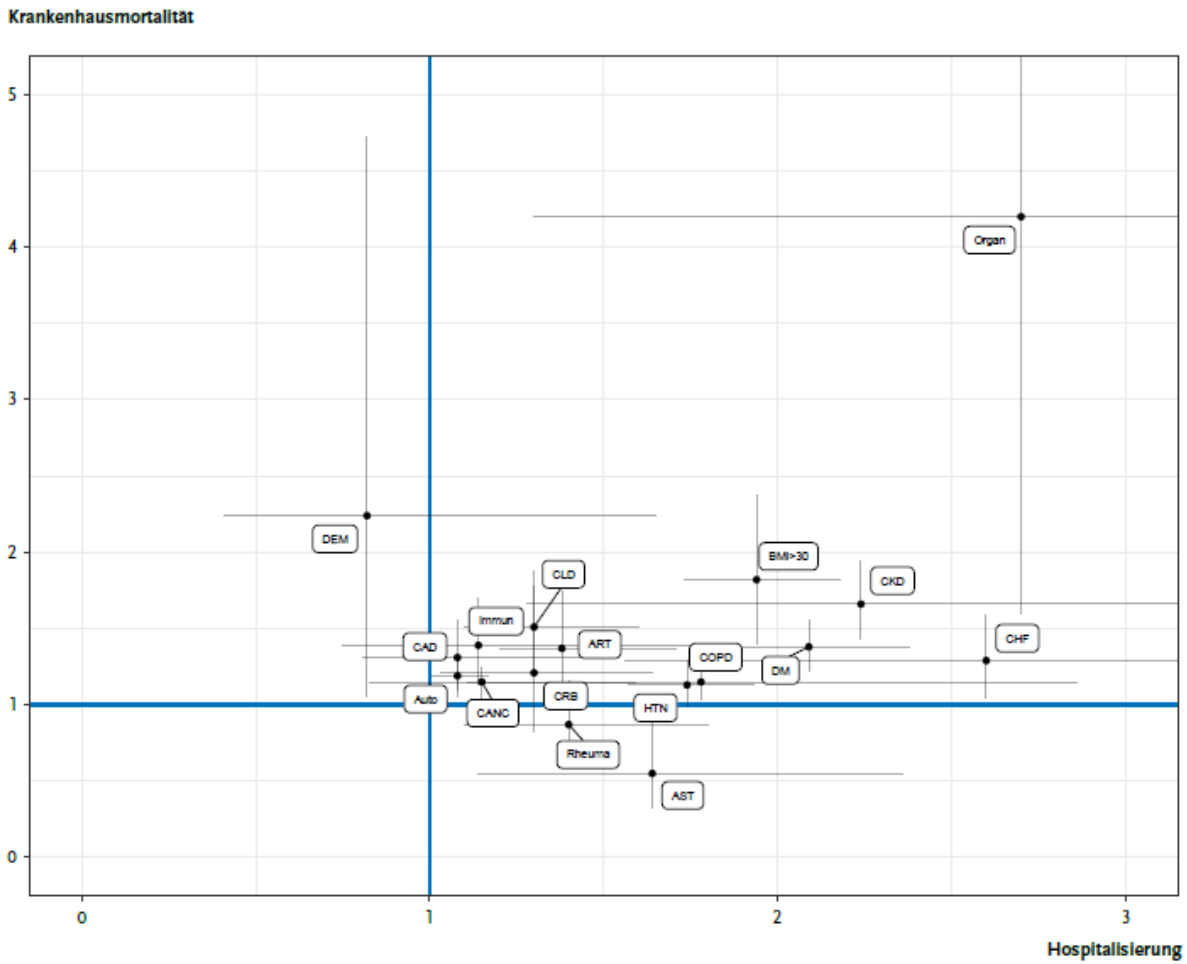
Severity	NVX-CoV2373 (n=2,206)	Placebo (n=2,200)
Total	**15**	**29**
Vaccine Efficacy (HIV negative)	**60.1 %** (95% CI: 19.9, 80.1)	
Vaccine Efficacy (overall)	**49.4%** (95% CI: 6.1, 72.8)	

- Sequencing data show 25/27 (93%) of cases attributable to SA 501Y.V2 escape variant

Prior COVID-19 Infection with Original Strain May Not Provide Protection Against South Africa 501Y.V2 Escape Variant

- Nearly 1/3 of study participants had prior COVID-19 infection
- COVID-19 case rate in placebo group not impacted by baseline anti-spike serostatus
- NVX-CoV2373 first vaccine with clinical data on protection against 501Y.V2 escape variant

Reihenfolge



ART, arrhythmia or atrial fibrillation; CHF, congestive heart failure; CAD, coronary artery disease; HTN, hypertension; DM, diabetes; BMI>30, obesity and overweight; CANC, cancer; AST, asthma; COPD, chronic obstructive pulmonary disease; CKD, chronic kidney disease; CLD, chronic liver disease; CRB, cerebrovascular or stroke; DEM, dementia; Auto, autoimmune condition; Immun, immunodeficiency or immuno-suppressed state; Rheuma, rheumatological disease; Organ, organ transplant history (Down-Syndrom wegen der besseren Übersichtlichkeit nicht dargestellt, s. Abb. 8)

Abb. 6 | Cluster-Analyse der Risiken von Vorerkrankungen auf Hospitalisation und Mortalität von COVID-19
Psychiatrische Erkrankungen werden bei der nächsten Aktualisierung berücksichtigt.

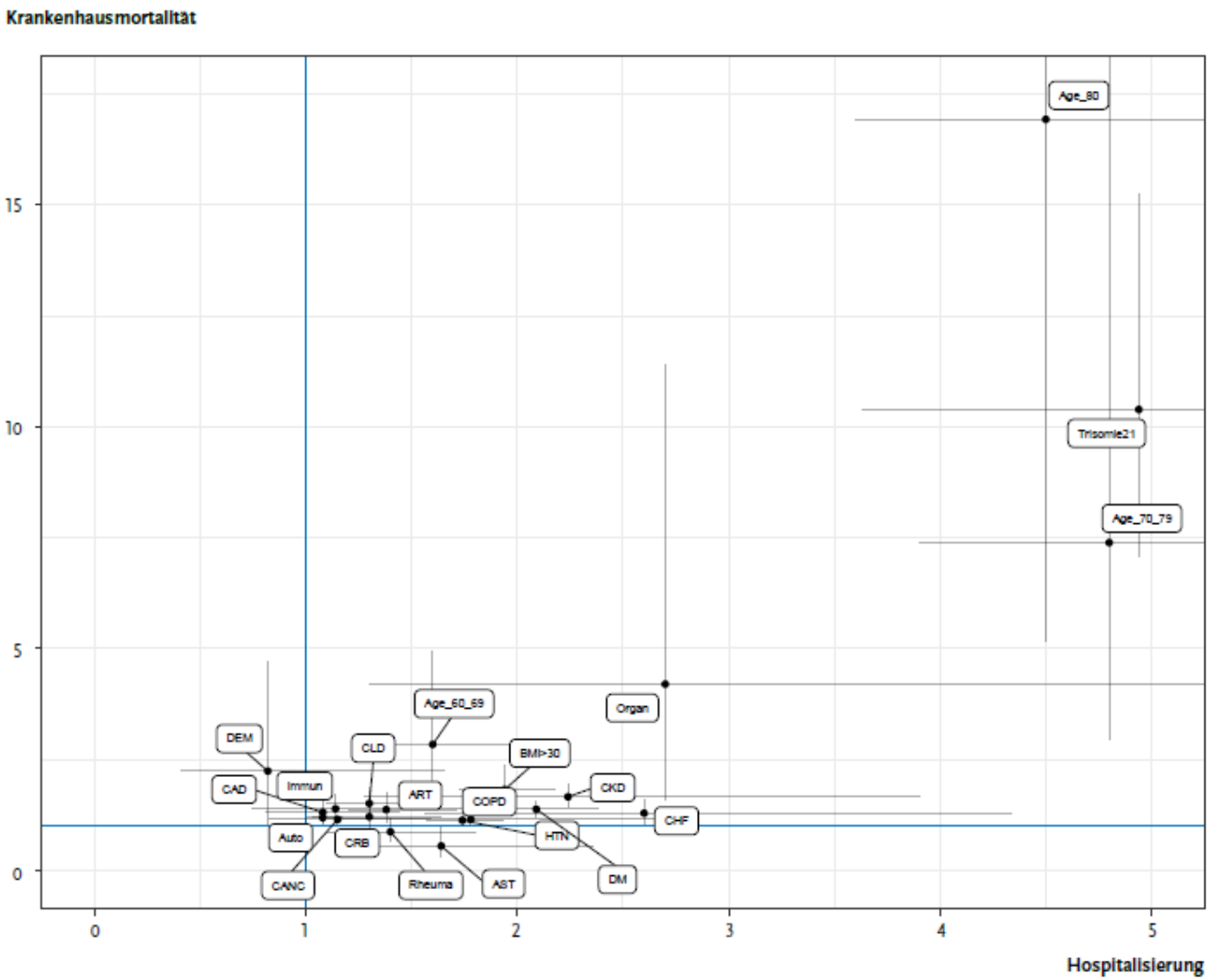


Abb. 7 | Cluster-Analyse der Risiken von Vorerkrankungen und Alter auf Hospitalisation und Mortalität von COVID-19 (Abkürzungen s. Abb. 6)

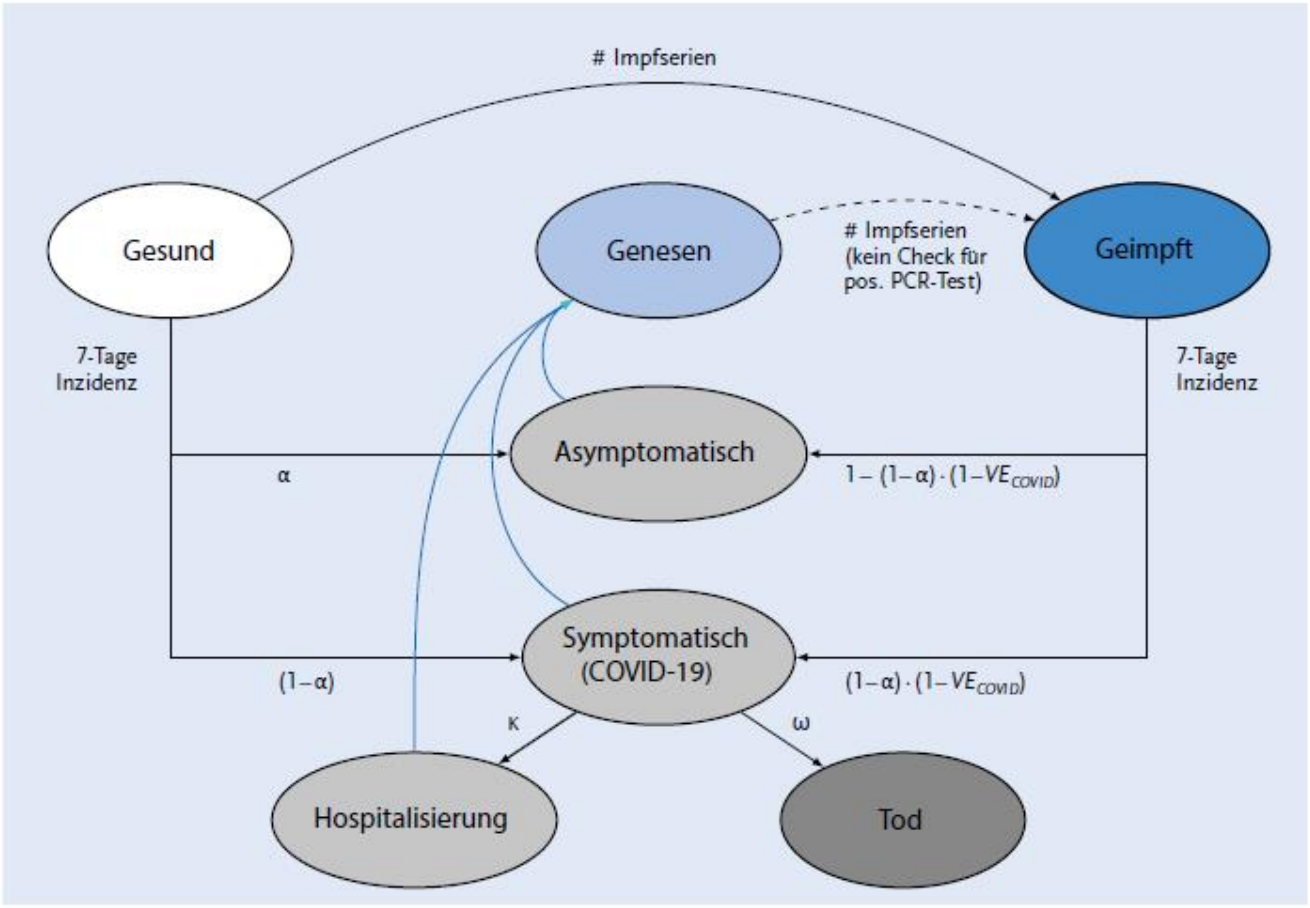


Abb. 8 | Schematische Darstellung des Markov Modells zur Berechnung der direkten Impfeffekte auf Bevölkerungsebene

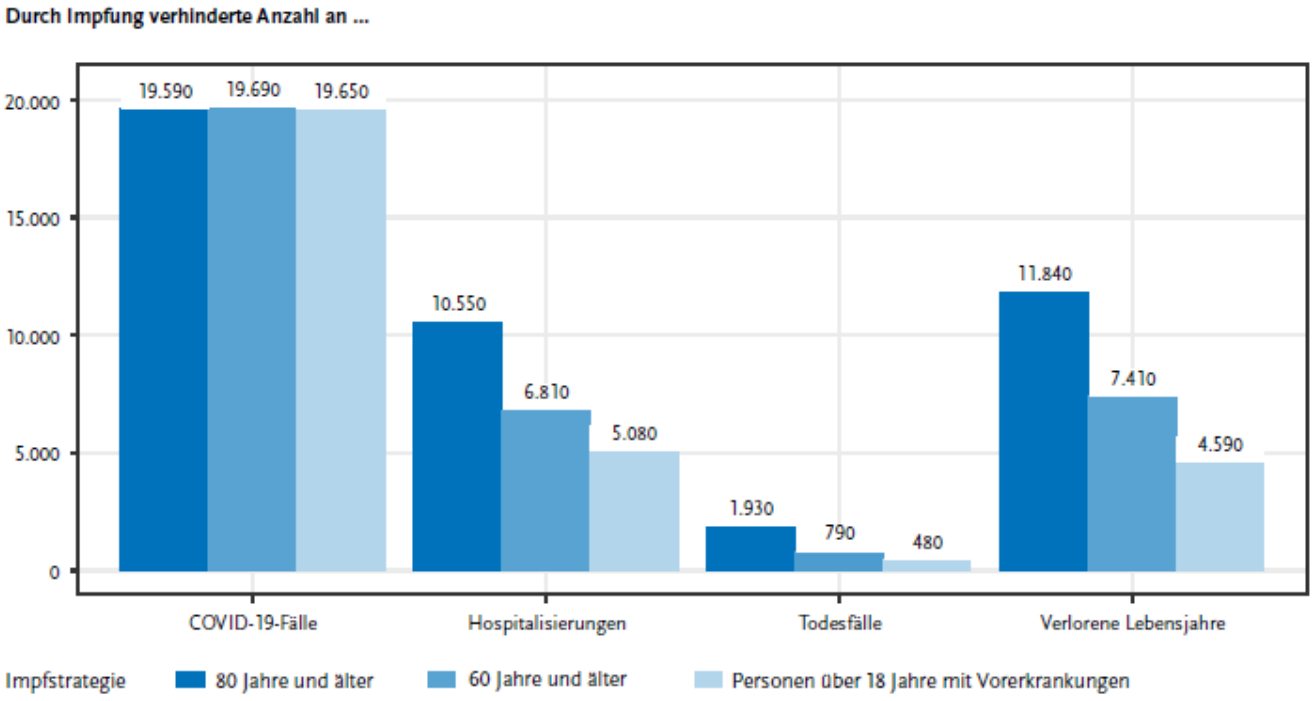


Abb. 10 | Kumulativer Impact von COVID-19-Impfstrategien bis 12 Wochen nach Impfstart (Basis-Szenario)

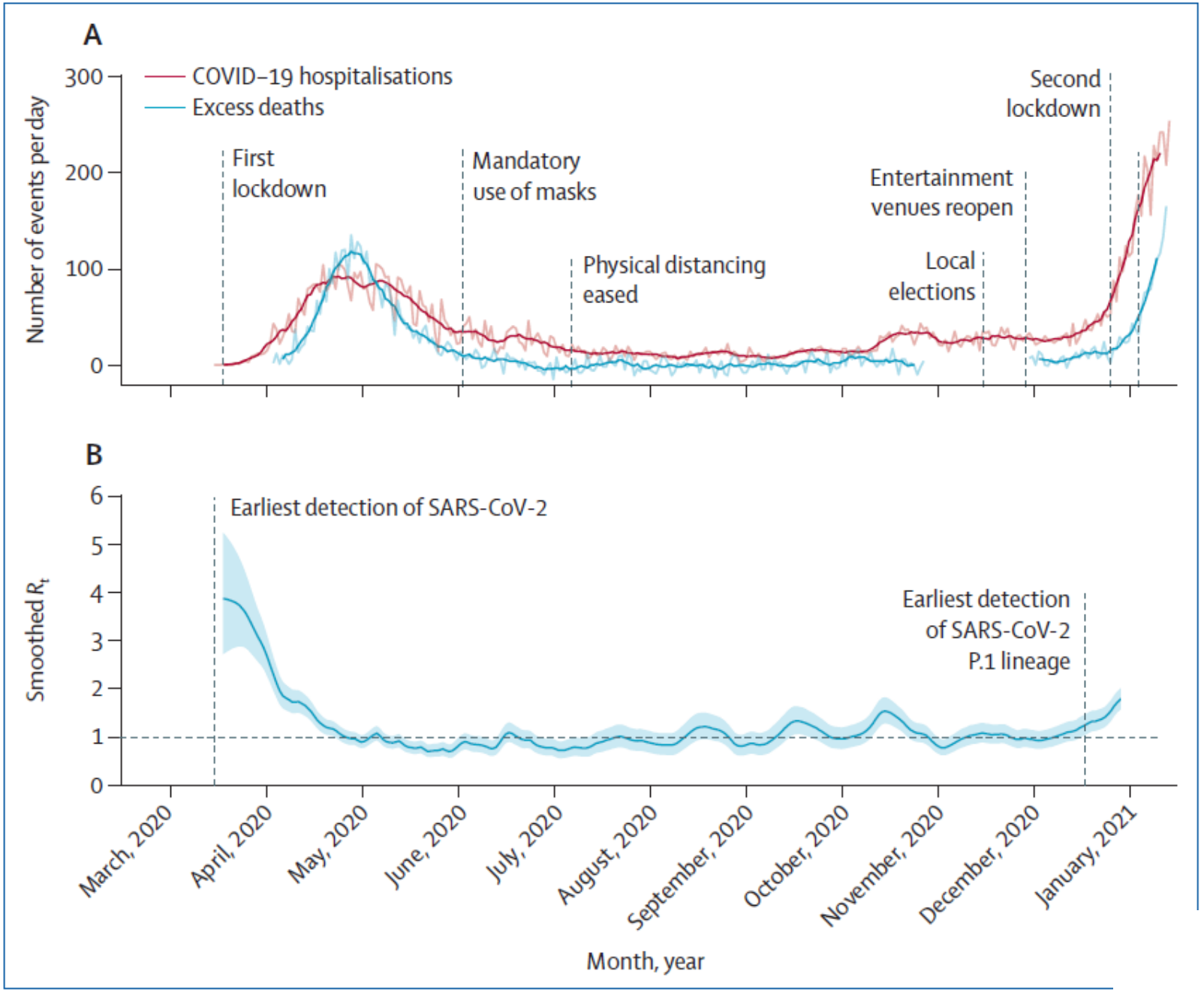


Figure: **COVID-19 hospitalisations, excess deaths, and R_t in Manaus, Brazil, 2020–21**

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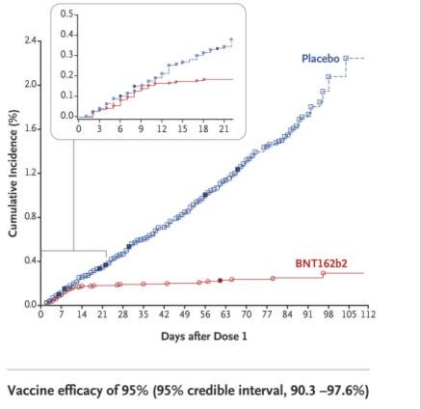
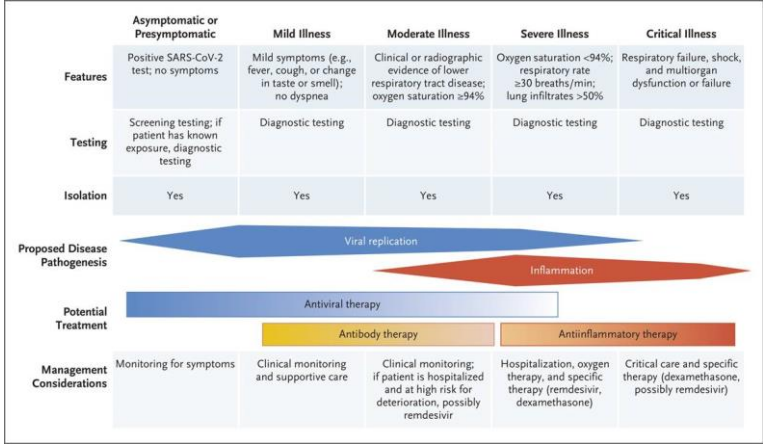


Corona-Trendwende 2021



- 2020:
  - Nicht-Pharmakologische Maßnahmen (Testen von Gesunden und Verbot des gesellschaftlichen Lebens)
  - Pharmakologische Maßnahmen nicht vorhanden
- 2021:
  - Pharmakologische Maßnahmen (Impfen und antivirale Therapien)
  - Nicht-Pharmakologische Maßnahmen (Fokus auf neue Varianten)