Vaccini e terapie specifiche, a che punto siamo

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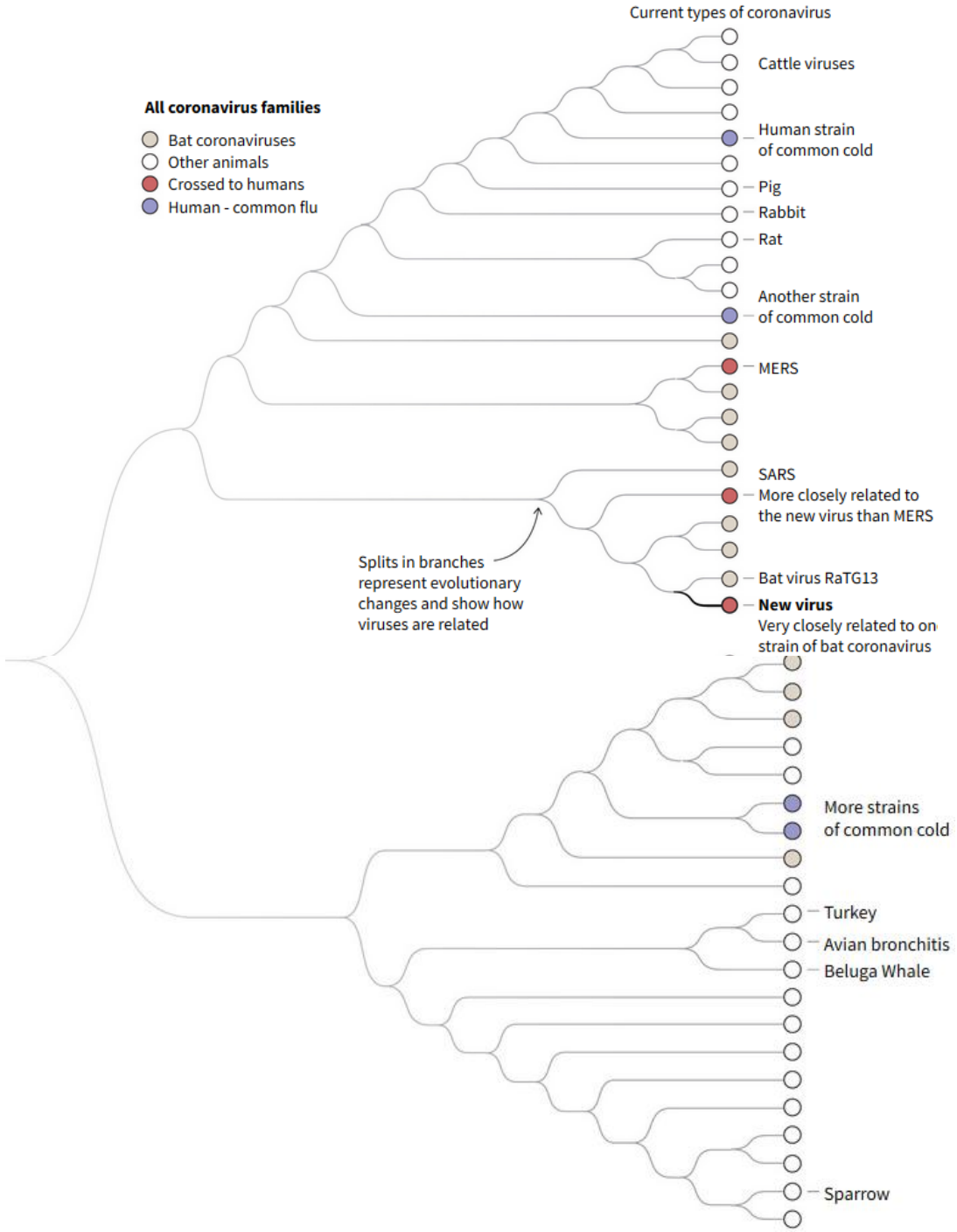
Loredana Sarmati disclosures

- Travel grants from Gilead, Merck, Gilead, Bristol, Pfizer
- Fee for lectures and expertise from Merck, Gilead, Bristol, Abbvie, Angelini
- Research funding from Gilead

WUHAN CORONAVIRUS
Genetics of the new virus
January 31, 2020



Coronaviruses are a group of viruses that cause diseases in mammals and birds.

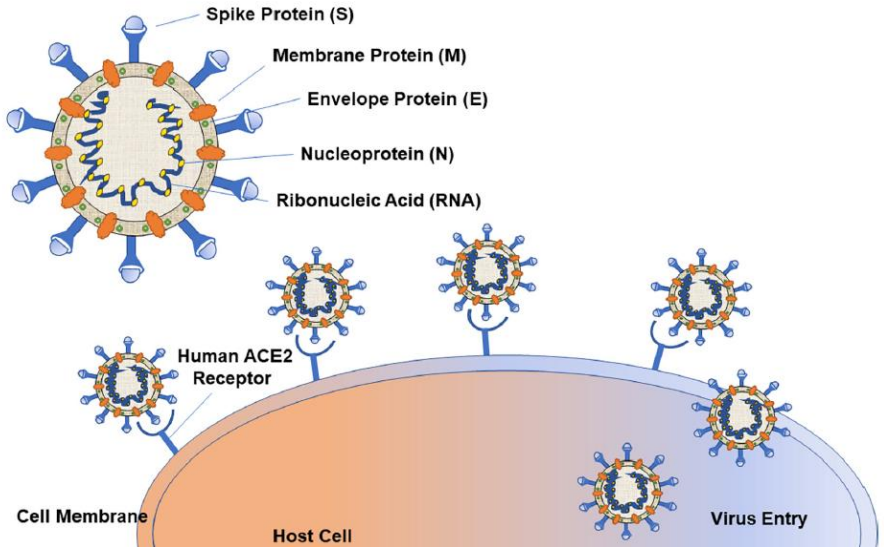
Coronaviruses are zoonotic:

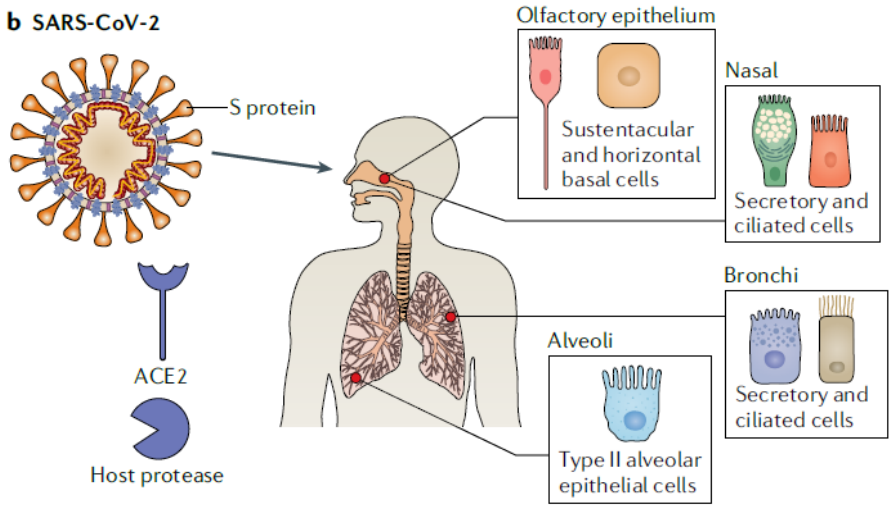
SARS probably originated in bats and passed through civet cats

MERS probably came from bats to camels to humans.

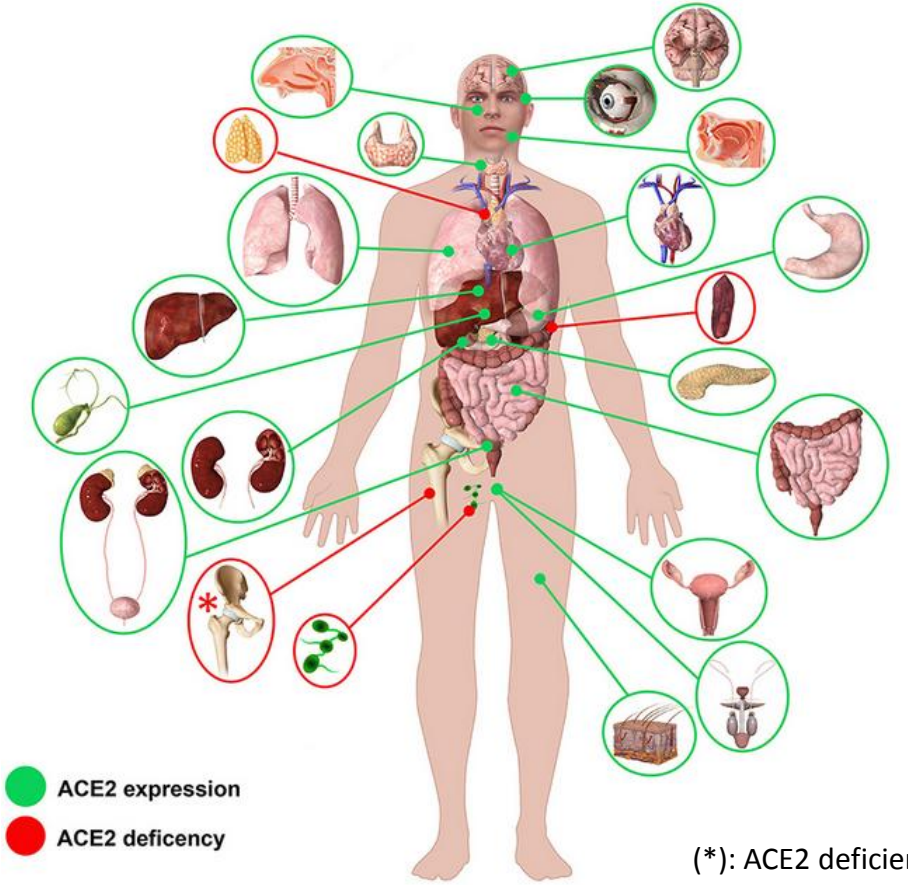
With the new coronavirus, it is unclear whether it was passed from bats to humans or if it passed via an intermediary species. The new coronavirus is the result of viral recombination -

The exact origin of the new coronavirus is yet to be confirmed but its genetic material say bat coronaviruses are its closest relative. The that the genome is 80% identical to the SARS virus but further away from the MERS virus.





La proteina spike (S) di SARS-CoV-2 lega l'enzima di conversione dell'angiotensina 2 (ACE2) sulla superficie di alcune cellule epiteliali olfattive e respiratorie distribuite lungo il tratto respiratorio umano, dopo l'attivazione da parte di proteasi cellulare (serina proteasi 2 transmembrana (TMPRSS2), catepsina L, neuropilina 1, furina).



(*): ACE2 deficiency hypothesized.

Brain: nuclei involved in the central regulation of cardiovascular function (brainstem cardiorespiratory neurons), non-cardiovascular areas (motor cortex and raphe)

Eyes: luminal surface of epithelial cells, retinal and retinal pigment epithelium

Nasal cavity: mucosal surface of the airway, basal layer of the non-keratinizing squa mous epithelium

Oral cavity: basal layer of the non-keratinizing squamous epithelium, tongue, buccal mucosa, saliva, gingiva, lymphocytes within oral mucosa, and oral cavity

Thyroid: Glandular cells

Heart and blood vessels: Pericytes, endothelial and smooth muscle cells of intra-myocardial vessels, thoracic aorta, carotid arteries, and veins. Endothelial cells from small and large arteries and veins

Lungs: Type I and II alveolar epithelial cells, bronchiolar epithelial cells, endothelial cells and arterial smooth muscle cells

Liver: Epithelial cells of the bile duct, perinuclear hepatocytes, cholangiocytes

Gallbladder: Gallbladder epithelium

Kidneys and bladder: Proximal tubular brush border, proximal renal tubular epithelium, distal tubules, bladder urothelial cells, luminal surface of tubular epithelial cells, glomeruli

Stomach: Esophagus upper and stratified epithelial cells

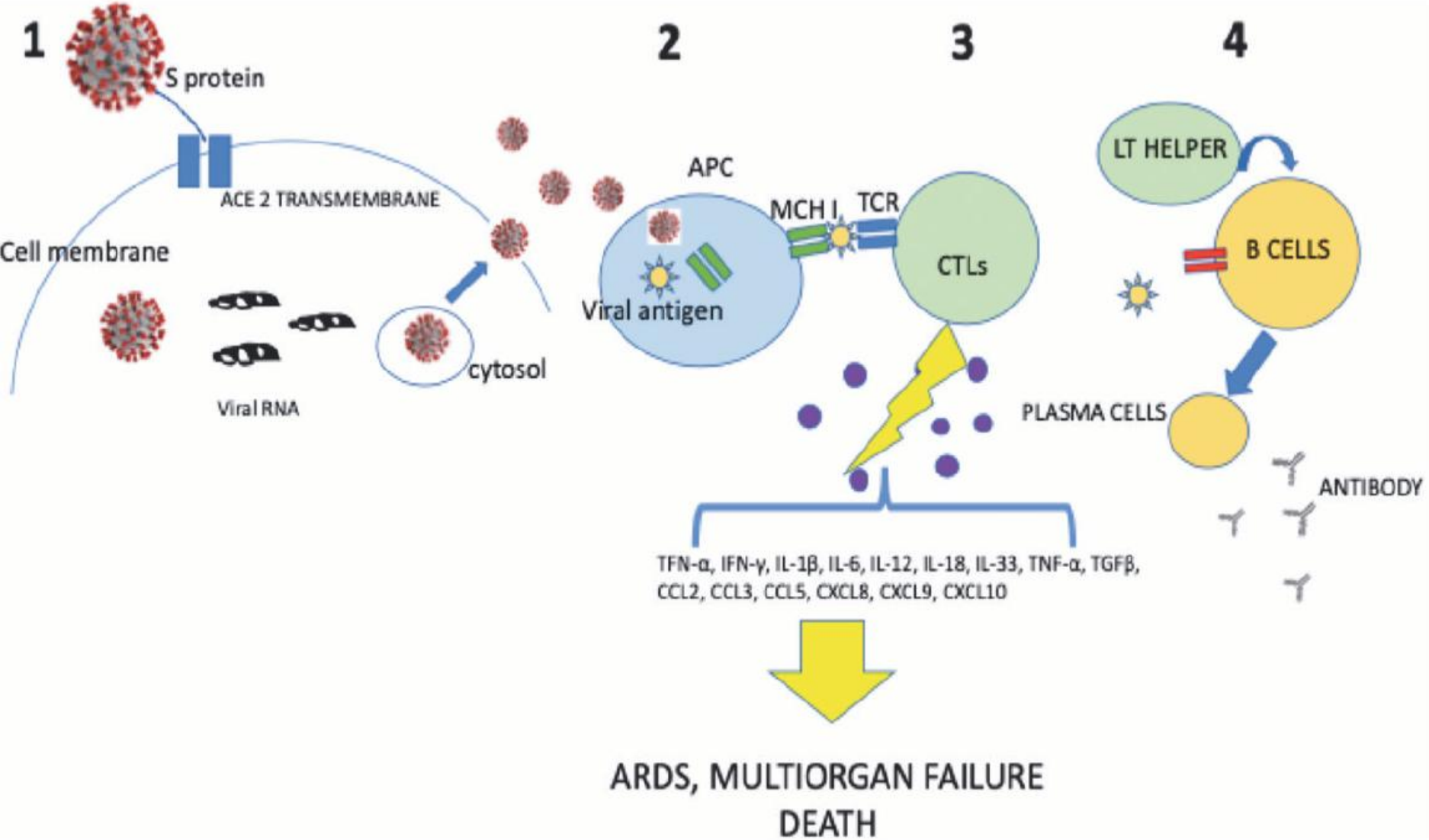
Pancreas: Exocrine gland (duct cells and acinar cells), and pancreatic islets (alpha, beta, delta and PP cells)

Intestines: intestinal epithelial cells, enterocytes of the small intestine, duodenum, absorptive enterocytes from ileum and colon, rectum endothelial cells

Reproductive system
Female: ovary, oocyte, uterus, vagina, placenta

Male: adult Leydig cells in the testis and in cells in the seminiferous ducts in testis

Skin: Basal epidermal layers and in sebaceous gland cells



1. **Inserimento, replica e rilascio di SARS-COV2**. Il virus si lega al suo recettore cellulare ACE2 tramite la glicoproteina spike (proteina S) e entra nel citoplasma cellulare dove rilascia il suo RNA, inizia a replicare, forma e rilascia nuovi virioni.
2. **Presentazione dell'antigene**. Le cellule presentanti l'antigene (APC) presentano i peptidi antigenici insieme al complesso maggiore di istocompatibilità (MHC). La presentazione dell'antigene stimola sia (3) l'immunità cellulare e (4) umorale.
3. **Tempesta citochinica**. Le cellule immunitarie effettrici rilasciano grandi quantità di citochine e chemochine che possono provocare rapidamente la sindrome da distress respiratorio acuto (ARDS), insufficienza di uno o più organi e infine la morte.

CLASSIFICAZIONE DELLA GRAVITA' CLINICA DI COVID19:

FORME ASINTOMATICHE O PRESINTOMATICHE

Tampone NF POSITIVO ma assenza di sintomi

QUADRO CLINICO LIEVE/MILD

Presenza di segni/sintomi (febbre, disgeusia, anosmia, etc.)
ma assenza di dispnea e RX negativo

QUADRO CLINICO DI MODERATA GRAVITA'/MODERATE

Polmonite di limitata gravità clinica,
SPO_2>94%

QUADRO CLINICO GRAVE/SEVERE

SpO_2 <94%, PaO_2/FiO_2 <300 mmHg,
RR >30 atti/min, infiltrati polmonari > 50%

QUADRO CLINICO CRITICO/CRITICAL

Insufficienza respiratoria, shock settico e/o disfunzione multiorganica

CONDIZIONI MEDICHE PRE-ESISTENTI CORRELATE CON LA GRAVITA' CLINICA DI COVID19 E LIVELLO DI EVIDENZA

Meta-analysis/systematic review: comorbidity having a significant association with risk of severe COVID-19 in at least 1 meta-analysis or systematic review.

- Cancer
- Cerebrovascular disease
- Chronic kidney disease*
- COPD (chronic obstructive pulmonary disease)
- Diabetes mellitus, type 1 and 2*
- Heart conditions (heart failure, coronary artery disease, or cardiomyopathies)
- Obesity (BMI ≥30 kg/m2)*
- Pregnancy and recent pregnancy
- Smoking, current and former

Observational studies, systematic review or meta-analysis with 1 in a group of conditions (kidney transplant in SOT or HSCT)

- Children with certain underlying conditions
- Down syndrome
- HIV
- Neurologic conditions including dementia
- Overweight (BMI ≥25 kg/m^2)
- Other lung disease (including interstitial lung disease, pulmonary fibrosis, pulmonary hypertension)*
- Sickle cell disease
- SOT or HSCT
- Substance use disorders
- Use of corticosteroids or other immunosuppressants

Case series, case reports, or small sample size

- Cystic fibrosis
- Thalassemia

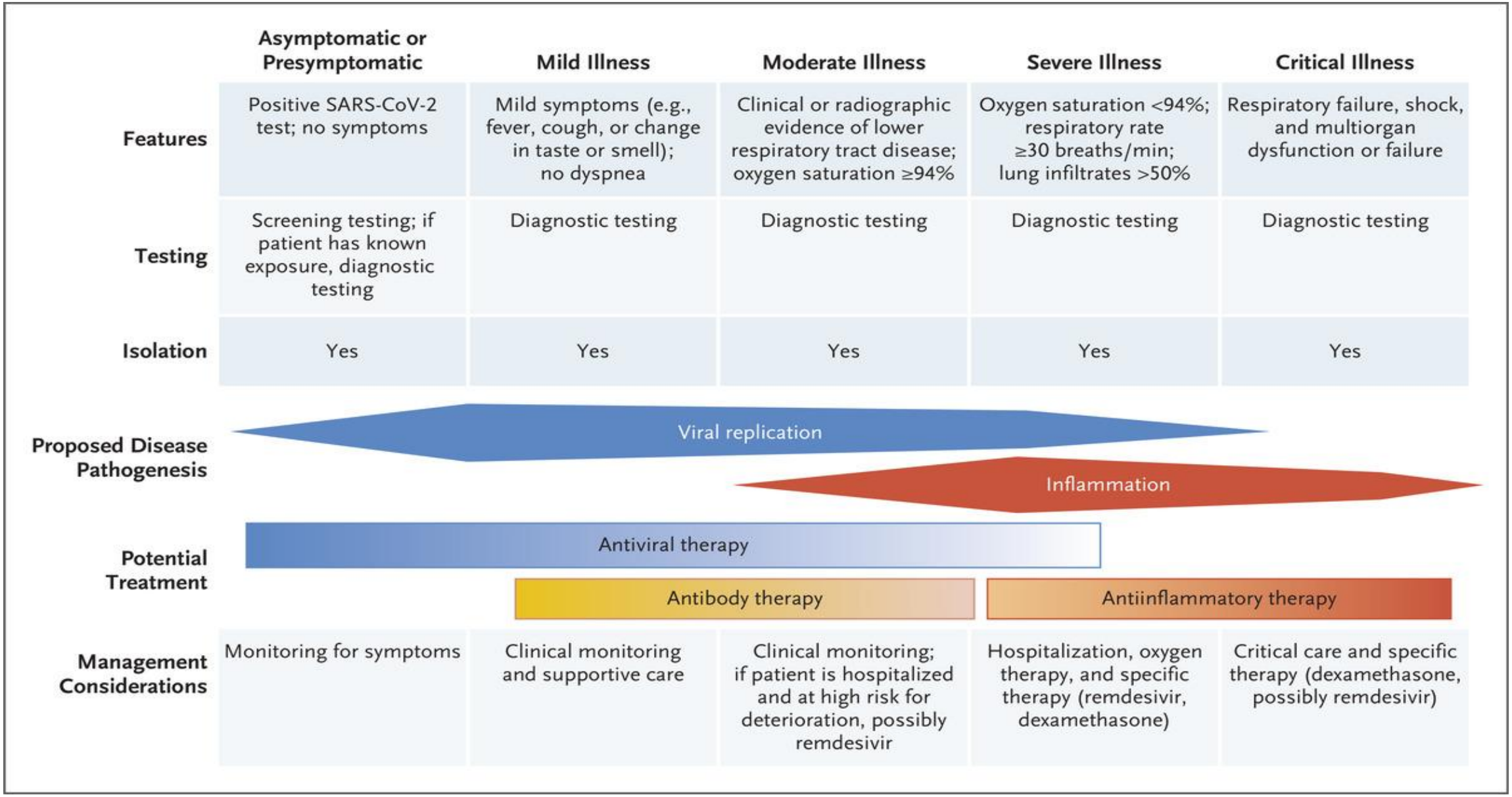
Co-morbidities that are supported by mixed evidence

- Asthma
- Hypertension*
- Immune deficiencies
- Liver disease

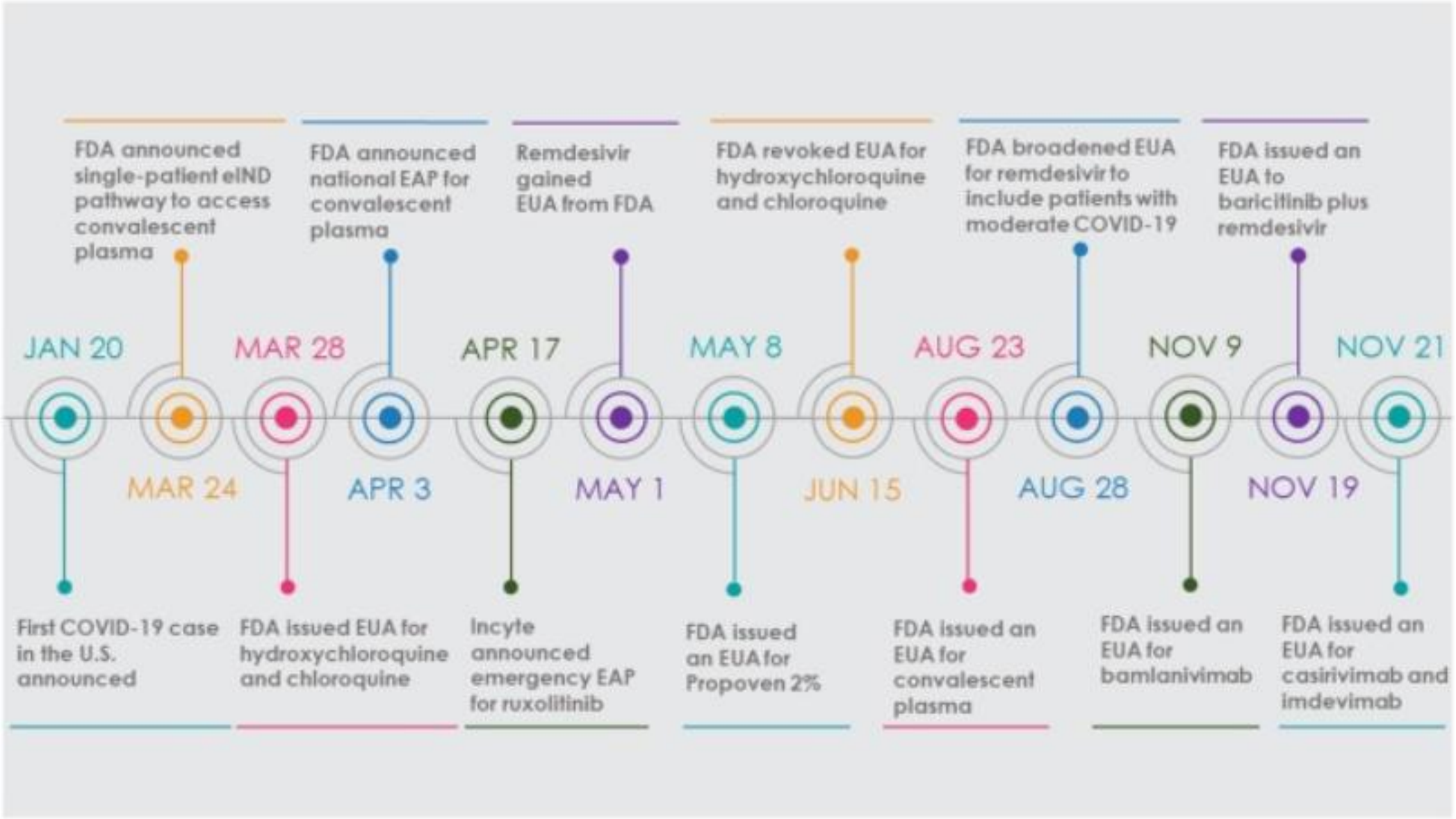
* for pregnant and non-pregnant people

https://www.cdc.gov/coronavirus/2019-ncov/hcp/clinical-care/underlyingconditions.html
Updated May 13, 2021

Caratteristiche, diagnosi, e gestione di Covid-19 in relazione allo stadio e gravità clinica.



Expanded Access Program (EAP) and Emergency Use Authorization (EUA) announcements and initiation over the duration of the Coronavirus 2019 (COVID-19) pandemic.



Abbreviations: eIND emergency investigational new drug; FDA, Food and Drug Administration

Drug Discovery Today 2021

Key Therapeutic Classes investigated for Treatment of COVID-19

Antivirals	Anticorpi	Immunomodulators
Baloxavir Favipiravir (Hydroxy)chloroquine Lopinavir/ritonavir Nitazoxanide Oseltamivir Remdesivir Ribavirin	Convalescent plasma Monoclonal antibodies	Corticosteroids (eg, dexamethasone) IL-1 inhibitors (eg, anakinra) IL-6 inhibitors (eg, tocilizumab) JAK inhibitors (eg, baricitinib)

Barlow. Pharmacotherapy. 2020;40:416. McCreary. Open Forum Infect Dis. 2020;7:ofaa105. Sanders. JAMA. 2020;323:1824.

Remdesivir

Antivirale studiato per la terapia delle infezioni da virus Ebola, attivo in vitro su cellule e su animali infetti con Sars-Cov-2 e MERS-cov

ACTT-1 : randomizzato doppio cieco, 1062 pts con polmonite remdesivir vs placebo 1:1. Remdesivir riduceva significativamente il tempo alla guarigione, maggiormente in chi aveva minor necessità di O2, nessun effetto sulla mortalità

SIMPLE: studio open label in paz ospedalizzati, 5 vs 10 giorni di remdesivir vantaggi simili. A confronto con popolazione non trattata ha mostrato una riduzione del 62% del rischio di mortalità nel gruppo in remdesivir

SOLIDARITY: studio randomizzato diversi trattamenti (fino a 4) compreso Remdesivir. Nessuna differenza in mortalità tra remdesivir e controllo, ma : non valutata la durata dei sintomi, SOC diverso nei diversi ospedali. Gli arruolati in ACTT-1 compresii in Solidarity confermano l'efficacia di remdesivir

Ulteriori 3 real-world studi (AETION AND HAELTH VERITY, PREMIER HEALTHCARE e SIMPLE-SEVERE) su Remdesivir minor richiesta di O_2, più breve durata di ricovero, e minor rischio di mortalità (54%)

Corticosteroidi

Generalmente non raccomandati per il trattamento della polmonite virale, trovano impiego nelle sepsi batteriche per temperare la risposta immune. L'uso di steroidi a basse dosi è raccomandato in situazioni specifiche (shock, ARDS, etc.)

RECOVERY: studio open label controllato di steroidi vs SOC, 2104 paz. Mortalità significativamente ridotta nei paz in terapia steroidea in MV o di O_2-terapia senza MV, ma non in quelli non di supporto ventilatorio.

REACT : studio WHO meta-analisi di 7 trials, 1703 paz, 678 ricevevano steroidi. Significativa riduzione della mortalità a 28 giorni di chi riceveva desametasone o idrocortisone

MV ventilazione meccanica

Farmaci autorizzati con Emergency Use Authorization (EUA)

Il programma Expanded Access (EA) della FDA consente usi compassionevoli di terapie e diagnostica non approvate al di fuori degli studi clinici e ha avuto un impatto significativo durante COVID-19 e molti farmaci sperimentali sono stati approvati con Emergency Use Authorization (EUA)

TOCILUZUMAB: IL-6 inibitore, non definitive evidenze di efficacia. Studi mostrano un vantaggio nel suo uso nei pazienti più gravi. IDSA e NIH ne raccomandano l'uso EUA in aggiunta a SOC in pazienti adulti e pediatrici (>2 anni) gravi, già in terapia steroidea e che necessitano o2, NIV, MV e ECMO

BARICITINIB: Janus Kinase-inibitore dell'endocitosi. Studi ne hanno dimostrato vs SOC una riduzione della durata del ricovero, della necessità di ossigeno e mortalità. Indicato EUA in pazienti con COVID-19 gravi che richiedono MV o ECMO

PLASMA IPERIMMUNE: raccolto da donatori guariti dal COVID-19 è un prodotto arricchito di anticorpi specifici, le poche segnalazioni d'uso non hanno dato risultati definitivi. FDA e NIH ne indicano l'uso EUA nelle fasi precoci della malattia e in pazienti con deficit umorali

MV ventilazione meccanica, NIV ventilazione non-invasiva, ECMO ossigeno-terapia extracorporea

TERAPIA DI COVID-19 COME DA LINEE GUIDA INTERNAZIONALI

GRAVITA' CLINICA COVID-19	REMDESIVIR			DESAMETASONE		
	IDSA	NIH	WHO	IDSA	NIH	WHO
Non grave Senza necessità di supplemento di O_2	✗ (C, VL)	*Insufficient data*	✗ (C)	✗ (C, L)	✗ (A,IIa)	✗ (C, L)
Grave Supplemento di O_2, SpO_2 <90-94%, RR>30, distress respiratorio	✓ (C, M)	✓ (B,IIa)*	✗	✓ (C, M)	✓ (B,I)*	✓ (S,M)
Critica MV o ECMO	✗ (C, VL)	✗	✗ (C)	✓ (S, SM)	✓ (AI)	✓ (S,M)

*Remdesivir + desametasone in paz con crescita di necessità di 0_2 o con NIV/alti flussi (BI). NIH raccomand. A forte, B moderata, C opzionale, I studi rand., IIa valutazioni studi rand., IIb non rand/osserv, III expert opinion.IDSA & WHO C condizionale, S forte, VL molto bassa, M moderata

MV ventilazione meccanica, ECMO ossigenazione extracorporea, RR respiratori rate

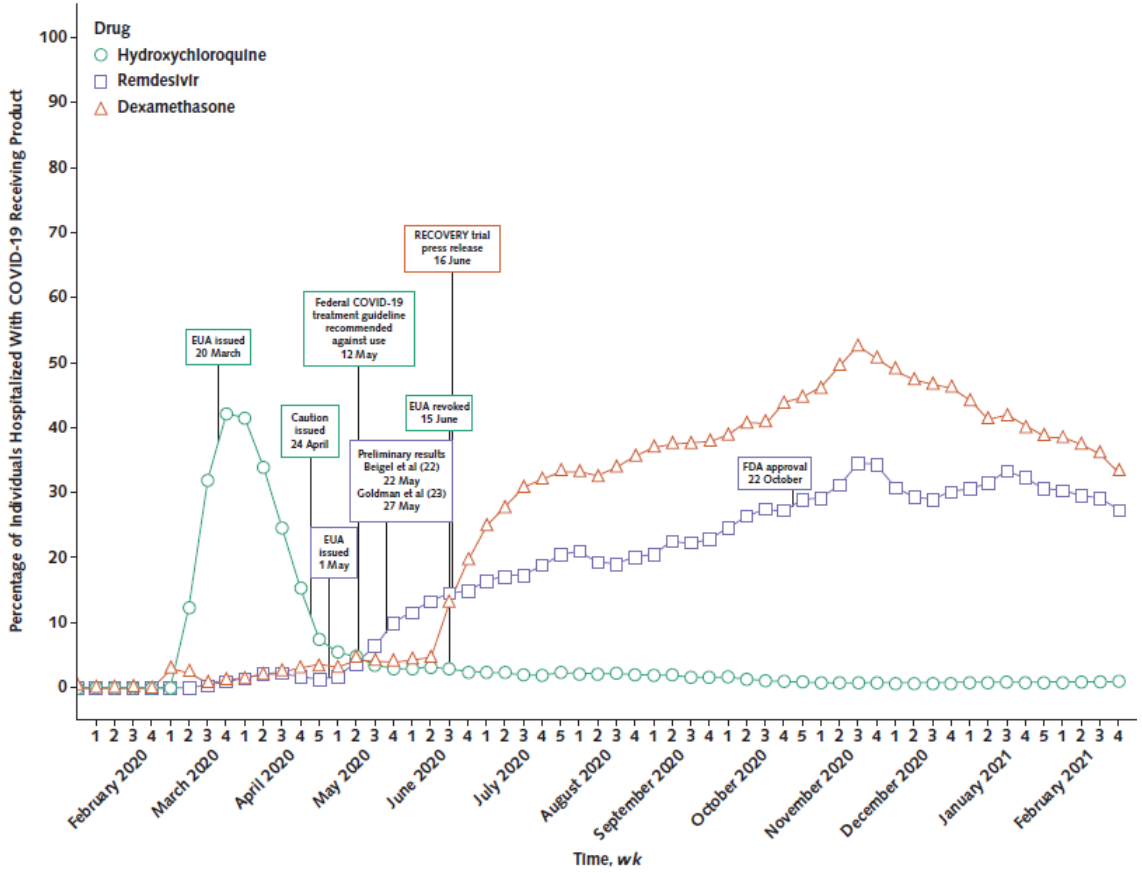
Annals of Internal Medicine *17 August 2021.* ORIGINAL RESEARCH

137 870 adults hospitalized with COVID-19 between 1 February 2020 and 28 February 2021.

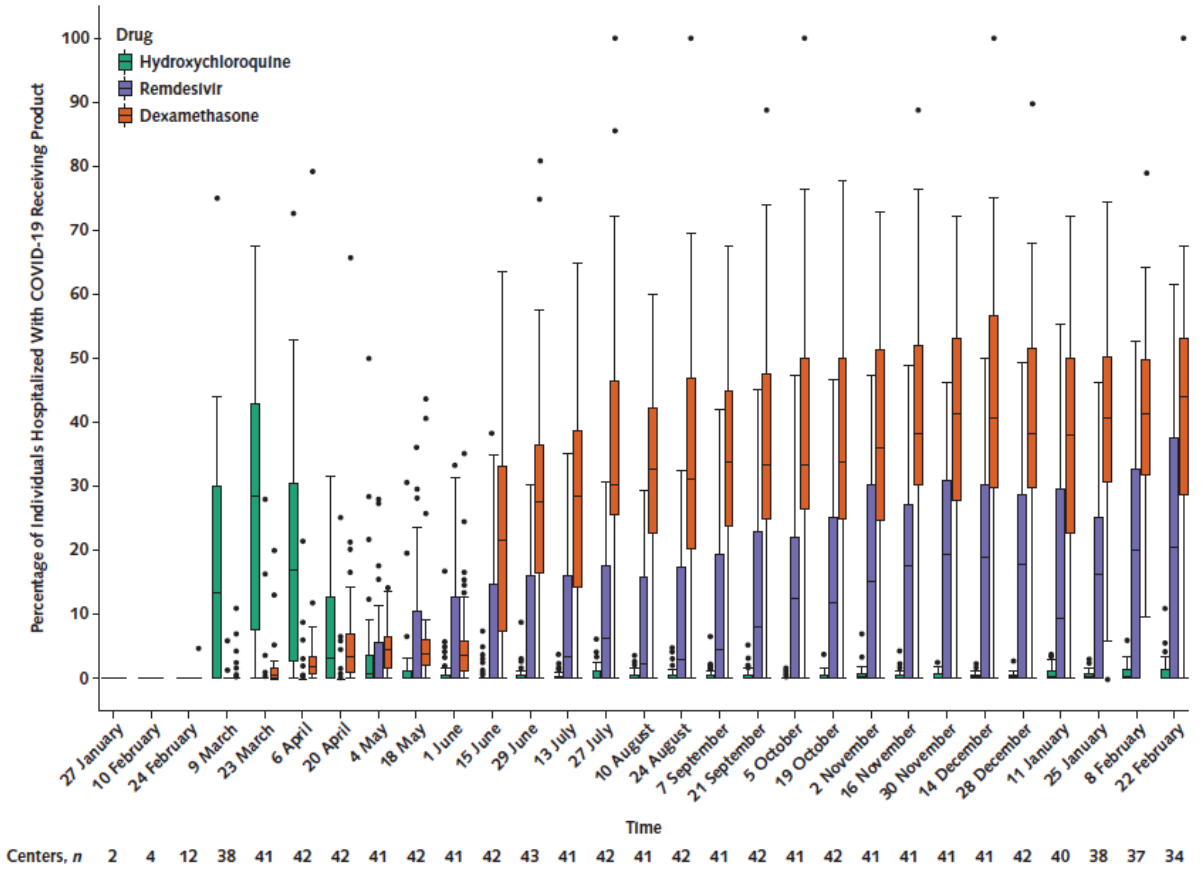
Use of Hydroxychloroquine, Remdesivir, and Dexamethasone Among Adults Hospitalized With COVID-19 in the United States

A Retrospective Cohort Study

Hemalkumar B. Mehta, MS, PhD; Huijun An, MS; Kathleen M. Andersen, MSc; Omar Mansour, MHS; Vithal Madhira, MS; Emaan S. Rashidi, MHS; Benjamin Bates, MD; Soko Setoguchi, MD, DrPH; Corey Joseph, MPH; Paul T. Kocis, PharmD, MPH; Richard Moffitt, PhD; Tellen D. Bennett, MD, MS; Christopher G. Chute, MD, DrPH; Brian T. Garibaldi, MD, MEHP; and G. Caleb Alexander, MD, MS; for the National COVID Cohort Collaborative (N3C)*

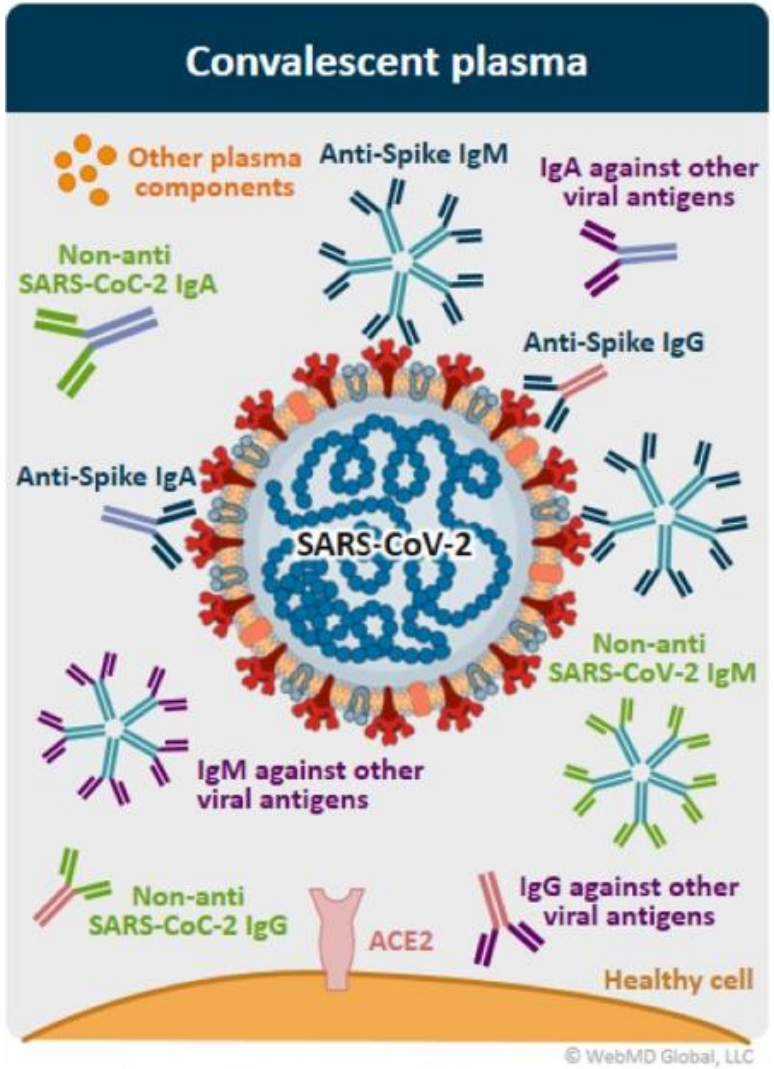


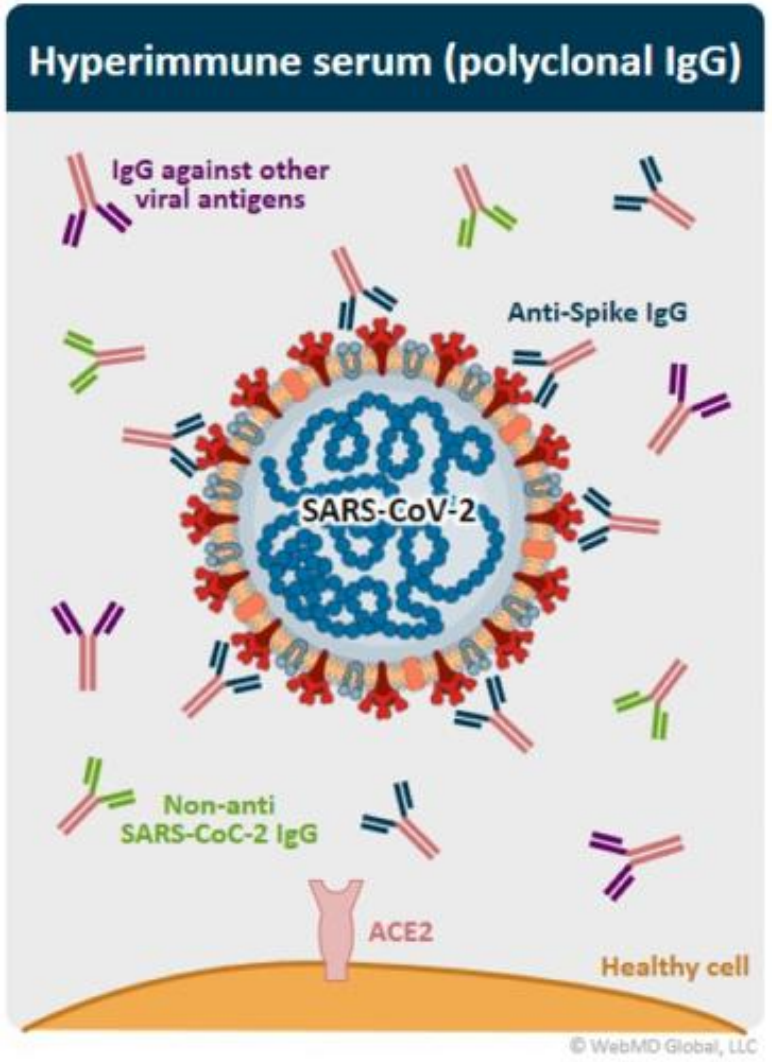
Use of hydroxychloroquine, remdesivir, and dexamethasone among individuals hospitalized with COVID-19, 1 February 2020 to 28 February 2021 (n= 137 870).

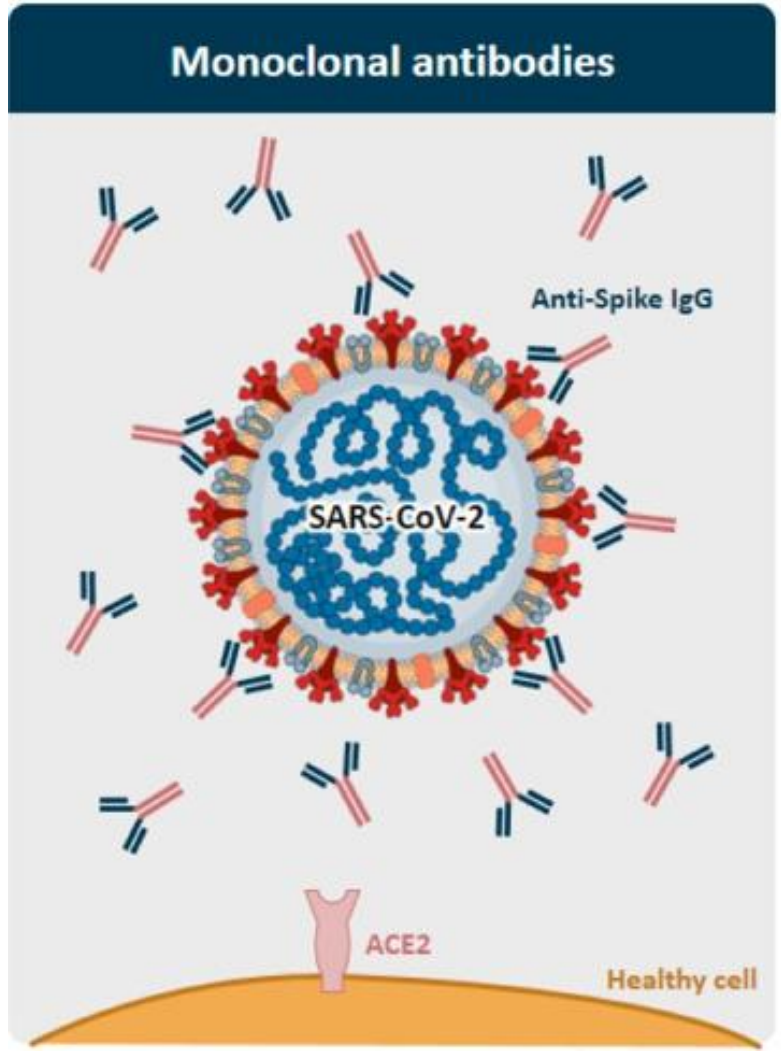


Variation in hydroxychloroquine, remdesivir, and dexamethasone use across health centers over time, 1 February 2020 to 28 February 2021 (n= 137 870).

ANTICORPI MONOCLONALI VS SARS-COV-2







Tuccori M. MoAbs 2020, 12, 1854149

ANTICORPI MONOCLONALI VS SARS-COV-2

- Anticorpi neutralizzanti selettivi del '*receptor binding domain*' (complesso proteico S) del virus
- Interferiscono con la capacità del virus di legarsi alla cellula e replicare
- Potenzialmente attivi (riduzione) sulla carica virale

USO DEGLI ANTICORPI MONOCLONALI VS SARS-COV-2

- Gli MoAb non sono indicati in pazienti con malattia grave e ospedalizzati
- Gli studi che hanno portato all'uso clinico hanno arruolato pazienti a 3 giorni dalla positività del tampone e 3-4 dall'inizio dei sintomi
- Prevenzione dello sviluppo di malattia grave

AIFA agosto 2021 'Trattamento di pazienti ospedalizzati per COVID-19, anche in ossigenoterapia supplementare (con l'esclusione dell'ossigenoterapia ad alti flussi, o in ventilazione meccanica), con sierologia negativa per gli anticorpi IgG anti- Spike di SARSCoV-2

ANTICORPI MONOCLONALI VS SARS-COV-2
quali e come li usiamo in Europa e negli USA

Europa

L'EMA ha raccomandato l'uso in specifiche categorie di pazienti dei seguenti monoclonali

- Carisivimab/imdevimab
- Bamlanivimab/etesevimab
- Regdavimab
- Sotrovimab

USA

- Carisivimab/imdevimab
- Bamlanivimab/etesevimab*
- Regdavimab (no EUA)
- Sotrovimab (no EUA)

- l'uso di Bamlanivimab/etesevimab e di etesevimab da solo è stato interrotto negli USA e anche in Italia per la minor efficacia di questi MoAb nei confronti di alcune varianti di Sar-Cov-2 (beta, gamma e delta)

Defining "High Risk" Patients With COVID-19

High risk is defined as a patient who meets ≥ 1 of the following criteria:

Patients of any age with:

- BMI ≥ 35 kg/m^2
- Chronic kidney disease
- Diabetes
- Immunosuppressive disease
- Current immunosuppressive therapy

Patients aged ≥ 65 y

Patients aged ≥ 55 y with:

- Cardiovascular disease *or*
- Hypertension *or*
- COPD/other chronic respiratory condition

Patients aged 12 to 17 y with:

- BMI > 85th percentile for age and sex
- Sickle cell disease *or*
- Congenital or acquired heart disease *or*
- Neurodevelopmental disorders (eg, cerebral palsy) *or*
- A medical-related technological dependence (eg, tracheostomy, gastrostomy, positive-pressure ventilation [not related to COVID-19]) *or*
- Asthma, reactive airway, or other chronic respiratory disease that requires daily medication for control

FDA. Factsheet: EUA of bamlanivimab and etesevimab. 2021.

Patient Monitoring and Follow-Up

Administration

- Monitor for serious hypersensitivity reaction including anaphylaxis.
- Slow or discontinue infusion if signs and symptoms of hypersensitivity emerge.

Infusion-Related reactions

- Fever, chills, nausea, headache, bronchospasm, hypotension, angioedema, throat irritation, rash/urticaria, pruritus, myalgia, or dizziness.

Patient Discharge

- Give them a copy of the FDA Patient Fact Sheet.
- Available in English and Spanish.

Follow-Up

- Phone the patients the next day to evaluate their experience.
- After MAb infusion, patients should wait 90 days before their next dose of COVID-19 vaccine.

Riepilogo nazionale e regionale per principio attivo (periodo: apertura monitoraggio – 15 luglio 2021)*

REGIONE	bamlanivimab	bamlanivimab e etesevimab	casirivimab e imdevimab	Totale per Regione*	Inc%	%Bam	%BamEte	%CasImd
LAZIO	21	455	374	850	13,6%	2,55	13,09	19,07
VENETO	201	508	103	812	13,0%	24,39	14,61	5,25
TOSCANA	33	434	291	758	12,1%	4	12,48	14,84
CAMPANIA	157	258	101	516	8,2%	19,05	7,42	5,15
PUGLIA	72	343	89	504	8,0%	8,74	9,86	4,54
LOMBARDIA	26	241	192	459	7,3%	3,16	6,93	9,79
SICILIA	73	157	140	370	5,9%	8,86	4,52	7,14
PIEMONTE	14	172	179	365	5,8%	1,7	4,95	9,13
LIGURIA	46	216	67	329	5,3%	5,58	6,21	3,42
MARCHE	37	188	69	294	4,7%	4,49	5,41	3,52
EMILIA ROMAGNA	1	142	63	206	3,3%	0,12	4,08	3,21
VALLE D'AOSTA	33	62	77	172	2,7%	4	1,78	3,93
ABRUZZO	0	43	95	138	2,2%	0	1,24	4,84
FRIULI VENEZIA GIULIA	40	75	5	120	1,9%	4,85	2,16	0,25
CALABRIA	0	54	61	115	1,8%	0	1,55	3,11
UMBRIA	51	25	21	97	1,5%	6,19	0,72	1,07
BASILICATA	3	47	14	64	1,0%	0,36	1,35	0,71
SARDEGNA	0	35	16	51	0,8%	0	1,01	0,82
PROV. AUTON. TRENTO	4	20	2	26	0,4%	0,49	0,58	0,1
MOLISE	12	1	0	13	0,2%	1,46	0,03	0
PROV. AUTON. BOLZANO	0	1	2	3	0,0%	0	0,03	0,1
ITALIA	824	3.477	1.961	6.262	100,0%	13,2%	55,5%	31,3%

* I numeri indicano le prescrizioni anticorpi monoclonali (RF=richieste farmaco) al netto di quelle senza dispensazione

mAbs in Trials for Pre- and Post-Exposure Prophylaxis

Pre-exposure prophylaxis

mAbs have been shown to reduce viral load, and therefore, may reduce transmission → prevent disease in people who would be at high risk of getting severe COVID-19

Post-exposure prophylaxis

Trials with exposed people who would be at high risk of severe disease have reported reductions in infection and disease progression (eg, care home setting)

Gottlieb RL, et al. *JAMA*. 2021;325:632-644; Weinreich DM, et al. *N Engl J Med*. 2021;384:238-251.

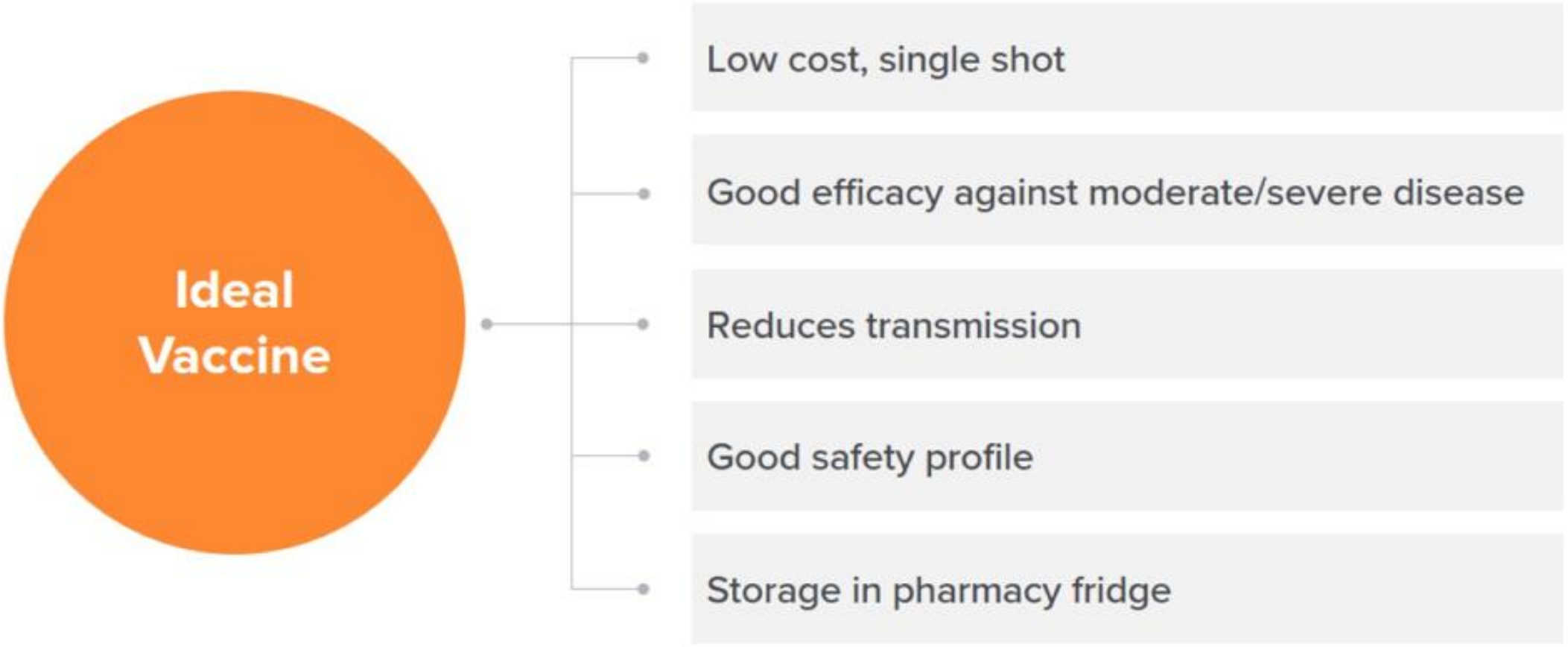
Table 9: Pseudotyped Virus-Like Particle Neutralization Data for SARS-CoV-2 Variant Substitutions with Casirivimab and Imdevimab Together

Lineage with Spike Protein Substitution	Country First Identified	WHO Nomenclature	Key Substitutions Tested	Fold Reduction in Susceptibility
B.1.1.7	UK	Alpha	N501Y[a]	no change[e]
B.1.351	South Africa	Beta	K417N, E484K, N501Y[b]	no change[e]
P.1	Brazil	Gamma	K417T, E484K, N501Y[c]	no change[e]
B.1.427/B.1.429	USA (California)	Epsilon	L452R	no change[e]
B.1.526[f]	USA (New York)	Iota	E484K	no change[e]
B.1.617.1/B.1.617.3	India	Kappa/no designation	L452R+E484Q	no change[e]
B.1.617.2/AY.3	India	Delta	L452R+T478K	no change[e]
AY.1/AY.2[g]	India	Delta [+K417N]	K417N, L452R, T478K[d]	no change[e]
B.1.621/B.1.621.1	Colombia	No designation	R346K, E484K, N501Y	no change[e]
C.37	Peru	Lambda	L452Q+F490S	no change[e]

a Pseudotyped VLP expressing the entire variant spike protein was tested. The following changes from wild-type spike protein are found in the variant: del69-70, del145, N501Y, A570D, D614G, P681H, T716I, S982A, D1118H**.. b Pseudotyped** VLP expressing the entire variant spike protein was tested. The following changes from wild-type spike protein are found in the variant: D80Y, D215Y, del241-243, K417N, E484K, N501Y, D614G, A701V. **. c Pseudotyped** VLP expressing the entire variant spike protein was tested. The following changes from wild-type spike protein are found in the variant: L18F, T20N, P26S, D138Y, R190S, K417T, E484K, N501Y, D614G, H655Y, T1027I, V1176F **d For AY.1: Pseudotyped VLP** expressing the entire variant spike protein was tested. The following changes from wild-type spike protein are found in the variant: (T19R, G142D, E156G, F157-, F158-, K417N, L452R, T478K, D614G, P681R, D950N).
e No change: ≤2-fold reduction in susceptibility**. f Not all isolates** of the New York lineage harbor the E484K substitution (as of February 2021). **g Commonly known as "Delta plus"**

VACCINI per *Sars-Cov-2*

VACCINI per *Sars-Cov-2*



JAMA. 2021;325(13):1318-1320

Table. SARS-CoV-2 Vaccines

Vaccine	Manufacturer	Vaccine type	Antigen	Dose	Dosage	Storage conditions	Efficacy against severe COVID-19[a]	Overall efficacy	Current approvals
mRNA-1273	Moderna (US)	mRNA	Full-length spike (S) protein with proline substitutions	100 µg	2 Doses 28 d apart	−25° to −15 °C; 2-8 °C for 30 d; room temperature ≤12 h	100% 14 d After second dose (95% CI, not estimable to 1.00)	92.1% 14 d After 1 dose (95% CI, 68.8%-99.1%); 94.1% 14 d after second dose (95% CI, 89.3%-96.8%)	EUA: the US, EU, Canada, and UK
BNT162b2	Pfizer-BioNTech (US)	mRNA	Full-length S protein with proline substitutions	30 µg	2 Doses 21 d apart	−80° to −60 °C; 2-8 °C for 5 d; room temperature ≤2 h	88.9% After 1 dose (95% CI, 20.1%-99.7%)	52% After 1 dose (95% CI, 29.5%-68.4%); 94.6% 7 d after second dose (95% CI, 89.9%-97.3%)	EUA: the US, EU, Canada, and UK
Ad26.CoV2.S	Janssen/ Johnson & Johnson (US)	Viral vector	Recombinant, replication-incompetent human adenovirus serotype 26 vector encoding a full-length, stabilized SARS-CoV-2 S protein	5×10^{10} Viral particles	1 Dose	−20 °C; 2-8 °C for 3 mo	85% After 28 d; 100% after 49 d	72% in the US; 66% in Latin America; 57% in South Africa (at 28 d)	EUA: the US, EU, and Canada
ChAdOx1 (AZS1222)	AstraZeneca/ Oxford (UK)	Viral vector	Replication-deficient chimpanzee adenoviral vector with the SARS-CoV-2 S protein	5×10^{10} Viral particles (standard dose)	2 Doses 28 d apart (intervals >12 wk studied)	2-8 °C for 6 mo	100% 21 d After first dose	64.1% After 1 dose (95% CI, 50.5%-73.9%); 70.4% 14 d after second dose (95% CI, 54.8%-80.6%)	EUA: WHO/Covax, the UK, India, and Mexico
NVX-CoV2373	Novavax, Inc (US)	Protein subunit	Recombinant full-length, prefusion S protein	5 µg of protein and 50 µg of Matrix-M adjuvant	2 Doses	2-8 °C for 6 mo	Unknown	89.3% in the UK after 2 doses (95% CI, 75.2%-95.4%); 60% in South Africa (95% CI, 19.9%-80.1%)	EUA application planned
CVnCoV	CureVac/ GlaxoSmithKline (Germany)	mRNA	Prefusion stabilized full-length S protein of the SARS-CoV-2 virus	12 µg	2 Doses 28 d apart	2-8 °C for 3 mo; room temperature for 24 h	Unknown	Phase 3 trial ongoing	
Gam-COVID-Vac (Sputnik V)	Gamaleya National Research Center for Epidemiology and Microbiology (Russia)	Viral vector	Full-length SARS-CoV-2 glycoprotein S carried by adenoviral vectors	10^{11} Viral particles per dose for each recombinant adenovirus	2 Doses (first, rAd26; second, rAd5) 21 d apart	−18 °C (Liquid form); 2-8 °C (freeze dried) for up to 6 mo	100% 21 d After first dose (95% CI, 94.4%-100%)	87.6% 14 d After first dose (95% CI, 81.1%-91.8%); 91.1% 7 d after second dose (95% CI, 83.8%-95.1%)	EUA: Russia, Belarus, Argentina, Serbia, UAE, Algeria, Palestine, and Egypt
CoronaVac	Sinovac Biotech (China)	Inactivated virus	Inactivated CN02 strain of SARS-CoV-2 created from Vero cells	3 µg With aluminum hydroxide adjuvant	2 Doses 14 d apart	2-8 °C; Lifespan unknown	Unknown	Phase 3 data not published; reported efficacy 14 d after dose 2: 50.38% (mild) and 78% (mild to severe) in Brazil, 65% in Indonesia, and 91.25% in Turkey	EUA: China, Brazil, Columbia, Bolivia, Brazil, Chile, Uruguay, Turkey, Indonesia, and Azerbaijan
BBIBP-CorV	Sinopharm 1/2 (China)	Inactivated virus	Inactivated HB02 strain of SARS-CoV-2 created from Vero cells	4 µg With aluminum hydroxide adjuvant	2 Doses 21 d apart	2-8 °C; Lifespan unknown	Unknown	Phase 3 data not published; unpublished reports of 79% and 86% efficacy	EUA: China, UAE, Bahrain, Serbia, Peru, and Zimbabwe

Piano vaccini anti Covid-19

- Vaccino Comirnaty di Pfizer/BioNTech
- Vaccino Spikevax (Moderna)
- Vaccino Vaxzevria di AstraZeneca
- Vaccino Janssen di Johnson&Johnson

La **Commissione Tecnico Scientifica (CTS) di AIFA** ha approvato l'estensione di indicazione di utilizzo del vaccino Comirnaty (BioNTech/Pfizer**) per la fascia di età tra i 12 e i 15 anni, accogliendo pienamente il parere espresso dall'Agenzia Europea dei Medicinali (EMA).** 31 maggio 2021

Solo a persone di età = o > 60 anni (ciclo completo). Per persone <**60 anni**, che hanno già ricevuto una prima dose del **vaccino Vaxzevria completare il ciclo vaccinale** con una **dose di vaccino a mRNA** (Comirnaty o Moderna).
Alla persona di età <60 anni che hanno ricevuto la prima dose di Vaxzevria, informati dei rischi di 2° dose, **rifiuta** 2° dose con vaccino a mRNA.. **può essere somministrata la seconda dose di Vaxzevria** (circolare 18 giugno 2021).

Uso preferenziale del **vaccino Janssen alle persone di età > 60 anni (Circolare 21 aprile 2021**). Il vaccino resta autorizzato per le persone sopra il 18 anni. L'EMA e l'AIFA ribadiscono che il rapporto rischio beneficio è estremamente ..estrema rarità degli eventi di trombosi associata a trombocitopenia, descritti a seguito della vaccinazione.

April 9, 2021, at NEJM.org. DOI: 10.1056/NEJMoa2104840

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Thrombotic Thrombocytopenia after ChAdOx1 nCov-19 Vaccination

Andreas Greinacher, M.D., Thomas Thiele, M.D., Theodore E. Warkentin, M.D., Karin Weisser, Ph.D., Paul A. Kyrle, M.D., and Sabine Eichinger, M.D.

11 patients in Germany and Austria in whom thrombosis or thrombocytopenia had developed after vaccination with ChAdOx1 nCov-19. We used a standard enzyme-linked immunosorbent assay to detect platelet factor 4 (PF4)–heparin antibodies and a modified (PF4-enhanced) platelet-activation test to detect platelet-activating antibodies under various reaction conditions

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Journal of Autoimmunity

journal homepage: www.elsevier.com/locate/jautimm

23 June 2021

Blood clots and bleeding events following BNT162b2 and ChAdOx1 nCoV-19 vaccine: An analysis of European data

Luigi Cari [a], Paolo Fiore [a], Mahdieh Naghavi Alhosseini [a], Gianni Sava [b], Giuseppe Nocentini [a,*]

We assessed the frequency of severe adverse events (SAEs) documented in the EudraVigilance European database up to April 16, 2021 related to thrombocytopenia, bleeding, and blood clots in recipients of ChA compared to that of recipients of the BNT162b2 Covid-19 (Pfizer/BioNTech) vaccine (BNT).

ChA administration was associated with a much higher frequency of SAEs in each AE Reaction Group as compared with that elicited by BNT. When considering AEs caused by thrombocytopenia, bleeding and blood clots, we observed 33 and 151 SAEs/1 million doses in BNT and ChA recipients, respectively. When considering patients with AEs related to cerebral/splanchnic venous thrombosis, and/or thrombocytopenia, we documented 4 and 30 SAEs and 0.4 and 4.8 deaths/1 million doses for BNT and ChA recipients, respectively. The highest risk following ChA vaccination is in young people and, likely, women of reproductive age, as suggested by hypothesized scenarios.

In conclusion, the immune reaction promoted by ChA vaccine may lead to not only thrombocytopenia and cerebral/splanchnic venous thrombosis but also other thrombotic and thromboembolic SAEs. These events are not favored by BNT vaccine. Our study may help in the evaluation of the benefit/risk profile of the ChA vaccine considering the epidemic curve present in a country.

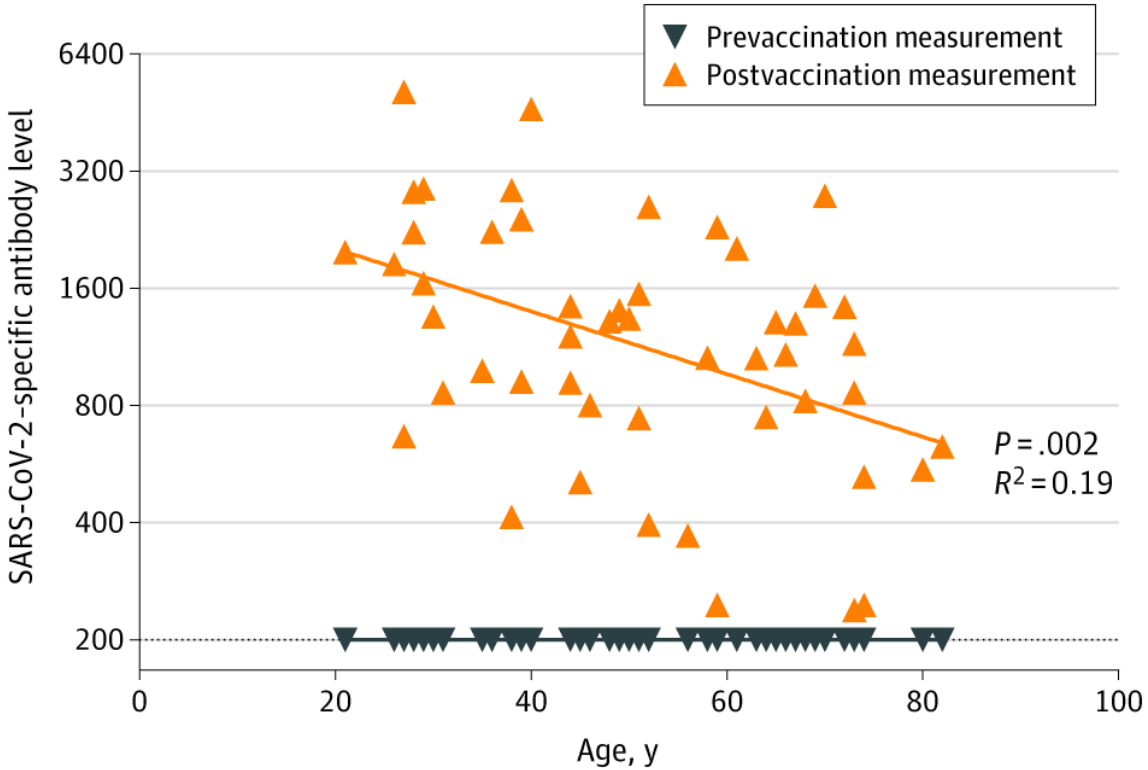
Thrombotic Events

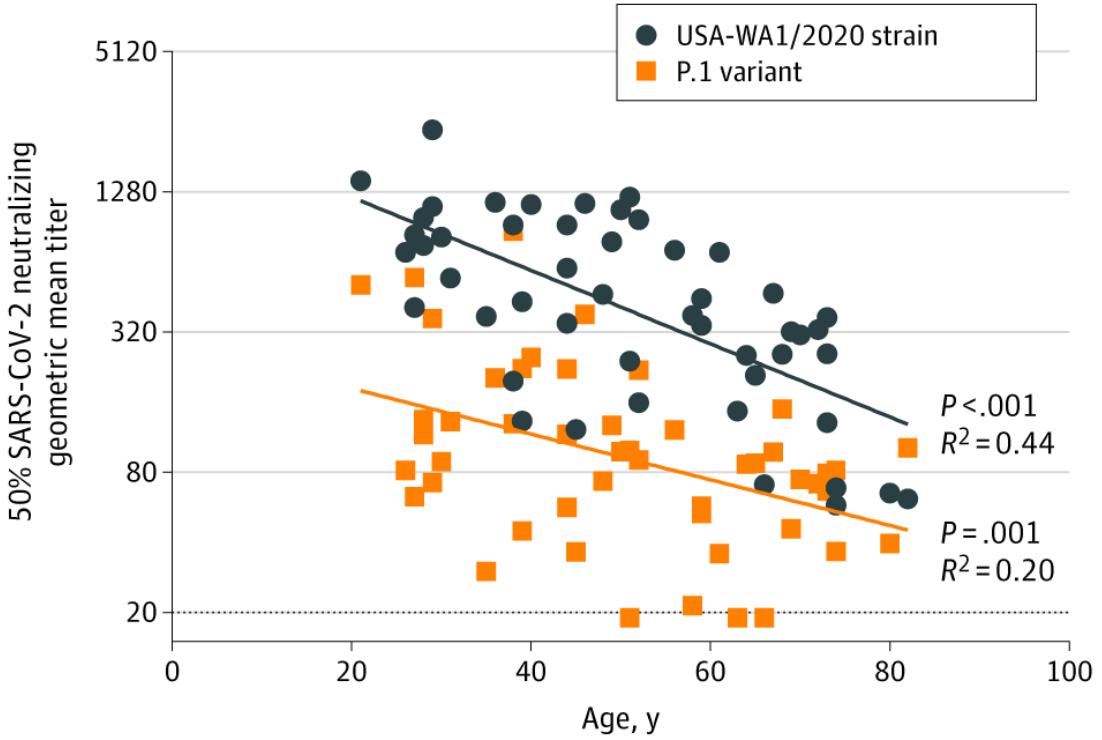
- Very rare side effect with no causal relationship established
  - UK: ~1 case per 250,000 from AZ vaccine[a]
  - US: ~1 case per 1,000,000 from J&J vaccine[b]
  - Most cases and deaths in women < 60 years of age
- Risk of thrombotic events from COVID-19 higher than from vaccine
- Benefits of vaccine outweigh risk of side effects

a. Mahase E. *BMJ.* 2021;373:n931; FDA. News release. April 23, 2021.

From: **Age-Dependent Neutralization of SARS-CoV-2 and P.1 Variant by Vaccine Immune Serum Samples**

JAMA. 2021;326(9):868-869. doi:10.1001/jama.2021.11656





SARS-CoV-2–Specific Antibody anti-SARS-CoV-2 spike receptor and association with age at time of vaccination for 50 participants 14 days after receiving their second vaccine dose. Prevaccination samples for all participants were below the limit of detection, indicating no prior exposure. **Postvaccination samples displayed a significant negative association with age.** The dotted line indicates the lower limit of quantification.

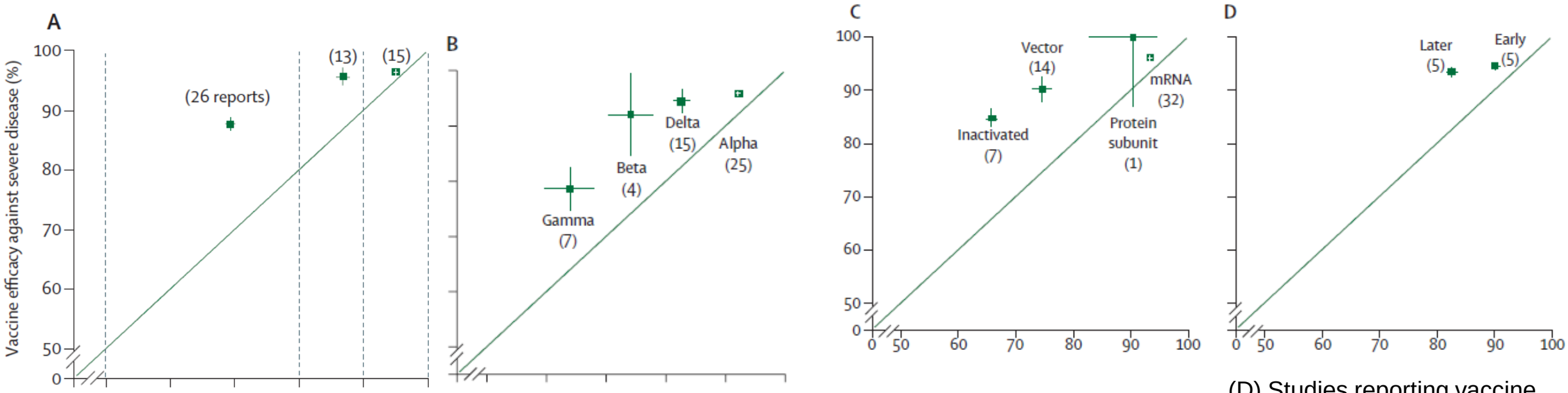
Neutralization experiments were performed with the USA-WA1/2020 strain and P.1 variant. Both show a significant negative association with participant age.

Considerations in boosting COVID-19 vaccine immune responses

Philip R Krause, Thomas R Fleming, Richard Peto, Ira M Longini, J Peter Figueroa, Jonathan A C Sterne, Alejandro Cravioto, Helen Rees, Julian P T Higgins, Isabelle Boutron, Hongchao Pan, Marion F Gruber, Narendra Arora, Fatema Kazi, Rogerio Gaspar, Soumya Swaminathan, Michael J Ryan, Ana-Maria Henao-Restrepo

The figure summarizes the reports that estimated vaccine efficacy separately for severe disease and for any confirmed SARS-CoV-2 infection.

- **A consistent finding is that vaccine efficacy is substantially greater against severe disease than against any infection;**
- **Vaccination appears to be substantially protective against severe disease from all the main viral variants.**
- **There is still high vaccine efficacy against both symptomatic and severe disease due to the delta variant.**



(A) Vaccine efficacy against any infection (50% to <80%, 80% to <90%, ≥90%).

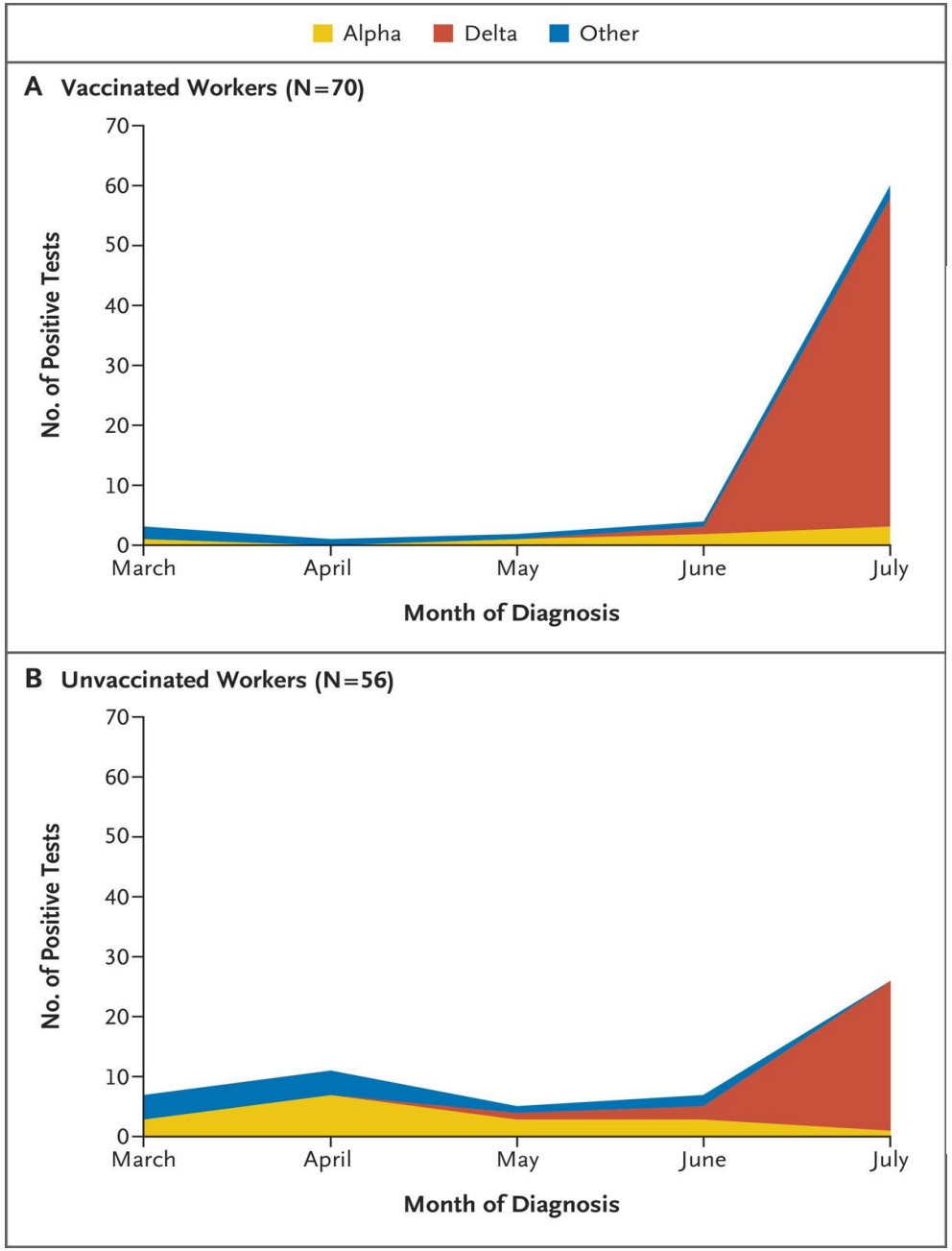
(B) Viral variant.

C) Type of vaccine (viral vector, inactivated SARS-CoV-2, adjuvanted protein subunit,or mRNA).

(D) Studies reporting vaccine efficacy early (more recently relative to vaccination) or later (less recently relative to vaccination) during the follow-up of the same observational study.

www.thelancet.com Published online September 13, 2021 https://doi.org/10.1016/S0140-6736(21)02046-8

J Keehner et al. N Engl J Med 2021. DOI: 10.1056/NEJMc2112981



The NEW ENGLAND JOURNAL of MEDICINE

CORRESPONDENCE

Resurgence of SARS-CoV-2 Infection in a Highly Vaccinated Health System Workforce

Table 1. Symptomatic SARS-CoV-2 Infection and mRNA Vaccine Effectiveness among UCSDH Health Workers, March through July 2021.*

	March	April	May	June	July
UCSDH workforce — no. of persons	18,964	18,992	19,000	19,035	19,016
Vaccination status — no. of persons					
Fully vaccinated†	14,470	15,510	16,157	16,426	16,492
mRNA-1273 (Moderna)	6,608	7,005	7,340	7,451	7,464
BNT162b2 (Pfizer–BioNTech)	7,862	8,505	8,817	8,975	9,028
Unvaccinated	3,230	2,509	2,187	2,059	1,895
Percentage of workers fully vaccinated	76.3	78.8	81.7	82.6	83.1
Symptomatic Covid-19					
Fully vaccinated workers	3	4	3	5	94
Unvaccinated workers	11	17	10	10	31
Percentage of cases in fully vaccinated workers	21.4	19.0	23.1	33.3	75.2
Attack rate per 1000 (95% CI)					
Fully vaccinated workers	0.21 (0.21–0.47)	0.26 (0.26–0.50)	0.19 (0.21–0.40)	0.30 (0.31–0.53)	5.7 (5.4–6.2)
Unvaccinated workers	3.4 (2.1–5.9)	6.8 (4.5–10.6)	4.6 (2.6–8.2)	4.9 (2.9–8.7)	16.4 (11.8–22.9)
Vaccine effectiveness — % (95% CI)	93.9 (78.2–97.9)	96.2 (88.7–98.3)	95.9 (85.3–98.9)	94.3 (83.7–98.0)	65.5 (48.9–76.9)

coincident with the end of California's mask mandate on June 15 and the rapid dominance of the B.1.617.2 (delta) variant that first emerged in mid-April and accounted for over 95% of UCSDH isolates by the end of July infections increased rapidly, including cases among fully vaccinated persons

ORIGINAL ARTICLE

N. Engl J Med Sept. 2021

Protection of BNT162b2 Vaccine Booster against Covid-19 in Israel

On **July 30, 2021**, the administration of **a third (booster) dose of the BNT162b2** messenger RNA vaccine (Pfizer–BioNTech) was approved in Israel for **1,137,804 persons who were 60 years of age or older** and **who had received a second dose of vaccine at least 5 months** earlier. Data are needed regarding the effect of the booster dose on the rate of confirmed coronavirus 2019 disease (Covid-19) and the rate of severe illness.

Table 2. Primary Outcomes of Confirmed Infection and Severe Illness.*

Outcome	Nonbooster Group	Booster Group	Adjusted Rate Ratio (95% CI)†
Confirmed infection			11.3 (10.4 to 12.3)
No. of cases	4439	934	
No. of person-days at risk	5,193,825	10,603,410	
Severe illness			19.5 (12.9 to 29.5)
No. of cases	294	29	
No. of person-days at risk	4,574,439	6,265,361	

* Listed are the results of the Poisson regression analysis in participants who received a booster vaccine and in those who did not receive a booster. The booster group includes data that were obtained at least 12 days after receipt of the booster dose.

† The rate ratio is the estimated factor reduction in the rate in the booster group as compared with the rate in the non-booster group.

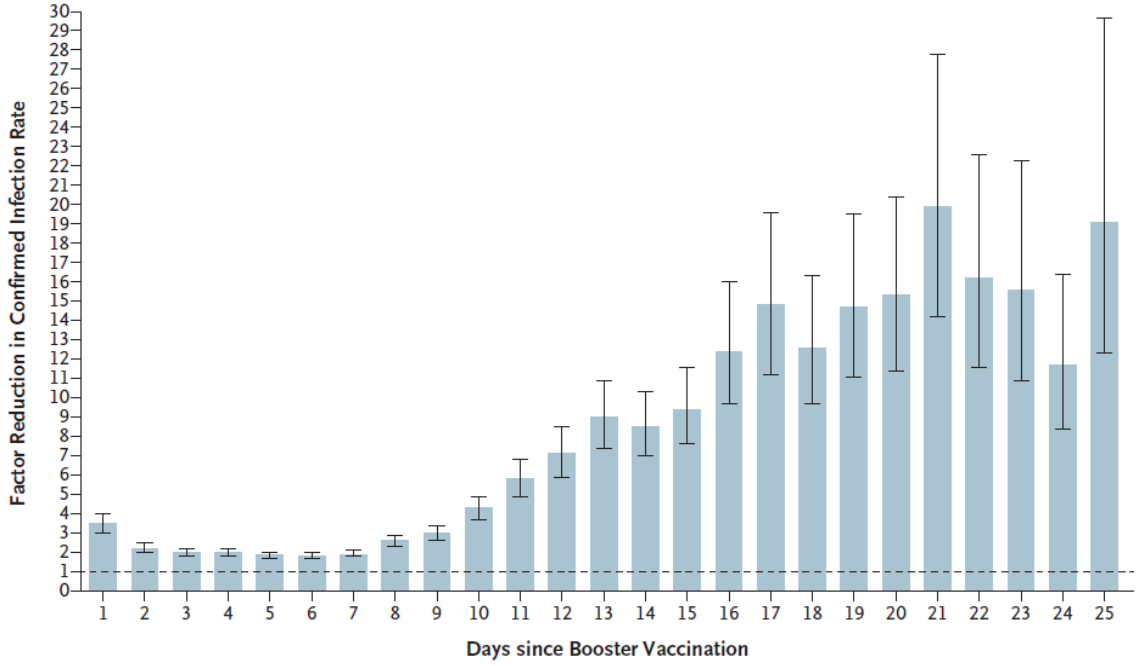


Figure 2. Reduction in Rate of Confirmed Infection in Booster Group as Compared with Nonbooster Group.

Shown is the factor reduction in the rate of confirmed infection among participants who received a third (booster) dose of the BNT162b2 vaccine as compared with those who did not receive a booster dose, according to the number of days after the administration of the booster dose. Because of wide confidence intervals, only days 1 through 25 are shown. The dashed horizontal line represents the level at which the booster dose provided no added protection. The I bars represent 95% confidence intervals, which have not been corrected for multiplicity.


obrigado
Dank U
Merci
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спасибо
Grazie
Thank you
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Takk
Gracias
Dziękuję
Děkuju
danke
Kiitos