THE COVID-19 PANDEMIC

Steve Kagen, M.D.
Allergy, Asthma + Immunology Specialist

The Kagen Allergy Clinic, S.C.
100 W. Lawrence Street
Appleton, Wisconsin 54911 USA

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Steve@KagenClinics.com

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SUMMARY

1. CoV-2 SPIKE PROTEINS INDUCE BLOOD CLOTS AND SCARS IN BLOOD VESSELS AND VITAL ORGANS.
2. EACH PATIENT IS UNIQUE REGARDING THEIR IMMUNE RESPONSES TO THE CoV-2 VIRUS.
3. CLINICAL OUTCOMES ARE DETERMINED BY THE INTENSITY OF YOUR IMMUNE RESPONSE TO CoV-2.
4. SUCCESSFUL TREATMENT REQUIRES EARLY USE OF ANTI-VIRAL, ANTI-INFLAMMATORY AND ANTI-COAGULANT DRUGS TO CONTROL YOUR IMMUNE AND COAGULATION RESPONSES TO A CoV-2 INFECTION.
5. WEARING MASKS AND SOCIAL DISTANCING WILL CONTINUE TO BE NECESSARY UNTIL EVERYONE IS VACCINATED.

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THE COVID-19 PANDEMIC
WE HAVE NOT YET WON

TOTAL CASES	DEATHS PAST 7 DAYS	TOTAL DEAD
30,814,955	4,707	557,093
+ 75,956 New Cases	APRIL 9, 2021	APRIL 9, 2021

UNITED STATES – CASES AND DEATHS REPORTED TO CDC

SINCE JANUARY 21, 2020

SOURCE: https://covid.cdc.gov/covid-data-tracker/#cases_totalcases

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COVID-19 DEATH RATE IN USA

138 TIMES WORSE THAN VIETNAM WAR

APRIL 7, 2021

EVENT Time	TOTAL DEAD	TOTAL DAYS	DEAD PER DAY	DEATH RATE COVID-19 VIETNAM
COVID-19 PANDEMIC January 19, 2020 April 7, 2021	555,231	447	1,242	$\frac{1242}{9}$ = 138
VIETNAM WAR 1956 - 1974	58,220	6,570	9	—

https://ourworldindata.org/covid-deaths

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COVID-19 FACTS

1. CoV-2 IS A HIGHLY INFECTIOUS CORONAVIRUS FOUND IN BATS, CATS BIRDS, CATTLE, MINK AND CAMELS 95% IDENTICAL TO SARS CORONAVIRUS.
2. CoV-2 SPIKE PROTEINS INDUCE CLOTS WITHIN INFECTED TISSUES.
3. 43% OF INFECTIONS ARE ASYMPTOMATIC, OTHERS MAY EXPERIENCE FEVER, COUGH, SORE THROAT, CHANGE IN SMELL AND TASTE, SKIN RASHES OR FATAL INFLAMMATORY REACTIONS.
4. CoV-2 VIRUSES INFECT CELLS IN THE NOSE, SINUS, LUNG, HEART, BRAIN, KIDNEY AND BLOOD VESSELS IN BOTH CHILDREN AND ADULTS.
5. VIRUS TRANSMISSION CAN OCCUR 2 DAYS BEFORE SYMPTOMS BEGIN, BUT CoV-2 CAN BE SPREAD FOR UP TO 33 DAYS IN THE AIR AND STOOL AFTER YOU ARE INFECTED.
6. THERE ARE NO "MILD" COVID INFECTIONS FOR INFECTED PATIENTS MAY EXPERIENCE LONGTERM DAMAGE TO THEIR HEARTS.

4--10-2021

COVID-19 FACTS

7. PATIENT OUTCOMES DEPEND ON THE INTENSITY OF ONE'S IMMUNE RESPONSE TO THE VIRUS AND EXTENT OF DAMAGE TO VITAL ORGANS.
8. 87% OF PATIENTS FEEL FATIGUE AND SHORTNESS OF BREATH FOR MONTHS AFTER "RECOVERING" FROM COVID-19 INFECTIONS.
9. REMDESIVIR DECREASES VIRUS NUMBERS BUT DOES NOT PREVENT DEATH. HYDROXYCHLOROQUINE FAILED TO IMPROVE CLINICAL OUTCOMES.
10. mRNA VACCINES ARE 95% EFFECTIVE IN PREVENTING CoV-2 INFECTIONS. INTRA-NASAL CoV-2 IMMUNIZATION MAY ALSO PREVENT CoV-2 INFECTIONS.
11. ANTI-SPIKE MONOCLONAL ANTIBODIES DECREASE COVID-19 SYMPTOMS IN ADULTS AND CHILDREN WITH MILD INFECTIONS IF GIVEN WITHIN THE FIRST 7 DAYS AFTER SYMPTOMS BEGIN.
12. CONTROLLING THE PANDEMIC REQUIRES TESTING EVERYONE, ISOLATION OF ALL THOSE INFECTED, TRACING EVERY CONTACT OF INFECTED INDIVIDUALS AND VACCINATING EVERYONE POSSIBLE.

4-10-2021

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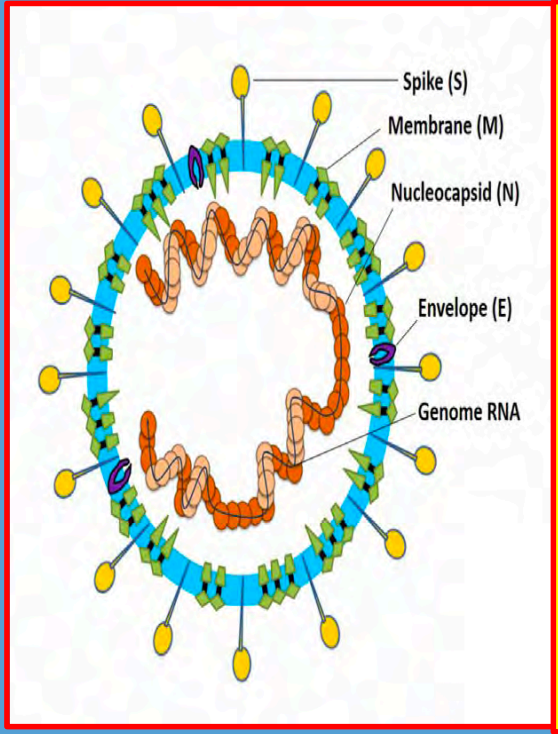
THE COVID-19 PANDEMIC



TO CONTROL THE PANDEMIC WE MUST

1. **TEST** EVERYONE REPEATEDLY.
2. **ISOLATE** EVERY POSITIVE PATIENT.
3. **TRACE** ALL CONTACTS OF POSITIVES.
4. **ALWAYS** WEAR FACE MASKS NEAR OTHERS.
5. **IMMUNIZE** ALL INDIVIDUALS

using CoV-2 spike proteins or spike mRNA (active immunity)
and anti-spike monoclonal antibodies (passive immunity)

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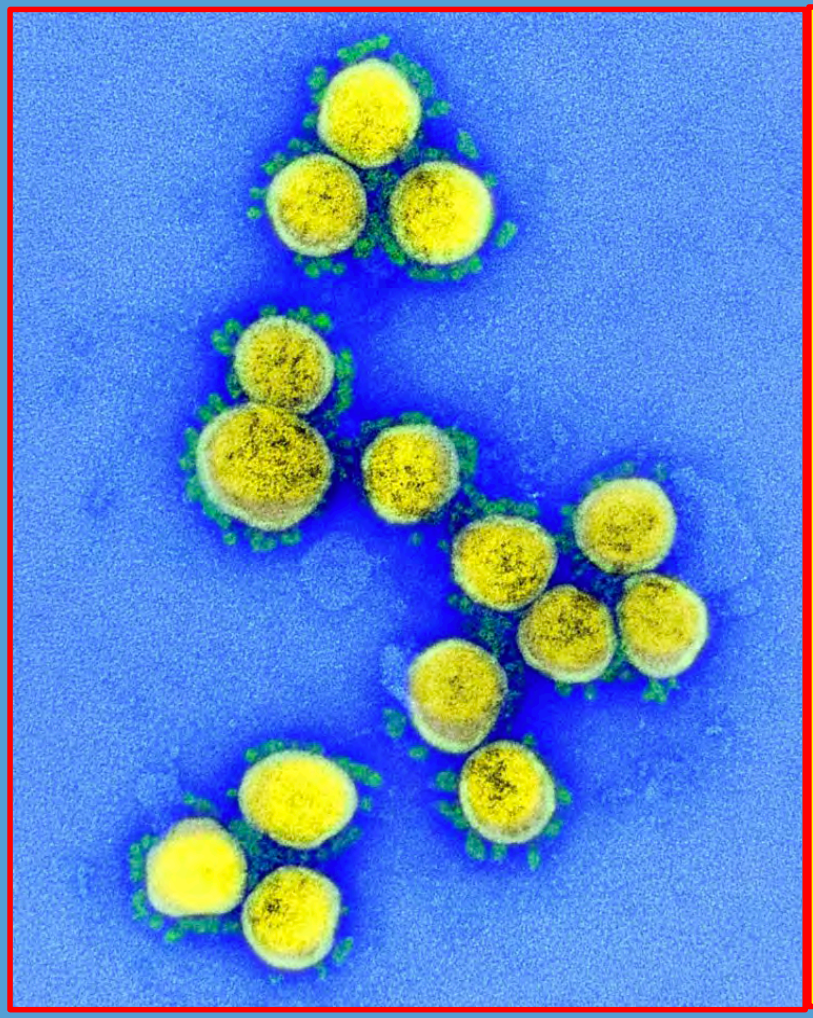

CORONAVIRUS

WHAT IS IT ?

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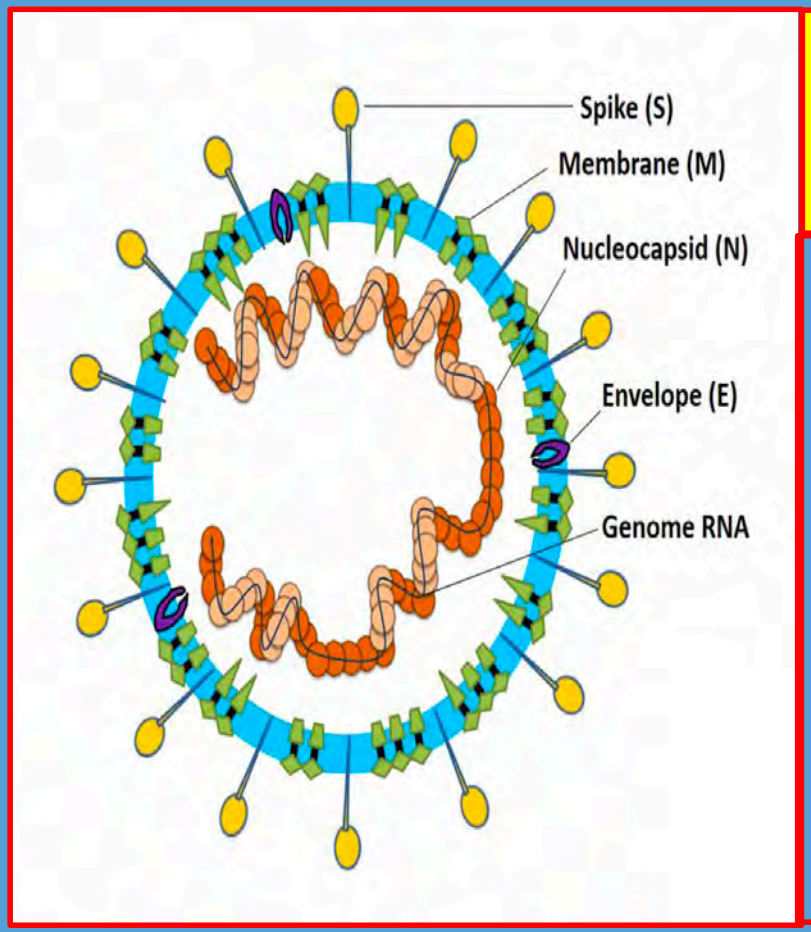
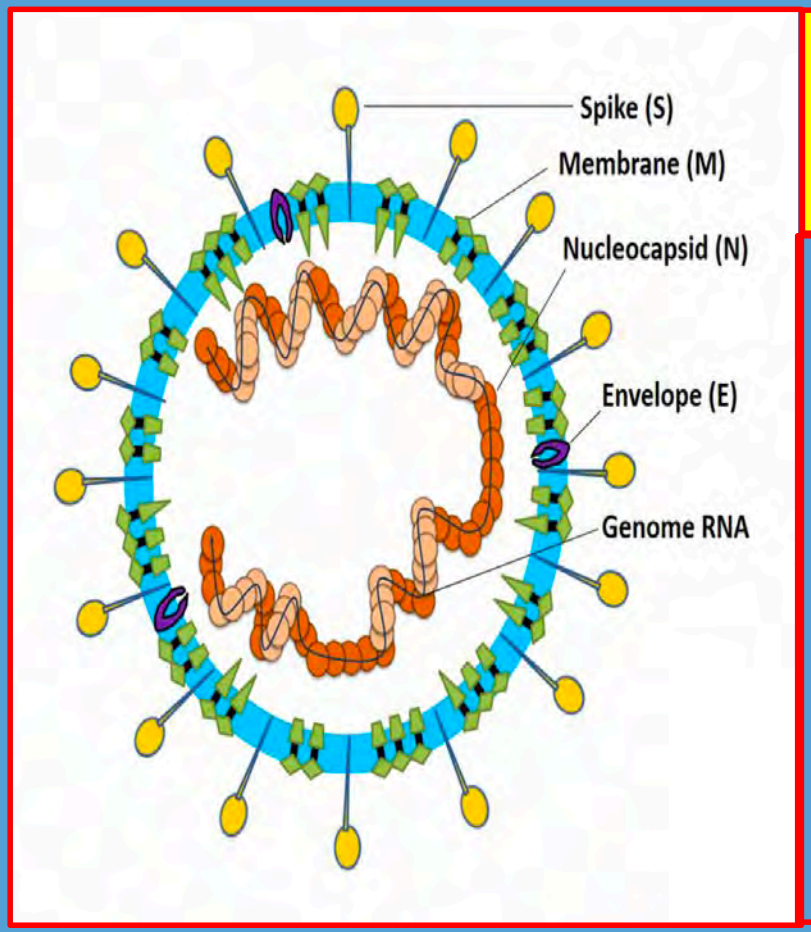


CORONAVIRUS

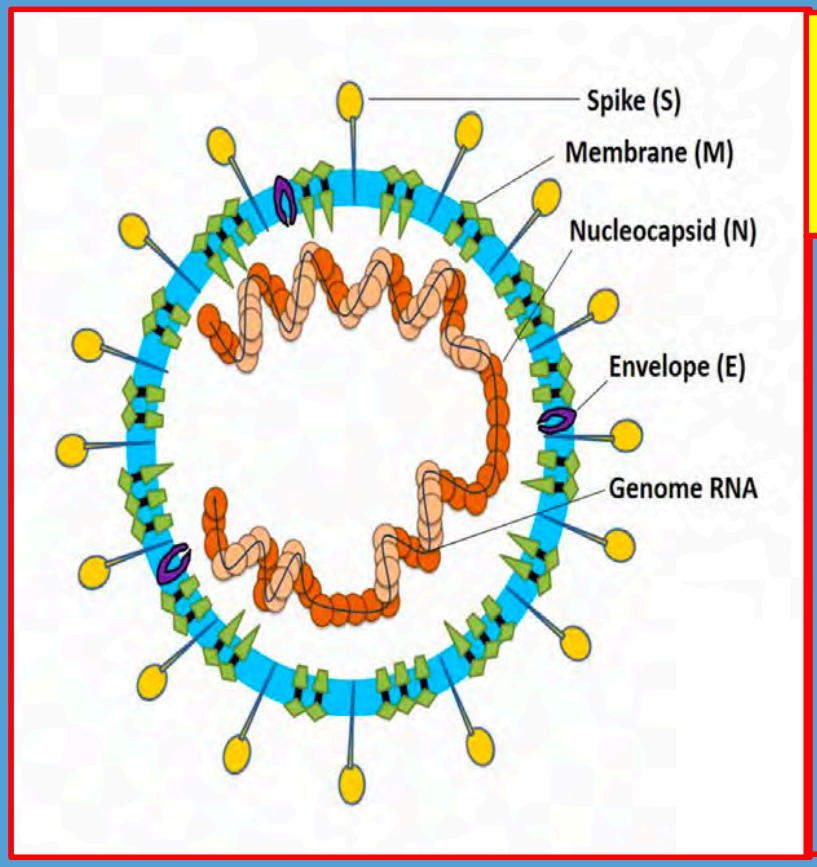
* FIRST DISCOVERED AS A CAUSE OF A COMMON COLD IN 1965
* ENCAPSULATED RNA VIRUSES
* 7 TYPES INFECT HUMANS
* IN BATS, CATTLE, PIGS, CATS, MINK, BIRDS
* INFECTIONS MAY BE FATAL IF YOUR IMMUNE SYSTEM OVERREACTS



CORONAVIRUS

THE COVID-19 VIRUS HAS CHANGED THE STRUCTURE OF ITS OUTER SPIKE PROTEIN, MAKING IT DIFFICULT FOR CURRENT VACCINES TO PROTECT US FROM BECOMING INFECTED.

THESE MUTATED FORMS OF COV-2 ARE MORE INFECTIOUS THAN THE ORIGINAL CORONAVIRUS AND CAN ALSO BE MORE DEADLY.



CORONAVIRUS

THREE PANDEMICS

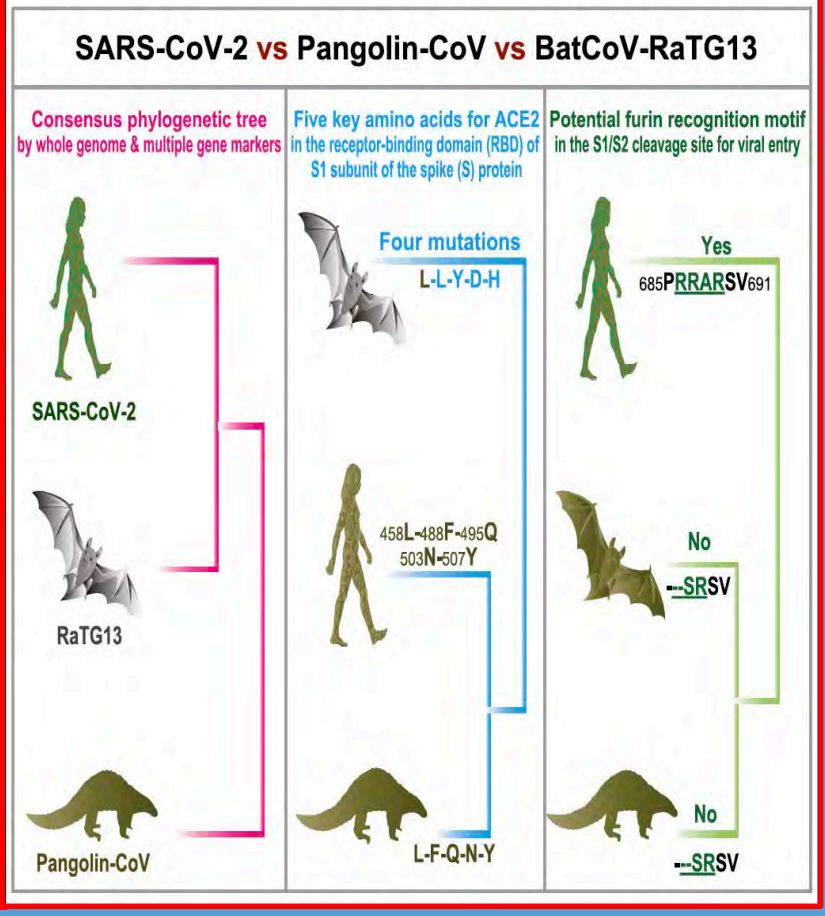
2003 SARS CHINA
SEVERE ACUTE RESPIRATORY SYNDROME

2012 MERS SAUDI ARABIA
MIDDLE EAST RESPIRATORY SYNDROME

2019 SARS-CoV-2 CHINA
SARS CORONAVIRUS-2 2019 = COVID-19

WHERE DID CoV-2 COME FROM ?

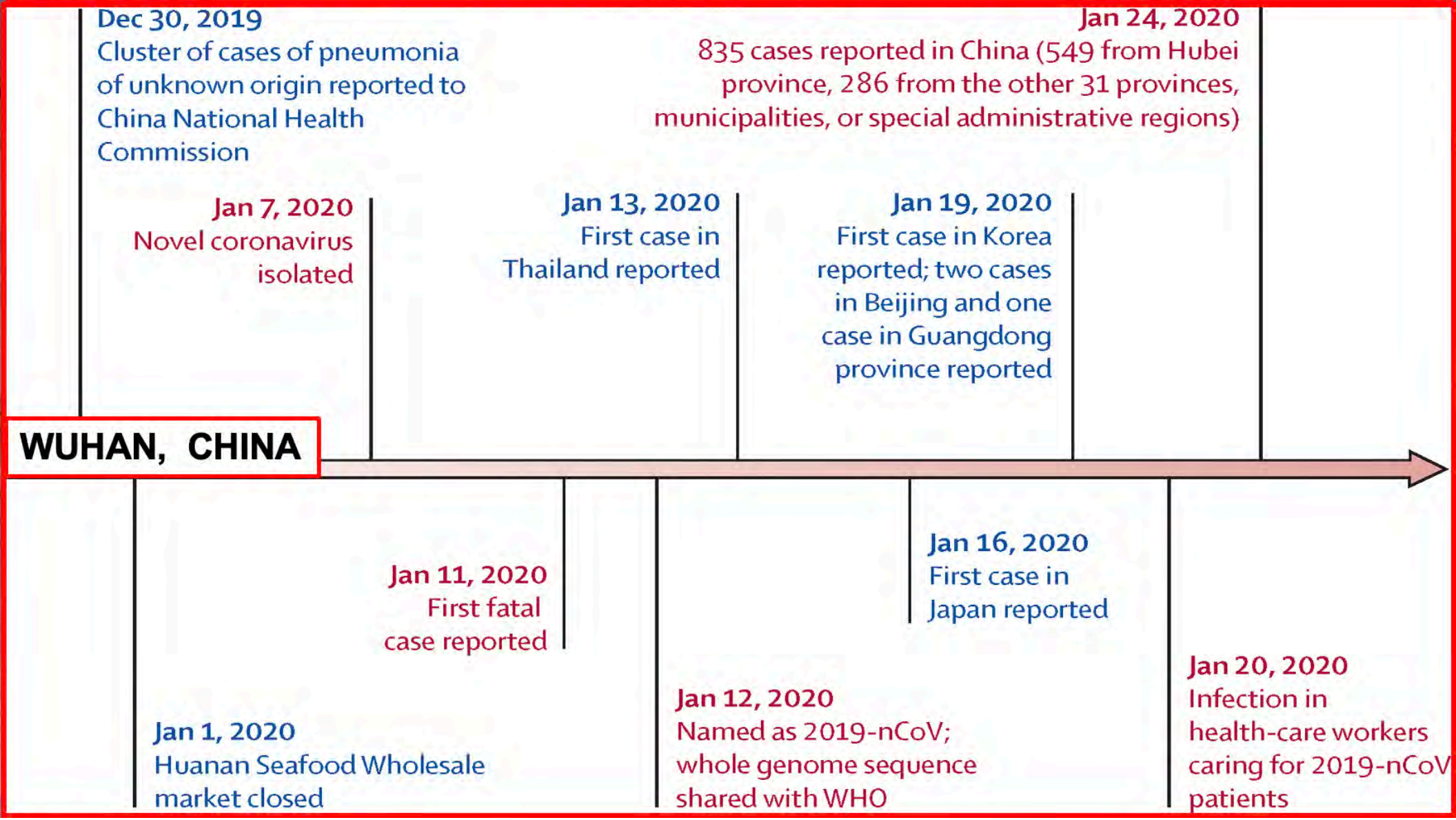
BATS AND PANGOLINS ARE NATURAL RESERVOIRS FOR THE CoV-2 VIRUS, WHICH IS 96% IDENTICAL TO THE BAT VIRUS *BATCOV RATG13*.



Zhang et al., Probable Pangolin Origin of SARS-CoV-2 Associated with the COVID-19 Outbreak, Current Biology 2020. https://doi.org/10.1016/j.cub.2020.03.022

Boni MF et. al. Evolutionary origins of the SARS-CoV-2 sarbecovirus lineage responsible for the COVID-19 pandemic. *Nat Microbiol* (2020). July 28, 2020. https://doi.org/10.1038/s41564-020-0771-4

WHEN DID IT BEGIN TO INFECT HUMANS ?



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IS IT A COLD, ALLERGY OR COVID-19 ?

SYMPTOMS	COMMON COLD	ALLERGY Hay Fever	COVID-19 SARS-CoV-2
RUNNY NOSE SNEEZING SORE THROAT	YES	YES	YES
ITCHING	NO	YES	NO
FEVER > 101^0 F	NO	NO	YES
SHORT OF BREATH	NO	NO	YES
MUSCLE ACHES	NO	NO	YES
COUGH	POSSIBLE	POSSIBLE	YES

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COVID-19 SYMPTOMS

FEVER

COUGH

SINUS PAIN

SORE THROAT

ALTERED TASTE OR SMELL

SHORTNESS OF BREATH

MUSCLE ACHES

NAUSEA + DIARRHEA

HIVES, RED TOES OR FINGERS

STROKE

Kluytmans-van den Bergh M et. al. Prevalence and Clinical Presentation of Health CareWorkers With Symptoms of Coronavirus Disease 2019 in 2 Dutch Hospitals During an Early Phase of the Pandemic. JAMA Network Open. 2020;3(5):e209673. doi:10.1001/jamanetworkopen.2020.9673

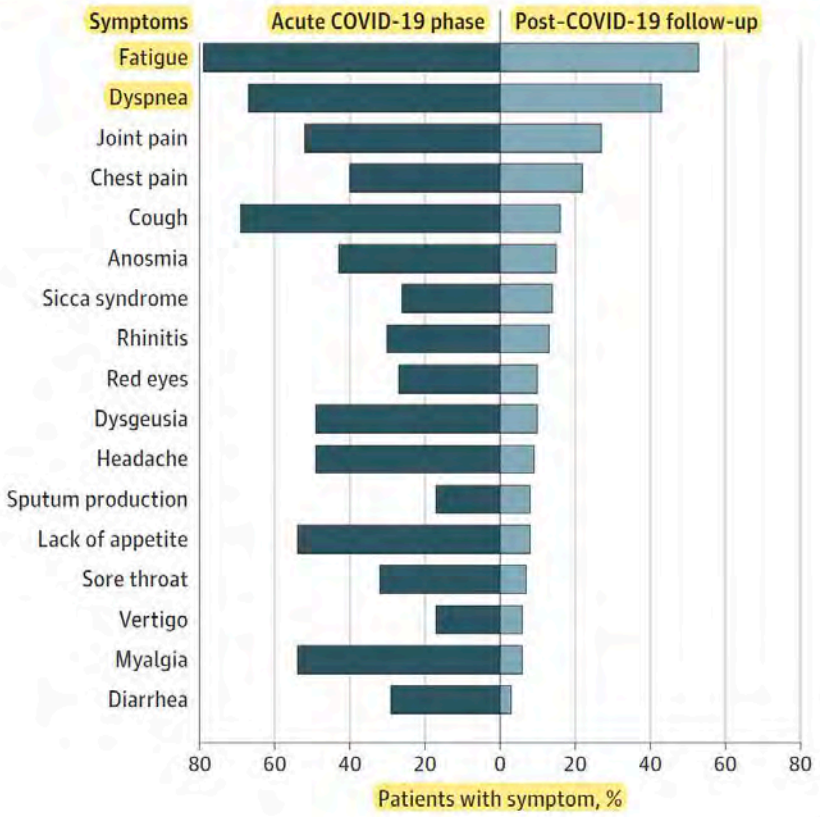
COVID-19 SYMPTOM FREQUENCY

SYMPTOM	% OF PATIENTS
FEVER	64
SINUS PAIN	50
COUGH	46
SMELL ALTERED	44
EXPECTORATION	32
STUFFY NOSE	25
CHILLS	18
FATIGUE	18
SORE THROAT	13
HEADACHE	13
DIFFICULTY BREATHING	11
JOINT or MUSCLE PAIN	10
DIARRHEA	6
VOMITING	3

Barnes M, Sax P. Challenges of "Return to Work" in an Ongoing Pandemic. NEJM 2020. June 18. DOI: 10.1056/NEJMsr2019953

CHRONIC COVID-19

Figure. COVID-19–Related Symptoms



60 DAYS AFTER ONSET OF CoV-2 INFECTION ONLY 13% OF PATIENTS WERE FREE OF SYMPTOMS.

87 % OF PATIENTS REPORTED PERSISTENT DECREASES IN THEIR QUALITY OF LIFE

FATIGUE
and
SHORTNESS OF BREATH

Carfì A, Bernabei R, Landi F. Persistent Symptoms in Patients After Acute COVID-19. *JAMA.* Published online July 09, 2020. doi:10.1001/jama.2020.12603

SILENT SPREADERS

30% - 43 % OF PEOPLE

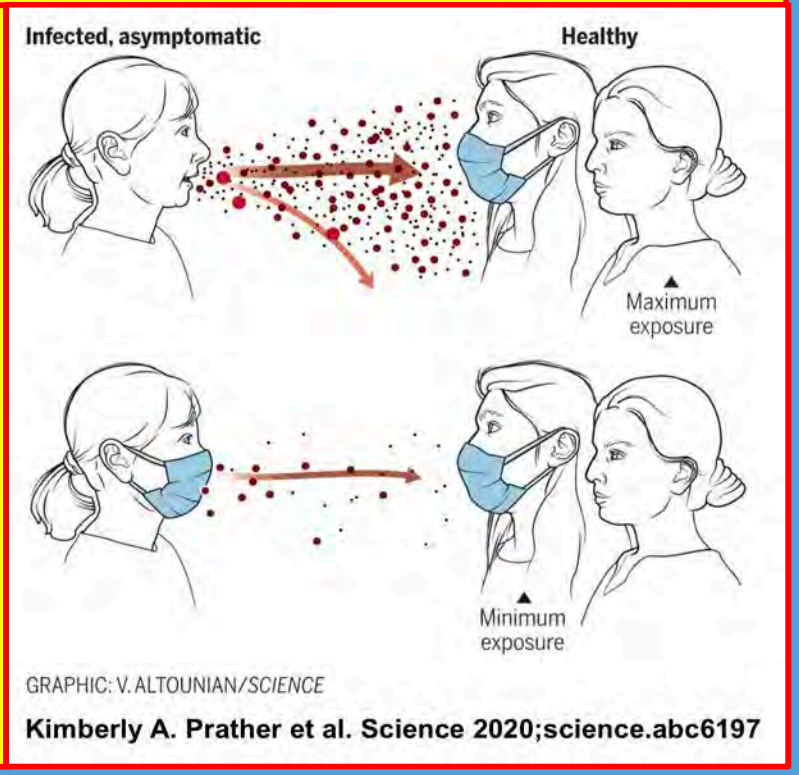
INFECTED ARE

SILENT SPREADERS

WITH NO SYMPTOMS.

YOU MUST ASSUME

EVERYONE IS INFECTED.



Yang R et. al. Comparison of Clinical Characteristics of Patients with Asymptomatic vs Symptomatic Coronavirus Disease 2019 in Wuhan, China. JAMA Network Open. 2020;3(5):e2010182. doi:10.1001/jamanetworkopen.2020.10182

Arons M et. al. Presymptomatic SARS-CoV-2 Infections and Transmission in a Skilled Nursing Facility. N Engl J Med 2020;382:2081-90. DOI: 10.1056/NEJMoa2008457

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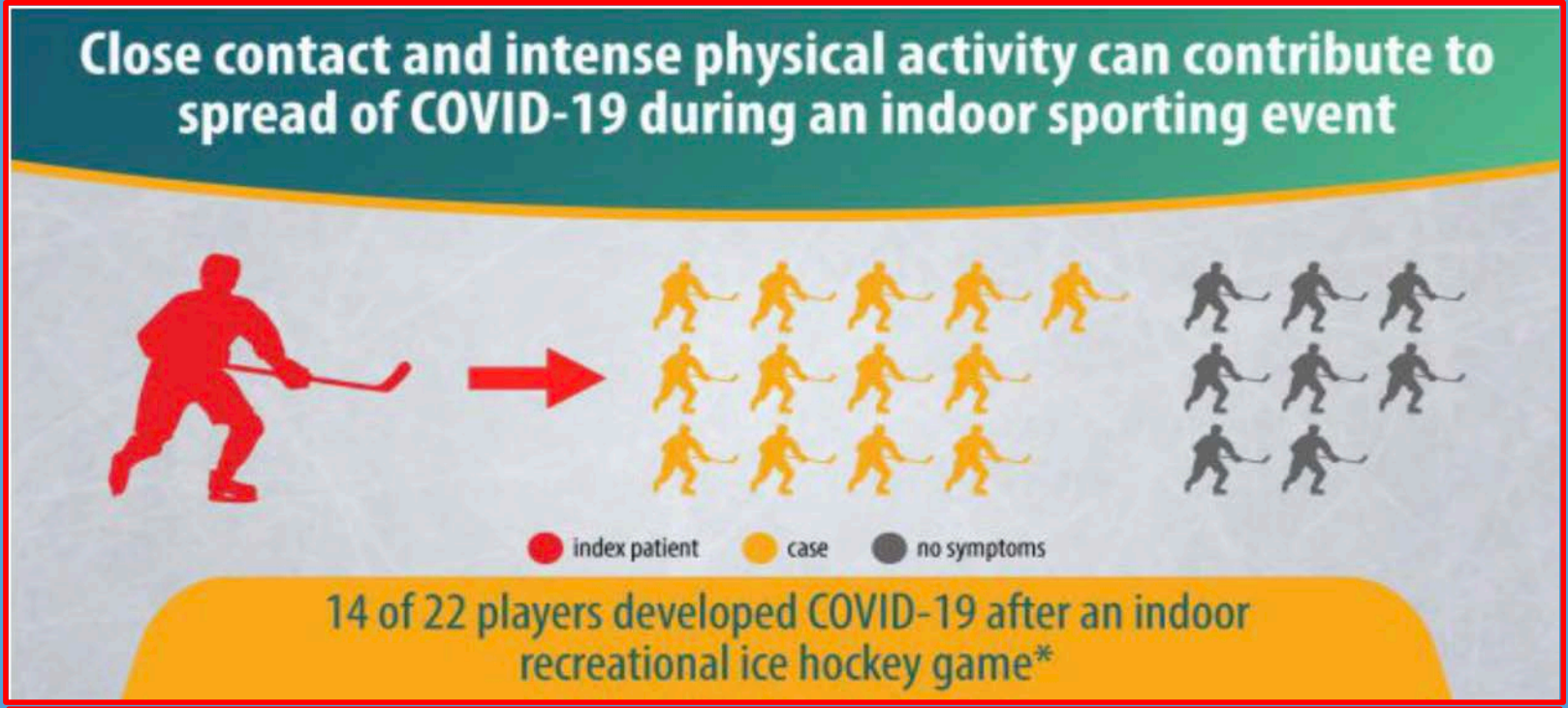
SILENT SPREADERS

CAUSE MORE THAN 50% OF NEW INFECTIONS

1. **SILENT DISEASE TRANSMISSION IN THE PRESYMPTOMATIC AND ASYMPTOMATIC STAGES IS RESPONSIBLE FOR MORE THAN 50% OF THE OVERALL ATTACK RATE IN COVID–19 OUTBREAKS.**
2. **EVEN IF ALL SYMPTOMATIC CASES ARE ISOLATED, A VAST OUTBREAK MAY STILL OCCUR.**
3. **TO BRING AN OUTBREAK BELOW 1% OF THE POPULATION, OVER 1/3 OF ALL SILENT INFECTIONS MUST BE ISOLATED.**
4. **SYMPTOM - BASED ISOLATION MUST BE COMBINED WITH RAPID CONTACT TRACING AND TESTING TO IDENTIFY ASYMPTOMATIC AND PRESYMPTOMATIC CASES BEFORE LIFTING RESTRICTIONS.**

Moghadas S. et. al. The implications of silent transmission for the control of COVID-19 outbreaks. PNAS Jul 2020, 202008373; DOI: 10.1073/pnas.2008373117

INDOOR SUPER SPREADING

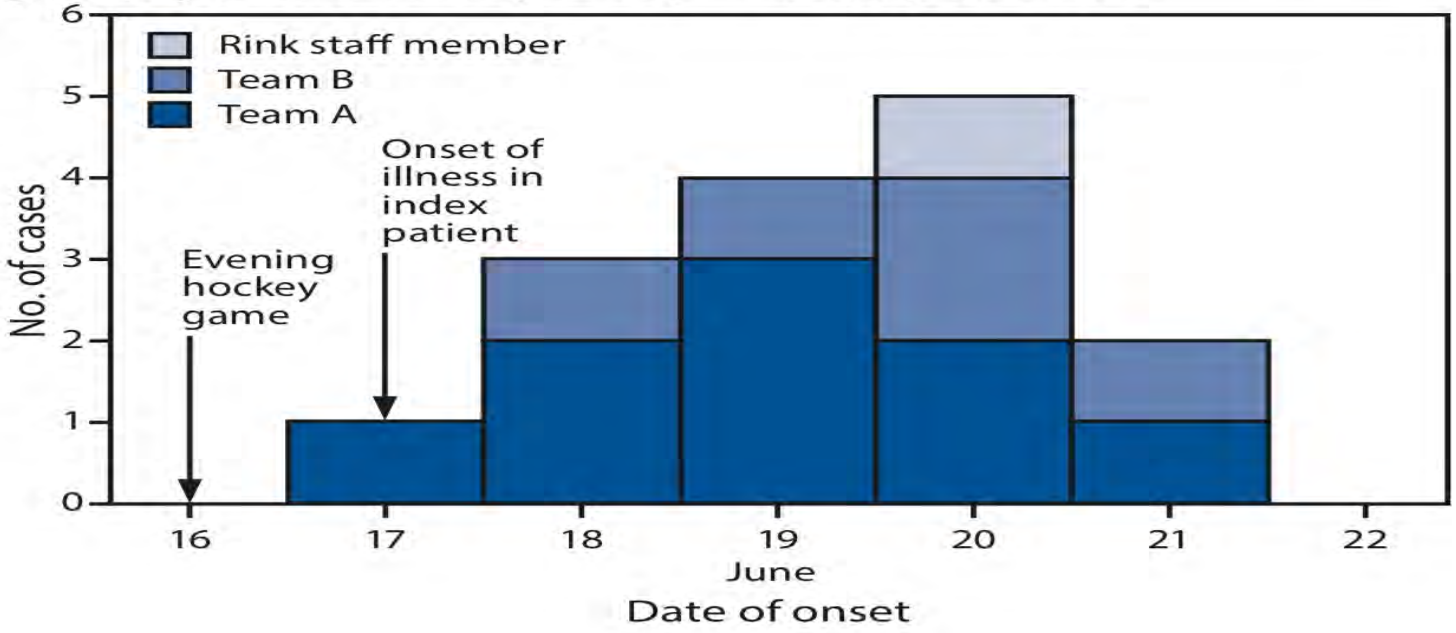


INDOOR ATHLETIC EVENTS PROVIDE A PERFECT ENVIRONMENT TO SPREAD THE COVID-19 VIRUS

Atrubin D, Wiese M, Bohinc B. An Outbreak of COVID-19 Associated with a Recreational Hockey Game — Florida, June 2020. MMWR Morb Mortal Wkly Rep 2020;69:1492–1493. DOI: http://dx.doi.org/10.15585/mmwr.mm6941a4external icon

INDOOR SUPER SPREADING

FIGURE. COVID-19 cases associated with a recreational ice hockey game, by date of onset (N = 15) — Florida, June 2020



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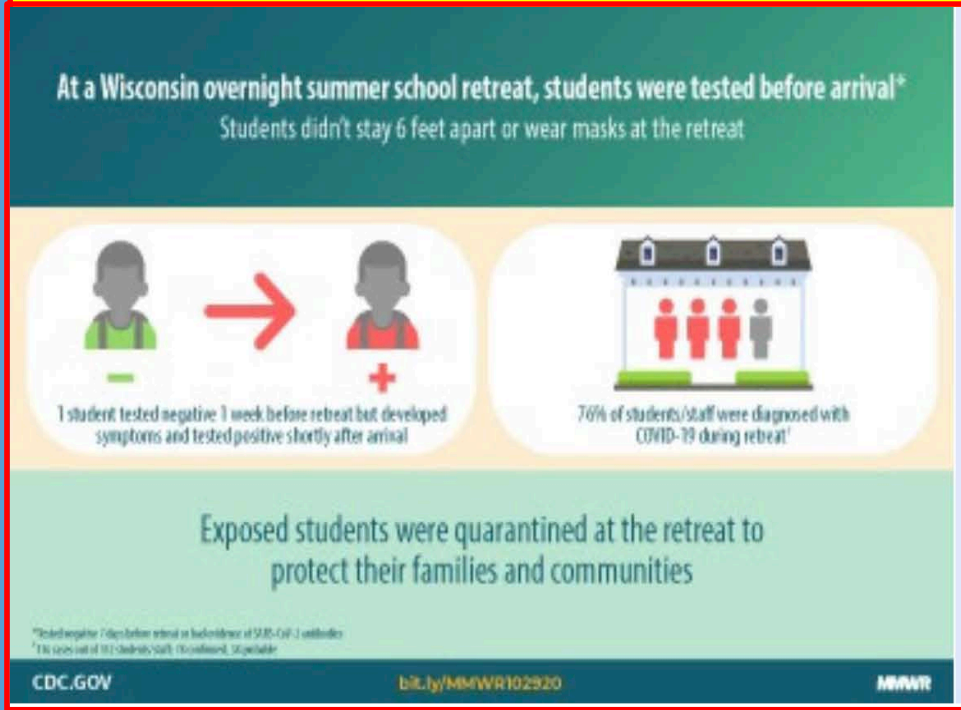
INDOOR SUPER SPREADING



COVID-19 Outbreak at an Overnight Summer School Retreat — Wisconsin, July-August 2020

During July 2-August 11, 2020, a COVID-19 outbreak at an overnight high school retreat likely began with a single student who had received a negative SARS-CoV-2 molecular test result <1 week before the retreat.

SARS-CoV-2 can spread rapidly among adolescents and young adults in a congregate setting with inadequate COVID-19 mitigation measures.

COVID-19 Outbreak at an Overnight Summer School Retreat — Wisconsin, July–August 2020. *Weekly* / October 30, 2020 / 69(43);1600–1604

MASKS PREVENT TRANSMISSION

Van Dyke ME, Rogers TM, Pevzner E, et al. Trends in County-Level COVID-19 Incidence in Counties With and Without a Mask Mandate — Kansas, June 1–August 23, 2020. MMWR Morb Mortal Wkly Rep. ePub: 20 November 2020. DOI: http://dx.doi.org/10.15585/mmwr.mm6947e2

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MASKS PREVENT TRANSMISSION

" AT THIS CRITICAL JUNCTURE
WHEN COVID-19 IS RESURGING, BROAD ADOPTION
OF CLOTH FACE COVERINGS IS A CIVIC DUTY,
A SMALL SACRIFICE RELIANT ON A HIGHLY EFFECTIVE
LOW - TECH SOLUTION THAT CAN HELP
TURN THE TIDE FAVORABLY IN NATIONAL
AND GLOBAL EFFORTS AGAINST COVID-19. "

Brooks JT, Butler JC, Redfield RR. Universal Masking to Prevent SARS-CoV-2 Transmission—The Time Is Now. *JAMA.* Published online July 14, 2020. doi:10.1001/jama.2020.13107

FECAL TRANSMISSION

43% OF COVID-19 INFECTED PATIENTS (934 / 2,149)

HAD COV-2 VIRUS IN STOOL SAMPLES FOR UP TO

70 DAYS AFTER SYMPTOM ONSET.

ASSUME ALL PUBLIC TOILETS ARE CONTAMINATED

van Doorn, AS, Meijer, B, Frampton, CMA, Barclay, ML, de Boer, NKH. Systematic review with meta-analysis: SARS-CoV-2 stool testing and the potential for faecal-oral transmission. *Aliment Pharmacol Ther.* 2020; 00: 1– 13. https://doi.org/10.1111/apt.16036

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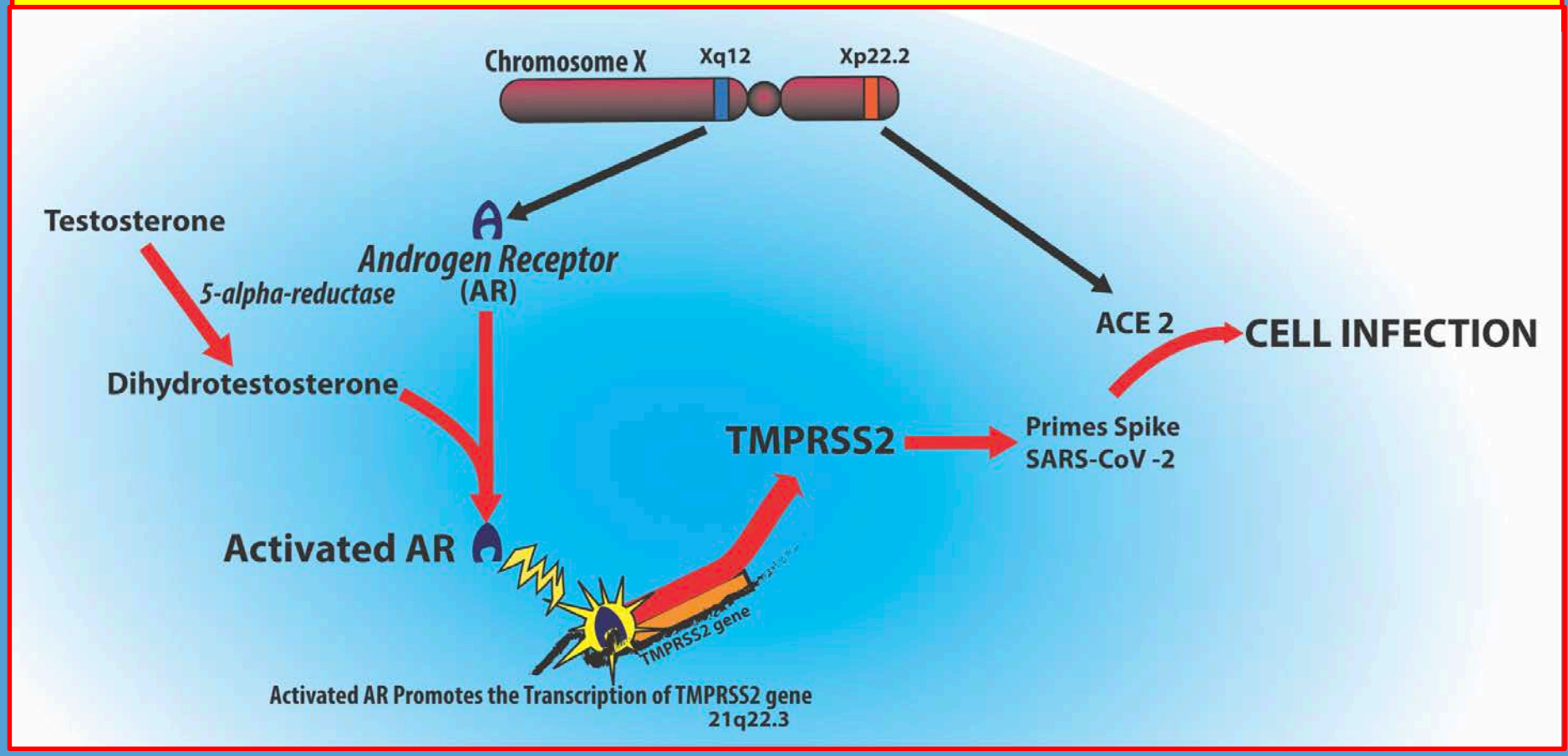
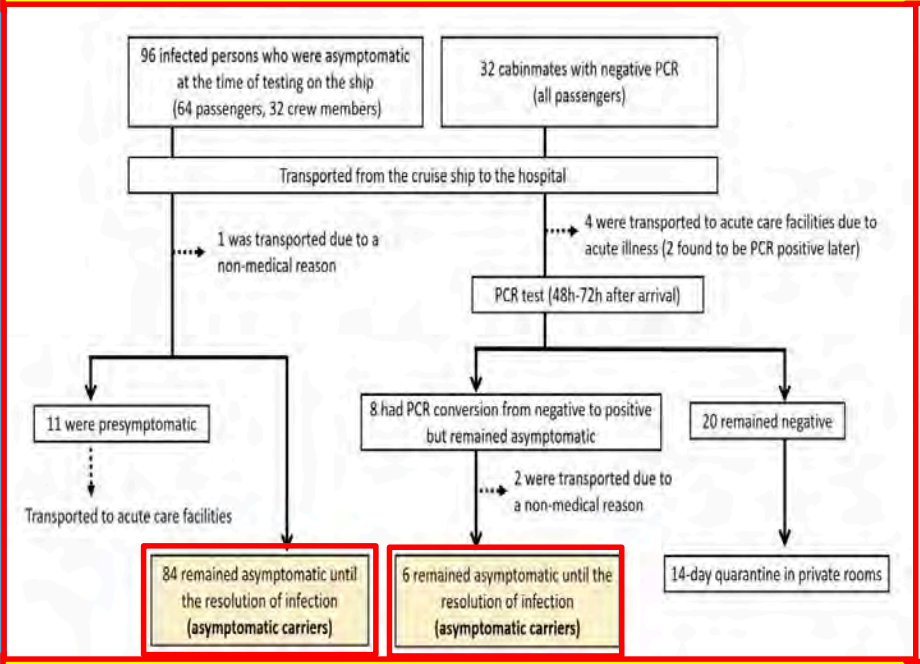
CoV-2 INFECTS MEN > WOMEN

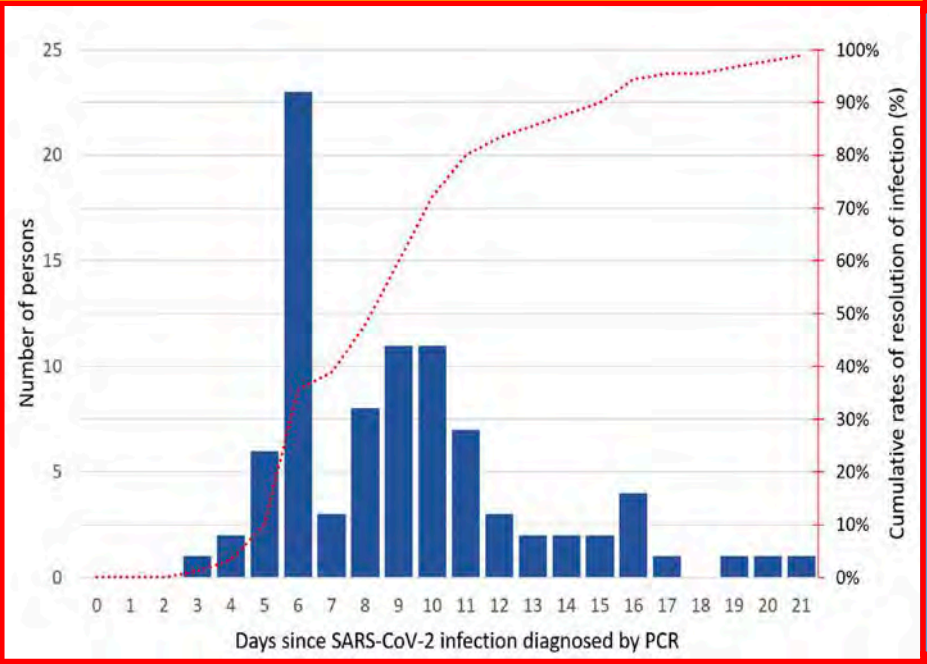


Wambier CG, Goren A, SARS-COV-2 infection is likely to be androgen mediated, J Am Acad Derm (2020). doi: https://doi.org/10.1016/ j.jaad.2020.04.032

THE COVID CRUISE SHIP

90 OF 104 INFECTED PASSENGERS REMAINED ASYMPTOMATIC





" THE MAJORITY OF ASYMPTOMATICALLY INFECTED PERSONS REMAINED ASYMPTOMATIC THROUGHOUT THE COURSE OF THE INFECTION. "

Sakurai A, Sasaki T, Kato S, et al. Natural history of asymptomatic SARS-CoV-2 infection. N Engl J Med. DOI: 10.1056/NEJMc2013020

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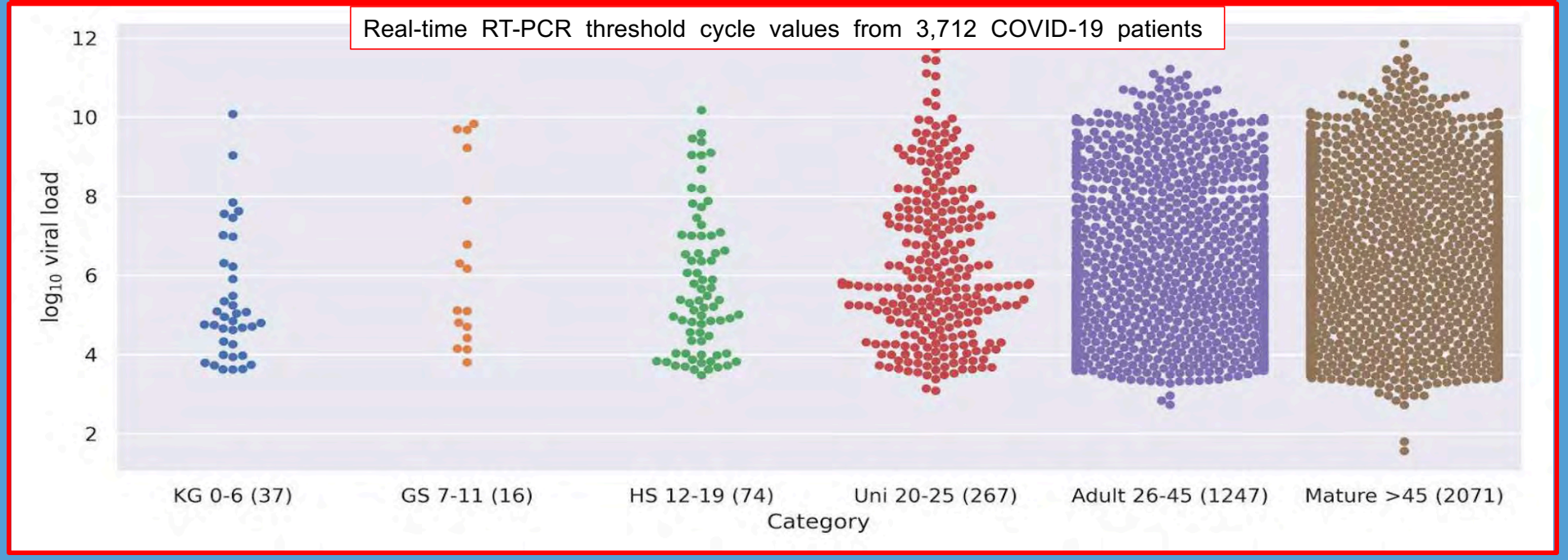
CoV-2 INFECTS CHILDREN + ADULTS

" VIRAL LOADS IN THE VERY YOUNG DO NOT DIFFER SIGNIFICANTLY FROM THOSE OF ADULTS. WE HAVE TO CAUTION AGAINST AN UNLIMITED RE-OPENING OF SCHOOLS AND KINDERGARTENS IN THE PRESENT SITUATION. CHILDREN MAY BE AS INFECTIOUS AS ADULTS. "



Jones T, Drosten C. et. al. An analysis of SARS-CoV-2 viral load by patient age.
https://zoonosen.charite.de/fileadmin/user_upload/microsites/m_cc05/virologie-ccm/dateien_upload/Weitere_Dateien/analysis-of-SARS-CoV-2-viral-load-by-patient-age.pdf

ASYMPTOMATIC CHILDREN

" SARS-CoV-2 Infection in Children "
New England Journal of Medicine April 23, 2020

" OF THE 1,391 CHILDREN ASSESSED AND TESTED FROM JANUARY 28 THROUGH FEBRUARY 26, 2020, A TOTAL OF 171 (12.3%) WERE CONFIRMED TO HAVE SARS - COV-2 INFECTION. "

"A TOTAL OF 27 PATIENTS (15.8%) DID NOT HAVE ANY SYMPTOMS OF INFECTION OR RADIOLOGIC FEATURES OF PNEUMONIA." [1]

ASYMPTOMATIC INFECTIONS IN CHILDREN ARE COMMON. [2]

1. Lu X. et. al. SARS-CoV-2 Infection in Children. NEJM 382;17. April 23, 2020.
2. Wu Z, McGoogan JM. Characteristics of and important lessons from the coronavirus disease 2019 (COVID-19) outbreak in China: summary of a report of 72,314 cases from the Chinese Center for Disease Control and Prevention. JAMA 2020 February 24.

ASYMPTOMATIC CHILDREN

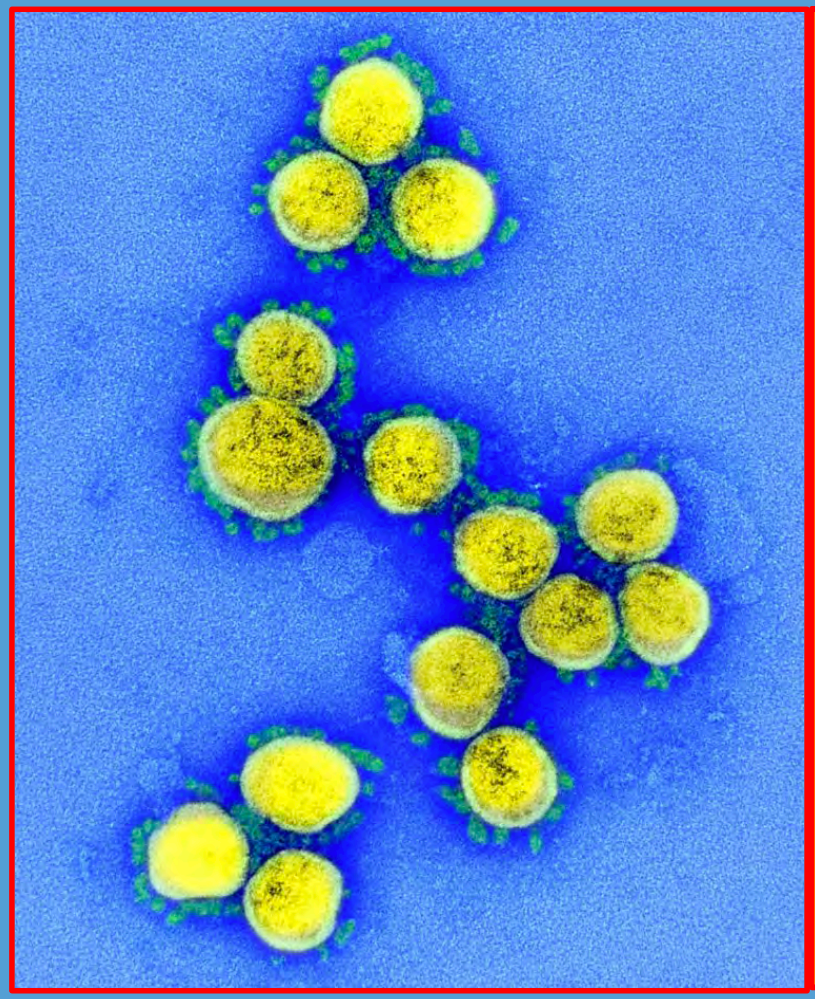
582 INDIVIDUALS WITH PCR - CONFIRMED COV-2 INFECTIONS WERE STUDIED IN 82 EUROPEAN MEDICAL CENTERS.

16% OF INFECTED CHILDREN WERE ASYMPTOMATIC.

" THIS STUDY CONFIRMS PREVIOUS REPORTS FROM CHINA SUGGESTING THAT THE CASE - FATALITY RATE OF COVID-19 IN CHILDREN IS SUBSTANTIALLY LOWER THAN IN OLDER ADULT PATIENTS.

HOWEVER, SOME CHILDREN DEVELOP SEVERE DISEASE AND REQUIRE PROLONGED INTENSIVE CARE SUPPORT… "

Gotzinger F. et. al. COVID-19 in children and adolescents in Europe: a multinational, multicentre cohort study. Lancet Child Adolesc Health 2020. June 25, 2020. https://doi.org/10.1016/S2352-4642(20)30177-2



HOW CAN YOU AVOID COVID-19 INFECTIONS ?

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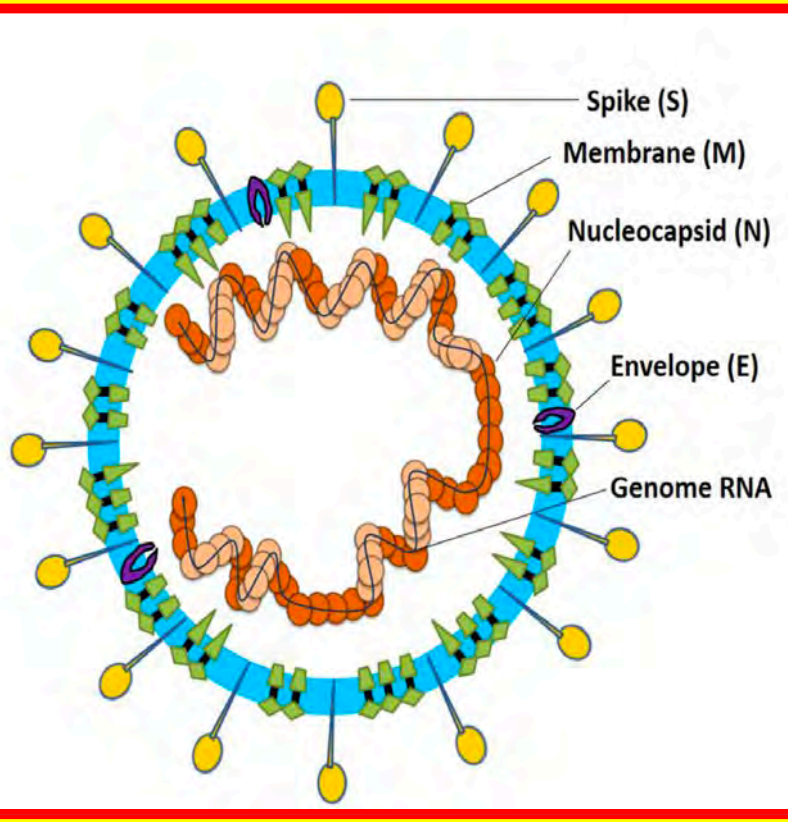
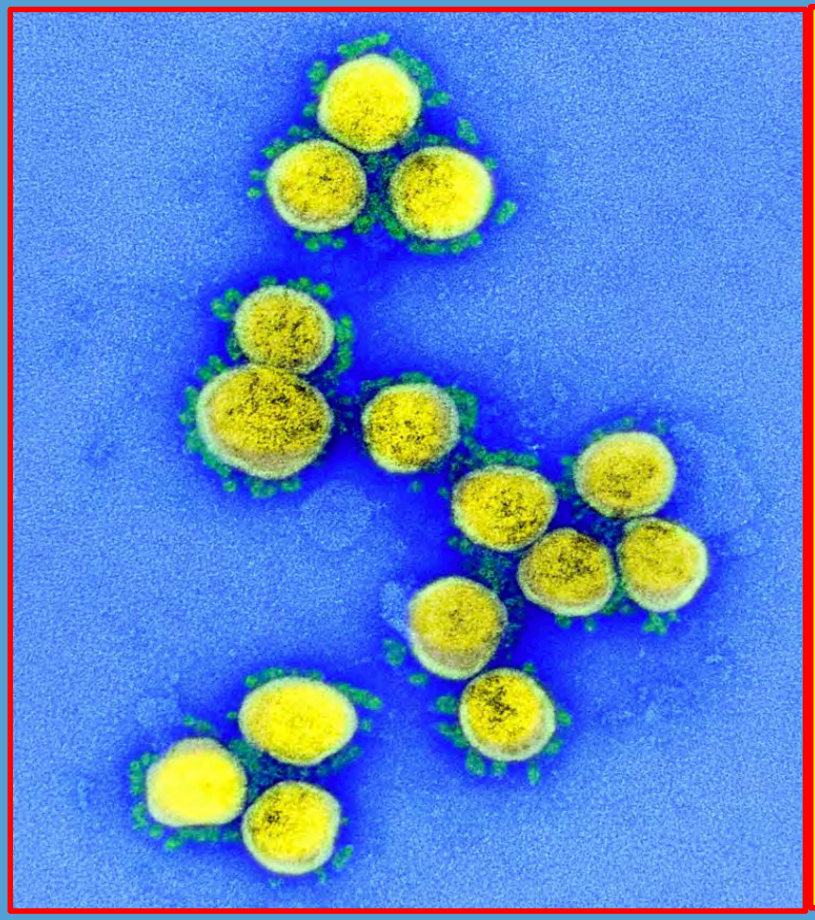
HOW TO AVOID CoV-2

1. WASH YOUR HANDS OFTEN
2. DO NOT TOUCH YOUR FACE
3. ALWAYS WEAR FACE MASK IN PUBLIC
4. AVOID CLOSE ENCOUNTERS 6 Feet from Others
5. THROW YOUR COLD AWAY Kleenex® tissues
6. DISINFECT YOUR HOME Toilet + Bathroom
7. STAY HOME + AVOID CROWDS



AVOIDANCE IS TREATMENT OF CHOICE



HOW DOES CoV-2 INFECT CELLS ?

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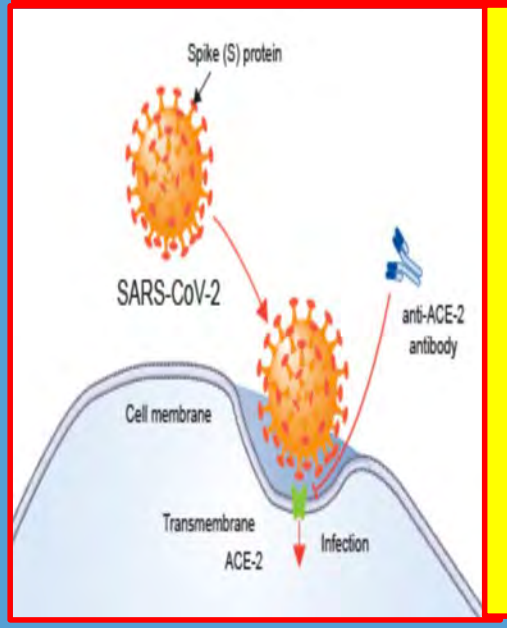
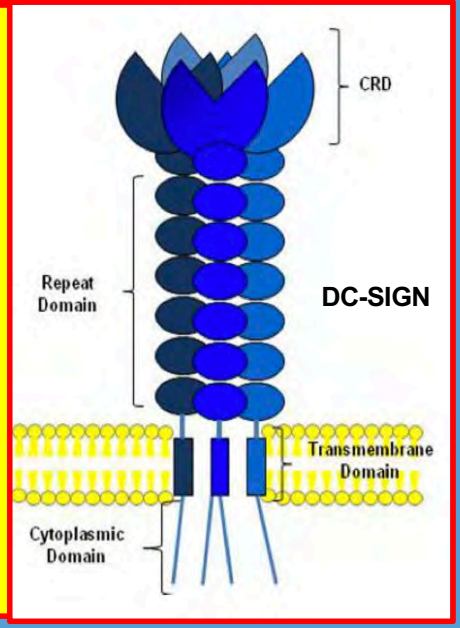
CoV-2 VIRUS ENTERS CELLS VIA ACE-2 + CD209 + TASTE RECEPTORS



THE SARS SPIKE PROTEIN BINDS TO ACE-2 RECEPTORS [1] IN HUMAN LUNG, HEART, BLOOD VESSELS, SKIN, KIDNEY, INTESTINES AND LIVER AFTER BEING PROCESSED BY A SERINE PROTEASE ENZYME TMPRSS2. [2]

INFECTIONS MAY BE INHIBITED BY ANTI-ACE-2 RECEPTOR ANTIBODIES.

CoV-2 SPIKE PROTEINS BIND TO DC-SIGN / CD209 AND TASTE RECEPTORS. [3, 4, 5]



1. Li W. et. al. Angiotensin-converting enzyme 2 is a functional receptor for the SARS coronavirus, Nature 426, 450-454 (2003).
2. Zhou Y, et. al. Protease inhibitors targeting coronavirus and filovirus entry. Viral Research 2015;116:76-84. https://doi.org/10.1016/j.antiviral.2015.01.011
3. Workman AD et. al. (2015) "The Role of Bitter and Sweet Taste Receptors in Upper Airway Immunity " Curr Allergy Asthma Rep. December; 15(12): 72. doi:10.1007/s11882-015-0571-8.
4. Marzi A. et. al. DC-SIGN and DC-SIGNR Interact with the Glycoprotein of Marburg Virus and the S Protein of Severe Acute Respiratory Syndrome Coronavirus. J Virol. 2004 Nov; 78(21): 12090–12095. doi: 10.1128/JVI.78.21.12090-12095.2004.
5. Jeffers S.A. et. al. (2006) Human Coronavirus 229E can Use CD209L (L-Sign) to Enter Cells. In: Perlman S., Holmes K.V. (eds) The Nidoviruses. Advances in Experimental Medicine and Biology, vol 581. Springer, Boston, MA

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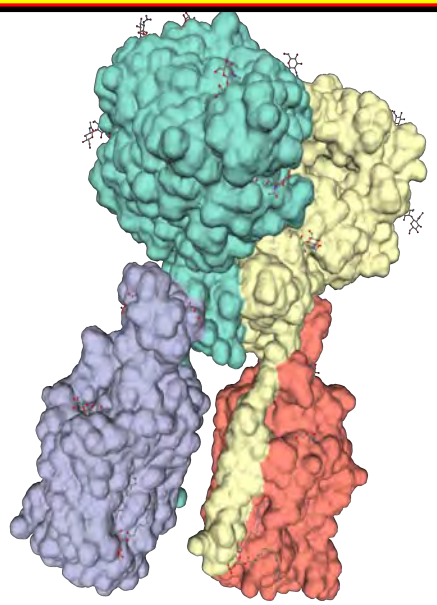
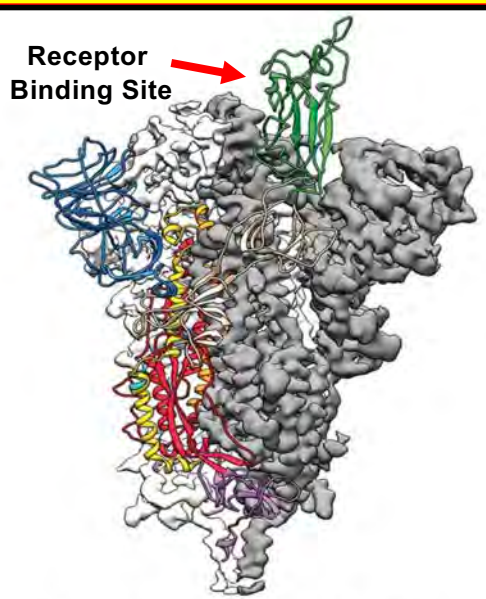
SPIKE PROTEINS BIND
ACE-2 AND C-LECTINS CD209 / DC-SIGN

IN RESPIRATORY + INTESTINAL + CARDIAC + NERVE + RENAL CELLS



ACE-2 Receptor



CoV-2 Spike

CD209 / DC-SIGN

Wrapp D et. al. Cryo-EM structure of the 2019-nCoV spike in the prefusion conformation. Science (2020) 367(6483):1260-1263. Spike.
https://swissmodel.expasy.org/repository/uniprot/Q9BYF1 ACE2. https://swissmodel.expasy.org/repository/uniprot/Q9NNX6 CD209 – DC-SIGN.
Chiodo F. et. al. Novel ACE2-Independent Carbohydrate-Binding of SARS-CoV-2 Spike Protein to Host Lectins and Lung Microbiota.
bioRxiv 2020.05.13.092478; doi: https://doi.org/10.1101/2020.05.13.092478

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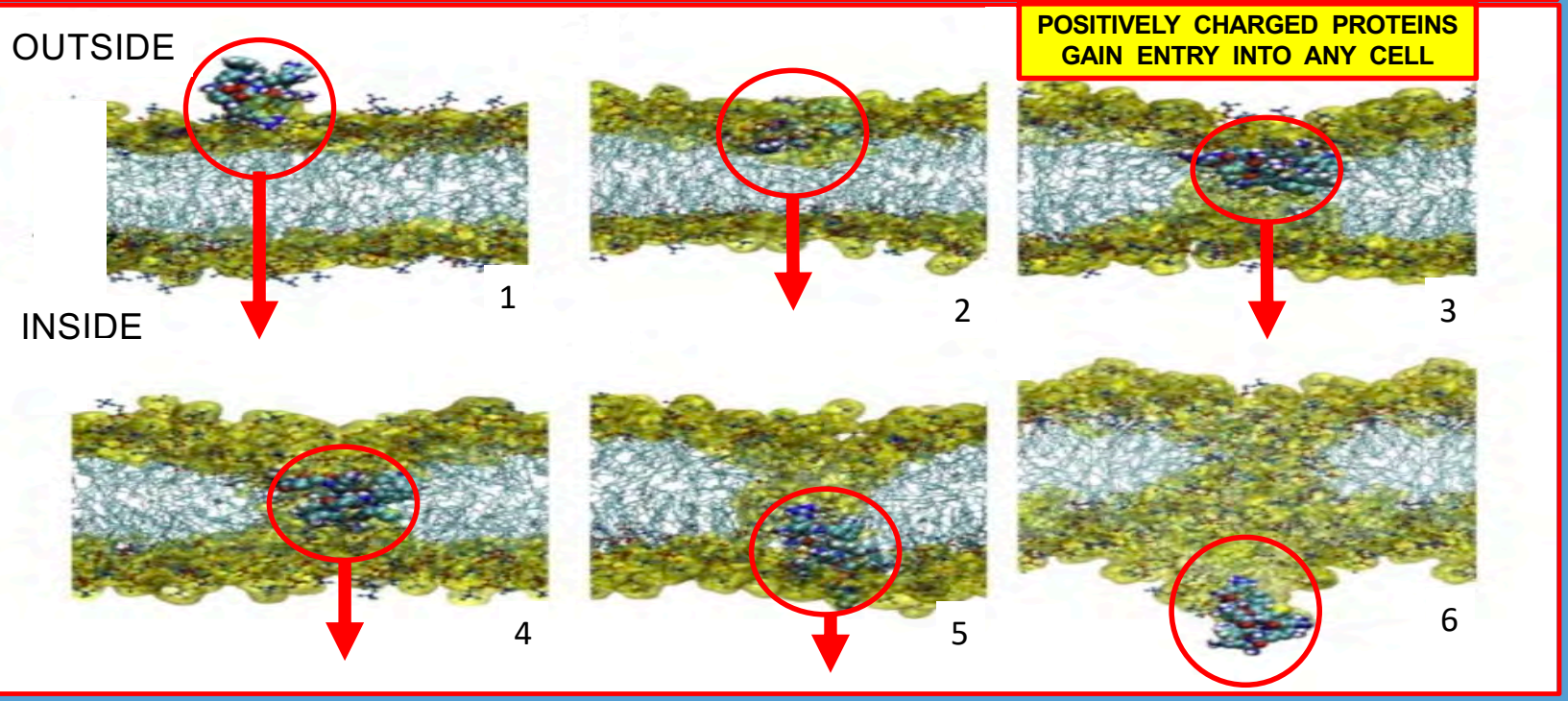
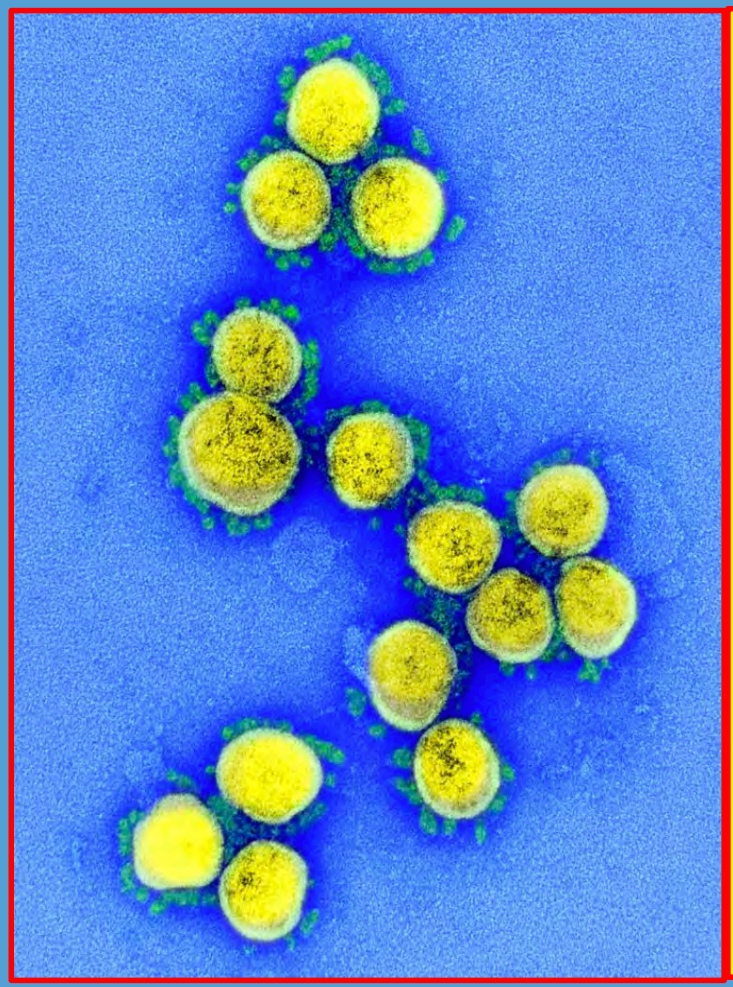
COV-2 SPIKE PROTEIN
IS HIGHLY POSITIVELY CHARGED
CoV-2 VIRUS CAN ENTER ANY CELL IN HUMAN BODY



Yesylevskyy S, Marrink SJ and Mark AE, (2009) "Alternative Mechanisms for the interaction of the Cell-Penetrating Peptides Penetration and the TAT Peptide with Lipid Bilayers", Biophysical Journal, Volume 97 July 2009, DOI:10.1016/j.bpj.2009.03.059



WHAT HAPPENS INSIDE INFECTED PATIENTS ?

https://www.flickr.com/photos/niaid/49645120251/in/album-72157712914621487

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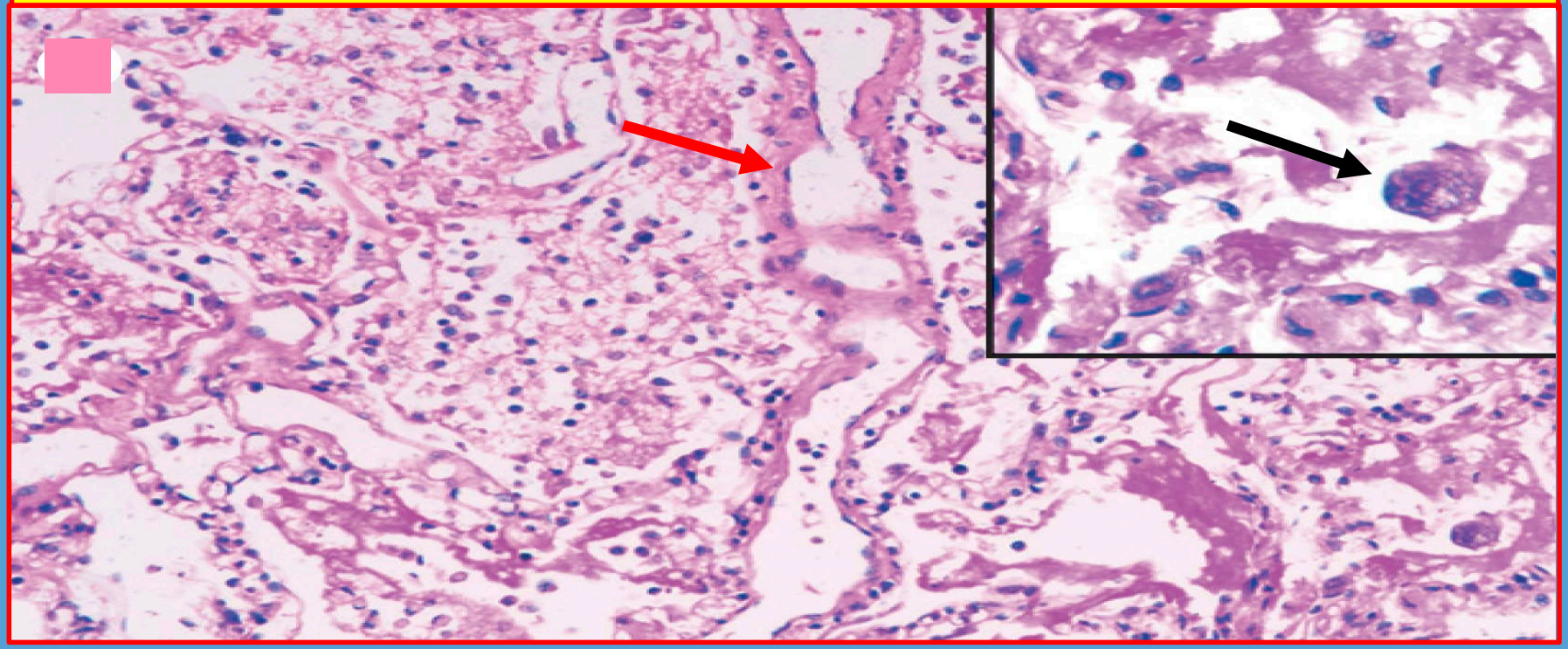
SARS-CoV-2 IN LUNGS

DESQUAMATION OF PNEUMOCYTES →

HYALINE MEMBRANE FORMATION →



Wu Z et. al. Pathological findings of COVID-19 associated with acute respiratory distress syndrome. Lancet Respir Med. 2020;8:420-22.
https://doi.org/10.1016/S2213-2600(20)30076-X

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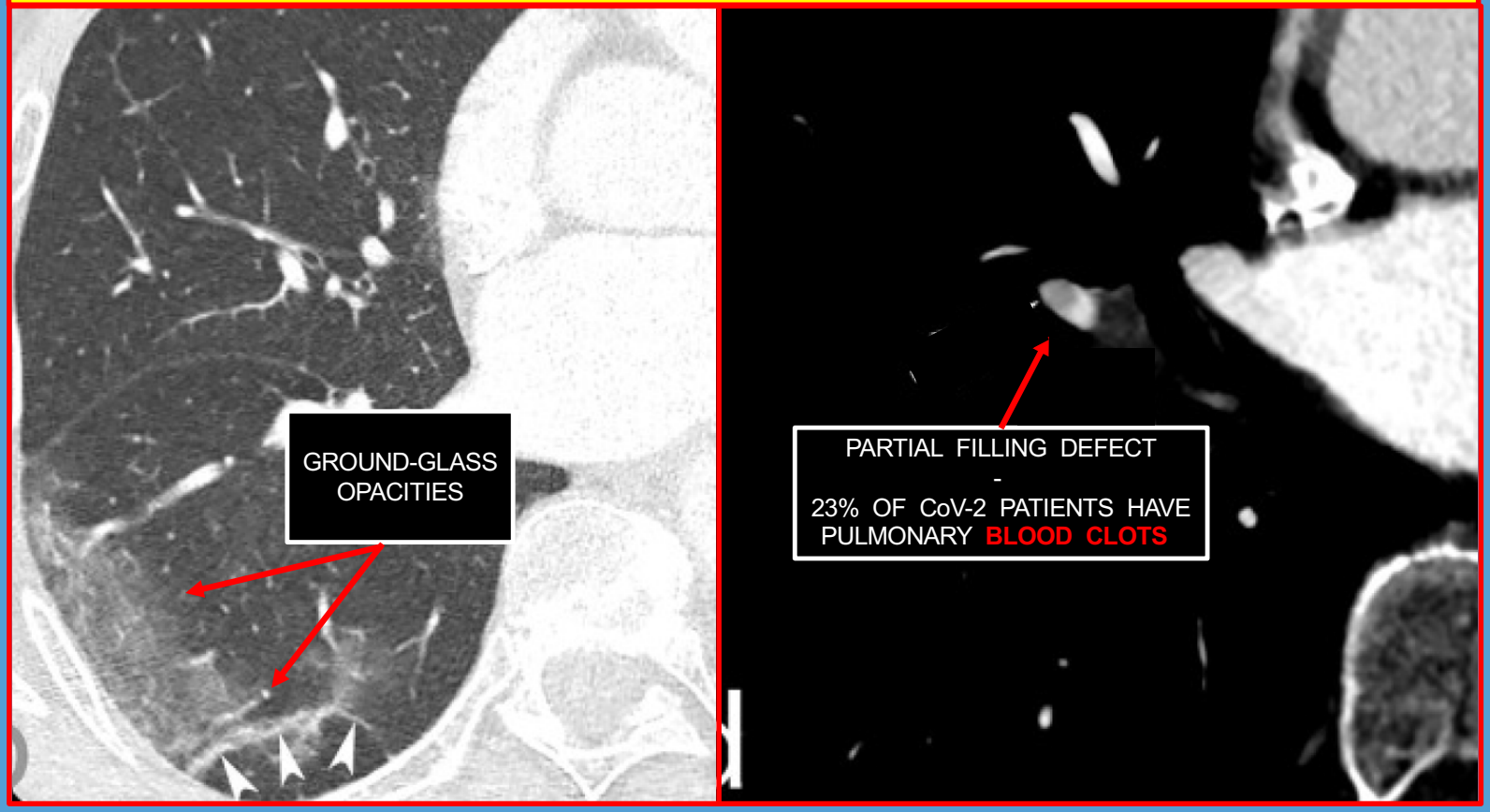
SARS-CoV-2 IN LUNGS

PULMONARY EMBOLI + ALVEOLAR BLOOD CLOTS



Rotzinger D et. al. Pulmonary embolism in patients with COVID-19: Time to change the paradigm of computed tomography Thromb Res. 2020 Jun; 190: 58–59. doi: 10.1016/j.thromres.2020.04.011

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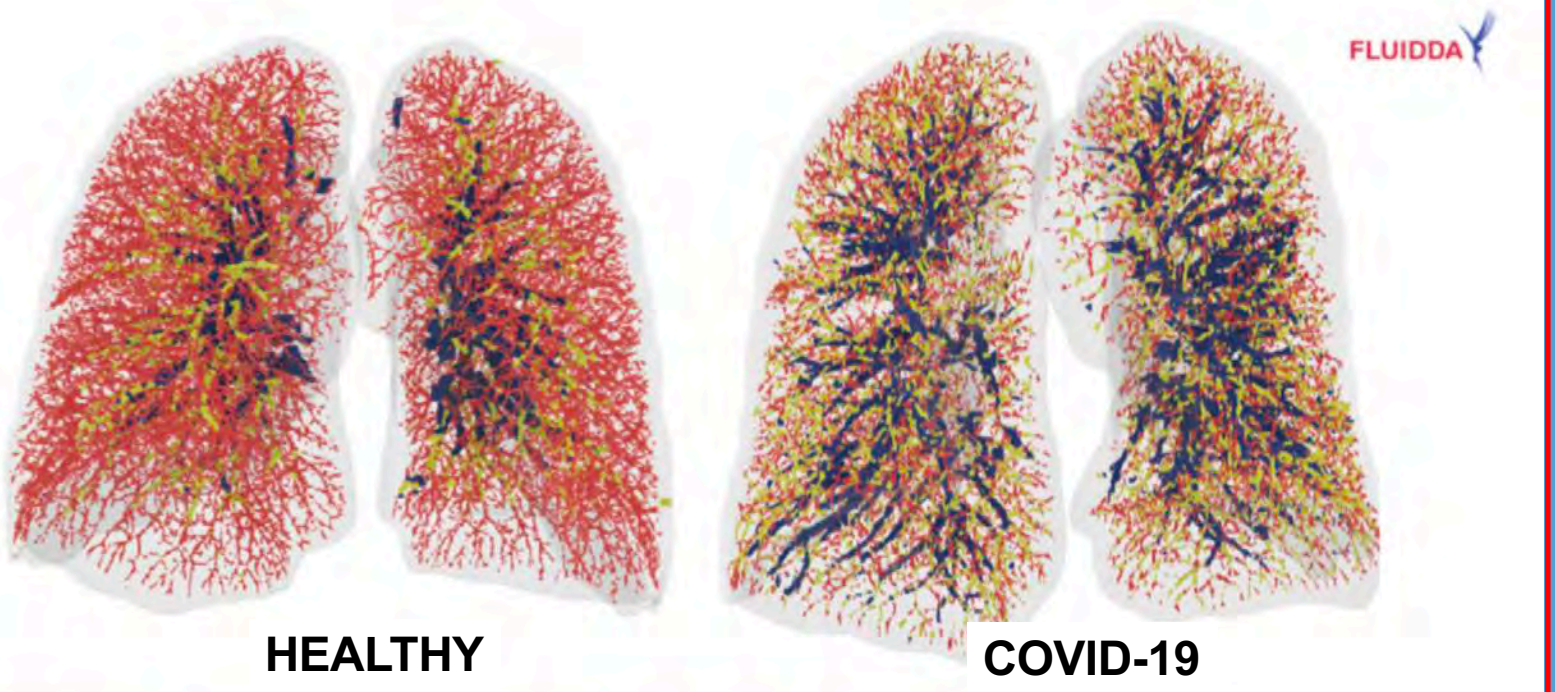
SARS-CoV-2 IN LUNGS



BLOOD VESSELS (red) **ARE DEPLETED IN COVID-19 LUNGS** right
HEALTHY LUNGS left

https://emcrit.org/wp-content/uploads/2020/05/Fluidda-Data.pdf

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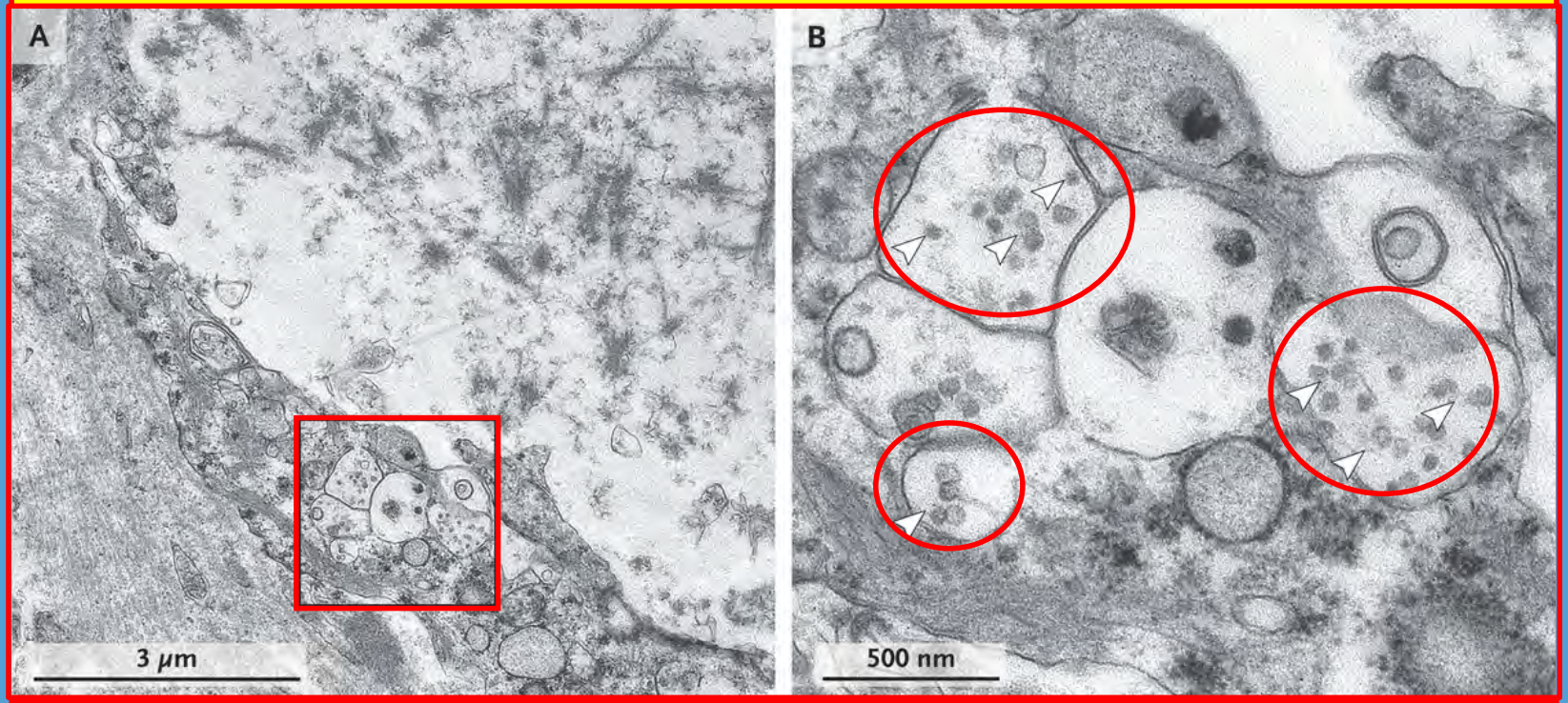
SARS-CoV-2 IN LUNGS

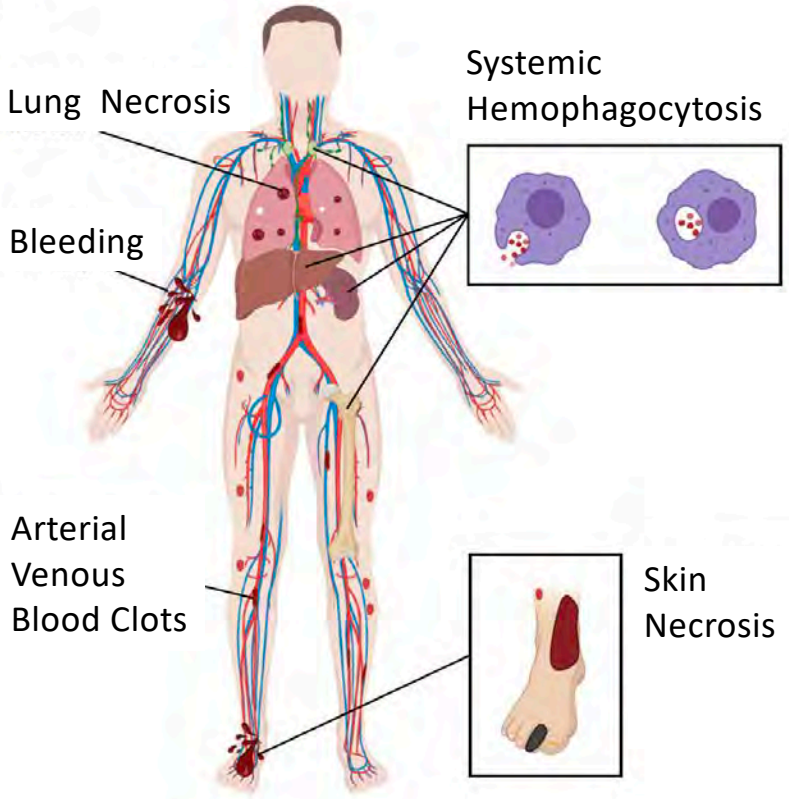


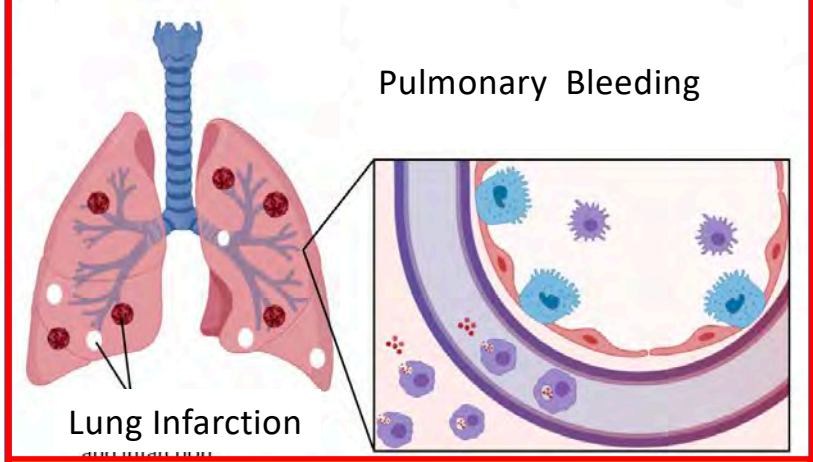
Virus Particles in Lung Endothelial Cells

Ackermann M. et. al. Pulmonary Vascular Pathology in Covid-19. N Engl J Med 2020. DOI: 10.1056/NEJMc2022068

SARS-CoV-2 IN LUNGS

LIFE - LONG PULMONARY CHANGES

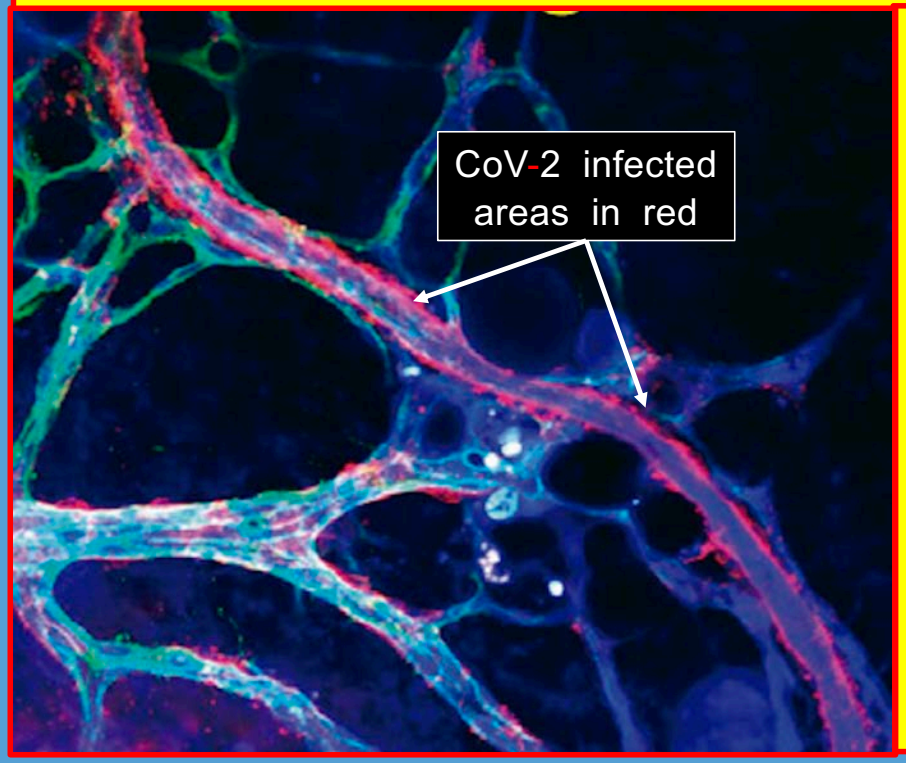




"We believe that this pulmonary intravascular coagulopathy, or pulmonary immunovascular coagulopathy, is the best explanation for the COVID-19 pneumonia risk factors for poor survival …"

McDonagle D. et. al. Immune mechanisms of pulmonary intravascular coagulopathy in COVID-19 pneumonia. Lancet Rheumatol 2020. https://doi.org/10.1016/S2665-9913(20)30121-1

SARS-CoV-2 IN BLOOD VESSELS



THE SARS-CoV-2 VIRUS INFECTS CELLS INSIDE HUMAN BLOOD VESSLES.

BLOOD CLOTS OCCUR AS BLOOD VESSELS BECOME INFLAMMED.

Monteil et al., Inhibition of SARS-CoV-2 Infections in Engineered Human Tissues Using Clinical-Grade Soluble Human ACE2. Cell (2020)
https://doi.org/10.1016/j.cell.2020.04.004

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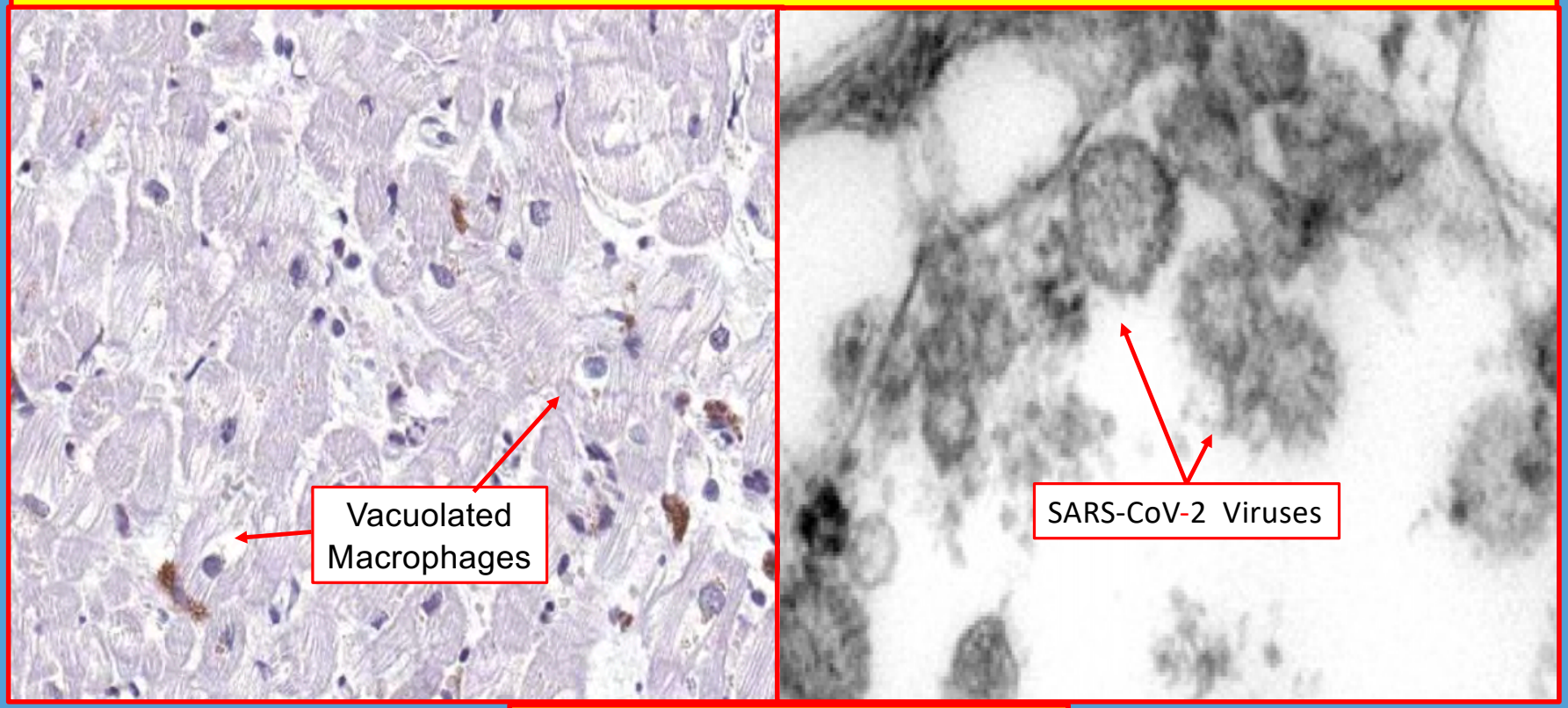
COVID-19 IN HEART

CORONAVIRUS-2 INFECTS CARDIAC TISSUE



CARDIAC MUSCLE BIOPSY

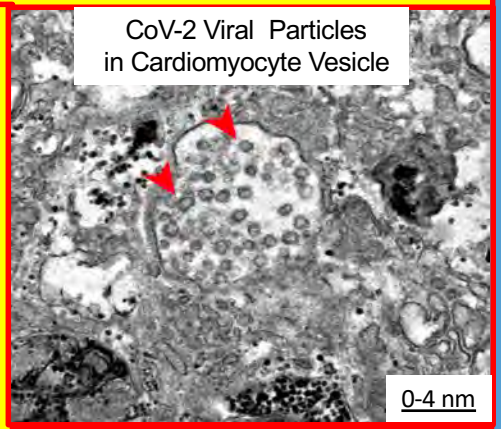
Tavazzi G et al. Myocardial localization of coronavirus in COVID-19 cardiogenic shock. Eur J Heart Fail. 2020;10.1002/ejhf.1828. doi:10.1002/ejhf.1828

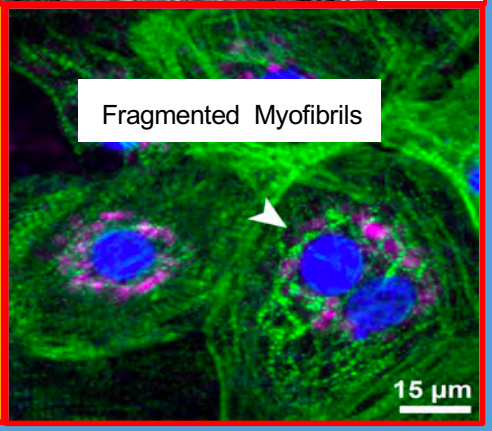
COVID-19 IN HEART

MILD INFECTIONS CAN CAUSE IRREVERSIBLE DAMAGE

MYOCARDIAL CELL DISRUPTION

1. COV-2 VIRUS INFECTS AND REPRODUCES IN CARDIOMYOCYTES, NOT IN ENDOTHELIAL CELLS OR FIBROBLASTS.
2. CARDIOMYOCYTES, ENDOTHELIAL CELLS AND FIBROBLASTS ALL EXHIBITED PATHOLOGIC EFFECTS – FRAGMENTED MYOFIBRILS ARE BROKEN INTO INDIVIDUAL SARCOMERES AND NUCLEAR DNA IS DISRUPTED.
3. MYOFIBRIL FRAGMENTATION CAUSES IRREVERSIBLE LOSS OF CARDIAC MUSCLE FUNCTION.





Perez-Bermejo JA et. al. SARS-CoV-2 infection of human iPSC-derived cardiac cells predicts novel cytopathic features in hearts of COVID-19 patients. bioRxiv preprint doi: https://doi.org/10.1101/2020.08.25.265561

COVID-19 IN HEART

MILD INFECTIONS CAN CAUSE IRREVERSIBLE DAMAGE

" A MAJORITY OF PATIENTS WHO RECOVER FROM COVID-19 DISPLAY SIGNIFICANT LEVELS OF CARDIAC DAMAGE (~80%) AND NEARLY HALF OF ALL MILDLY ILL COVID-19 PATIENTS HAVE ECHO ABNORMALITIES. "

" DUE TO THE HEART'S INNATE LACK OF REGENERATIVE CAPACITY, THESE RESULTS SUGGEST THAT A MAJORITY OF PATIENTS COULD SUFFER LONG-TERM CONSEQUENCES OF COVID-19 ON CARDIAC FUNCTION, AND THAT EVEN THE MILDEST CASES COULD CAUSE PERMANENT HEART DAMAGE. " Juan Perez-Bermejo

Perez-Bermejo JA et. al. SARS-CoV-2 infection of human iPSC-derived cardiac cells predicts novel cytopathic features in hearts of COVID-19 patients. bioRxiv preprint doi: https://doi.org/10.1101/2020.08.25.265561

Li, Y., Li, H., Li, M., Zhang, L. & Xie, M. The prevalence, risk factors and outcome of cardiac dysfunction in hospitalized patients with COVID-19. Intensive Care Medicine 1–3 (2020). https://doi:10.1007/s00134-020-06205-0

Xu, H. et al. Clinical Characteristics and Risk Factors of Cardiac Involvement in COVID-19. J. Am. Heart Assoc. e016807 (2020). https://doi:10.1161/JAHA.120.016807

COVID-19 IN HEART

MILD INFECTIONS CAN CAUSE CARDIAC DYSFUNCTION

RECEIVER OPERATING CHARACTERICTIC CURVE DATA

COVID PATIENTS vs. HEALTHY CONTROLS

Characteristic	AUC (95% CI)	*P* value	Cutoff value
Native T1	0.83 (0.76-0.91)	<.001	1100 ms
Native T2	0.82 (0.75-0.90)	<.001	38 ms
LVEF	0.68 (0.59-0.78)	.001	54%
LVEDV index	0.66 (0.49-0.71)	.07	NA
LV mass index	0.60 (0.49-0.72)	.12	NA
RVEF	0.68 (0.58-0.78)	.001	45%
hsTnT	0.81 (0.74-0.89)	<.001	6.8 pg/dL
NT-proBNP	0.53 (0.48-0.62)	.81	NA

LOWER VENTRICUALR EJECTION FRACTIONS CORRELATE WITH HIGH TROPONIN LEVELS AND ABNORMAL MRI

Puntmann VO, Carerj ML, Wieters I, et al. Outcomes of Cardiovascular Magnetic Resonance Imaging in Patients Recently Recovered From Coronavirus Disease 2019 (COVID-19). JAMA Cardiol. July 27, 2020. doi:10.1001/jamacardio.2020.3557

COVID-19 IN HEART

MILD INFECTIONS CAN CAUSE CARDIAC DYSFUNCTION

ECHO-CARDIOGRAM	PATIENTS n = 1,216	TROPONIN n = 239	BNP n = 129
Normal	549 (44%)	75 (31%)	32 (25%)
Abnormal	667 (53%)	↑164 (69%)	↑97 (75%)
Left Ventricle Normal	745 (61%)	109 (46%)	45 (35%)
Left Ventricle Mild – Severe Abnormal	455 (37%)	124 (52%)	83 (64%)
Right Ventricle Normal	842 (69%)	158 (66%)	79 (61%)
Right Ventricle Mild – Severe Abnormal	313 (26%)	75 (32%)	46 (36%)

ECHOCARDIOGRAMS WERE OBTAINED ON 1,216 PATIENTS WITH PROVEN OR SUSPECTED CoV-2 INFECTIONS IN 69 NATIONS.

ABNORMAL FINDINGS WERE PRESENT IN OVER HALF THE POPULATION WITH CLINICAL DISEASE VARYING FROM MILD TO SEVERE.

MILD COV-2 INFECTIONS MAY CAUSE SEVERE CARDIAC DYSFUNCTION WHICH MAY LAST A LIFETIME.

Dweck MR et. al. Global evaluation of echocardiography in patients with COVID-19.
European Heart Journal - Cardiovascular Imaging (2020) 0, 1–10. doi:10.1093/ehjci/jeaa178

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CoV-2 IN BRAIN

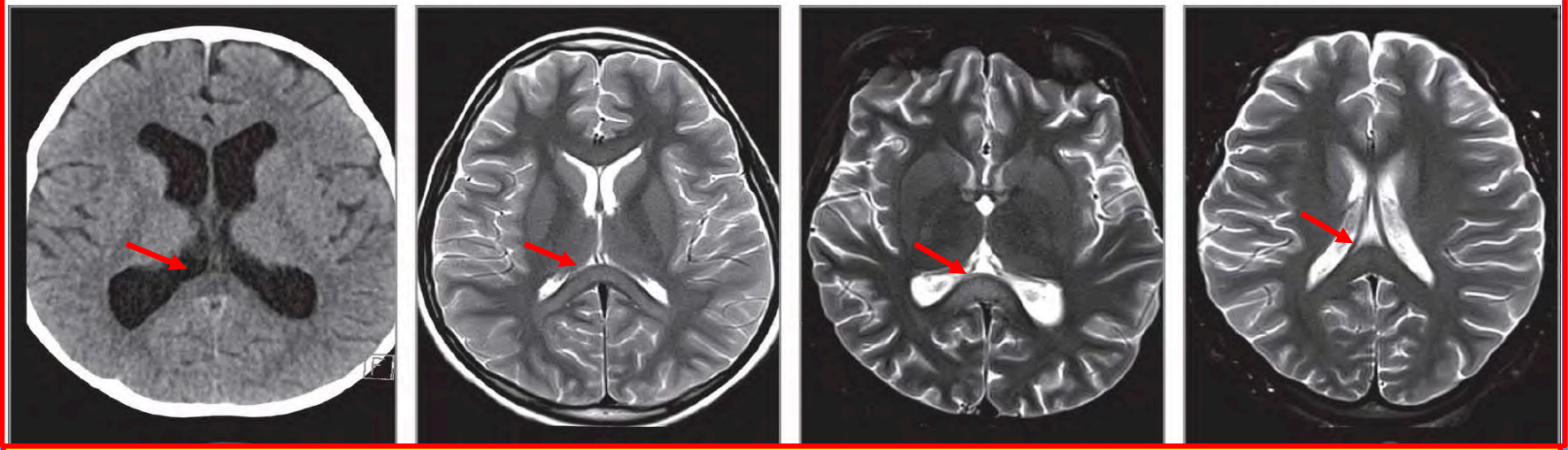
PEDIATRIC IMMUNONEUROLOGIC SYNDROME

Computed tomography of patient 1 on day 5 and day 12

Magnetic resonance imaging of patient 2 on day 1

Magnetic resonance imaging of patient 3 on day 21

Magnetic resonance imaging of patient 4 on day 5



4 CHILDREN MULTISYSTEM INFLAMMATORY SYNDROME AND CoV-2 EXPERIENCED CENTRAL AND PERIPHERAL NERVOUS SYSTEM DYSFUNCTION WITH SPLENIAL CHANGES ON IMAGING.

Abdel-Mannan O. et. al. Neurologic and Radiographic Findings Associated With COVID-19 Infection in Children. JAMA Neurol. doi:10.1001/jamaneurol.2020.2687. Published online July 1, 2020.

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SARS-CoV-2 IN SKIN

VASCULAR COAGULATION + COMPLEMENT ACTIVATION

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SARS-CoV-2 IN SKIN

COVID-19 PATIENTS
WITH NO SYMPTOMS
OTHER THAN SKIN RASH

Guarneri C et al. Silent COVID-19: what your skin can reveal. Lancet Infect Dis 2020. May 18. https://doi.org/10.1016/S1473-3099(20)30143-2. © 2020 Elsevier Ltd

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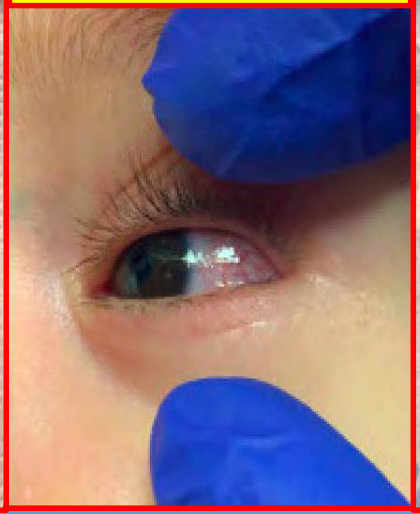
COVID-19 + KAWASAKI DISEASE

MULTISYSTEM INFLAMMATORY SYNDROME

KAWASAKI

* **Fever > 5 days**
* **Conjunctivitis**
* **Erythema Hands**
* **Erythema Feet**
* **Cervical Lymph-adenopathy**



Jones VG, Mills M, Suarez D, et al. COVID-19 and Kawasaki disease: novel virus and novel case. Hosp Pediatr. 2020; doi: 10.1542/hpeds.2020-0123

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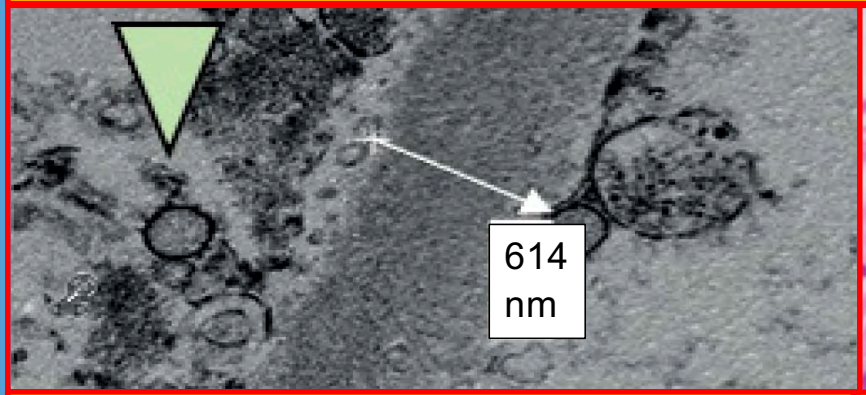
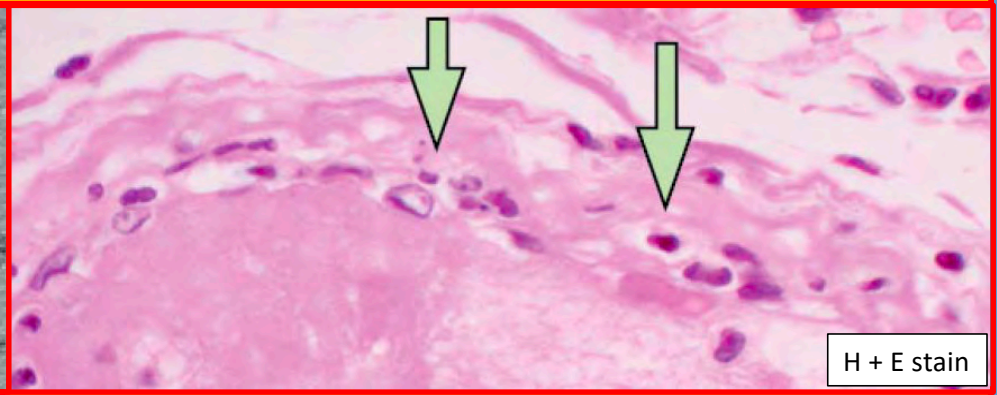
CoV-2 COAGULOPATHY

ENDOTHELIAL INFLAMMATION + COAGULOPATHY

" WE FOUND EVIDENCE OF DIRECT VIRAL INFECTION OF THE ENDOTHELIAL CELL AND DIFFUSE ENDOTHELIAL INFLAMMATION."





KIDNEY

Glomerular basement membrane and viral particle. Green Arrow

SMALL INTESTINE

Endotheliitis in submucosal vessels and apoptotic bodies. Green Arrow

Varga Z. et. al. Endothelial cell infection and endotheliitis in COVID-19, Lancet 395 (2020) 1417–1418.

CoV-2 COAGULOPATHY

ENDOTHELIAL INFLAMMATION + COAGULOPATHY

Haematological parameters of COVID-19 patients.

Parameter	Normal	Patient 1		Patient 2		Patient 3
		Day 31[a]	Day 38[a]	Day 11[a]	Day 18[a]	Day 14[a]
D-dimer, mg/L	< 0.5	20.63	6.26	1.1	1.74	2.19
ESR, mm/h	0–20	135	125	> 100	65	98
VWF:activity, %	42–168	520	405	374	303	352
VWF:antigen, %	42–136	555	413	329	251	396
FVIII:C, %	55–164	369	332	310	232	432
ADAMTS13 activity, %	> 51	[b]	56	> 100	83	81

" **COVID-19 COAGULOPATHY MAY BE A DISTINCT ENTITY OF HIGHLY PROTHROMBOTIC ALTERATIONS AND – IN LIGHT OF THE PERSISTENTLY AND EXCESSIVELY ELEVATED LEVELS OF VON WILLEBRAND FACTOR AND FACTOR VIII – MOST PROBABLY AN ENDOTHELIAL DISEASE. "** R. Escher

Escher R. et. al. ADAMTS13 activity, von Willebrand factor, factor VIII and D-dimers in COVID-19 inpatients. Thrombosis Research 192 (2020) 174–175. https://doi.org/10.1016/j.thromres.2020.05.032

CoV-2 COAGULOPATHY

ENDOTHELIOPATHY and COAGULOPATHY

Assay	Standard Reference Range, or Measurements from Controls (n = 13)	ICU (n = 48)	Non- ICU (n = 20)	p value
D-dimer, mg/L FEU	< 0.55	4.2 (2.6 – 6.9)	0.7 (0.4 - 1.2)	<0.0001
TAT, µg/L	< 4	10.6 (7.1 – 18.4)	7.2 (4.7 - 11.3)	0.020
Anti-thrombin activity	70-133%	102% (32)	111% (13)	0.12
Protein C activity	81-145%	121% (97 - 150)	106% (92-130)	0.46
Protein S activity	62-166%	100% (30)	93% (22)	0.32
a_2-anti-plasmin activity	72- 122%	112% (24)	113% (10)	0.77
PAI-1, ng/ ml	4 - 43	58 (47 - 88)	54 (44-89)	0.65
VWF Antigen	62 - 175%	565% (199)	278% (133)	<0.0001
VWF Activity	58 - 163%	390% (390 - 390)	260% (145-323)	<0.0001
Factor VIII Activity	66 - 143%	398% (111)	251% (90)	<0.0001
Soluble P-Selectin ng/ml *	9.5 (8.5 - 11.3) t	15.9 (4.8)	11.2 (3.1)	0.0014
Soluble thrombomodulin, ng/ ml *	2.5 (2.2 - 3.3) t	4.2 (2.6 – 6.5)	3.0 (2.6 - 3.2)	0.23
sCD40L, pg/ ml *	67 (33- 98) t	136 (82-228)	157 (85-211)	0 - 80

COV-2 INDUCED

COAGULOPATHY IS

AN ENDOTHELIOPATHY

RESULTING IN

HYPERCOAGULABILITY

Goshua G. et. al. Endotheliopathy in COVID-19-associated coagulopathy: evidence from a single-centre, cross-sectional study. Lancet Haematol. June 30, 2020. https://doi.org/10.1016/ S2352-3026(20)30216-7 VWF = von WILLEBRAND FACTOR

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CoV-2 COAGULOPATHY

SPIKE PROTEIN BINDS TO VON WILLEBRAND FACTOR

POSITIVELY CHARGED

AMINO ACIDS AND SUGARS

ON CoV-2 SPIKE PROTEINS

BIND TO

VON WILLEBRAND FACTOR

TABLE 1
PLASMA FVIII/vWF LECTIN ACTIVITY
INHIBITION OF HAEMAGGLUTINATION BY SUGARS AND AMINO ACIDS

TEST MATERIAL	RECIPROCAL TITRE
BUFFER	128
GLUCOSE	128
GALACTOSE	128
MANNOSE	8
GLUCOSAMINE	64
GALACTOSAMINE	0
MANNOSAMINE	0
N-ACETYL GLUCOSAMINE	128
N-ACETYL GALACTOSAMINE	64
N-ACETYL MANNOSAMINE	128
ARGININE	0
LYSINE	32
GLUTAMINE	64
GLYCINE	64
ASPARTIC ACID	128

The final concentration of FVIII/vWF in the first well of each row is 10 µg/ml; final concentration of sugar or amino acid is 50 mM in all tests. Buffer is Tris-buffered saline, pH 7.4.

Booth W. et. al. Factor VIII-von Willebrand Factor has potent lectin activity. Biochem and Biophys Res Communication. 1984:118; 495-501.

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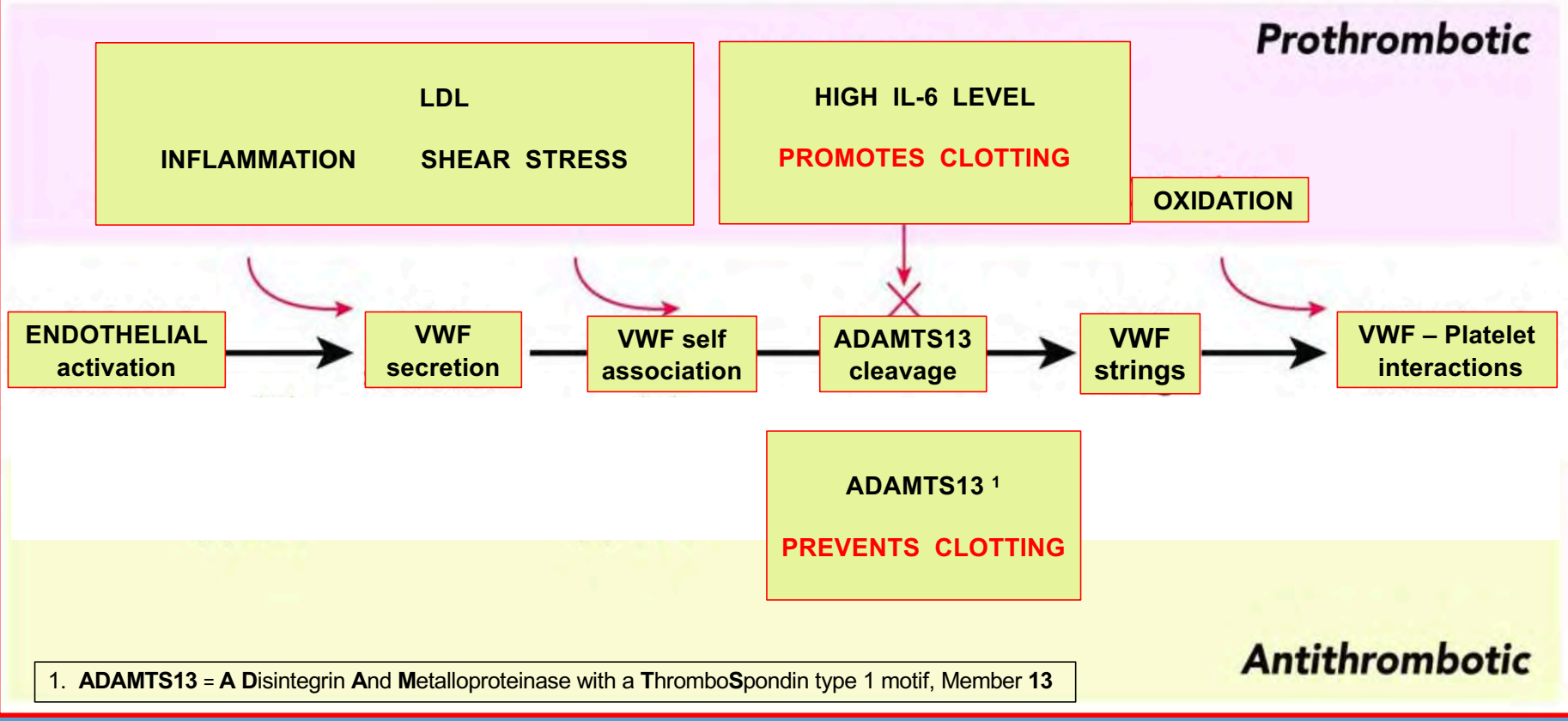
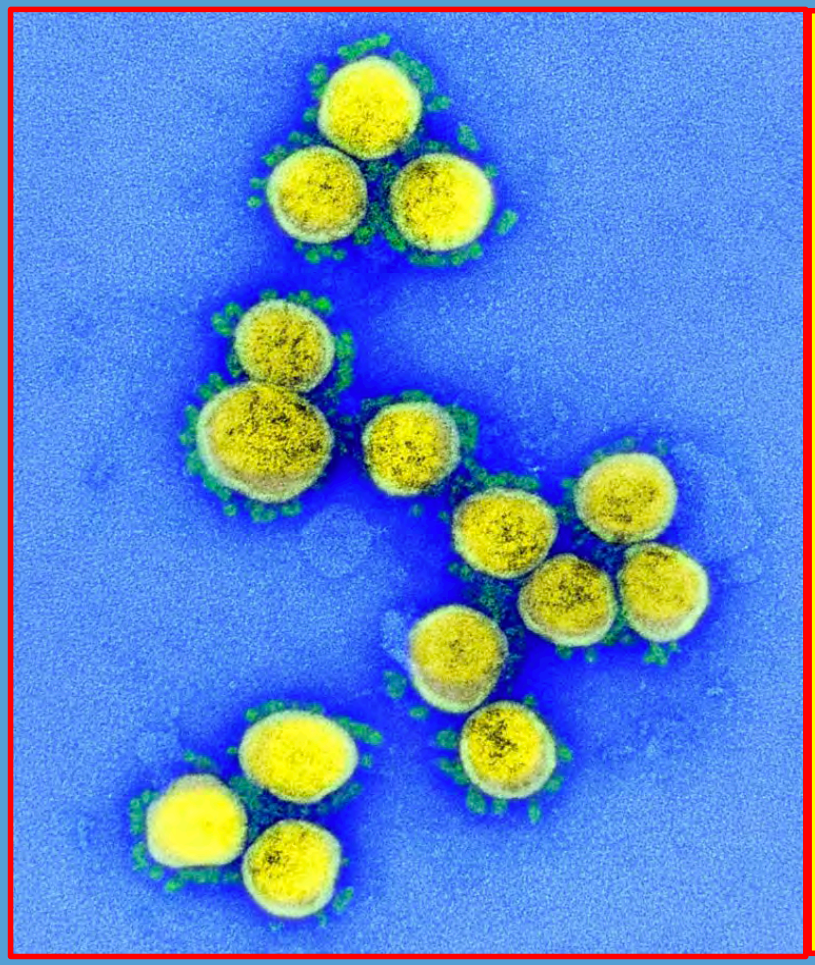
CoV-2 COAGULOPATHY

RECOMBINANT HUMAN ADAMTS13 MAY PREVENT COAGULOPATHY



1. **ADAMTS13** = **A** **D**isintegrin **A**nd **M**etalloproteinase with a **T**hrombo**S**pondin type 1 motif, Member **13**

Chen J. And Chung D. Inflammation, von Willebrand factor, and ADAMTS13. Blood. 2018Jul 12; 132(2): 141-147. doi: 10.1182/blood-2018-02-769000



HOW DO CELLS STOP FLU VIRUS INFECTIONS ?

IFITM3 PROTEINS LOCK NEW CoV-2 VIRUSES INSIDE INFECTED CELLS

1. **VIRUS INDUCES INTERFERON PRODUCTION IN PATIENT.**
2. **INTERFERON INDUCES IFITM3 GENE PROTEIN PRODUCTION.**
3. **IFITM3 PROTEIN DISRUPTS CHOLESTEROL PROCESSING INSIDE INFECTED CELLS.**
4. **NEW VIRUSES ARE LOCKED INSIDE THE INFECTED CELL'S ENDOSOMES, BECAUSE VIRAL ENVELOPES CANNOT FUSE WITH CHOLESTEROL – DEPLETED ENDOSOME MEMBRANES.**

IFITM3 PROTEINS

DEFEND CELLS FROM INFLUENZA AND CORONAVIRUS INFECTIONS

https://www.rcsb.org/pdb/explore/jmol.do?structureId=1z2m&bionumber=1&jmolMode=HTML5

IFITM3 PROTEIN

IFITM3-T/T GENE PRODUCT
INHIBITS MANY VIRAL INFECTIONS

* INFLUENZA A + B	
* CORONAVIRUS	SARS-CoV-1
* MARBURG	MARV
* EBOLA	EBOV
* DENGUE	DNV
* WEST NILE	WNV
* VESICULAR STOMATITIS	VSV
* HUMAN IMMUNODEFIENCY	HIV-1

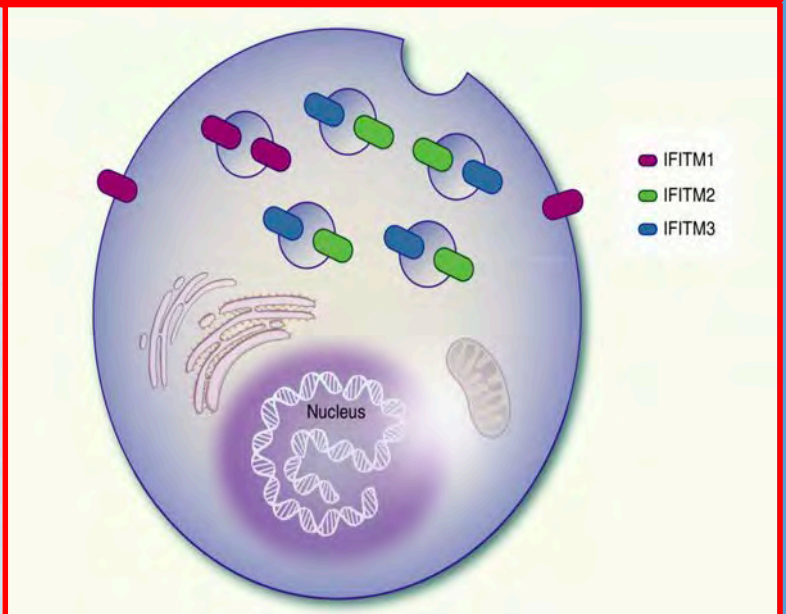
https://www.genecards.org/cgi-bin/carddisp.pl?gene=IFITM3

IFITM3 LOCKS NEWLY MADE VIRUS PARTICLES INSIDE INFECTED CELLS

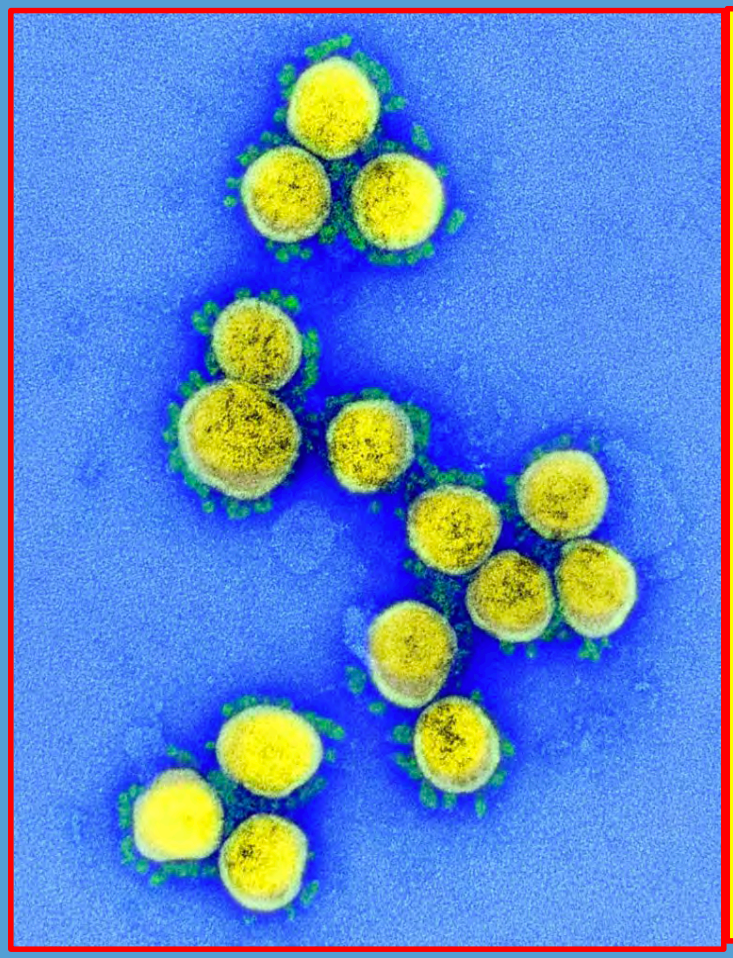
IFITM3 Inhibits Influenza A Virus Infection by Preventing Cytosolic Entry

Eric M. Feeley[1], Jennifer S. Sims[1☯], Sinu P. John[1☯], Christopher R. Chin[1], Thomas Pertel[1], Li-Mei Chen[2], Gaurav D. Gaiha[1], Bethany J. Ryan[1], Ruben O. Donis[2], Stephen J. Elledge[3,4], Abraham L. Brass[1,5*]

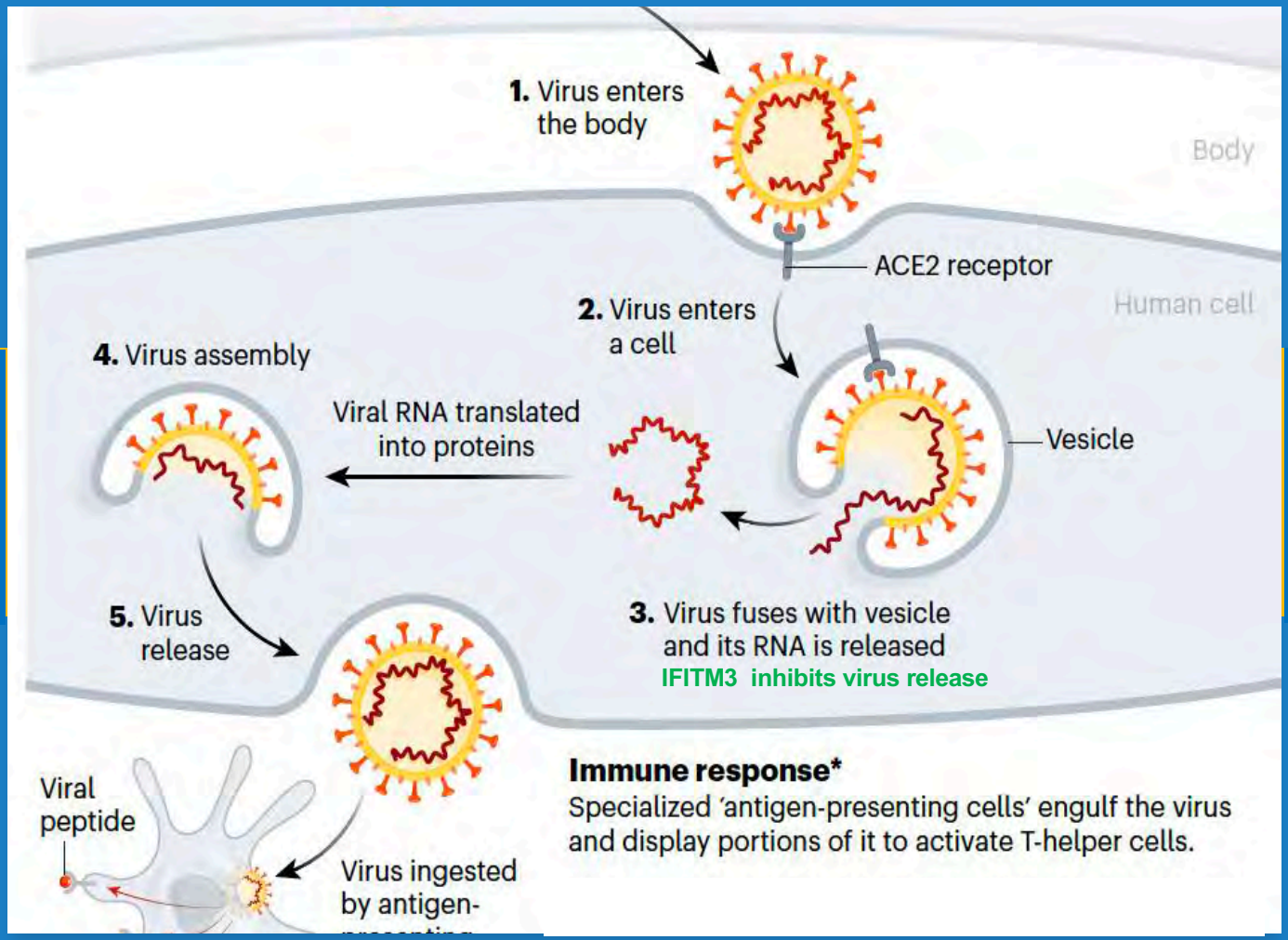
Influenza epidemics exact a great toll on world health. Thus research to identify new anti-influenza virus strategies would be useful. Each of our cells contains antiviral factors that work to inhibit infection. A large component of this antiviral program is regulated by the interferon family of signaling molecules. Here, we seek to better understand how one of these antiviral factors, IFITM3, contributes to both baseline, as well as interferon-induced, antagonism of influenza A viral infection. We found that interferon prevents influenza A virus from entering our cells by blocking the virus' fusion with the cellular membrane. Furthermore, we learned that IFITM3 is required for this antiviral action of interferon, and that high levels of IFITM3 alone can produce a similar viral inhibition. Together, these results improve our understanding of how IFITM3 serves to defend us against viral invasion at a very early stage of infection.



Feeley EM et al. (2011) IFITM3 Inhibits Influenza A Virus Infection by Preventing Cytosolic Entry. PLoS Pathog 7(10):e1002337. doi:10.1371/journal.ppat.1002337



HOW DOES YOUR IMMUNE SYSTEM RESPOND ?



https://www.nature.com/articles/d41586-020-01221-y

CoV-2 INDUCES INNATE, T-CELL and ANTIBODY IMMUNE RESPONSES

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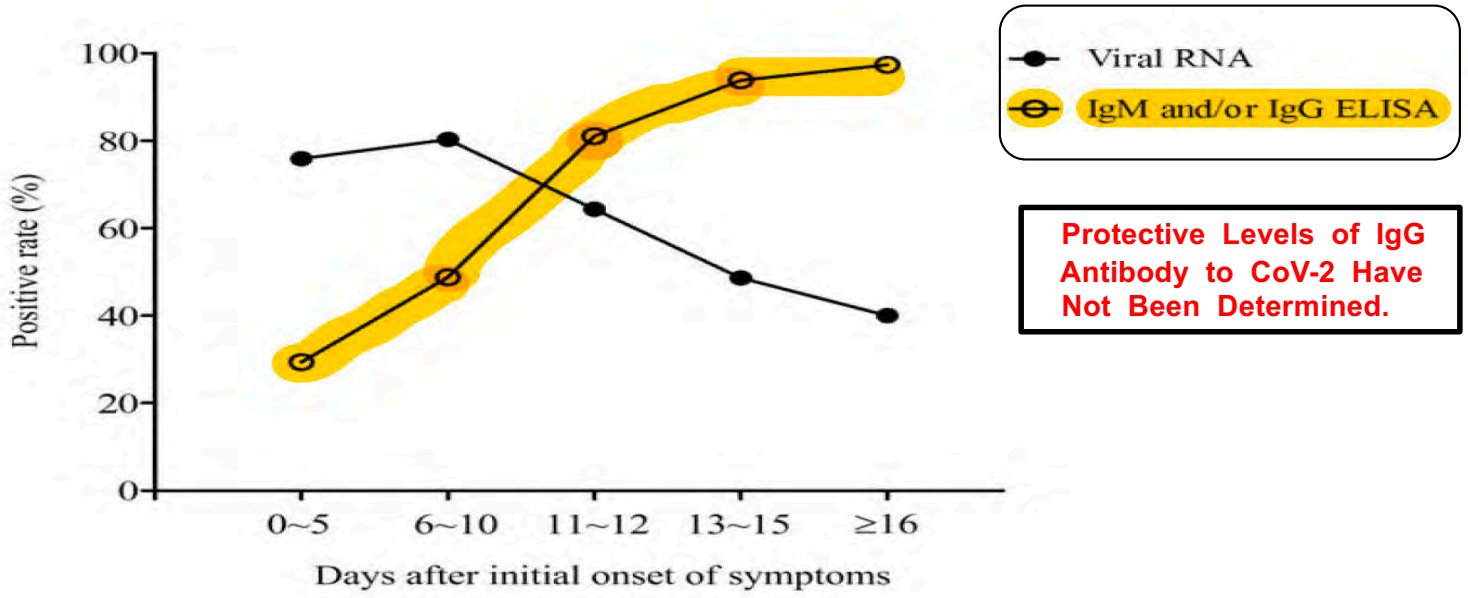
ANTIBODY RESPONSE TO CoV-2

A preliminary study on serological assay for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) in 238 admitted hospital patients

Lie L et. al.

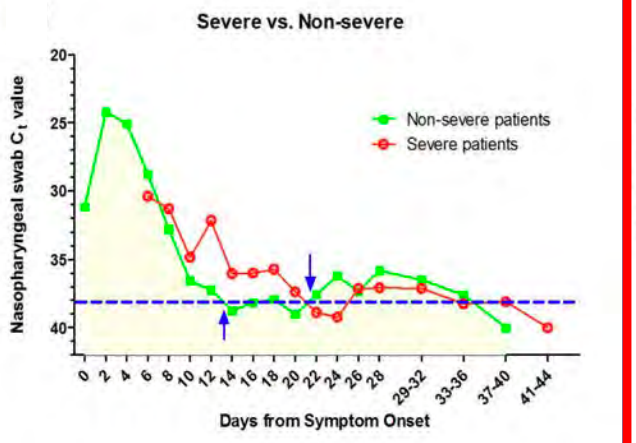


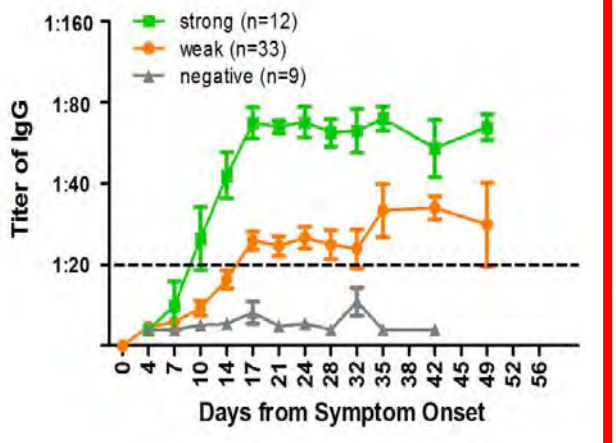
Protective Levels of IgG Antibody to CoV-2 Have Not Been Determined.

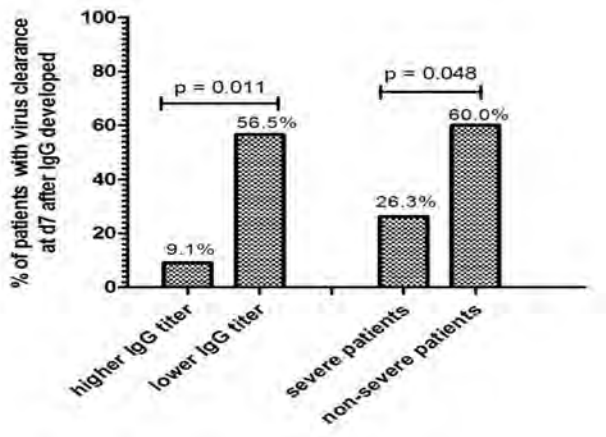
https://doi.org/10.1101/2020.03.06.20031856.

Kagen MD

WEAK IgG RESPONSE = BETTER OUTCOME







" **SARS-CoV-2 Viral Shedding** in the nasopharyngeal swabs, sputum and stools appeared in the early phase (3 - 5 days after onset of symptoms), peaked in the first week, decreased in the second week, and persisted up to 38 days from illness onset. "

↑ IgG = POOR OUTCOMES

" … earlier response, higher antibody titer and higher proportion of strong responders for IgM and IgG were significantly associated with disease severity. "

VIRAL CLEARANCE

"**weak responders** for IgG antibodies had a significantly **higher viral clearance rate** than that of strong responders."

LOW ANITIBODY RESPONSE = BETTER OUTCOME

Tan w. et. al. Viral Kinetics and Antibody Responses in Patients with Covid-19. doi: https://doi.org/10.1101/2020.03.24.20042382

CoV-2 ANTIBODY RESPONSES
TO SARS-CoV-2

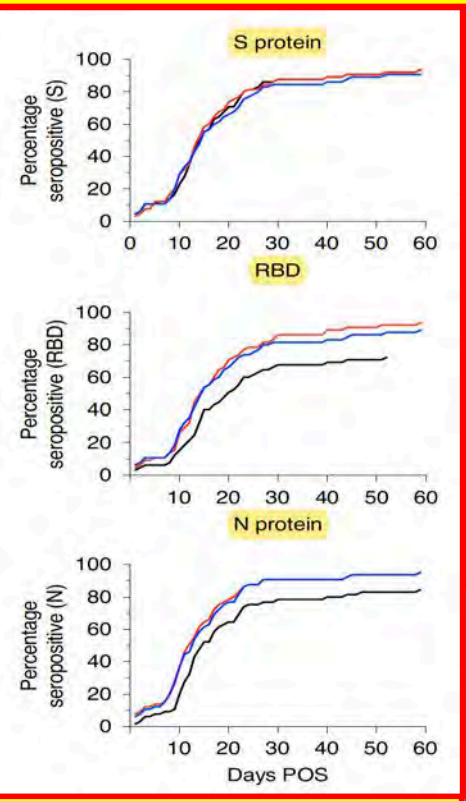
USING SEQUENTIAL SAMPLES FROM SARS-COV-2 INFECTED INDIVIDUALS COLLECTED UP TO 94 DAYS PAST ONSET OF SYMPTOMS, SEOW FOUND TYPICAL ANTIVIRAL ANTIBODY RESPONSE AFTER CORONAVIRUS-2 INFECTIONS WITH A PEAK RESPONSE DETECTED 3 – 4 WEEKS POST-INFECTION, WHICH THEN DECLINED OVER SEVERAL MONTHS.

IN PATIENTS WHO DEVELOPED A LOW NEUTRALIZING ANTIBODY RESPONSE (ID50 100–300), TITERS RETURNED TO BASELINE OVER A RELATIVELY SHORT PERIOD, WHEREAS THOSE WHO DEVELOPED A ROBUST NEUTRALIZING ANTIBODY RESPONSE MAINTAINED TITERS >1,000 DESPITE INITIAL DECLINES.

STUDIES USING SAMPLES COLLECTED FROM INDIVIDUALS AT EXTENDED TIMEPOINTS ARE REQUIRED TO DETERMINE THE DURATION OF NEUTRALIZING ANTIBODY RESPONSES, AND PROTECTIVE LEVELS OF NEUTRALIZING ANTIBODY THAT MAY PREVENT INITIAL INFECTIONS AND REINFECTION.

Seow J, Graham C. et. al. Longitudinal observation and decline of neutralizing antibody responses in the three months following SARS-CoV-2 infection in humans. Nature Microbiology. Published online October 20, 2020. https://doi.org/10.1038/s41564-020-00813-8

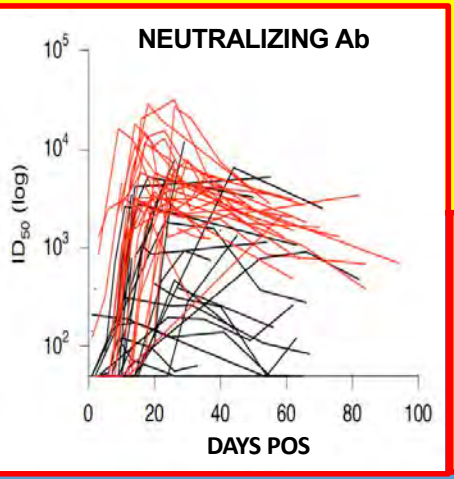
CoV-2 ANTIBODY RESPONSES
ARE UNIQUE IN EACH PATIENT



KINETICS

TYPICAL ANTIBODY RESPONSES AFTER ACUTE VIRAL INFECTIONS INCLUDE A PEAK RESPONSE AT 3 – 4 WEEKS POST - INFECTION, WHICH THEN WANES.

THOSE WHO DEVELOP LOW NEUTRALIZING ANTIBODY RESPONSES (ID50 100–300) SEE TITERS RETURN TO BASELINE OVER A SHORT PERIOD, WHEREAS THOSE WHO DEVELOP A ROBUST NEUTRALIZING ANTIBODY RESPONSE MAINTAIN TITERS > 1,000 DESPITE THE INITIAL DECLINE.

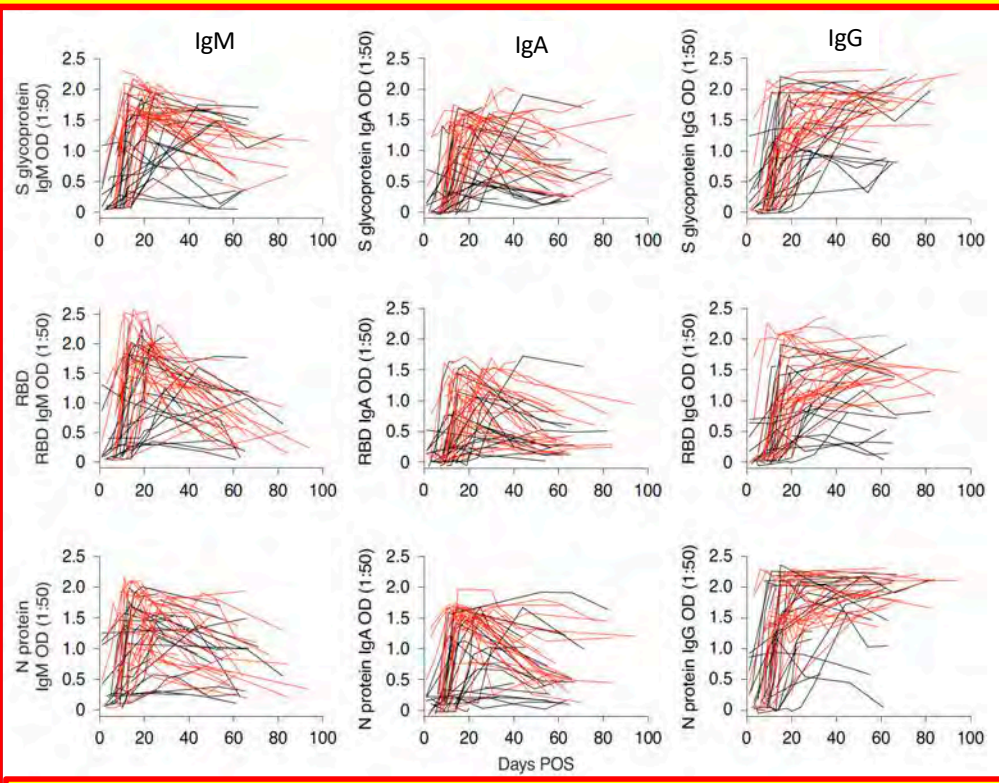


SERUM LEVELS OF NEUTRALIZING ANTIBODY ARE UNIQUE IN EACH OF THE PATIENTS STUDIED.

Seow J, Graham C. et. al. Longitudinal observation and decline of neutralizing antibody responses in the three months following SARS-CoV-2 infection in humans. Nature Microbiology. Published online October 20, 2020. https://doi.org/10.1038/s41564-020-00813-8

CoV-2 ANTIBODY RESPONSES

EACH PATIENT IS UNIQUE



IgM, IgA and IgG NEUTRALIZING ANTIBODY KINETICS

IN SEQUENTIAL SERUM SAMPLES COLLECTED FROM 65 PATIENTS FOR UP TO 94 DAYS POST ONSET OF SYMPTOMS, ANTI-CoV-2 IgM, IgA and IgG WAS PRESENT IN > 95% OF CASES, AS WAS NEUTRALIZING ANTIBODY IN SERA OBTAINED BEYOND 8 DAYS POST ONSET OF SYMPTOMS.

DECLINES IN NEUTRALIZING ANTIBODY LEVELS WERE SEEN IN 31 ASYMPTOMATIC SEROPOSITIVE HEALTH CARE WORKERS.

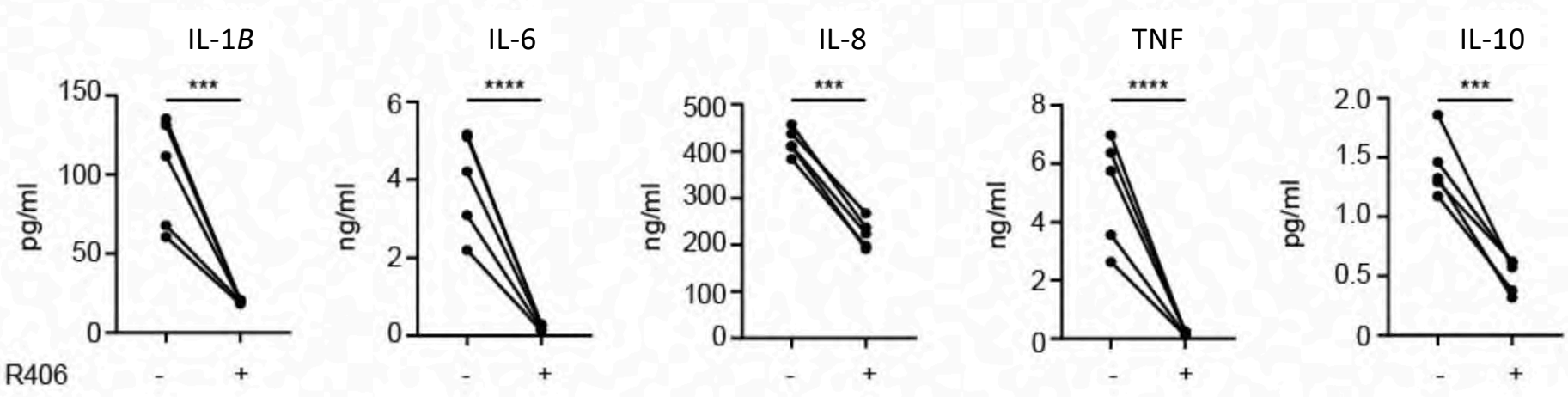
Seow J, Graham C. et. al. Longitudinal observation and decline of neutralizing antibody responses in the three months following SARS-CoV-2 infection in humans. Nature Microbiology. Published online October 20, 2020. https://doi.org/10.1038/s41564-020-00813-8

ANTI - SPIKE IgG INDUCES CYTOKINE STORM

DEGLYCOSYLATED ANTI-CoV-2 IgG – COV-2 IMMUNE COMPLEXES INDUCE AN INFLAMMATORY RESPONSE

Anti-Spike IgG – CoV-2 Immune Complexes Bind to FcγRII Receptors on Macrophages Releasing IL-6, TNF, IL-1*B* and IL-8.

Inhibition of FcγRII Receptors Prevents Inflammatory Mediator Release



FOSTAMATINIB (R406 = Syk inhibitor) **PREVENTS RELEASE OF INFLAMMATORY CYTOKINES**

Hoepel W, et. al. Anti-SARS-CoV-2 IgG from severely ill COVID-19 patients promotes macrophage hyper-inflammatory responses. bioRxiv 2020.07.13.190140; doi: https://doi.org/10.1101/2020.07.13.190140

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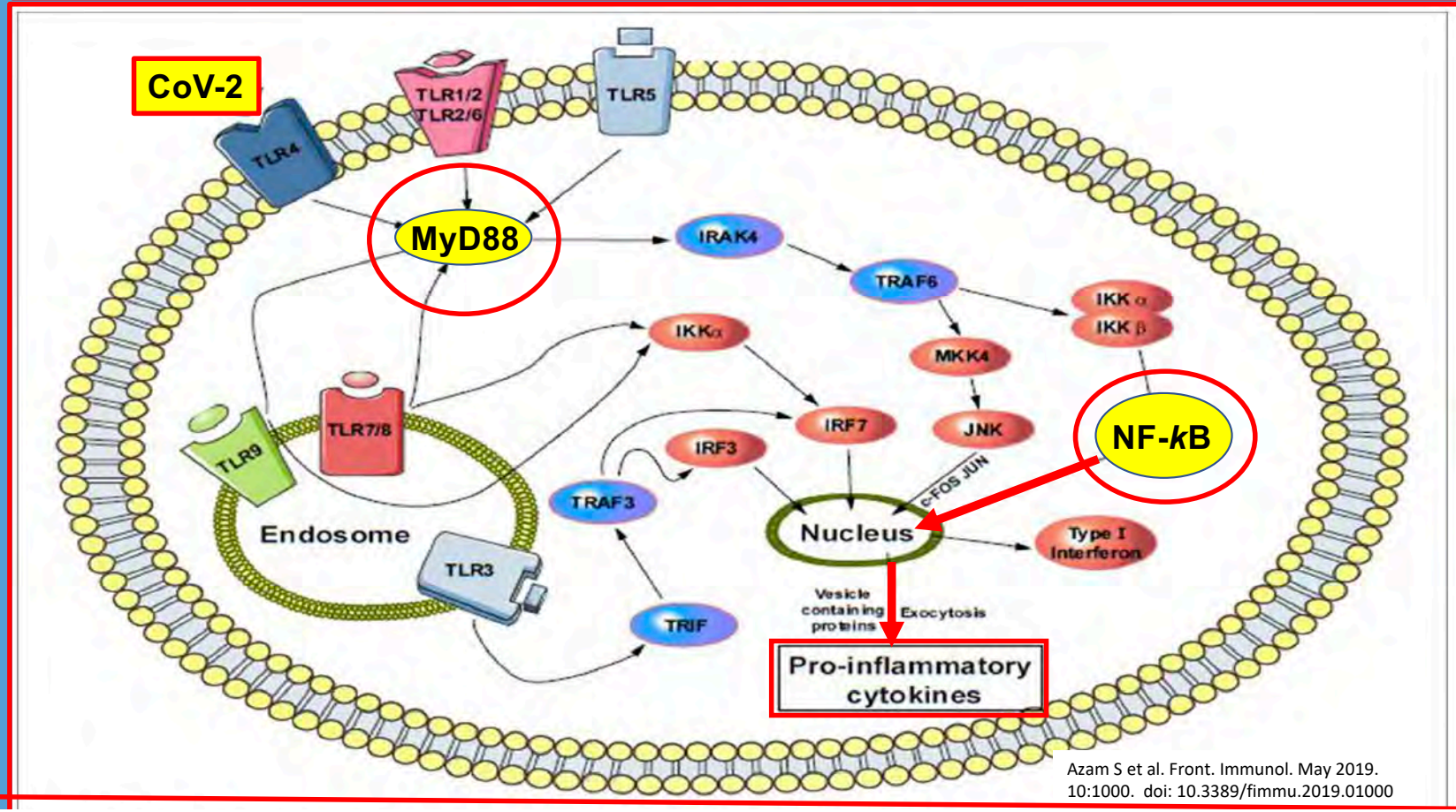
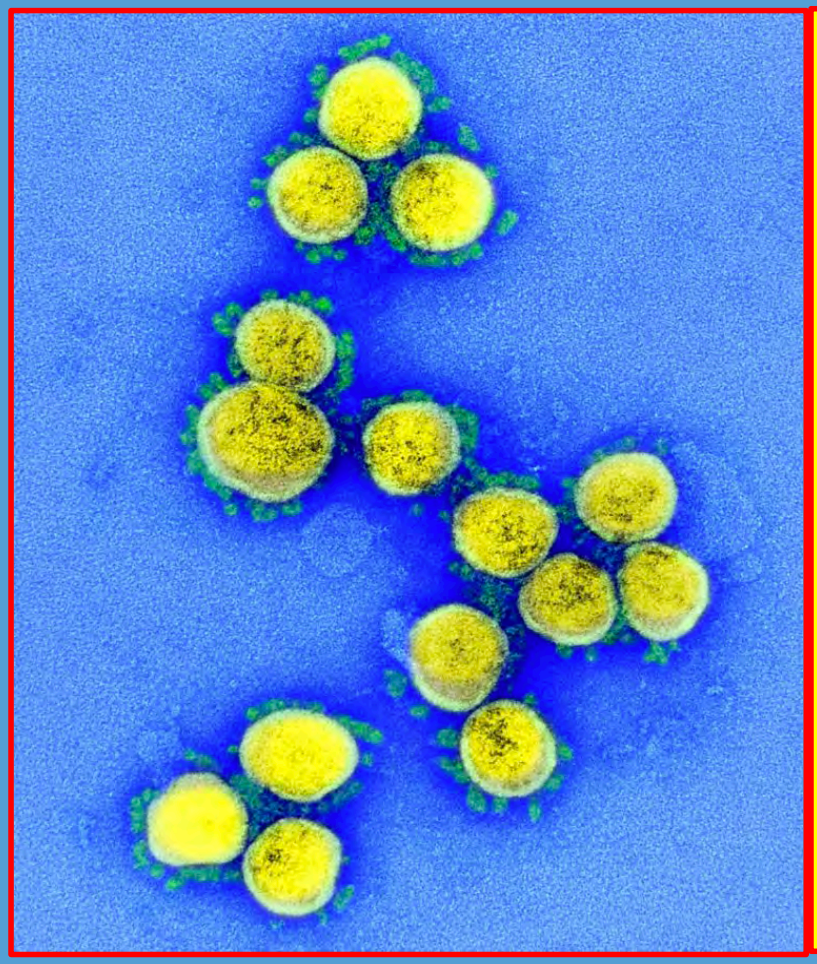
INNATE IMMUNITY

CoV-2 → TLR4 → NF-*k*B → INFLAMMATION



Azam S et al. Front. Immunol. May 2019. 10:1000. doi: 10.3389/fimmu.2019.01000



MAKING THE DIAGNOSIS ?

https://www.flickr.com/photos/niaid/49645120251/in/album-72157712914621487

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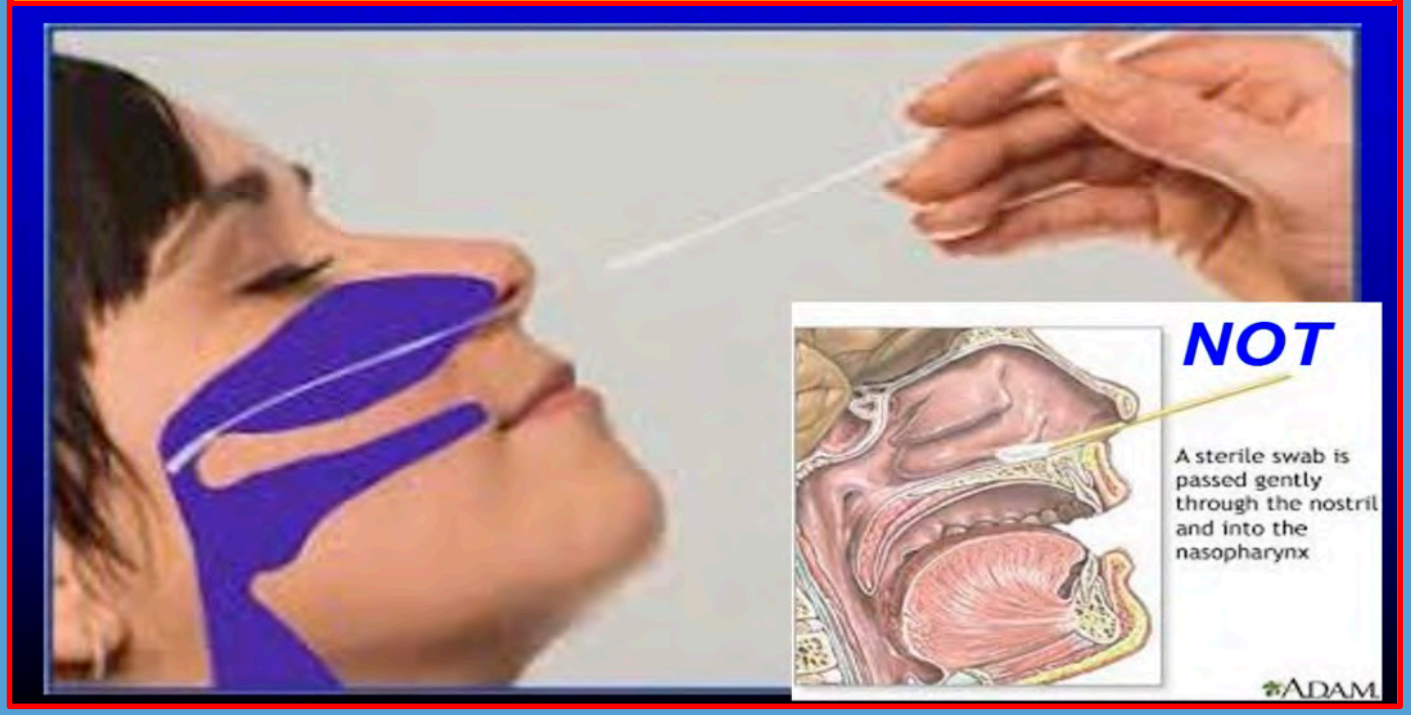
NASOPHARYNGEAL SWAB FOR CoV-2 RNA



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COVID-19 PCR TEST

PCR TESTS DETECT CoV-2 RNA

A POSTIVE PCR TEST MEANS

1. YOU HAVE CoV-2 RNA IN YOUR BODY, AND YOU MAY OR MAY NOT BE CONTAGIOUS.
2. CoV-2 VIRUS PARTICLES ARE PRESENT, BUT VIRUS MAY NOT BE ABLE TO INFECT ANYONE.

A NEGATIVE PCR TEST MEANS

1. THERE IS NO CoV-2 RNA IN THE SAMPLE or
2. CoV-2 VIRUS IS PRESENT, BUT NOT CAPTURED.

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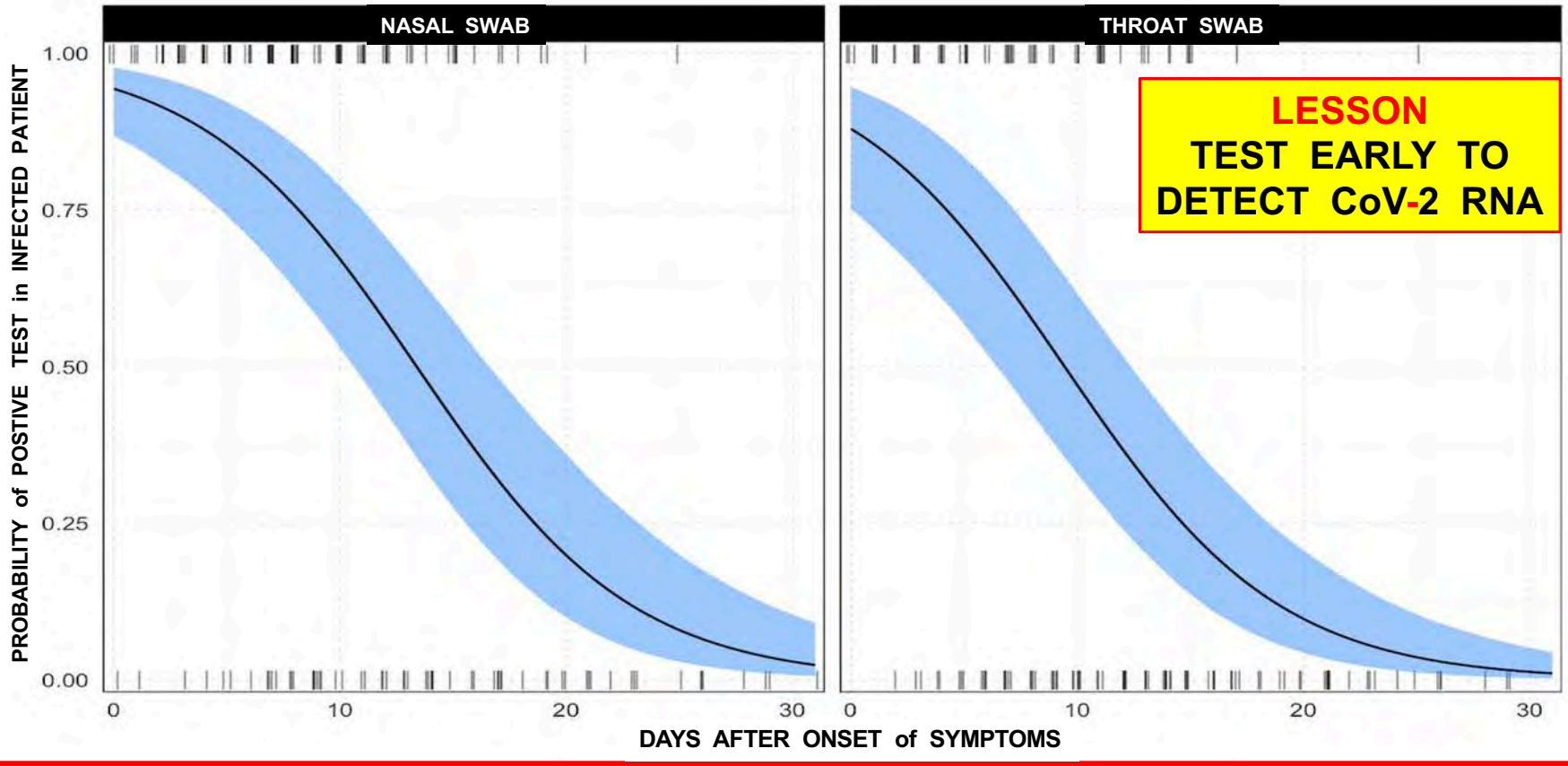
CoV-2 RT-PCR TEST



Wikramaratna R. et. al. Estimating false-negative detection rate of SARS-CoV-2 by RT-PCR. https://doi.org/10.1101/2020.04.05.20053355

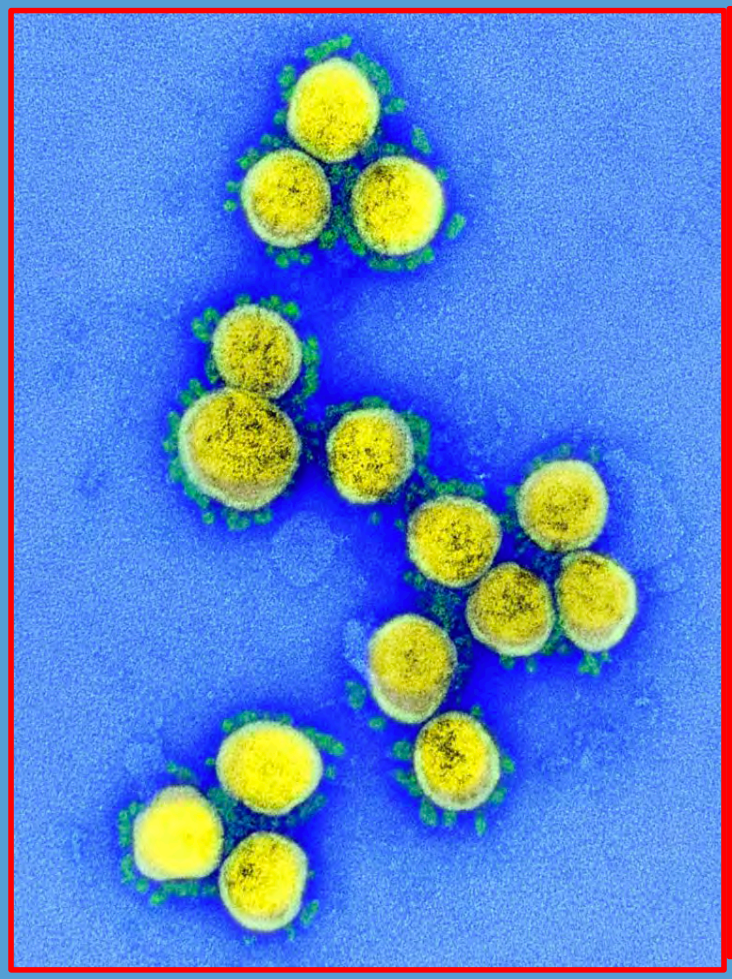
CoV-2 RT-PCR TEST

REPEAT TESTING IS OFTEN NECESSSARY

CoV-2 PATIENTS HAVE A 33% CHANCE OF TESTING NEGATIVE ON DAY 10 OF INFECTION

NASAL SWAB	SYMPTOMS DAY #	% PROBABILITY POSITIVE
"	0	94 %
"	10	67 %
"	31	2 %

Wikramaratna R. et. al. Estimating false-negative detection rate of SARS-CoV-2 by RT-PCR. https://doi.org/10.1101/2020.04.05.20053355



ANTIBODY TESTS FOR COVID-19

https://www.flickr.com/photos/niaid/49645120251/in/album-72157712914621487

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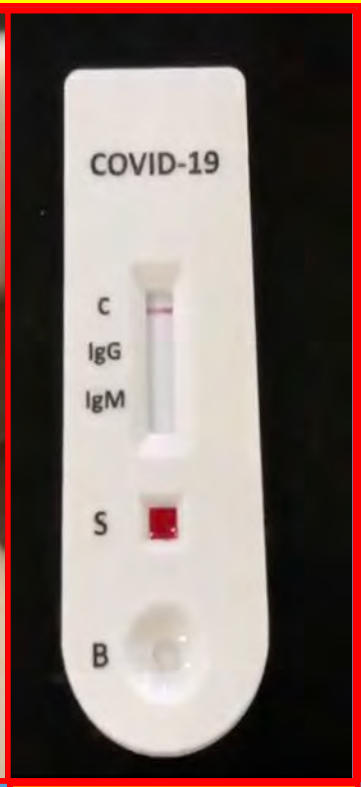
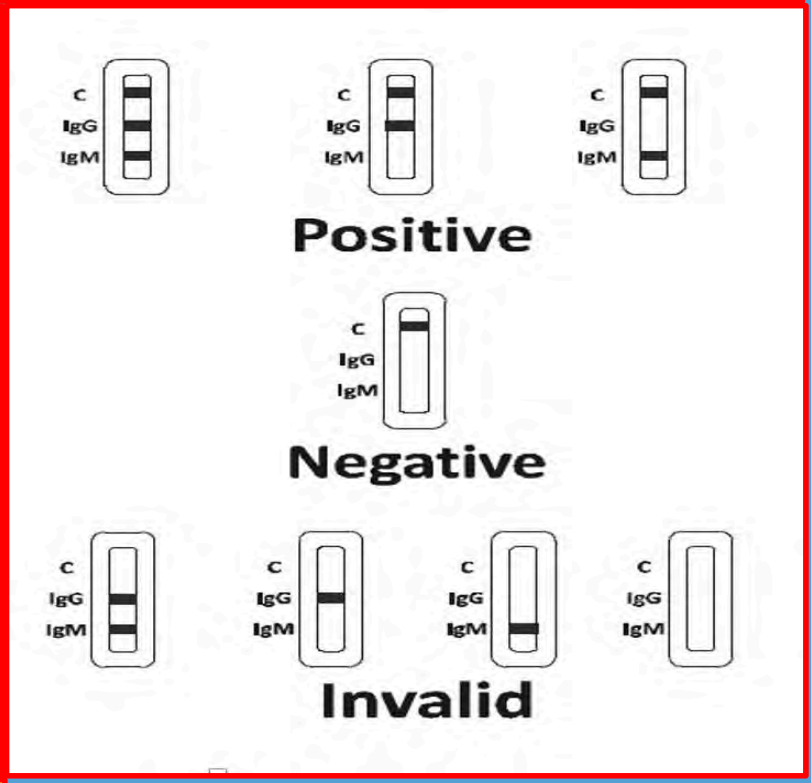
LATERAL FLOW CoV-2 ANTIBODY TEST



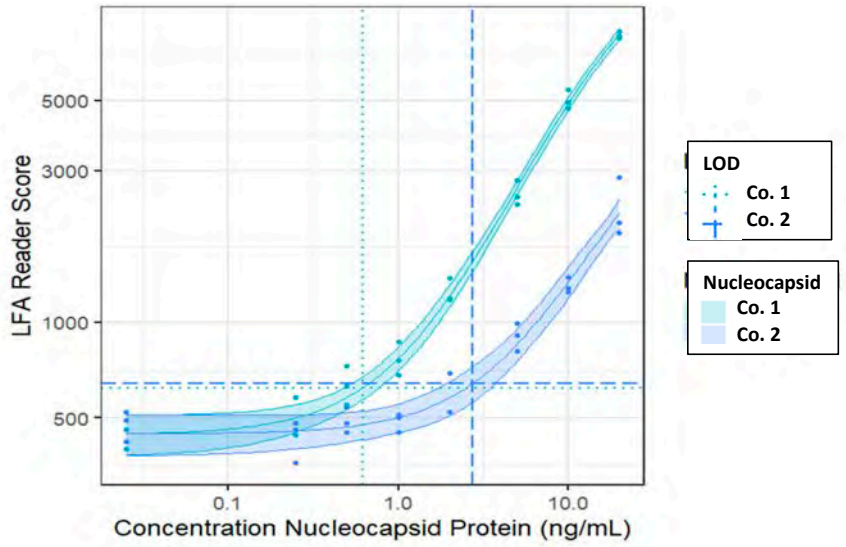


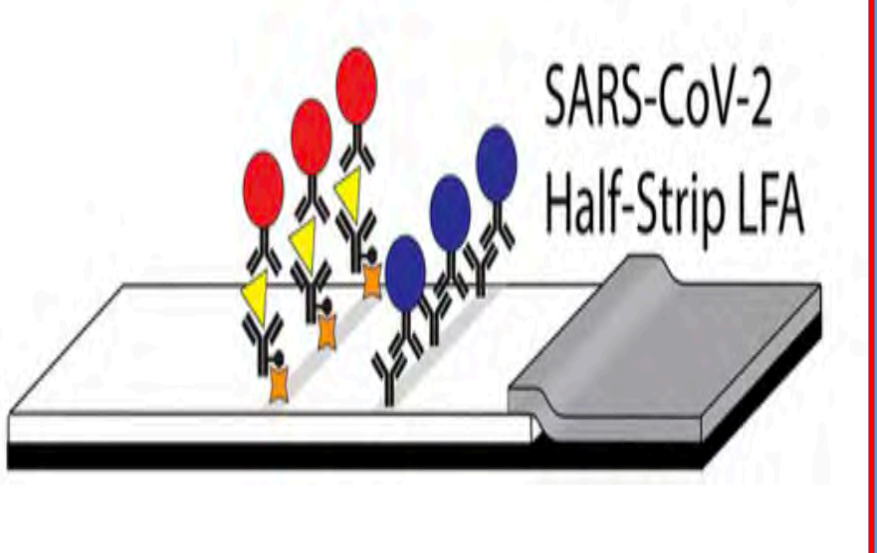
NEGATIVE TEST

Li Z. et. al. Development and Clinical Application of A Rapid IgM-IgG Combined Antibody Test for SARS-CoV-2 Infection Diagnosis. J Med Virology. Feb. 2020. 2020 https://doi.org/10.1002/jmv.25727

IN-HOME TEST

NUCLEOCAPSID PROTEIN TEST





LIMITS OF DETECTION

Company 1 0.65 ng/mL

Company 2 3.03 ng/mL

LATERAL FLOW ASSAY (LFA)

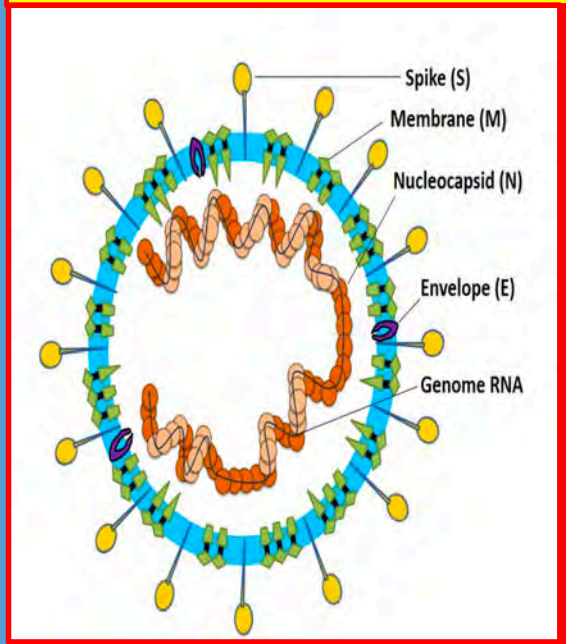
Red = Test line

Blue = Control line

Grant DB et. al. SARS-CoV-2 Coronavirus Nucleocapsid Antigen-Detecting Half-Strip Lateral Flow Assay Toward the Development of Point of Care Tests Using Commercially Available Reagents. Analytical Chemistry Article ASAP. DOI: 10.1021/acs.analchem.0c01975. https://pubs.acs.org/doi/full/10.1021/acs.analchem.0c01975

RAPID COVID-19 ANTIGEN TESTS

QUIDEL AND BECTON - DICKENSON



NUCLEOCAPSID ANTIGEN IMMUNOASSAY IMMEDIATELY REVEALS THE PRESENCE OF AN ACTIVE COV-2 INFECTION.

https://www.bd.com/en-us/offerings/capabilities/microbiology-solutions/point-of-care-testing/bd-veritor-plus-system-for-rapid-covid-19-sars-cov-2-testing

https://www.fda.gov/news-events/press-announcements/coronavirus-covid-19-update-fda-authorizes-first-antigen-test-help-rapid-detection-virus-causes

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RAPID COVID-19 NUCLEOCAPSID NASAL SWAB TEST

ABBOTT

IN PATIENTS SUSPECTED OF COVID-19

IN THE FIRST 7 DAYS OF SYMPTOMS

THE BinaxNOW COVID-19 CARD HAS A

SENSITIVITY OF 97.1%

(POSITIVE % AGREEMENT)

SPECIFICITY OF 98.5%

(NEGATIVE % AGREEMENT)

FDA - https://www.fda.gov/media/141567/download

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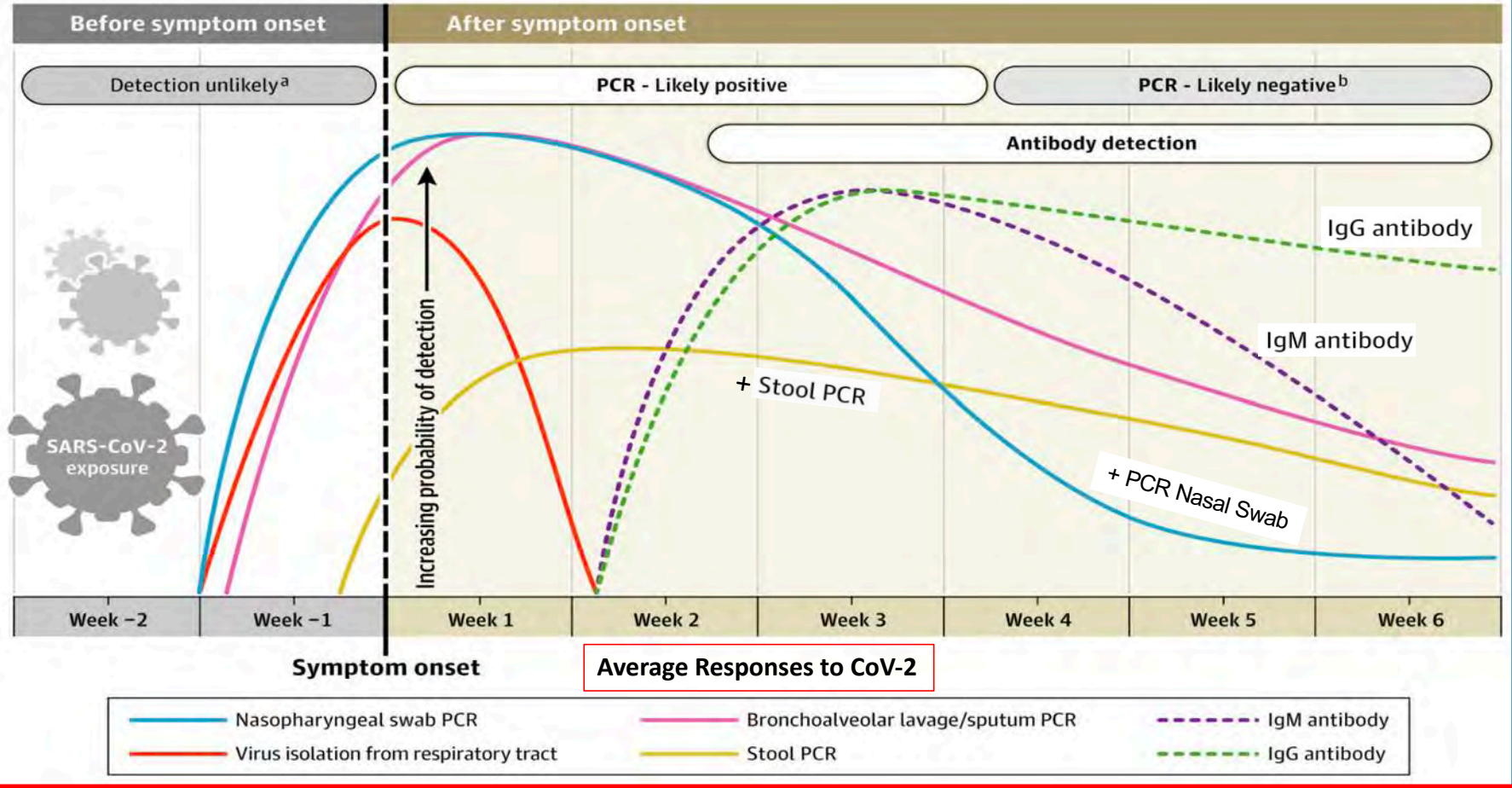
COVID - 19 TIMELINE



Sethuraman N, Jeremiah SS, Ryo A. Interpreting Diagnostic Tests for SARS-CoV-2. *JAMA.* Published online May 06, 2020. doi:10.1001/jama.2020.8259

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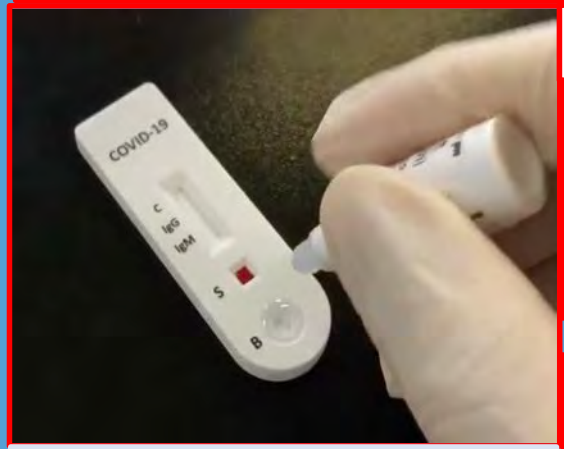
INTERPRETATION OF ANTIBODY TESTS



ANTIBODY TESTS REFLECT WHAT YOU WERE EXPOSED TO AT SOME UNKNOWN TIME IN THE PAST.

HOW DO I INTERPRET A CoV-2 IgM TEST ?

A POSITIVE IgM TEST MEANS YOU WERE EXPOSED TO CoV-2 RECENTLY, AND YOU MAY OR MAY NOT BE INFECTED NOW.
A NEGATIVE IgM TESTS = NO RECENT EXPOSURE TO CoV-2.

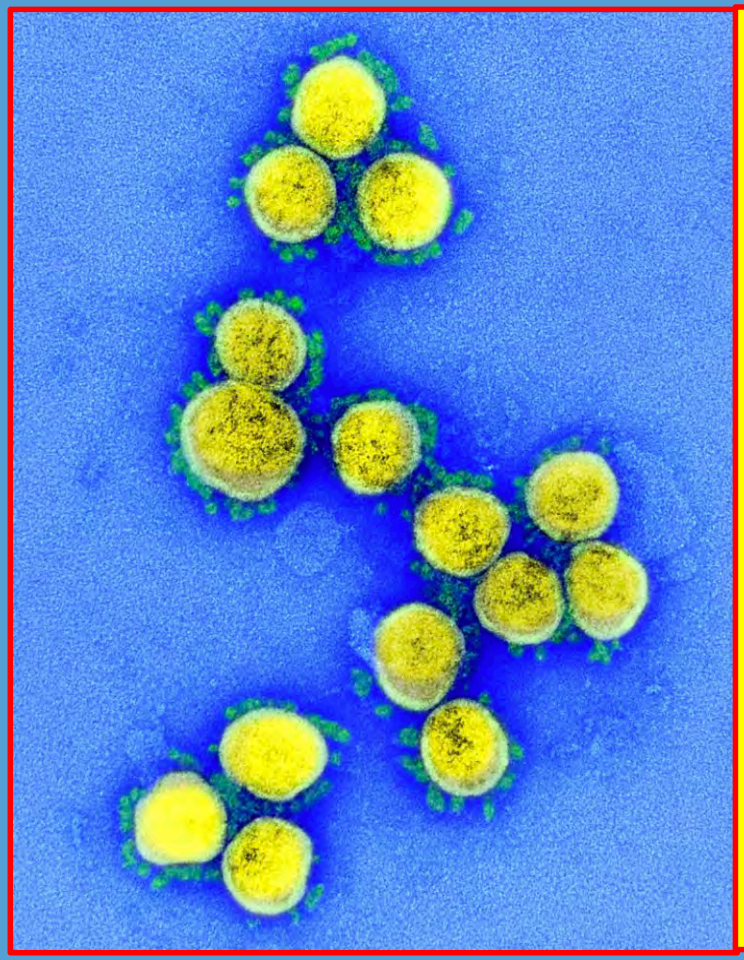
WHAT DOES A NEGATIVE IgG TEST MEAN ?

A NEGATIVE IgG TEST INDICATES YOUR IMMUNE SYSTEM HAS NOT RECENTLY SEEN THE CoV-2 VIRUS.

WHAT DOES A POSITIVE IgG TEST MEAN ?

A POSITIVE CoV-2 IgG TEST MEANS YOUR IMMUNE SYSTEM WAS EXPOSED AT SOME UNKNOWN TIME.
TODAY, THERE IS NO TEST AVAILABLE TO TELL IF YOU ARE PROTECTED FROM FUTURE INFECTIONS.

November 14, 2020



WHO IS AT RISK OF DEATH ?

IFITM3 - C/C ALLELES

THE IFITM3 - C/C GENE PREDICTS FATAL H7N9 INFLUENZA INFECTIONS

A T → C NUCLEOTIDE MUTATION AT SNP12252 POSITION ALLOWS 3 FORMS OF IFITM3 TO APPEAR.

IFITM3 – C / C ENABLES CYTOKINE STORM
IFITM3 – T / T PREVENTS INFECTION
IFITM3 – T / C PREVENTS INFECTION

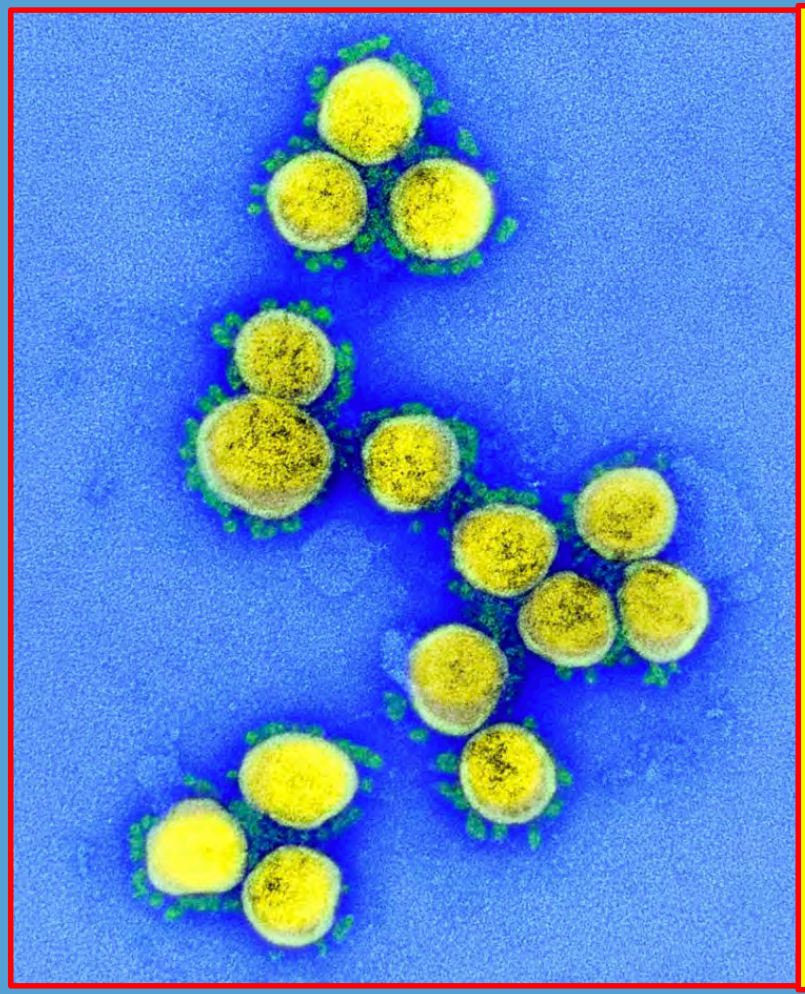
IFITM3 PROTEIN

Wang Z. et. al. 2014:111;769-774. doi/10.1073/pnas.1321748111

IFITM3 - C/C GENOTYPE PREDICTS POTENTIALLY FATAL FLU INFECTIONS

A unique avian-origin H7N9 influenza virus caused 134 human infections with 44 deaths. The host factors contributing to moderate vs. severe disease are not clear. Here, we show that H7N9 severity was associated with a higher level of cytokines/chemokines. We demonstrate that the cytokines in the infected lung were 100- to 1,000-fold higher than those in the plasma. Furthermore, we found that the IFN-induced transmembrane protein-3 (IFITM3) C/C genotype was associated with severe clinical outcome, as reflected by reduced time in seeking medical aid; more rapid progression to acute respiratory distress syndrome; and higher viral load, cytokine/chemokine levels, and mortality rate. Overall, our data suggest that the IFITM3 genotype is a primary driver of the observed differences in clinical outcome after H7N9 infection.

Z. Wang et. al. 2014:111;769-774. doi/10.1073/pnas.1321748111



6% OF HEALTHCARE WORKERS BECOME INFECTED

Kluytmans-van den Bergh M et. al. Prevalence and Clinical Presentation of Health CareWorkers With Symptoms of Coronavirus Disease 2019 in 2 Dutch Hospitals During an Early Phase of the Pandemic. JAMA Network Open. 2020;3(5):e209673. doi:10.1001/jamanetworkopen.2020.9673

MEDICAL MASKS FOR COVID-19

"Spatter Mask"

Surgical Mask

N95 Respirator Mask

PAPRs

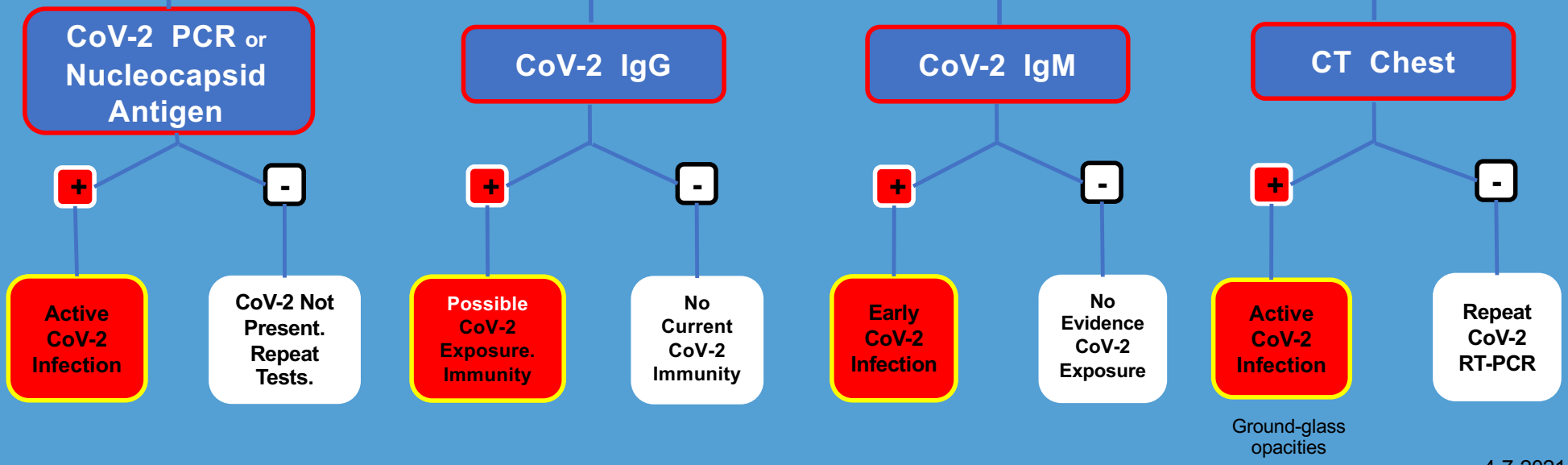
Dennis Maki M.D. UW-Madison

Kagen MD

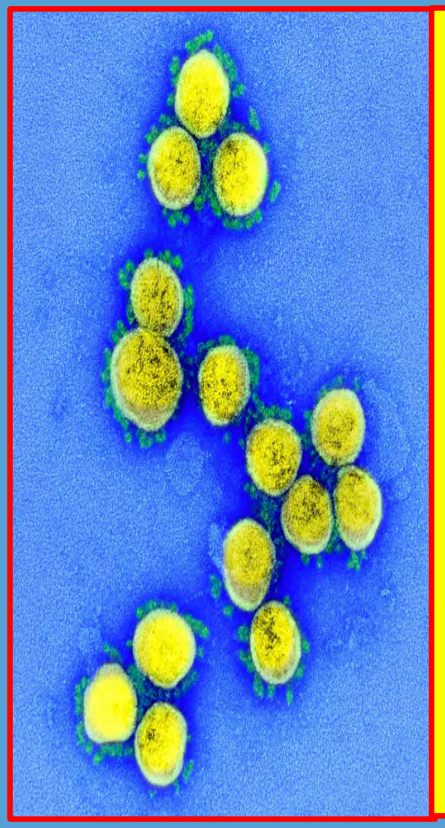
PATIENT EVALUATION

SYMPTOMS

COUGH FEVER FATIGUE SHORTNESS OF BREATH
MUSCLE ACHES HYPOSMIA RHINORRHEA HIVES
DVT DIARRHEA



4-7-2021



TREATMENT

1. **VIRUS SUPPRESSION** — Anti-Spike MAb
2. **CONTROL INFLAMMATION** — Dexamethasone
3. **ANTICOAGULATION** — Enoxaparin
4. **PREVENTION** — Immunization, Face Mask
   using CoV-2 mRNA, DNA, viral proteins without inducing de-fucosylated IgG

Kagen MD

PATIENT MANAGEMENT

4-10-2021

PREVENTION

1. **HAND WASHING**
2. **SOCIAL DISTANCING**
3. **FACE MASKS**
4. **PAPR**
5. **GLOVES and GOWNS**
6. **VITAMINS C + D**
7. **VACCINE** Spike mRNA or Peptides

* **DO NOT TAKE IBUPROFEN OR COUGH SUPPRESSANTS w/ DEXTROMETHORPHAN IF YOU HAVE SARS-CoV-2.**

TREATMENT

A. VIRUS SUPPRESSION

1. **ANTI-SPIKE MONOCLONAL ANTIBODIES**
2. **REMDESIVIR** FDA approved in first few days of infection

B. ANTI – INFLAMMATION

1. **METHYLPREDNISOLONE** Clinical Decision
2. **FOSTAMATINIB** Oral Syk inhibitor Investigational

C. ANTICOAGULATION Enoxaparin / Heparin
? Rec - Human ADAMTS13

INF beta-1-b, RIBAVIRON, LOPINAVIR, RITONAVIR. https://doi.org/10.1016/S0140-6736(20)31042-4

NIH COVID-19 Rx Guidelines https://www.covid19treatmentguidelines.nih.gov/introduction/

Kagen MD

PATIENT MANAGEMENT

Hospitalized Patient

Positive PCR CoV-2
or Nucleocapsid Antigen
or
Person of Interest

Negative RT-PCR

No Evidence of Cytokine Storm
Vital Signs Stable

Risks for Cytokine Storm
IFITM3 - C/C allele
deglycosylated anti-CoV-2 IgG
ID or Pulmonary Consult

Repeat RT-PCR or Nucleocapsid Antigen Tests if Symptoms Persist

2L O_2 with No Risk Factors
≥ 2L O_2 with Risk Factors*

Supportive Care
Close Monitoring
Statin ?
ACE-2 Inhibitor ?

ANTICOAGULATION
Lovenox enoxaparin

VIRUS SUPPRESSION

Anti-Spike Monoclonal Antibody Bamlanivimab
Casirivimab + Imdevimab

Remdesivir 200 mg IV at onset of symptoms
then 100 mg IV / day x 9 days.

Consider Interferon beta-1b, **Ribavirin, Lopinavir-Ritonavir**

INFLAMMATION CONTROL

Cytokine Storm present when IL-6 > 7 pg/mL CRP > 20
Fever > 100.4 F Ferritin > 1,000 NT-proBNP ≥ 88.64 pg/ml

Methylprednisolone 40 mg – 80 mg IV q day
Consider IVIG if serum IgG < 400 mg / ml

Remdesivir is only drug approved by the FDA to treat SARS-CoV-2.

* **RISK FACTORS**
Age > 60. BMI > 40. Diseases Heart, Lung, Kidney, Diabetes, CVD, Hypertension, Steroid Dependent (> 20 mg/day > 12 days), HIV, Immunosuppression (anti-TNF or other immune suppressant agents, CD4 <400 cells/ml).

(1) https://www.massgeneral.org/assets/MGH/pdf/news/coronavirus/mass-general-COVID-19-treatment-guidance.pdf (2) https://covid19criticalcare.com/treatment-protocol/

4-10-2021

VITAMIN D REDUCES INFLAMMATION

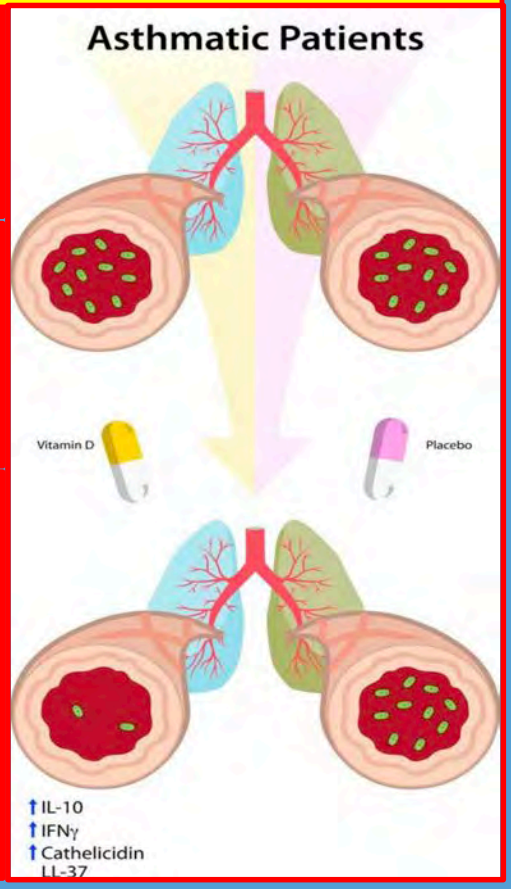
Vitamin D and the Immune System

Cynthia Aranow, MD
Feinstein Institute for Medical Research, Manhasset, N.Y.

Vitamin D also has effects on monocytes and dendritic cells (DCs). It inhibits monocyte production of inflammatory cytokines such as IL-1, IL-6, IL-8, IL-12 and TNFα[42]. It additionally inhibits DC differentiation and maturation with preservation of an immature phenotype as evidenced by a decreased expression of MHC class II molecules, co-stimulatory molecules and IL12[43-45] (Figure 1B).

Conclusions

Vitamin D has important functions beyond those of calcium and bone homeostasis which include modulation of the innate and adaptive immune responses. Vitamin D deficiency is prevalent in autoimmune disease. Cells of the immune system are capable of synthesizing and responding to vitamin D. Immune cells in autoimmune diseases are responsive to the ameliorative effects of vitamin D suggesting that the beneficial effects of supplementing vitamin D deficient individuals with autoimmune disease may extend beyond effects on bone and calcium homeostasis.



Aranow C. Vitamin D and the immune system. J Investig Med. 2011 Aug;59(6):881-6. doi: 10.2310/JIM.0b013e31821b8755. PMID: 21527855; PMCID: PMC3166406.

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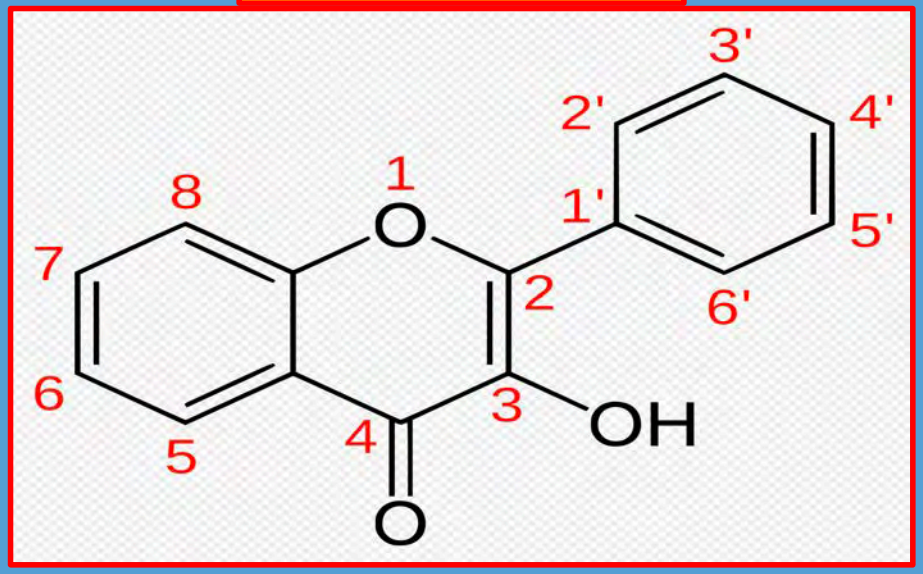
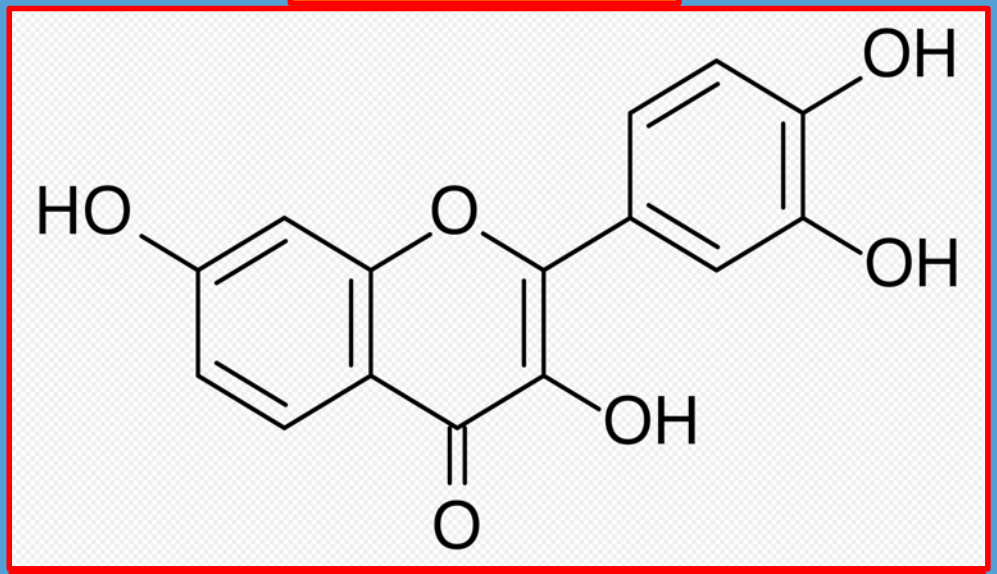
FISETIN REDUCES INFLAMMATION

FLAVONE



FISETIN



FISETIN REDUCES INFLAMMATION BY INHIBITING NF-*k*B

Azam S, Jakaria M et. al. (2019) Regulation of Toll-Like Receptor (TLR) Signaling Pathway by Polyphenols in the Treatment of Age-Linked Neurodegenerative Diseases: Focus on TLR4 Signaling. Front. Immunol. 10:1000. doi: 10.3389/fimmu.2019.01000

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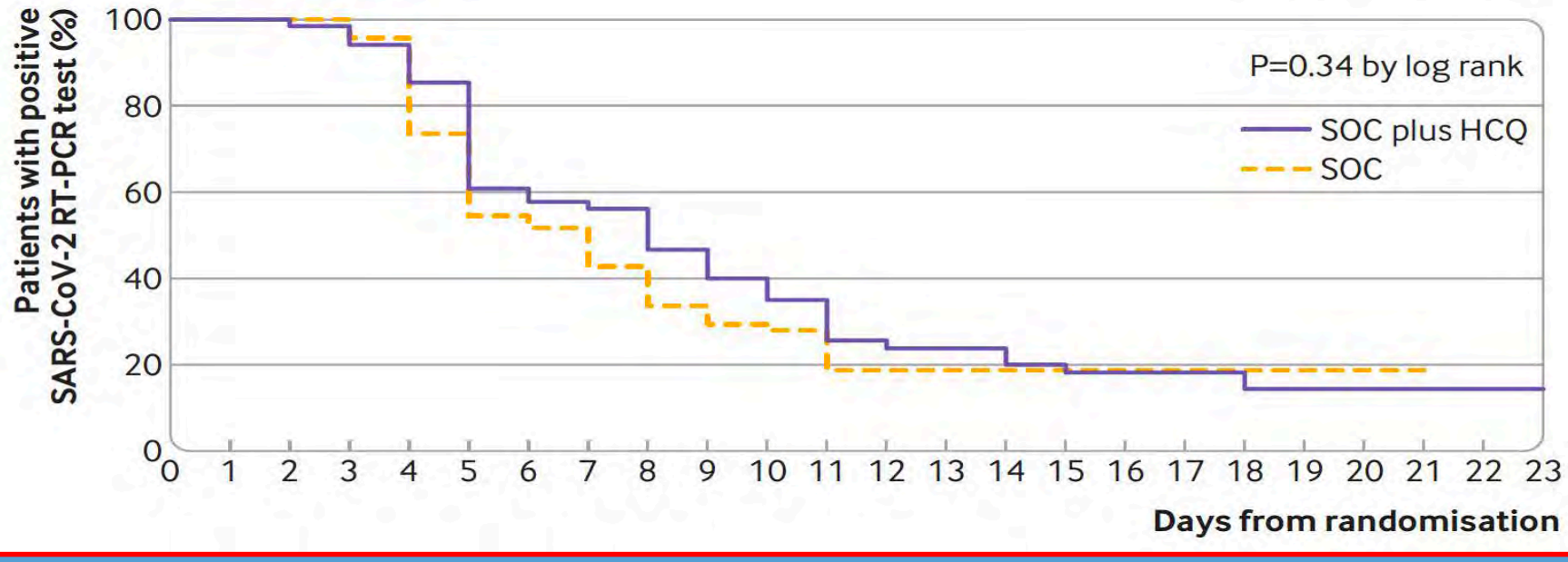
HYDROXYCHLOROQUINE

PLACEBO CONTROLLED STUDIES DO NOT SUPPORT USE OF HYDROXYCHLOROQUINE IN PATIENTS WITH MILD TO MODERATE COVID-19



Tang W. Hydroxychloroquine in patients with mainly mild to moderate coronavirus disease 2019: open label, randomised controlled trial. BMJ 2020;369:m1849 | doi: 10.1136/bmj.m1849

IL–6 REFLECTS DISEASE SEVERITY

"… OUR RESULTS SUGGEST THAT SERIAL MEASUREMENT OF CIRCULATING IL-6 LEVELS MAY BE IMPORTANT IN IDENTIFYING DISEASE PROGRESSION AMONG COVID-19 INFECTED PATIENTS.

THEREFORE, IT IS REASONABLE THAT IMMEDIATE INITIAL EVALUATION OF IL-6 LEVEL BE PERFORMED UPON HOSPITAL ADMISSION OF COVID-19 PATIENTS, DUE TO ITS POTENTIAL BENEFITS TO ASSESS WORSENING CLINICAL FEATURES AND DISEASE PROGRESSION IN COVID-19. "

	Severe			Non-severe				Std. Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI
Chen et al	64	63.92	17	10.4	20.14	21	8.2%	1.16 [0.47, 1.86]
Gao et al	36.1	26.81	15	10.6	14.11	28	8.2%	1.29 [0.60, 1.98]
Liu et al (1)	3.3	1.18	25	4.7	2.44	25	8.9%	-0.72 [-1.29, -0.15]
Liu et al (2)	4.6	20.88	7	0	5.4	44	7.6%	0.51 [-0.29, 1.31]
Liu et al (a)	52	11	9	34	7	15	6.3%	2.00 [0.97, 3.04]
Liu et al (b)	108	12	5	34	7	15	1.5%	8.46 [5.37, 11.56]
Qin et al	25.2	33.25	286	13.3	27.55	166	10.5%	0.38 [0.19, 0.57]
Wang et al	17.2	24.96	50	9.7	13.18	115	10.0%	0.42 [0.09, 0.76]
Wu et al (a)	7.4	3.64	63	6.76	4	48	9.9%	0.17 [-0.21, 0.54]
Wu et al (b)	7.4	3.64	63	7.36	2.62	77	10.0%	0.01 [-0.32, 0.35]
Yang et al	14.61	16.23	34	8.06	7.57	21	9.0%	0.47 [-0.08, 1.03]
Zhou et al	11	5.11	54	6.3	2.14	137	10.0%	1.44 [1.09, 1.78]
Total (95% CI)			628			712	100.0%	**0.71 [0.31, 1.12]**

Heterogeneity: Tau² = 0.39; Chi² = 100.24, df = 11 (P < 0.00001); I² = 89%
Test for overall effect: Z = 3.46 (P = 0.0005)

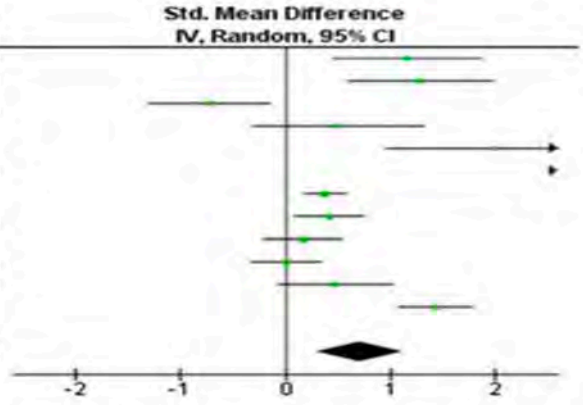


Fig. 1. Forest plot for pooled standardized mean difference (SMD) and 95% confidence interval (95% CI) of circulating IL-6 levels in COVID-19-infected patients with severe and non-severe condition.

Ulhaq ZS, Soraya GV. Interleukin-6 as a potential biomarker of COVID-19 progression. Med Mal Infect (2020) https://doi.org/10.1016/j.medmal.2020.04.002

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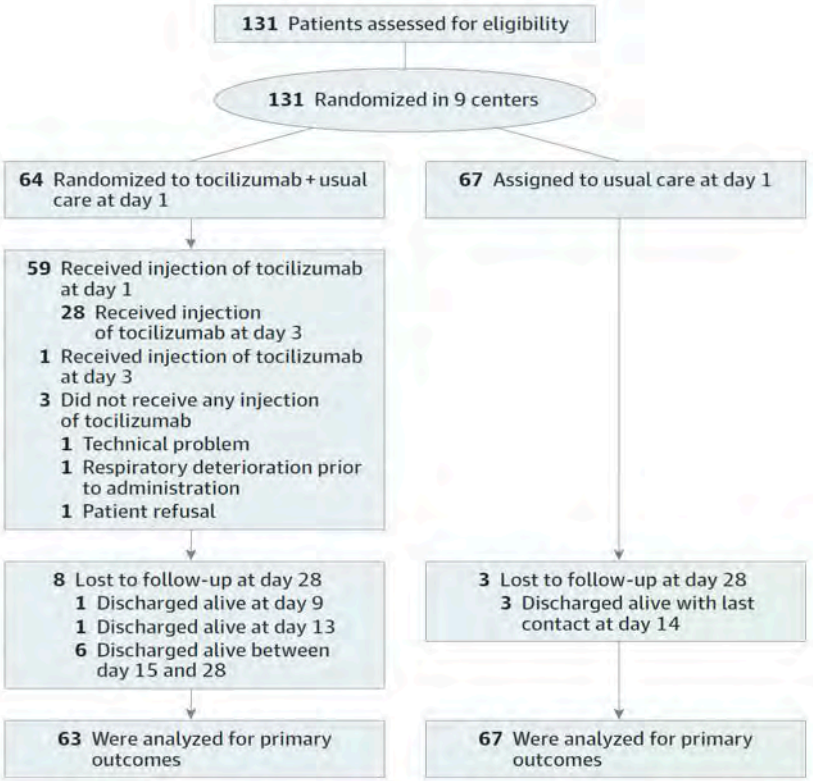
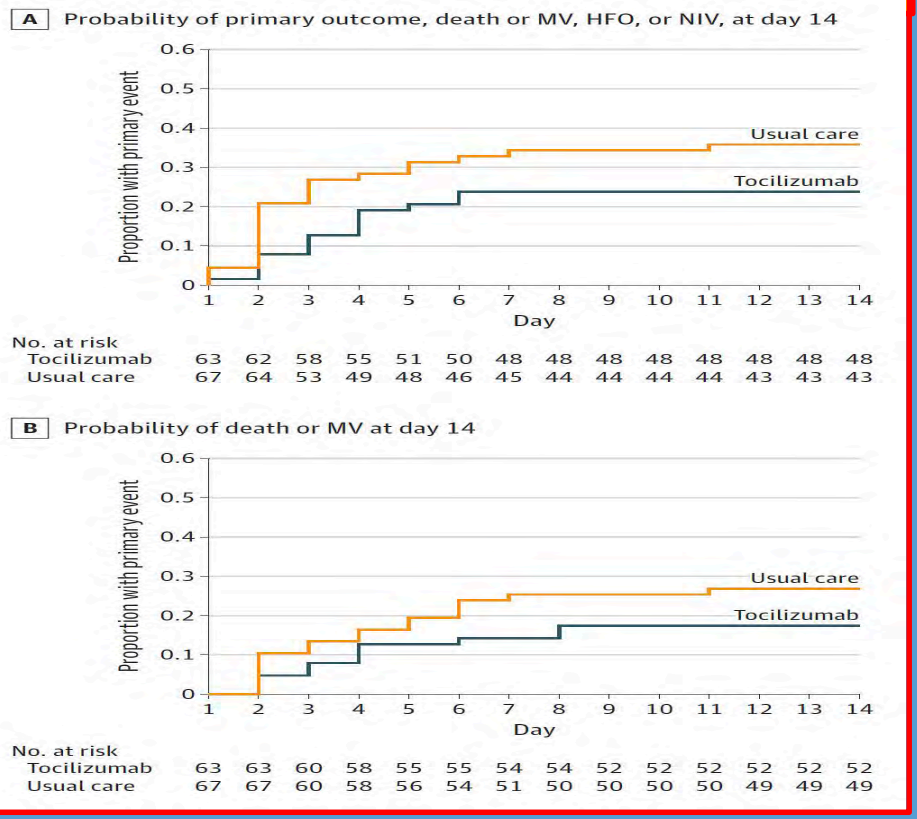
TOCILIZUMAB

TOCILIZUMAB FAILED TO MEET ENDPOINTS IN CLINICAL TRIALS.

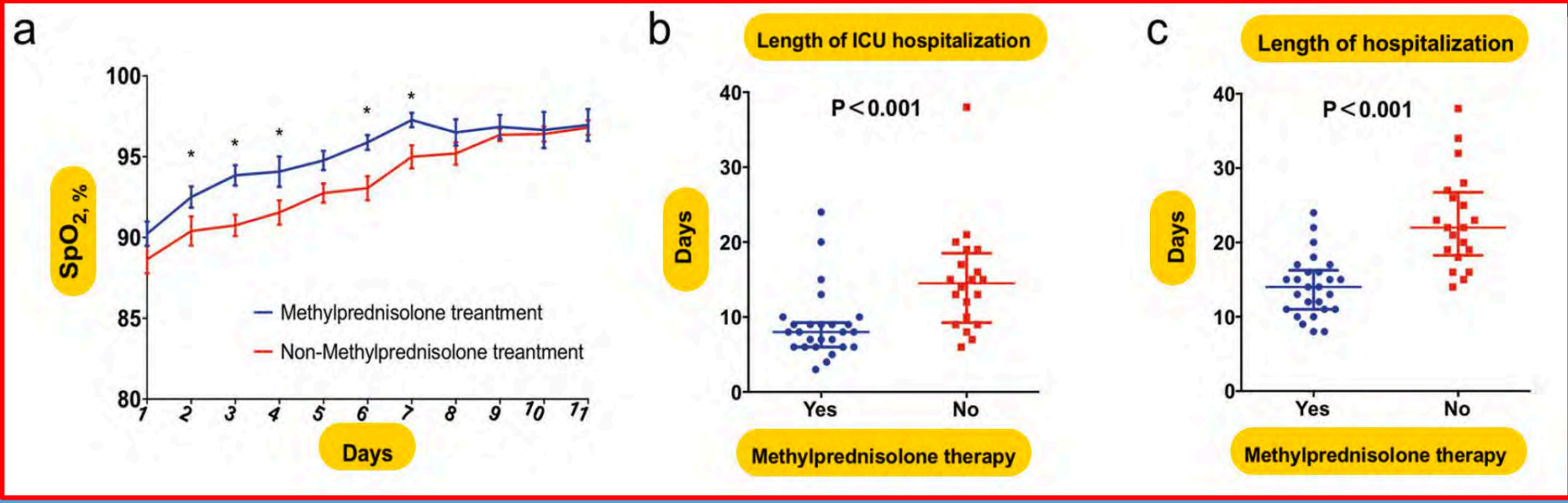




1. Hermine O., Mariette X, et. al. Effect of tocilizumab vs usual care in adults hospitalized with COVID-19 and moderate or severe pneumonia. A randomized clinical trial. JAMA Intern Med. doi:10.1001/jamainternmed.2020.6820. Published online October 20, 2020.
2. Parr J. Time to reassess tocilizumab's role in COVID-19 pneumonia. *JAMA Intern Med.* Published online October 20, 2020. doi:10.1001/jamainternmed.2020.6557

METHYLPREDNISOLONE

" …EARLY, LOW-DOSE AND SHORT-TERM APPLICATION OF METHYLPREDNISOLONE WAS ASSOCIATED WITH BETTER CLINICAL OUTCOMES IN SEVERE PATIENTS WITH COVID-19 PNEUMONIA, AND SHOULD BE CONSIDERED BEFORE THE OCCURRENCE OF ARDS."



Wang Y, Jiang W, He Q, et al. A retrospective cohort study of methylprednisolone therapy in severe patients with COVID-19 pneumonia.
Signal Transduct Target Ther. 2020;5(1):57. Published 2020 Apr 28. doi:10.1038/s41392-020-0158-2

METHYLPREDNISOLONE

" SUMMARY – IN THIS MULTI-CENTER QUASI-EXPERIMENTAL STUDY OF 213 PATIENTS, WE DEMONSTRATE EARLY SHORT COURSE OF METHYLPREDNISOLONE IN MODERATE TO SEVERE COVID-19 PATIENTS REDUCED THE COMPOSITE ENDPOINTS OF ESCALATION OF CARE FROM WARD TO ICU, NEW REQUIREMENT FOR MECHANICAL VENTILATION AND MORTALITY. "

" … EARLY USE OF A SHORT COURSE OF METHYLPREDNISOLONE, AN INEXPENSIVE AND READILY AVAILABLE AGENT, IN PATIENTS WITH MODERATE TO SEVERE COVID-19 MAY PREVENT PROGRESSION OF DISEASE AND IMPROVE OUTCOMES."

See Medical Experts Discuss This Critical Treatment

https://www.youtube.com/watch?v=XfDWjPxhKcE&utm_source=silverchair&utm_campaign=jama_network&utm_content=car_weekly_highlights&cmp=1&utm_medium=email

Fadel R. et. al. Henry Ford COVID-19 Management Task Force. Early Short Course Corticosteroids in Hospitalized Patients with COVID-19. medRxiv 2020.05.04.20074609; doi: https://doi.org/10.1101/2020.05.04.20074609

REMDESIVIR IMPROVED CLINICAL OUTCOMES

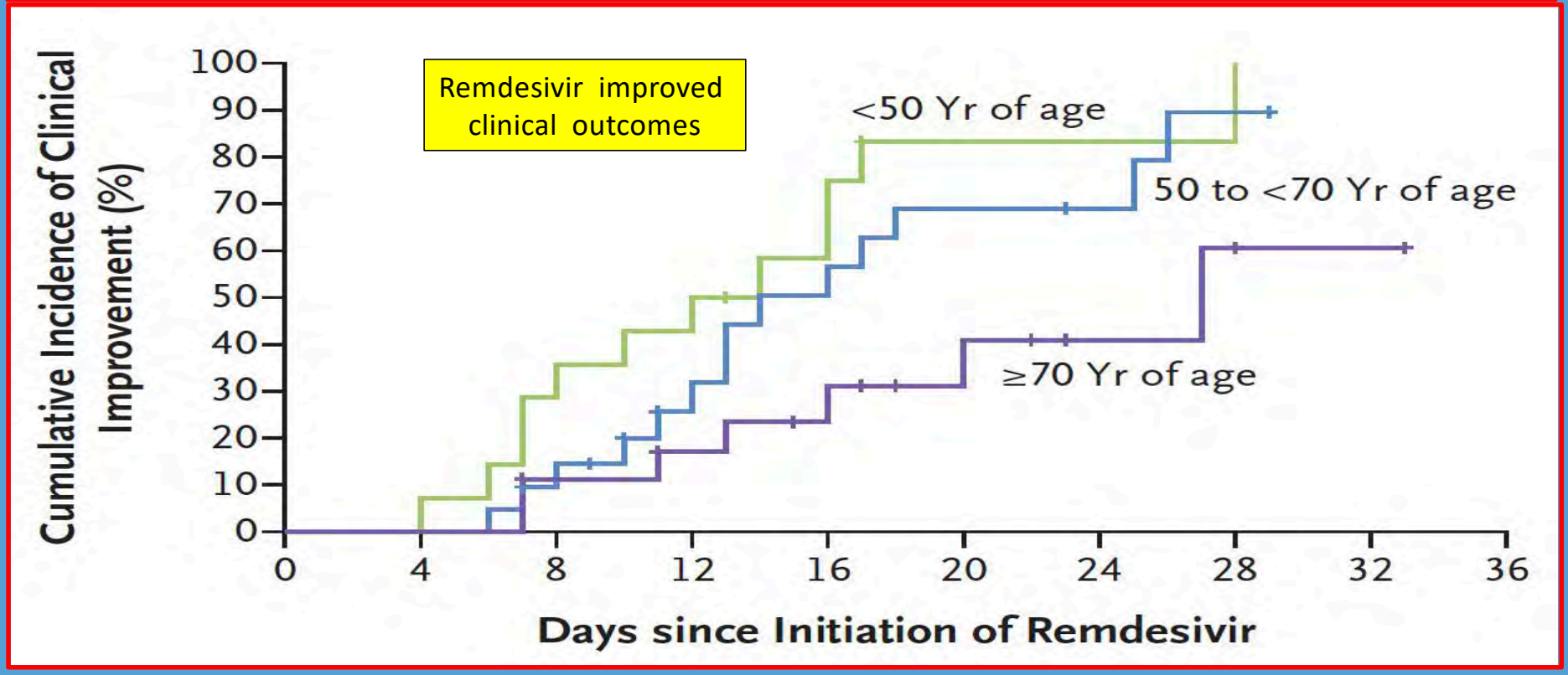
53 SARS-CoV-2 PATIENTS ON MECHANICAL VENTILATION +/- ECMO RECEIVED AT LEAST ONE DOSE OF REMDESIVIR (200 MG IV). FOR A MEDIAN OF 18 DAYS. THEY WERE EVALUATED RETROSPECTIVELY AND ASSESSED FOR CLINICAL OUTCOMES.

" IN THIS COHORT OF PATIENTS HOSPITALIZED FOR SEVERE COVID-19 WHO WERE TREATED WITH COMPASSIONATE - USE REMDESIVIR, CLINICAL IMPROVEMENT WAS OBSERVED IN 36 OF 53 PATIENTS (68%). MEASUREMENT OF EFFICACY WILL REQUIRE ONGOING RANDOMIZED, PLACEBO CONTROLLED TRIALS OF REMDESIVIR THERAPY. "

FUNDED BY GILEAD SCIENCES.

Grein J, et. al. Compassionate Use of Remdesivir for Patients with Severe Covid-19. NEJM 2020. DOI: 10.1056/NEJMoa2007016 https://www.nejm.org/doi/full/10.1056/NEJMoa2007016

REMDESIVIR
COVID-19 PATIENTS



Grein J, et. al. Compassionate Use of Remdesivir for Patients with Severe Covid-19. NEJM 2020. DOI: 10.1056/NEJMoa2007016
https://www.nejm.org/doi/full/10.1056/NEJMoa2007016

REMDESIVIR

DID NOT CURE or PREVENT DEATH

PROTOCOL

1,059 HOSPITALIZED COVID-19 PATIENTS RANDOMIZED INTO REMDESIVIR TREATMENT (538) AND NON - TREATMENT (521) GROUPS.

OUTCOMES

" REMDESIVIR WAS SUPERIOR TO PLACEBO IN SHORTENING THE TIME TO RECOVERY IN ADULTS HOSPITALIZED WITH COVID-19 AND EVIDENCE OF LOWER RESPIRATORY TRACT INFECTION."

" GIVEN HIGH MORTALITY DESPITE THE USE OF REMDESIVIR, IT IS CLEAR THAT TREATMENT WITH AN ANTIVIRAL DRUG ALONE IS NOT LIKELY TO BE SUFFICIENT. "

Beigel J, et. al. Remdesivir for the Treatment of Covid-19. NEJM May 22, 2020. https://www.nejm.org/doi/full/10.1056/NEJMoa2007764

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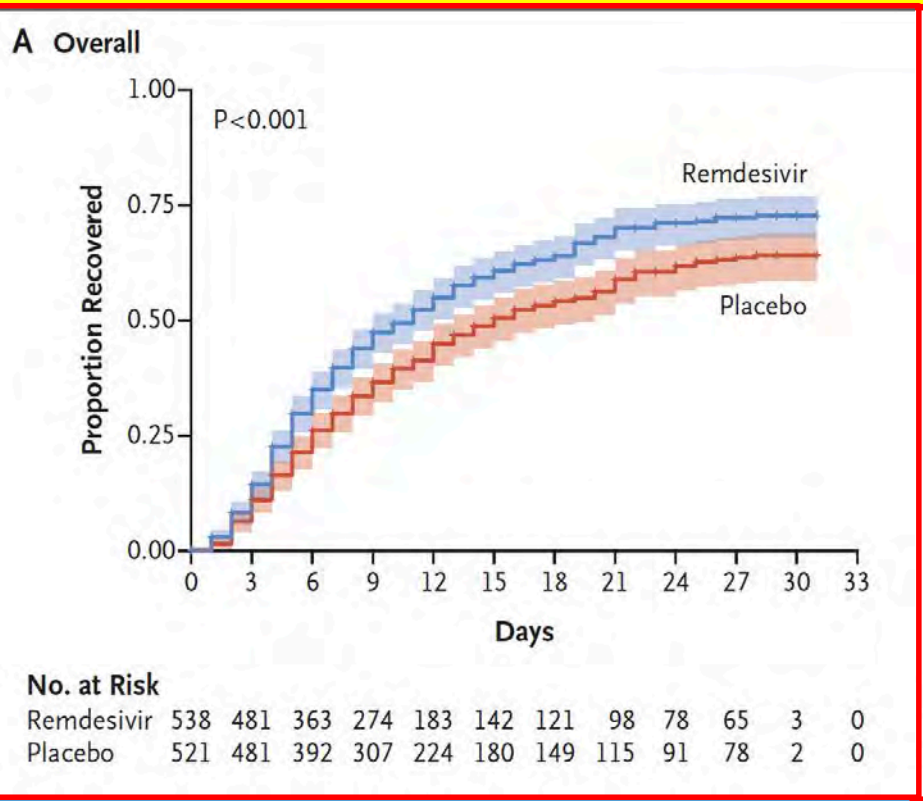
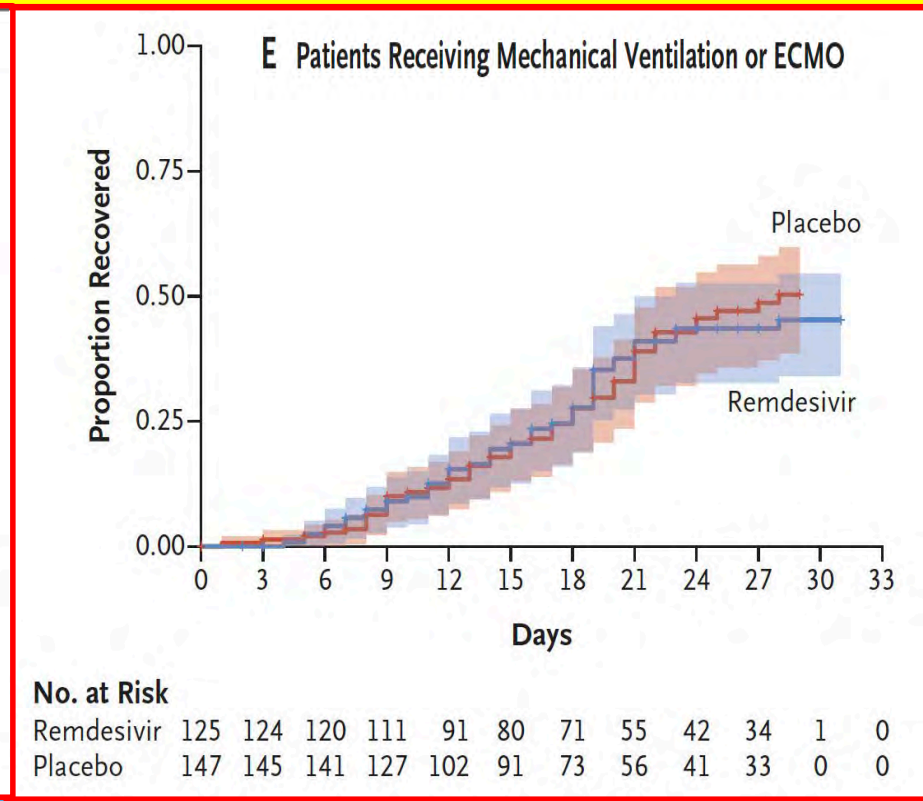
REMDESIVIR

DID NOT CURE OR PREVENT DEATH WHEN GIVEN LATE





Beigel J, et. al. Remdesivir for the Treatment of Covid-19 — Preliminary Report. NEJM May 22, 2020.
https://www.nejm.org/doi/full/10.1056/NEJMoa2007764

CONVALESCENT PLASMA

CONVALESCENT PLASMA IS ALLOWED BY FDA

AS AN INVESTIGATIONAL BLOOD. PRODUCT

DONORS OF CONVALESCENT PLASMA

1. SYMPTOMS MUST BE COMPLETELY GONE FOR ≥ 28 DAY, or
2. SYMPTOMS MUST BE GONE FOR AT LEAST 14 DAYS PRIOR TO DONATION and CoV-2 RT-PCR TESTS MUST BE NEGATIVE.
3. FEMALE DONORS MUST BE NEGATIVE FOR HLA ANTIBODIES.
4. DONORS MUST BE SCREENED FOR TRANSFUSION TRANSMITTED INFECTIONS AND PERHAPS DEGLYCOSYLATED ANTI-COV-2 IgG.

https://www.fda.gov/vaccines-blood-biologics/investigational-new-drug-ind-or-device-exemption-ide-process-cber/recommendations-investigational-covid-19-convalescent-plasma

CONVALESCENT PLASMA

OPEN-LABEL, MULTICENTER, RANDOMIZED CLINICAL TRIAL
52 Patients on Standard Treatment + Convalescent Plasma
51 Patients on Standard Treatment Alone. Wuhan, China

ELIMINATION OF CoV-2 RNA AT 72 Hours
Plasma Treatment = 87.2%
Control Patients = 37.5%

MORTALITY + TIME TO DISCHARGE
No Difference in Mortality
No Difference in Time to Discharge

CONVALESCENT PLASMA HELPED ELIMINATE THE VIRUS BUT MADE NO DIFFERENCE IN MORTALITY.

Li L et. al. Effect of Convalescent Plasma Therapy on Time to Clinical Improvement in Patients With Severe and Life-threatening COVID-19: A Randomized Clinical Trial. JAMA. doi:10.1001/jama.2020.10044

CONVALESCENT PLASMA

HELPED ELIMINATE VIRUS, BUT MADE NO DIFFERENCE IN MORTALITY.

CONVALESCENT PLASMA IMPROVED RESOLUTION OF SHORTNESS OF BREATH AND FATIGUE IN PATIENTS WITH MODERATE COVID-19 AND LED TO HIGHER NEGATIVE CONVERSION OF SARS-COV-2 RNA ON DAY 7 POST-ENROLMENT, BUT THIS DID NOT TRANSLATE INTO A REDUCTION IN 28 DAY MORTALITY OR PROGRESSION TO SEVERE DISEASE.

CONVALESCENT PLASMA WAS NOT ASSOCIATED WITH A REDUCTION IN PROGRESSION TO SEVERE COVID-19 OR ALL CAUSE MORTALITY. THIS TRIAL HAS HIGH GENERALIZABILITY AND APPROXIMATES CONVALESCENT PLASMA USE IN REAL LIFE SETTINGS WITH LIMITED LABORATORY CAPACITY.

MEASUREMENT OF NEUTRALIZING ANTIBODY TITERS IN DONORS AND PARTICIPANTS MIGHT CLARIFY THE ROLE OF CONVALESCENT PLASMA IN THE MANAGEMENT OF COVID-19.

Agarwal A., et. al. Convalescent plasma in the management of moderate covid-19 in adults in India: open label phase II multicentre randomised controlled trial (PLACID Trial). BMJ 2020;371:m3939. http://dx.doi.org/10.1136/bmj.m3939

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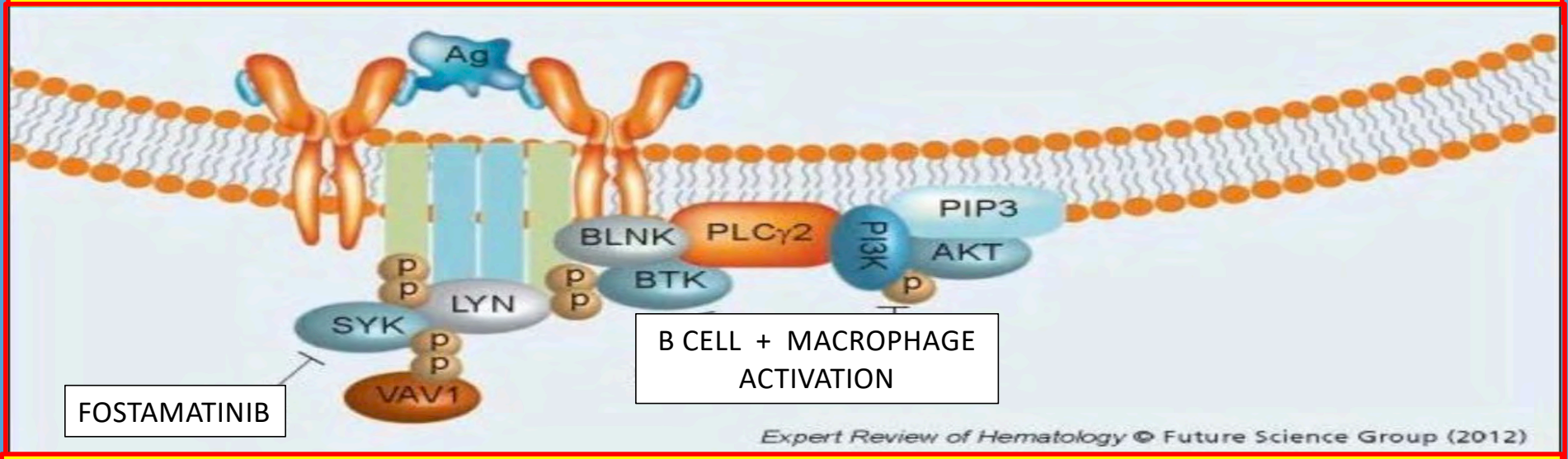
FOSTAMATINIB

DEGLYCOSYLATED ANTI-CoV-2 IgG : COV-2 IMMUNE COMPLEXES INDUCE RELEASE OF MACROPHAGE IL-6, TNF, IL-1*B* and IL-8.



FOSTAMATINIB INHIBITS RELEASE OF INFLAMMATORY CYTOKINES BY INHIBITING SPLEEN TYROSINE KINASE (Syk)

Hoepel W, et. al. Anti-SARS-CoV-2 IgG from severely ill COVID-19 patients promotes macrophage hyper-inflammatory responses. bioRxiv 2020.07.13.190140; doi: https://doi.org/10.1101/2020.07.13.190140

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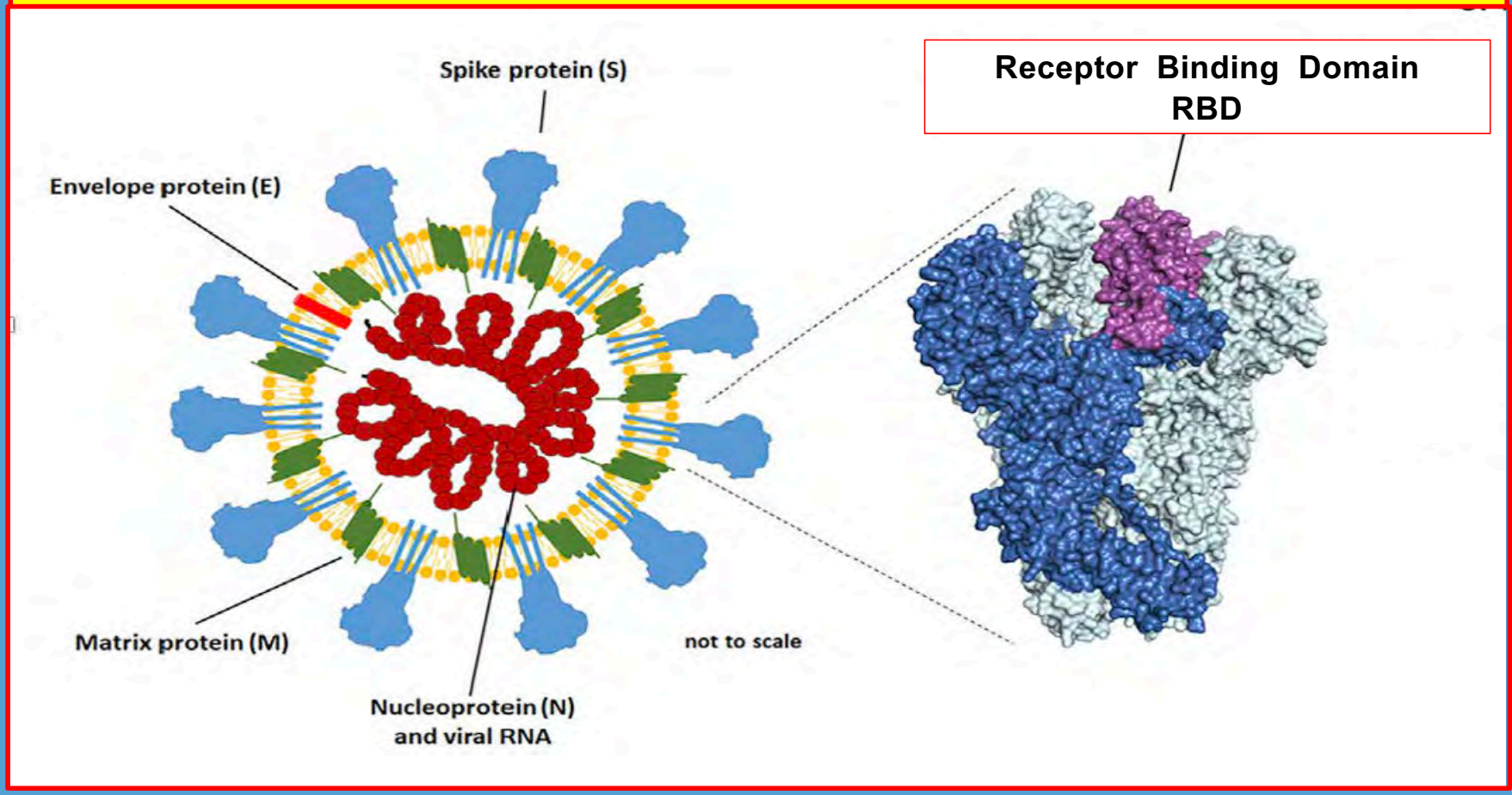
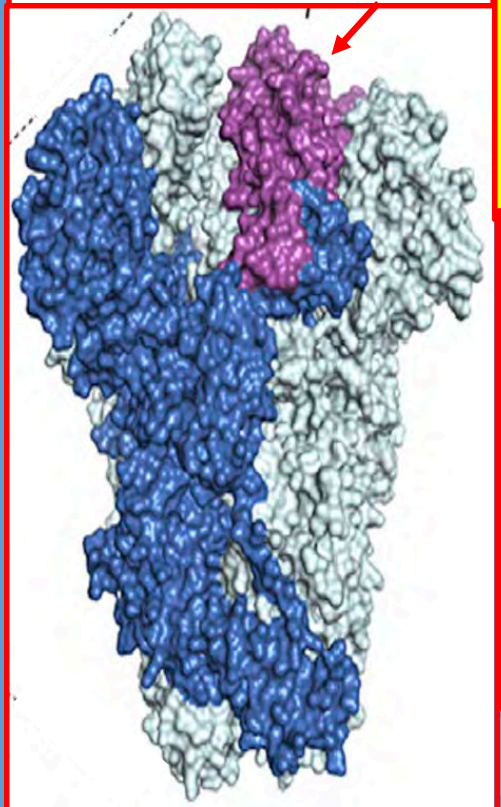
ANTI-CoV-2 MONOCLONAL ANTIBODY



ANTI-CoV-2 MONOCLONAL ANTIBODY

Receptor Binding Domain (RBD)



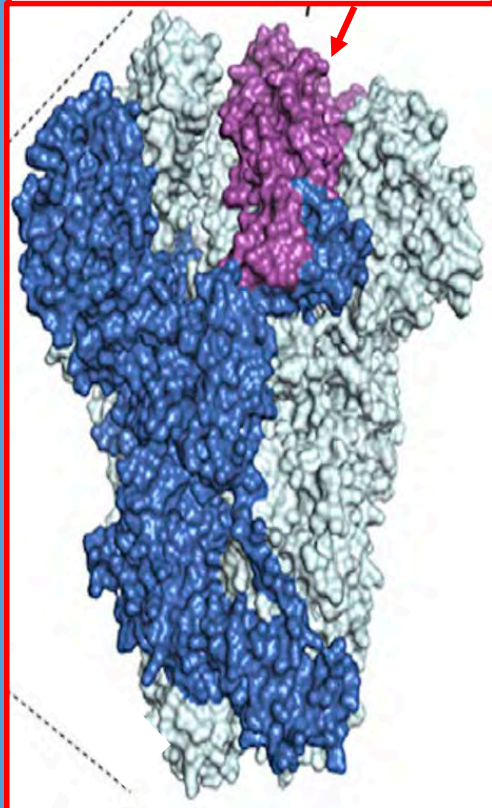
452 COV-2 INFECTED PATIENTS WERE RANDOMIZED TO RECEIVE A SINGLE INTRAVENOUS INFUSION OF A PLACEBO OR HIGH AFFINITY ANTI-SPIKE RBD ANTIBODY, BAMLANIVIMAB (LY-CoV555), IN ONE OF THREE DOSES: 700 mg, 2800 mg or 7000 mg.

THE PERCENTAGE OF COVID-19 PATIENTS WHO REQUIRED HOSPITALIZATION OR VISITS TO AN EMERGENCY DEPARTMENT WAS 1.6% IN PATIENTS RECEIVING 2800 mg OF BAMLANIVIMAB VS. 6.3% IN THE PLACEBO GROUP. HOSPITALIZATION RATES FOR HIGH RISK PATEINTS WAS 4.2% IN THE TREATMENT GROUP, AND 14.6% IN THE PLACEBO GROUP.

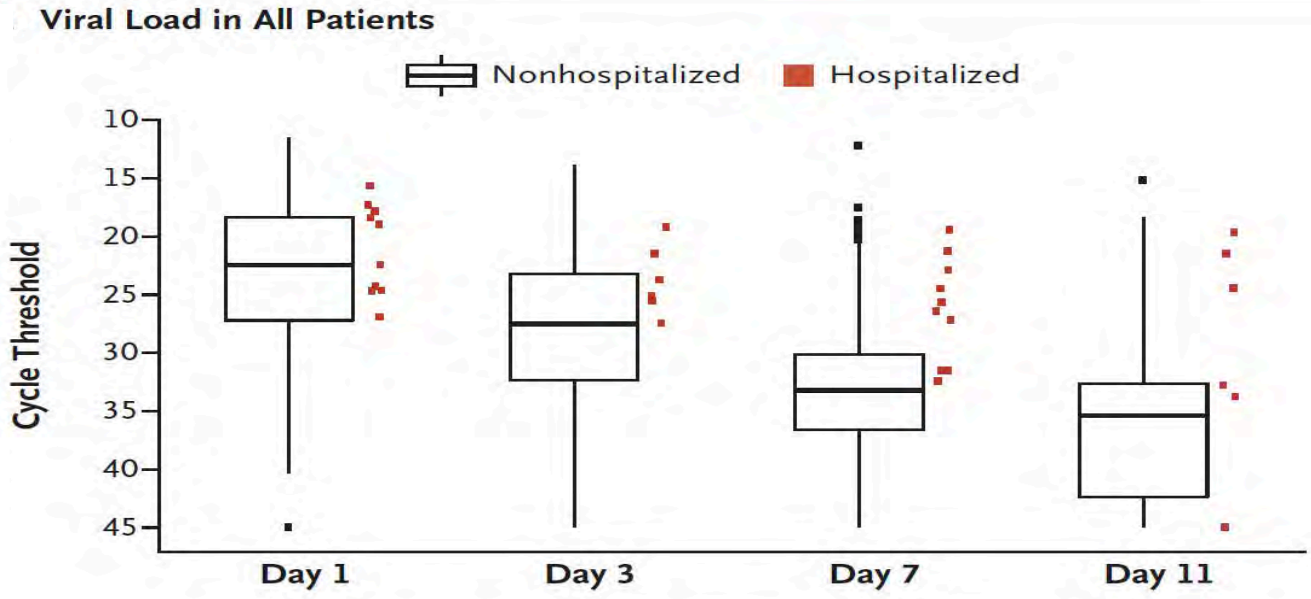
Chen P. et. al. SARS-CoV-2 Neutralizing Antibody LY-CoV555 in Outpatients with Covid-19. N Engl J Med. 2020 Oct 28. doi: 10.1056/NEJMoa2029849. Epub ahead of print. PMID: 33113295.

ANTI-CoV-2 MONOCLONAL ANTIBODY

Receptor Binding Domain (RBD)



VIRAL RNA DECLINED BY A MEAN OF 99.97% IN PATIENTS WHO RECEIVED 2,800 mg OF LY-CoV555.



Chen P. et. al. SARS-CoV-2 Neutralizing Antibody LY-CoV555 in Outpatients with Covid-19. N Engl J Med. 2020 Oct 28. doi: 10.1056/NEJMoa2029849. Epub ahead of print. PMID: 33113295.

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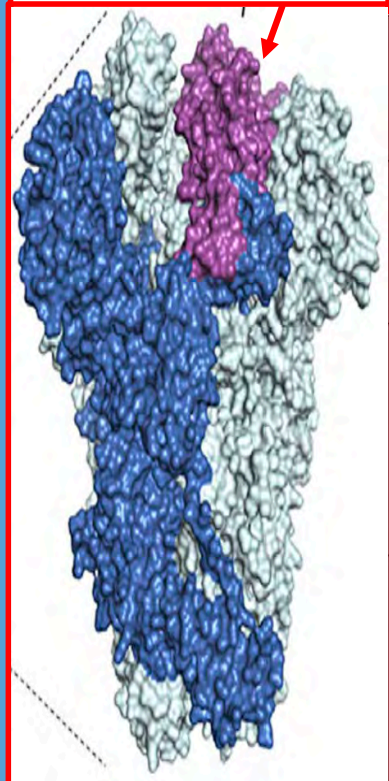
Receptor Binding Domain (RBD)



ANTI-SPIKE MONOCLONAL ANTIBODIES

SOURCE	PRODUCT	ANTIBODY	INDICATION Early Onset CoV-2 Infection	DOSE	FDA EUA
AstraZeneca	AZD7442 [1, 2]	AZD8895 AZD1061 long half-life	Investigational	TBD	--
Eli Lilly	Bamlanivimab		Mild to Moderate Age ≥ 12 years ≥ 40 kg High Risk Patient	700 mg	Yes [3]
Regeneron	Casirivimab Imdevimab	REGN10933 REGN10987	Mild to Moderate Age ≥ 12 years ≥ 40 kg High Risk Patient	1,200 mg each	Yes [4]

1. https://clinicaltrials.gov/ct2/show/NCT04507256?term=NCT04507256&draw=2&rank=1
2. Zost, S.J. *et al.* Potently neutralizing and protective human antibodies against SARS-CoV-2. *Nature* 584, 443–449 (2020). https://doi.org/10.1038/s41586-020-2548-6
3. Eli Lilly: Bamlanivimab Emergency Use Authorization https://www.fda.gov/media/143602/download
4. Regeneron: FDA Approval for Casirivimab and Imdevimab. https://www.fda.gov/media/143891/download

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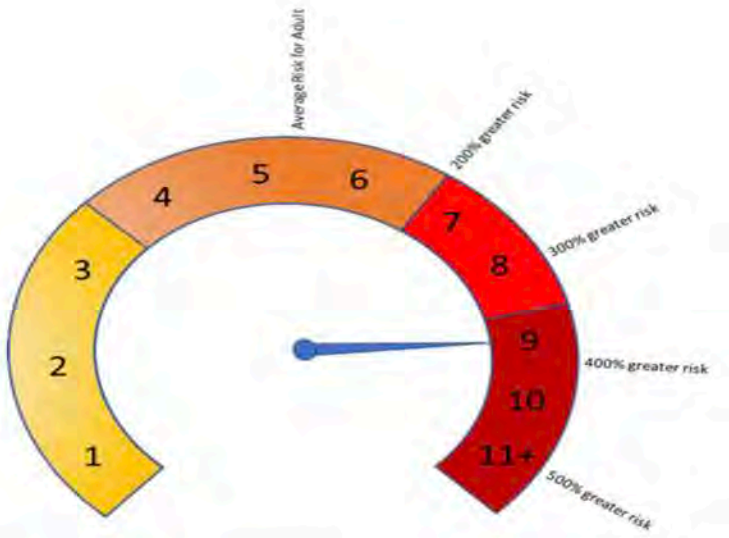
ANTI-SPIKE MONOCLONAL ANTIBODY

PATIENT SELECTION – IF SUPPLY IS LIMITED

COVID-19 Risk Calculator

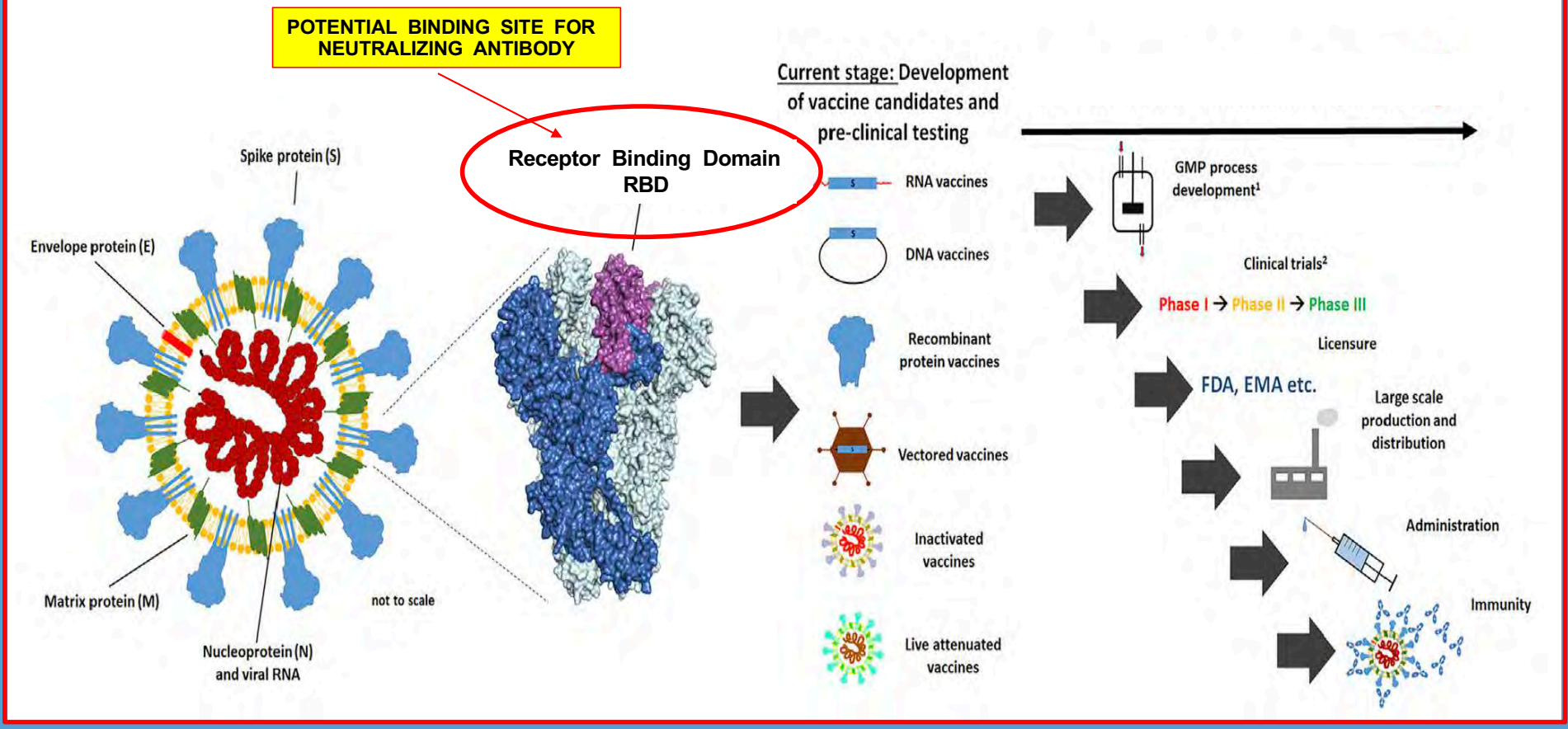
Risk Factor	Points
Demographic Factors	
Age	0.5 pts / decade
Male	1
Non-White Race or Hispanic/Latinx	2
Symptom Factor	
Shortness of breath	1
Major Comorbidities	
Diabetes mellitus	2
Immunocompromised	2
Obesity	2
Other Comorbidities	
Hypertension	1
Coronary artery disease (MI)	1
Cardiac Arrhythmia	1
Congestive Heart Failure	1
Chronic Kidney Disease	1
Chronic Pulmonary Disease	1
Chronic Liver Disease	1
Cerebrovascular disease	1
Chronic Neurologic disease	1



	Derivation Cohort N=16,030, Hospitalized N=990 (6.2%)		Validation Cohort N=5976, Hospitalized N=408 (6.8%)	
	AUROC	95% CI	AUROC	95% CI
Hospitalization	0.82	0.81-0.84	0.8	0.78-0.82
28-day Mortality	0.91	0.83-0.94	0.8	0.69-0.9

Intermountain Healthcare

SPIKE PROTEIN VACCINE



Amanat F, Krammer F. SARS-CoV-2 Vaccines: Status Report. *Immunity*. 2020;52(4):583–589. doi:10.1016/j.immuni.2020.03.007

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VACCINES + BIOLOGICS

Platform	Type	Source	Phase	FDA EUA	WARP
Simian Non-Rep. Virus	Chimpanzee ChAdOx1-S AZD1222	University of Oxford AstraZeneca		No	Yes
Non-Rep Virus	Adenovirus Type 5 Vector Ad5-nCoV	CanSino Biological Inc. Beijing Inst Biotech	3	-	
Human Non-Replicating Viral Vector	Adenovirus 26 Ad26.COVS1 JNJ-78436735	Johnson + Johnson Janssen		Yes	Yes
Stomatitis Virus Nonreplicating	Replication Defective Stomatitis Viral Vector	Merck International AIDS Vaccine Initiative		DISCONTINUED	
mRNA	LNP-mRNA	Moderna		Yes	Yes
mRNA	LNP-mRNAs	Pfizer BioNTech		Yes	Yes
mRNA	CV07050101	CureVac	2	-	
mRNA	MRT5500	Sanofi Translate Bio	2	-	Yes

Platform	Type	Source	Phase	FDA EUA	WARP
Long Half-Life Monoclonal Ab	2 Anti-Spike Monoclonal	AstraZeneca AZD7442	3	-	Yes
Monoclonal Ab	Anti-Spike Monoclonal Ab	Eli Lilly *Bamlanivimab*		Yes	Yes
Monoclonal Ab	Anti-Spike Monoclonal Ab	Regeneron *REGEN-CoV2*		Yes	Yes
DNA	DNA Plasmid Vaccine with Electroporation	Inovio Pharmaceuticals	2	-	Yes
Inactivated Virus	Inactivated + Alum CoronaVac	Sinovac	3	-	
Inactivated Virus	Inactivated Virus Covaxin	Bharat Biotech India	3	-	
Spike Rec. Nanoparticles + Adjuvant	Full length Spike Recombinant Nanoparticles + Matrix-M adjuvant	Novavax	3	-	Yes

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VACCINES + BIOLOGICALS

Platform	Type	Source	Phase	EUA	WARP
Simian Non-Replicating Virus	**Chimpanzee ChAdOx1-S** AZD1222	**AstraZeneca** University of Oxford	**3**	Suspended	**Yes**
mRNA	**LNP-mRNA**	**Moderna**		Yes	**Yes**
mRNA	**LNP-mRNAs**	**Pfizer** BioNTech		Yes	**Yes**
Monoclonal Ab Long Half-Life	**Anti-Spike Monoclonals** AZD7442 *AZD8895 + AZD1061*	**AstraZeneca**	**3**		**Yes**
Monoclonal Ab	**Anti-Spike Monoclonal** *Bamlanivimab*	**Eli Lilly**		**Yes**	**Yes**
Monoclonal Ab	**Anti-Spike Monoclonals** *Casirivimab + Imdevimab*	**Regeneron**		**Yes**	**Yes**

https://www.raps.org/news-and-articles/news-articles/2020/3/covid-19-vaccine-tracker

RISKS ASSOCIATED WITH COVID-19 VACCINE DEVELOPMENT

Potential risks associated with vaccine development for COVID-19

Antibodies that bind virus without neutralizing infectivity can cause disease through increased viral replication or formation of immune complexes that deposit in tissue and activate complement pathways associated with inflammation. T helper 2 cell (T_H2)–biased responses have also been associated with ineffective vaccines that lead to enhanced disease after subsequent infection. Antibody-dependent enhancement (ADE) of viral replication has occurred in viruses with innate macrophage tropism. Virus-antibody immune complexes and T_H2-biased responses can both occur in vaccine-associated enhanced respiratory disease (VAERD).

	Antibody-mediated		T cell–mediated
	ADE	**VAERD**	**VAERD**
Mechanism	Fc-mediated increase in viral entry	Immune complex formation and complement deposition	T_H2-biased immune response
Effectors	Macrophage activation and inflammatory cytokines	Complement activation and inflammatory cytokines	Allergic inflammation and T_H2 cytokines
Mitigation	Conformationally correct antigens and high-quality neutralizing antibody		T_H1-biasing immunization and $CD8^+$ T cells

Barney S. Graham Science 2020;368:945-946

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Science AAAS

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RISKS ASSOCIATED WITH COVID-19

POLYETHYLENE GLYCOL (PEG) + POLYSORBATE

Pfizer-BioNTech COVID-19 Vaccine (FDA)

mRNA (nucleoside-modified messenger RNA encoding the viral spike glycoprotein (S) of SARS-CoV-2).

Other ingredients include:

4-hydroxybutyl)azanediyl)bis(hexane-6,1-diyl)bis(2-hexyldecanoate)
2 [(**polyethylene glycol**) **- 2000**]-N,N-ditetradecylacetamide
1,2-Distearoyl-sn-glycero-3- phosphocholine
Cholesterol
Potassium chloride
Monobasic K PO_4
Sodium chloride Sucrose.
Dibasic sodium phosphate dehydrate and

Moderna COVID-19 Vaccine (FDA)

mRNA (Nucleoside-modified mRNA encoding the viral spike (S) glycoprotein of SARS-CoV-2)

Other ingredients include:

SM-102 (an ionizable lipid used to form lipid nanoparticles)
1,2-dimyristoyl-rac-glycero3-methoxy**polyethylene glycol-2000** [PEG2000-DMG]
1,2-distearoyl-snglycero-3-phosphocholine [DSPC]
Cholesterol
Tromethamine
Tromethamine hydrochloride
Acetic acid
Sodium acetate
Sucrose.

RISKS ASSOCIATED WITH COVID-19

POLYETHYLENE GLYCOL (PEG) + POLYSORBATE

Janssen – Johnson & Johnson COVID-19 Vaccine (CDC.gov)

One dose (0.5 ml) contains recombinant, replication-incompetent **Adenovirus 26** vector, encoding a stabilized variant of the SARS-CoV-2 Spike protein.

Other ingredients include:

Polysorbate - 80
2-hydroxypropyl-β-cyclodextrin
Sodium chloride
Hydrochloric acid
Water for injection.
Trisodium citrate dihydrate
Citric acid monohydrate
Sodium hydroxide
Ethanol

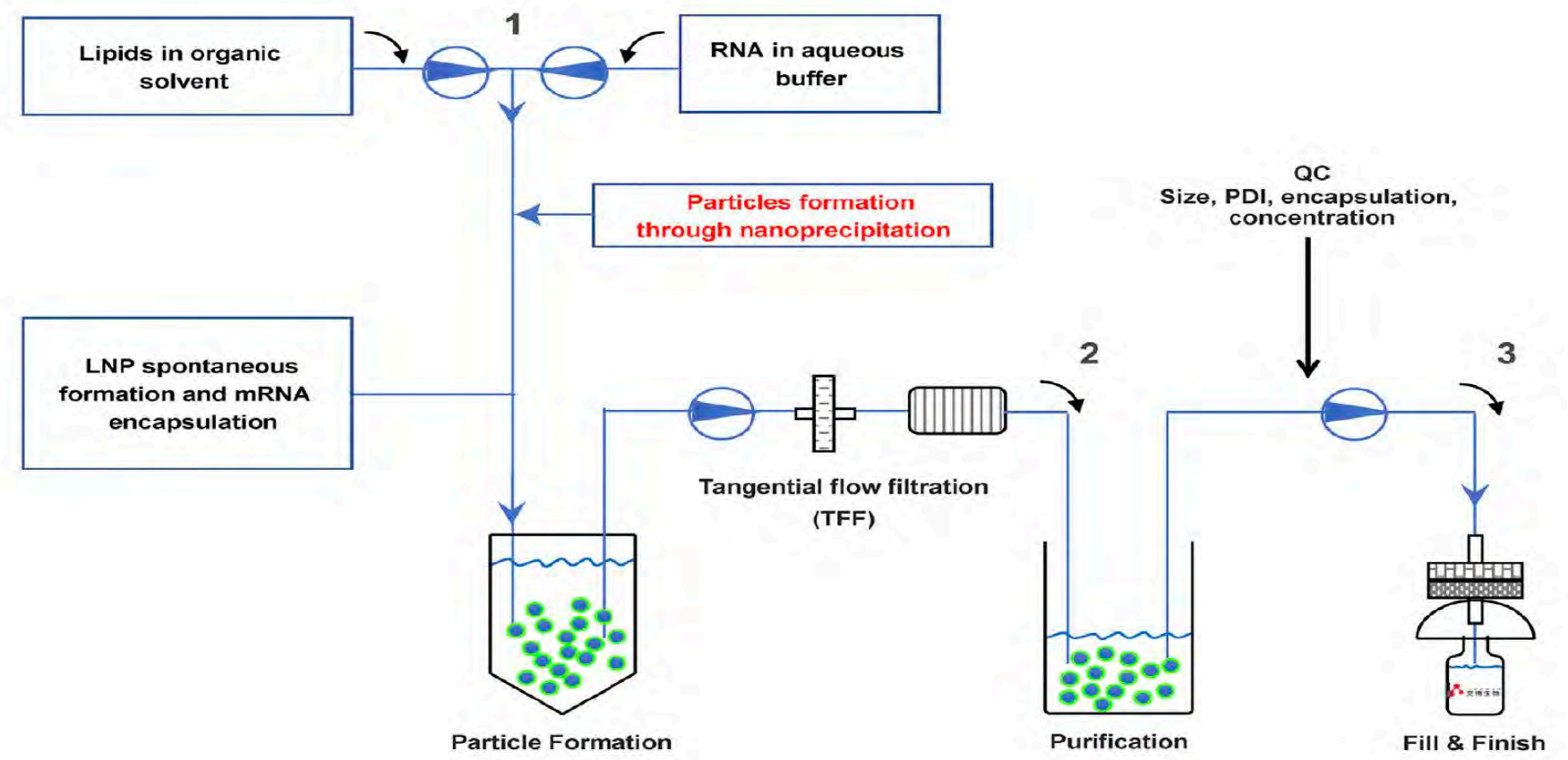
AstraZeneca COVID-19 Vaccine (Gov UK).

One dose (0.5 ml) contains: 5×10^{10} viral particles of recombinant, replication-deficient **Chimpanzee Adenovirus** vector encoding the SARS CoV 2 Spike (S) glycoprotein produced in genetically modified human embryonic kidney cells (HEK).

Other ingredients include:

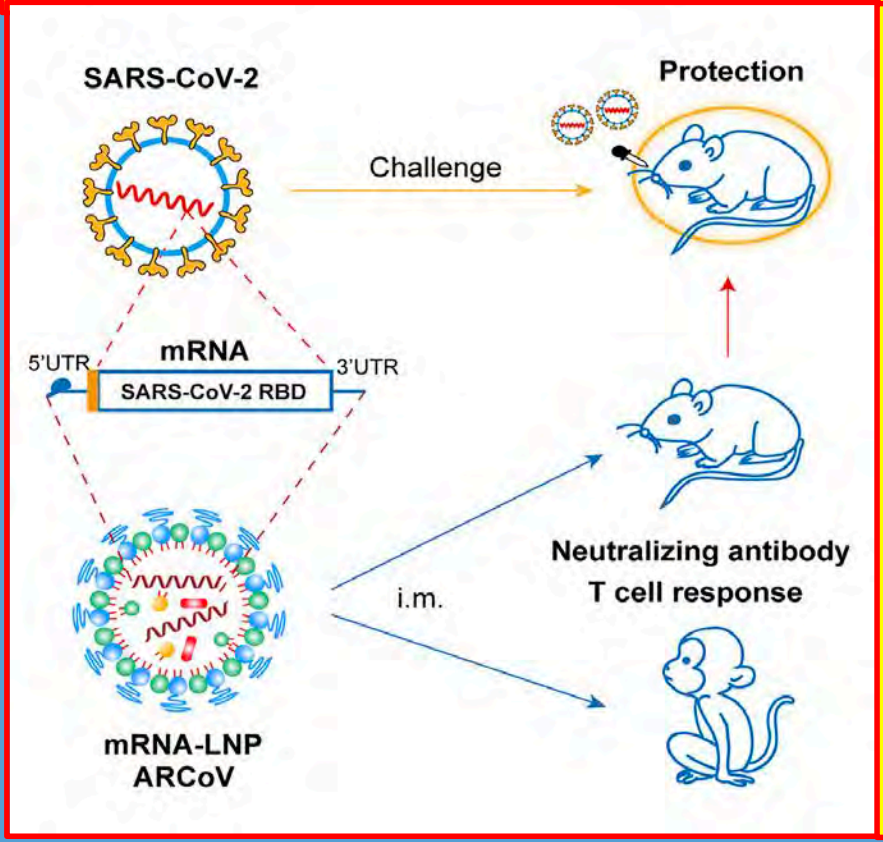
Polysorbate – 80
Citric acid monohydrate
Sodium chloride
Hydrochloric acid
Water for injection.
2-hydroxypropyl-β-cyclodextrin
Trisodium citrate dihydrate
Sodium hydroxide
Ethanol

LIPID NANOPARTICLE ENCAPSULATION



Zhang et al., A Thermostable mRNA Vaccine against COVID-19, Cell (2020). https://doi.org/10.1016/j.cell.2020.07.024 j.cell.2020.07.024

THERMOSTABLE LIPID NANOPARTICLE CoV-2-RBD VACCINE



THERMOSTABLE

LNP - ENCAPSULATED mRNA VACCINE (ARCoV) USING THE SPIKE RECEPTOR BINDING DOMAIN SEQUENCE.

EFFECTIVE ANTIGEN

INDUCED NEUTRALIZING ANTIBODIES AND T - CELL IMMUNITY IN MICE AND MONKEYS.

PROTECTION

VACCINATION CONFERRED FULL PROTECTION AGAINST COV-2 CHALLENGE IN MICE.

Zhang et al., A Thermostable mRNA Vaccine against COVID-19, Cell (2020). https://doi.org/10.1016/j.cell.2020.07.024 j.cell.2020.07.024

MODERNA CoV-2 mRNA
SPIKE PROTEIN VACCINE STUDY

Safety and Immunogenicity Study of 2019-nCoV Vaccine (mRNA-1273) for Prophylaxis SARS CoV-2 Infection

Study Description — **IN PHASE 3**

Brief Summary: **Volunteers produced neutralizing anti-SARS-CoV-2 IgG with minimal side effects.**

This is a phase I, open-label, dose ranging clinical trial in males and non-pregnant females, 18 to 55 years of age, inclusive, who are in good health and meet all eligibility criteria. This clinical trial is designed to assess the safety, reactogenicity and immunogenicity of **mRNA-1273** manufactured by ModernaTX, Inc. **mRNA-1273** is a novel lipid nanoparticle (LNP)-encapsulated mRNA-based vaccine that encodes for a full-length, prefusion stabilized spike (S) protein of SARS-CoV-2. Enrollment will occur at one domestic site. Forty-five subjects will be enrolled into one of three cohorts and will receive an intramuscular (IM) injection of **mRNA-1273** on Days 1 and 29 in the deltoid muscle. Subjects will be followed through 12 months post second vaccination (Day 394). The primary objective is to evaluate the safety and reactogenicity of a 2-dose vaccination schedule of **mRNA-1273**, given 28 days apart, across 3 dosages in healthy adults.

https://clinicaltrials.gov/ct2/show/NCT04283461

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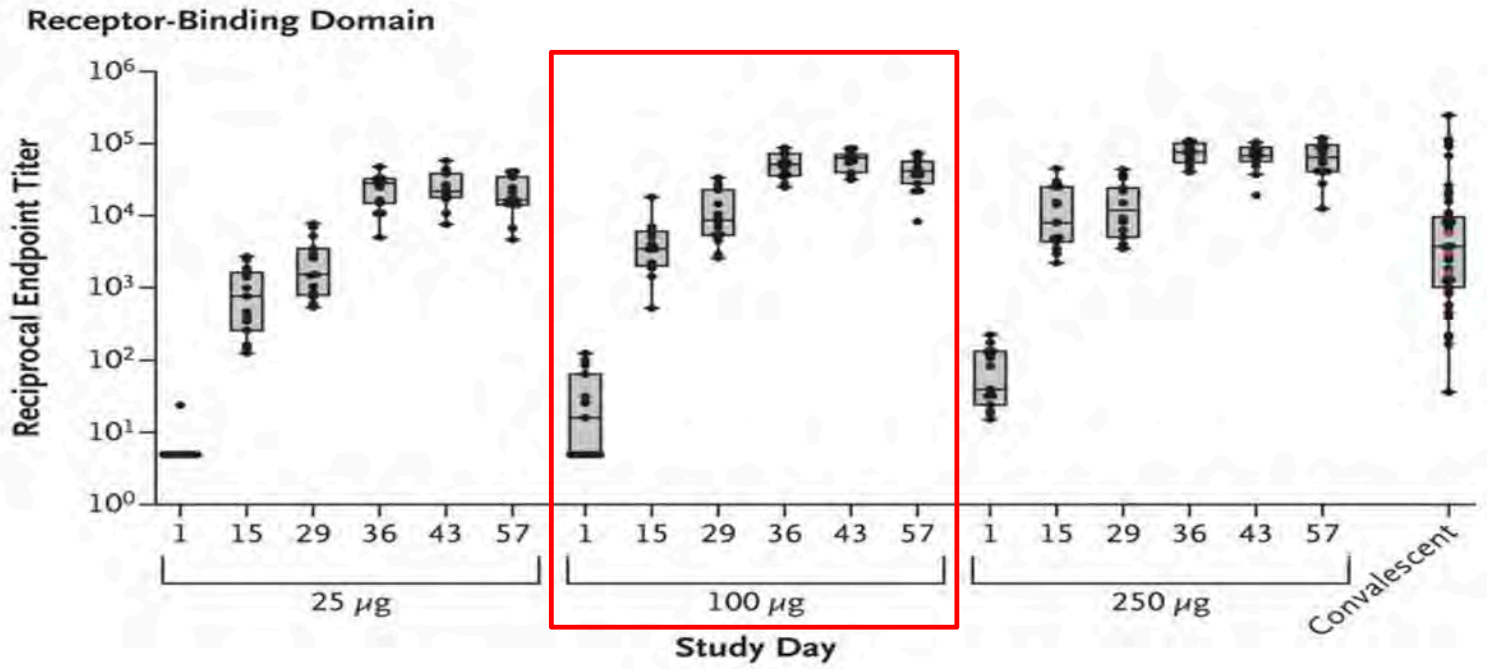
MODERNA CoV-2 mRNA VACCINE



100 ug DOSE PRODUCED BEST IMMUNE RESPONSE WITH MODERATE LOCAL SYMPTOMS AFTER 2nd DOSE

Jackson LA et. al., An mRNA Vaccine against SARS-CoV-2 — Preliminary Report. NEJM July 14, 2020. DOI: 10.1056/NEJMoa2022483

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MODERNA CoV-2 mRNA VACCINE

MOST COMMON ADVERSE REACTIONS

PAIN INJECTION SITE	**91.6 %**
FATIGUE	**68.5 %**
HEADACHE	**63.0 %**
MUSCLE PAIN	**59.6 %**
JOINT PAIN	**44.8 %**
CHILLS	**43.4 %**

https://www.fda.gov/media/144434/download

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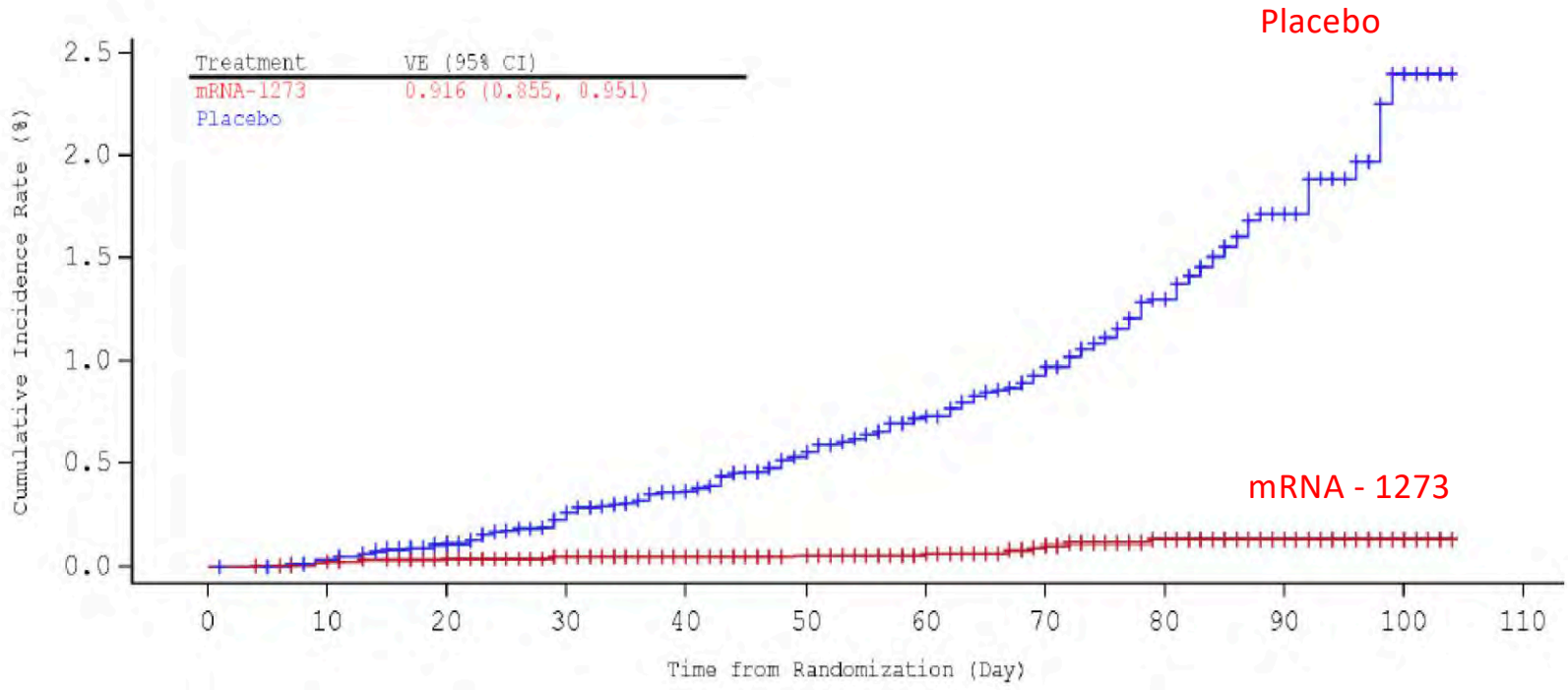
MODERNA CoV-2 mRNA VACCINE

Figure 2. Cumulative Incidence Curves for the First COVID-19 Occurrence After Randomization, mITT Set



https://www.fda.gov/media/144434/download

MODERNA CoV-2 mRNA VACCINE

Table 9. Interim Analysis[a] for Primary Efficacy Endpoint, COVID-19 Starting 14 Days After the 2nd Dose, Per-Protocol Set

Primary Endpoint: COVID-19 (per adjudication committee assessment)	Vaccine Group N=13934 Cases n (%) (Incidence rate per 1,000 person-years)	Placebo Group N=13883 Cases n (%) (Incidence rate per 1,000 person-years)	Vaccine Efficacy (VE) % (95% CI)*	Met Predefined Success Criterion**
All participants	5 (<0.1) 1.840	90 (0.6) 33.365	94.5% (86.5%, 97.8%)	Yes
18 to <65	5 / 10407 (<0.1) 2.504	75 / 10384 (0.7) 37.788	93.4% (83.7%, 97.3%)	NA
65 and older	0 / 3527	15 / 3499 (0.4) 21.046	100%	NA

https://www.fda.gov/media/144434/download

MODERNA CoV-2 mRNA VACCINE

Table 14. Severe COVID-19 Cases Starting 14 Days After Second Dose Based on Adjudication Committee Assessment, Per-Protocol Set

	Vaccine Group N=13934 Cases n (%)	Placebo Group N=13883 Cases n (%) Incidence rate per 1,000 person-years	Vaccine Efficacy (VE) % (95% CI)*
Severe COVID-19	0	11 (<0.1); 4.072	100%

There were 4 additional severe COVID-19 cases which met the protocol-defined severe COVID-19 endpoint but were not able to be adjudicated in time for the interim analysis. All 4 cases were in the placebo group.

https://www.fda.gov/media/144434/download

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MODERNA CoV-2 mRNA VACCINE

Table 15. Vaccine Efficacy[a] of mRNA-1273 to Prevent COVID-19 From Dose 1 by Time Period in Participants Who Only Received One Dose, mITT Set

First COVID-19 Occurrence After Dose 1	Vaccine Group N=996 Case n (%)	Placebo Group N=1079 Case n (%)	VE (%) (95% CI)*
After dose 1	7/996 (87.5)	39/1079 (96.7)	80.2% (55.2%, 92.5%)
After dose 1 to 14 days after dose 1	5/996 (38.0)	11/1079 (41.1)	50.8% (-53.6%, 86.6%)
>14 days after dose 1**	2/983 (87.2)	28/1059 (96.2)	92.1% (68.8%, 99.1%)

https://www.fda.gov/media/144434/download

MODERNA CoV-2 mRNA VACCINE

Table 17. Final Scheduled Efficacy Analysis, Primary Endpoint, COVID-19 Starting 14 Days After the Second Dose per Adjudication Committee Assessments, Per-Protocol Set

Primary Endpoint: COVID-19 (per adjudication committee assessment)	Vaccine Group N=13934 Cases n (%) (Incidence Rate per 1,000 person-years)*	Placebo Group N=13883 Cases n (%) (Incidence Rate per 1,000 person-years)*	Vaccine Efficacy (VE) % (95% CI)**	Met Predefined Success Criterion***
All participants	11 (<0.1) 3.328	185 (1.3) 56.510	94.1% (89.3%, 96.8%)	Yes
18 to <65 years[1]	7/10551 (<0.1) 2.875	156/10521 (1.5) 64.625	95.6%; (90.6%, 97.9%)	NA
65 years and older[2]	4/3583 (0.1); 4.595	29/3552 (0.8); 33.728	86.4%; (61.4%, 95.5%)	NA

https://www.fda.gov/media/144434/download

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MODERNA CoV-2 mRNA VACCINE

Table 18. Secondary Efficacy Analysis, Severe COVID-19 Starting 14 Days After the Second Dose per Adjudication Committee Assessments, Per-Protocol Set

Severe Cases 14 Days After Dose 2 Based on Adjudication Committee Assessments	Vaccine Group N=13934 Cases n (%) (Incidence rate per 1,000 person-years)	Placebo Group N=13883 Cases n (%) (Incidence rate per 1,000 person-years)	Vaccine Efficacy (VE) % (95% CI)*
All participants	0	30 (0.2) 9.138	100%

[a] EUA request (primary analysis): November 21, 2020 efficacy data cutoff.

https://www.fda.gov/media/144434/download

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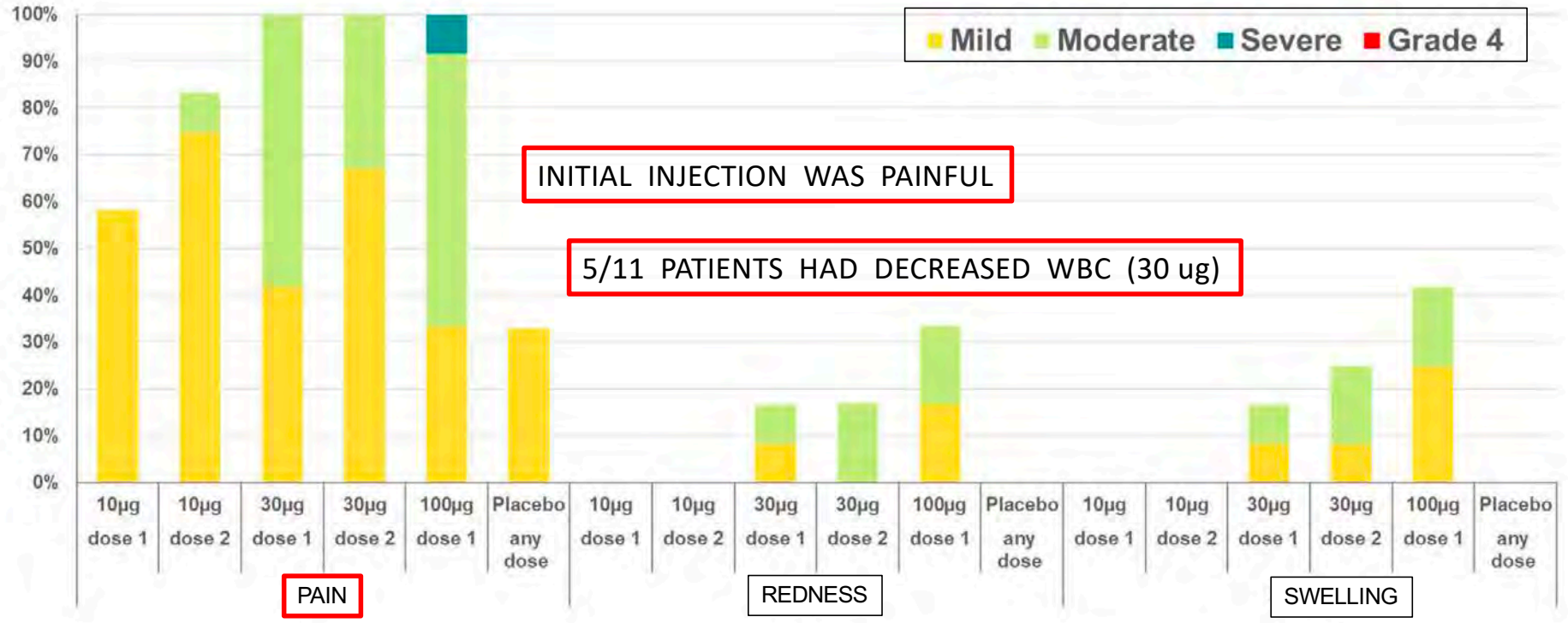
PFIZER CoV-2 mRNA

SPIKE PROTEIN VACCINE STUDY



Mulligan M. et. al. Phase 1/2 Study to Describe the Safety and Immunogenicity of a COVID-19 RNA Vaccine Candidate (BNT162b1) in Adults 18 to 55 Years of Age: Interim Report. doi: https://doi.org/10.1101/2020.06.30.20142570.

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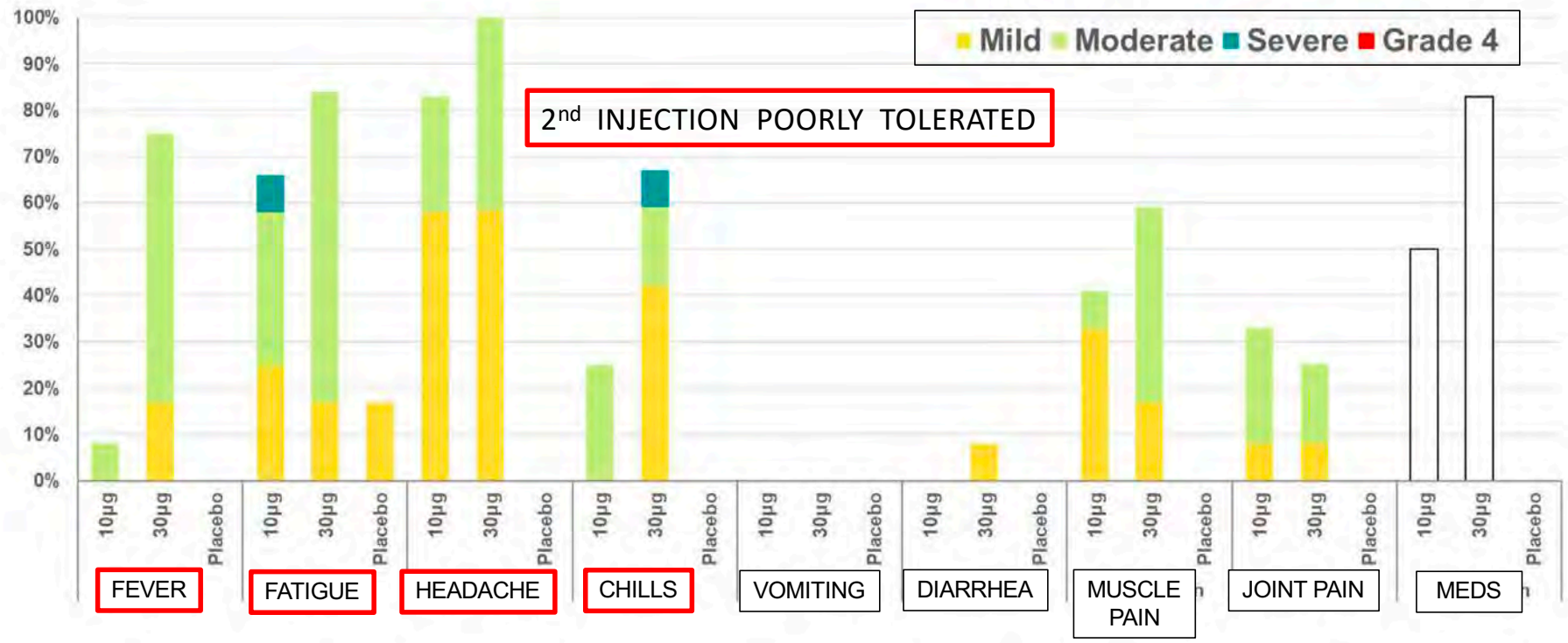
PFIZER CoV-2 mRNA

SPIKE PROTEIN VACCINE STUDY



Mulligan M. et. al. Phase 1/2 Study to Describe the Safety and Immunogenicity of a COVID-19 RNA Vaccine Candidate (BNT162b1) in Adults 18 to 55 Years of Age: Interim Report. doi: https://doi.org/10.1101/2020.06.30.20142570.

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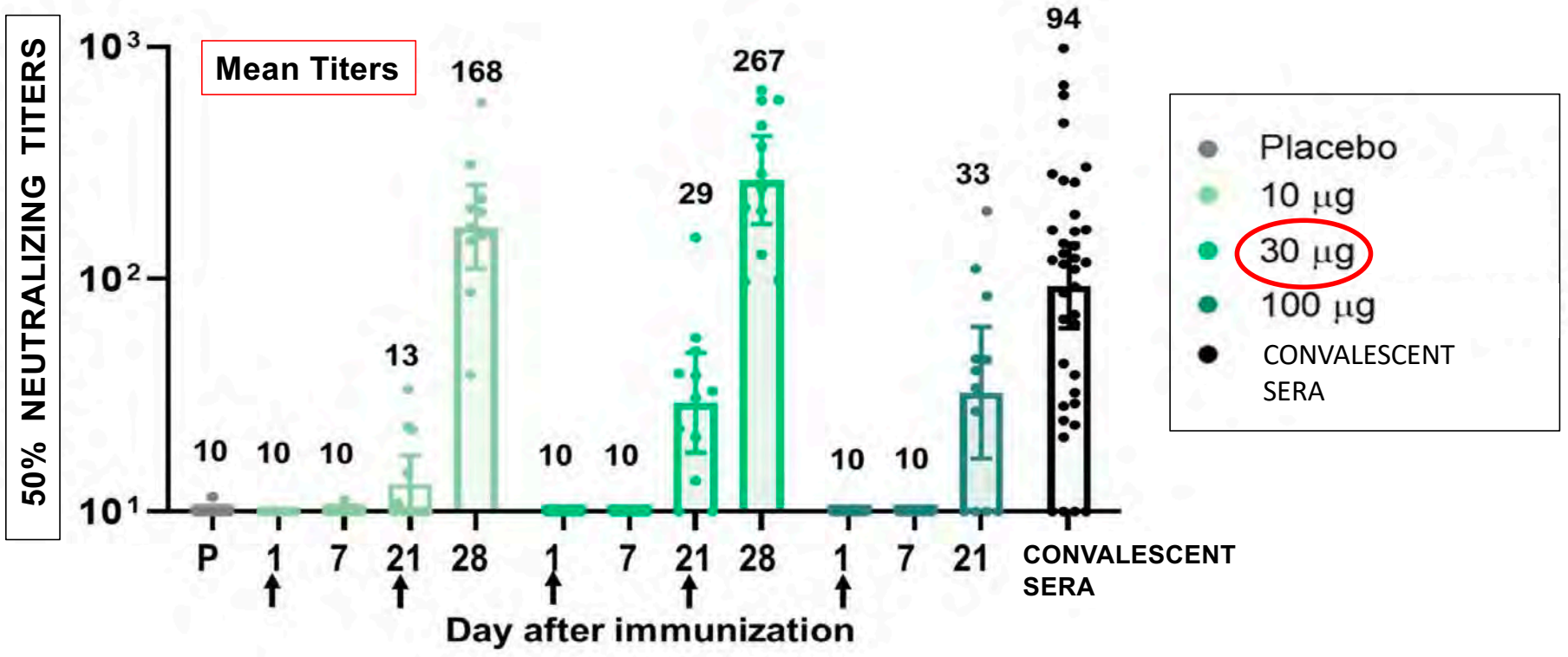
PFIZER CoV-2 mRNA

SPIKE PROTEIN VACCINE STUDY



Mulligan M. et. al. Phase 1/2 Study to Describe the Safety and Immunogenicity of a COVID-19 RNA Vaccine Candidate (BNT162b1) in Adults 18 to 55 Years of Age: Interim Report. doi: https://doi.org/10.1101/2020.06.30.20142570.

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PFIZER CoV-2 mRNA

SPIKE PROTEIN VACCINE STUDY

The BNT162b2 vaccine is based on SARS-CoV-2 spike glycoprotein antigen encoded by mRNA and formulated in lipid nanoparticles given in 2 doses, 30 µg each, administered 21 days apart.

MOST COMMON ADVERSE REACTIONS

INJECTION SITE REACTION	**84.1 %**
FATIGUE	**62.9 %**
HEADACHE	**55.1 %**
MUSCLE PAIN	**38.3 %**
CHILLS	**31.9 %**
JOINT PAIN	**23.6 %**
FEVER	**14.2 %**

https://www.fda.gov/media/144245/download

PFIZER CoV-2 mRNA

SPIKE PROTEIN VACCINE STUDY

Table 13. Primary Efficacy Endpoint –All-Available Efficacy Population

Efficacy Endpoint	BNT162b2 N[a]=21669 Cases n1[b] Surveillance Time[c] (n2[d])	Placebo N[a]=21686 Cases n1[b] Surveillance Time[c] (n2[d])	Vaccine Efficacy % (95% CI)
First COVID-19 occurrence after Dose 1 – Dose 1	50 4.015 (21314)	275 3.982 (21258)	82.0 (75.6, 86.9)[f]
After Dose 1 to before Dose 2	39	82	52.4 (29.5, 68.4)
Dose 2 to 7 days after Dose 2	2	21	90.5 (61, 98.9)
≥7 Days after Dose 2	9	172	94.8 (89.8, 97.6)

https://www.fda.gov/media/144245/download

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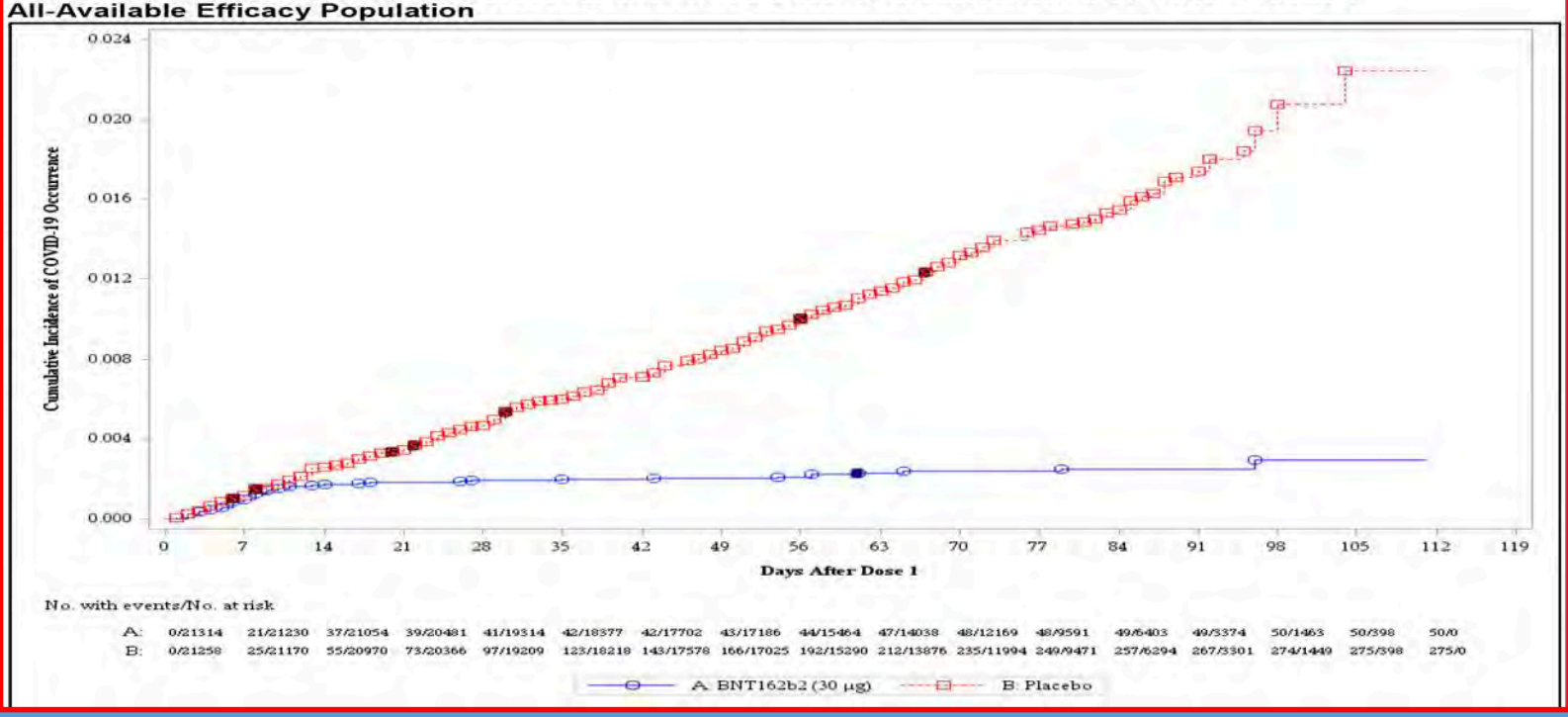
PFIZER CoV-2 mRNA

SPIKE PROTEIN VACCINE STUDY

Pfizer-BioNTech COVID-19 Vaccine
VRBPAC Briefing Document

Figure 2. Cumulative Incidence Curves for the First COVID-19 Occurrence After Dose 1, Dose 1 All-Available Efficacy Population



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PFIZER CoV-2 mRNA

SPIKE PROTEIN VACCINE STUDY

Table 6. Final Analysis of Efficacy of BNT162b2 Against Confirmed COVID-19 From 7 Days After Dose 2 in Participants Without Evidence of Prior SARS-CoV-2 Infection - Evaluable Efficacy Population

Pre-specified Age Group	BNT162b2 N[a] = 18198 Cases n1[b] Surveillance Time[c] (n2[d])	Placebo N[a] =18325 Cases n1[b] Surveillance Time[c] (n2[d])	Vaccine Efficacy % (95% CI)	Met Predefined Success Criterion*
All participants	8 2.214 (17411)	162 2.222 (17511)	95.0 (90.3, 97.6)[e]	Yes
16 to 55 years	5 1.234 (9897)	114 1.239 (9955)	95.6 (89.4, 98.6)[f]	NA
> 55 years and older	3 0.980 (7500)	48 0.983 (7543)	93.7 (80.6, 98.8)[f]	NA

https://www.fda.gov/media/144245 download

PFIZER mRNA

BNT162B2 NEUTRALIZES

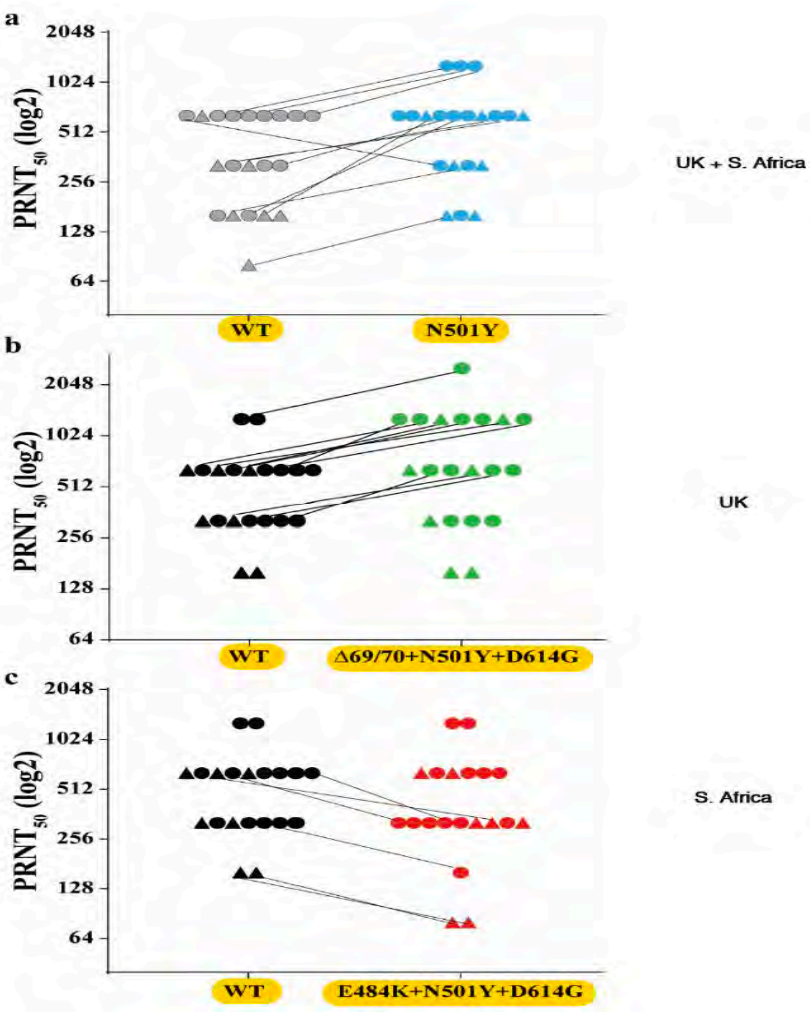
VARIANT STRAINS

IN UK AND SOUTH AFRICA

PRNT50s of twenty BNT162b2-vaccinated human sera against wild-type (WT) and mutant SARS-CoV-2.

(a) WT (USA-WA1/2020) and mutant N501Y.
(b) WT and Δ69/70+N501Y+D614G.
(c) WT and E484K+N501Y+D614G.

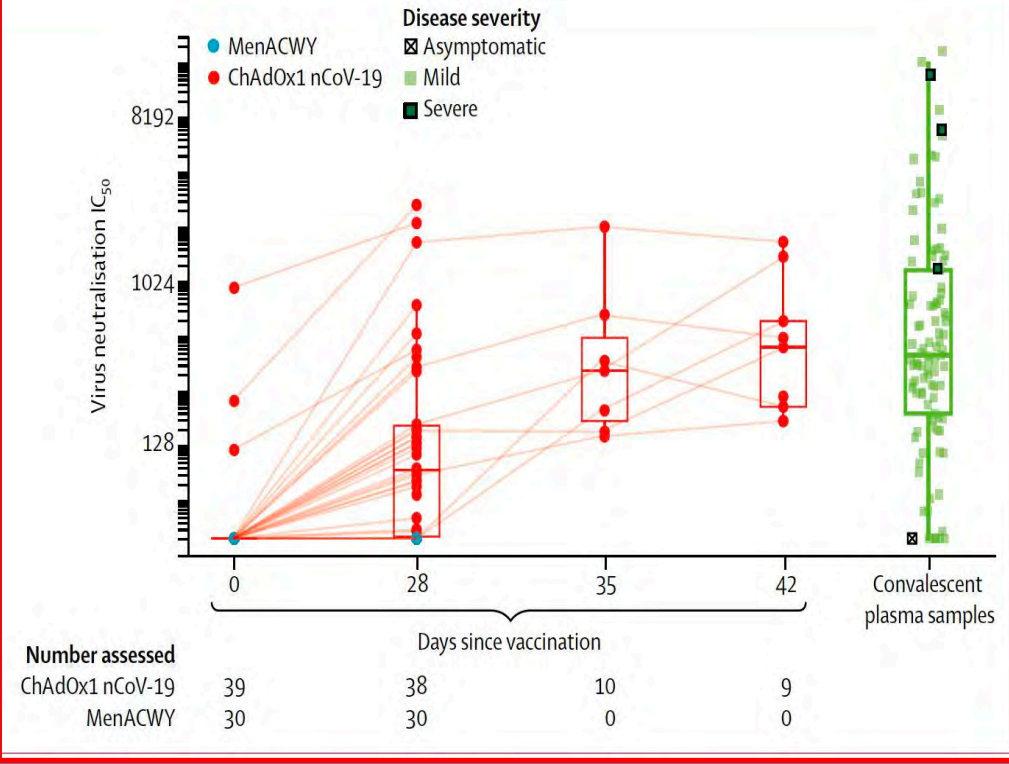
Seven (triangles) and thirteen (circles) sera were drawn 2 and 4 weeks after the second dose of vaccination, respectively. Sera with different PRNT50s against WT and mutant viruses are connected by lines. Results in (a) were from one experiment; results in (b) and (c) were from another set of experiments. Each data point is the average of duplicate assay results.



doi: https://doi.org/10.1101/2021.01.27.427998

OXFORD UNIVERSITY + ASTRAZENECA

CHIMPANZEE ADENOVIRUS VECTOR – CoV-2 SPIKE PROTEIN



5 X 10^{10} viral particles of a chimpanzee adenovirus-vectored vaccine (ChAdOx1 nCoV-19) were injected into 543 participants. Neutralising antibody responses against SARS-CoV-2 were detected in 32 (91%) of 35 participants after a single dose when measured in MNA80, and in 35 (100%) participants when measured in PRNT50.

After a booster dose, all participants had neutralizing antibody activity.

Safety and immunogenicity of the ChAdOx1 nCoV-19 vaccine against SARS-CoV-2: a preliminary report of a phase 1/2, single-blind, randomised controlled trial. Folegatti P et. al. Lancet July 20, 2020. https://doi.org/10.1016/S0140-6736(20)31604-4

JANSSEN - JOHNSON + JOHNSON

Table 16. Vaccine Efficacy Against Adjudicated Severe/Critical COVID-19 With Onset at Least 14 or at Least 28 Days After Vaccination, Per-Protocol Set, Study 3001

	Onset at Least 14 Days			Onset at Least 28 Days		
	Ad26.COV2.S Cases (N) Person-yrs	Placebo Cases (N) Person-yrs	VE% (95% CI)	Ad26.COV2.S Cases (N) Person-yrs	Placebo Cases (N) Person-yrs	VE% (95% CI)
Centrally confirmed cases[a]						
Overall	14 (19514) 3125.1	60 (19544) 3122.0	76.7% (54.6, 89.1)[b]	5 (19306) 3106.2	34 (19178) 3082.6	85.4% (54.2, 96.9)[b]
18-59 years	8 (12750) 2114.3	41 (12782) 2115.1	80.5% (57.8, 92.1)	2 (12617) 2101.0	24 (12527) 2086.7	91.7% (66.7, 99.1)
≥60	6 (6764) 1010.7	19 (6762) 1006.9	68.5% (18.1, 89.7)	3 (6689) 1005.1	10 (6651) 995.9	70.3% (-15.5, 94.7)

https://www.fda.gov/media/146338/download

https://www.fda.gov/emergency-preparedness-and-response/coronavirus-disease-2019-covid-19/janssen-covid-19-vaccine

JANSSEN - JOHNSON + JOHNSON

Table 17. Vaccine Efficacy of First Occurrence COVID-19 Requiring Medical Intervention Based on MRU, With Onset at Least 14 or at Least 28 Days After Vaccination, Per-Protocol Set, Study 3001

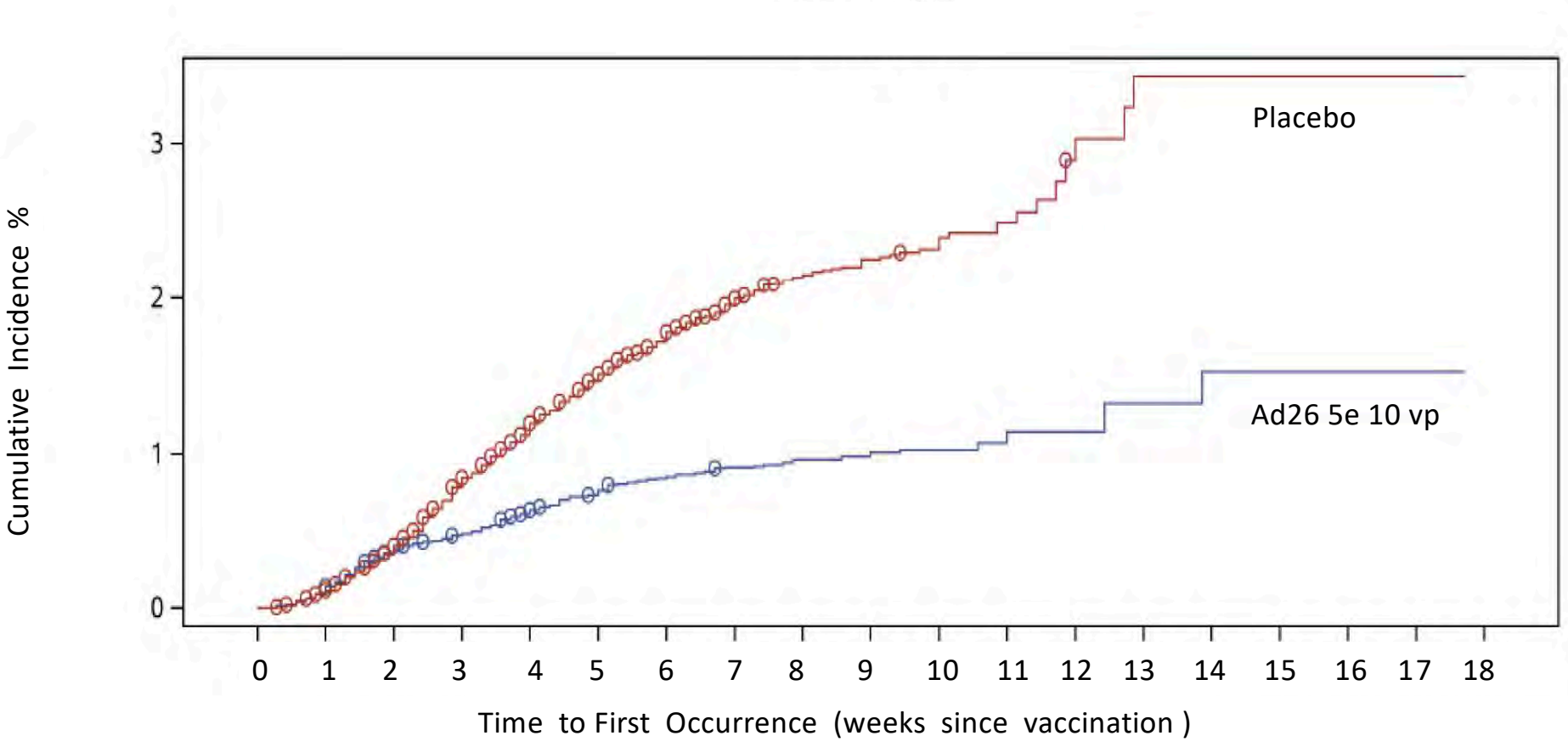
	Onset at Least 14 Days			Onset at Least 28 Days		
	Ad26.COV2.S Cases (N) Person-yrs	Placebo Cases (N) Person-yrs	VE% (95% CI)	Ad26.COV2.S Cases (N) Person-yrs	Placebo Cases (N) Person-yrs	VE%[a] (95% CI)
Centrally Confirmed	2 (19514) 3126.9	8 (19544) 3126.1	75.0% (-25.3, 97.4)	0 (19306) 3106.4	5 (19178) 3084.4	
Any positive PCR	2 (19514) 3125.9	14 (19544) 3125.8	85.7% (37.8, 98.4)	0 (19306) 3106.4	7 (19178) 3084.4	100% (31.1, 100.0)

https://www.fda.gov/media/146338/download

https://www.fda.gov/emergency-preparedness-and-response/coronavirus-disease-2019-covid-19/janssen-covid-19-vaccine

Kagen MD

JANSSEN - JOHNSON + JOHNSON



https://www.fda.gov/media/146338/download
https://www.fda.gov/emergency-preparedness-and-response/coronavirus-disease-2019-covid-19/janssen-covid-19-vaccine

OXFORD UNIVERSITY + ASTRAZENECA

CHIMPANZEE ADENOVIRUS VECTOR – CoV-2 SPIKE PROTEIN

AZD1222 CLINICAL TRIALS RESUMED IN THE UK.

AZD1222 WAS CO-INVENTED BY THE UNIVERSITY OF OXFORD AND ITS SPIN-OUT COMPANY, VACCITECH. IT USES A REPLICATION - DEFICIENT CHIMPANZEE VIRAL VECTOR BASED ON A WEAKENED VERSION OF A COMMON COLD VIRUS (ADENOVIRUS) THAT CAUSES INFECTIONS IN CHIMPANZEES, WHICH CONTAINS GENETIC MATERIAL OF THE SARS-COV-2 SPIKE PROTEIN.

THE ASTRAZENECA TRIAL WAS HALTED WHEN ONE VACCINE RECIPIENT EXPERIENCED TRANVERSE MYELITIS, AND SUBSEQUENTLY RESTARTED.

https://www.astrazeneca.com/content/astraz/media-centre/press-releases/2020/covid-19-vaccine-azd1222-clinical-trials-resumed-in-the-uk.html

OXFORD UNIVERSITY + ASTRAZENECA

ChAdOx1 nCov-19 VACCINE INDUCED AUTOIMMUNE THROMBOCYTOPENIA

" VACCINATION WITH ChAdOx1 nCov-19 CAN RESULT IN THE RARE DEVELOPMENT OF IMMUNE THROMBOTIC THROMBOCYTOPENIA MEDIATED BY PLATELET - ACTIVATING ANTIBODIES AGAINST PF4, WHICH CLINICALLY MIMICS AUTOIMMUNE HEPARIN - INDUCED THROMBOCYTOPENIA. "

Greinacher A et. al. Thrombotic Thrombocytopenia after ChAdOx1 nCov-19 Vaccination. NEJM April 9, 2021. DOI: 10.1056/NEJMoa2104840

OXFORD UNIVERSITY + ASTRAZENECA

ChAdOx1 nCov-19 VACCINE INDUCED AUTOIMMUNE THROMBOCYTOPENIA

'A previously healthy 49-year-old health care worker received her first dose of ChAdOx1 nCov-19 in mid-February 2021 (day 0).

Over the next few days, she reported having minor symptoms (fatigue, myalgia, and headache).

Beginning on day 5, she reported having chills, fever, nausea, and epigastric discomfort; she was admitted to a local hospital on day 10.'

Table 1. Laboratory Characteristics of the Index Patient.*

Laboratory Analysis	Reference Value	Day 10		Day 11	
		8:00 a.m.	8:00 p.m.	8:00 a.m.	8:00 p.m.
Hemoglobin (g/dl)	12.0–16.0	12.3	11.3	10.9	9.1
Platelet count (per mm^3)	150,000–350,000	18,000	37,000	25,000	13,000
Leukocytes (per mm^3)	4000–10,000	6,600	7,100	10,900	15,500
Activated partial thromboplastin time (sec)	<35	34	41.6	37.9	32.3
International normalized ratio	0.9–1.1	1.4	1.3	1.2	1.3
Thrombin time (sec)	<21	NA	25.7	NA	23.7
Fibrinogen (mg/dl)	200–400	NA	101	126	78
D-dimer (mg/liter)	<0.5	35	142	NA	NA
Aspartate aminotransferase (U/liter)	<35	33	88	160	98
Alanine aminotransferase (U/liter)	<35	46	94	167	155
γ-Glutamyltransferase (U/liter)	<40	141	110	103	78
Lactate dehydrogenase (U/liter)	<250	NA	337	NA	344
C-reactive protein (mg/dl)	<0.5	8.8	7.6	8.7	6.8
Lactate (mmol/liter)	<1.6	0.9	NA	1.7	3.6

Greinacher A et. al. Thrombotic Thrombocytopenia after ChAdOx1 nCov-19 Vaccination. NEJM April 9, 2021. DOI: 10.1056/NEJMoa2104840

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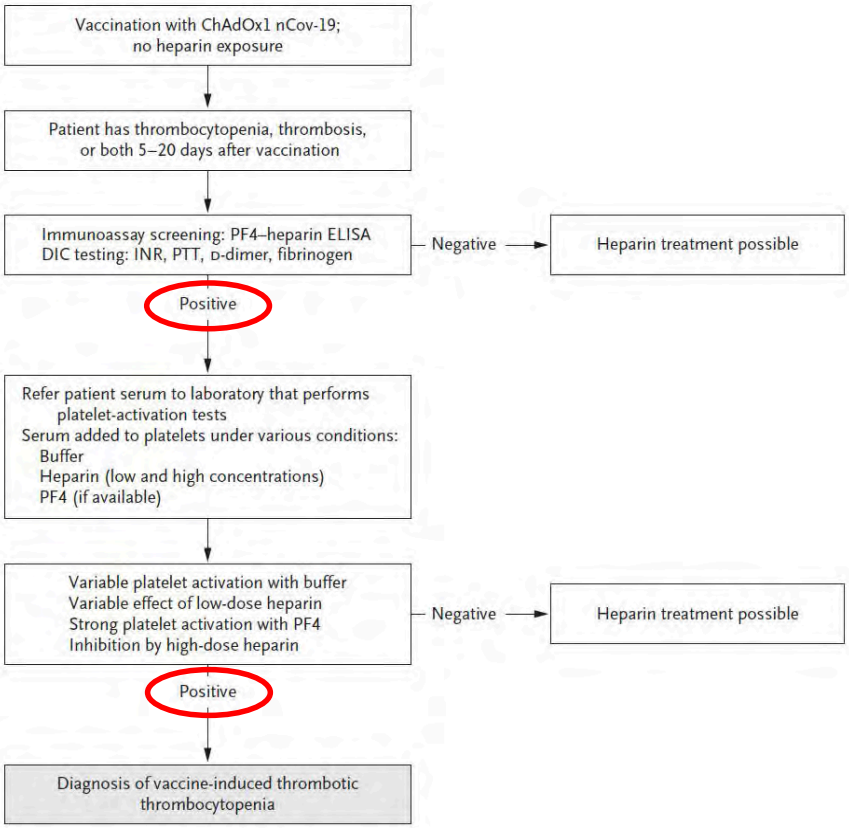
ChAdOx1 nCov-19 VACCINE – INDUCED THROMBOTIC THROMBOCYTOPENIA



Treatment Options	Comment
High-dose intravenous immune globulin (1 g per kg for 2 days)	Raises platelet count and decreases hypercoagulability (by analogy with autoimmune HIT); inhibits platelet activation by platelet-activating anti-PF4 antibodies (platelet Fcγ receptors)
Anticoagulants often used to treat heparin-induced thrombocytopenia	Direct oral Xa inhibitors (apixaban, rivaroxaban) Direct thrombin inhibitors (argatroban, bivalirudin) Indirect (antithrombin-dependent) Xa inhibitors: danaparoid (not available in U.S.), fondaparinux
Platelet transfusions	Avoid unless presence of bleeding (theoretical prothrombotic risk)
Vitamin K antagonist	Contraindicated during acute thrombocytopenia and disseminated intravascular coagulation (microthrombosis associated with protein C depletion)

Greinacher A et. al. Thrombotic Thrombocytopenia after ChAdOx1 nCov-19 Vaccination. NEJM April 9, 2021. DOI: 10.1056/NEJMoa2104840

CoV-2 VACCINE COMPARISONS

	Moderna	Pfizer	Johnson + Johnson	AstraZeneca	Novavax
FDA Approved	Yes	Yes	Yes	No	No
Doses	2	2	1	2	2
COVID-19 Antigen Source	Spike mRNA	Spike mRNA	Spike mRNA in Adenovirus	Spike mRNA ChAdOx1 nCoV-19 Adenovirus	Recombinant Spike Nanoparticle
Ages	≥18 yrs	≥16 yrs	≥18 yrs	≥18 yrs	≥18 yrs
Efficacy					
Overall	90% 14 d post 2nd dose	90% 14 d post 2nd dose	72% 28 d post 1st dose	76% 15 d post 2nd dose	90% 7 d post 2nd dose
Elderly	86 % >65 yrs	95 % >65 yrs	66 % >60 yrs	Unknown	Unknown
Prevents Death	100 %	100 %	100 %	100 %	100 %
Prevents Severe Disease	100 %	90 %	88 %	100 %	100 %
Variant Coverage					
UK B.1.1.7	Partial coverage in lab tests	Partial coverage in lab tests	60 % – 75 %	75 %	86 %
South Africa B.1.351	Low coverage in lab tests	Low coverage in lab tests	64 %	10 %	49 %
Brazil P1	Low	Low	68 %	Yes (preliminary)	Unknown

Source:
The Medical Letter. 3-31-2021

VACCINES ARE IMPERFECT

VACCINE - SPECIFIC IgG

VACCINE	NON-IMMUNE / IMMUNE	% NON-IMMUNE
MEASLES	17 / 85	17%
DIPHTH.	26 / 56	32%
TETANUS	26 / 56	32%
RUBELLA	13 / 69	16%
HIB	1 / 85	1%

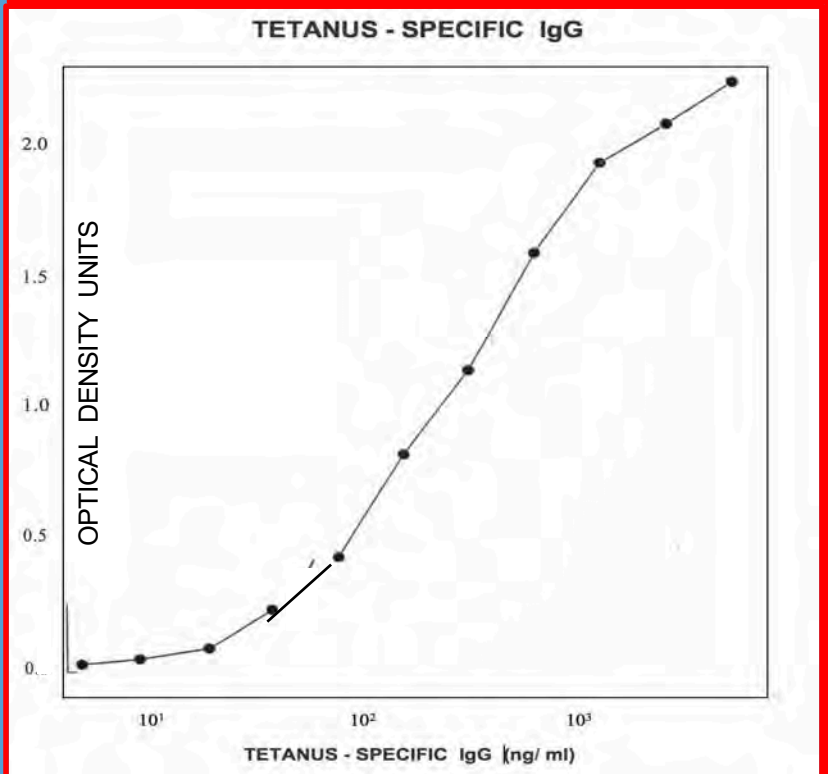
VACCINE	UNITS	ug VACCINE SP. IgG
TETANUS	1 UNIT	43.63 ug
RUBELLA	1 I.UNIT	0.445 ug
DIPHTHERIA	1 UNIT	943.0 ug

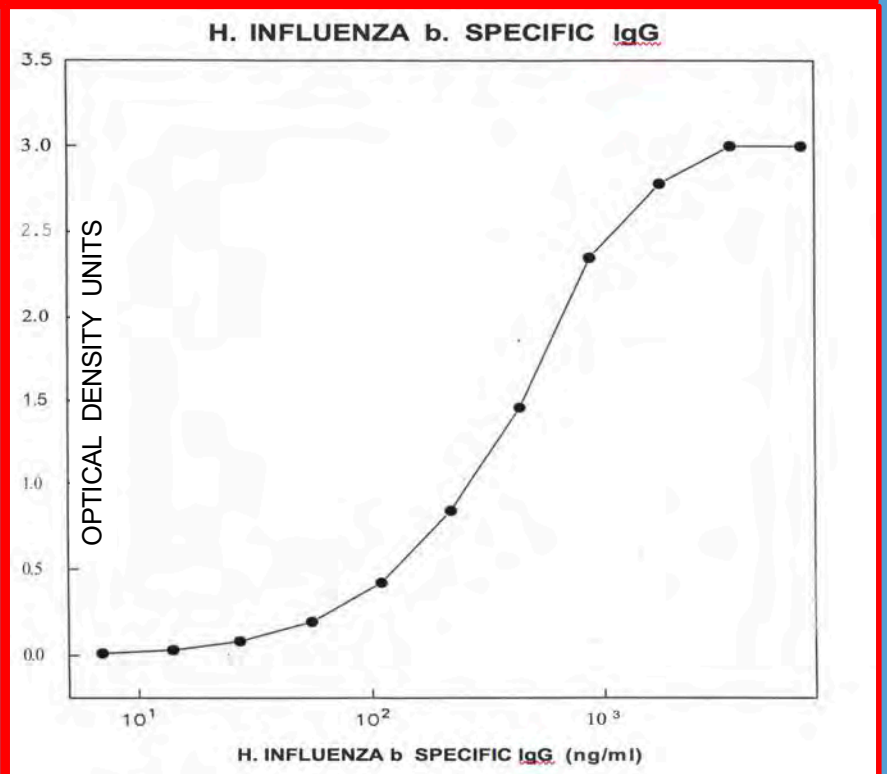
1. **EACH PATIENT IS UNIQUE** AND WILL RESPOND DIFFERENTLY TO VACCINE ANTIGENS BOTH INITIALLY AND OVER TIME. MANY PATIENTS WILL NOT ACHIEVE OR MAINTAIN PROTECTIVE LEVELS OF VACCINE - SPECIFIC NEUTRALIZING ANTIBODIES.
2. **EACH VACCINE IS UNIQUE** IN ITS ABILITY TO PROTECT PATIENTS AGAINST ITS INTENDED TARGET.

Muthiah R, Kagen S, Hildeman D and Knoll R. New Immunization screen reveals under-immunization of patients attending allergy & asthma clinics. J Allergy Clin Immunol. 1992;89:490.

PROTECTIVE IgG ANTIBODY LEVELS

TETANUS + H. INFLUENZA b - SPECIFIC IgG



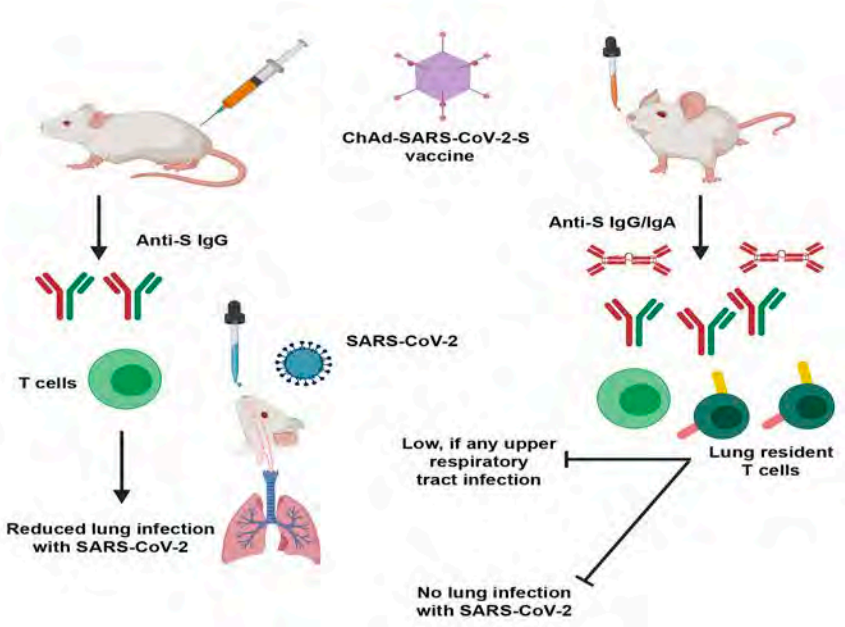


STANDARD CURVES TO QUANTITATE VACCINE – SPECIFIC IgG LEVELS

Muthiah R, Kagen S et. al. New Immunization screen reveals under-immunization of patients attending allergy & asthma clinics. J Allergy Clin Immunol. 1992;89:490.

INTRANASAL CHIMPANZEE ADENOVIRUS ENCODING PRE-FUSION STABILIZED SPIKE PROTEIN PREVENTS SARS-CoV-2 INFECTION

UNIVERSITY OF WASHINGTON, ST. LOUIS



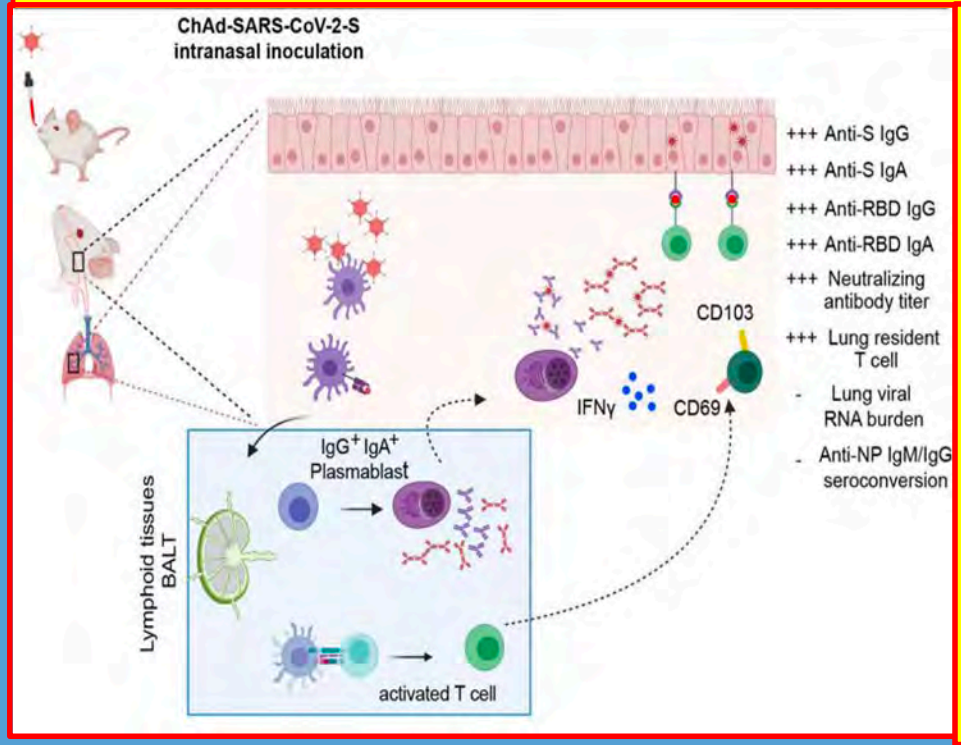
A single intranasal dose of ChAd-SARS-CoV-2-S induced high levels of CoV-2-S neutralizing RBD-specific IgG and IgA.

Intramuscular injection of this vector failed to generate an IgA antibody response.

ChAd-SARS-CoV-2-S has the potential to control infection at the site of inoculation, which may prevent both virus - induced disease and transmission.

Hassan, A.O., Kafai, NM, Diamond MS, et. al. A single-dose intranasal ChAd vaccine protects upper and lower respiratory tracts against SARS-CoV-2. Cell (2020). doi: https://doi.org/10.1016/j.cell.2020.08.026

INTRANASAL CHIMPANZEE ADENOVIRUS ENCODING PRE-FUSION STABILIZED SPIKE PROTEIN PREVENTED CoV-2 INFECTION



ChAd-SARS-CoV-2-S Vaccine

* Induces Neutralizing IgG and IgA.
* Protects Against SARS-CoV-2 Infection and Pneumonia.
* Generates Mucosal B and T Cell Responses.
* Prevents Upper and Lower CoV-2 Respiratory Tract Infections.

Hassan, A.O., Kafai, NM, Diamond MS, et. al. A single-dose intranasal ChAd vaccine protects upper and lower respiratory tracts against SARS-CoV-2. Cell (2020). doi: https://doi.org/10.1016/j.cell.2020.08.026

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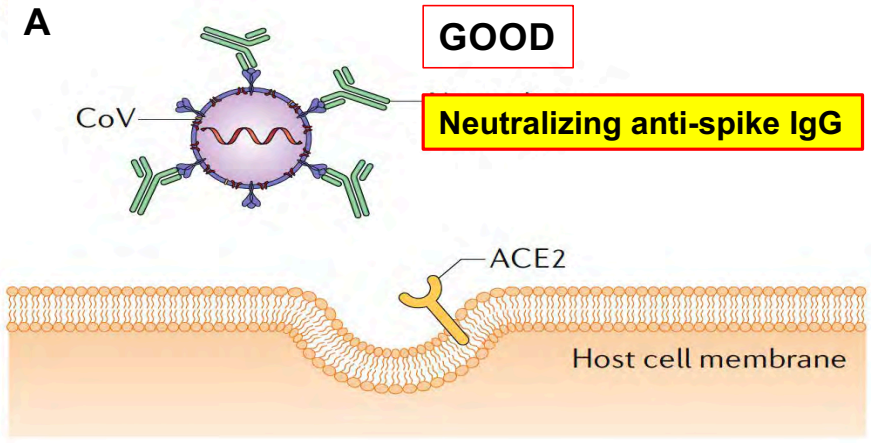
ARE ANTI-SPIKE VACCINES GOOD OR BAD ?

A

GOOD

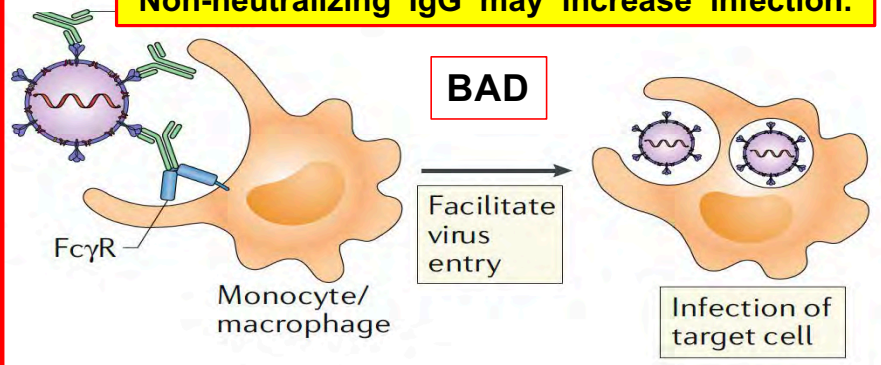


Neutralizing anti-spike IgG

B

Non-neutralizing IgG may increase infection.

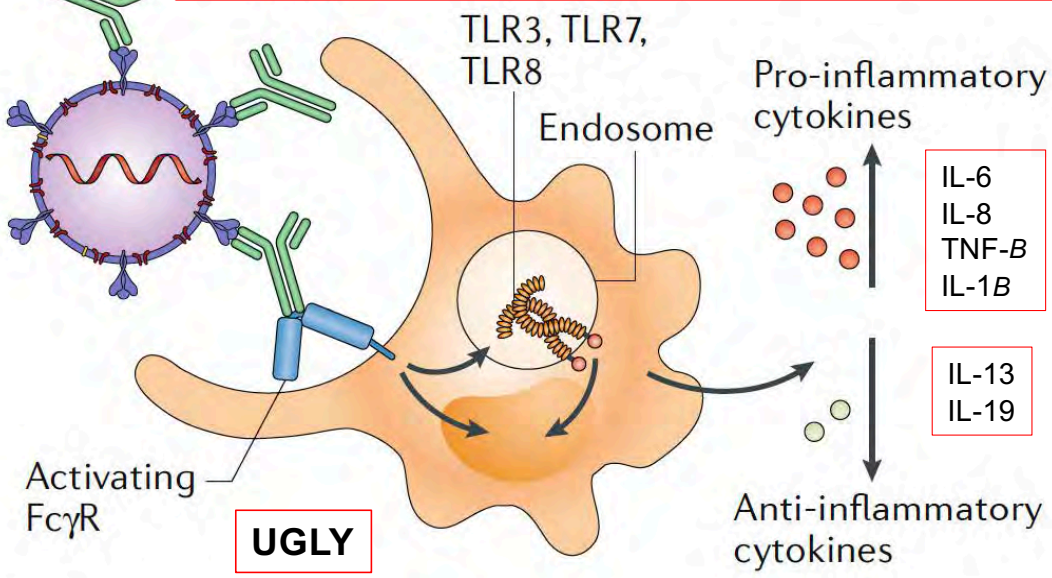
BAD



A. **NEUTRALIZING ANTIBODY IS PREFERRED.**
B. **NON-NEUTRALIZING ANTIBODY MAY ENHANCE INFECTION.**
C. **DEGLYCOSYLATED IgG INDUCES CYTOKINE STORM.**

C

Deglycosylated anti-spike IgG: CoV-2 immune complex induced macrophage activated Cytokine Storm.



UGLY

Iwasaki, A., Yang, Y. The potential danger of suboptimal antibody responses in COVID-19. *Nat Rev Immunol* 20, 339–341 (2020). https://doi.org/10.1038/s41577-020-0321-6

PATIENT MANAGEMENT

4-10-2021

PREVENTION

1. **HAND WASHING**
2. **SOCIAL DISTANCING**
3. **FACE MASKS**
4. **PAPR**
5. **GLOVES and GOWNS**
6. **VITAMINS C + D**
7. **VACCINE** Spike mRNA or Peptides

* **DO NOT TAKE IBUPROFEN OR COUGH SUPPRESSANTS w/ DEXTROMETHORPHAN IF YOU HAVE SARS-CoV-2.**

TREATMENT

A. VIRUS SUPPRESSION

1. **ANTI-SPIKE MONOCLONAL ANTIBODIES**
2. **REMDESIVIR** FDA approved in first few days of infection

B. ANTI – INFLAMMATION

1. **METHYLPREDNISOLONE** Clinical Decision
2. **FOSTAMATINIB** Oral Syk inhibitor Investigational

C. ANTICOAGULATION Enoxaparin / Heparin
Rec - Human ADAMTS13 ?

INF beta-1-b, RIBAVIRON, LOPINAVIR, RITONAVIR. https://doi.org/10.1016/S0140-6736(20)31042-4

NIH COVID-19 Rx Guidelines https://www.covid19treatmentguidelines.nih.gov/introduction/

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COVID-19 FACTS

1. CoV-2 IS A HIGHLY INFECTIOUS CORONAVIRUS FOUND IN BATS, CATS BIRDS, CATTLE, MINK AND CAMELS 95% IDENTICAL TO SARS CORONAVIRUS.
2. CoV-2 SPIKE PROTEINS INDUCE CLOTS WITHIN INFECTED TISSUES.
3. 43% OF INFECTIONS ARE ASYMPTOMATIC, OTHERS MAY EXPERIENCE FEVER, COUGH, SORE THROAT, CHANGE IN SMELL AND TASTE, SKIN RASHES OR FATAL INFLAMMATORY REACTIONS.
4. CoV-2 VIRUSES INFECT CELLS IN THE NOSE, SINUS, LUNG, HEART, BRAIN, KIDNEY AND BLOOD VESSELS IN BOTH CHILDREN AND ADULTS.
5. VIRUS TRANSMISSION CAN OCCUR 2 DAYS BEFORE SYMPTOMS BEGIN, BUT CoV-2 CAN BE SPREAD FOR UP TO 33 DAYS IN THE AIR AND STOOL AFTER YOU ARE INFECTED.
6. THERE ARE NO "MILD" COVID INFECTIONS FOR INFECTED PATIENTS MAY EXPERIENCE LONGTERM DAMAGE TO THEIR HEARTS.

4--10-2021

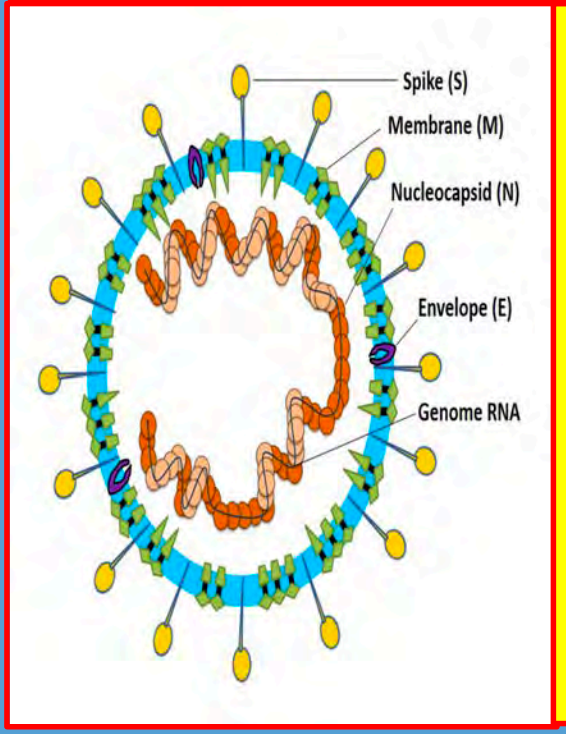
COVID-19 FACTS

7. PATIENT OUTCOMES DEPEND ON THE INTENSITY OF ONE'S IMMUNE RESPONSE TO THE VIRUS AND EXTENT OF DAMAGE TO VITAL ORGANS.
8. 87% OF PATIENTS FEEL FATIGUE AND SHORTNESS OF BREATH FOR MONTHS AFTER "RECOVERING" FROM COVID-19 INFECTIONS.
9. REMDESIVIR DECREASES VIRUS NUMBERS BUT DOES NOT PREVENT DEATH. HYDROXYCHLOROQUINE FAILED TO IMPROVE CLINICAL OUTCOMES.
10. mRNA VACCINES ARE 95% EFFECTIVE IN PREVENTING CoV-2 INFECTIONS. INTRA-NASAL CoV-2 IMMUNIZATION MAY ALSO PREVENT CoV-2 INFECTIONS.
11. ANTI-SPIKE MONOCLONAL ANTIBODIES DECREASE COVID-19 SYMPTOMS IN ADULTS AND CHILDREN WITH MILD INFECTIONS IF GIVEN WITHIN THE FIRST 7 DAYS AFTER SYMPTOMS BEGIN.
12. CONTROLLING THE PANDEMIC REQUIRES TESTING EVERYONE, ISOLATION OF ALL THOSE INFECTED, TRACING EVERY CONTACT OF INFECTED INDIVIDUALS AND VACCINATING EVERYONE POSSIBLE.

4-10-2021

Kagen MD

THE COVID-19 PANDEMIC



TO CONTROL THE PANDEMIC WE MUST

1. **TEST** EVERYONE REPEATEDLY.
2. **ISOLATE** EVERY POSITIVE PATIENT.
3. **TRACE** ALL CONTACTS OF POSITIVES.
4. **ALWAYS** WEAR FACE MASKS NEAR OTHERS.
5. **IMMUNIZE** ALL INDIVIDUALS

using CoV-2 spike proteins or spike mRNA (active immunity) or
long half-life humanized anti-spike monoclonal antibodies (passive immunity)

SUMMARY

1. SPIKE PROTEINS ON CoV-2 INDUCE BLOOD CLOTS AND SCARS IN INFECTED BLOOD VESSELS AND VITAL ORGANS.
2. EACH PATIENT IS UNIQUE REGARDING THEIR IMMUNE RESPONSES TO CoV-2 VIRAL ANTIGENS.
3. CLINICAL OUTCOMES ARE DETERMINED BY THE INTENSITY OF YOUR IMMUNE RESPONSE TO CoV-2.
4. SUCCESSFUL TREATMENT REQUIRES EARLY USE OF ANTI-VIRAL, ANTI-INFLAMMATORY AND ANTI-COAGULANT AGENTS IN DOSES NECESSARY TO CONTROL INFLAMMATORY AND COAGULATION EVENTS.
5. WEARING MASKS AND SOCIAL DISTANCING WILL CONTINUE TO BE NECESSARY UNTIL EVERYONE IS VACCINATED.

RESOURCES

NATIONAL INSTITUTE OF ALLERGY AND INFECTIOUS DISEASE (NIAID)

https://www.niaid.nih.gov/ https://www.coronavirus.gov/

NATIONAL INSTITUTE OF HEALTH (NIH)

https://www.nih.gov/health-information/coronavirus

CENTER FOR DISEASE CONTROL AND PREVENTION (CDC)

https://www.cdc.gov/coronavirus/2019-nCoV/index.html

https://www.cdc.gov/coronavirus/2019-ncov/community/strategy-discontinue-isolation.html?deliveryName=USCDC_2067-DM27395

CENTERS OF EXCELLENCE FOR INFLUENZA RESEARCH AND SURVEILLANCE (CEIRS)

https://www.niaidceirs.org/covid-19/

VACCINE TRACKER

https://www.covid-19vaccinetracker.org/

MASSACHUCETTS GENERAL HOSPITAL (MGH)

https://www.massgeneral.org/news/coronavirus/treatment-guidance/inpatient-care-recommendations