CDC/IDSA COVID-19 Clinician Call

February 20, 2021

Welcome & Introductions

Dana Wollins, DrPH, MGC
Vice President, Clinical Affairs & Guidelines
IDSA

- 55th in a series of weekly calls, initiated by CDC as a forum for information sharing among frontline clinicians caring for patients with COVID-19
- The views and opinions expressed here are those of the presenters and do not necessarily reflect the official policy or position of the CDC or IDSA. Involvement of CDC and IDSA should not be viewed as endorsement of any entity or individual involved.
- This webinar is being recorded and can be found online at www.idsociety.org/cliniciancalls.

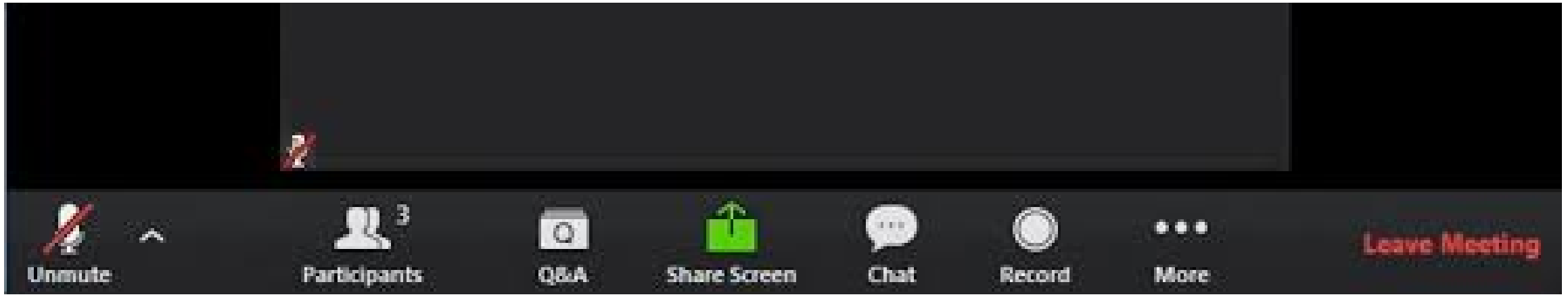
TODAY'S TOPICS

- Updated SCCM Guidelines on the Management of Adults with COVID-19in the ICU

- Emerging SARS-CoV-2 Variants: Updates & Implications

Question?
Use the “Q&A” Button

Comment?
Use the “Chat” Button



Updated Guidelines on the Management of Adults with COVID-19 in the ICU

Greg Martin, MD, MSc, FCCM
President, Society of Critical Care Medicine
Professor and Executive Associate Division Director
Pulmonary, Allergy, Critical Care and Sleep Medicine
Emory University

Surviving Sepsis Campaign: Updated Guidelines on the Management of Critically Ill Adults with Coronavirus Disease 2019 (COVID-19)

Surviving Sepsis Campaign

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COI Disclosures

- President, Society of Critical Care Medicine
- Research funding to Emory University: BARDA, NIH (NHLBI, NIBIB, NIGMS, NIDDK, OD)
- Research funding to Emory University: Siemens, Marcus Foundation
- Research consultant/DSMB: Genentech, Grifols, Regeneron, MIRACLE trial

Surviving Sepsis Campaign: Guidelines on the Management of Critically Ill Adults with Coronavirus Disease 2019 (COVID-19)

Surviving Sepsis Campaign Guidelines on the Management of Adults With Coronavirus Disease 2019 (COVID-19) in the ICU: First Update

Guideline Scope and Definitions

First update:

- Focus on therapeutics
- 9 topics updated:
  - 3 new recommendations
  - 6 updated recommendations

Category	Definition
Severe COVID-19	Clinical signs of pneumonia (fever, cough, dyspnea, fast breathing) and one of the following: - Respiratory rate >30 breaths/minute - Severe respiratory distress -SpO2 <90% on room air
Critical COVID-19	Presence of ARDS or respiratory failure requiring ventilation; sepsis or septic shock

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Awake Prone Positioning

Quality assessment		№ of patients		Effect		Quality
№ of studies	Study design	awake proning	no awake proning	Relative (95% CI)	Absolute (95% CI)	
Intubation/invasive mechanical ventilation						
29	observational studies	108/364 (29.7%)	0/0	not estimable		⨁◯◯◯ VERY LOW
Mortality - COVID-19 exclusively (assessed with: No control group)						
29	observational studies	37/364 (10.2%)	0/0	not estimable		⨁◯◯◯ VERY LOW
Mortality COVID-19 ICU						
11	observational studies	4/104 (3.8%)	0/0	not estimable		⨁◯◯◯ VERY LOW
Mortality (follow up: mean 90 days; assessed with: Zang et al control group. Unadjusted estimates.)						
1	observational studies	10/23 (43.5%)	28/37 (75.7%)	not estimable		⨁◯◯◯ VERY LOW
Complications						
29		Adverse events reporting was variable. Most commonly reported adverse events were discomfort, nosebleeds, sternal pain, back pain, and intolerance of awake prone positioning.				-
Oxygenation						
29	observational studies	All 29 COVID-19 studies (n=364) reported improvement in oxygenation in prone position. However, the improvement in oxygenation was not sustained in supine position in 28 studies (n=349) Only 1 study (n=15) showed sustained improvement in oxygenation in supine position however, using NIV.				⨁◯◯◯ VERY LOW

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Awake Prone Positioning

- There is insufficient evidence to issue a recommendation on the use of awake prone positioning in non-intubated adults with severe COVID-19

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Evidence Profile: Corticosteroids

Studies		№ of patients		Effect		Quality
№ of studies	Study design	Systemic corticosteroids	no corticosteroids	Relative (95% CI)	Absolute (95% CI)	
28 days mortality (subgroup: invasive mechanical ventilation)						
7	randomised trials	208/608 (34.2%)	397/951 (41.7%)	OR 0.69 (0.55 to 0.86)	87 fewer per 1,000 (from 135 fewer to 36 fewer)	⊕⊕⊕◯ MODERATE
28 day Mortality (all critically ill)						
7	randomised trials	222/678 (32.7%)	425/1025 (41.5%)	OR 0.66 (0.53 to 0.82)	96 fewer per 1,000 (from 142 fewer to 47 fewer)	⊕⊕⊕⊕ HIGH
28 day Mortality – Dexamethasone						
3	randomised trials	166/459 (36.2%)	361/823 (43.9%)	OR 0.64 (0.50 to 0.82)	105 fewer per 1,000 (from 158 fewer to 48 fewer)	⊕⊕⊕◯ MODERATE
28 day Mortality - Hydrocortisone						
3	randomised trials	43/195 (22.1%)	51/179 (28.5%)	OR 0.69 (0.43 to 1.12)	69 fewer per 1,000 (from 139 fewer to 24 more)	⊕⊕◯◯ LOW
28 day Mortality – Methylprednisone						
2	randomised trials	85/218 (39.0%)	89/222 (40.1%)	RR 0.97 (0.77 to 1.22)	12 fewer per 1,000 (from 92 fewer to 88 more)	⊕⊕⊕◯ MODERATE

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Corticosteroids

- For adults with severe or critical COVID-19, we recommend using a short-course of systemic corticosteroids, over not using corticosteroids
  - Strong Recommendation, moderate quality evidence

- For adults with severe or critical COVID-19 who are considered for systemic corticosteroids, we suggest using dexamethasone over other corticosteroids
  - Weak recommendation, very low quality evidence

Remark: If dexamethasone is not available, clinicians may use other corticosteroids in doses equivalent to 6 mg daily of dexamethasone for up to 10 days.

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Evidence Profile: Hydroxychloroquine

Studies		№ of patients		Effect		Quality
№ of studies	Study design	Hydroxychloroquine (HCQ)	No HCQ	Relative (95% CI)	Absolute (95% CI)	
Mortality 28-30 days						
3	randomised trials	431/1817 (23.7%)	799/3425 (23.3%)	RR 1.07 (0.97 to 1.19)	16 more per 1,000 (from 7 fewer to 44 more)	⊕⊕⊕◯ MODERATE
Mortality D14-28 (RCTs) by severity - SUBGROUP: Invasive mechanical ventilation at baseline						
1	randomised trials	110/261 (42.1%)	216/532 (40.6%)	RR 1.04 (0.87 to 1.24)	16 more per 1,000 (from 53 fewer to 97 more)	⊕⊕⊕⊕ HIGH
Invasive Mechanical Ventilation						
2	randomised trials	130/1459 (8.9%)	227/2796 (8.1%)	RR 1.11 (0.90 to 1.36)	9 more per 1,000 (from 8 fewer to 29 more)	⊕⊕⊕◯ MODERATE
Progression to severe illness						
1	randomised trials	0/31 (0.0%)	4/31 (12.9%)	RR 0.11 (0.01 to 1.98)	115 fewer per 1,000 (from 128 fewer to 126 more)	⊕◯◯◯ VERY LOW
Adverse events						
3	randomised trials	27/116 (23.3%)	10/121 (8.3%)	RR 2.63 (1.36 to 5.09)	135 more per 1,000 (from 30 more to 338 more)	⊕⊕◯◯ LOW

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Hydroxychloroquine

- For adults with severe or critical COVID-19, we recommend against using hydroxychloroquine
  - Strong recommendation, moderate quality evidence

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Evidence Profile: Convalescent Plasma

Studies		№ of patients		Effect		Quality
№ of studies	Study design	convalescent plasma	no convalescent plasma	Relative (95% CI)	Absolute (95% CI)	
Mortality at hospital discharge (or 28 days)						
4	randomised trials	48/367 (13.1%)	58/365 (15.9%)	RR 0.77 (0.48 to 1.24)	37 fewer per 1,000 (from 83 fewer to 38 more)	⊕⊕◯◯ LOW
Mortality (Indirect evidence from other viral illnesses)						
4	randomised trials	0/0	5.0%	RR 0.94 (0.49 to 1.80)	3 fewer per 1,000 (from 26 fewer to 40 more)	⊕⊕◯◯ LOW
			10.0%		6 fewer per 1,000 (from 51 fewer to 80 more)	
			20.0%		12 fewer per 1,000 (from 102 fewer to 160 more)	

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Convalescent Plasma

- For adults with severe or critical COVID-19, we suggest against the use of convalescent plasma outside clinical trials
  - Weak recommendation, low quality evidence

Note: 88% agreed with this recommendation, 12% thought we should issue no recommendation due to insufficient evidence

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Evidence Profile: Remdesivir (**severe**)

Quality assessment							№ of patients		Effect		Quality	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Remdesivir	No Remdesivir	Relative (95% CI)	Absolute (95% CI)		
Mortality at 28 days (Severe COVID-19 not receiving invasive mechanical ventilation)												
3	randomised trials	not serious	not serious	not serious	serious [a]	none	231/3309 (7.0%)	282/3277 (8.6%)	RR 0.80 (0.63 to 1.01)	17 fewer per 1,000 (from 32 fewer to 1 more)	⊕⊕⊕◯ MODERATE	CRITICAL
								20.0%		40 fewer per 1,000 (from 74 fewer to 2 more)		
Serious adverse events												
3	randomised trials	serious [b]	not serious	not serious	not serious	none	152/886 (17.2%)	179/799 (22.4%)	RR 0.76 (0.62 to 0.92)	54 fewer per 1,000 (from 85 fewer to 18 fewer)	⊕⊕⊕◯ MODERATE	CRITICAL
Time to clinical improvement in blinded trials (all hospitalized patients)												
2 [c]	randomised trials	serious [b]	not serious	not serious	not serious	none	699	599	-	MD 3.8 days fewer (5.7 fewer to 1.9 fewer)	⊕⊕⊕◯ MODERATE	CRITICAL
Time to clinical recovery (all hospitalized patients)												
1 [d]	randomised trials	serious [e]	not serious	not serious	serious [f]	none	541	521	-	MD 4 days fewer (7.15 fewer to 0.85 fewer)	⊕⊕◯◯ LOW	

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Remdesivir (**severe** COVID-19)

- For adults with **severe** COVID-19 who do not require mechanical ventilation, we suggest using intravenous remdesivir, over not using it
  - Weak recommendation, moderate quality evidence

Remark: Remdesivir should *ideally* be started within 72 hours of a positive SARS-CoV-2 polymerase chain reaction or antigen testing

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Evidence Profile: Remdesivir (**critical**)

Quality assessment							№ of patients		Effect		Quality	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Remdesivir	No Remdesivir	Relative (95% CI)	Absolute (95% CI)		
Mortality at 28 days (Critical COVID-19 on invasive mechanical ventilation)												
3	randomised trials	not serious	not serious	not serious [a]	serious [b]	none	156/509 (30.6%)	126/505 (25.0%)	RR 1.16 (0.85 to 1.60)	40 more per 1,000 (from 37 fewer to 150 more)	⨁⨁⨁◯ MODERATE	CRITICAL
								50.0%		80 more per 1,000 (from 75 fewer to 300 more)		
Serious adverse events (All patients)												
3	randomised trials	serious [c]	not serious	not serious	not serious	none	152/886 (17.2%)	179/799 (22.4%)	RR 0.76 (0.62 to 0.92)	54 fewer per 1,000 (from 85 fewer to 18 fewer)	⨁⨁⨁◯ MODERATE	CRITICAL
Time to clinical improvement (all patients)												
3	randomised trials	serious [c]	serious [d]	not serious	not serious	none	889	799	-	MD 4.84 days fewer (5.25 fewer to 4.43 fewer)	⨁⨁◯◯ LOW	CRITICAL

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Remdesivir (**critical** COVID-19)

- For adults undergoing mechanical ventilation for critical COVID-19, we suggest against starting intravenous remdesivir
  - Weak recommendation, low quality evidence

Note: A majority of the panel (97.6%) agreed with this recommendation, one panel member preferred to issue a neutral recommendation

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VTE Prophylaxis

- For adults with severe or critical COVID-19, we recommend using pharmacologic venous thromboembolism (VTE) prophylaxis over not using prophylaxis.
  - Strong recommendation, moderate quality evidence

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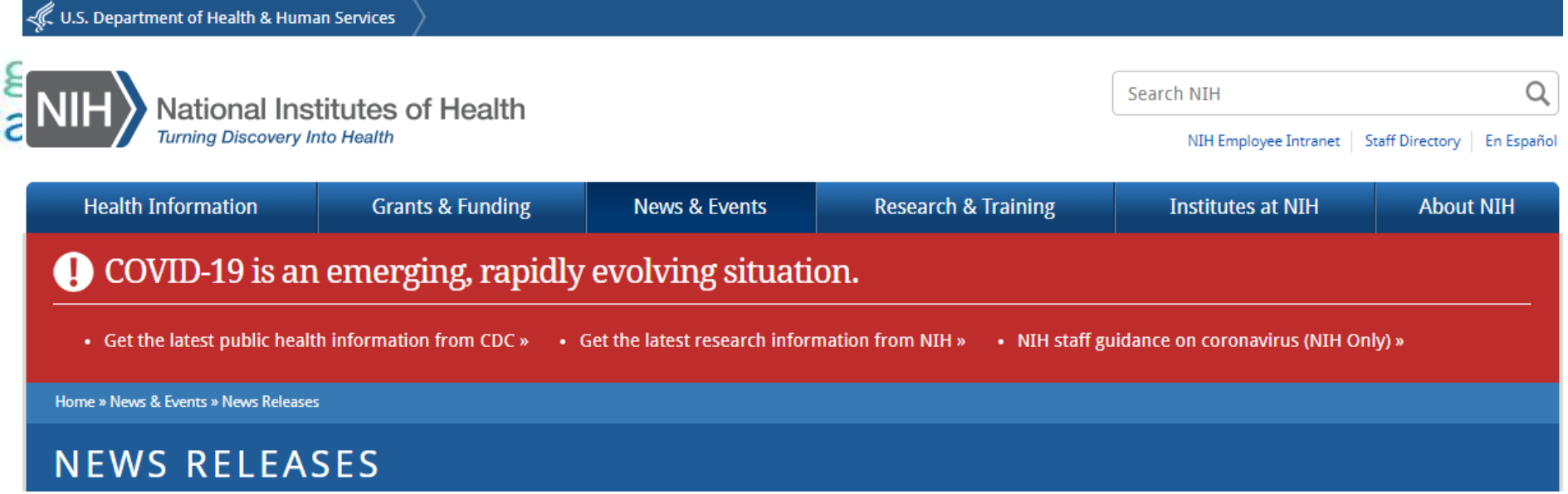
Evidence Profile: Anticoagulation

Quality assessment		№ of patients		Effect		Quality	Importance
№ of studies	Study design	therapeutic anticoagulation	prophylactic dosing anticoagulation	Relative (95% CI)	Absolute (95% CI)		
Mortality: in mechanically ventilated patients (OR)							
3	observational studies		15.0%	OR 0.25 (0.11 to 0.58)	108 fewer per 1,000 (from 131 fewer to 57 fewer)	⊕◯◯◯ VERY LOW	CRITICAL
			50.0%		300 fewer per 1,000 (from 401 fewer to 133 fewer)		
Pulmonary embolism							
1	observational studies		8.0%	OR 0.09 (0.02 to 0.41)	72 fewer per 1,000 (from 78 fewer to 46 fewer)	⊕◯◯◯ VERY LOW	CRITICAL
			18.0%		161 fewer per 1,000 (from 176 fewer to 97 fewer)		
			22.0%		195 fewer per 1,000 (from 214 fewer to 116 fewer)		
Major bleeding							
1	-	Risk of major bleeding with VTE prophylaxis is 1.95% and is 3.3% with therapeutic anticoagulation				-	



Three clinical trial platforms working together to test the effects of full doses of anticoagulants (blood thinners) in COVID-19 patients have paused enrollment for one group of patients. Among critically ill COVID-19 patients requiring intensive care unit (ICU) support, therapeutic anticoagulation drugs did not reduce the need for organ support. Enrollment continues for moderately ill hospitalized COVID-19 patients in the trials.

As is normal for clinical trials, these trials are overseen by independent boards that routinely review the data and are composed of experts in ethics, biostatistics, clinical trials, and blood clotting disorders. Informed by the deliberations of these oversight boards, all the trial sites have paused enrollment of the most critically ill hospitalized patients with COVID-19. A potential for harm in this sub-group could not be excluded. Increased bleeding is a known complication of full-dose anticoagulation. The trials are working urgently to undertake additional analyses which will be made available as soon as possible.

group could not be excluded. Increased bleeding is a known complication of full-dose anticoagulation. The trials are working urgently to undertake additional analyses which will be made available as soon as possible.

At the recommendation of the oversight boards, patients who do not require ICU care at the time of enrollment will continue to be enrolled in the trial. Whether the use of full-dose compared to low-dose blood thinners leads to better outcomes in hospitalized

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Anticoagulation

- For adults with severe or critical COVID-19 and no evidence of VTE, we suggest against the routine use of therapeutic anticoagulation outside of clinical trials.
  - Weak recommendation, very low quality evidence

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Summary of recommendations of the COVID-19 guidelines therapeutic update

Severe COVID-19	Critical COVID-19
✔ DO: Systemic corticosteroids	
⚠ CONSIDER: Dexamethasone over other corticosteroids	
✔ DO: Pharmacologic VTE prophylaxis	
⚠ CONSIDER: Remdesivir	⚠ CONSIDER avoiding: Remdesivir
⚠ CONSIDER avoiding: Convalescent plasma outside of clinical trials	
⚠ CONSIDER avoiding: Full anticoagulation in patients without VTE outside of clinical trials	
⛔ DON'T DO: Hydroxychloroquine	
? UNCERTAIN: Awake proning	

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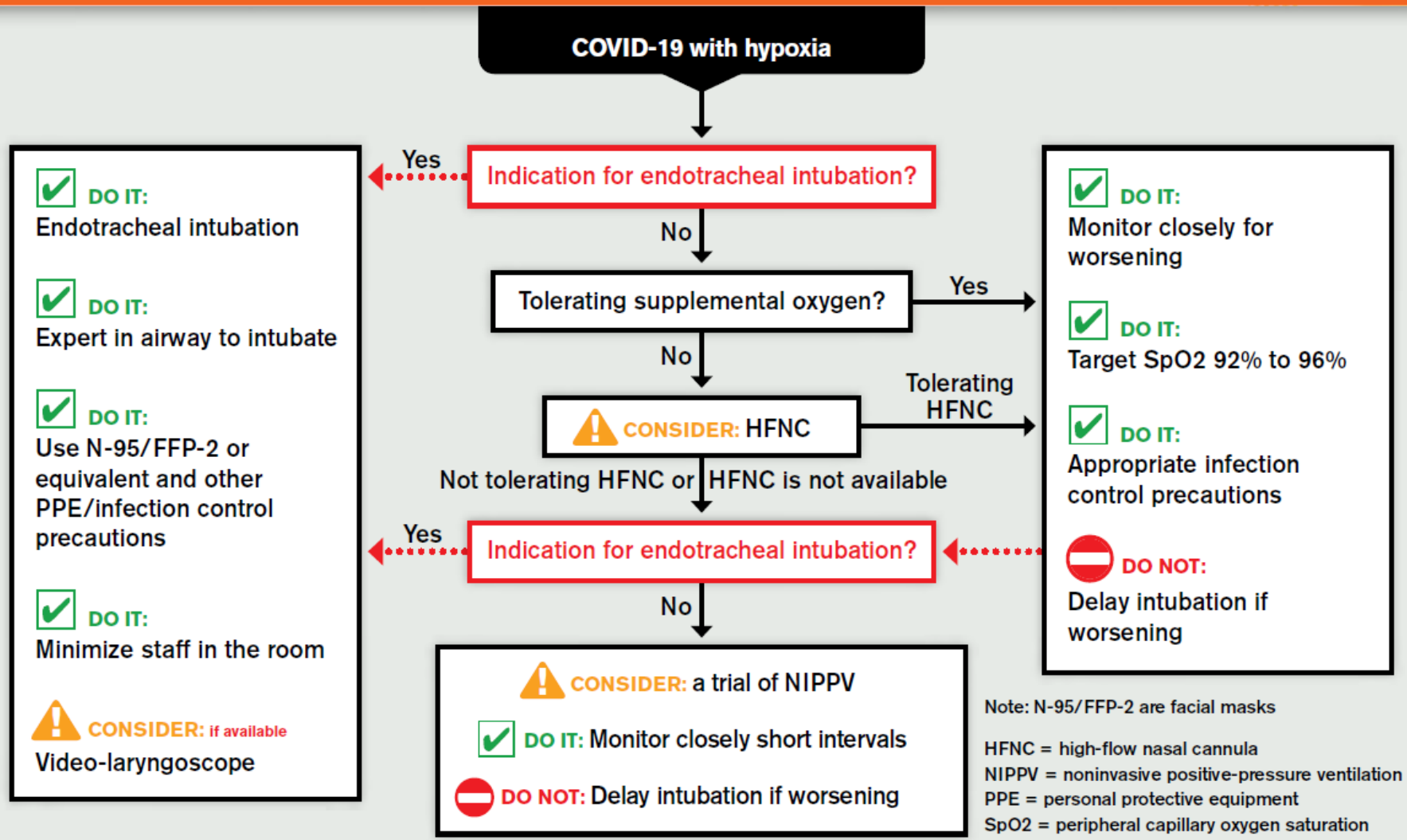
COVID-19 Guidelines

Summary of recommendations on the initial management of hypoxic COVID-19 patients



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Summary of recommendations on the management of patients with COVID-19 and ARDS

COVID-19 with mild ARDS

- ✔ **DO:** Vt 4-8 ml/kg and P_{plat} < 30 cm H_2O
- ✔ **DO:** Investigate for bacterial infection
- ✔ **DO:** Target SpO2 92% - 96%
- ⚠ **CONSIDER:** Conservative fluid strategy
- ⚠ **CONSIDER:** Empiric antibiotics

COVID-19 with mod to severe ARDS

- ⚠ **CONSIDER:** Higher PEEP
  PEEP should be tailored to individual response
- ⚠ **CONSIDER:** NMBA boluses to facilitate ventilation targets
- ⚠ **CONSIDER:**
  if PEEP responsive
  Traditional recruitment maneuvers
- ⚠ **CONSIDER:** Prone ventilation 12 -16 h
- ⚠ **CONSIDER:**
  if proning, high P_{plt} asynchrony
  NMBA infusion for 24 h
- ⛔ **DON'T DO:** Staircase recruitment maneuvers

Rescue/adjunctive therapy

- ⚠ **CONSIDER:**
  if proning, high P_{plt} asynchrony
  NMBA infusion for 24 h
- ⚠ **CONSIDER:** Prone ventilation 12 -16 h
- ⚠ **CONSIDER:** A trial of inhaled nitric oxide
  STOP if no quick response
- ⚠ **CONSIDER:** V-V ECMO or referral to ECMO center
  follow local criteria for ECMO

Mod = moderate
ARDS = adult respiratory distress syndrome
P_{plat} = plateau pressure
SpO2 = peripheral capillary oxygen saturation
PEEP = positive end-expiratory pressure
NMBA = neuromuscular blocking agents
ECMO = extracorporeal membrane oxygenation

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Thank you!

SSC COVID Guidelines First Update Panel Members

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Allison McGeer
Leonard Mermel
Manoj J. Mammen
Sheila Nainan Myatra
Amy Arrington
Ruth Kleinpell
Giuseppe Citerio
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Massimo Antonelli
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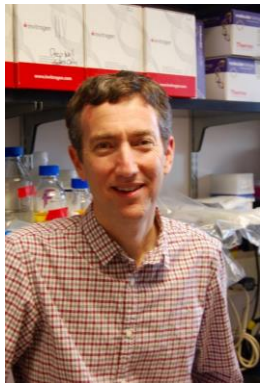
Emerging SARS-CoV-2 Variants: Updates & Implications

Angela L. Rasmussen, PhD
Georgetown Center for Global Health Science and Security
VIDO-InterVac, University of Saskatchewan (soon)



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Mastering the Mutants:
A primer on COVID-19 variants

Angela L. Rasmussen, Ph.D.

Georgetown Center for Global Health Science and Security

(soon: VIDO-InterVac, University of Saskatchewan)

Disclosures

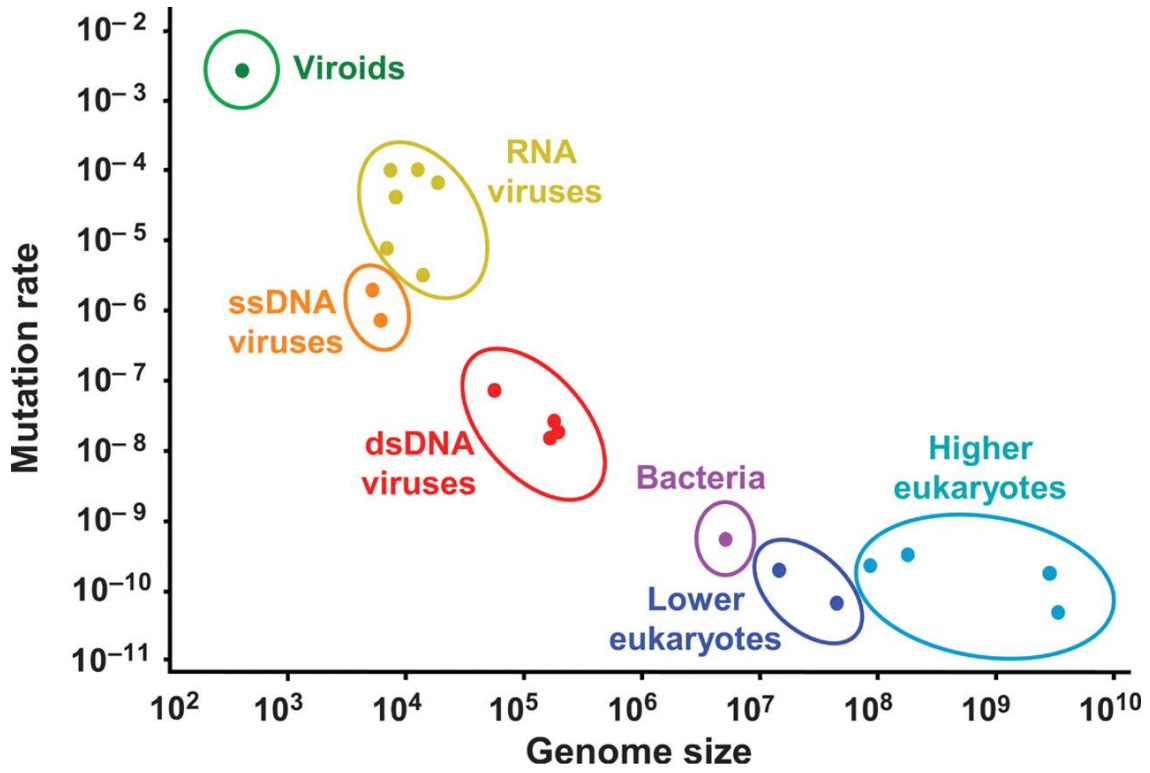
- Paid consultant for W2O, Edelman, Guidepoint, and IMG Expert Services
- Paid advisor for Siemens Healthineers
- Member of MJH Life Sciences COVID-19 Coalition
- Own stock in Illumina, Pacific Biosciences, ThermoFisher Scientific, & NanoString Technologies
- Research funded by DARPA, DTRA, NIAID, and FastGrants

Territorial Acknowledgement and Equity Statement

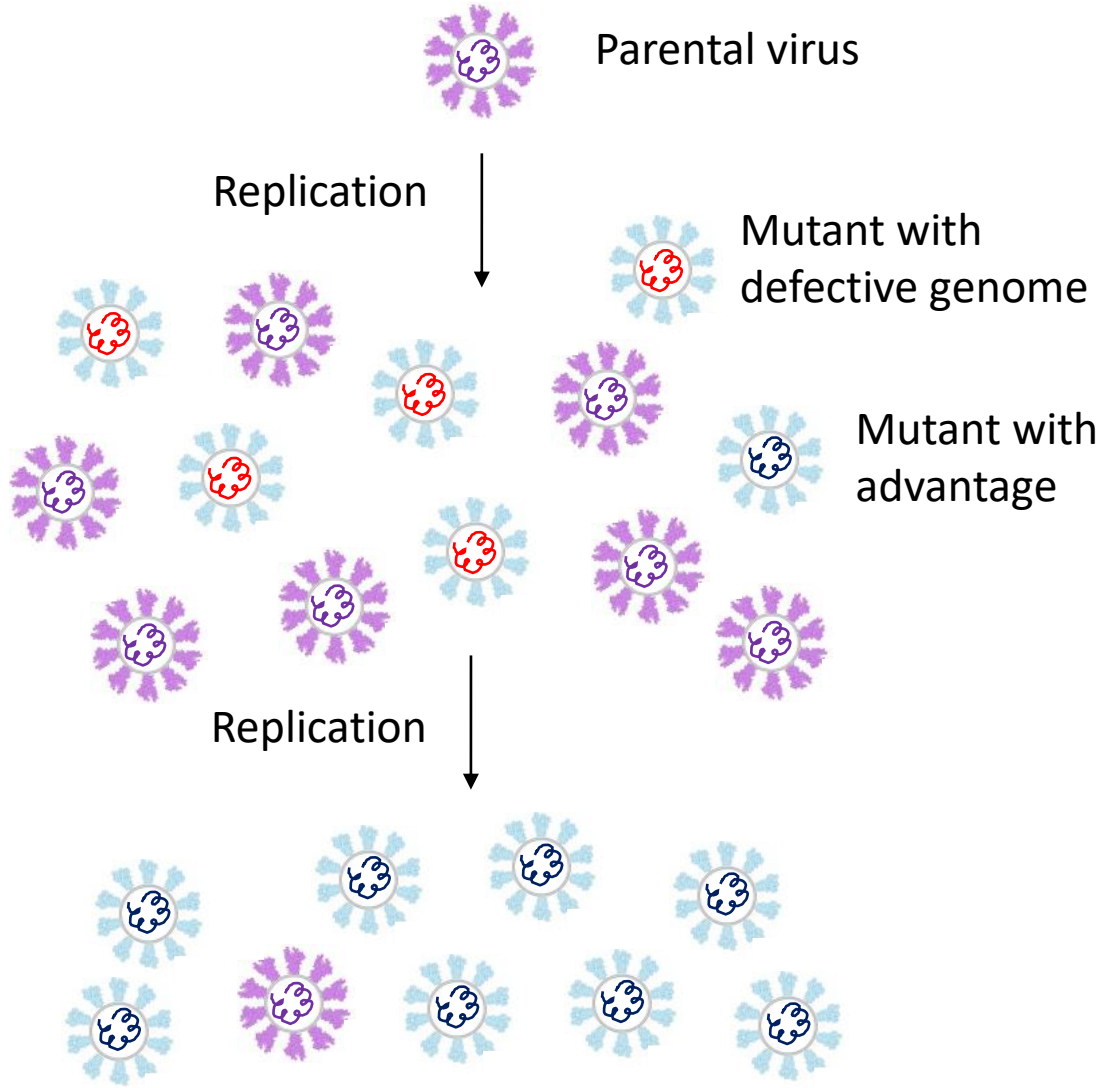
I am presenting today from the unceded ancestral homelands of the Duwamish people. I acknowledge and honor the First people of these territories and their Tribal governments, their histories and ancestry, and their roles today in caring for these lands.

I also would like to acknowledge that there is a history of systemic inequity in academic science that spans centuries. My prior institution, Columbia University, and my current institution, Georgetown University, were founded using profits from the trans-Atlantic slave trade and the sale of enslaved people. In addition, they excluded women and people of color from the academic community for more than 200 years, leaving a long and painful legacy of racial and gender-based inequality that continues to this day. I encourage all to consider how they can contribute to making scientific research a more equitable enterprise.

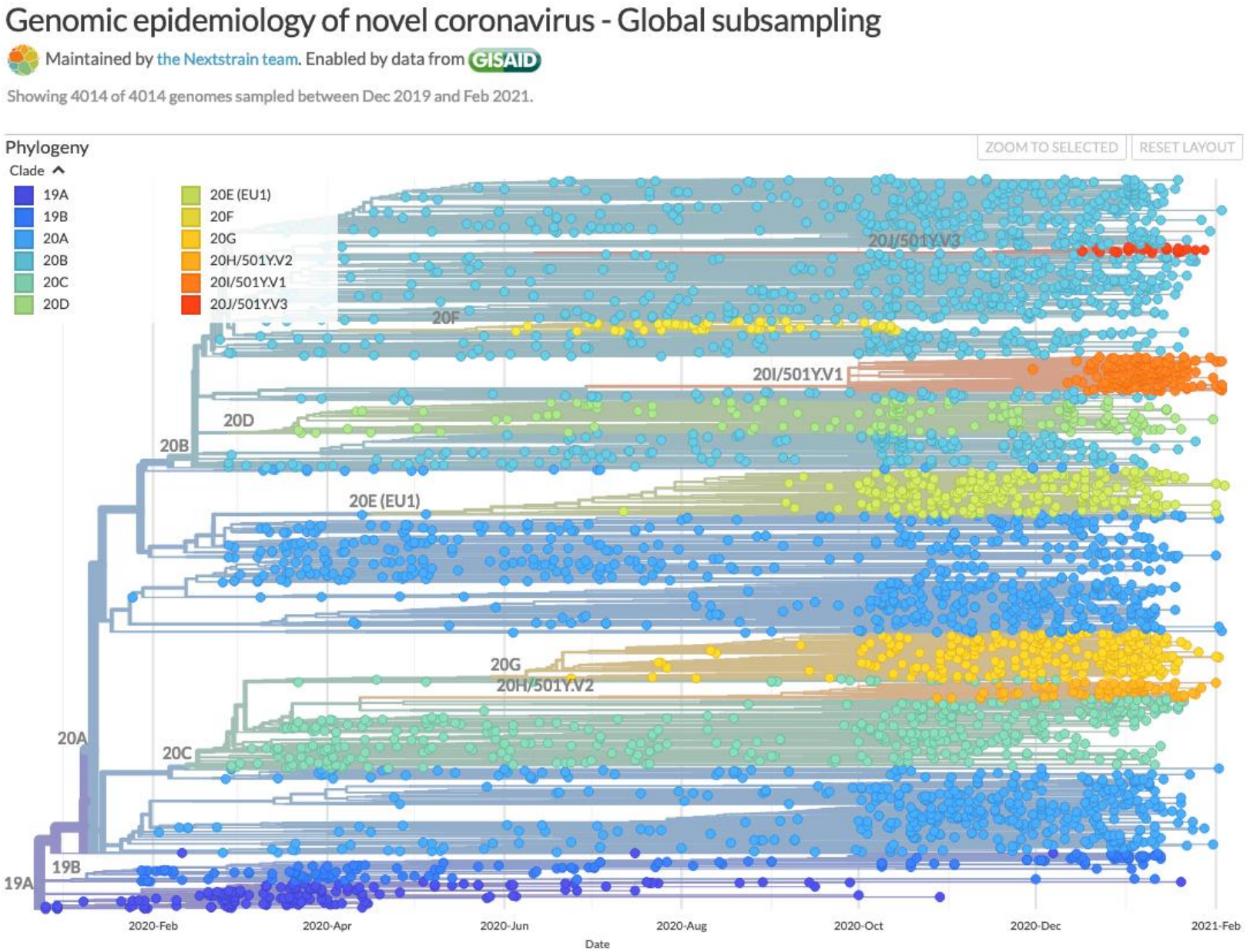
Mutation and virus evolution



Gago *et al*, *Science*, 2009

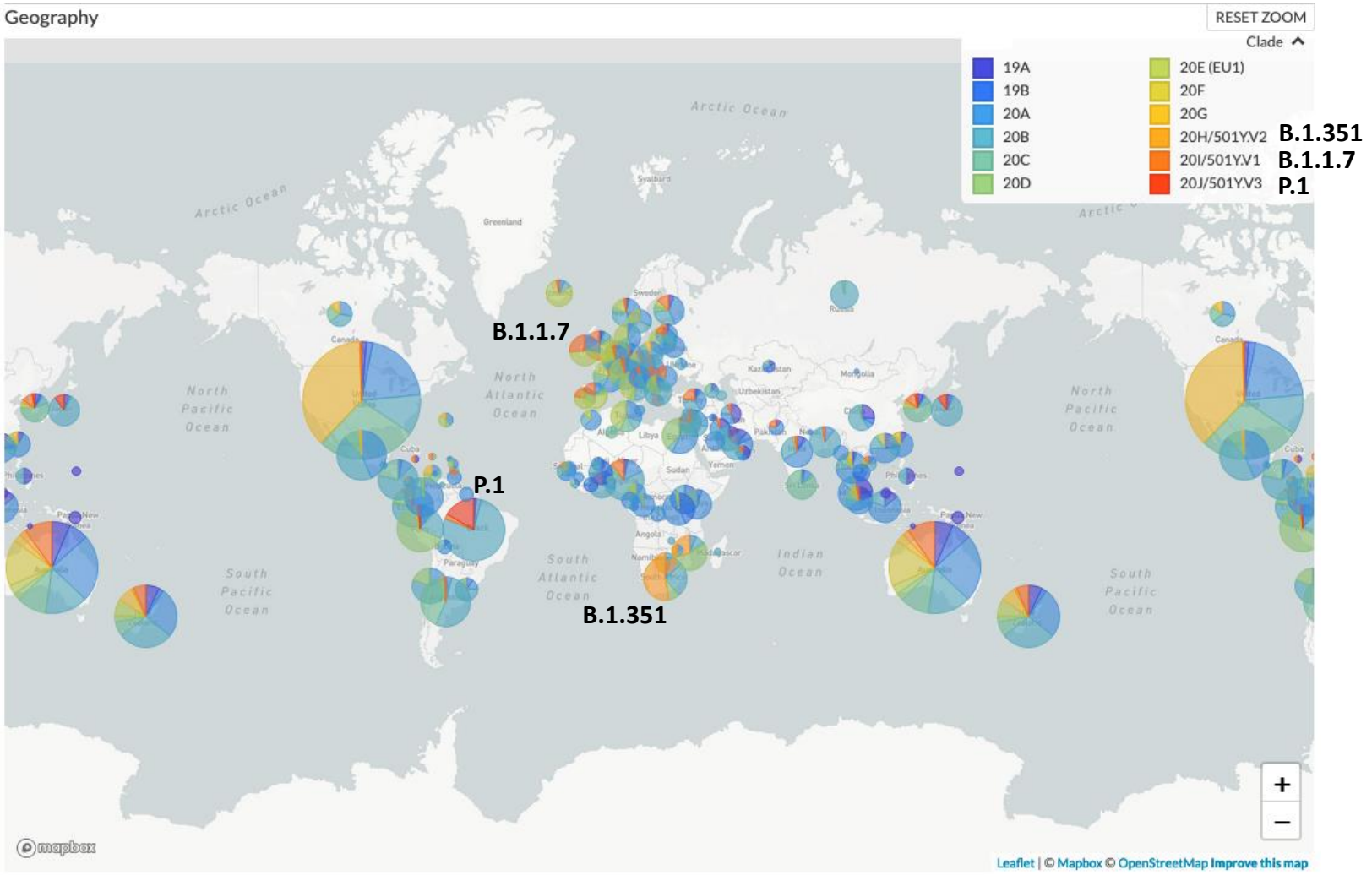


There are many variants



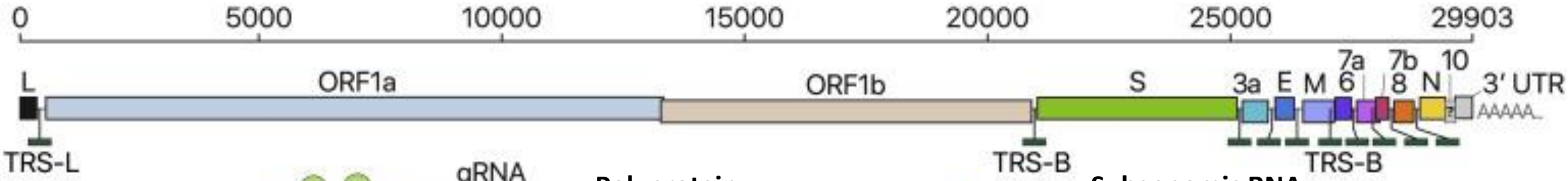
nextstrain.org

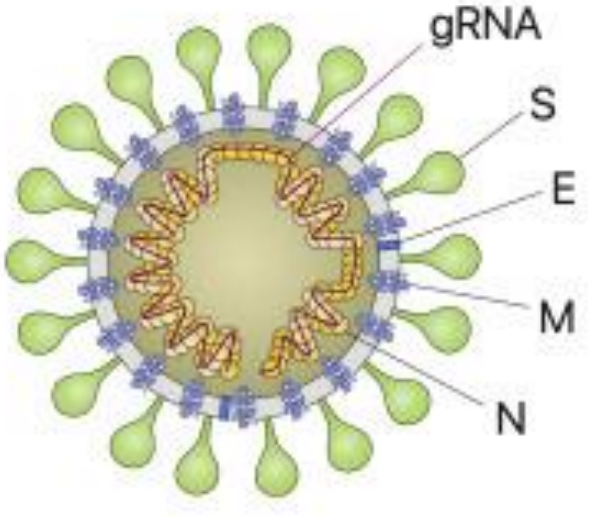
Global distribution of SARS-CoV-2 variants



nextstrain.org

SARS-CoV-2 genome organization

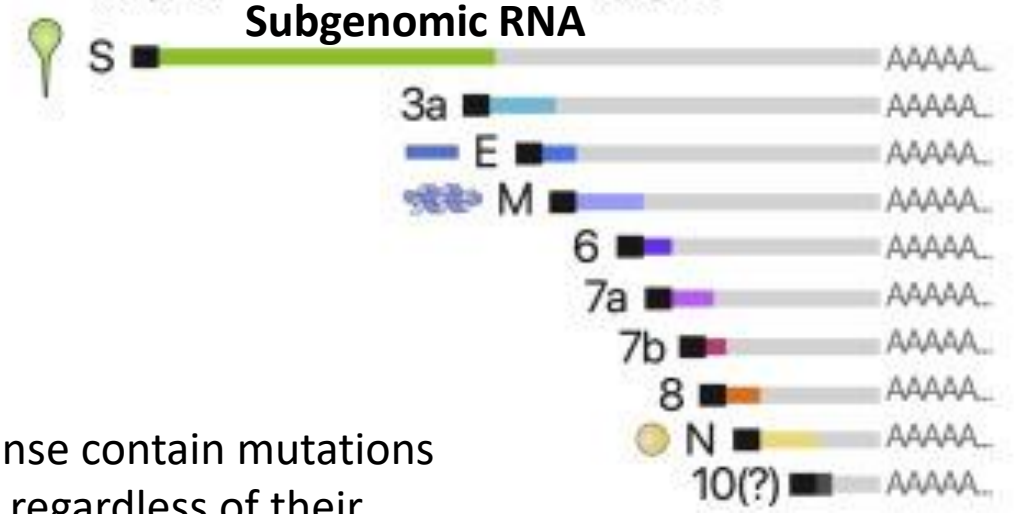




Virion architecture

Polyprotein

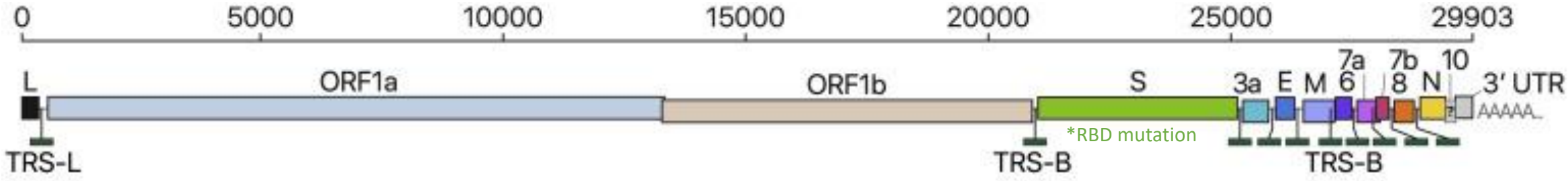
Subgenomic RNA



Variants in the strictest sense contain mutations anywhere in the genome, regardless of their function (or lack thereof)

Kim *et al*, *Cell*, 2020

Variants of concern



B.1.1.7 (501Y.V1)

T1001I (nsp3/PL2pro)
A1708D (nsp3/PL2pro)
I2230T (nsp3/PL2pro)
3675-3677del (nsp6)

P4715L (nsp12/RdRp)

69/70del
144del
N501Y*
A570D
D614G
P681H
T716I
S982A
D1118H
Q27Stop
R52I
Y73C
D3E
R203K
G204R
S235F

B.1.351 (501Y.V2)

T265I (nsp2)
H417N (nsp2)
K1655N (nsp3/PL2pro)
K3353R (nsp5/3CLpro)

P4715L (nsp12/RdRp)

D80A
241del
K417N*
E484K*
N501Y*
D614G
A701V
Q57H
P71L
P80A
T205I

P.1 (501Y.V3)

H417T (nsp2)
S1188S (nsp3/PL2pro)
K1795Q (nsp3/PL2pro)
3675-3677del (nsp6)

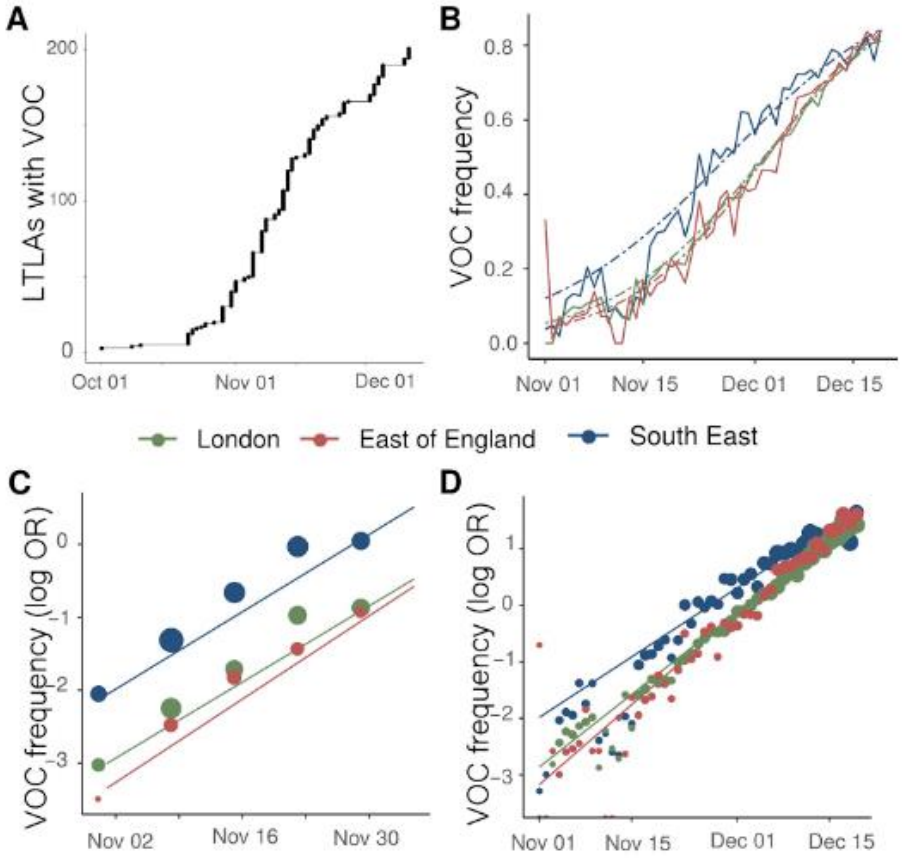
P4715L (nsp12/RdRp)
E5665D (nsp13/Helicase)

L18F
T20N
P26S
D80R
D138Y
R190S
K417N*
E484K*
N501Y*
D614G
H655Y
T1027I
V1176F
S253P
E92K
G18F
P80R
S202C
R203K
G204R

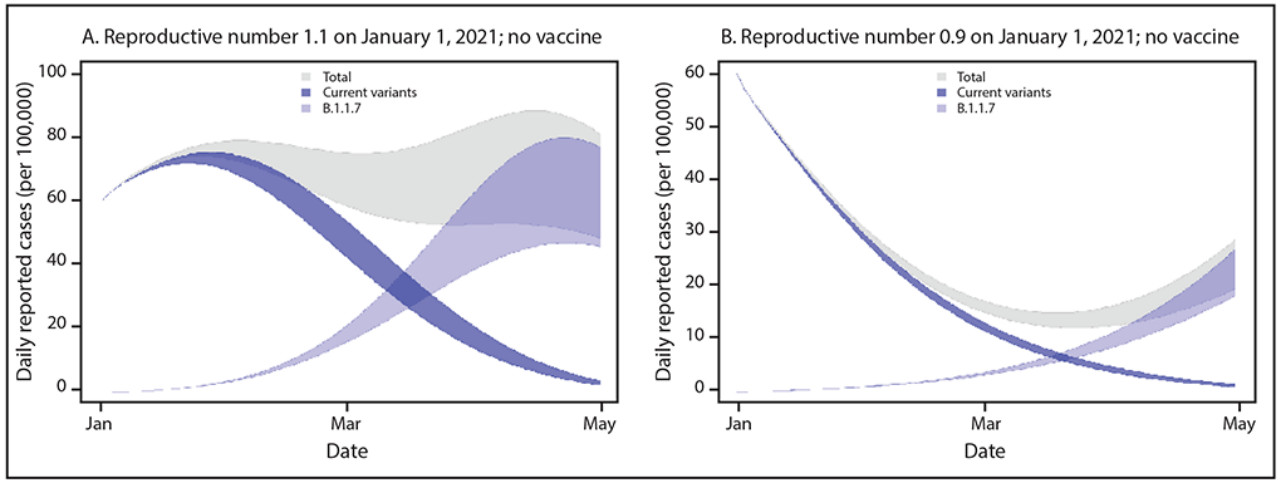
Present in 2/3 variants

Present in 3/3 variants

Evidence for increased transmissibility



Volz *et al*, *medRxiv*, 2020



Galloway *et al*, *MMWR*, 2021

Evidence for increased pathogenicity (?)

a. LSHTM: reported that the relative hazard of death within 28 days of test for VOC-infected individuals compared to non-VOC was 1.58 (95%CI 1.40–1.79), or 1.71 (95% CI 1.48- 1.97) if adjustment is made for misclassification of SGTF and missingness of data.

b. Imperial College London: mean ratio of case fatality ratio (CFR) for VOC-infected individuals compared to non-VOC was 1.36 (95%CI 1.18-1.56) by a case-control weighting method, 1.29 (95%CI 1.07-1.54) by a standardised CFR method.

c. University of Exeter: an updated analysis estimated the mortality hazard ratio for VOC-infected individuals compared to non-VOC was 1.7 (95% CI 1.3 – 2.2) in a matched cohort study.

d. Public Health England: an updated matched cohort analysis has reported a death risk ratio for VOC-infected individuals compared to non-VOC of 1.65 (95%CI 1.21-2.25).

e. Public Health Scotland: the REACT-SCOT study found that the hazard ratio was 1.08 (95% CI 0.78-1.49) for death and 1.40 (95% CI 1.28-1.53) for death or hospital admission in SGTF compared to non-SGTF cases.

f. Public Health Scotland: the EAVE-II study found the risk of being admitted to hospital is higher for cases with SGTF than for those who are S Gene positive - risk Ratio 1.63 (95% CI 1.48, 1.80). The relative risk of death within 28 days of a positive test was 1.37 (95% CI 1.02, 1.84) for SGTF compared to S Gene positive.

g. The Hospital Onset Covid Infection (HOCI) study: found the overall HR for in-hospital mortality of B.1.1.7 was 1.09 (95% CI 0.86-1.36, P=0.48). Increased mortality was only observed with the VOC in women over 65 years. The overall HR for ITU admission for B.1.1.7 was 1.15 (95% CI 0.86-1.53, P=0.35).

h. ICNARC and QRESEARCH: found a higher risk of ICU admission for VOC-patients (HR: 1.44; 95% CI: 1.25, 1.67) compared to non-VOC patients and no significant difference in the hazard of ICU mortality between the two groups (HR: 0.94; 95% CI: 0.82, 1.09).

i. ONS analysis: found that whilst the hazard ratio suggests that the B.1.1.7 variant is associated with higher risk of all-cause mortality, the number of deaths are too low for reliable inference.

j. CO-CIN (hospitalised patients only): found no statistically significant change in in-hospital CFR comparing proven B.1.1.7 (n=32) with non-VOC (n=184) (OR 0.63, 95%CI 0.20 – 1.69).

k. CO-CIN (hospitalised patients only): a repeat analysis with an updated dataset did not provide evidence to suggest that the variant of concern is linked to a higher risk of in-hospital case fatality (OR 0.67, 95%CI 0.32, 1.40).

l. LSHTM: a population-level analysis at the level of upper-tier local authorities resulted in estimates of a 1.4 (1.3-1.5) times higher number of hospitalisations per case and 1.4 (1.2-1.5) times higher number of fatalities per hospitalisation associated with VOC.

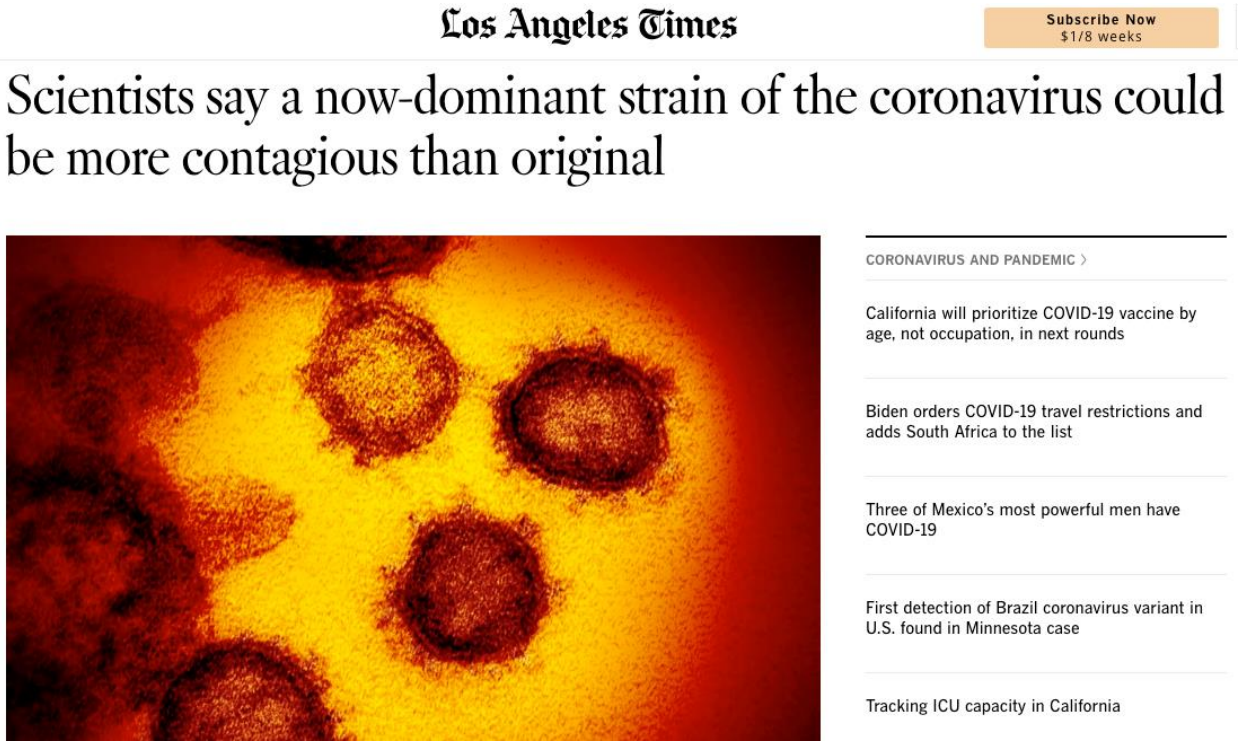
B.1.1.7 (as identified by SGTF) is associated with a higher risk of hospitalization and mortality in multiple studies

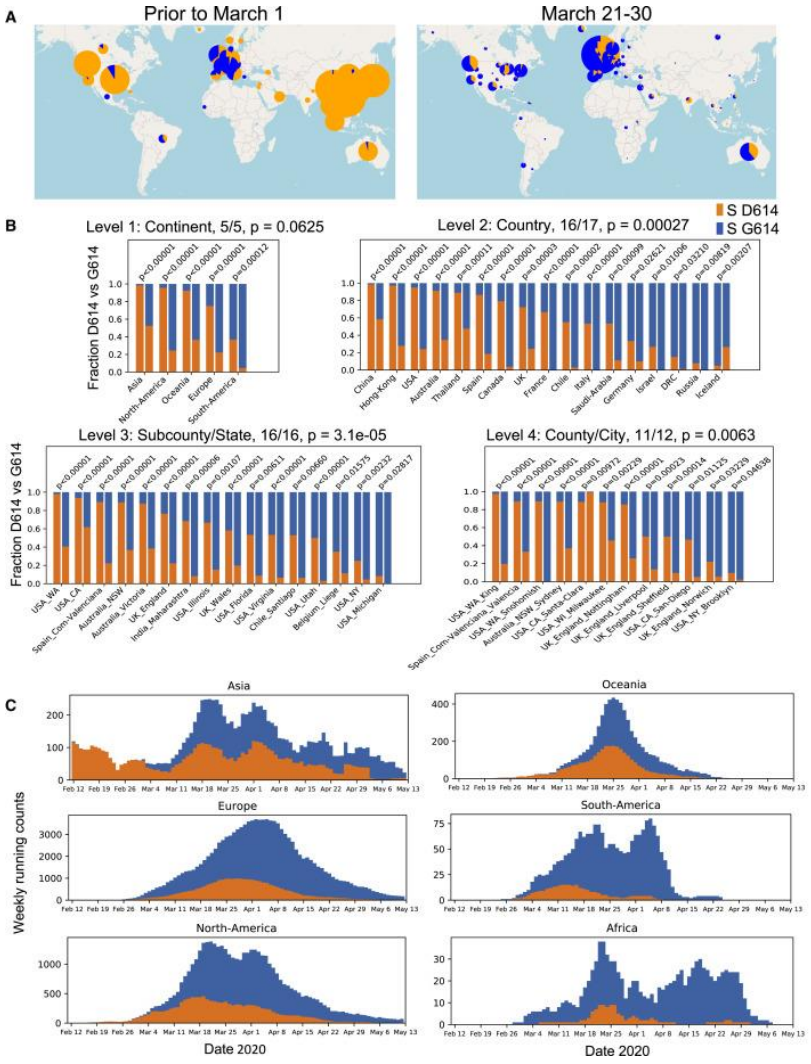
Studies limited to community testing or population-based analyses, thus are limited by:
-Sampling bias
-Representativeness
-Statistical power
-Inability to control for confounders

No observed increase in disease severity in hospitalized B.1.1.7 patients so there is no clear mechanism for increased pathogenicity

NERVTAG report:
https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/961042/S1095_NERVTAG_update_note_on_B.1.1.7_severity_20210211.pdf

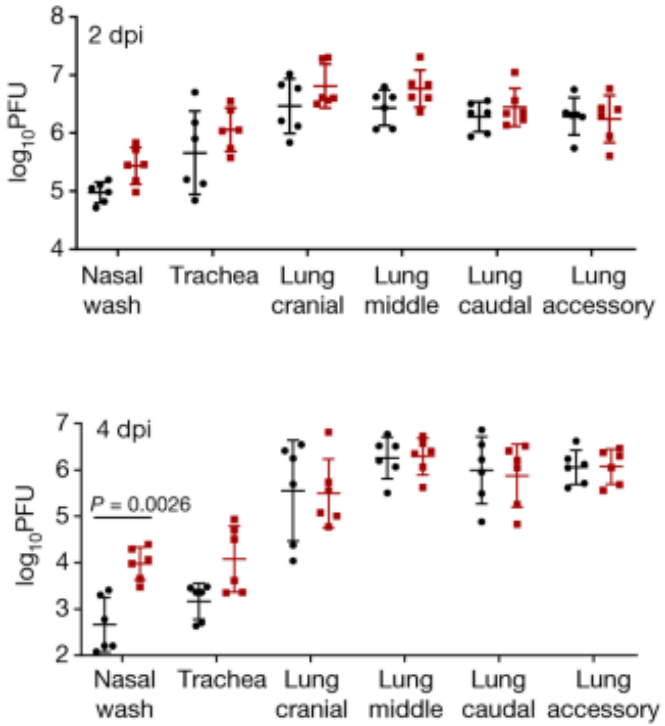
D614G: a harbinger of more transmissible variants



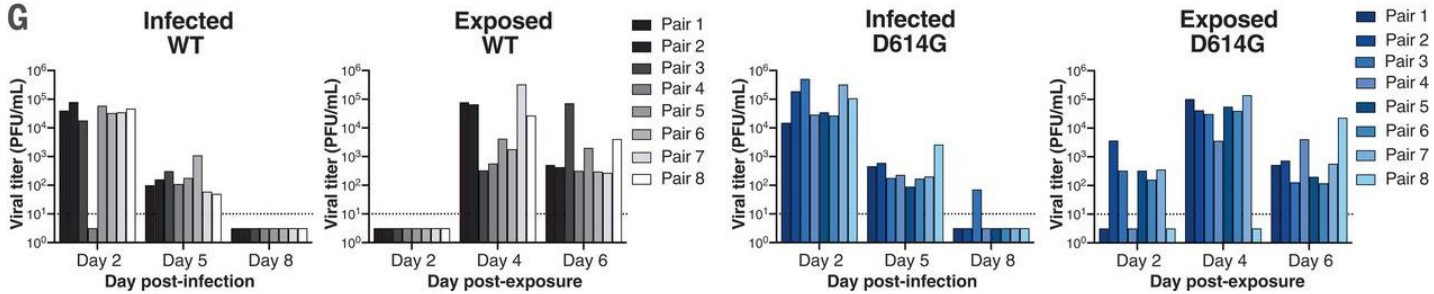


Korber *et al*, *Cell*, 2020

But is D614G more transmissible?



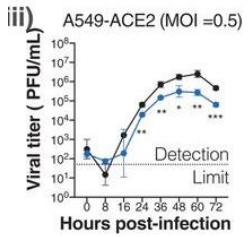
Plante *et al*, *Nature*, 2020



Hou *et al*, *Science*, 2020

Possible mechanisms of increased transmissibility

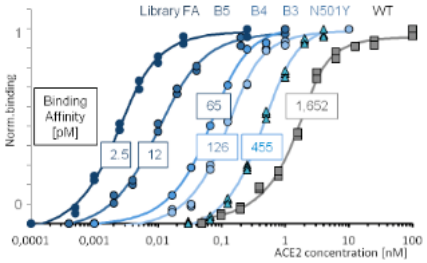
Increased fitness



Increased viral shedding

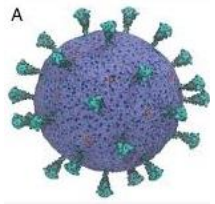
Longer interval of contagiousness

Receptor binding affinity



Increased infectivity

Increased virion stability



Increased environmental stability

DAILY COMMENT

CAN THE COVID-19 VACCINE BEAT THE PROLIFERATION OF NEW VIRUS MUTATIONS?

By Lawrence Wright

January 21, 2021

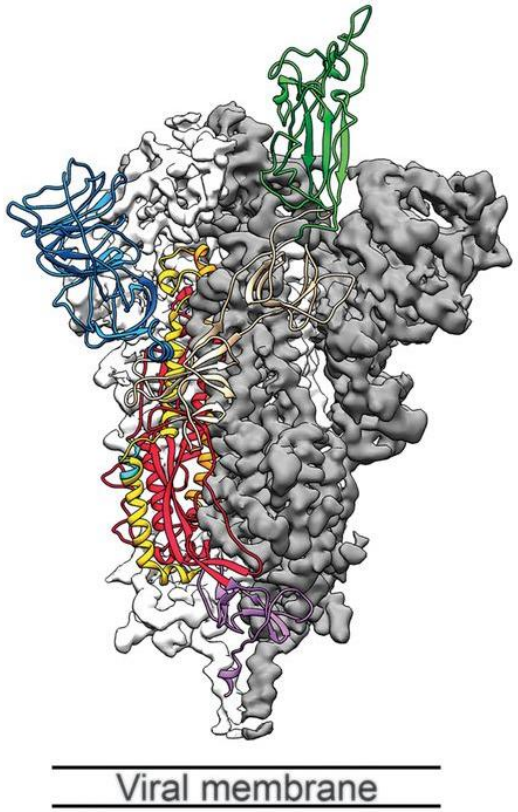
Adam Lauring, MD, PhD
Department of Medicine, Infectious Diseases
Department of Microbiology and Immunology
University of Michigan

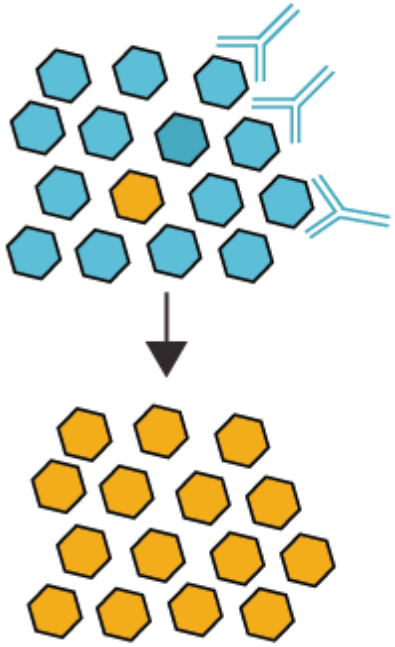
Disclosures

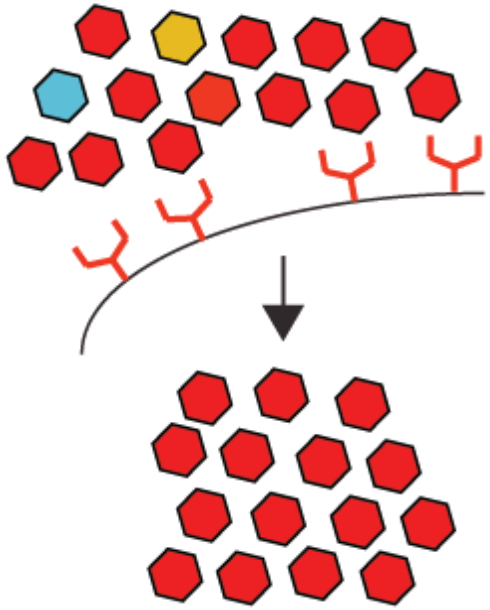
- Paid consultant on antiviral drugs for Sanofi

- Paid member of Steering Committee for Roche clinical trial, ongoing CENTERSTONE: a global phase IIIb, randomized, double-blind, placebo-controlled clinical efficacy study of baloxavir marboxil for the reduction of direct transmission of influenza from otherwise healthy patients to household contacts

Spike is *the* antigen





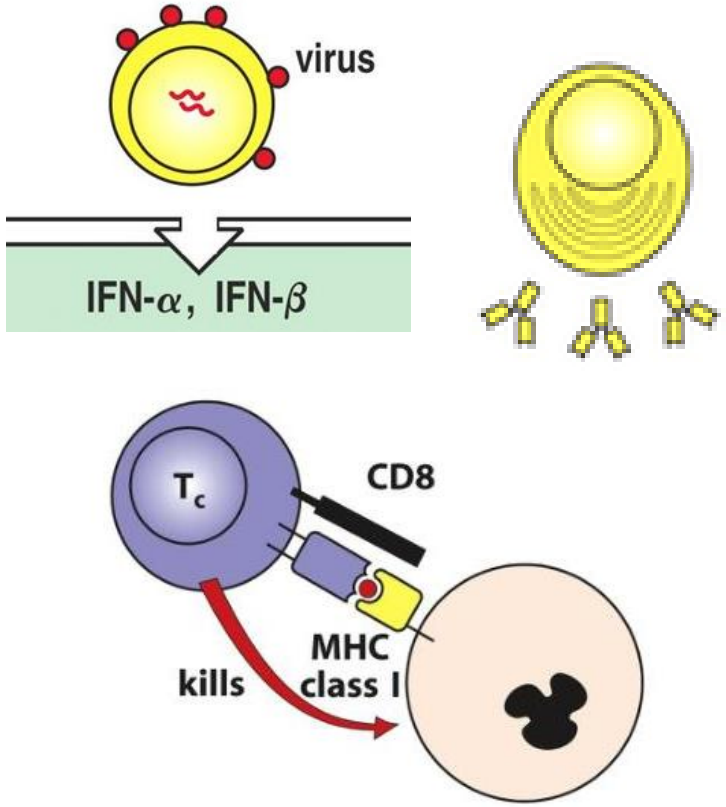


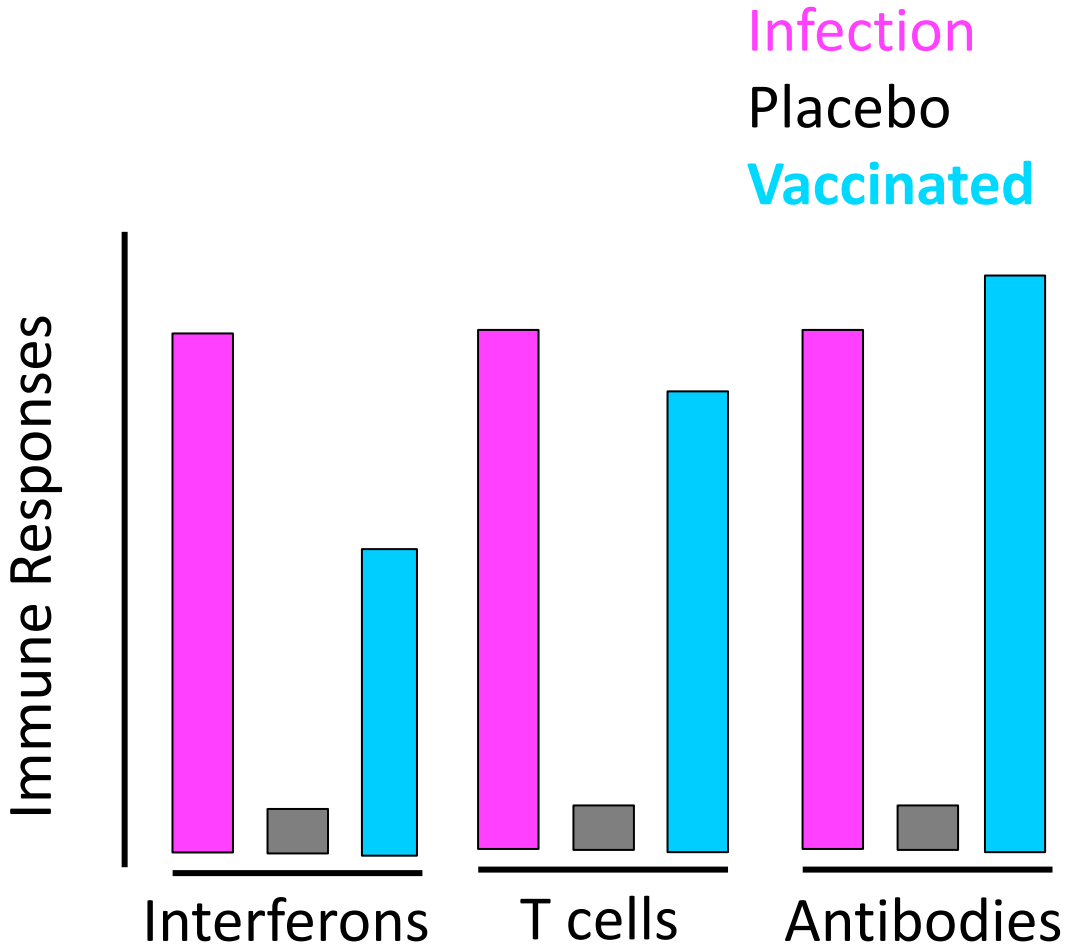
Wrapp et al. Science 2020

Will the flu vaccine protect this ID physician?

A/HongKong/2014	”cell”	1:160
A/HongKong/2014	“egg”	1:2560
A/Singapore/2016	“cell”	1:160
A/Singapore/2016	“egg”	1:5120

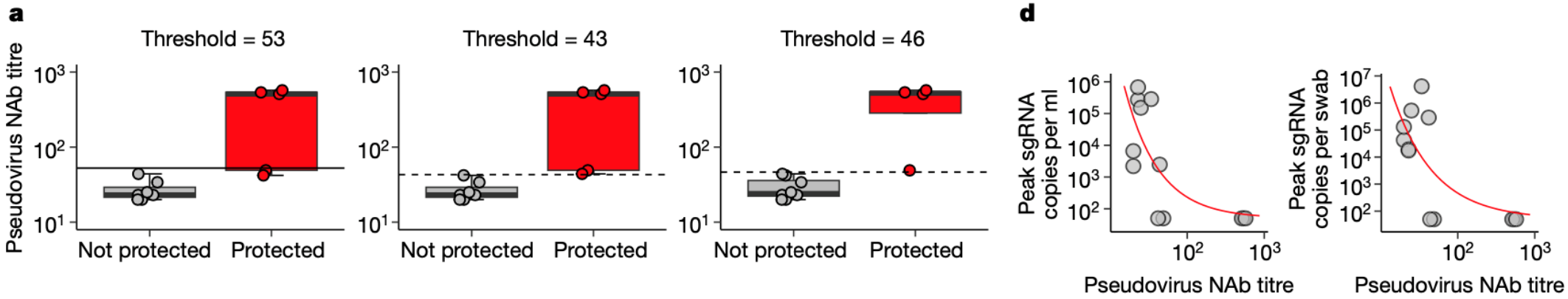
Defining correlates of protection





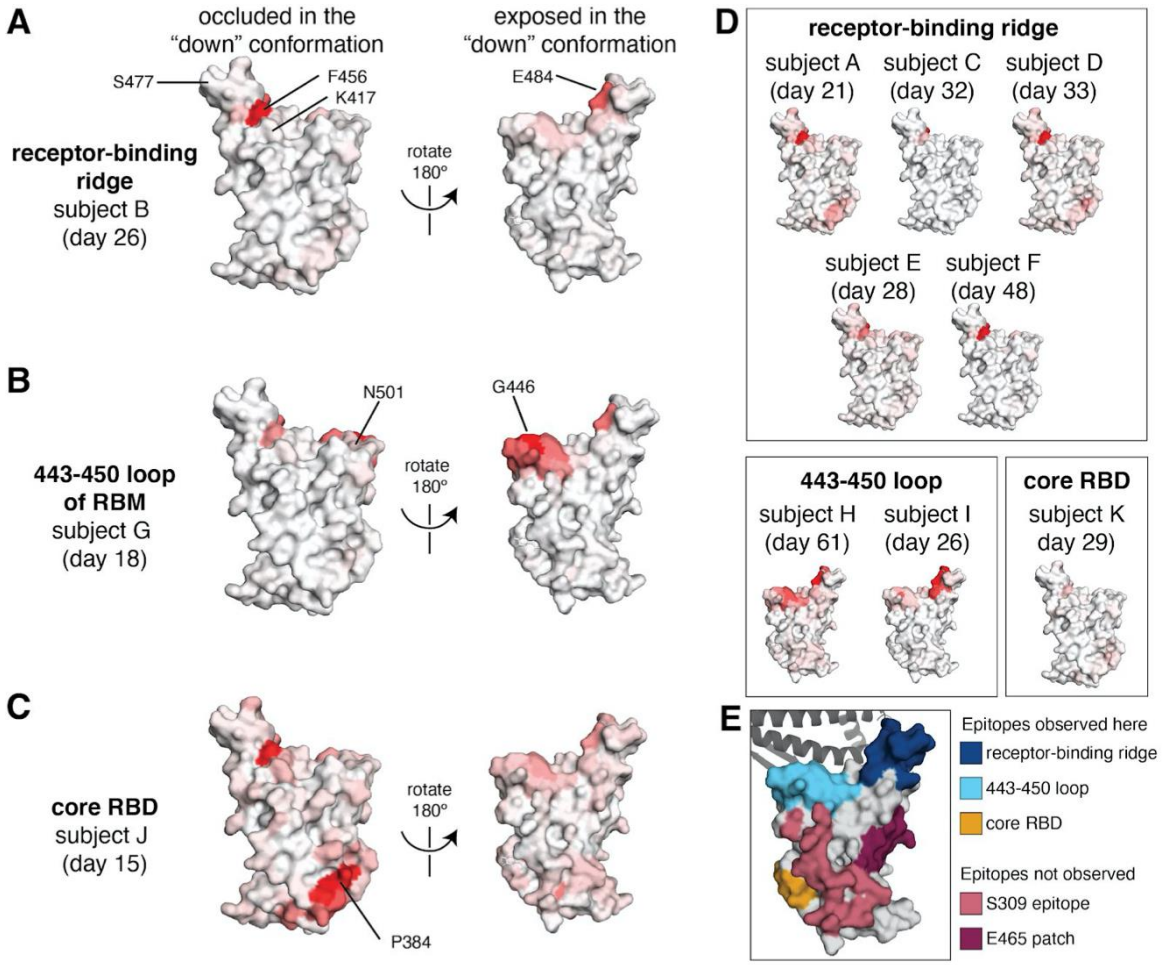
Graphics from Janeway's Immunobiology

What serum titer is “protective”?



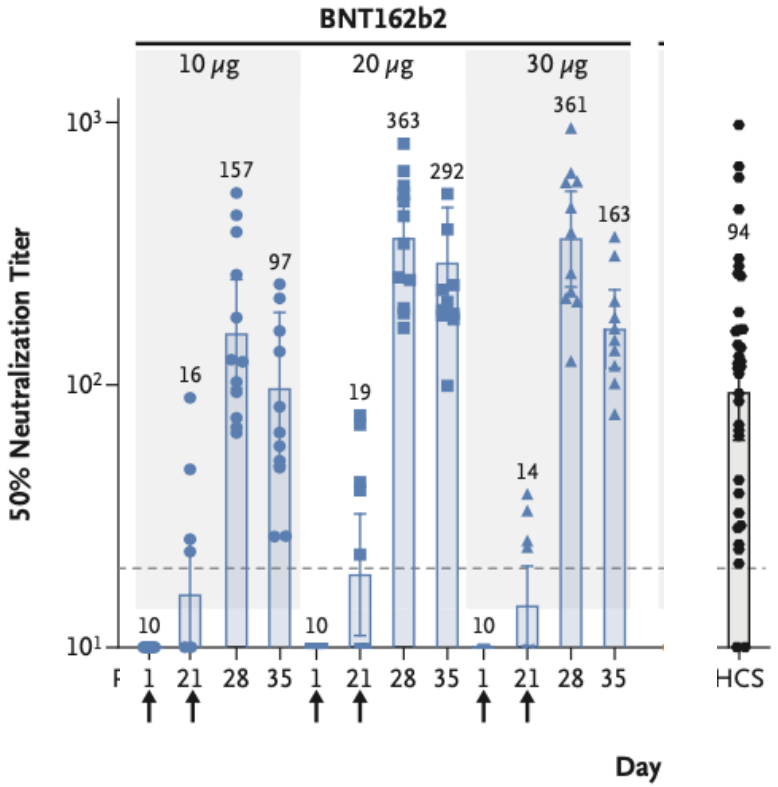
MacMahon et al. Nature 2020

Serological responses are complex…and dynamic



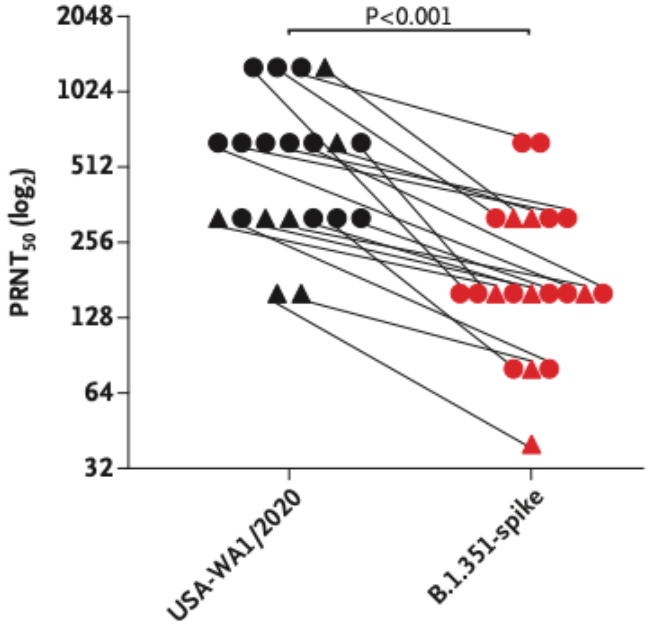
Greaney et al. bioRxiv 2020

Serological responses to vaccines are strong

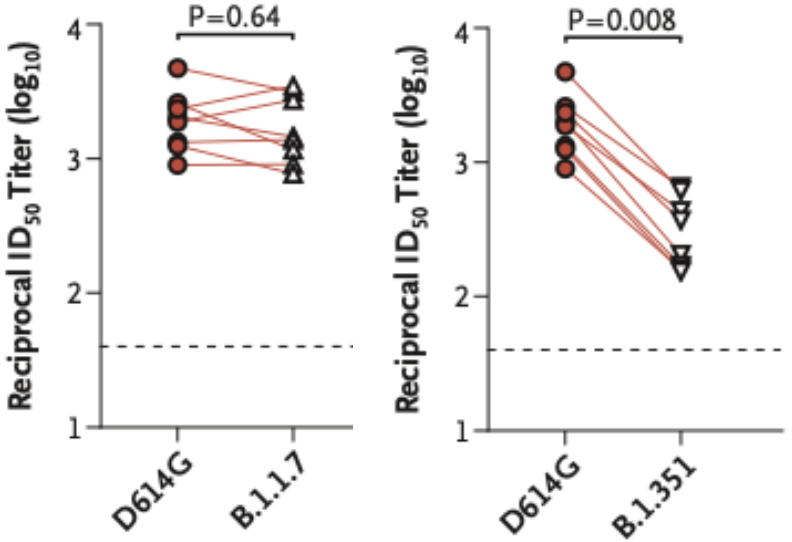


Walsh et al. NEJM 2020

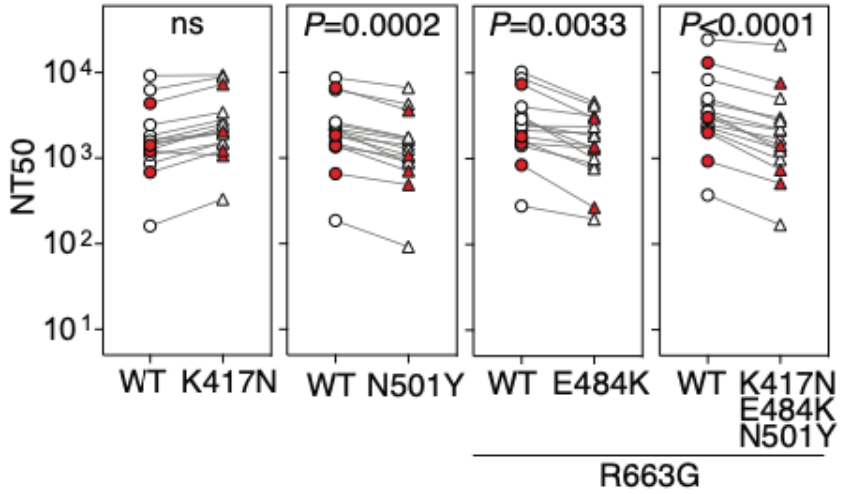
Are post-vaccination responses strong enough?



Liu et al. NEJM 2021
Pfizer/BioNTech



Werner et al. NEJM 2021
Moderna



Wang et al. Nature 2021
Moderna and Pfizer/BioNTech

Serology is only part of the story

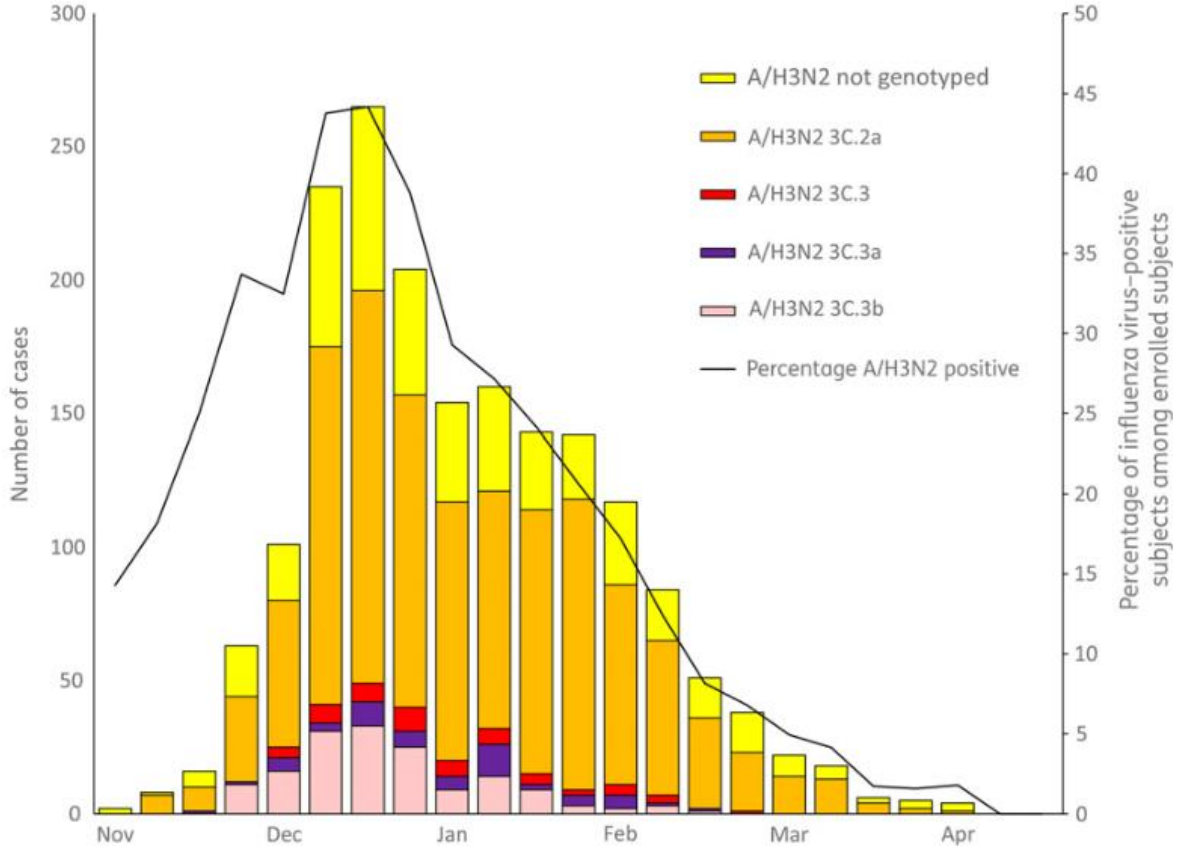
Adam Kucharski 
@AdamJKucharski

A few people have asked "do new variants mean vaccines won't work"? Important to avoid simple categories of 'works' and 'doesn't work'. Some variants may alter the extent of protection (and some probably won't) and question is whether this change matters (and at what scale)... 1/

7:34 AM · Jan 19, 2021 · Twitter Web App

A/HongKong/2014	”cell”	1:160
A/HongKong/2014	“egg”	1:2560
A/Singapore/2016	“cell”	1:160
A/Singapore/2016	“egg”	1:5120

How do you know when a variant reduces vaccine effectiveness?



Genetic Group, Age	VE, % (95% CI)[a]
Overall[b]	
All ages	7 (–5 to 17)
6 mo–8 y	20 (–3 to 37)
9–49 y	–5 (–24 to 12)
≥50 y	9 (–14 to 28)
Genetic group 3C.2a	
All ages	1 (–14 to 14)
6 mo–8 years	16 (–13 to 37)
9–49 y	–15 (–41 to 7)
≥50 y	8 (–21 to 30)
Genetic group 3C.3b	
All ages	44 (16 to 63)
6 mo–8 y	NR
9–49 y	35 (–13 to 63)
≥50 y	NR
Genetic group 3C.3a	
All ages	–48 (–169 to 19)
Genetic group 3C.3	
All ages	1 (–87 to 48)

Flannery et al. JID 2016

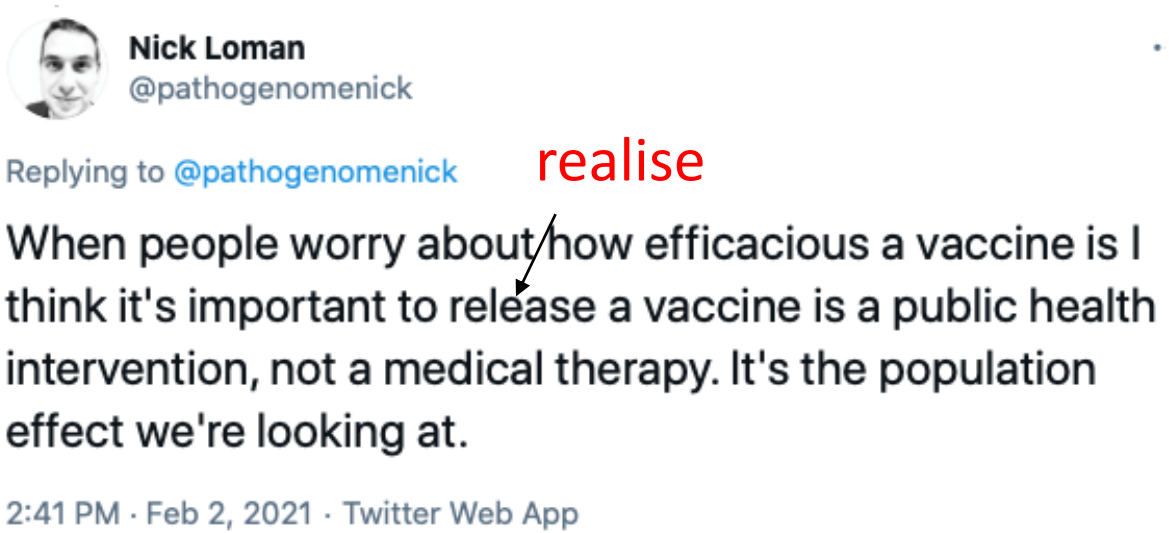
What do the trials say?

- J&J (Ad26), press release
  - VE against moderate to severe COVID-19 infection: 72% in US, 66% in Latin America (P1?) and 57% in South Africa (B.1.351?)

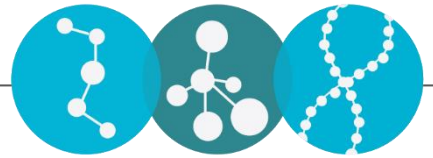
- Novavax (Spike nanoparticle), press release
  - UK phase 3 trial, overall VE against symptomatic disease 89.3% (75.2;95.4)
    Post hoc analysis showed similar efficacy against B.1.1.7
  - South Africa phase 2b trial, VE in HIV (-) 60.1% (19.9; 80.1)
    93% of cases due to B.1.1351

- AZ/Oxford (Chimp Ad), medRxiv
  - Phase 1b/2 trial in South Africa, June-November
  - Overall VE against symptomatic disease 21.9% (-49.9; 59.8)
  - 92.9% of cases meeting endpoint were B.1351 (VE 10.4%, -76.8; 54.8)

What does this mean for the future of SARS-CoV-2 vaccines?



Imgflip.com



Surveillance for SARS-CoV-2 Variants in the US

Gregory Armstrong, MD, FIDSA
Director, Advanced Molecular Detection Program
Centers for Disease Control and Prevention

No Disclosures to Report

Objectives for Sequence-Based Surveillance of SARS-CoV-2

National Level

- detect and track variants with implications for
  - vaccines
  - therapeutics
  - diagnostics
- … or that have important epidemiologic implications, such as:
  - increased transmissibility
  - increased severity

(random sampling)

State/Local level

- more granular understanding of local epidemiology
- identify clusters
- investigate outbreaks
- support other public health operations

(targeted sampling)

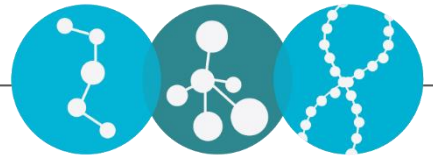
SARS-CoV-2 Sequence-Based Surveillance

National SARS-CoV-2 Strain Surveillance (NS3):	**750/wk (also provides samples)**
National diagnostics labs:	**~4,000/wk currently, expanding to 25,000**
State/local public health labs:	**~4,000/wk currently**
Other US labs:	**~4,000/wk currently**
Total:	***~13,000/wk currently*** ***(~2.6% of 503,000 US cases in 3rd wk of Feb)***

Variants and Mutations of Highest Concern

- Variants of concern
  - B.1.1.7: increased transmission, probably increased severity
  - B.1.351: probably increased transmission, decreased neutralization
  - P.1: probably increased transmission, decreased neutralization
- Variants of interest
  - B.1.427/.429 (L452R): possible increased transmission
- Mutations (examples)
  - N501Y: in all 3 VOCs, increases receptor binding
  - E484K: *in vitro,* has most impact on neutralization*
  - Q677P/H: 7 emergences in US (and others elsewhere)†

*Greaney *et al.*, 2021, *Cell Host & Microbe* (https://doi.org/10.1016/j.chom.2021.02.003)
†Hodcroft EB *et al.*, *medRxiv* 2021 (https://doi.org/10.1101/2021.02.12.21251658)



cdc.gov/coronavirus
cdc.gov/amd*

* “Covid-19 Genomic Epidemiology Toolkit” (short tutorials on molecular epidemiology)

COVID-19 Vaccine FAQs

Go to www.COVID19LearningNetwork.org and click on “Vaccines FAQ”

CDC-IDSA Partnership: COVID-19 Clinical Management Call Support

FOR WHOM?

Clinicians who have questions about the clinical management of COVID-19

WHAT?

Calls from clinicians will be answered by CDC personnel and/or triaged by CDC to a group of IDSA volunteer clinicians for peer-to-peer support

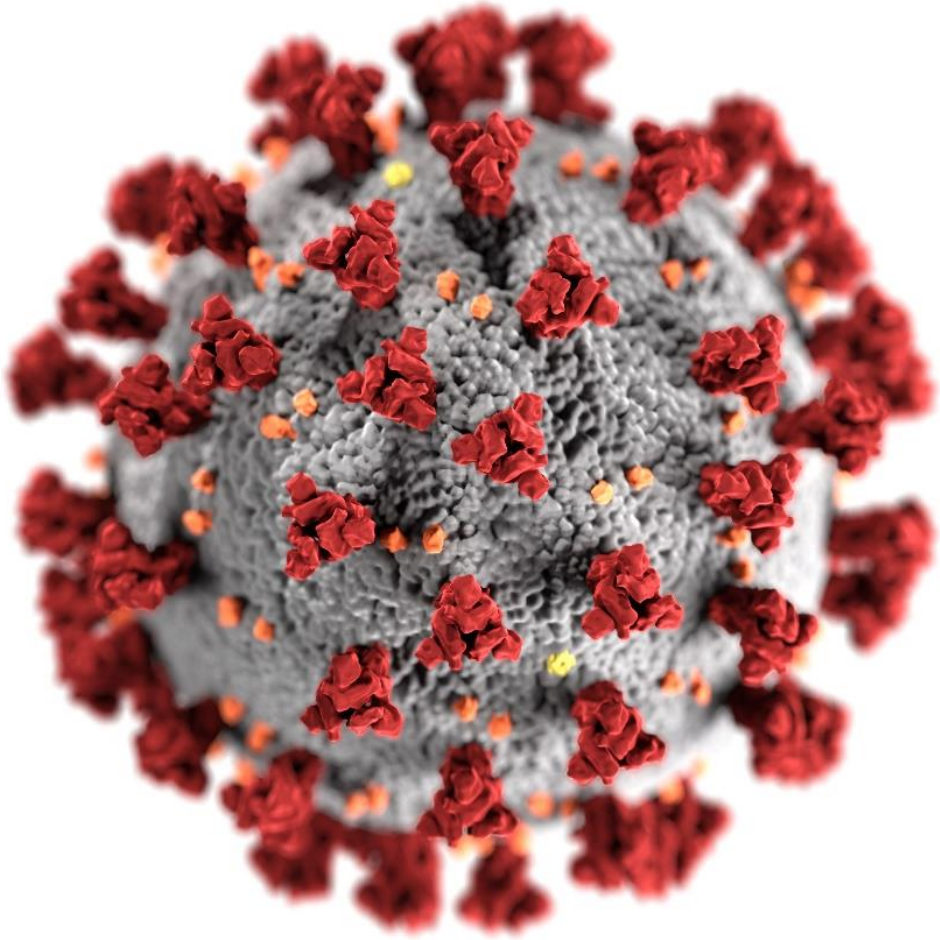
HOW?

Call 800-CDC-INFO (800-232-4636)

Or Submit Your Question in Writing:

www.cdc.gov/cdc-info

Click on Contact Form



IDSA
Infectious Diseases Society of America

cdc.gov/coronavirus

Continue the conversation on Twitter

@RealTimeCOVID19
#RealTimeCOVID19

We want to hear from you! Please complete the post-call survey.

Next Call: **Saturday, Feb. 27th**

A recording of this call will be posted at **www.idsociety.org/cliniciancalls**

-- library of all past calls now available --

Contact Us:

Dana Wollins (dwollins@idsociety.org)
Deirdre Lewis (dlewis@idsociety.org)