COVID-19 / SARS-COV2 /CORONAVIRUS

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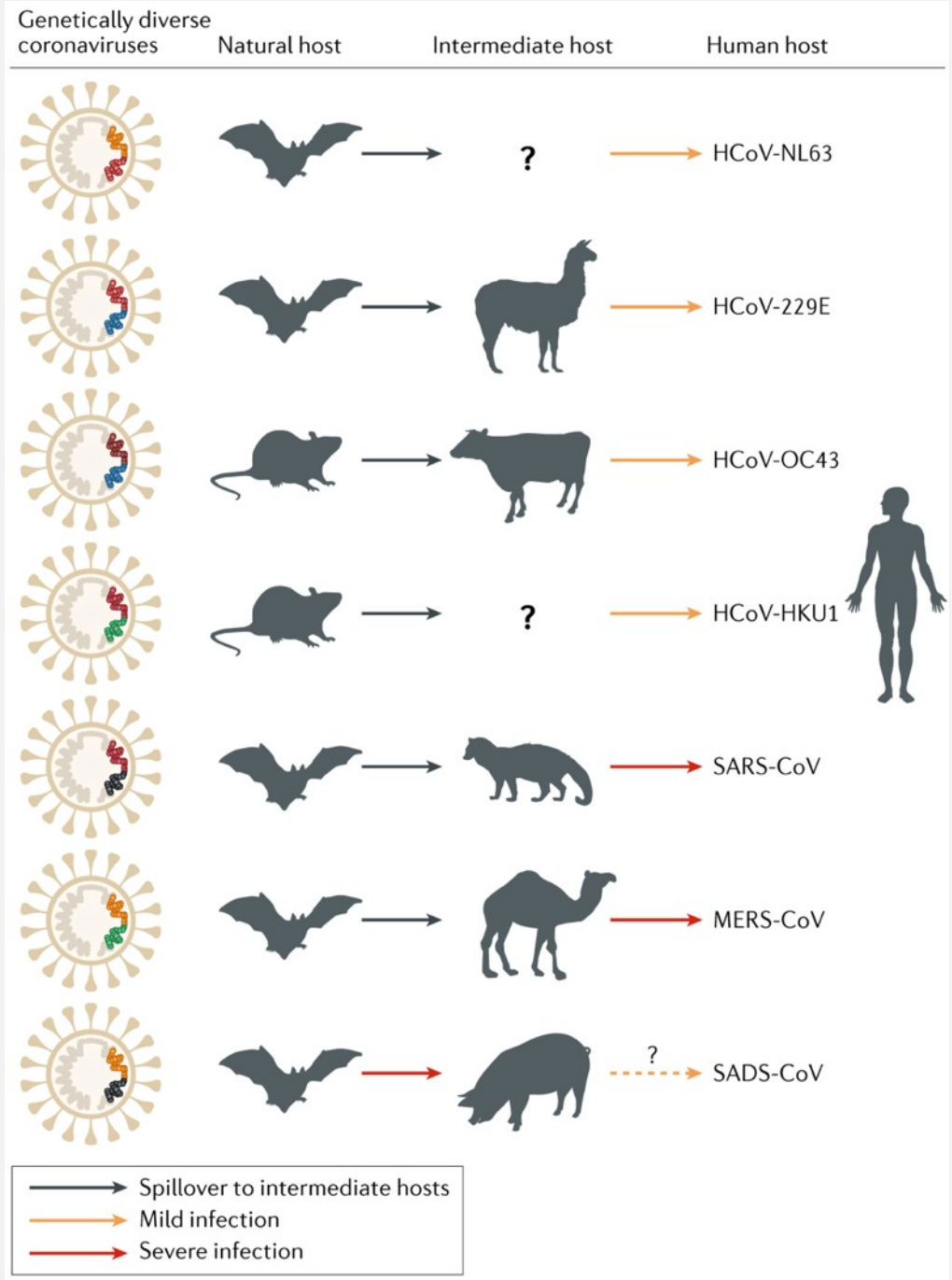
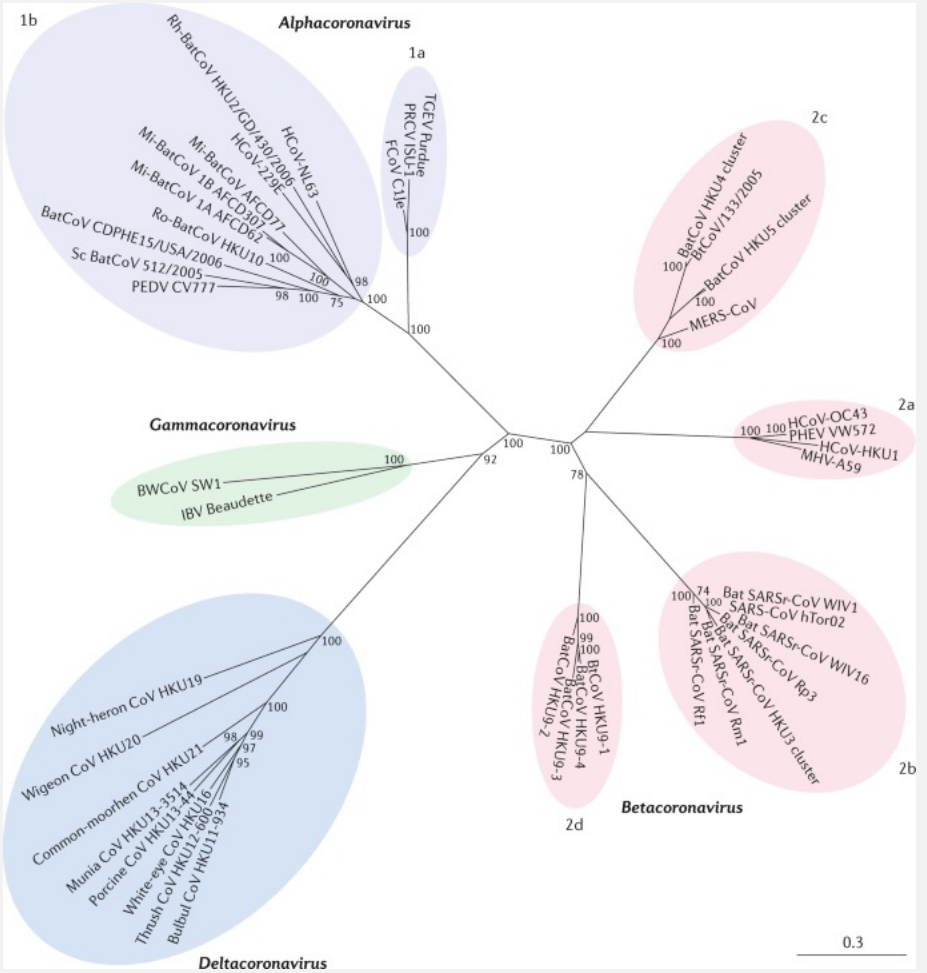
OBJECTIVES

- Microbiology of SARS-CoV 2 / Origin
- Acquisition / Epidemiology – Airborne/Contact; Days of infectiousness, Role of children / schools, Hotspots
- Clinical features of COVID 19: my personal observations
- Diagnosis and Testing: Pitfalls
- Treatment: State of the Art 9/2021
- Vaccines: hope and misinformation

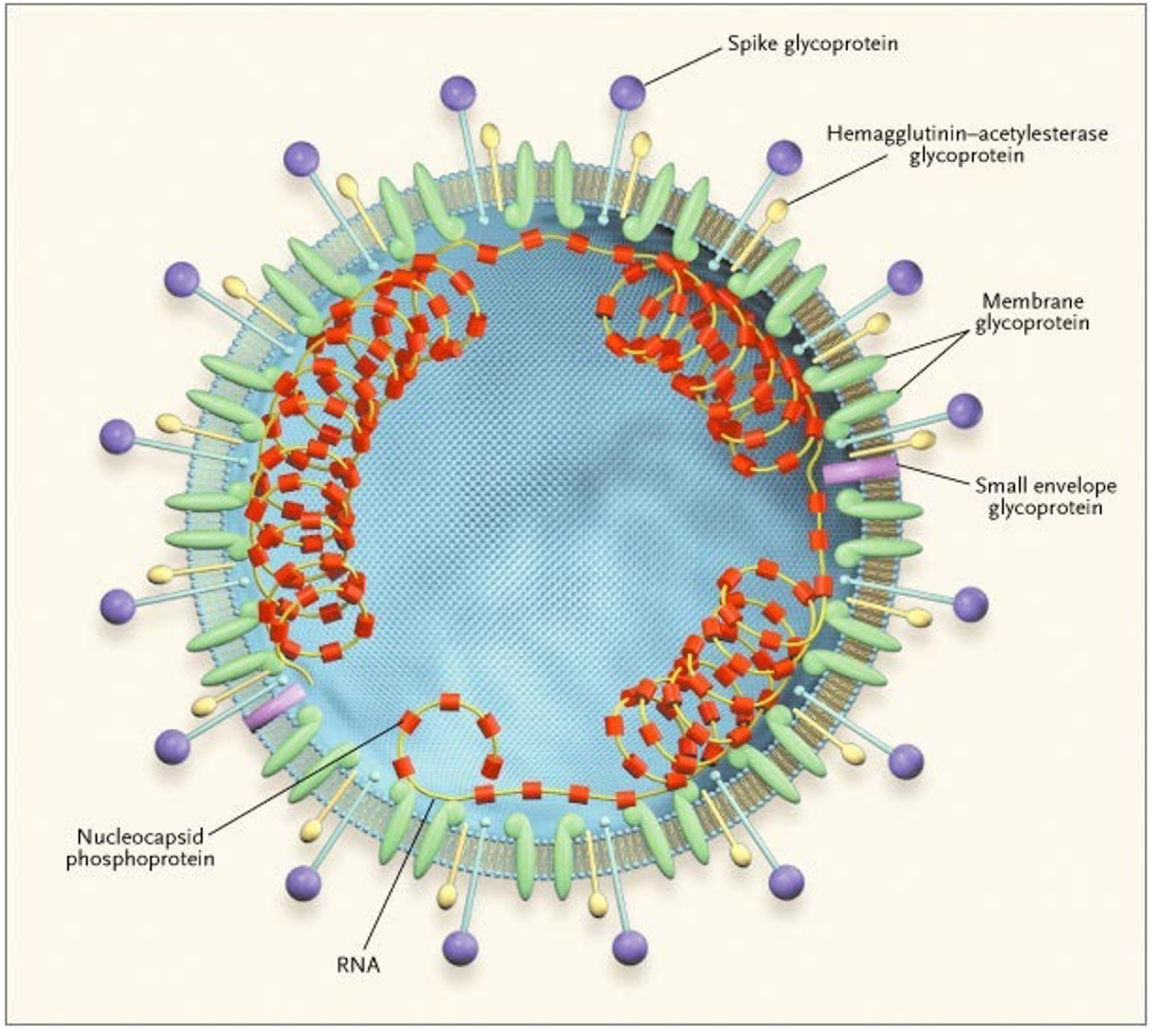




Cui, J., Li, F. & Shi, Z. Origin and evolution of pathogenic coronaviruses. *Nat Rev Microbiol* **17,** 181–192 (2019).

MICROBIOLOGY

- Novel Coronavirus – RNA virus, Positive sense, encodes a polyprotein
- Non-structural proteins including RNA dependent RNA polymerase: inhibited by remdesivir, Protease
- Structural proteins – Spike, Nucleocapsid, Envelope, HA, Membrane
- Human receptor – ACE 2
- Binding element – Spike glycoprotein (S) protein (RBD-receptor binding domain)
- Replication in Alveolar Pneumocytes, type II



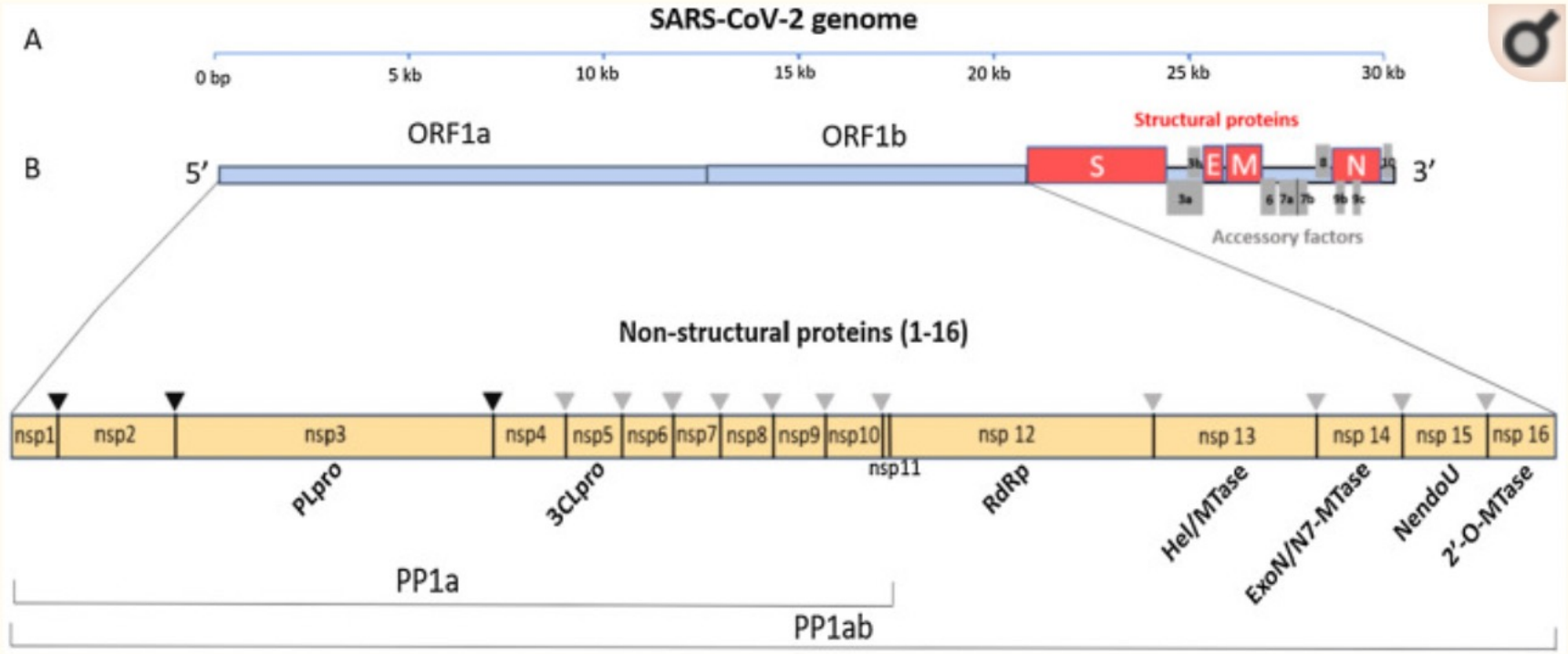


Figure 1

The SARS-CoV-2 genome has many ORFs and encodes as far as 50 non-structural, structural, and accessory proteins. Source: Romano et al.[7].

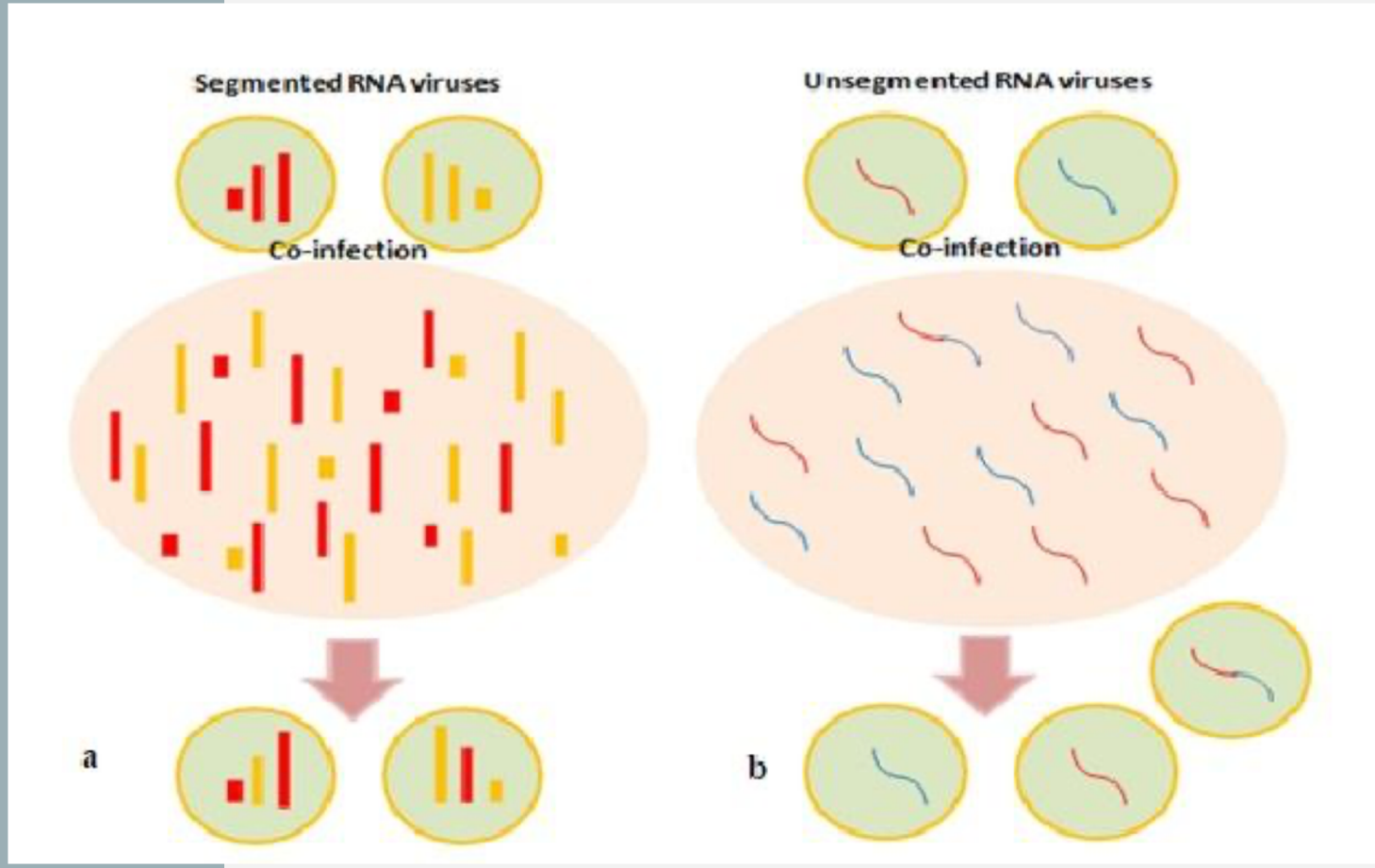
SARS- CoV 2 Genome

VIRAL EVOLUTION – EMERGENCE OF NEW VIRUSES

High rates of mutation

Homologous recombination

Heterologous recombination



MAR 05, 2020

First U.S. Confirmed Case of 2019-nCoV Infection

M.L. Holshue and Others
N Engl J Med 2020; 382:929-936

A healthy 35-year-old man who had visited Wuhan, China, presented with cough and fever that progressed to pneumonia. This report describes the diagnosis, clinical course, and management of the condition. The case highlights the importance of close coordination between clinicians and public health authorities at the local, state, and federal levels.

Correspondence First Case of Covid-19 in the United States

See Also Chinese Translation in NEJM 医学前沿

FREE

CORRESPONDENCE MAR 05, 2020

2019-nCoV Transmission from Asymptomatic Patient

C. Rothe and Others
N Engl J Med 2020; 382:970-971

In this report, investigators in Germany detected the spread of the novel coronavirus (2019-nCoV) from a person who had recently traveled from China to Germany for a business trip. This transmission occurred before the apparent onset of illness in the index patient and was associated with additional transmission events in Germany.

Indoor / enclosed spaces with Congregation

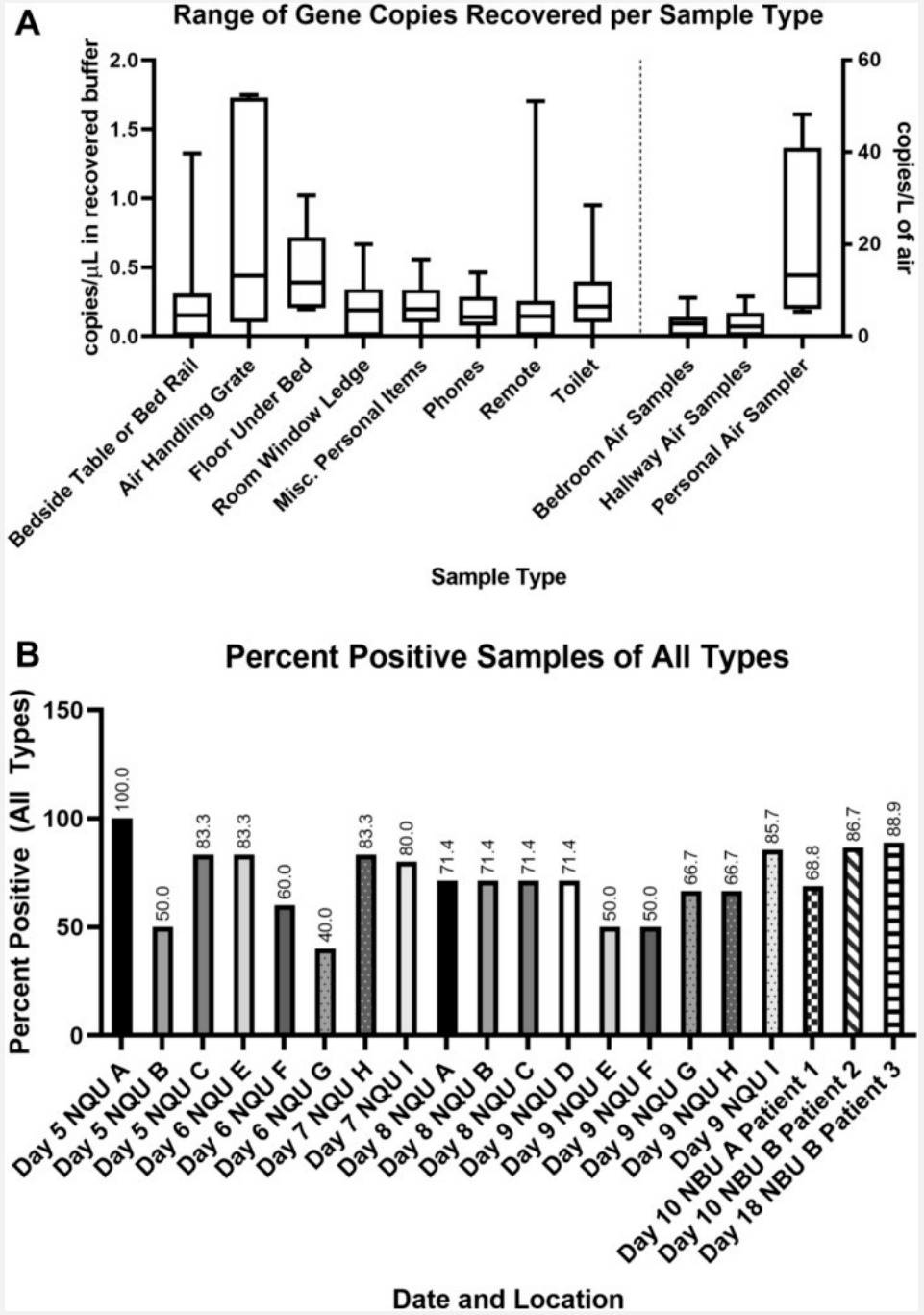
-- Churches
-- Gyms
-- Restaurants / indoor dining / Bars
-- Gathering with friends / family
-- Work place transmission
-- Nursing homes: employees
-- Assisted living
-- Colleges: eg. UNC, parties, no masking

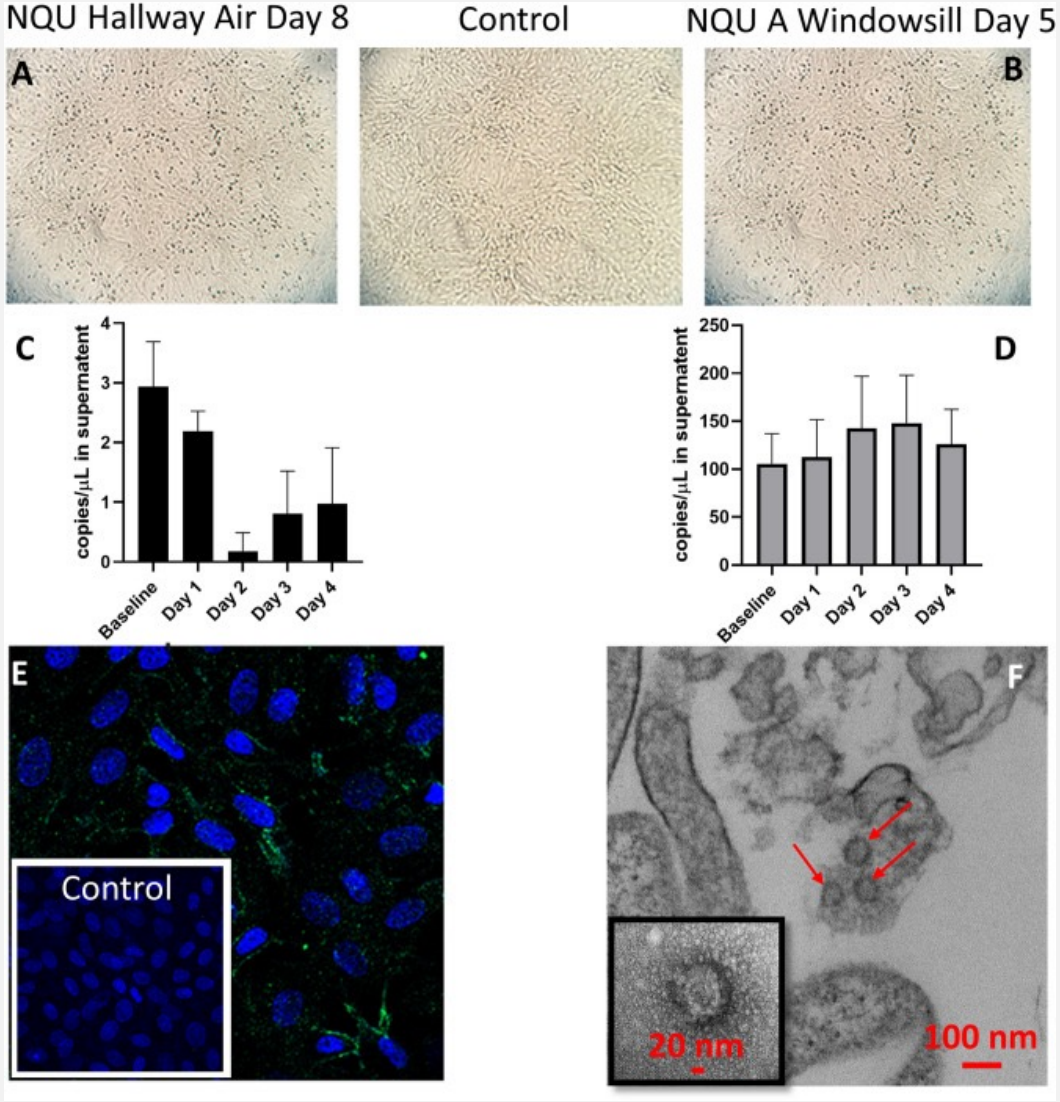
Transmission Routes

-- Primarily Airborne AND Droplet
-- Not likely much conjunctival
-- Not likely much fecal
-- Not likely much contagion / touch

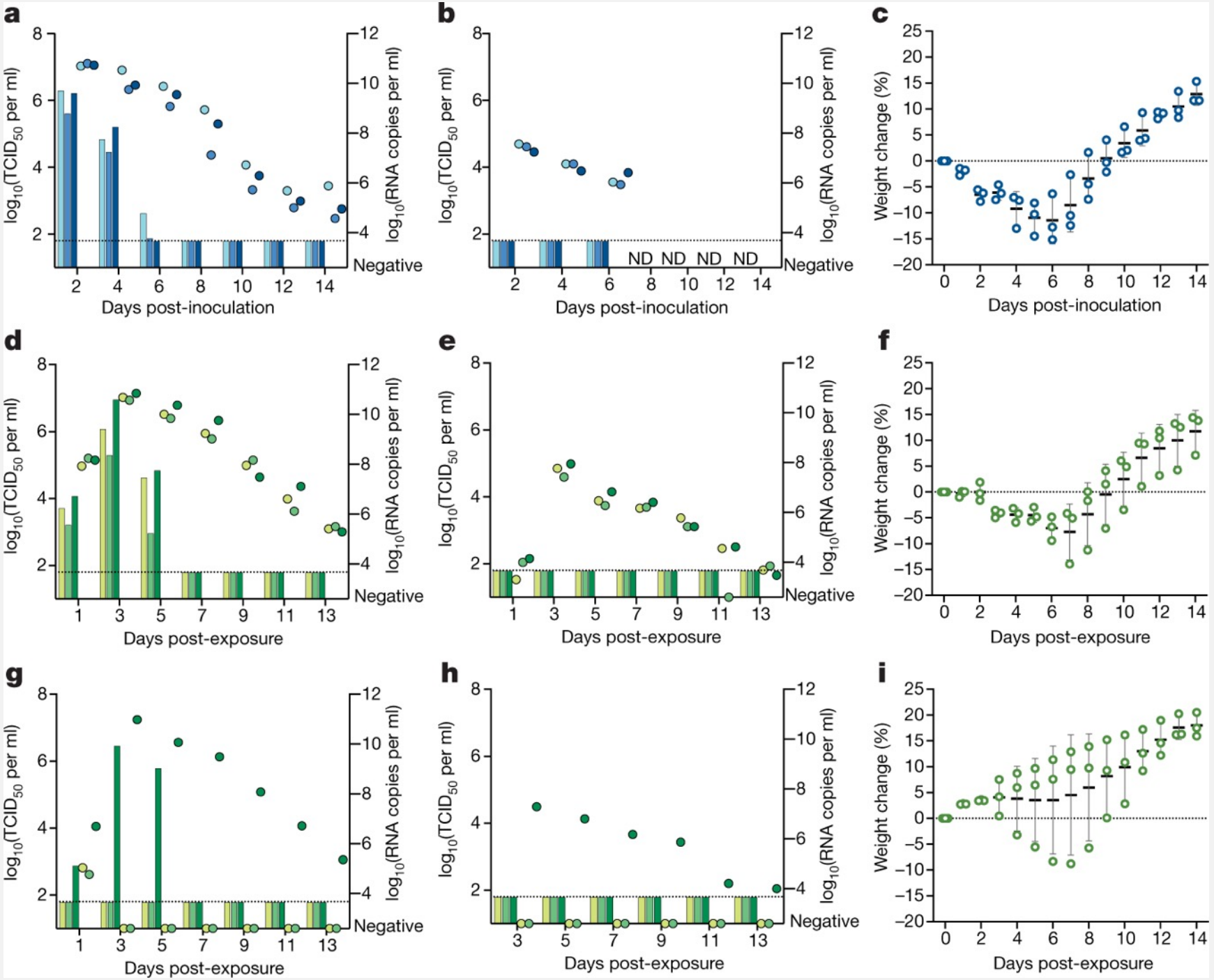
Duration of Infectiousness

-- mild to severe cases – 10 days
-- critical cases – 20 days
-- immune compromised cases – 20 days





Santarpia JL, Rivera DN, Herrera VL, et al. Aerosol and surface contamination of SARS-CoV-2 observed in quarantine and isolation care [published correction appears in Sci Rep. 2020 Aug 12;10(1):13892]. *Sci Rep*. 2020;10(1):12732. Published 2020 Jul 29. doi:10.1038/s41598-020-69286-3



A, b, c – donor hamsters

D, e, f – co-housed hamsters

G, h, I – single housed in donor cage

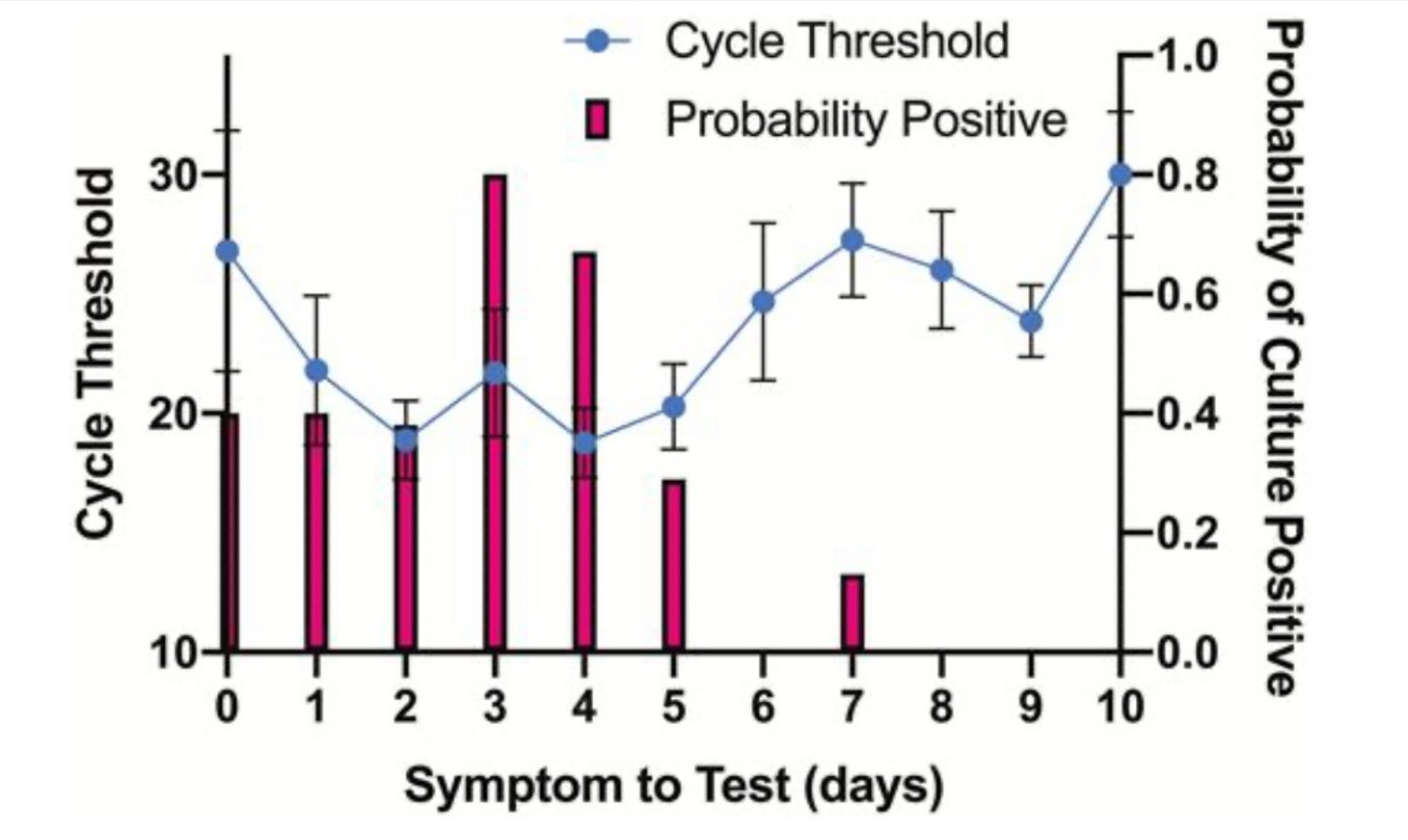
Panel 1 – nasal washes
Panel 2 – fecal samples
Panel 3 – weight plotted versus days

Each shade is a unique animal
Blue – inoculated hamster
Green – naïve hamster

Sia, S.F., Yan, L., Chin, A.W.H. *et al.* Pathogenesis and transmission of SARS-CoV-2 in golden hamsters. *Nature* **583,** 834–838 (2020). https://doi.org/10.1038/s41586-020-2342-5

Duration of Virus Culture Positivity

- 90 RT-PCR positive samples incubated on cell culture
- 26 samples showed viral growth
- No viral growth past 8 days symptom to test



Jared Bullard, Kerry Dust, Duane Funk, James E Strong, David Alexander, Lauren Garnett, Carl Boodman, Alexander Bello, Adam Hedley, Zachary Schiffman, Kaylie Doan, Nathalie Bastien, Yan Li, Paul G Van Caeseele, Guillaume Poliquin, Predicting Infectious Severe Acute Respiratory Syndrome Coronavirus 2 From Diagnostic Samples, *Clinical Infectious Diseases*,

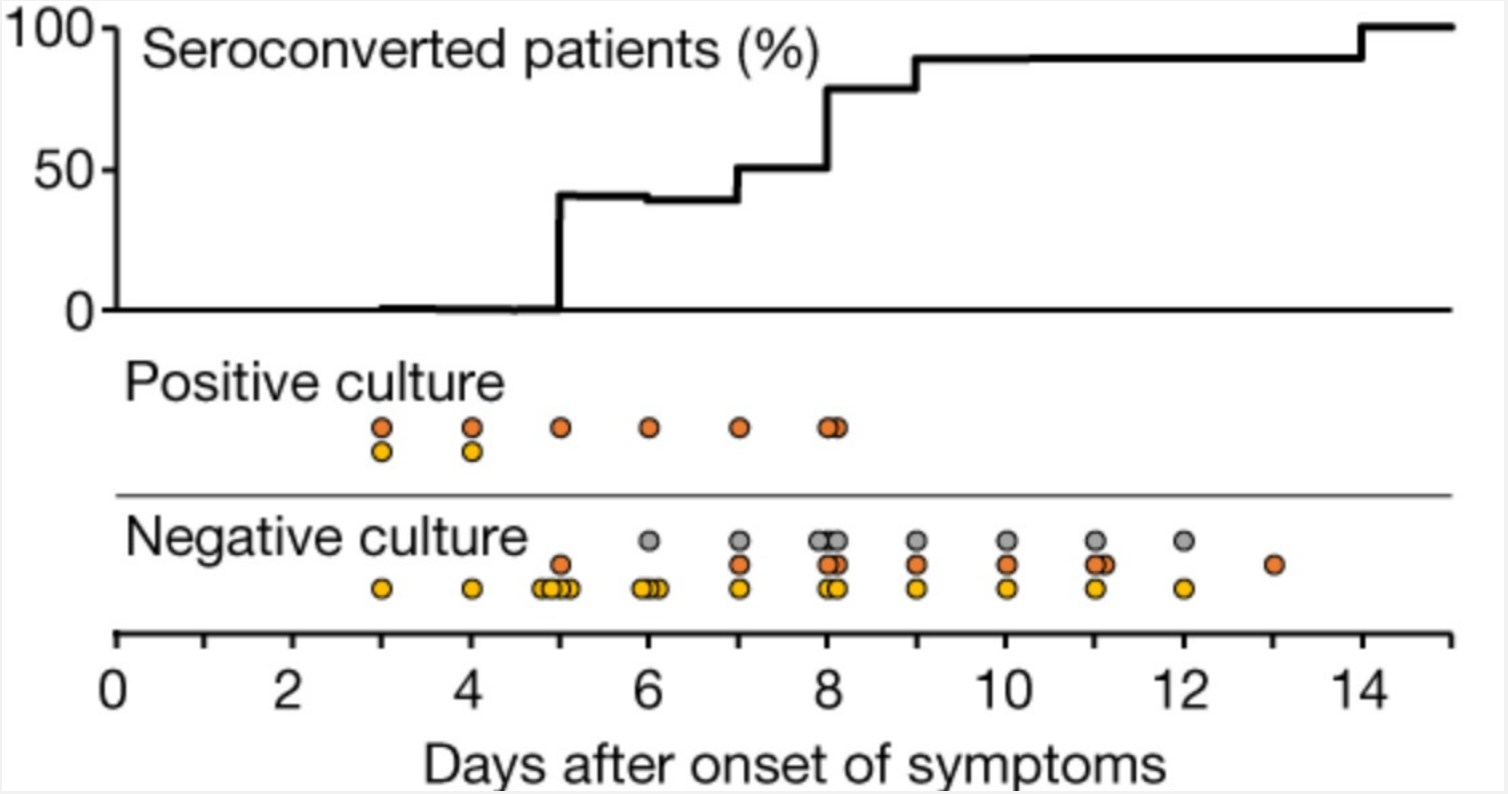
-- seroconversion by 14 days in all

-- negative cultures in all specimen Types by day 9

-- stool cultures always negative

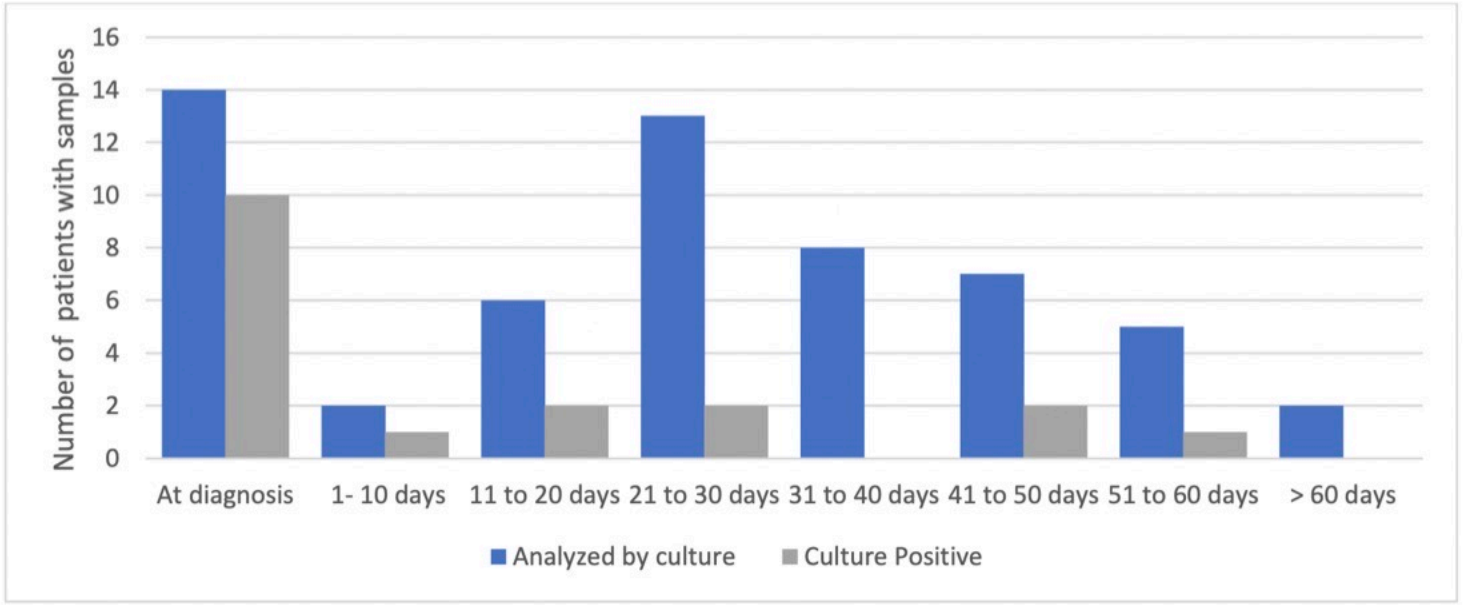
-- mild to moderate disease only

-- grey: stool
-- yellow: NP swab/ OP swab
-- orange: Sputum

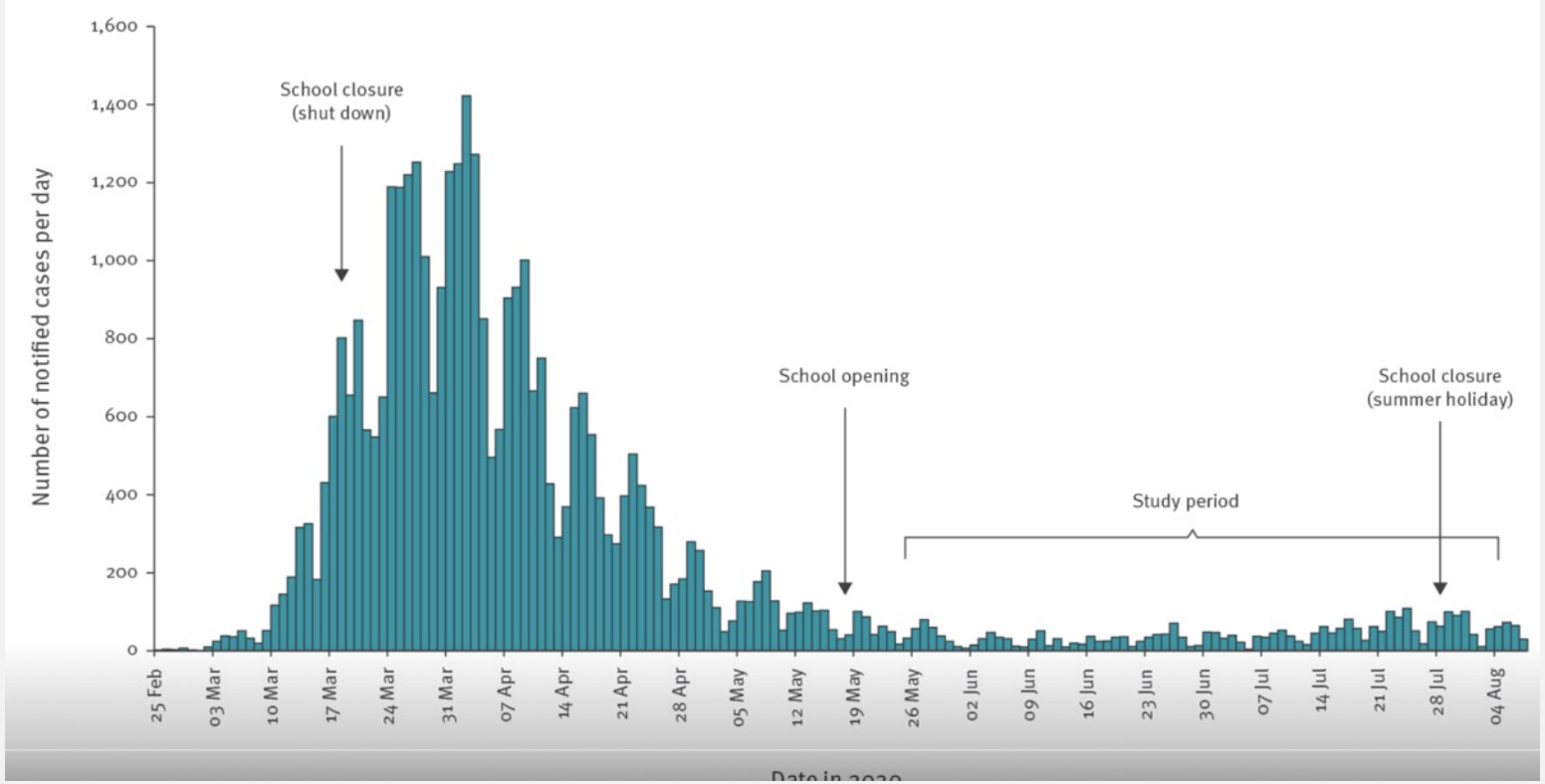


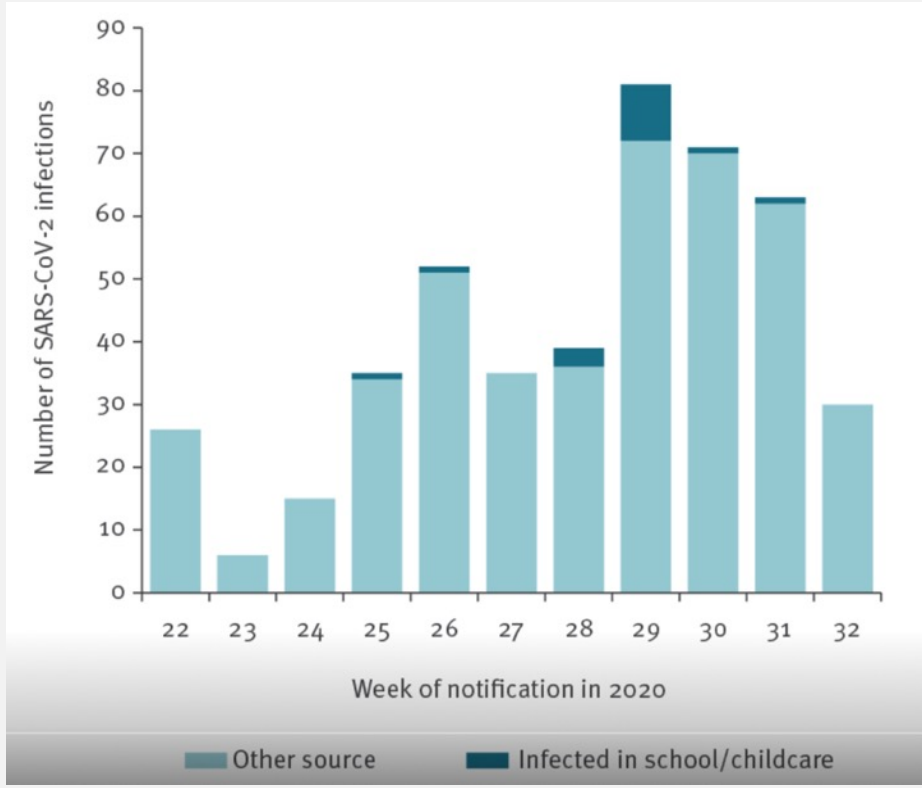
Wölfel, R., Corman, V.M., Guggemos, W. *et al.* Virological assessment of hospitalized patients with COVID-2019. *Nature* **581,** 465–469 (2020).

Figure S1 Graph showing collection time of 57 analyzed samples from 20 patients relative to the time of laboratory confirmation of SARS CoV-2 by PCR. At diagnosis, 10/14 patients with samples had viral isolation in culture. Eight additional samples from five patients were positive as shown in the grey bars. Overall, 11 unique patients had at least one positive isolation.



Children may not acquire and transmit SARS-CoV 2 as readily





Ehrhardt J, Ekinci A, Krehl H, et al. Transmission of SARS-CoV-2 in children aged 0 to 19 years in childcare facilities and schools after their reopening in May 2020, Baden-Württemberg, Germany. *Euro Surveill*. 2020;25(36):10.2807/1560-7917.ES.2020.25.36.2001587. doi:10.2807/1560-7917.ES.2020.25.36.2001587

Secondary attack rates of SARS-CoV-2 infection by educational setting and testing approach

	Secondary attack
All settings, all contacts, including single ECEC outbreak	1·2% (18/1448)
All settings, all contacts, excluding single ECEC outbreak[*–]	0·4% (5/1411)
All settings, all child case to child contacts	0·3% (2/649)
All settings, all child case to staff member contacts	1·0% (1/103)
All settings, all staff member case to child contacts	1·5% (8/536)
All settings, all staff member case to staff member contacts	4·4% (7/160)
All settings, all staff member case to child contact, excluding single ECEC outbreak[*–]	0·2% (1/511)
All settings, all staff member case to staff member contacts, excluding single ECEC outbreak[*–]	0·7% (1/148)
All settings, tested population	2·8% (18/633)
All settings, tested population, excluding single ECEC outbreak	0·8% (5/598)
All schools, all contacts	0·5% (5/914)
All schools, tested population	1·3% (5/375)
Single ECEC outbreak,[*–] all contacts	35·1% (13/37)
Child close contacts	28·0% (7/25)
Staff close contacts	50·0% (6/12)

Macartney K, Quinn HE, Pillsbury AJ, et al. Transmission of SARS-CoV-2 in Australian educational settings: a prospective cohort study [published online ahead of print, 2020 Aug 3]. *Lancet Child Adolesc Health*. 2020;S2352-4642(20)30251-0. doi:10.1016/S2352-4642(20)30251-0

COVID-19 in schools and early childhood education and care services – the Term 2 experience in NSW

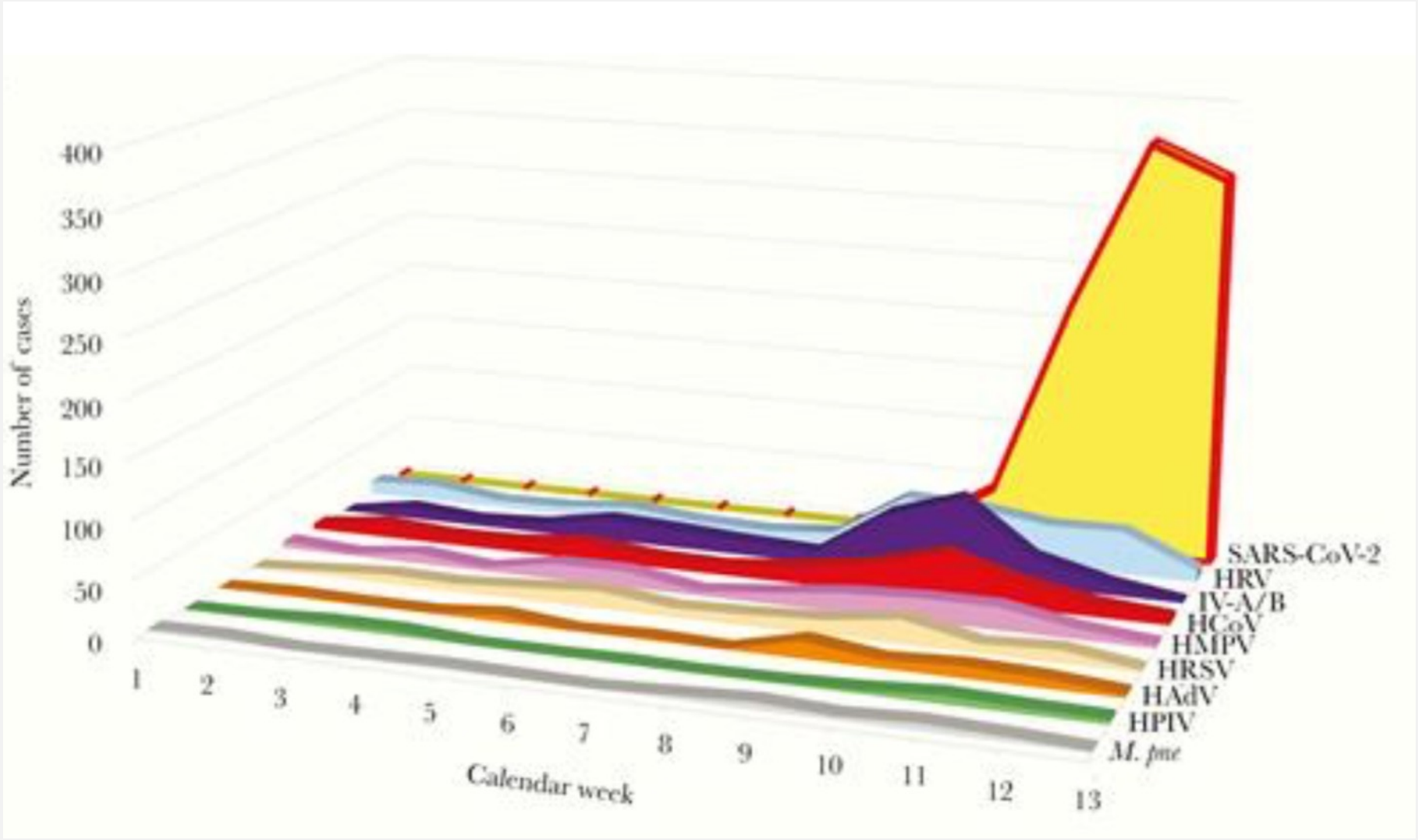
Prepared by the National Centre for Immunisation Research and Surveillance (NCIRS)

31 July 2020

Overview

- This report provides an overview of investigation into all COVID-19 cases in the state of New South Wales (NSW), Australia in all schools and early childhood education and care (ECEC) services between 10 April 2020 and 3 July 2020 (school term 2 of the academic year).
- 6 individuals (4 students and 2 staff members) from 6 educational settings (5 schools and 1 ECEC service) were confirmed as primary COVID-19 cases who had an opportunity to transmit the SARS-CoV-2 virus to others in their school or ECEC service.
- 521 individuals (459 students and 62 staff members) were identified as close contacts of these primary 6 cases.
- No secondary cases were reported in any of the 6 educational settings.
- In Term 2 no student or staff member contracted COVID-19 from a school or ECEC setting.

Replacing other Viruses



Karoline Leuzinger, Tim Roloff, Rainer Gosert, et al. Epidemiology of Severe Acute Respiratory Syndrome Coronavirus 2 Emergence Amidst Community-Acquired Respiratory Viruses, *The Journal of Infectious Diseases*, Volume 222, Issue 8, 15 October 2020, Pages 1270–1279.

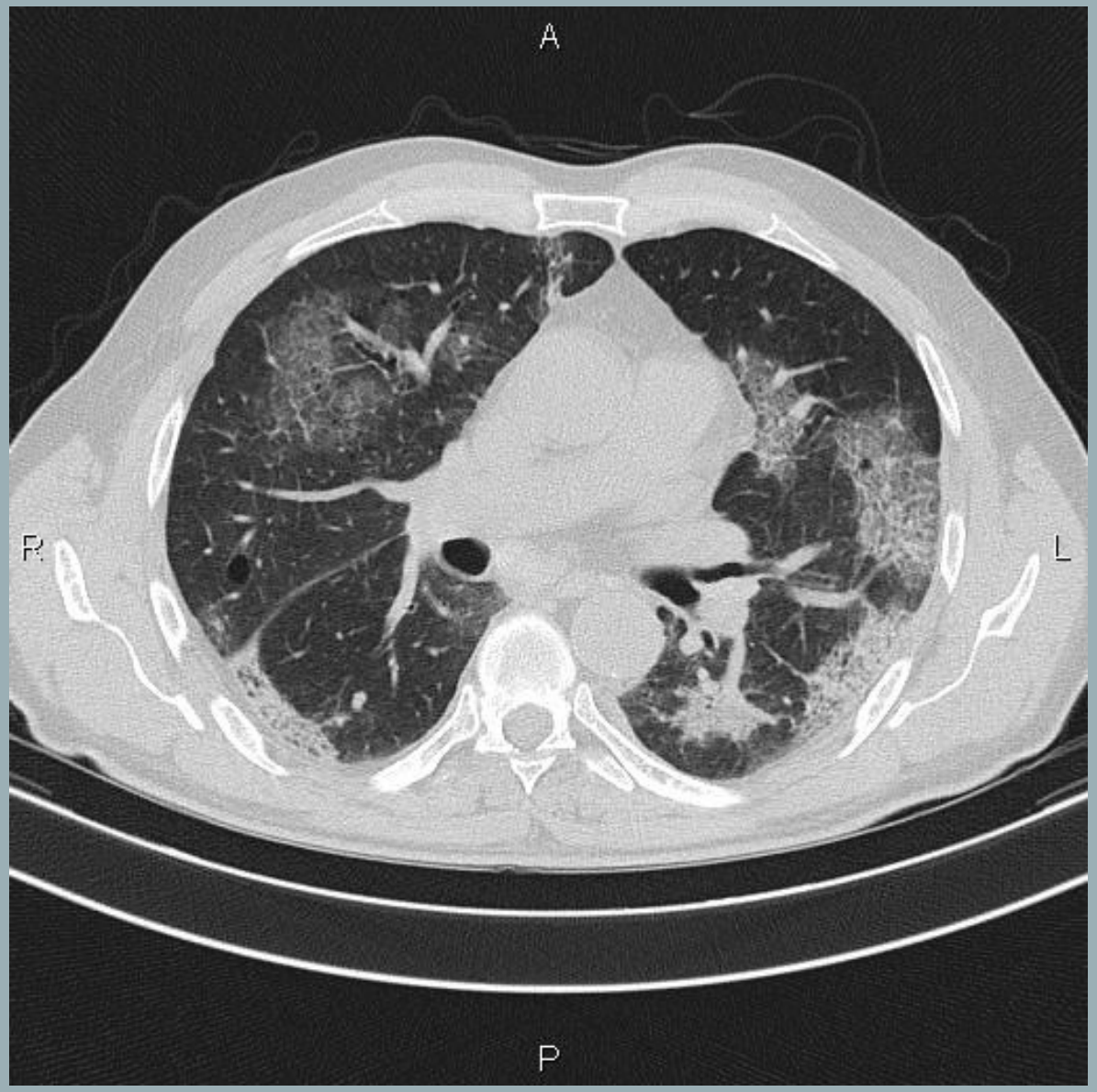
CLINICAL FEATURES – COVID 19

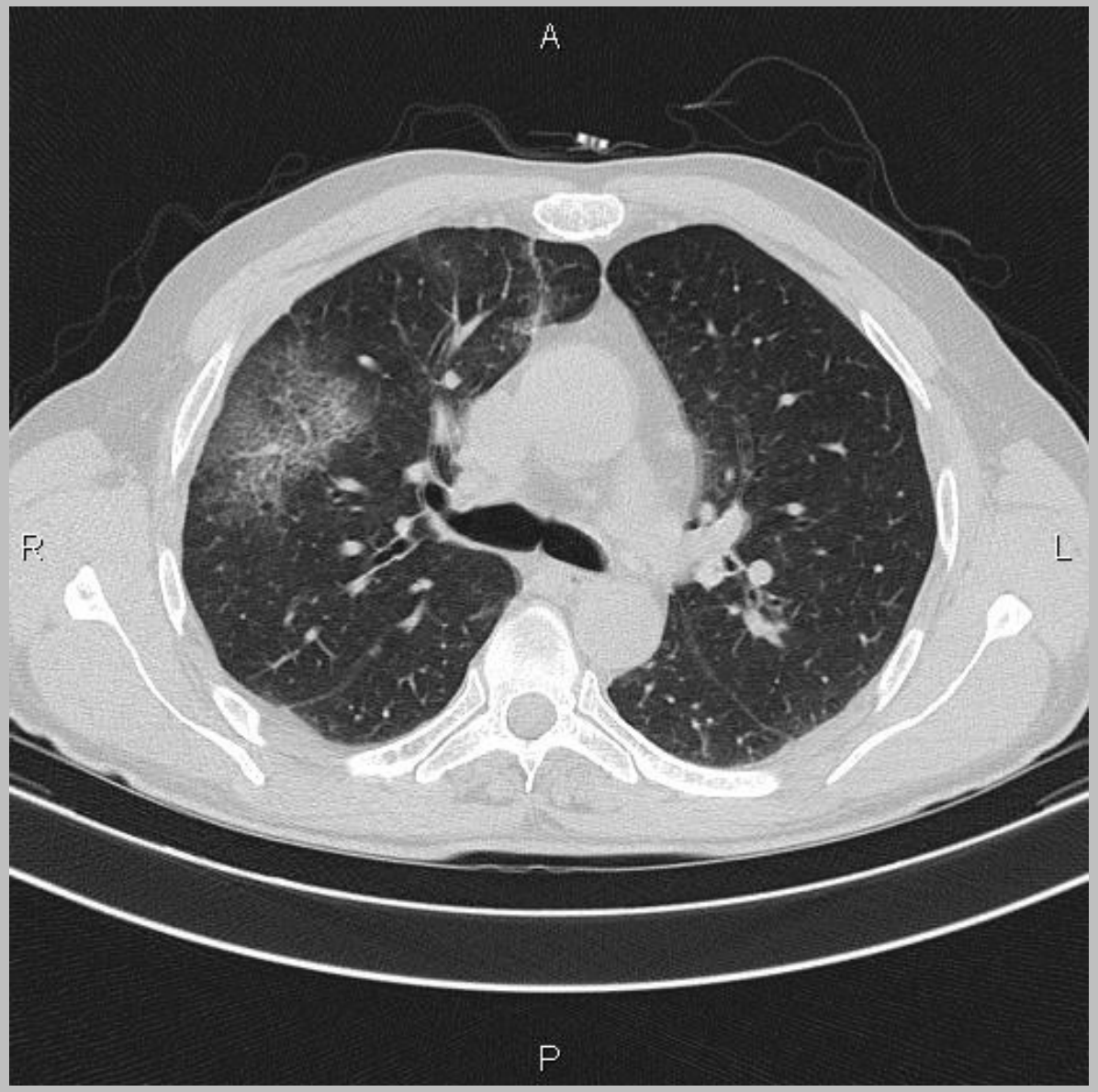
- Fever, chills, sweats, hot/cold feeling
- Malaise, myalgias, arthralgias, immense fatigue – “laid up in bed”
- Headache – sometimes quite severe
- Nasal congestion or ”allergies acting up” / “Sinus infection”
- Sore throat
- Loss of appetite, taste and smell alteration, nausea/vomiting
- Cough, particularly with deep breathing and activity
- Shortness of breath with minor activity or at rest
- Initial 5-7 days of general symptoms, then dyspnea: “viral replication phase” and “inflammatory phase” / ARDS phase
- Cutaneous manifestations - chill blain like lesions, livedo reticularis, purpurae

LABORATORY FEATURES

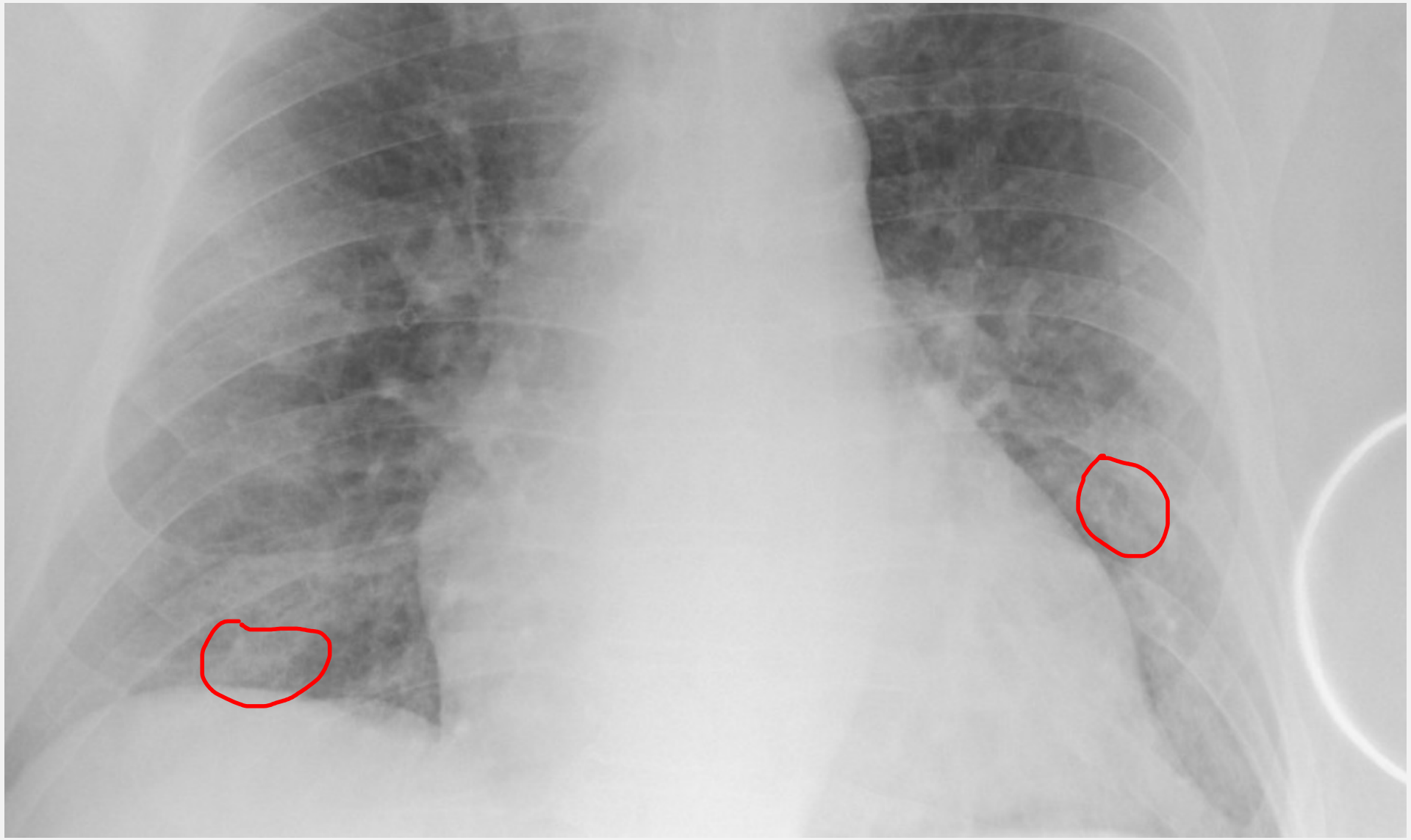
- Procalcitonin almost always less than 0.25, CRP always elevated
- Absolute lymphopenia about 80% of patients, less than 1000 cells/microliter
- Elevations in AST, ALT, Bilirubin: 10-20%
- Elevation in Cr (mild, moderate, severe): 1%, 4%, 9%
- Leukocytosis: 6%, uncommon, tends to develop late, signals deterioration
- Leukopenia: 33%
- Elevated Ferritin in most active patients, sometimes dramatic
- High LDH and Fibrinogen, D dimer, in almost all active patients

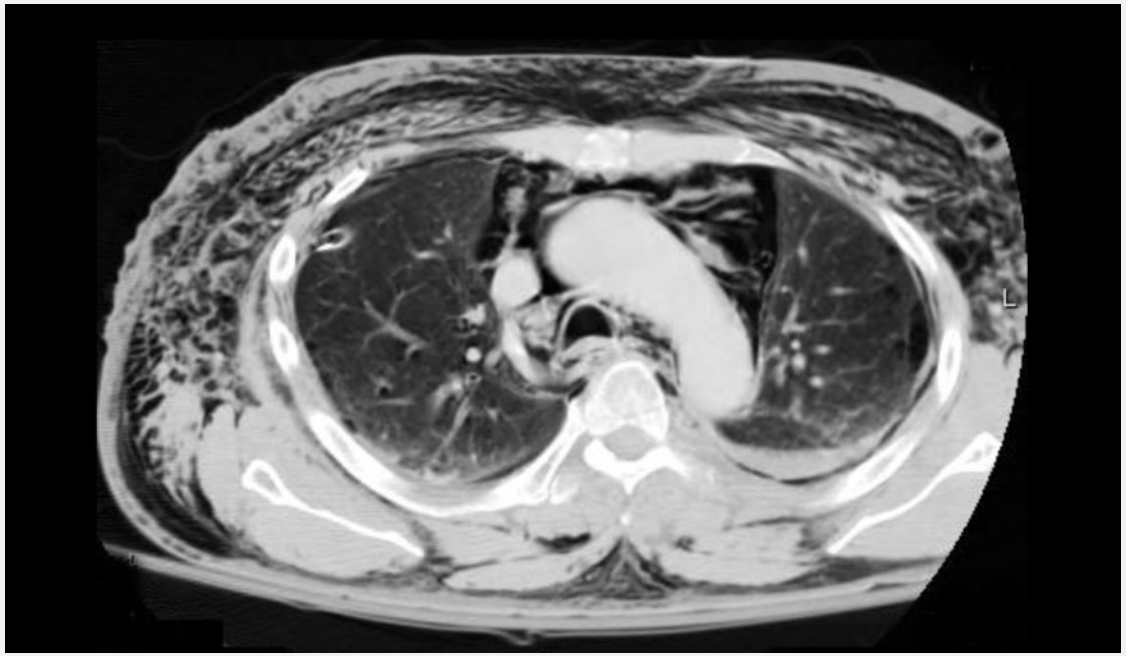
RADIOGRAPHIC FEATURES – CT scan

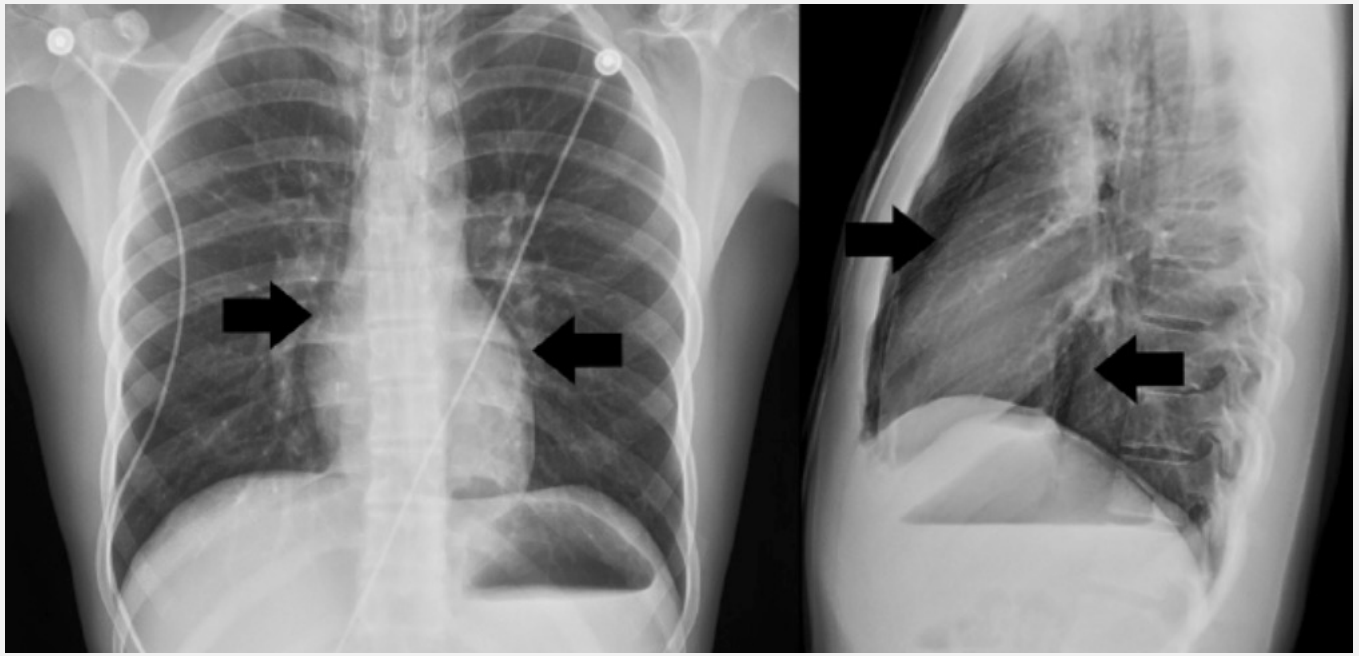




CHEST X RAY







Pneumomediastinum / Pneumothorax

DAD		28	230 (87)	
	Acute			53 (23)
	Acute-Proliferative			77 (33)
	Proliferative			18 (8)
	Proliferative-Fibrotic			1 (0)
	Fibrotic			1 (0)
Interstitial/alveolar edema				86 (33)
Interstitial lymphocytic infiltrate				152 (58)
Pneumocyte reactive hyperplasia				143 (54)
Multinucleated giant cells				52 (20)
Alveolar/capillary megakaryocytes				50 (19)
Arteriolar vascular microthrombi				123 (47)
Alveolar/interstitial thickening				52 (20)
Pulmonary/alveolar hemorrhage				52 (20)
Vasculitis necrotizing/non-necrotizing				44 (17)
Bronchial/bronchiolar inflammation				21 (8)
Tracheobronchial inflammation				64 (24)
Acute bronchopneumonia (aspiration or secondary infection)				30 (11)

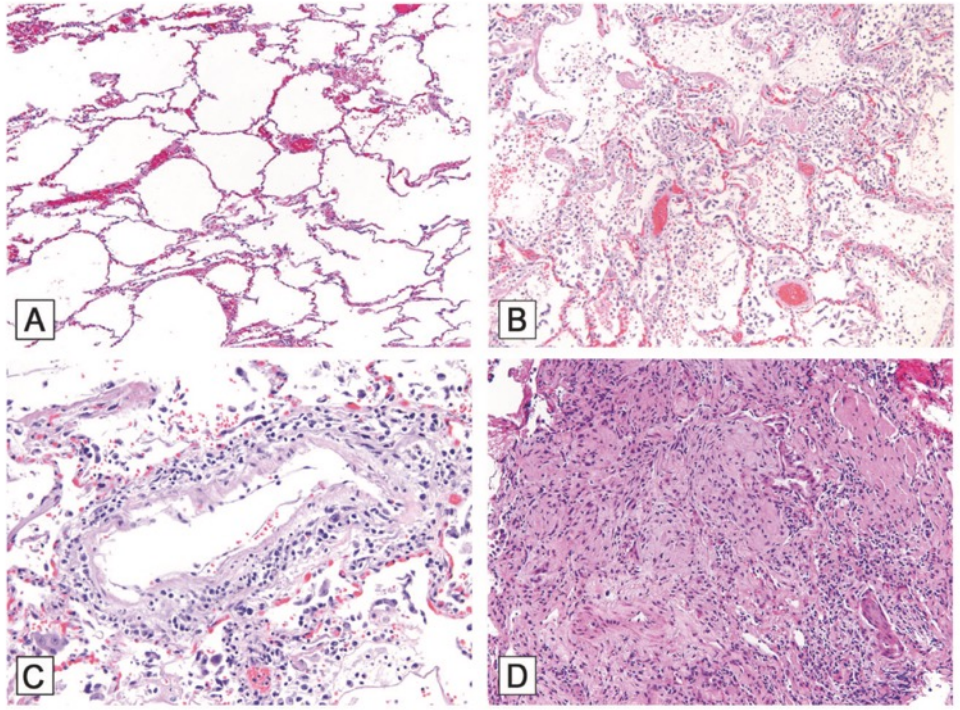
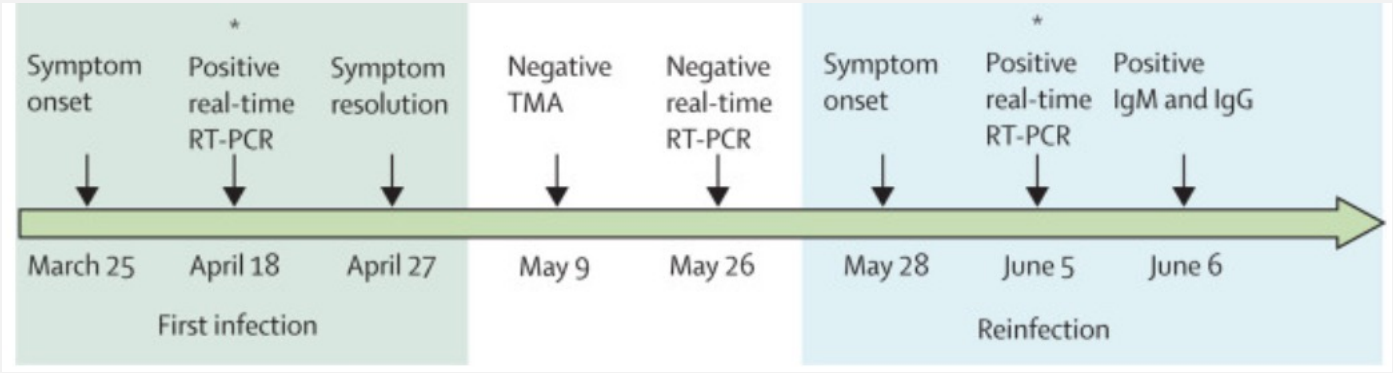


Fig. 1 Histopathologic findings of COVID-19 in the lung. A Normal lung with open alveoli and delicate alveolar septa containing thin capillaries lined by an attenuated alveolar epithelium (hematoxylin-eosin; original magnification ×200). **B** Acute diffuse alveolar damage (DAD) with hyaline membranes lining alveolar spaces, pneumocyte hyperplasia, desquamation of alveolar epithelial cells into the alveolar spaces, inflammatory infiltrates, and capillary congestion (hematoxylin-eosin; original magnification ×200). **C** Perivascular inflammation (hematoxylin-eosin; original magnification ×400). **D** Organizing pneumonia with granulation tissue plugs within the lumen of respiratory bronchioles (hematoxylin-eosin; original magnification ×200).

Caramaschi S, Kapp ME, Miller SE, Eisenberg R, Johnson J, Epperly G, Maiorana A, Silvestri G, Giannico GA. Histopathological findings and clinicopathologic correlation in COVID-19: a systematic review. Mod Pathol. 2021 Sep;34(9):1614-1633. doi: 10.1038/s41379-021-00814-w. Epub 2021 May 24. PMID: 34031537; PMCID: PMC8141548.



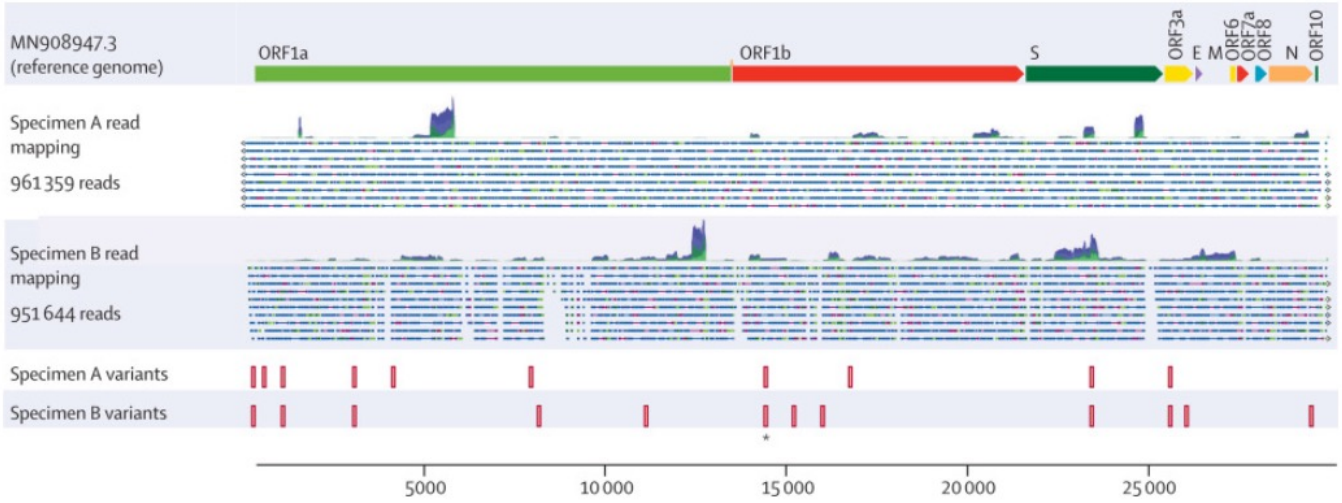
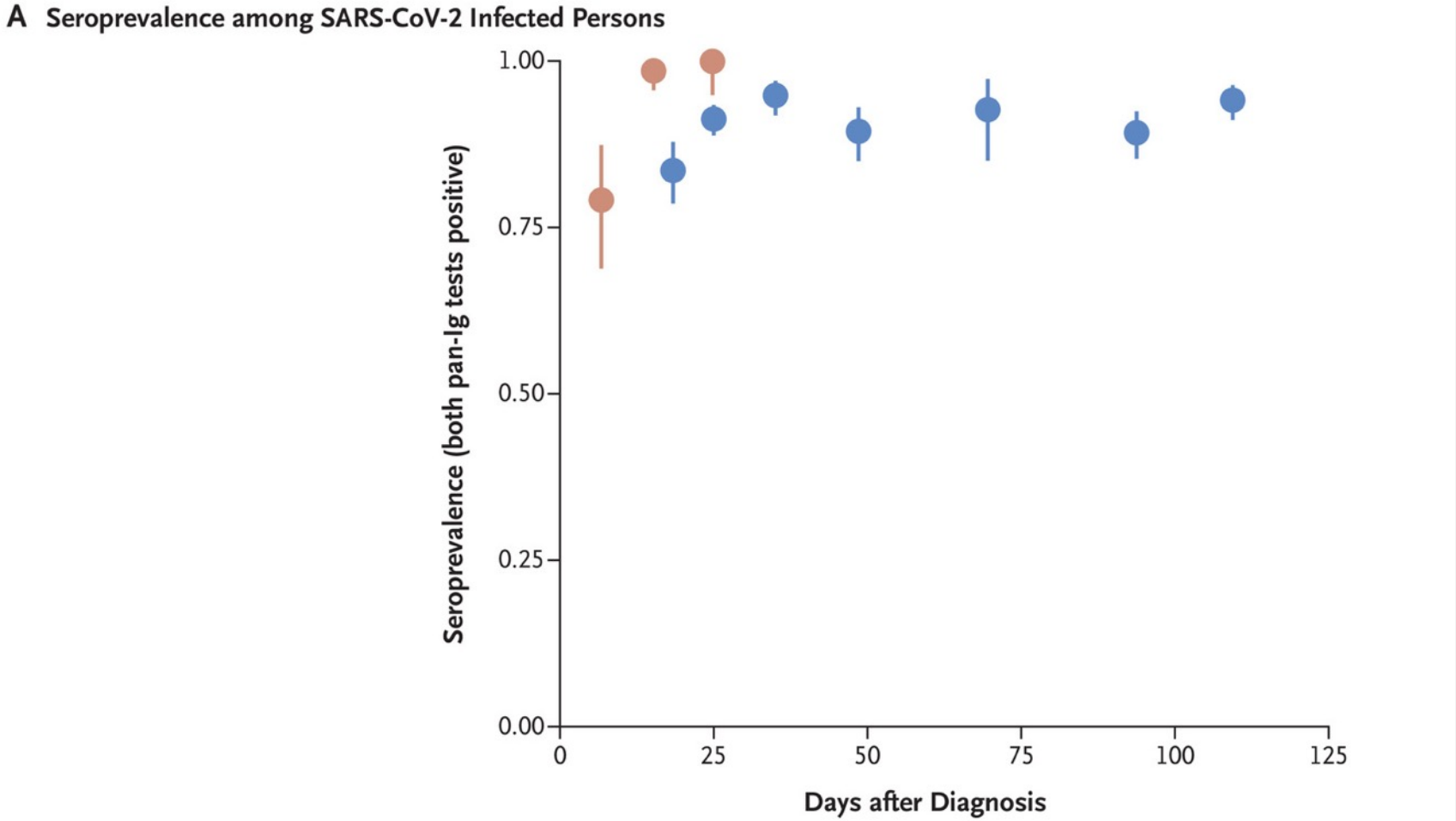


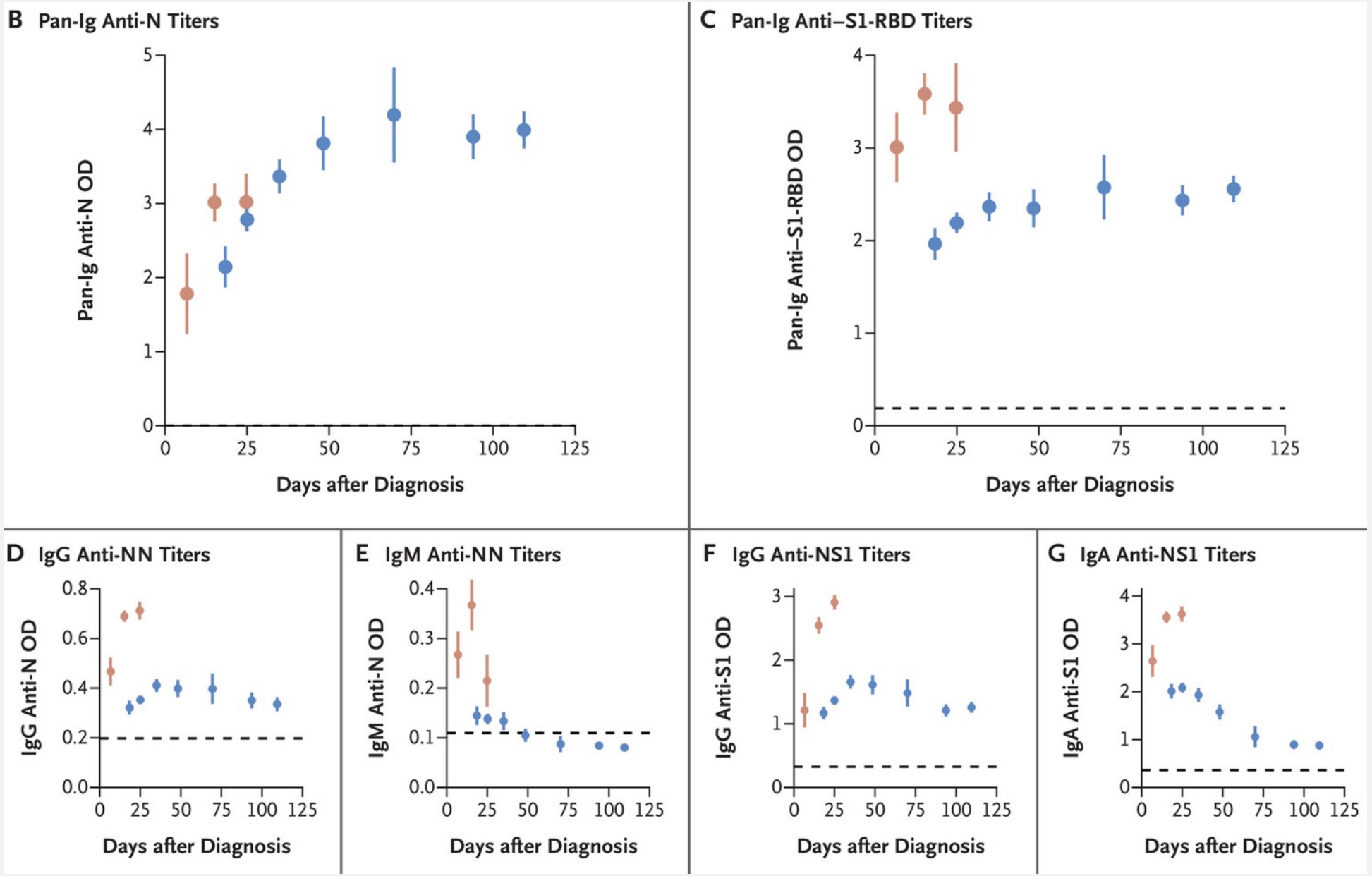
Figure 2 Variant mapping of specimens A and B against the reference genome

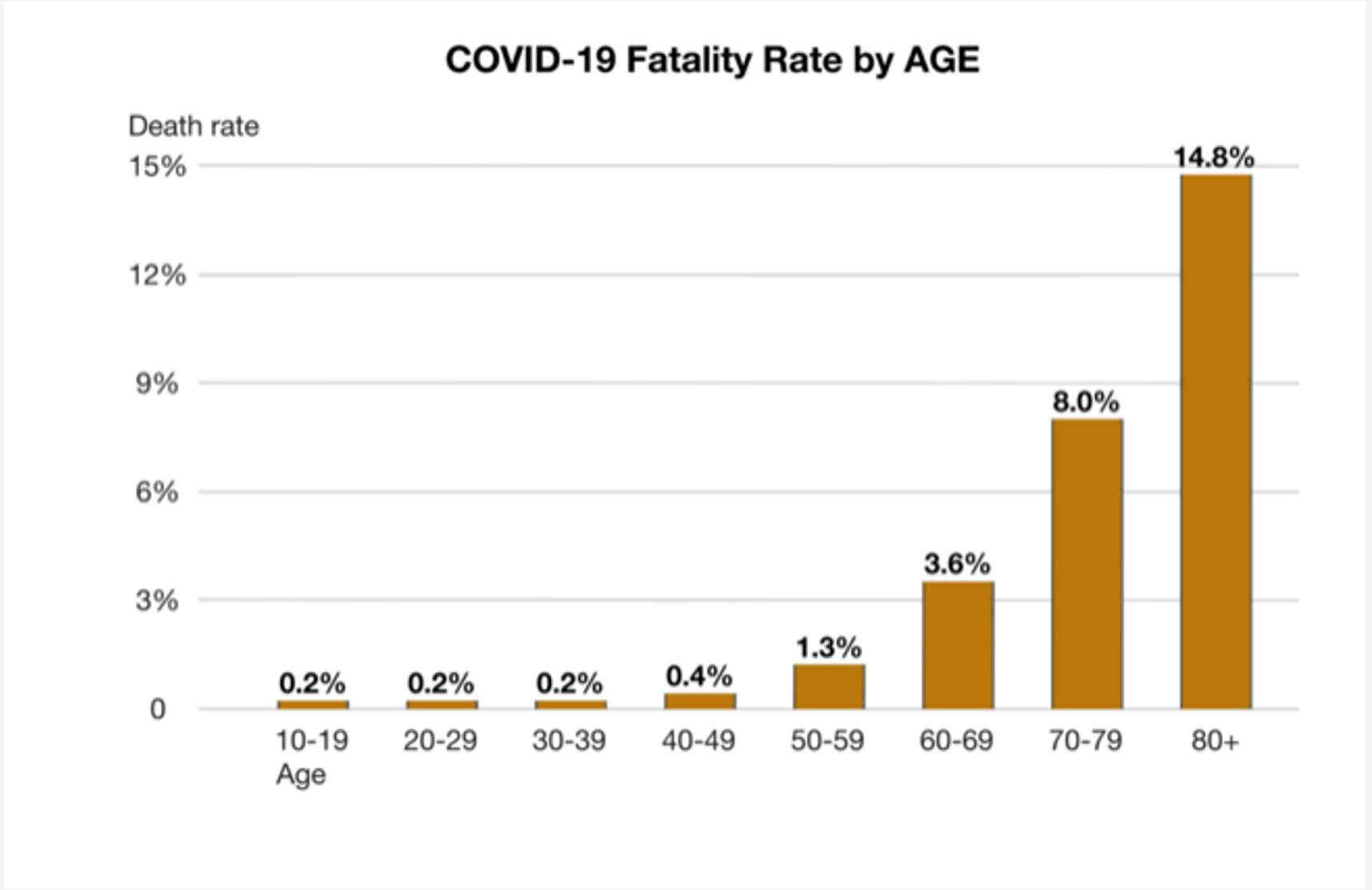
Genomic evidence for reinfection with SARS-CoV-2: a case study
Richard L Tillett, PhD Joel R Sevinsky, PhD Paul D Hartley, PhD Heather Kerwin, MPH Natalie Crawford, MD Andrew Gorzalski, PhD. Lancet. Oct 12, 2020

- 2102 samples, 1237 individuals
- Two Pan Ig assays
- Anti N Pan Ig
- Anti S1 –RBD Pan Ig
- Antibodies persist
- Mortality estimate 0.3%
- Total infected estimate 0.9%



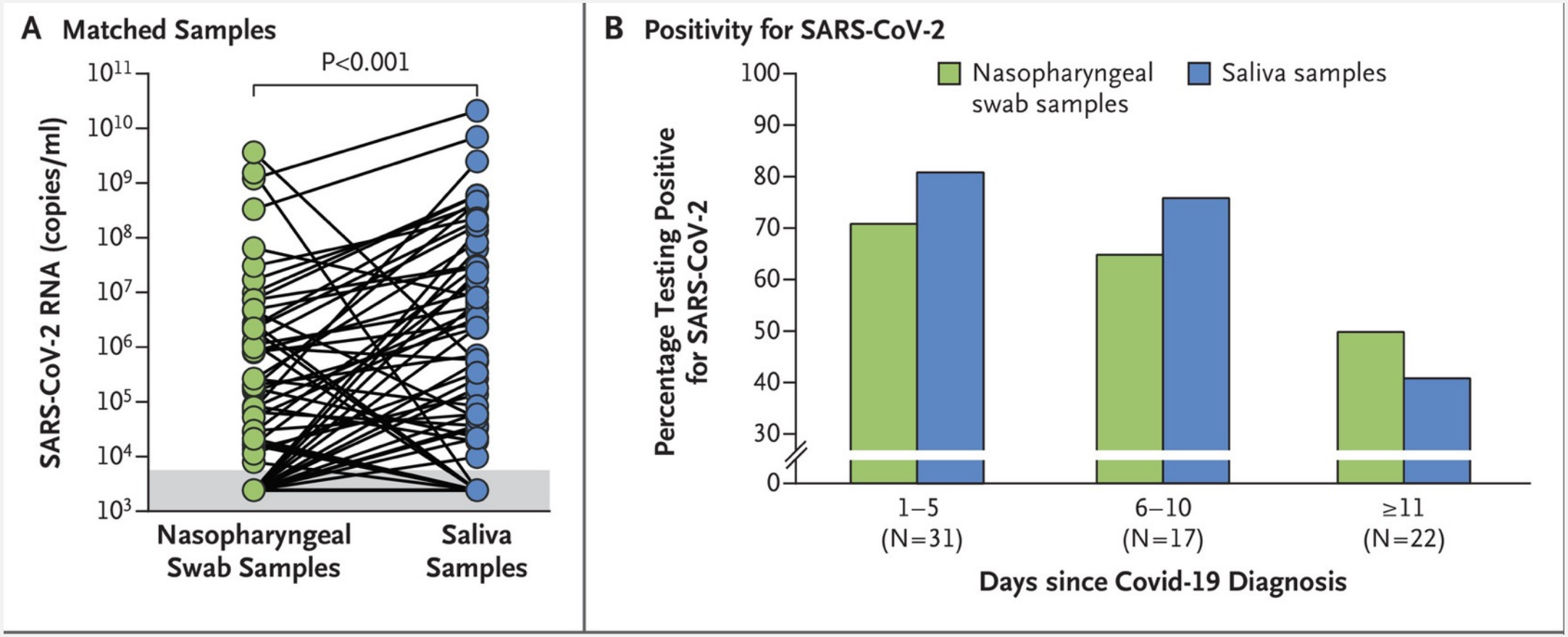
Daniel F. Gudbjartsson, Ph.D., Gudmundur L. Norddahl, Ph.D., Pall Melsted, Ph.D.,
Humoral Immune Response to SARS-CoV-2 in Iceland. NEJM. September 1, 2020
DOI: 10.1056/NEJMoa2026116


B Pan-Ig Anti-N Titers
Pan-Ig Anti-N OD
Days after Diagnosis
C Pan-Ig Anti–S1-RBD Titers
Pan-Ig Anti–S1-RBD OD
Days after Diagnosis
D IgG Anti-NN Titers
IgG Anti-N OD
Days after Diagnosis
E IgM Anti-NN Titers
IgM Anti-N OD
Days after Diagnosis
F IgG Anti-NS1 Titers
IgG Anti-S1 OD
Days after Diagnosis
G IgA Anti-NS1 Titers
IgA Anti-S1 OD
Days after Diagnosis


COVID-19 Fatality Rate by AGE
Death rate
15%
12%
9%
6%
3%
0
0.2%
0.2%
0.2%
0.4%
1.3%
3.6%
8.0%
14.8%
10-19
20-29
30-39
40-49
50-59
60-69
70-79
80+
Age

Chinese CDC

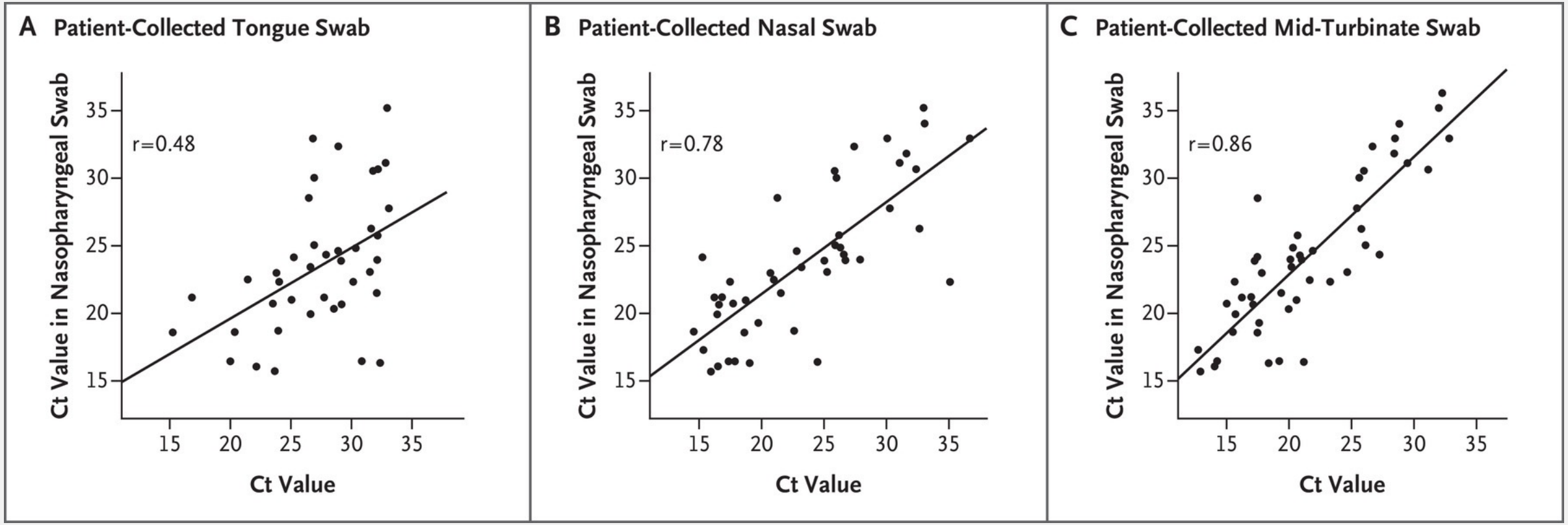
Acceptable sensitivity and specificity of saliva samples instead of NP samples in patients with COVID 19: active disease, not asymptomatic persons



A.L Willey et al. Saliva specimens to detect SARS-CoV – 2 Infection. NEJM. Aug 28, 2020.

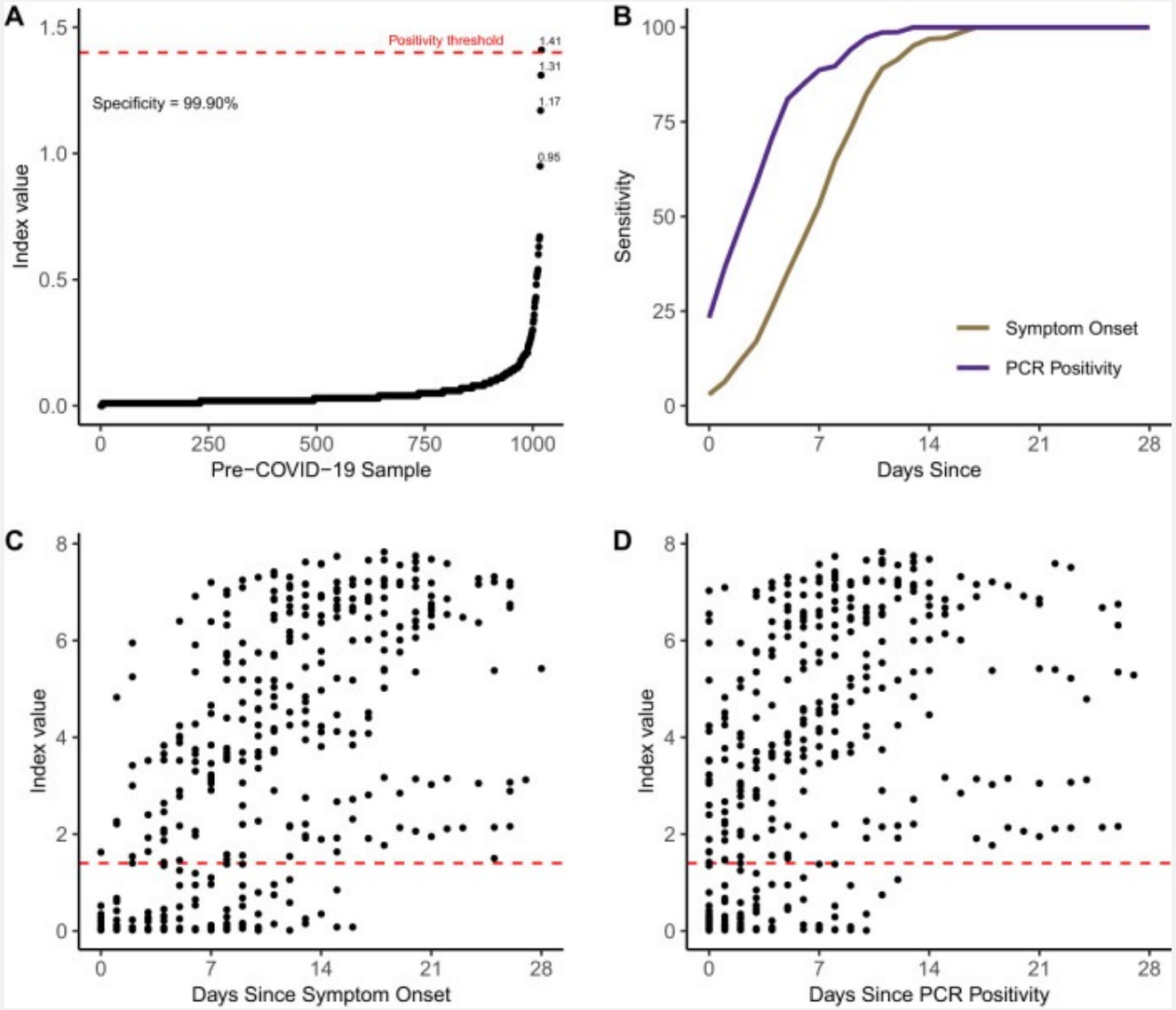
Patient-collected swabs from tongue, nose or mid-turbinate are nearly equivalent in sensitivity to HCP collected NP swabs

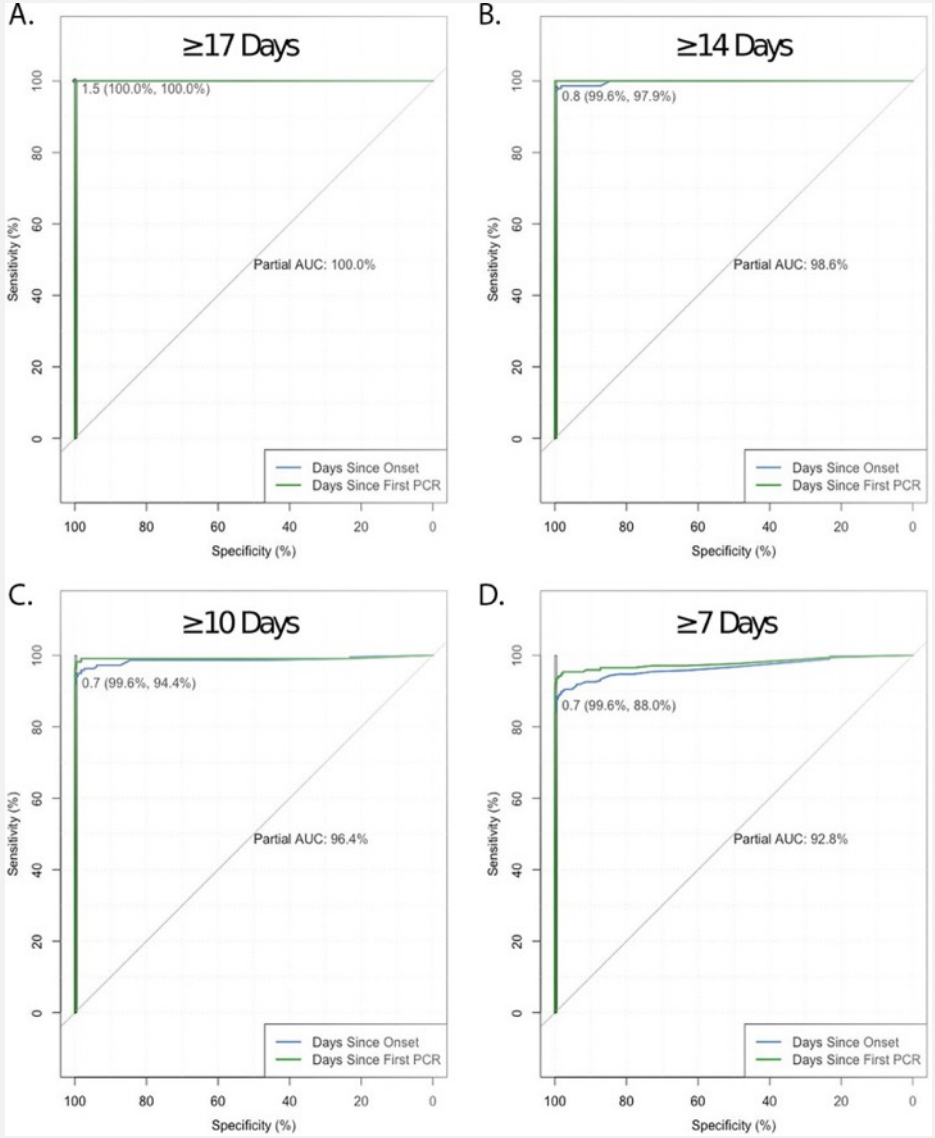
Approximately 90% sensitivity of self collected specimens relative to HCP collected specimens.



Y.P. Tu et al. Patient – collected swabs for SARS-CoV 2 testing. N Engl J Med 2020; 383:494-496

The ABBOTT Antibody test / IgG is nearly 100% sensitive and specific at 17 days





Bryan A, Pepper G, Wener MH, et al. Performance Characteristics of the Abbott Architect SARS-CoV-2 IgG Assay and Seroprevalence in Boise, Idaho. *J Clin Microbiol*. 2020;58(8):e00941-20. Published 2020 Jul 23. doi:10.1128/JCM.00941-20

Rapid Testing: Abbott ID NOW / Cepheid Xpert Xpress

ABBOTT RELEASES INTERIM CLINICAL STUDY DATA ON ID NOW COVID-19 RAPID TEST SHOWING STRONG AGREEMENT TO LAB-BASED MOLECULAR PCR TESTS

- Urgent care clinic study shows ID NOW test performance of ≥94.7% positive agreement (sensitivity) and ≥98.6% negative agreement (specificity) compared to lab-based PCR reference tests

- The Everett Clinic study shows 91.3% positive agreement and 100% negative agreement

- Ongoing study of hospitalized and nursing home patients tested with late symptom onset shows ≥83.3% positive agreement and ≥96.5% negative agreement

- Abbott's studies suggest ID NOW performs best in patients tested earlier post symptom onset

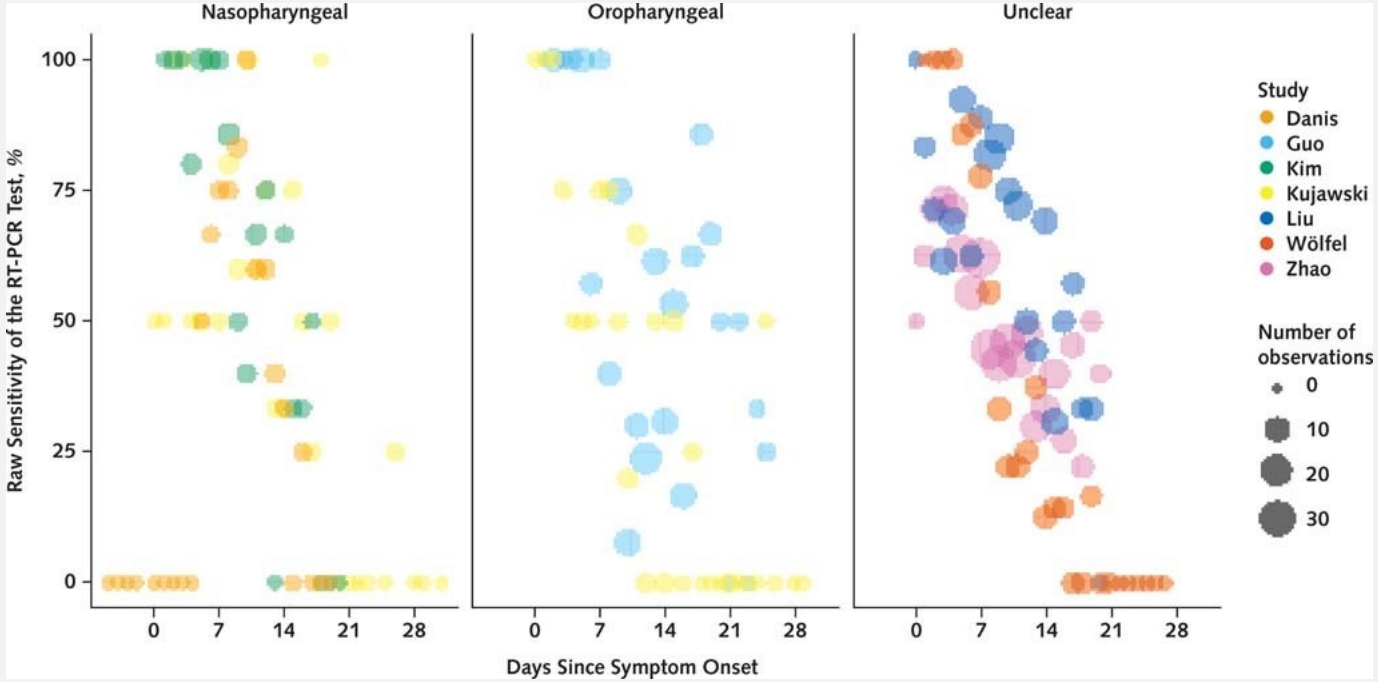
- ID NOW delivers results in minutes rather than days and is helping reduce the spread of infection by detecting more positive patients faster than would otherwise be the case

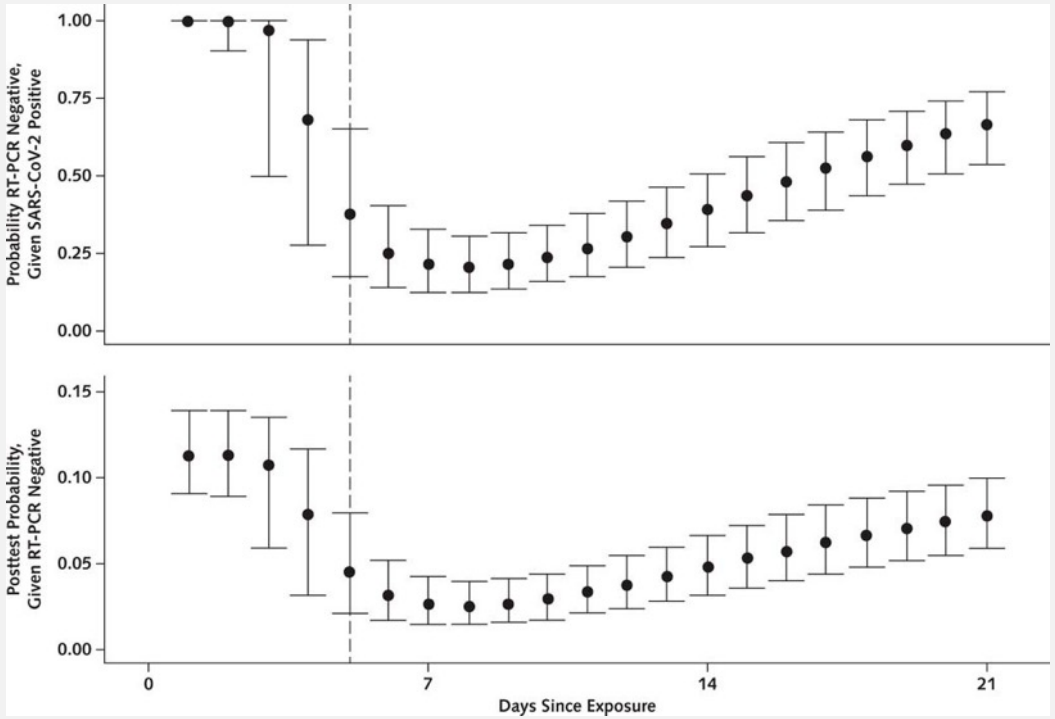
Cepheid Receives Emergency Use Authorization For SARS-CoV-2, Flu A, Flu B and RSV Combination Test

Challenged by Similar Clinical Presentations, Accurate Detection & Differentiation of all 4 Viruses is Critical for Clinicians This Flu Season

SUNNYVALE, Calif., Sept. 29, 2020 /PRNewswire/ -- Cepheid today announced it has received Emergency Use Authorization (EUA) from the U.S. Food & Drug Administration (FDA) for Xpert® Xpress **SARS-CoV-2/Flu/RSV**, a rapid molecular diagnostic test for qualitative detection of the viruses causing COVID-19, Flu A, Flu B, and RSV infections from a single patient sample. The four-in-one test is designed for use on any of Cepheid's over 26,000 GeneXpert® Systems placed worldwide, with results delivered in approximately 36 minutes.

False Negative RT-PCR from upper respiratory samples in COVID 19 patients





L.M. Kucirka M.D., Ph.D et al. Variation in False-Negative Rate of Reverse Transcriptase Polymerase Chain Reaction–Based SARS-CoV-2 Tests by Time Since Exposure. Annals of Internal Medicine 2020 173:4, 262-267

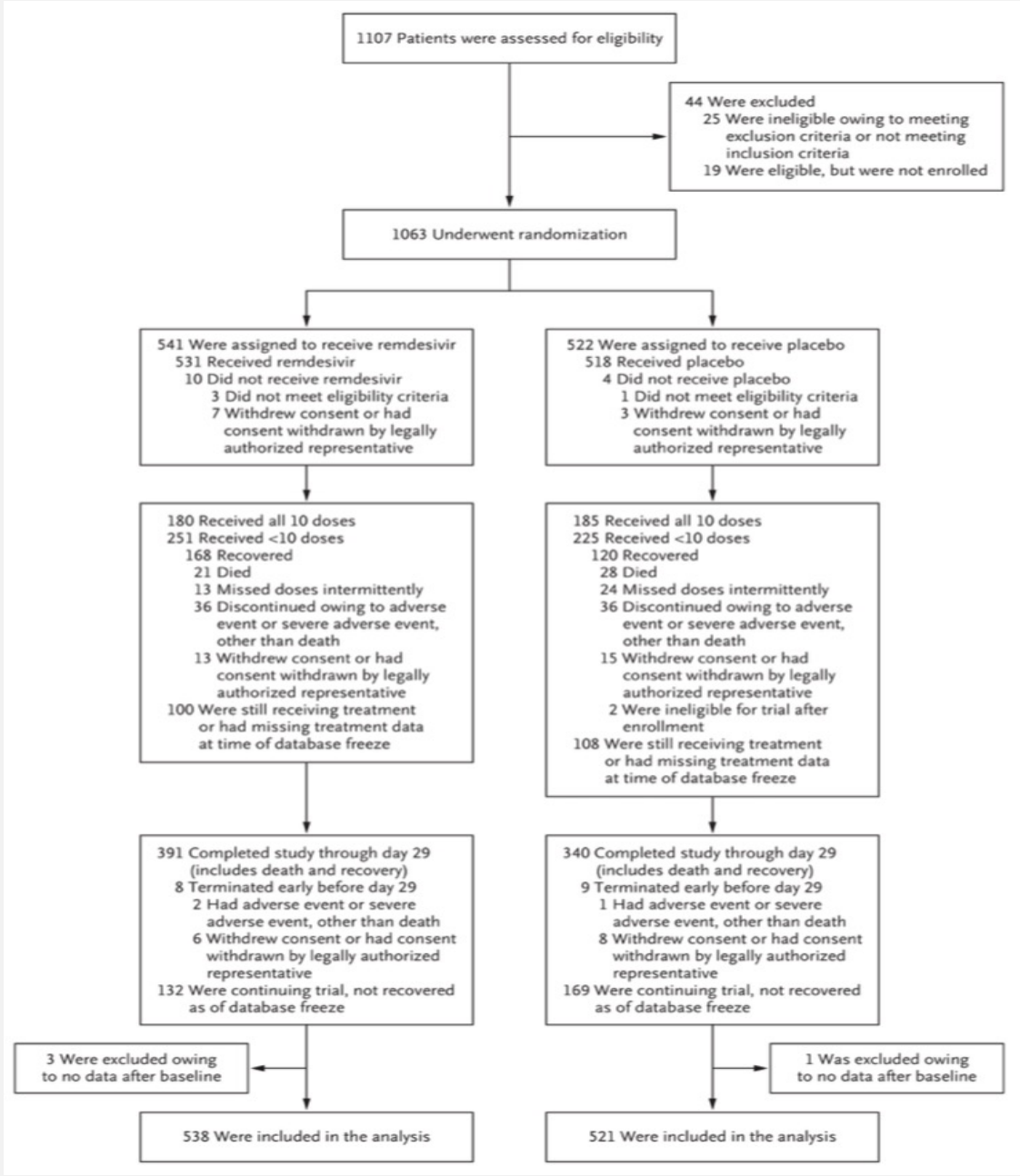
State of the Art Management

- Anti-viral therapy: Remdesivir, Convalescent plasma, Lopinavir-Ritonavir, HCQ, Ivermectin, mAb
- Anti-inflammatory therapy: dexamethasone, IL – 6 inhibition, JAK inhibition
- Anti-coagulation: therapeutic versus prophylactic, or somewhere in between!
- Supportive care – euglycemia, GI prophylaxis
- Laboratory and Imaging suggested

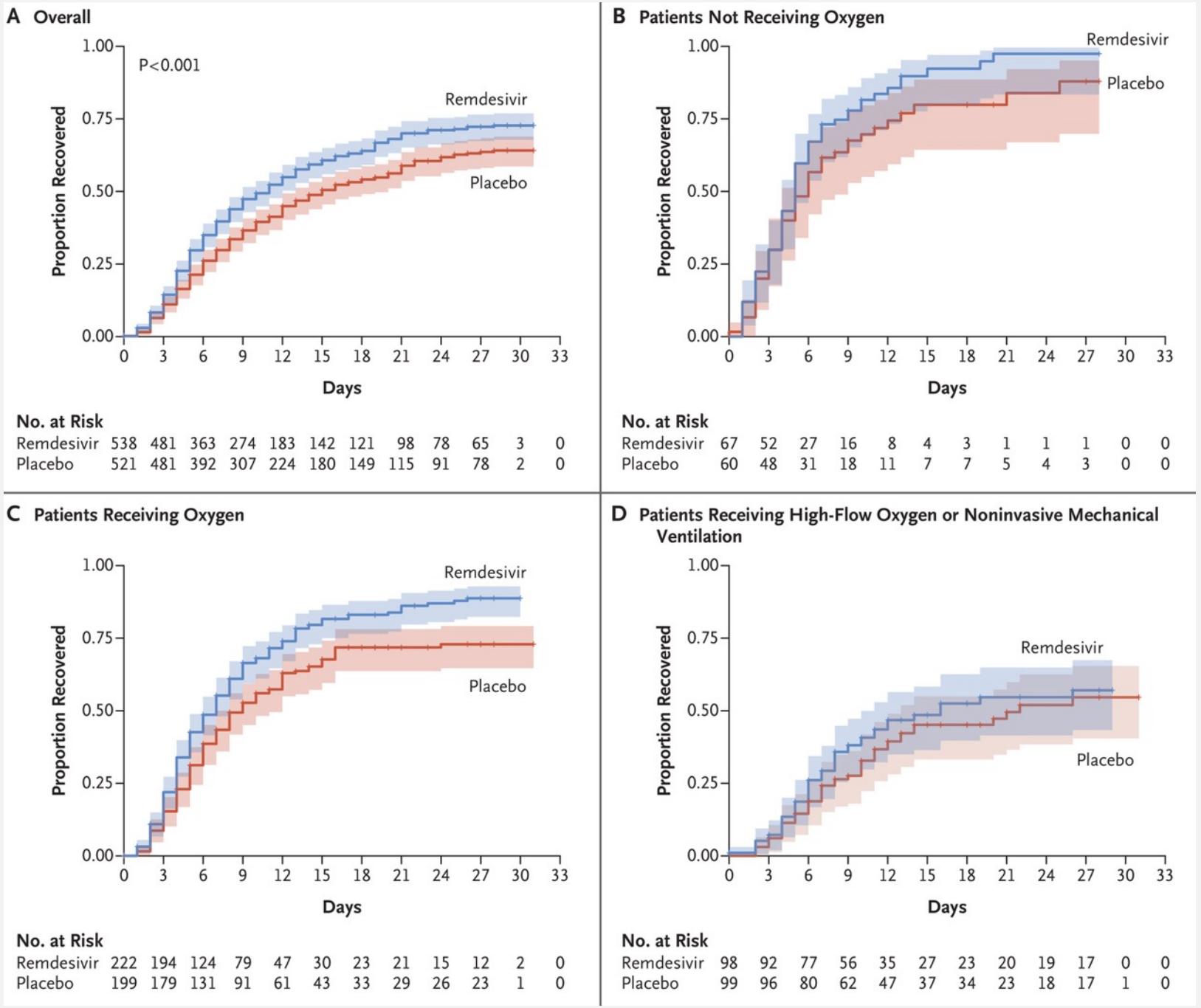
-- ACTT - 1
-- Broadly generalizable
-- similar degree of drop outs, withdrawn consent, adverse effects
-- study ongoing at the time of interim data analysis led to stopping

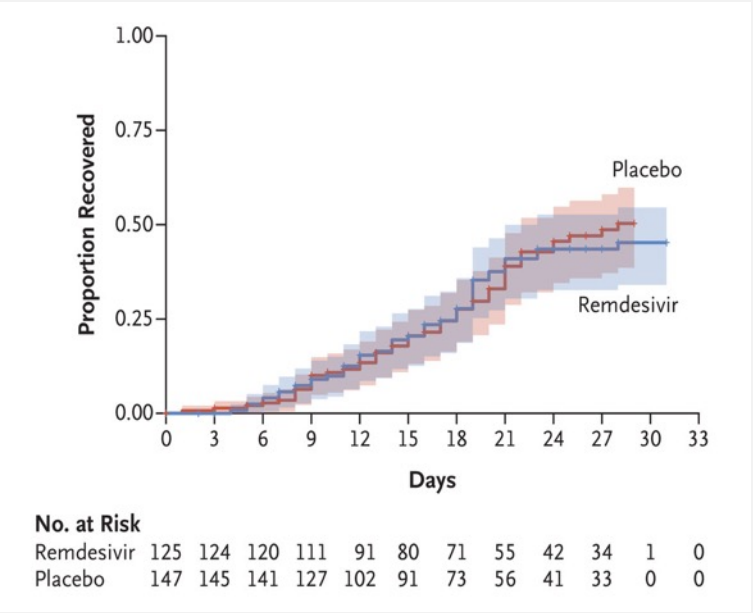
Baseline status well balanced between active and placebo groups

Characteristic	All (N=1063)	Remdesivir (N=541)	Placebo (N=522)
Score on ordinal scale — no. (%)			
4. Hospitalized, not requiring supplemental oxygen, requiring ongoing medical care (Covid-19–related or otherwise)	127 (11.9)	67 (12.4)	60 (11.5)
5. Hospitalized, requiring supplemental oxygen	421 (39.6)	222 (41.0)	199 (38.1)
6. Hospitalized, receiving noninvasive ventilation or high-flow oxygen devices	197 (18.5)	98 (18.1)	99 (19.0)
7. Hospitalized, receiving invasive mechanical ventilation or ECMO	272 (25.6)	125 (23.1)	147 (28.2)

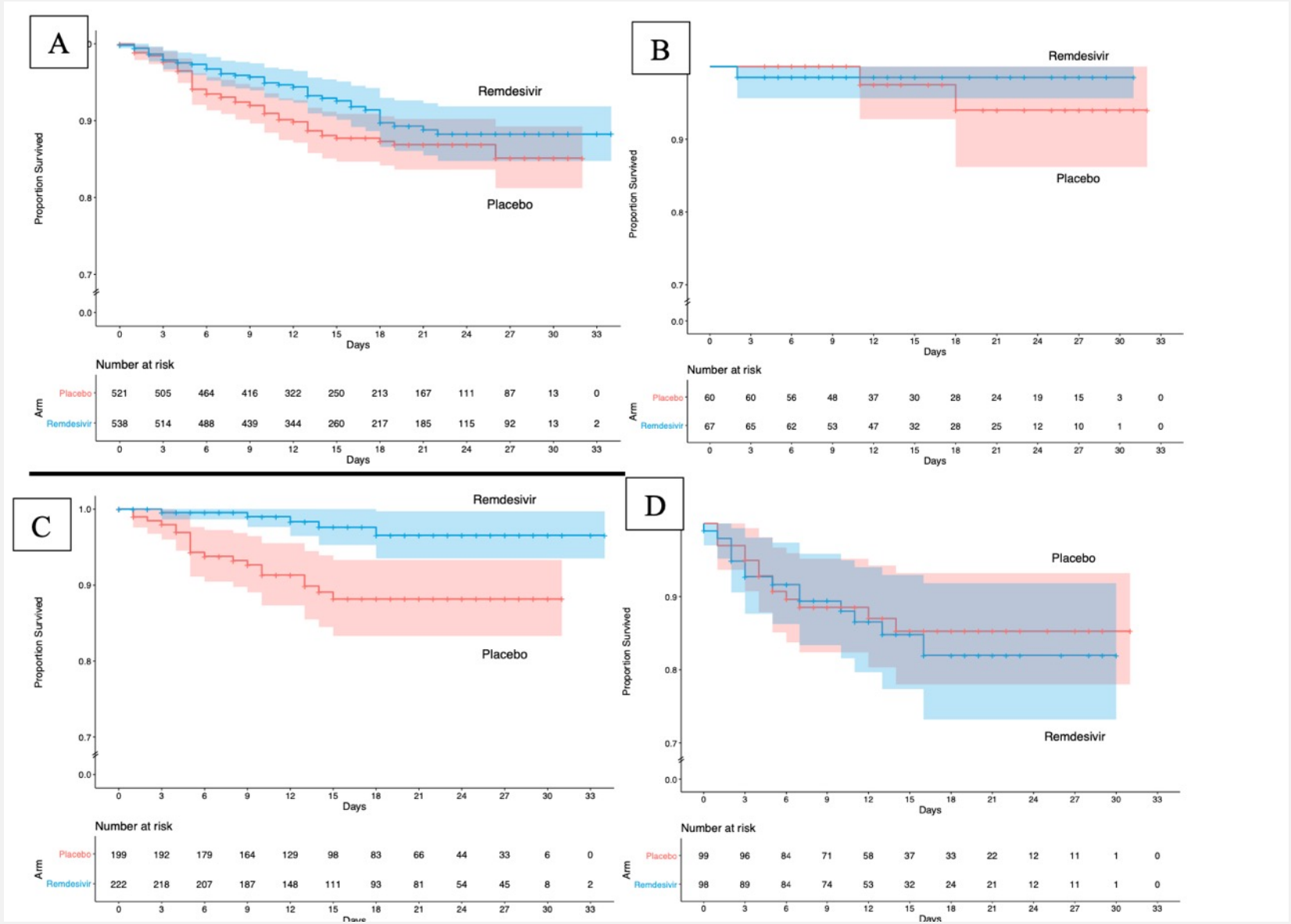


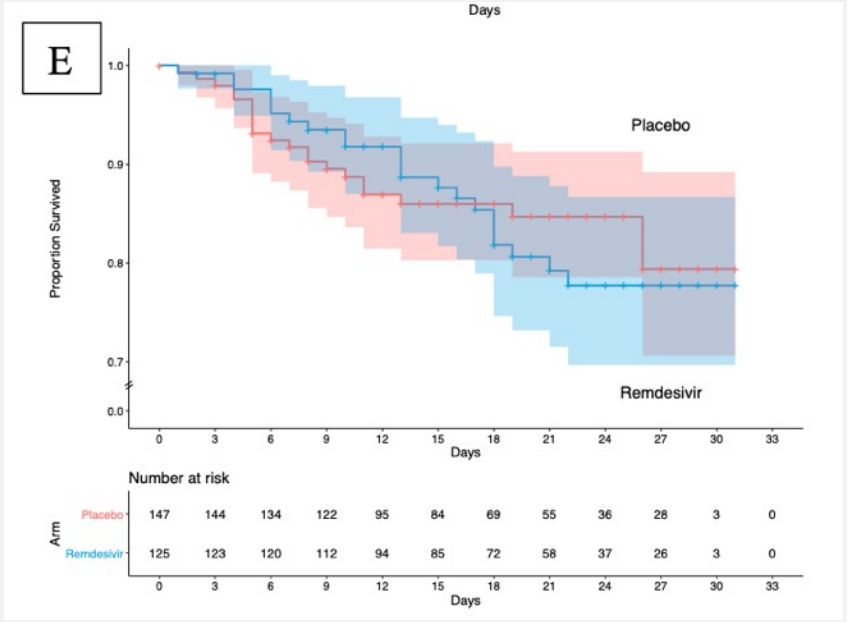
J. H. Biegel MD, K.M. Tomashek MD, L.E. Dodd PhD et al.
Remdesivir for the treatment of COVID-19 – Preliminary report.
NEJM. May 22, 2020. ACCT-1 Study Group.





-- overall faster recovery 11 vs. 15 days
-- p value < 0.001
-- statistically significant: time to recovery





A – overall population
B – hospitalized but no oxygen
C - hospitalized with low flow oxygen
D – high flow / BIPAP
E – mechanical ventilation / ECMO

	Overall		Ordinal Score at Baseline							
			4		5		6		7	
	Remdesivir (N=541)	Placebo (N=521)	Remdesivir (N=75)	Placebo (N=63)	Remdesivir (N=232)	Placebo (N=203)	Remdesivir (N=95)	Placebo (N=98)	Remdesivir (N=131)	Placebo (N=154)
Recovery										
No. of recoveries	399	352	73	58	206	156	57	61	63	77
Median time to recovery (95% CI) — days	10 (9–11)	15 (13–18)	5 (4–6)	6 (4–7)	7 (6–8)	9 (7–10)	15 (10– 27)	20 (14– 26)	29 (24–NE)	28 (24–NE)
Rate ratio (95% CI)†	1.29 (1.12–1.49 [P<0.001])		1.29 (0.91–1.83)		1.45 (1.18–1.79)		1.09 (0.76–1.57)		0.98 (0.70–1.36)	
Mortality through day 14‡										
Hazard ratio for data through day 15 (95% CI)	0.55 (0.36–0.83)		0.42 (0.04–4.67)		0.28 (0.12–0.66)		0.82 (0.40–1.69)		0.76 (0.39–1.50)	
No. of deaths by day 15	35	61	1	2	7	21	13	17	14	21
Kaplan–Meier estimate of mortality by day 15 — % (95% CI)	6.7 (4.8–9.2)	11.9 (9.4–15.0)	1.3 (0.2–9.1)	3.2 (0.8–12.1)	3.1 (1.5–6.4)	10.5 (7.0–15.7)	14.2 (8.5–23.2)	17.3 (11.2–26.4)	10.9 (6.6–17.6)	13.8 (9.2–20.4)
Mortality over entire study period‡										
Hazard ratio (95% CI)	0.73 (0.52–1.03)		0.82 (0.17–4.07)		0.30 (0.14–0.64)		1.02 (0.54–1.91)		1.13 (0.67–1.89)	
No. of deaths by day 29	59	77	3	3	9	25	19	20	28	29
Kaplan–Meier estimate of mortality by day 29 — % (95% CI)	11.4 (9.0–14.5)	15.2 (12.3–18.6)	4.1 (1.3– 12.1)	4.8 (1.6–14.3)	4.0 (2.1–7.5)	12.7 (8.8–18.3)	21.2 (14.0–31.2)	20.4 (13.7–29.8)	21.9 (15.7–30.1)	19.3 (13.8–26.5)
Ordinal score at day 15 (±2 days) — no. (%)§										
1	157 (29.0)	115 (22.1)	38 (50.7)	28 (44.4)	90 (38.8)	62 (30.5)	18 (18.9)	14 (14.3)	11 (8.4)	11 (7.1)
2	117 (21.6)	102 (19.6)	20 (26.7)	15 (23.8)	70 (30.2)	58 (28.6)	22 (23.2)	19 (19.4)	5 (3.8)	10 (6.5)
3	14 (2.6)	8 (1.5)	8 (10.7)	4 (6.3)	6 (2.6)	4 (2.0)	0	0	0	0
4	38 (7.0)	33 (6.3)	3 (4.0)	7 (11.1)	17 (7.3)	13 (6.4)	12 (12.6)	4 (4.1)	6 (4.6)	9 (5.8)
5	58 (10.7)	60 (11.5)	3 (4.0)	5 (7.9)	25 (10.8)	18 (8.9)	2 (2.1)	14 (14.3)	28 (21.4)	23 (14.9)
6	28 (5.2)	24 (4.6)	1 (1.3)	0	5 (2.2)	7 (3.4)	12 (12.6)	11 (11.2)	10 (7.6)	6 (3.9)
7	95 (17.6)	121 (23.2)	1 (1.3)	3 (4.8)	13 (5.6)	21 (10.3)	16 (16.8)	20 (20.4)	57 (43.5)	74 (48.1)
8	34 (6.3)	58 (11.1)	1 (1.3)	1 (1.6)	6 (2.6)	20 (9.9)	13 (13.7)	16 (16.3)	14 (10.7)	21 (13.6)
Odds ratio (95% CI)	1.5 (1.2–1.9)		1.5 (0.8–2.7)		1.6 (1.2–2.3)		1.4 (0.9–2.3)		1.2 (0.8–1.9)	

JAMA Network

QUESTION Does remdesivir provide a benefit on clinical status for patients hospitalized with moderate COVID-19 pneumonia?

CONCLUSION This clinical trial found that hospitalized patients with moderate COVID-19 randomized to a 5-day course, but not a 10-day course, of remdesivir had a statistically significant better clinical status vs standard care at 11 days, but the difference was of uncertain clinical importance.

POPULATION

357 Men
227 Women

Patients hospitalized with moderate COVID-19 pneumonia (pulmonary infiltrates plus room air oxygen >94%)

Median age: **57** years

LOCATIONS

105 Hospitals in the United States, Europe, and Asia

INTERVENTION

596 Patients randomized
584 Patients analyzed

193
10-Day remdesivir
IV remdesivir, 200 mg on day 1, followed by 100 mg/d

191
5-Day remdesivir
IV remdesivir, 200 mg on day 1, followed by 100 mg/d

200
Standard care

PRIMARY OUTCOME

Clinical status on day 11 rated on a categorical scale (1 = death , 7 = discharged) reported as odds ratio (OR >1 indicates difference in clinical status toward category 7 for remdesivir)

FINDINGS

Clinical status on day 11

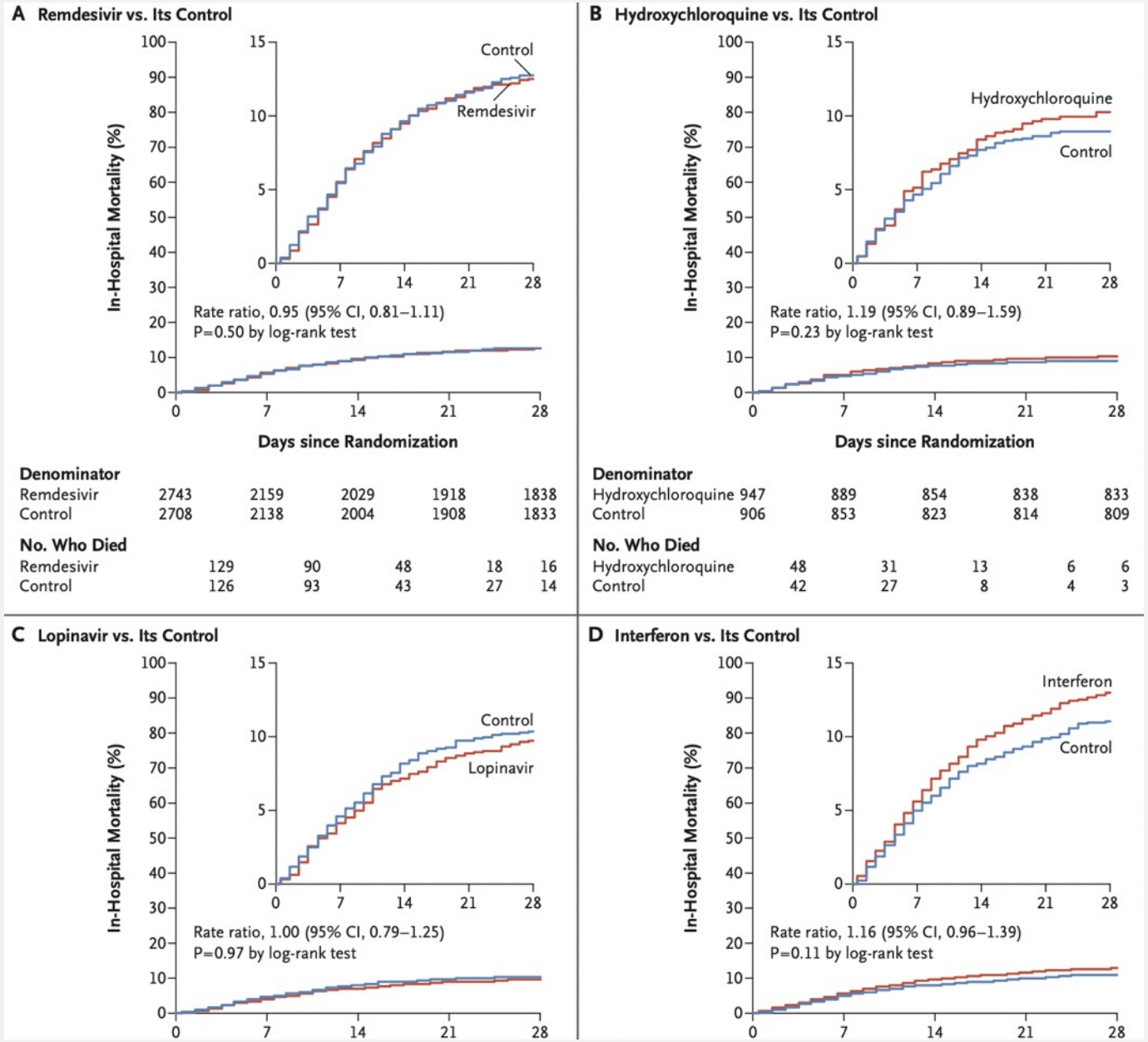
The difference in the primary outcome indicating better clinical status at day 11 was **statistically significant** for the 5-day remdesivir group compared with the standard care group:

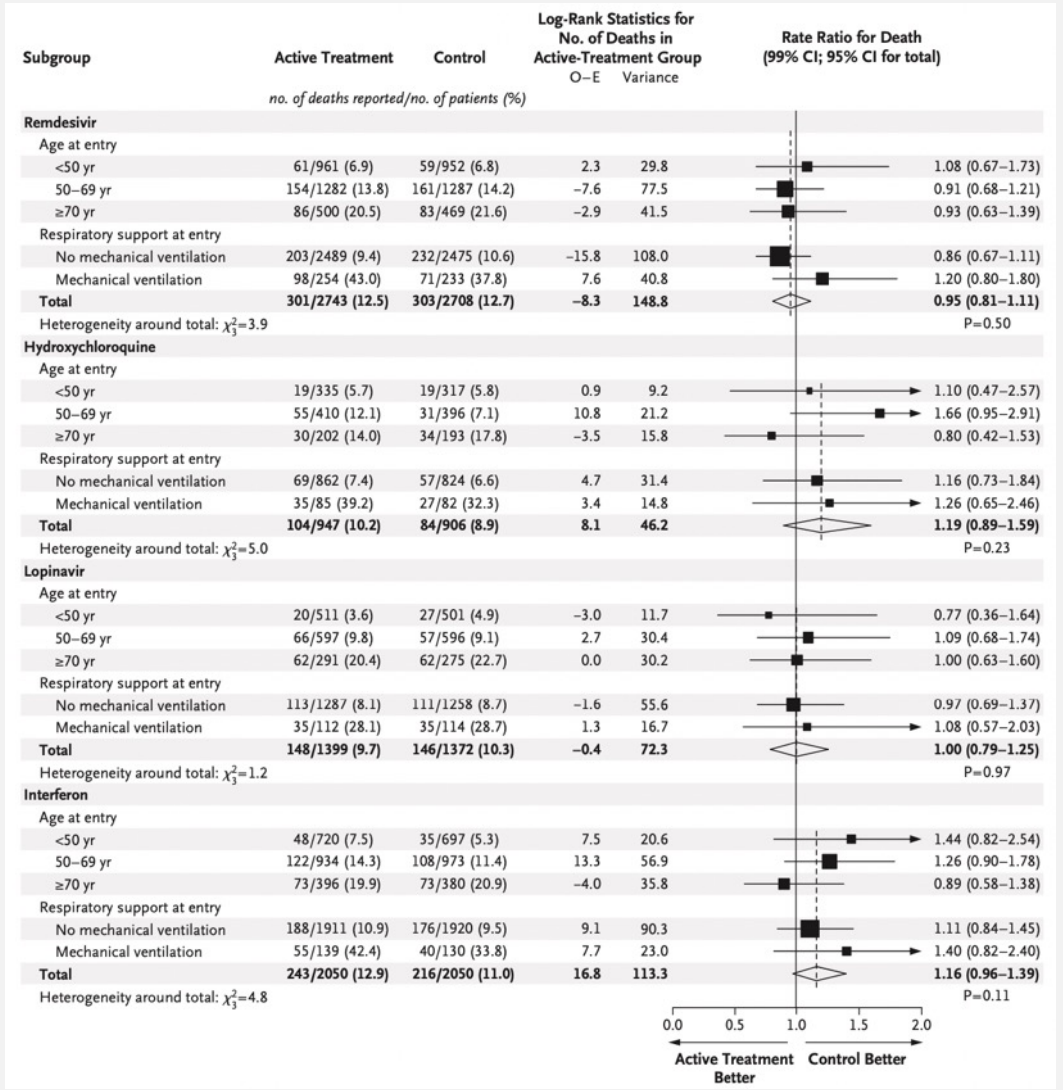
OR = **1.65** (95% CI, 1.09 to 2.48);
5-day remdesivir vs standard care, *P* = .02

The difference in the primary outcome indicating better clinical status at day 11 was **not statistically significant** for the 10-day remdesivir group compared with the standard care group:

10-day remdesivir vs standard care, *P* = .18

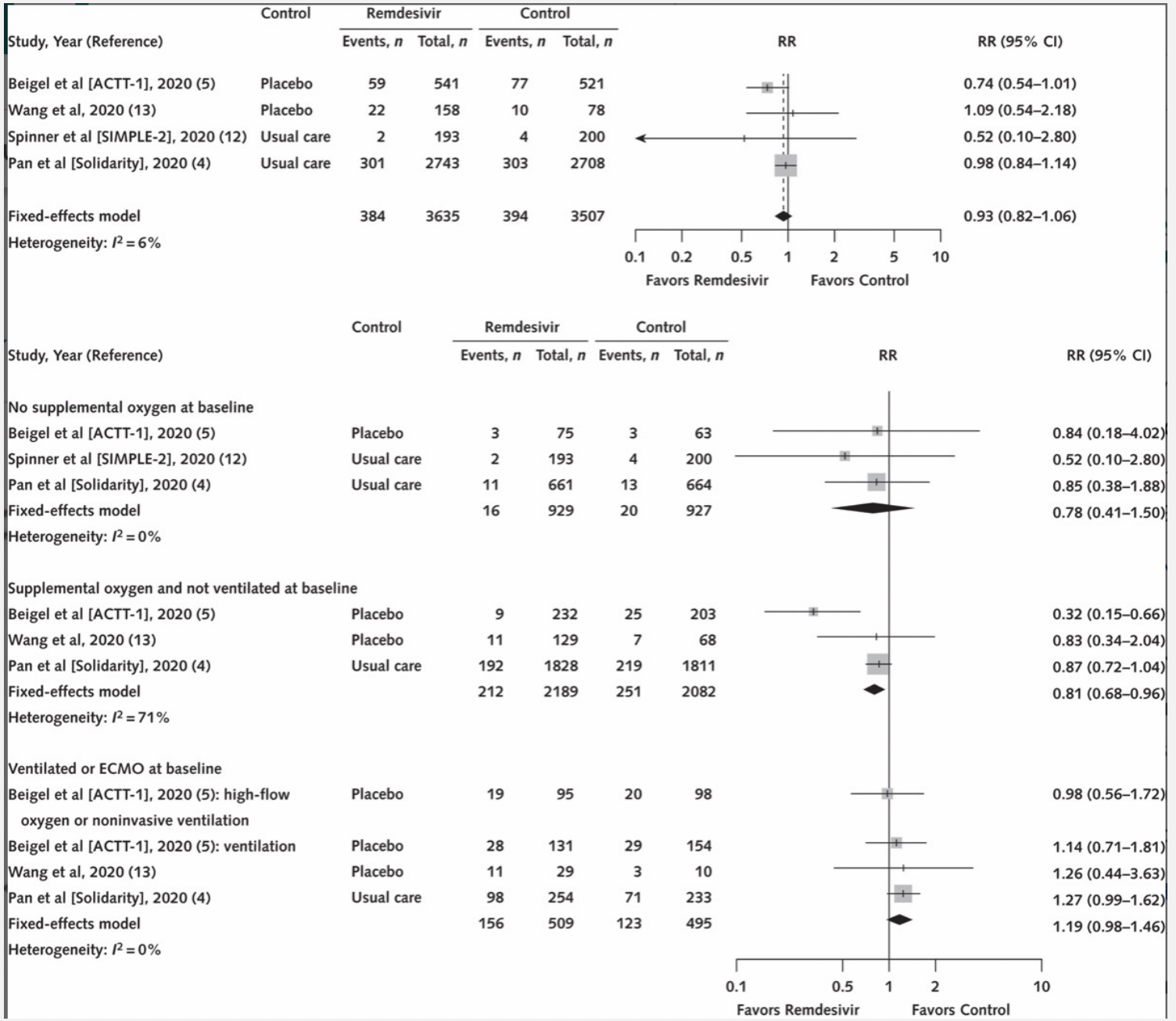
Spinner CD, Gottlieb RL, Criner GJ, et al; for the GS-US-540-5774 Investigators. Effect of remdesivir vs standard care on clinical status at 11 days in patients with moderate COVID-19: a randomized clinical trial. *JAMA*. Published online August 21, 2020. doi:10.1001/jama.2020.16349





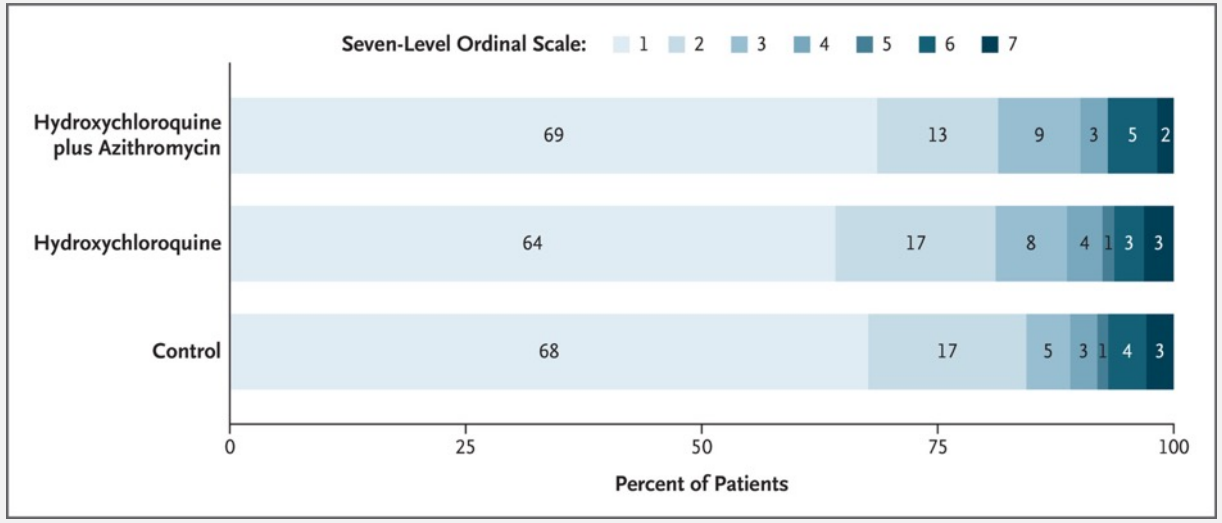
WHO Solidarity Trial Consortium, Pan H, Peto R, Henao-Restrepo AM et al. Repurposed Antiviral Drugs for Covid-19 - Interim WHO Solidarity Trial Results. N Engl J Med. 2021 Feb 11;384(6):497-511. doi: 10.1056/NEJMoa2023184. Epub 2020 Dec 2. PMID: 33264556; PMCID: PMC7727327

- SOLIDARITY trial used unambiguous end point of mortality
- Other trials used improvement, hospitalization duration
  and need for IMV – surrogate outcomes
- The surrogate outcomes are subject to misclassification
- My personal opinion – any real benefit is marginal
- Not cost effective



Kaka AS, MacDonald R, Greer N, Vela K, Duan-Porter W, Obley A, Wilt TJ. Major Update: Remdesivir for Adults With COVID-19 : A Living Systematic Review and Meta-analysis for the American College of Physicians Practice Points. Ann Intern Med. 2021 May;174(5):663-672. doi: 10.7326/M20-8148. Epub 2021 Feb 9. Erratum in: Ann Intern Med. 2021 Mar 16;: PMID: 33560863; PMCID: PMC7901604.

Hydroxychloroquine: The distraction.



Analysis	Intubation or Death
No. of events/no. of patients at risk (%)	
Hydroxychloroquine	262/811 (32.3)
No hydroxychloroquine	84/565 (14.9)
Crude analysis — hazard ratio (95% CI)	2.37 (1.84–3.02)
Multivariable analysis — hazard ratio (95% CI)*	1.00 (0.76–1.32)
Propensity-score analyses — hazard ratio (95% CI)	
With inverse probability weighting†	1.04 (0.82–1.32)
With matching‡	0.98 (0.73–1.31)
Adjusted for propensity score§	0.97 (0.74–1.28)

View full size

-- mild to moderate disease: either no oxygen or oxygen less than 4 liters via low flow nasal cannula
-- 15 day ordinal scale assessment
-- early initiation of therapy: 7 days

Observational Study of Hydroxychloroquine in Hospitalized Patients with Covid-19. Geleris J., Sun Y., Platt J., et al.|N Engl J Med 2020; 382:2411-2418

Hydroxychloroquine with or without Azithromycin in Mild-to-Moderate Covid-19
Cavalcanti A.B., Zampieri F.G., Rosa R.G., et al.|10.1056/NEJMoa2019014

CONVALESCENT PLASMA

- Trials using high titer plasma – a
- Trials using low, medium and high titer plasma – b
- **Bottom line**
- does not work in the general hospitalized
- May have utility in seronegative patients treated within

Three days of illness onset with high titer plasma only

- CP does not have a place in prevention of hospitalization
- Does not have a place in prevention of acquisition

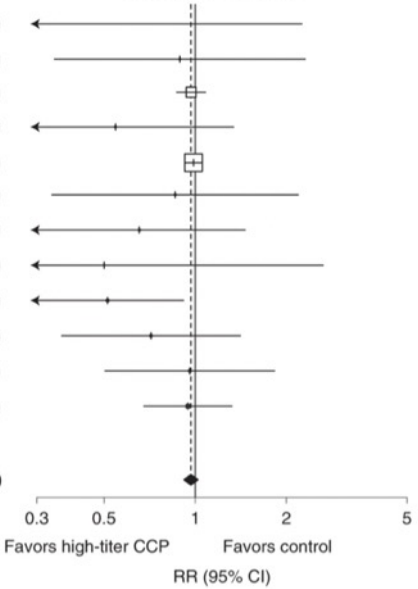
Fig. 5: Meta-analysis of mortality at 30 d in CONCOR-1 and other trials according to convalescent plasma selection strategy.

From: Convalescent plasma for hospitalized patients with COVID-19: an open-label, randomized controlled trial

a

Study	High-titer CCP Sample size	Events	Control Sample size	Events	RR (95% CI)
Avendaño-Solà 2020	38	0	43	4	0.13 (0.01, 2.26)
Bennett-Guerrero 2020	59	14	15	4	0.89 (0.34, 2.31)
Estcourt 2021	1,078	401	904	347	0.97 (0.87, 1.09)
Gharbharan 2020	43	6	43	11	0.55 (0.22, 1.34)
Horby 2021	5,795	1,398	5,763	1,408	0.99 (0.93, 1.05)
Körper 2021	53	7	52	8	0.86 (0.34, 2.20)
Li 2020	52	8	51	12	0.65 (0.29, 1.47)
Libster 2020	80	2	80	4	0.50 (0.09, 2.65)
O'Donnell 2021	150	19	73	18	0.51 (0.29, 0.92)
Ray 2020	40	10	40	14	0.71 (0.36, 1.41)
Simonovich 2020	228	25	105	12	0.96 (0.50, 1.83)
CONCOR-1 blood supplier 1	343	75	173	40	0.95 (0.67, 1.33)
Total (95% CI)	7,959		7,342		0.97 (0.92, 1.02)

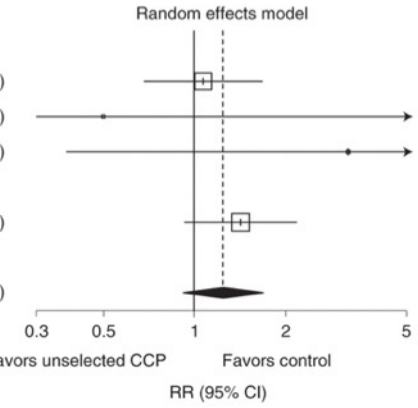
Heterogeneity: $Tau^2 = 0$; $Chi^2 = 10.80$, df = 11 ($P = 0.46$); $I^2 = 0\%$



b

Study	Unselected CCP Sample size	Events	Control Sample size	Events	RR (95% CI)
Agarwal 2020	235	34	229	31	1.07 (0.68, 1.68)
AlQahtani 2020	20	1	20	2	0.50 (0.05, 5.08)
Bajpai 2020	14	3	15	1	3.21 (0.38, 27.40)
Hamdy Salman 2020	15	0	15	0	
CONCOR-1 blood supplier 2/3/4	271	66	134	23	1.42 (0.93, 2.17)
Total (95% CI)	555		413		1.25 (0.92; 1.69)

Heterogeneity: $Tau^2 = 0$; $Chi^2 = 2.15$, df = 3 ($P = 0.54$); $I^2 = 0\%$



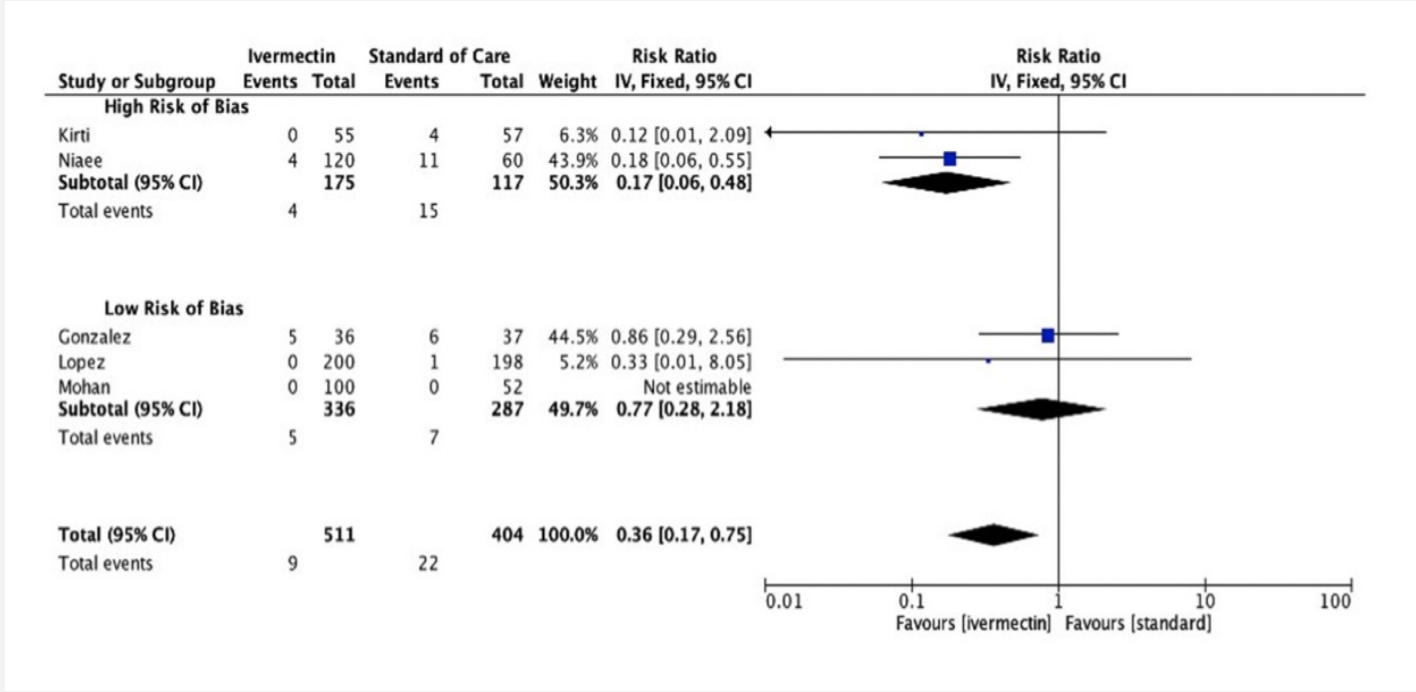
a, Meta-analysis of trials that used high-titer plasma. **b**, Meta-analysis of trials that used a mix of low-, medium- and high-titer plasma. df, degrees of freedom.

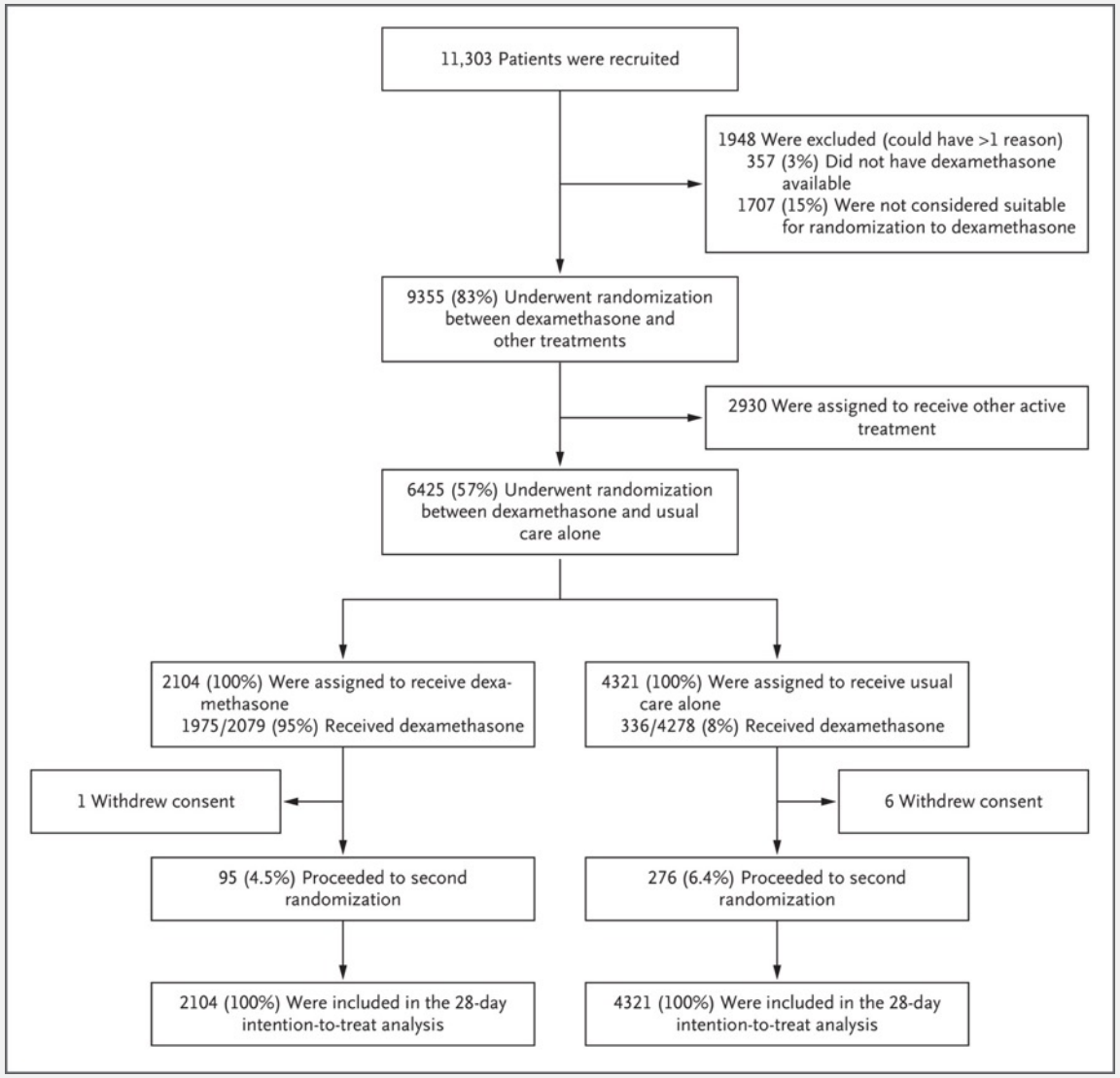
Bégin P, Callum J, Jamula E, Cook R, Heddle NM, Tinmouth A, Zeller MP, Beaudoin-Bussières G, Amorim L, Bazin R, Loftsgard KC, Carl R, Chassé M, Cushing MM, Daneman N, Devine DV, Dumaresq J, Fergusson DA, Gabe C, Glesby MJ, Li N, Liu Y, McGeer A, Robitaille N, Sachais BS, Scales DC, Schwartz L, Shehata N, Turgeon AF, Wood H, Zarychanski R, Finzi A; CONCOR-1 Study Group, Arnold DM. Convalescent plasma for hospitalized patients with COVID-19: an open-label, randomized controlled trial. Nat Med. 2021 Sep 9. doi: 10.1038/s41591-021-01488-2. Epub ahead of print. PMID: 34504336.

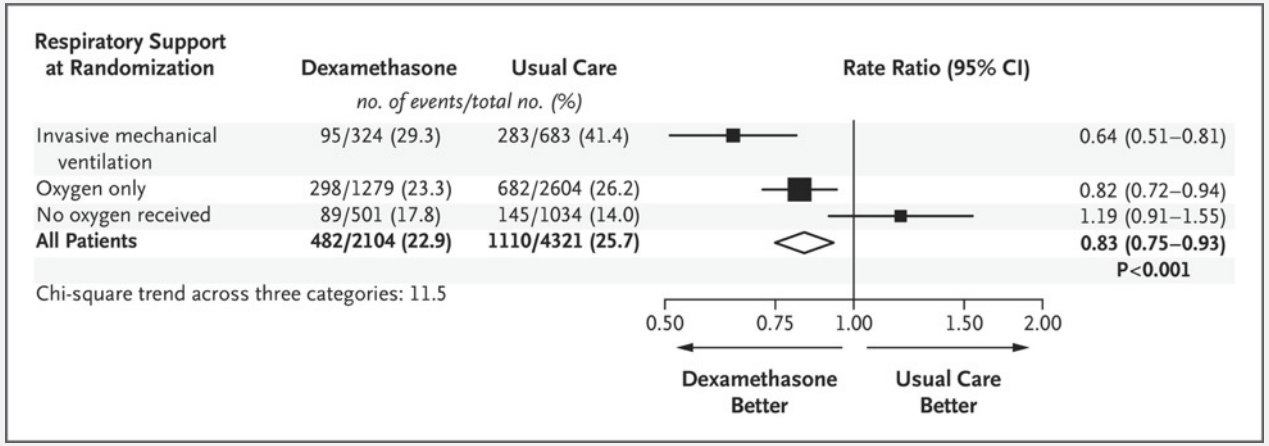
Ivermectin – magic bullet or the new hydroxychloroquine

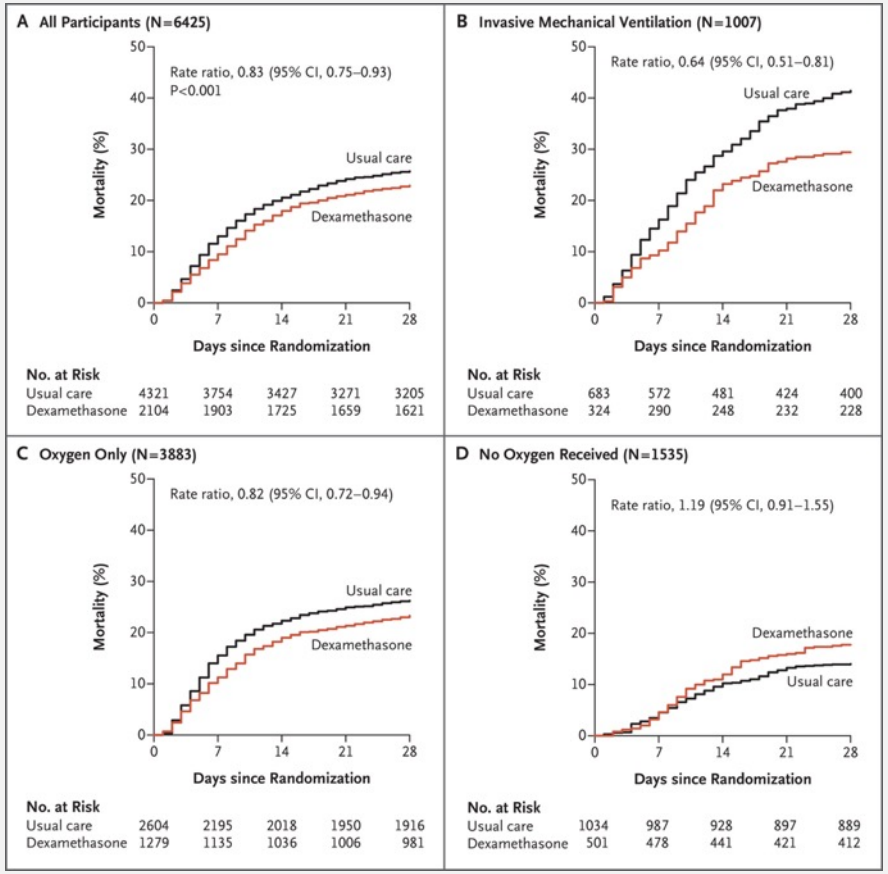
Ivermectin is an antiparasitic agent that interferes with nerve and muscle function of helminths through binding glutamate-gated chloride channels *(32)*. Based on in vitro experiments, some have postulated that ivermectin may have a direct antiviral effect against SARS-CoV-2. However, in humans the concentrations needed for in vitro inhibition are unlikely to be achieved by the doses proposed for COVID-19 *(33)(34)(35)*. Ivermectin had no impact on SARS-CoV-2 viral RNA in the Syrian golden hamster model of SARS-CoV-2 infection *(36)*. The proposed mechanism remains unclear: multiple targets have been proposed based upon either analogy to other viruses with very different life cycles, or, like several hundred other candidates, simulations indicating molecular docking with multiple viral targets including spike, RdRp and 3CLpro *(37)(38)(39)(40)(41)*. No direct evidence for any mechanism of antiviral action against SARS-CoV-2 currently exists.

- Professional medical associations of repute and governmental agencies recommend the use of Ivermectin only in a clinical trial.
- The studies done have been small, subject to bias, lack of data transparency, and outright fraud leading to withdrawal of the largest Study by El Nazzar et al.
- The effect on mortality described is inconsistent with any anti-viral strategy for an acute infectious viral condition and with other Anti-viral strategies used in severe hospitalized patients for influenza and COVID 19 for example, or CMV in immune compromised Persons.
- The doses required to achieve neutralization of virus based on in-vitro studies would have to be about 100 times higher than those Used for anti-parasitic applications.
- The issue is political and not settled but I doubt the studies are meaningful and I doubt that any intervention can work so well as Claimed.









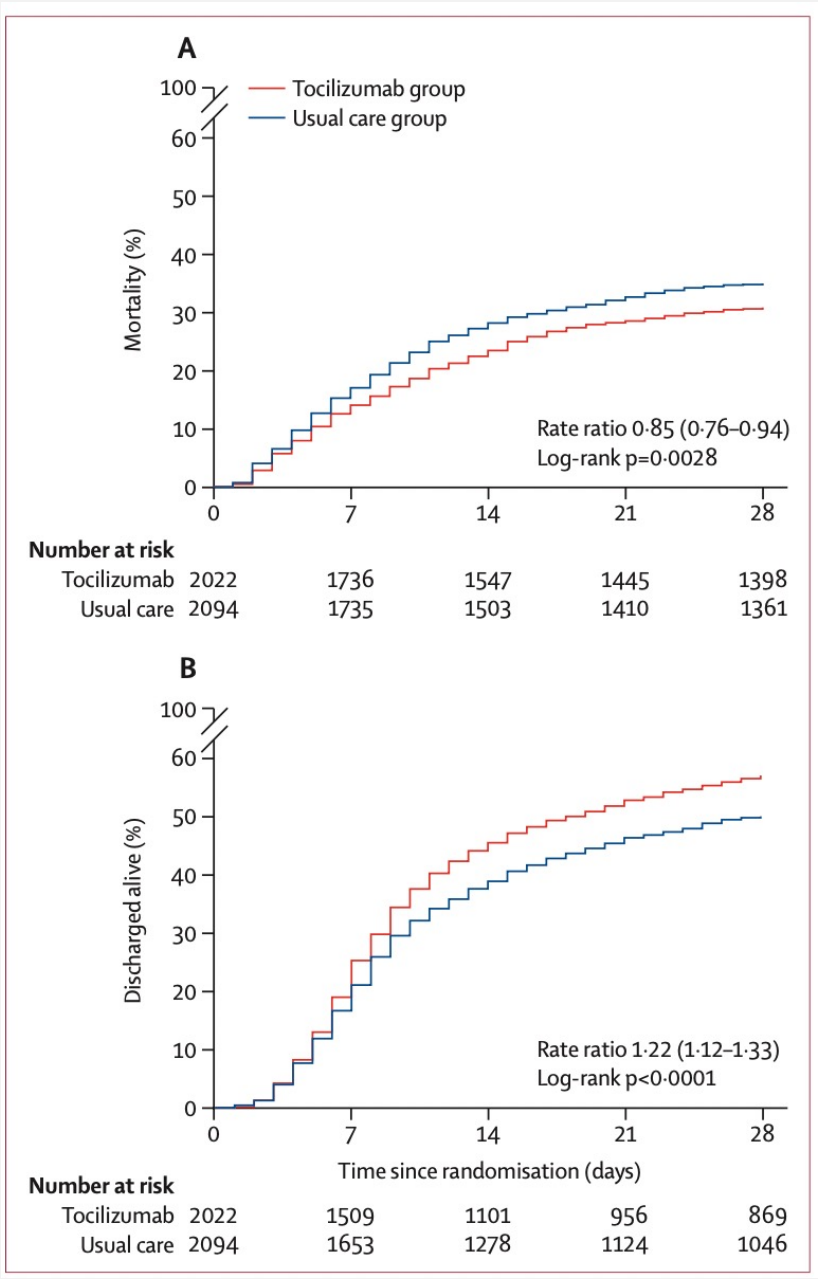
Recovery Trial Group. Dexamethasone in Hospitalized patients with COVID -19 - Preliminary Report. NEJM, Jul 17, 2020.

RECOVERY TRIAL-TOCILIZUMAB

- 4116 randomized
- 2022 toci
- 2094 SOC
- Open label
- Over 18
- CRP > 7.5
- SaO2 < 92% RA
- Both ICU and non-ICU patients

	Treatment allocation		RR (95% CI)	p value
	Tocilizumab group (n=2022)	Usual care group (n=2094)		
Primary outcome				
28-day mortality	621 (31%)	729 (35%)	0·85 (0·76–0·94)	0·0028
Secondary outcomes				
Median time to being discharged, days	19	>28	..	..
Discharged from hospital within 28 days	1150 (57%)	1044 (50%)	1·22 (1·12–1·33)	<0·0001
Receipt of invasive mechanical ventilation or death*	619/1754 (35%)	754/1800 (42%)	0·84 (0·77–0·92)	<0·0001
Invasive mechanical ventilation	265/1754 (15%)	343/1800 (19%)	0·79 (0·69–0·92)	0·0019
Death	490/1754 (28%)	580/1800 (32%)	0·87 (0·78–0·96)	0·0055
Subsidiary clinical outcomes				
Receipt of ventilation†	290/935 (31%)	323/933 (35%)	0·90 (0·79–1·02)	0·10
Non-invasive ventilation	281/935 (30%)	309/933 (33%)	0·91 (0·79–1·04)	0·15
Invasive mechanical ventilation	67/935 (7%)	86/933 (9%)	0·78 (0·57–1·06)	0·11
Successful cessation of invasive mechanical ventilation‡	95/268 (35%)	98/294 (33%)	1·08 (0·81–1·43)	0·60
Use of haemodialysis or haemofiltration§	120/1994 (6%)	172/2065 (8%)	0·72 (0·58–0·90)	0·0046

Data are n (%), n/N (%), or median (IQR) unless stated otherwise. RR=rate ratio for the outcomes of 28-day mortality, hospital discharge, and successful cessation of invasive mechanical ventilation, and risk ratio for other outcomes. *Analyses include only those on no ventilator support or non-invasive ventilation at second randomisation. †Analyses include only those on no ventilator support at second randomisation. ‡Analyses restricted to those on invasive mechanical ventilation at second randomisation. §Analyses exclude those on haemodialysis or haemofiltration at second randomisation.

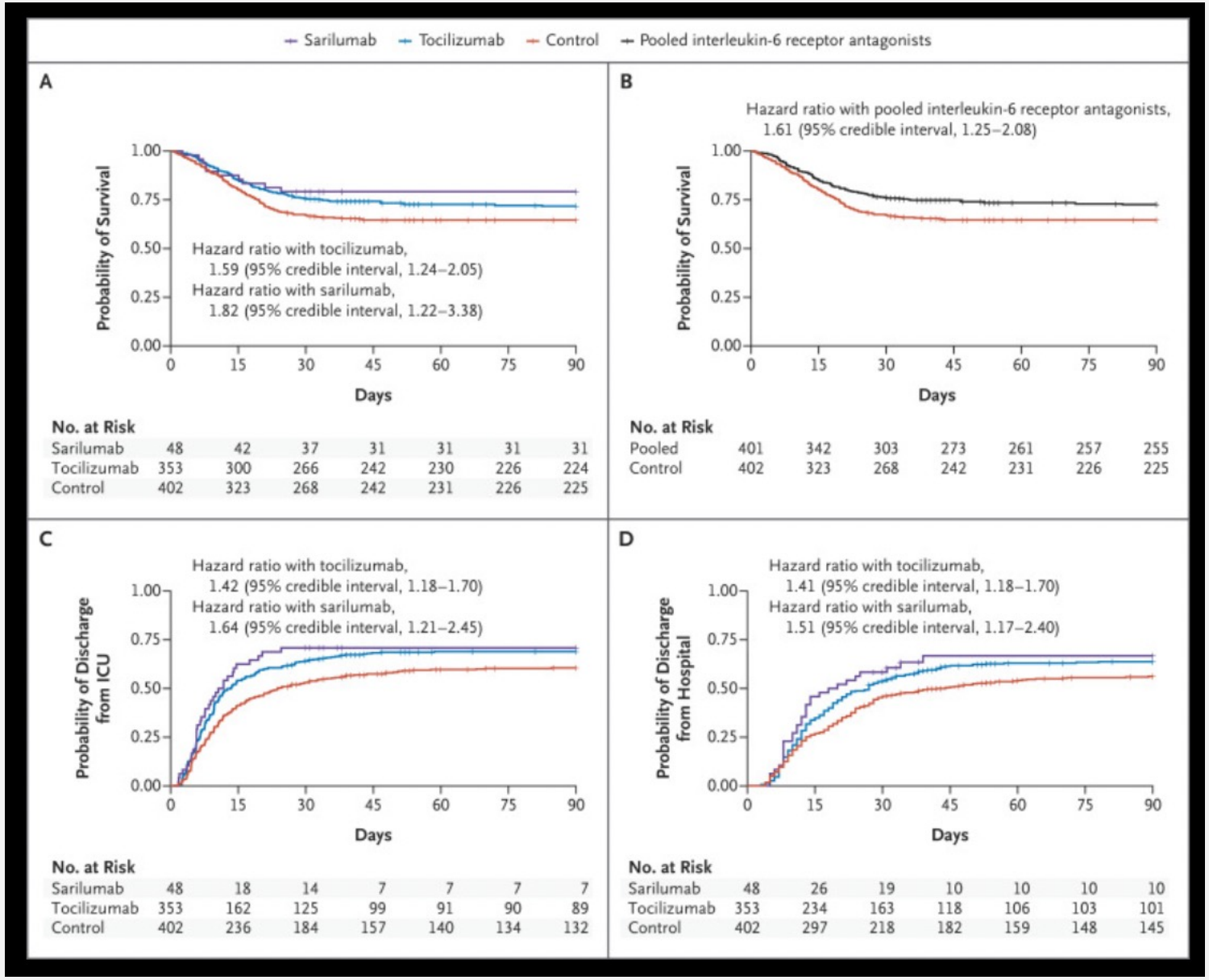


RECOVERY Collaborative Group. Tocilizumab in patients admitted to hospital with COVID-19 (RECOVERY): a randomised, controlled, open-label, platform trial. Lancet. 2021 May 1;397(10285):1637-1645. doi: 10.1016/S0140-6736(21)00676-0. PMID: 33933206; PMCID: PMC8084355.

REMAP-CAP STUDY: IL-6R inhibitors

Critically ill patients, 18 years of age or older, with either clinically suspected or microbiologically confirmed Covid-19 who were admitted to an intensive care unit (ICU) and receiving respiratory or cardiovascular organ support were classified as having a severe disease state and were eligible for enrollment in the Covid-19 Immune Modulation Therapy domain. Respiratory organ support was defined as invasive or noninvasive mechanical ventilation, including through high-flow nasal cannula if the flow rate was more than 30 liters per minute and the fraction of inspired oxygen was more than 0.4.

- Toci 353, Sari 48, 402 control
- 90-95% patients received glucocorticoids
- Remdesivir use balanced
- Other clinical features balanced
- **Result:** improved organ support free days and mortality
- ADR not significantly different



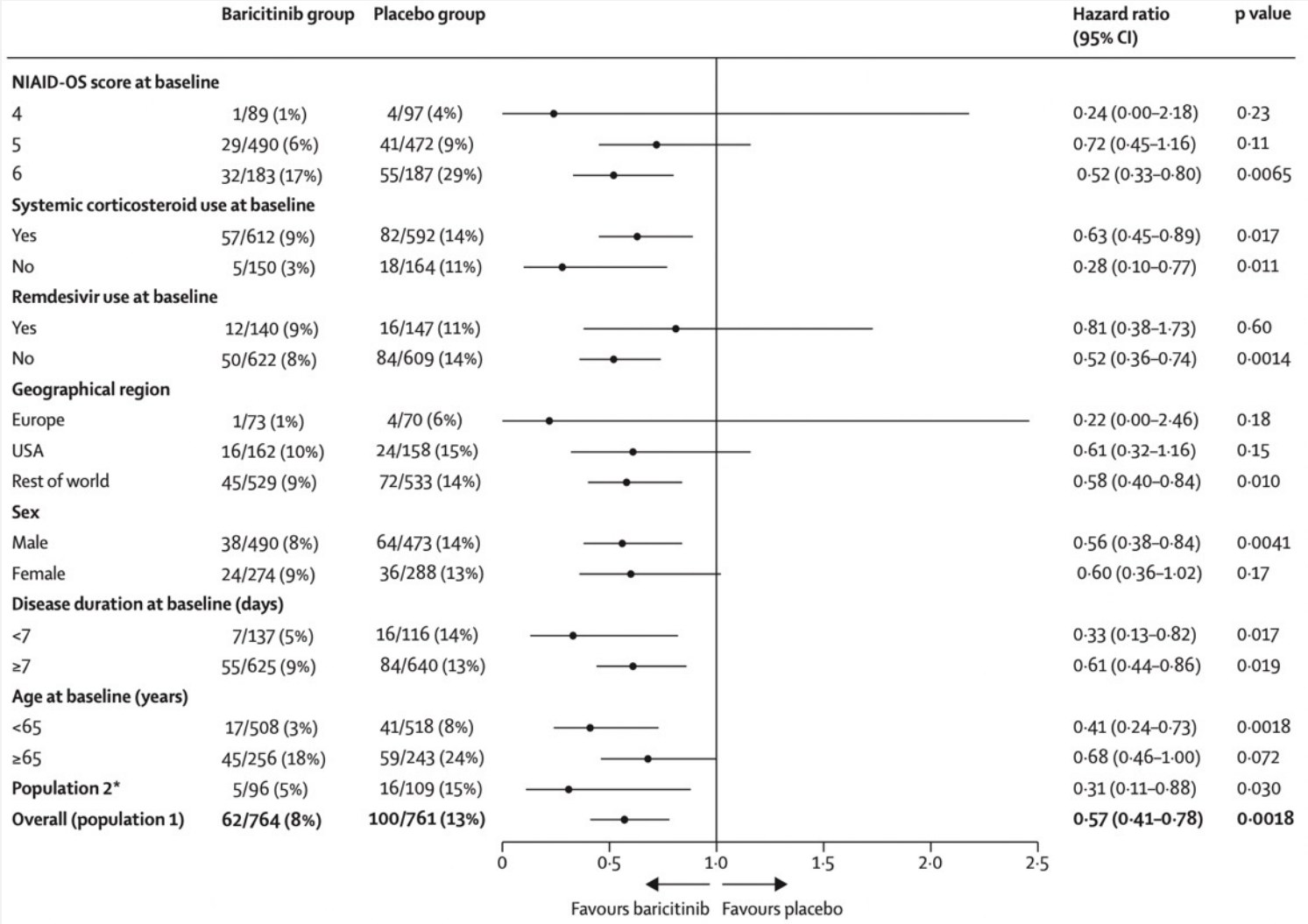
REMAP-CAP Investigators, Gordon AC, Mouncey PR, Al-Beidh F, Rowan KM, Nichol AD, Arabi YM, Annane D, Beane A, van Bentum-Puijk W, Berry LR, Bhimani Z, Bonten MJM, Bradbury CA, Brunkhorst FM, Buzgau A, Cheng AC, Detry MA, Duffy EJ, Estcourt LJ, Fitzgerald M, Goossens H, Haniffa R, Higgins AM, Hills TE, Horvat CM, Lamontagne F, Lawler PR, Leavis HL, Linstrum KM, Litton E, Lorenzi E, Marshall JC, Mayr FB, McAuley DF, McGlothlin A, McGuinness SP, McVerry BJ, Montgomery SK, Morpeth SC, Murthy S, Orr K, Parke RL, Parker JC, Patanwala AE, Pettilä V, Rademaker E, Santos MS, Saunders CT, Seymour CW, Shankar-Hari M, Sligl WI, Turgeon AF, Turner AM, van de Veerdonk FL, Zarychanski R, Green C, Lewis RJ, Angus DC, McArthur CJ, Berry S, Webb SA, Derde LPG. Interleukin-6 Receptor Antagonists in Critically Ill Patients with Covid-19. N Engl J Med. 2021 Apr 22;384(16):1491-1502. doi: 10.1056/NEJMoa2100433. Epub 2021 Feb 25. PMID: 33631065; PMCID: PMC7953461.

Inclusion Criteria – 18 or older
Positive PCR
Hospitalized
CRP or other marker elevated
Bilateral infiltrates on XR
Excluded if IVIG or CP
Need for mechanical vent
Immunosuppressive treatment
LFT > 5 ULN
Randomized 1525 pts

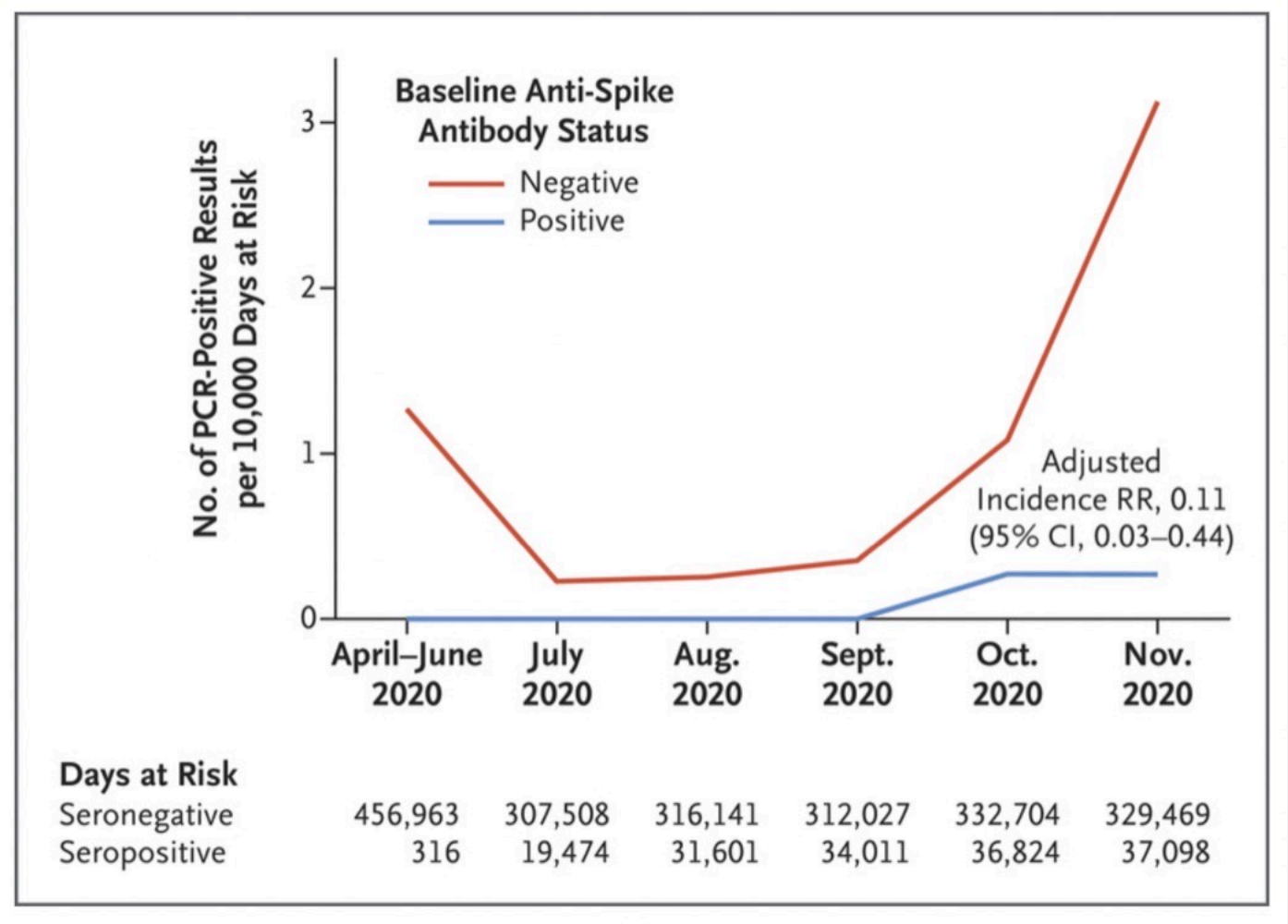
Results
12% Reduction in mortality in OrdS 6
None in OrdS 4/5
Treating 8 pts in OrdS saves 1 life

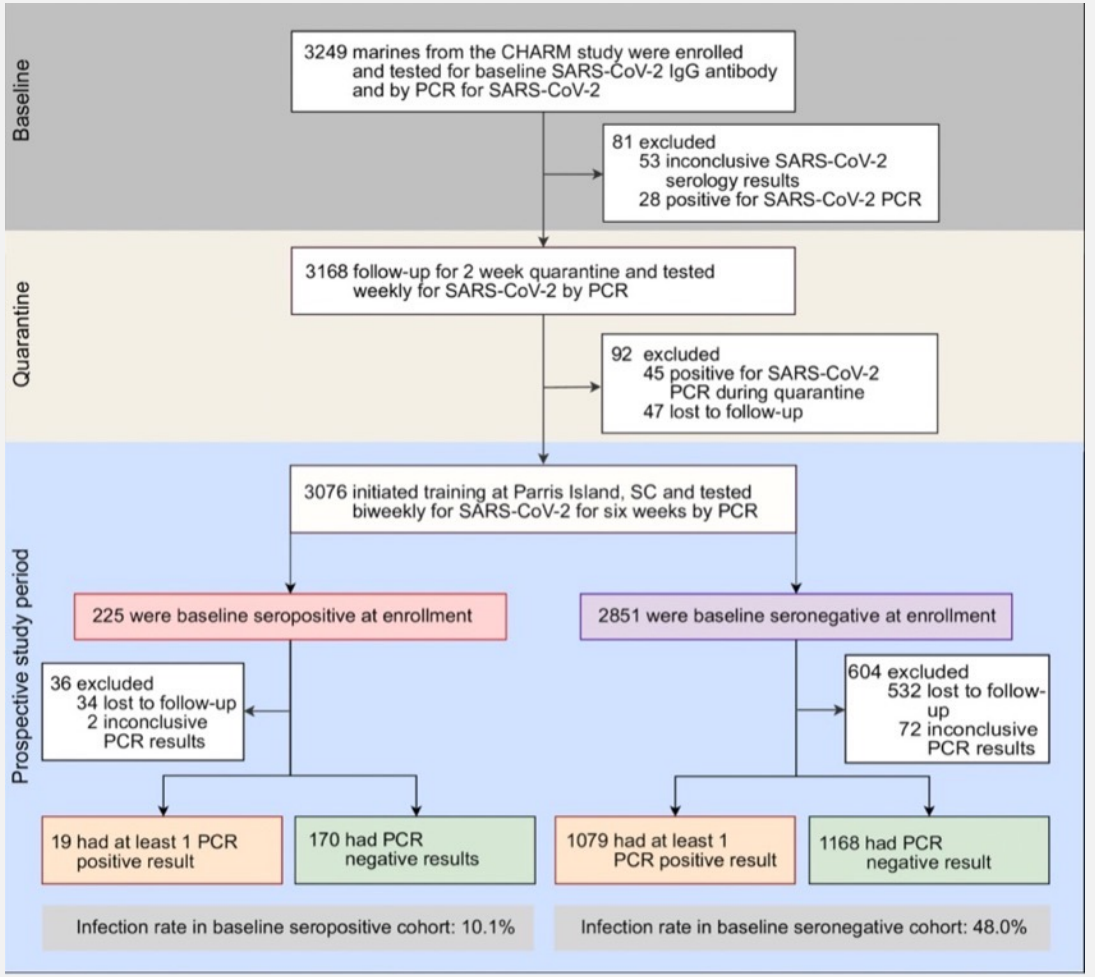
Other conclusions
Baseline groups balanced
ADR not significantly different

BOTTOM LINE – in HHFNC patients
Baricitinib reduces mortality with and
Without concomitant steroid treatment



Marconi VC, Ramanan AV, de Bono S, Kartman CE, Krishnan V, Liao R, Piruzeli MLB, Goldman JD, Alatorre-Alexander J, de Cassia Pellegrini R, Estrada V, Som M, Cardoso A, Chakladar S, Crowe B, Reis P, Zhang X, Adams DH, Ely EW; COV-BARRIER Study Group. Efficacy and safety of baricitinib for the treatment of hospitalised adults with COVID-19 (COV-BARRIER): a randomised, double-blind, parallel-group, placebo-controlled phase 3 trial. Lancet Respir Med. 2021 Aug 31:S2213-2600(21)00331-3. doi: 10.1016/S2213-2600(21)00331-3. Epub ahead of print. Erratum in: Lancet Respir Med. 2021 Sep 8;: PMID: 34480861; PMCID: PMC8409066.





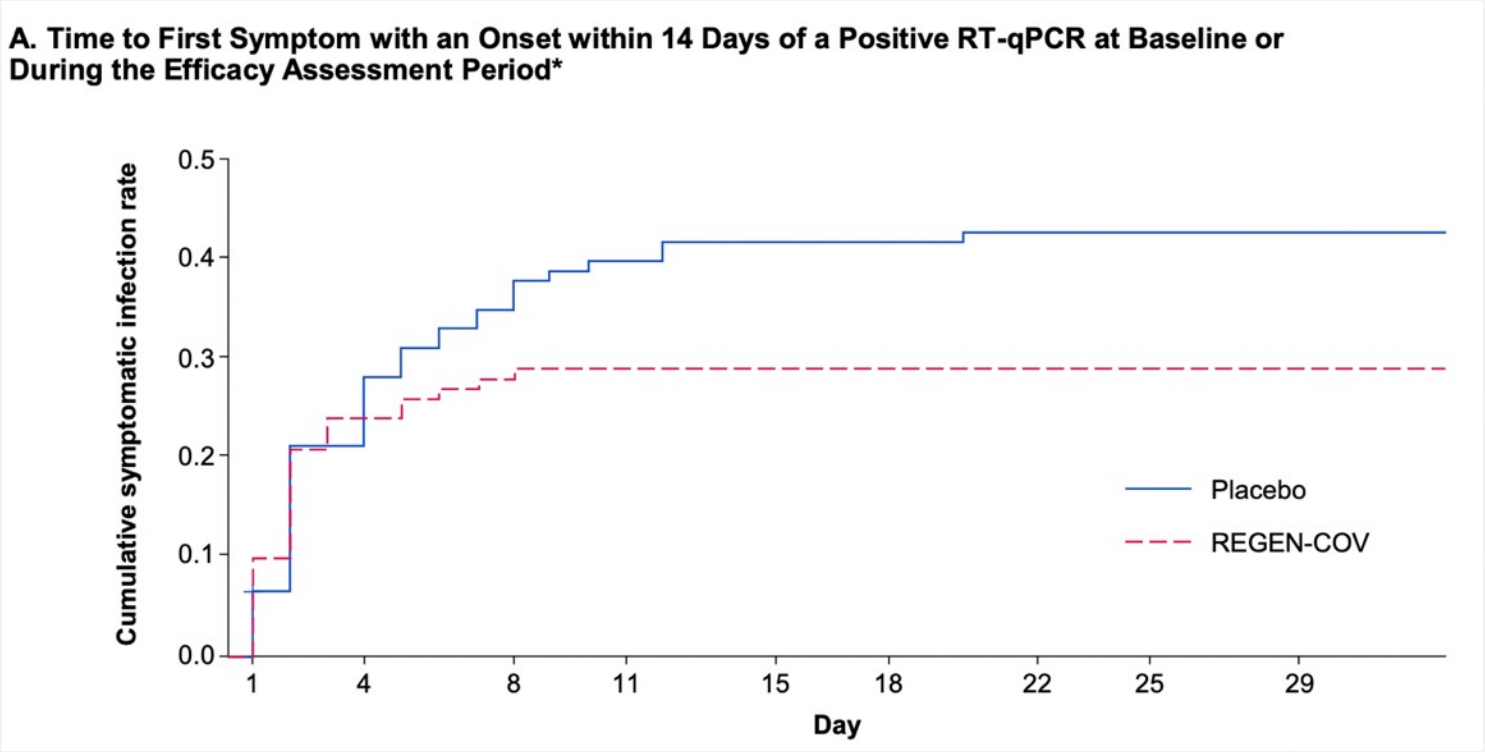
Lumley SF, et al. Oxford University Hospitals Staff Testing Group. Antibody Status and Incidence of SARS-CoV-2 Infection in Health Care Workers. N Engl J Med. 2021 Feb 11;384(6):533-540.

Primary Endpoint: Proportion of Patients with ≥ 1 COVID-19 Related Hospitalization or All-Cause Death Through Day 29 (COV-2067)

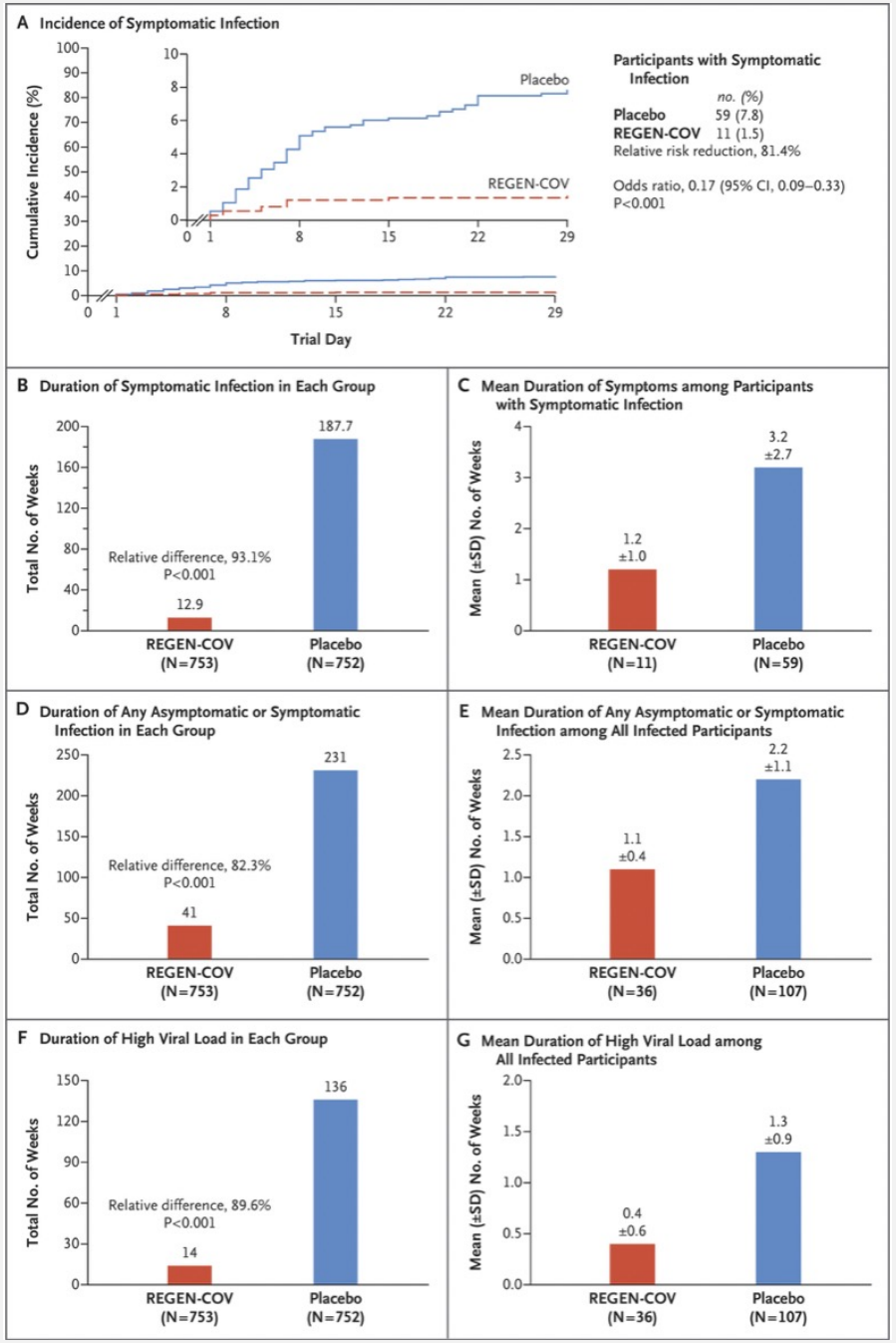
	REGEN-COV 600 mg of casirivimab and 600 mg of imdevimab (intravenous) (n=736)	**Placebo** (n=748)	1,200 mg of casirivimab and 1,200 mg of imdevimab (intravenous) (n=1,335)	Placebo (n=1,341)
# of patients with events	7 (1.0%)	24 (3.2%)	18 (1.3%)	62 (4.6%)
Risk reduction	70% compared to placebo *(P=0.0024)*		71% compared to placebo *(P<0.0001)*	

Results were consistent across subgroups of patients including nasopharyngeal viral load >10^6 copies/mL or serologic status at baseline.

https://www.regencov.com/hcp/clinical-information/primary-endpoint, accessed 9/20/21.



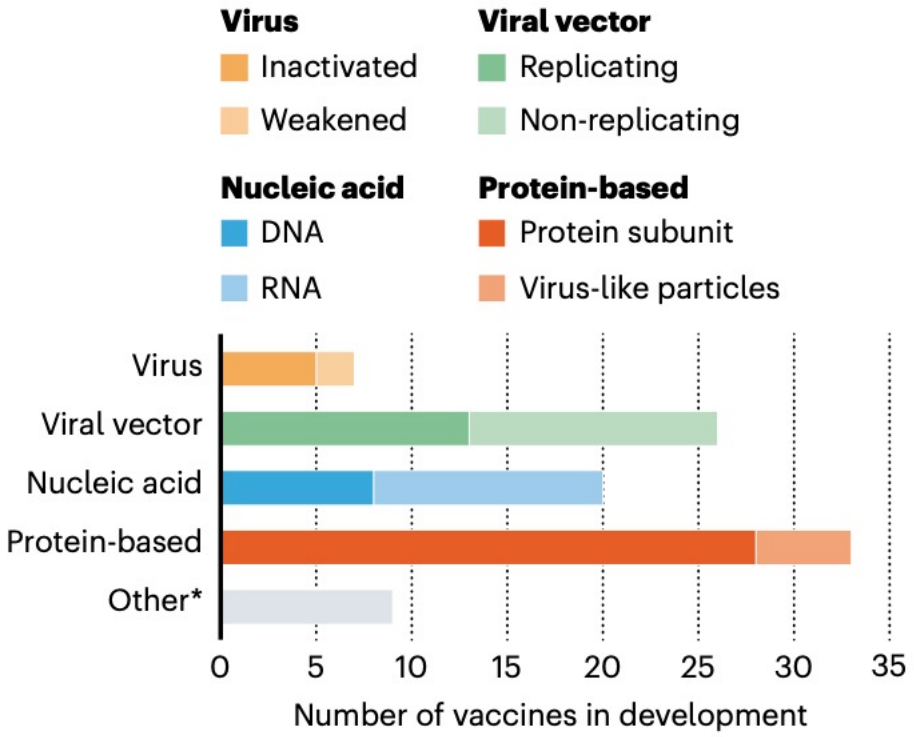
O'Brien MP, Forleo-Neto E, Sarkar N, et al. Covid-19 Phase 3 Prevention Trial Team. Subcutaneous REGEN-COV Antibody Combination in Early SARS-CoV-2 Infection. medRxiv [Preprint]. 2021 Jun 14:2021.06.14.21258569.



O'Brien MP et al. Covid-19 Phase 3 Prevention Trial Team. Subcutaneous REGEN-COV Antibody Combination to Prevent Covid-19. N Engl J Med. 2021 Aug 4:NEJMoa2109682.

AN ARRAY OF VACCINES

All vaccines aim to expose the body to an antigen that won't cause disease, but will provoke an immune response that can block or kill the virus if a person becomes infected. There are at least eight types being tried against the coronavirus, and they rely on different viruses or viral parts.

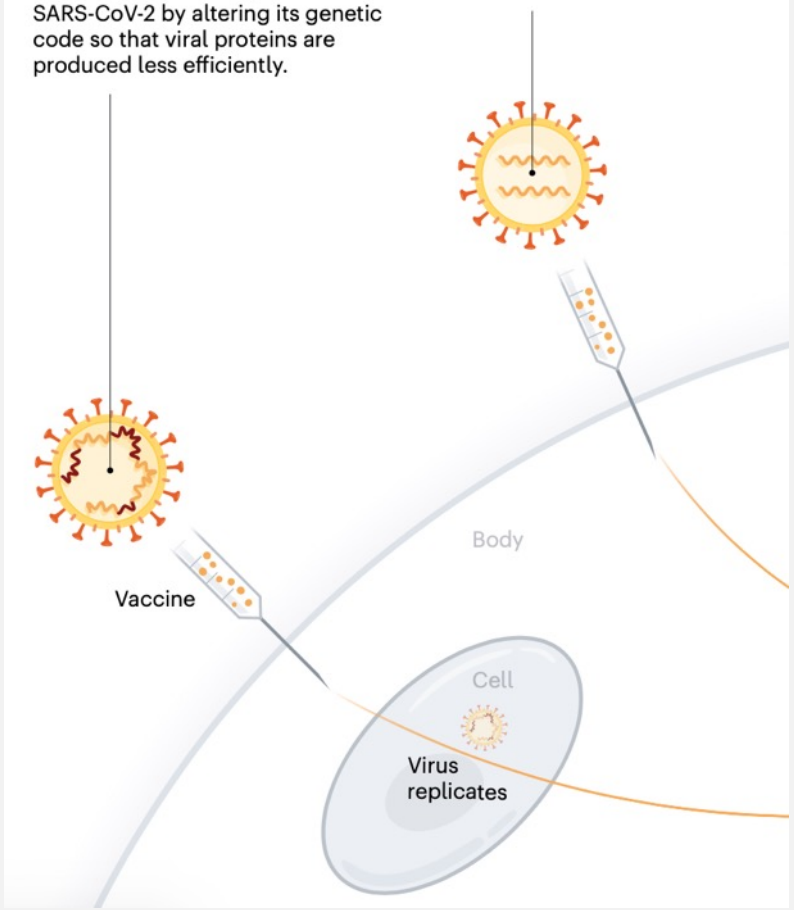


Weakened virus

A virus is conventionally weakened for a vaccine by being passed through animal or human cells until it picks up mutations that make it less able to cause disease. Codagenix in Farmingdale, New York, is working with the Serum Institute of India, a vaccine manufacturer in Pune, to weaken SARS-CoV-2 by altering its genetic code so that viral proteins are produced less efficiently.

Inactivated virus

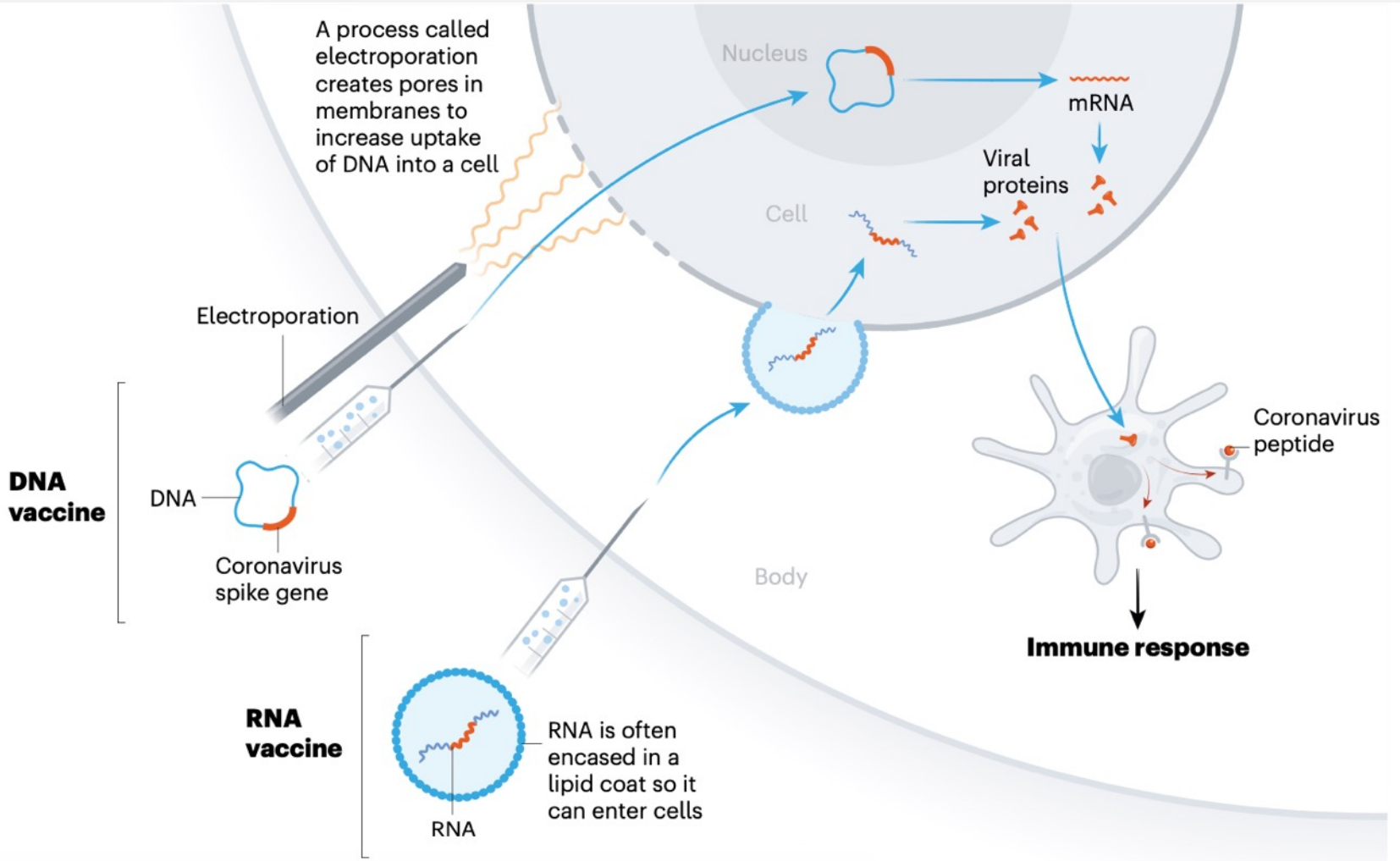
In these vaccines, the virus is rendered uninfectious using chemicals, such as formaldehyde, or heat. Making them, however, requires starting with large quantities of infectious virus.

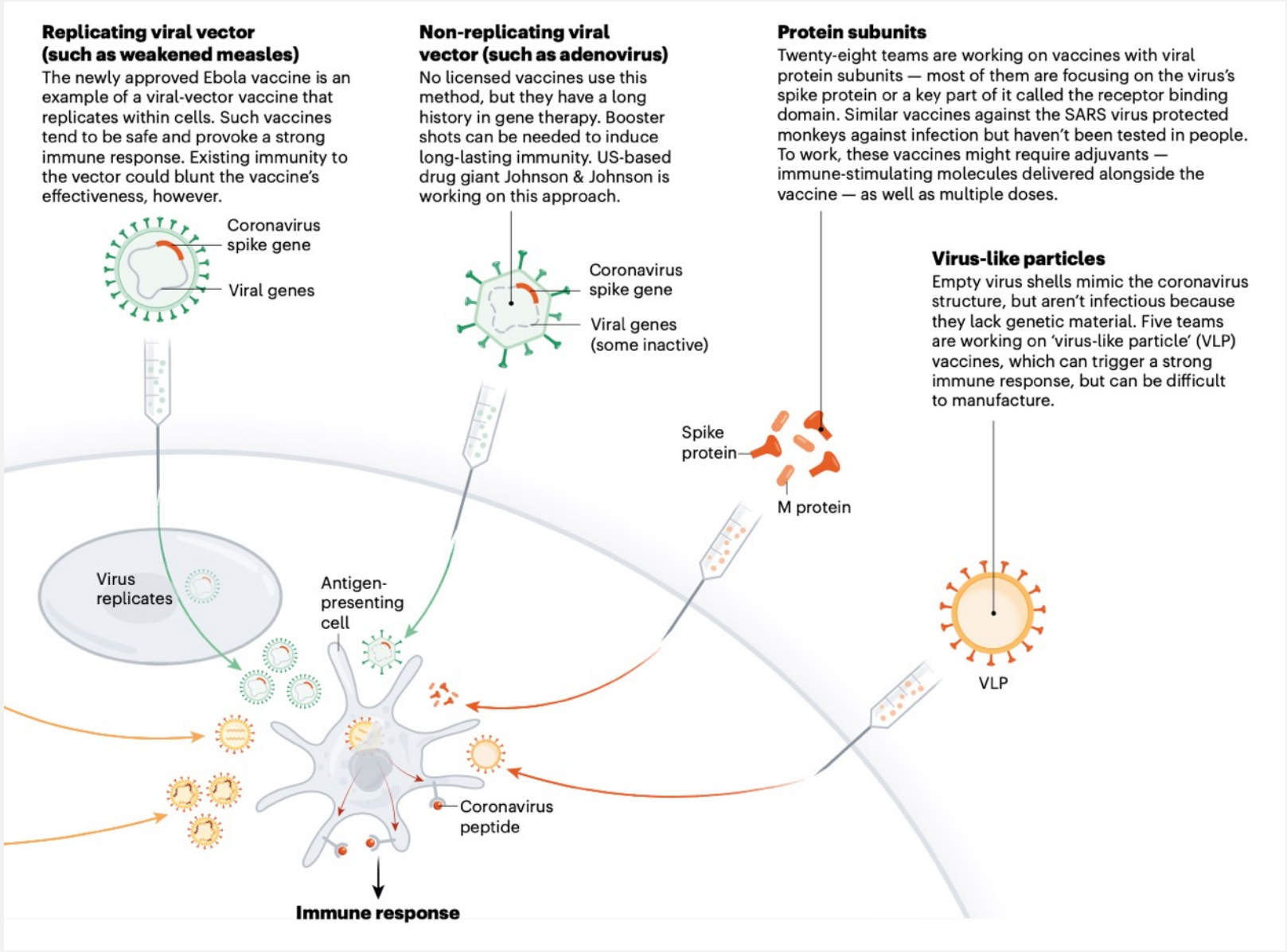


NUCLEIC-ACID VACCINES

At least 20 teams are aiming to use genetic instructions (in the form of DNA or RNA) for a coronavirus protein that prompts an immune response. The nucleic acid is inserted into human cells, which then churn out copies of the virus protein; most of these vaccines encode the virus's spike protein.

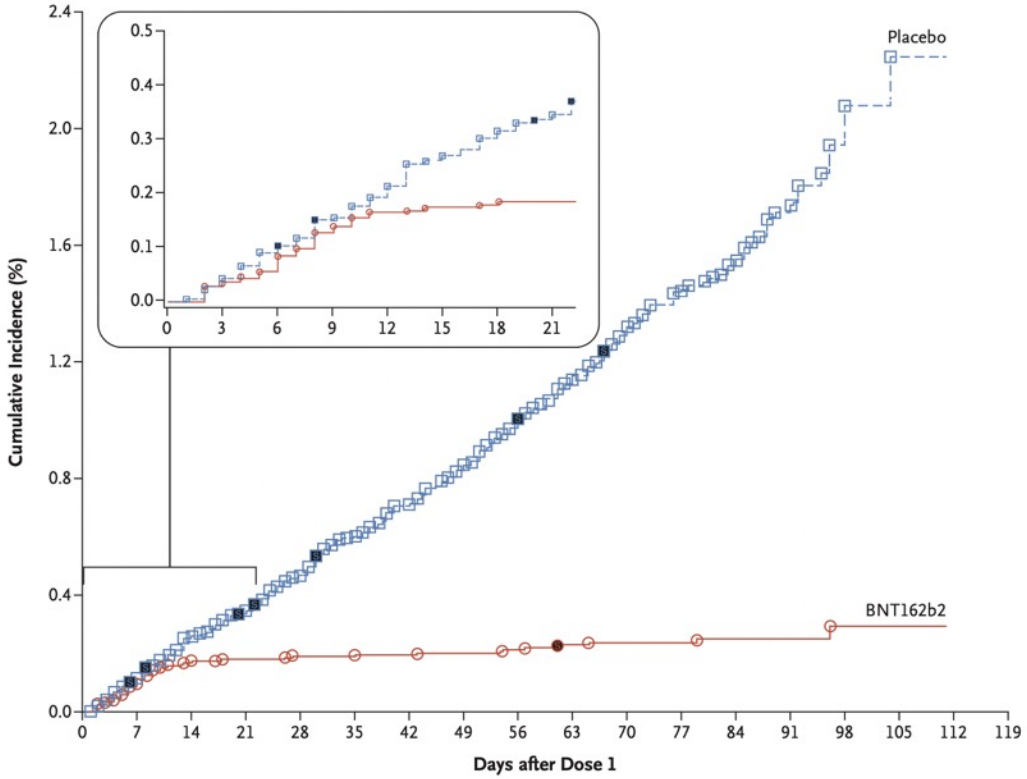
RNA- and DNA-based vaccines are safe and easy to develop: to produce them involves making genetic material only, not the virus. But they are unproven: no licensed vaccines use this technology.




Replicating viral vector (such as weakened measles)
The newly approved Ebola vaccine is an example of a viral-vector vaccine that replicates within cells. Such vaccines tend to be safe and provoke a strong immune response. Existing immunity to the vector could blunt the vaccine's effectiveness, however.
Coronavirus spike gene
Viral genes
Non-replicating viral vector (such as adenovirus)
No licensed vaccines use this method, but they have a long history in gene therapy. Booster shots can be needed to induce long-lasting immunity. US-based drug giant Johnson & Johnson is working on this approach.
Coronavirus spike gene
Viral genes (some inactive)
Protein subunits
Twenty-eight teams are working on vaccines with viral protein subunits — most of them are focusing on the virus's spike protein or a key part of it called the receptor binding domain. Similar vaccines against the SARS virus protected monkeys against infection but haven't been tested in people. To work, these vaccines might require adjuvants — immune-stimulating molecules delivered alongside the vaccine — as well as multiple doses.
Spike protein
M protein
Virus-like particles
Empty virus shells mimic the coronavirus structure, but aren't infectious because they lack genetic material. Five teams are working on 'virus-like particle' (VLP) vaccines, which can trigger a strong immune response, but can be difficult to manufacture.
VLP
Virus replicates
Antigen-presenting cell
Coronavirus peptide
Immune response

The first Pfizer VACCINE trial

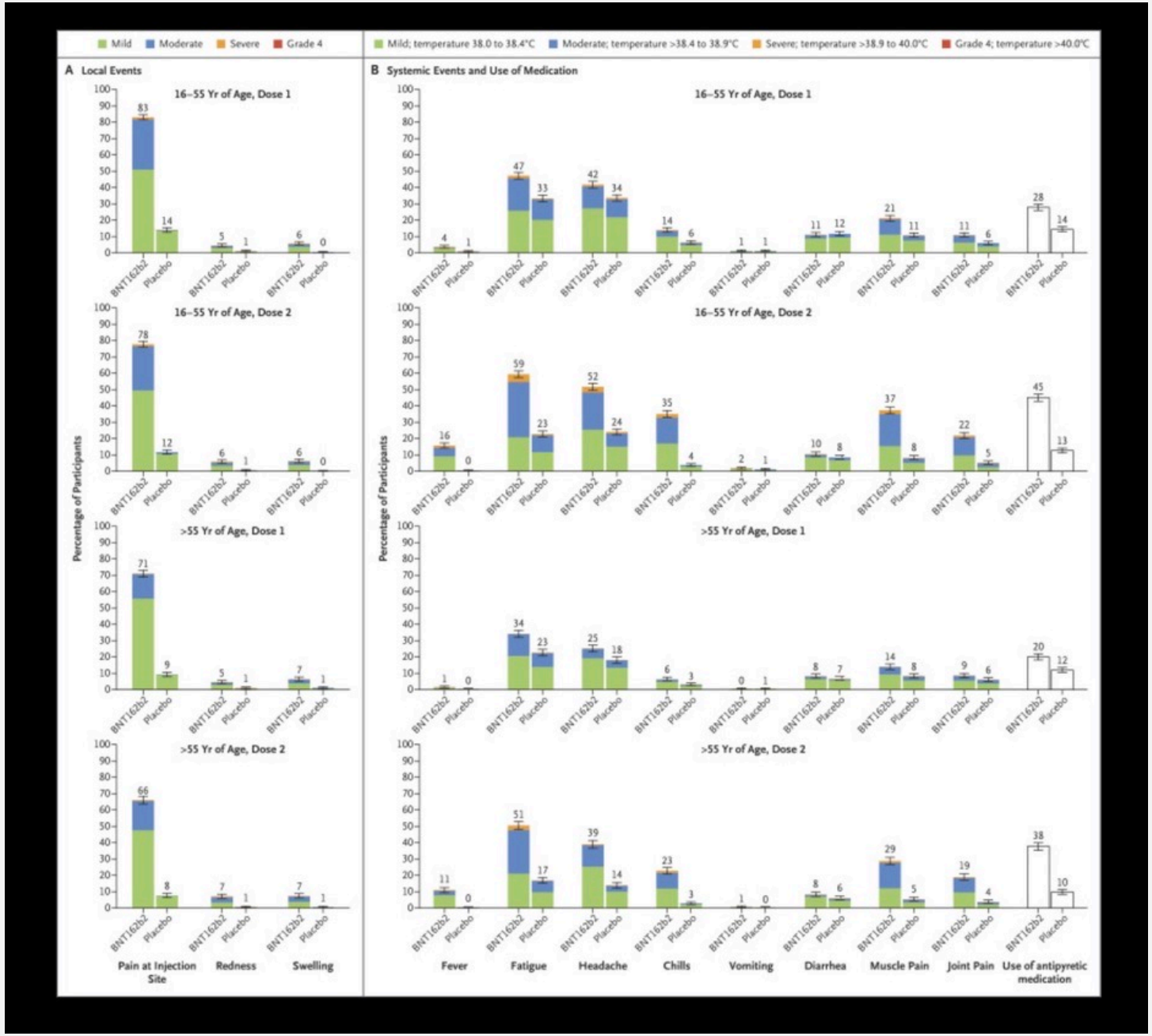
Efficacy End Point	BNT162b2		Placebo		Vaccine Efficacy, % (95% Credible Interval)‡	Posterior Probability (Vaccine Efficacy >30%)§
	No. of Cases	Surveillance Time (n)†	No. of Cases	Surveillance Time (n)†		
		(N=18,198)		(N=18,325)		
Covid-19 occurrence at least 7 days after the second dose in participants without evidence of infection	8	2.214 (17,411)	162	2.222 (17,511)	95.0 (90.3–97.6)	>0.9999
		(N=19,965)		(N=20,172)		
Covid-19 occurrence at least 7 days after the second dose in participants with and those without evidence of infection	9	2.332 (18,559)	169	2.345 (18,708)	94.6 (89.9–97.3)	>0.9999



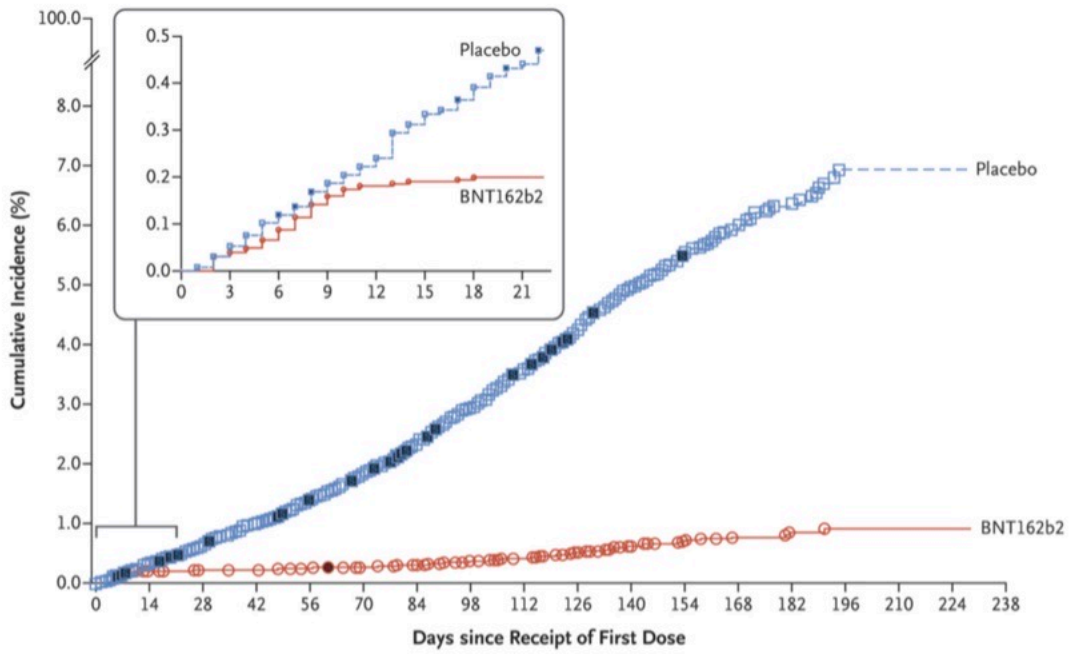
Efficacy End-Point Subgroup	BNT162b2, 30 μg (N=21,669)		Placebo (N=21,686)		VE (95% CI)
	No. of participants	Surveillance time *person-yr (no. at risk)*	No. of participants	Surveillance time *person-yr (no. at risk)*	*percent*
Covid-19 occurrence					
After dose 1	50	4.015 (21,314)	275	3.982 (21,258)	82.0 (75.6–86.9)
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 (61.0–98.9)
≥7 Days after dose 2	9		172		94.8 (89.8–97.6)

Polack FP, Thomas SJ, Kitchin N, Absalon J, Gurtman A, Lockhart S, Perez JL, Pérez Marc G, Moreira ED, Zerbini C, Bailey R, Swanson KA, Roychoudhury S, Koury K, Li P, Kalina WV, Cooper D, Frenck RW Jr, Hammitt LL, Türeci Ö, Nell H, Schaefer A, Ünal S, Tresnan DB, Mather S, Dormitzer PR, Şahin U, Jansen KU, Gruber WC; C4591001 Clinical Trial Group. Safety and Efficacy of the BNT162b2 mRNA Covid-19 Vaccine. N Engl J Med. 2020 Dec 31;383(27):2603-2615. doi: 10.1056/NEJMoa2034577. Epub 2020 Dec 10. PMID: 33301246; PMCID: PMC7745181.

Adverse Effects



Pfizer BNT 162b2 vaccine efficacy up to 6 months of follow up



Efficacy End Point	BNT162b2 (N=23,040) No. of cases	BNT162b2 Surveillance time 1000 person-yr	BNT162b2 No. at risk	Placebo (N=23,037) No. of cases	Placebo Surveillance time 1000 person-yr	Placebo No. at risk	Vaccine Efficacy % (95% CI)
Overall: first occurrence of Covid-19 after receipt of first dose	131	8.412	22,505	1034	8.124	22,434	87.8 (85.3 to 89.9)
After receipt of first dose up to receipt of second dose	46	1.339	22,505	110	1.331	22,434	58.4 (40.8 to 71.2)
<11 Days after receipt of first dose	41	0.677	22,505	50	0.675	22,434	18.2 (−26.1 to 47.3)
≥11 Days after receipt of first dose up to receipt of second dose	5	0.662	22,399	60	0.656	22,369	91.7 (79.6 to 97.4)
After receipt of second dose to <7 days after	3	0.424	22,163	35	0.422	22,057	91.5 (72.9 to 98.3)
≥7 Days after receipt of second dose	82	6.649	22,132	889	6.371	22,001	91.2 (88.9 to 93.0)
≥7 Days after receipt of second dose to <2 mo after	12	2.923	22,132	312	2.884	22,001	96.2 (93.3 to 98.1)
≥2 Mo after receipt of second dose to <4 mo after	46	2.696	20,814	449	2.593	20,344	90.1 (86.6 to 92.9)
≥4 Mo after receipt of second dose	24	1.030	12,670	128	0.895	11,802	83.7 (74.7 to 89.9)

Efficacy End Point	BNT162b2 No. of Cases	BNT162b2 Surveillance Time† 1000 person-yr	BNT162b2 No. at Risk	Placebo No. of Cases	Placebo Surveillance Time† 1000 person-yr	Placebo No. at Risk	Vaccine Efficacy (95% CI)‡ percent
		(N=20,998)			(N=21,096)		
First occurrence of Covid-19 from 7 days after receipt of the second dose among participants without evidence of previous infection	77	6.247	20,712	850	6.003	20,713	91.3 (89.0–93.2)
		(N=22,166)			(N=22,320)		
First occurrence of Covid-19 from 7 days after receipt of the second dose among participants with or without evidence of previous infection	81	6.509	21,642	873	6.274	21,689	91.1 (88.8–93.0)

In an ongoing, placebo-controlled, observer-blinded, multinational, pivotal efficacy trial, we randomly assigned 44,165 participants 16 years of age or older and 2264 participants 12 to 15 years of age to receive two 30-µg doses, at 21 days apart, of BNT162b2 or placebo. The trial end points were vaccine efficacy against laboratory-confirmed Covid-19 and safety, which were both evaluated through 6 months after vaccination.

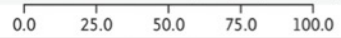
Safety: **No new safety signals**

Thomas SJ, Moreira ED Jr, Kitchin N, Absalon J, Gurtman A, Lockhart S, Perez JL, Pérez Marc G, Polack FP, Zerbini C, Bailey R, Swanson KA, Xu X, Roychoudhury S, Koury K, Bouguermouh S, Kalina WV, Cooper D, Frenck RW Jr, Hammitt LL, Türeci Ö, Nell H, Schaefer A, Ünal S, Yang Q, Liberator P, Tresnan DB, Mather S, Dormitzer PR, Şahin U, Gruber WC, Jansen KU; C4591001 Clinical Trial Group. Safety and Efficacy of the BNT162b2 mRNA Covid-19 Vaccine through 6 Months. N Engl J Med. 2021 Sep 15. doi: 10.1056/NEJMoa2110345. Epub ahead of print. PMID: 34525277.

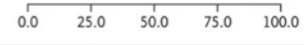
Test neg design
COVID like illness pts
Tested for SARS-COV2
Vaccination status
compared between the groups

VACCINE EFFICACY: Ambulatory and Inpatient Settings

Subgroup	No. of Patients	Positive for SARS-CoV-2 no. (%)	Vaccine Effectiveness (95% CI) %
Effectiveness against hospitalization			
BNT162b2 vaccine			
Unvaccinated (referent)	20,406	3695 (18.1)	
Partially vaccinated			
Dose 1	1,444	140 (9.7)	33 (18–46)
Dose 2	1,348	57 (4.2)	73 (63–81)
Fully vaccinated — 2 doses	8,500	163 (1.9)	87 (85–90)
mRNA-1273 vaccine			
Unvaccinated (referent)	20,406	3695 (18.1)	
Partially vaccinated			
Dose 1	1,639	91 (5.6)	68 (59–75)
Dose 2	1,134	50 (4.4)	74 (64–82)
Fully vaccinated — 2 doses	6,374	95 (1.5)	91 (89–93)
Ad26.COV2.S vaccine			
Unvaccinated (referent)	10,761	2006 (18.6)	
Fully vaccinated — 1 dose	707	30 (4.2)	68 (50–79)
Effectiveness against ICU admission			
BNT162b2 vaccine or mRNA-1273 vaccine			
Unvaccinated (referent)	4,024	692 (17.2)	
Partially vaccinated			
Dose 1	512	39 (7.6)	56 (35–70)
Dose 2	388	15 (3.9)	75 (58–86)
Fully vaccinated — 2 doses	2,359	38 (1.6)	90 (86–93)
Effectiveness against emergency department or urgent care visit			
BNT162b2 vaccine			
Unvaccinated (referent)	11,812	2847 (24.1)	
Partially vaccinated			
Dose 1	912	88 (9.6)	58 (46–68)
Dose 2	711	31 (4.4)	82 (74–88)
Fully vaccinated — 2 doses	3,589	105 (2.9)	89 (85–91)
mRNA-1273 vaccine			
Unvaccinated (referent)	11,812	2847 (24.1)	
Partially vaccinated			
Dose 1	1,008	67 (6.6)	73 (64–79)
Dose 2	558	35 (6.3)	72 (59–81)
Fully vaccinated — 2 doses	2,476	49 (2.0)	92 (89–94)
Ad26.COV2.S vaccine			
Unvaccinated (referent)	8,461	2200 (26.0)	
Fully vaccinated — 1 dose	456	29 (6.4)	73 (59–82)



Subgroup	No. of Patients	Positive for SARS-CoV-2 no. (%)	Vaccine Effectiveness (95% CI) %
Effectiveness against hospitalization			
≥50 yr of age			
Unvaccinated (referent)	20,406	3695 (18.1)	
Partially vaccinated			
Dose 1	3,083	231 (7.5)	54 (47–61)
Dose 2	2,482	107 (4.3)	73 (66–79)
Fully vaccinated — 2 doses	14,874	258 (1.7)	89 (87–91)
≥85 yr of age			
Unvaccinated (referent)	2,960	447 (15.1)	
Partially vaccinated			
Dose 1	549	41 (7.5)	38 (11–57)
Dose 2	448	27 (6.0)	56 (32–72)
Fully vaccinated — 2 doses	3,306	68 (2.1)	83 (77–87)
≥50 yr of age with ≥1 chronic respiratory condition			
Unvaccinated (referent)	13,018	2359 (18.1)	
Partially vaccinated			
Dose 1	2,033	140 (6.9)	56 (47–64)
Dose 2	1,634	62 (3.8)	76 (68–82)
Fully vaccinated — 2 doses	10,257	152 (1.5)	90 (88–92)
≥50 yr of age with ≥1 chronic nonrespiratory condition			
Unvaccinated (referent)	18,089	3043 (16.8)	
Partially vaccinated			
Dose 1	2835	201 (7.1)	54 (45–61)
Dose 2	2302	97 (4.2)	71 (62–77)
Fully vaccinated — 2 doses	13,999	240 (1.7)	88 (86–90)
Black and ≥50 yr of age			
Unvaccinated (referent)	2,393	436 (18.2)	
Partially vaccinated			
Dose 1	269	21 (7.8)	47 (10–69)
Dose 2	194	7 (3.6)	75 (36–90)
Fully vaccinated — 2 doses	961	20 (2.1)	86 (75–92)
Hispanic and ≥50 yr of age			
Unvaccinated (referent)	2,376	656 (27.6)	
Partially vaccinated			
Dose 1	307	36 (11.7)	56 (35–70)
Dose 2	264	16 (6.1)	80 (63–89)
Fully vaccinated — 2 doses	1,540	35 (2.3)	90 (85–93)
Effectiveness against ICU admission			
≥50 yr of age			
Unvaccinated (referent)	4,024	692 (17.2)	
Partially vaccinated			
Dose 1	512	39 (7.6)	56 (35–70)
Dose 2	388	15 (3.9)	75 (58–86)
Fully vaccinated — 2 doses	2,359	38 (1.6)	90 (86–93)



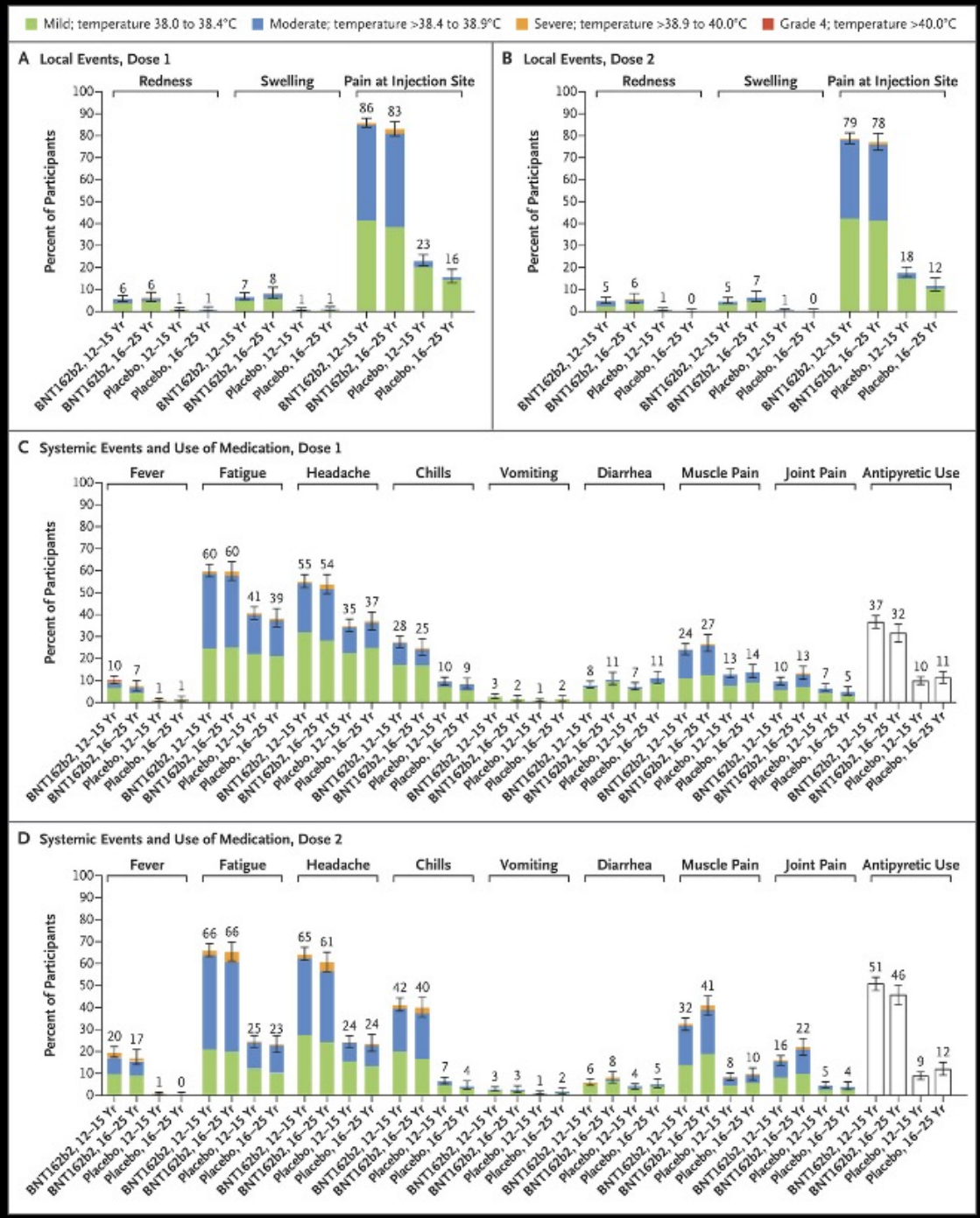
Thompson MG, Stenehjem E, Grannis S, Ball SW, at al. Effectiveness of Covid-19 Vaccines in Ambulatory and Inpatient Care Settings. N Engl J Med. 2021 Sep 8. doi: 10.1056/NEJMoa2110362. Epub ahead of print. PMID: 34496194.

BNT 162b2 vaccine efficacy in adolescents

Table 3. Vaccine Efficacy against Covid-19 in Participants 12 to 15 Years of Age.*

Efficacy End Point†	BNT162b2		Placebo		% Vaccine Efficacy (95% CI)‡
	No. of Participants with Event/Total No.§	Surveillance Time (No. at Risk)¶	No. of Participants with Event/Total No.§	Surveillance Time (No. at Risk)¶	
Covid-19 occurrence at least 7 days after dose 2 in participants without evidence of previous infection	0/1005	0.154 (1001)	16/978	0.147 (972)	100 (75.3–100)
Covid-19 occurrence at least 7 days after dose 2 in participants with or without evidence of previous infection	0/1119	0.170 (1109)	18/1110	0.163 (1094)	100 (78.1–100)

Frenck RW Jr, Klein NP, Kitchin N, Gurtman A, Absalon J, Lockhart S, Perez JL, Walter EB, Senders S, Bailey R, Swanson KA, Ma H, Xu X, Koury K, Kalina WV, Cooper D, Jennings T, Brandon DM, Thomas SJ, Türeci Ö, Tresnan DB, Mather S, Dormitzer PR, Şahin U, Jansen KU, Gruber WC; C4591001 Clinical Trial Group. Safety, Immunogenicity, and Efficacy of the BNT162b2 Covid-19 Vaccine in Adolescents. N Engl J Med. 2021 Jul 15;385(3):239-250. doi: 10.1056/NEJMoa2107456. Epub 2021 May 27. PMID: 34043894; PMCID: PMC8174030.


Mild; temperature 38.0 to 38.4°C
Moderate; temperature >38.4 to 38.9°C
Severe; temperature >38.9 to 40.0°C
Grade 4; temperature >40.0°C
A Local Events, Dose 1
B Local Events, Dose 2
C Systemic Events and Use of Medication, Dose 1
D Systemic Events and Use of Medication, Dose 2
Redness
Swelling
Pain at Injection Site
Fever
Fatigue
Headache
Chills
Vomiting
Diarrhea
Muscle Pain
Joint Pain
Antipyretic Use
Percent of Participants
BNT162b2, 12–15 Yr
BNT162b2, 16–25 Yr
Placebo, 12–15 Yr
Placebo, 16–25 Yr

Effectiveness of Covid-19 Vaccines against the B.1.617.2 (Delta) Variant

Lopez Bernal J et al. DOI: 10.1056/NEJMoa2108891

CLINICAL PROBLEM

The B.1.617.2 (delta) variant of SARS-CoV-2 became the dominant variant in India as of mid-April 2021, amid a Covid-19 surge there, and has spread rapidly around the world. The effectiveness of available vaccines in preventing symptomatic disease with this variant is unknown.

CLINICAL TRIAL

Design: A test-negative case–control study was conducted to estimate the effectiveness of the BNT162b2 (Pfizer–BioNTech) and ChAdOx1 nCoV-19 (AstraZeneca) vaccines against symptomatic disease from the delta variant of SARS-CoV-2.

Methods: Researchers examined data from symptomatic persons 16 years of age or older who underwent Covid-19 testing in England between October 2020 and May 2021. To estimate vaccine effectiveness, they assessed vaccination status in 4272 persons who tested positive for the delta variant and in 14,837 who tested positive for the B.1.1.7 (alpha) variant (the predominant strain in England at the time), as compared with test-negative controls.

RESULTS

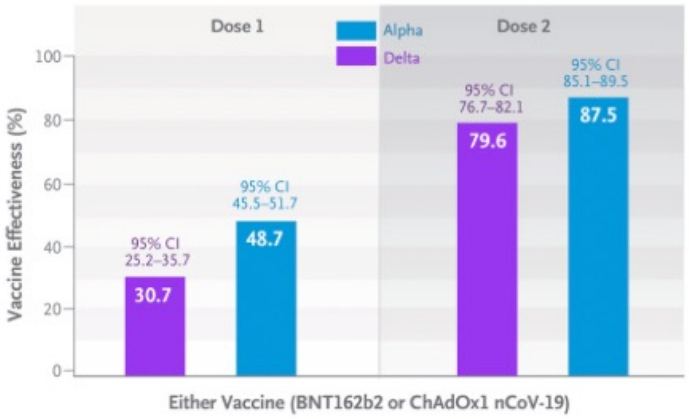
Effectiveness: After one dose of either vaccine, the estimated effectiveness was lower against delta than against alpha. After two doses, however, vaccine effectiveness was high, with only modest differences between the variants. The effectiveness of two doses against delta was lower with ChAdOx1 nCoV-19 than with BNT162b2.

LIMITATIONS AND REMAINING QUESTIONS

- How well do Covid-19 vaccines protect against severe disease, including hospitalization and death, from infection with the delta variant?

Links: Full Article | NEJM Quick Take | Editorial

Vaccine Effectiveness against the Delta and Alpha Variants



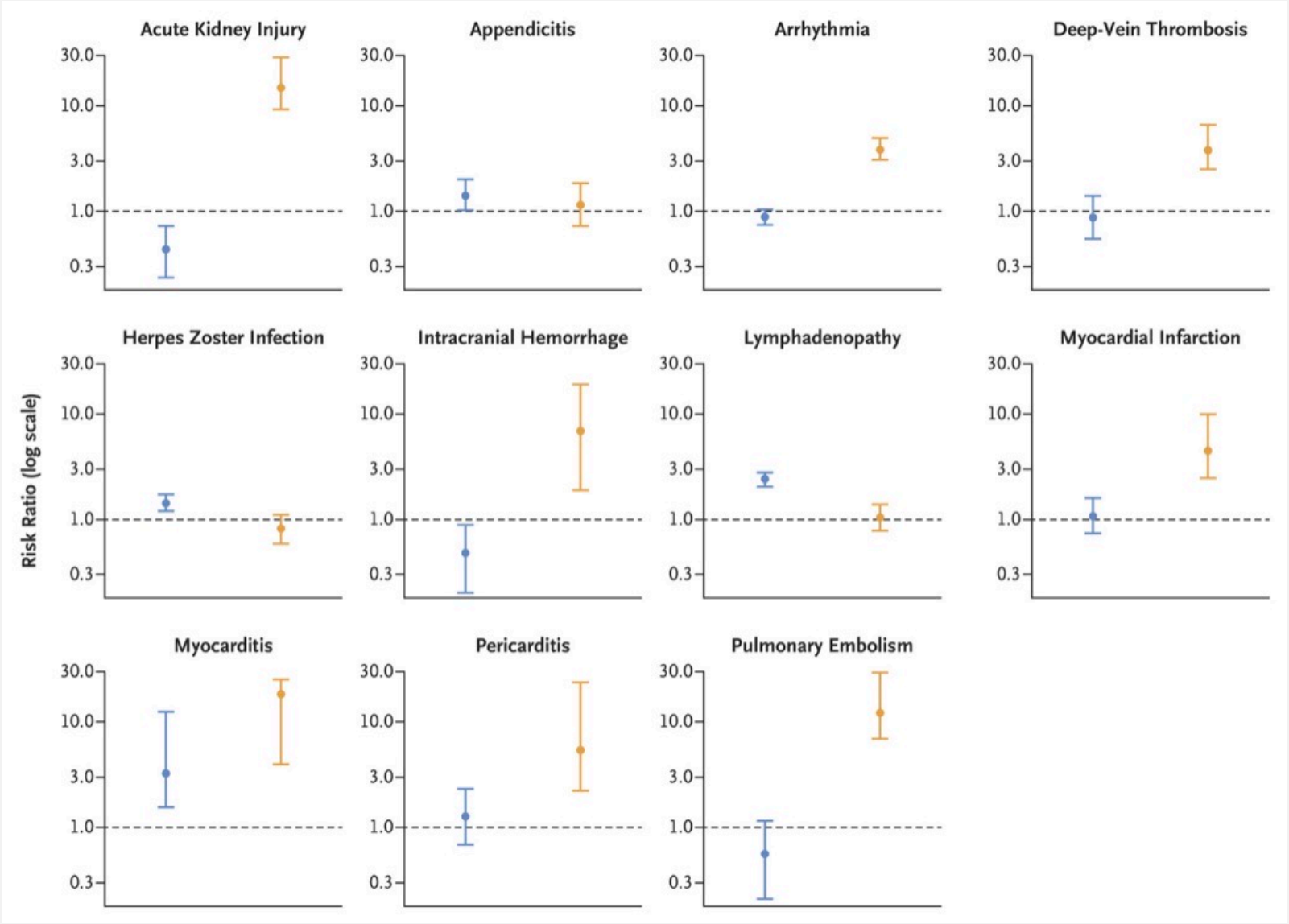
Vaccine Effectiveness against the Delta Variant after Dose 2

CONCLUSIONS

Two doses of the BNT162b2 or ChAdOx1 nCoV-19 vaccine were highly effective against the delta variant of SARS-CoV-2, although slightly less so than against the alpha variant.

Comparison of Adverse events after Vaccination (blue) v SARS-COV2 infection ()

- 880,000 vaccinated persons and similar number of controls
- 173, 000 SARS-COV2 infection persons and similar number of controls



Barda N, Dagan N, Ben-Shlomo Y, Kepten E, Waxman J, Ohana R, Hernán MA, Lipsitch M, Kohane I, Netzer D, Reis BY, Balicer RD. Safety of the BNT162b2 mRNA Covid-19 Vaccine in a Nationwide Setting. N Engl J Med. 2021 Sep 16;385(12):1078-1090. doi: 10.1056/NEJMoa2110475. Epub 2021 Aug 25. PMID: 34432976; PMCID: PMC8427535.

Vaccine Related Adverse Events versus Control persons in Israel – Nationwide setting

Event	Adverse-Event Cohort in Each Group	Vaccinated Group	Control Group	Risk Ratio (95% CI)	Risk Difference (95% CI)
	no. of persons	*no. of events*			*no. of events/100,000 persons*
Acute kidney injury	912,019	20	45	0.44 (0.23 to 0.73)	−4.6 (−7.8 to −1.8)
Anemia	709,267	298	378	0.79 (0.67 to 0.93)	−18.7 (−32.1 to −6.1)
Appendicitis	900,289	95	66	1.40 (1.02 to 2.01)	5.0 (0.3 to 9.9)
Arrhythmia	856,152	254	284	0.89 (0.74 to 1.04)	−6.1 (−14.7 to 1.8)
Arthritis or arthropathy	731,340	64	70	0.95 (0.65 to 1.34)	−0.8 (−6.3 to 4.2)
Bell's palsy	923,692	81	59	1.32 (0.92 to 1.86)	3.5 (−1.1 to 7.8)
Cerebrovascular accident	917,598	45	55	0.84 (0.54 to 1.27)	−1.6 (−5.3 to 2.0)
Deep-vein thrombosis	925,380	39	47	0.87 (0.55 to 1.40)	−1.1 (−4.5 to 2.7)
Herpes simplex infection	876,328	219	205	1.13 (0.95 to 1.38)	4.8 (−1.9 to 12.4)
Herpes zoster infection	888,647	283	204	1.43 (1.20 to 1.73)	15.8 (8.2 to 24.2)
Intracranial hemorrhage	933,130	13	30	0.48 (0.20 to 0.89)	−2.9 (−5.6 to −0.5)
Lymphadenopathy	823,006	660	279	2.43 (2.05 to 2.78)	78.4 (64.1 to 89.3)
Lymphopenia	938,939	2	7	0.26 (0.00 to 1.03)	−0.9 (−2.0 to <0.1)
Myocardial infarction	892,785	59	60	1.07 (0.74 to 1.60)	0.8 (−3.3 to 5.2)
Myocarditis	938,812	21	6	3.24 (1.55 to 12.44)	2.7 (1.0 to 4.6)
Neutropenia	919,291	20	22	0.87 (0.46 to 1.66)	−0.5 (−2.8 to 1.8)
Other thrombosis†	932,469	12	22	0.46 (0.19 to 0.91)	−2.2 (−4.6 to −0.3)
Paresthesia	827,478	552	496	1.12 (0.98 to 1.24)	10.8 (−1.8 to 21.4)
Pericarditis	936,197	27	18	1.27 (0.68 to 2.31)	1.0 (−1.6 to 3.4)
Pulmonary embolism	937,116	10	17	0.56 (0.21 to 1.15)	−1.5 (−3.6 to 0.4)
Seizure	913,091	36	35	0.99 (0.62 to 1.64)	−0.4 (−3.0 to 3.1)
Syncope	858,068	326	267	1.12 (0.94 to 1.34)	6.2 (−3.2 to 15.4)
Thrombocytopenia	923,123	56	60	0.94 (0.63 to 1.27)	−0.6 (−4.6 to 2.3)
Uveitis	933,217	26	20	1.27 (0.68 to 2.67)	1.0 (−1.5 to 3.8)
Vertigo	773,263	433	395	1.12 (0.97 to 1.28)	9.3 (−2.5 to 20.0)

Barda N, Dagan N, Ben-Shlomo Y, Kepten E, Waxman J, Ohana R, Hernán MA, Lipsitch M, Kohane I, Netzer D, Reis BY, Balicer RD. Safety of the BNT162b2 mRNA Covid-19 Vaccine in a Nationwide Setting. N Engl J Med. 2021 Sep 16;385(12):1078-1090. doi: 10.1056/NEJMoa2110475. Epub 2021 Aug 25. PMID: 34432976; PMCID: PMC8427535.

Waning of Immunity / Boosters

Figure 3: Rate of documented SARS-CoV-2 infection (per 1,000 persons) from July 11, 2021 to July 31, 2021, stratified by period of second dose of COVID-19 vaccine and age group. White bars represent periods at which only persons at higher risk were allowed to receive vaccination.

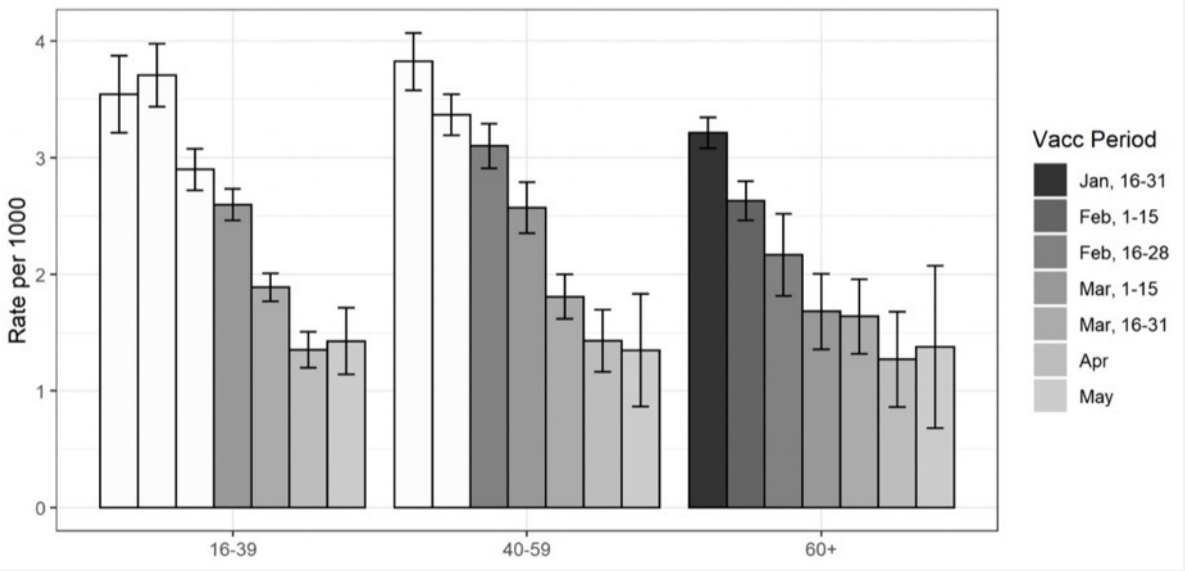
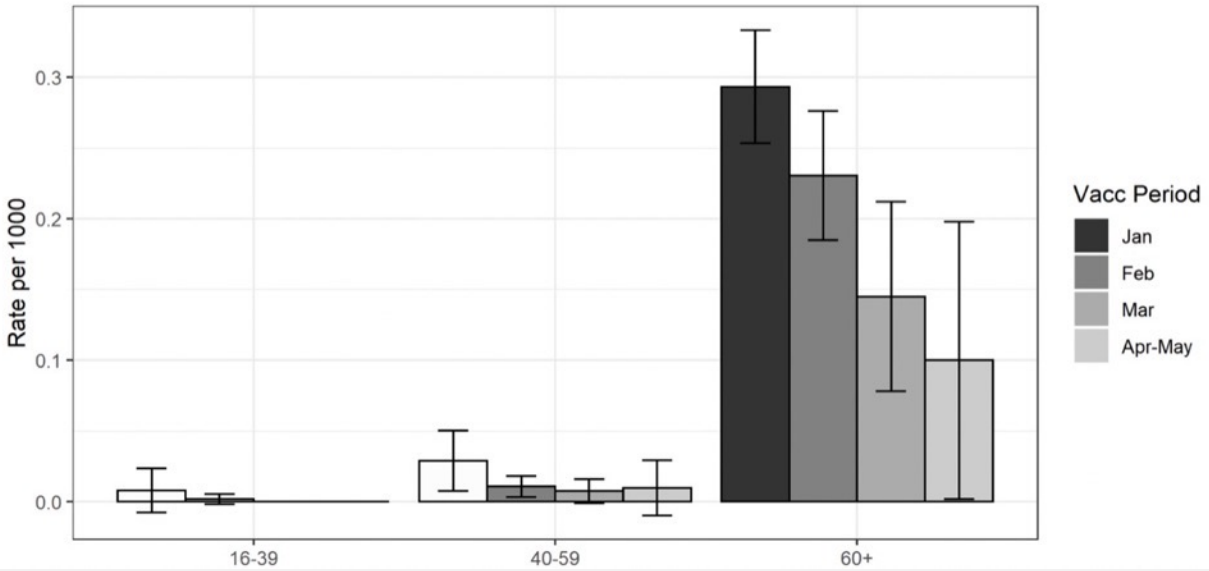


Figure 4: Rate of severe COVID-19 (per 1,000 persons) from July 11, 2021 to July 31, 2021, stratified by period of second dose of COVID-19 vaccine and age group. White bars represent periods at which only persons at higher risk were allowed to receive vaccination.



Waning immunity of the BNT162b2 vaccine: A nationwide study from Israel

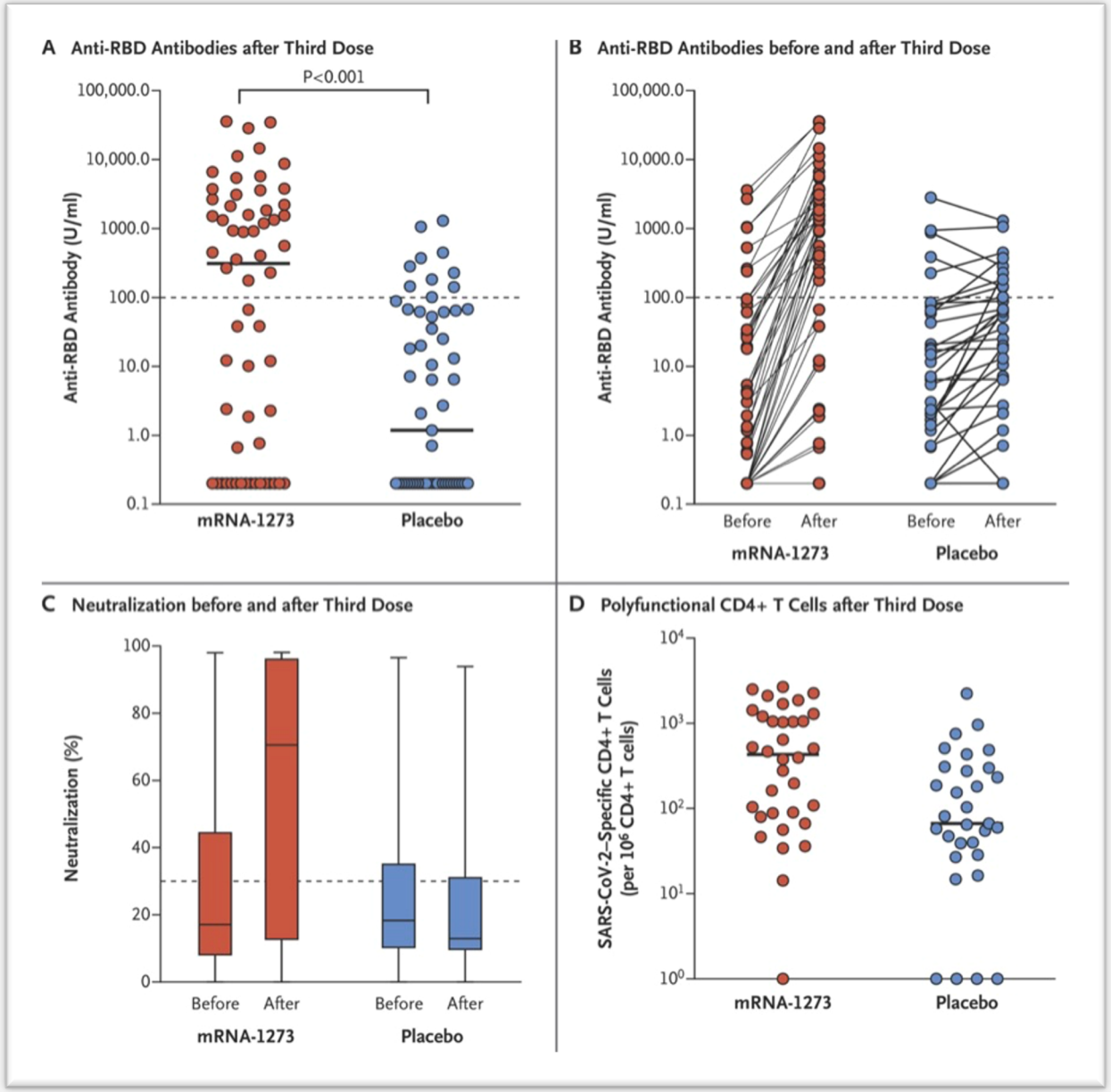
Yair Goldberg, Micha Mandel, Yinon M. Bar-On, Omri Bodenheimer, LaurenceFreedman, Eric J. Haas, Ron Milo, Sharon Alroy-Preis, Nachman Ash, Amit Hupper

medRxiv 2021.08.24.21262423; doi:https://doi.org/10.1101/2021.08.24.21262423

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

Bar-On YM, Goldberg Y, Mandel M, Bodenheimer O, Freedman L, Kalkstein N, Mizrahi B, Alroy-Preis S, Ash N, Milo R, Huppert A. Protection of BNT162b2 Vaccine Booster against Covid-19 in Israel. N Engl J Med. 2021 Sep 15. doi: 10.1056/NEJMoa2114255. Epub ahead of print. PMID: 34525275.

Immunology Case for Boosters in Immune Compromised Individuals

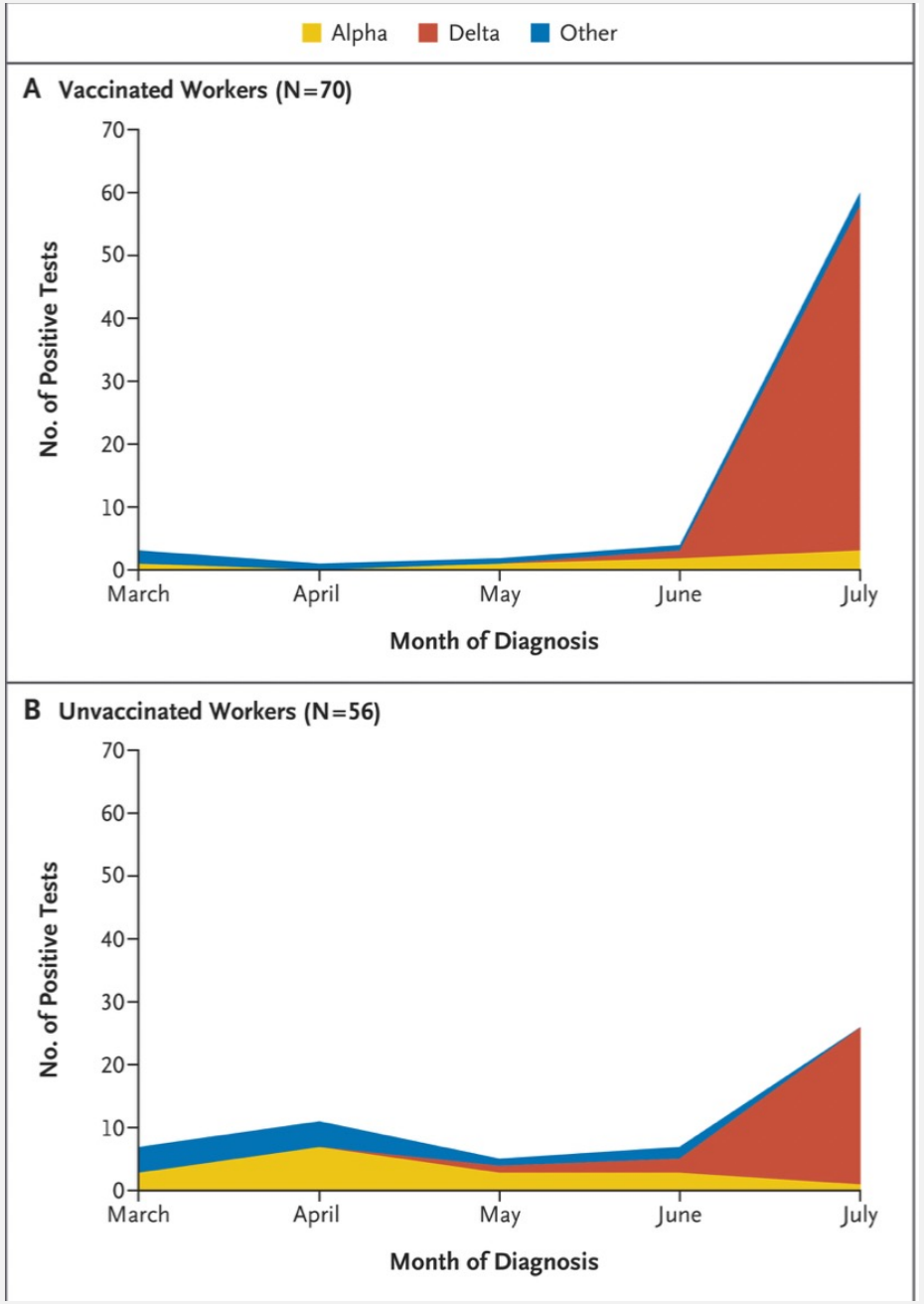


Hall VG, Ferreira VH, Ku T, Ierullo M, Majchrzak-Kita B, Chaparro C, Selzner N, Schiff J, McDonald M, Tomlinson G, Kulasingam V, Kumar D, Humar A. Randomized Trial of a Third Dose of mRNA-1273 Vaccine in Transplant Recipients. N Engl J Med. 2021 Aug 11:NEJMc2111462. doi: 10.1056/NEJMc2111462. Epub ahead of print. PMID: 34379917; PMCID: PMC8385563.

Drop in Vaccine Efficacy: UCSD experience

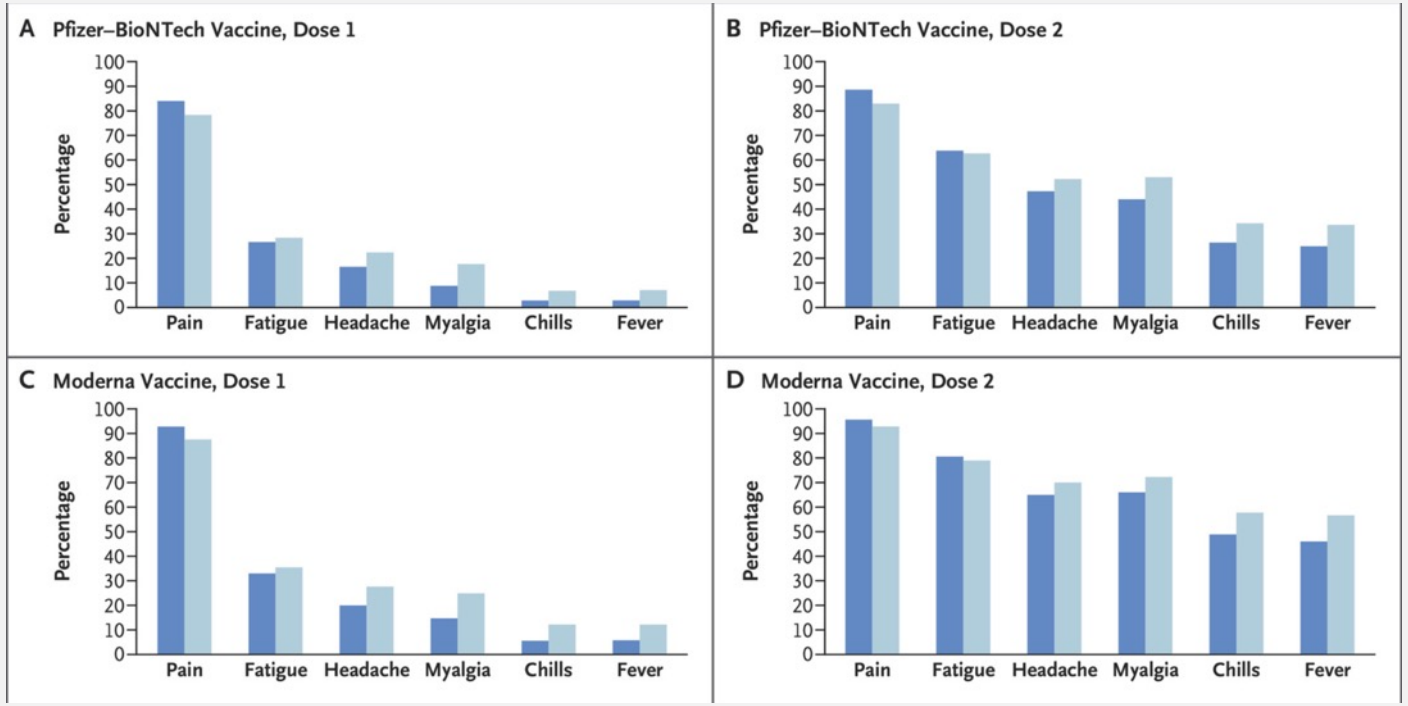
Table 1. Symptomatic SARS-CoV-2 Infection and mRNA Vaccine Effectiveness among UCSDH Health Workers, March through July 2021.*

	March	April	May	June	July
UCSDH workforce — no. of persons	18,964	18,992	19,000	19,035	19,016
Vaccination status — no. of persons					
Fully vaccinated†	14,470	15,510	16,157	16,426	16,492
mRNA-1273 (Moderna)	6,608	7,005	7,340	7,451	7,464
BNT162b2 (Pfizer–BioNTech)	7,862	8,505	8,817	8,975	9,028
Unvaccinated	3,230	2,509	2,187	2,059	1,895
Percentage of workers fully vaccinated	76.3	81.7	85.0	86.3	86.7
Symptomatic Covid-19					
Fully vaccinated workers	3	4	3	5	94
Unvaccinated workers	11	17	10	10	31
Percentage of cases in fully vaccinated workers	21.4	19.0	23.1	33.3	75.2
Attack rate per 1000 (95% CI)					
Fully vaccinated workers	0.21 (0.21–0.47)	0.26 (0.26–0.50)	0.19 (0.21–0.40)	0.30 (0.31–0.53)	5.7 (5.4–6.2)
Unvaccinated workers	3.4 (2.1–5.9)	6.8 (4.5–10.6)	4.6 (2.6–8.2)	4.9 (2.9–8.7)	16.4 (11.8–22.9)
Vaccine effectiveness — % (95% CI)	93.9 (78.2–97.9)	96.2 (88.7–98.3)	95.9 (85.3–98.9)	94.3 (83.7–98.0)	65.5 (48.9–76.9)



Keehner J, Horton LE, Binkin NJ, Laurent LC, Pride D, Longhurst CA, Abeles SR, Torriani FJ. Resurgence of SARS-CoV-2 Infection in a Highly Vaccinated Health System Workforce. N Engl J Med. 2021 Sep 1. doi: 10.1056/NEJMc2112981. Epub ahead of print. PMID: 34469645.

Vaccine Safety in Pregnant Women – approximately 3900 pregnancies



Participant-Reported Outcome	Published Incidence*	V-safe Pregnancy Registry†
	%	*no./total no. (%)*
Pregnancy loss among participants with a completed pregnancy		
Spontaneous abortion: <20 wk[15-17]‡	Not applicable	104
Stillbirth: ≥ 20 wk[18-20]	<1	1/725 (0.1)§
Neonatal outcome among live-born infants		
Preterm birth: <37 wk[21,22]	8–15	60/636 (9.4)¶
Small size for gestational age[23,24]‖	3.5	23/724 (3.2)
Congenital anomalies[25]**	3	16/724 (2.2)
Neonatal death[26]††	<1	0/724

Characteristic	Pfizer–BioNTech Vaccine	Moderna Vaccine	Total
		number (percent)	
Total	19,252 (53.9)	16,439 (46.1)	35,691 (100)
Age at first vaccine dose			
16–19 yr	23 (0.1)	36 (0.2)	59 (0.2)
20–24 yr	469 (2.4)	525 (3.2)	994 (2.8)
25–34 yr	11,913 (61.9)	9,960 (60.6)	21,873 (61.3)
35–44 yr	6,002 (31.2)	5,011 (30.5)	11,013 (30.9)
45–54 yr	845 (4.4)	907 (5.5)	1,752 (4.9)
Pregnancy status			
Pregnant at time of vaccination	16,522 (85.8)	14,365 (87.4)	30,887 (86.5)
Positive pregnancy test after vaccination	2,730 (14.2)	2,074 (12.6)	4,804 (13.5)
Race and ethnic group†			
Participants with available data	14,320	13,232	27,552
Non-Hispanic White	10,915 (76.2)	9,982 (75.4)	20,897 (75.8)
Hispanic	1,289 (9.0)	1,364 (10.3)	2,653 (9.6)
Non-Hispanic Asian	972 (6.8)	762 (5.8)	1,734 (6.3)
Non-Hispanic Black	371 (2.6)	338 (2.6)	709 (2.6)
Non-Hispanic multiple races	315 (2.2)	292 (2.2)	607 (2.2)
Non-Hispanic other race	76 (0.5)	56 (0.4)	132 (0.5)
Non-Hispanic American Indian or Alaska Native	40 (0.3)	54 (0.4)	94 (0.3)
Non-Hispanic Native Hawaiian or other Pacific Islander	33 (0.2)	31 (0.2)	64 (0.2)
Unknown race or unknown ethnic group	309 (2.2)	353 (2.7)	662 (2.4)

Shimabukuro TT, Kim SY, Myers TR, Moro PL, Oduyebo T, Panagiotakopoulos L, Marquez PL, Olson CK, Liu R, Chang KT, Ellington SR, Burkel VK, Smoots AN, Green CJ, Licata C, Zhang BC, Alimchandani M, Mba-Jonas A, Martin SW, Gee JM, Meaney-Delman DM; CDC v-safe COVID-19 Pregnancy Registry Team. Preliminary Findings of mRNA Covid-19 Vaccine Safety in Pregnant Persons. N Engl J Med. 2021 Jun 17;384(24):2273-2282. doi: 10.1056/NEJMoa2104983. Epub 2021 Apr 21.

No difference in cumulative risk of spontaneous abortion in pregnant women vaccinated before or during pregnancy compared to historical cohorts

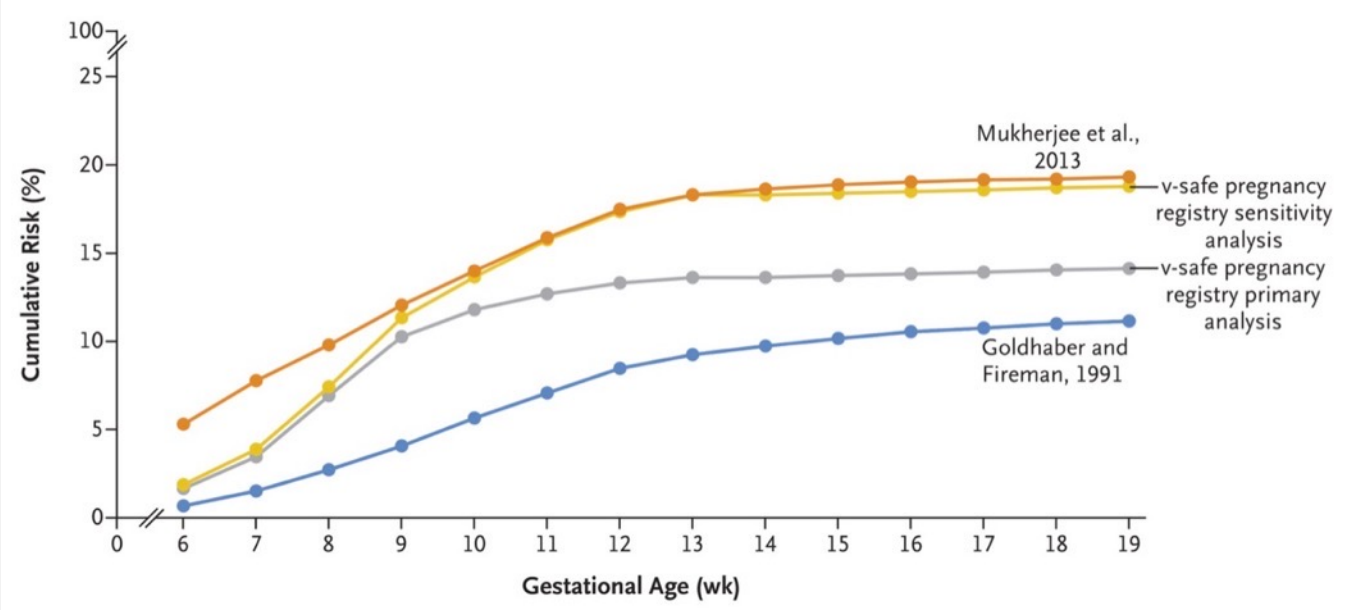


Table 1. Risk of Spontaneous Abortion among Participants in the v-safe Covid-19 Vaccine Pregnancy Registry, December 14, 2020, through July 19, 2021.

Gestational Age	Participants at Risk	Participants Who Reported Spontaneous Abortion	Week-Specific Risk	Cumulative Risk
	number of persons		*percent*	*percent (95% CI)*
6 to <7 weeks	904	15	1.7	1.7 (0.8–2.5)
7 to <8 weeks	982	18	1.8	3.5 (2.3–4.6)
8 to <9 weeks	1032	37	3.6	6.9 (5.4–8.5)
9 to <10 weeks	1087	39	3.6	10.3 (8.4–12.0)
10 to <11 weeks	1118	19	1.7	11.8 (9.9–13.7)
11 to <12 weeks	1184	12	1.0	12.7 (10.7–14.6)
12 to <13 weeks	1274	9	0.7	13.3 (11.3–15.2)
13 to <14 weeks	1394	5	0.4	13.6 (11.6–15.6)
14 to <15 weeks	1534	0	0	13.6 (11.6–15.6)
15 to <16 weeks	1632	2	0.1	13.7 (11.7–15.7)
16 to <17 weeks	1742	2	0.1	13.8 (11.8–15.8)
17 to <18 weeks	1848	2	0.1	13.9 (11.9–15.9)
18 to <19 weeks	1941	3	0.2	14.0 (12.0–16.0)
19 to <20 weeks	2052	2	0.1	14.1 (12.1–16.1)

Zauche LH, Wallace B, Smoots AN, Olson CK, Oduyebo T, Kim SY, Petersen EE, Ju J, Beauregard J, Wilcox AJ, Rose CE, Meaney-Delman DM, Ellington SR; CDC v-safe Covid-19 Pregnancy Registry Team. Receipt of mRNA Covid-19 Vaccines and Risk of Spontaneous Abortion. N Engl J Med. 2021 Sep 8. doi: 10.1056/NEJMc2113891. Epub ahead of print. PMID: 34496196.