University of Washington
Public Health Capacity Building Center

COVID-19 Clinical Update

I-TECH Videoconference March 15, 2021

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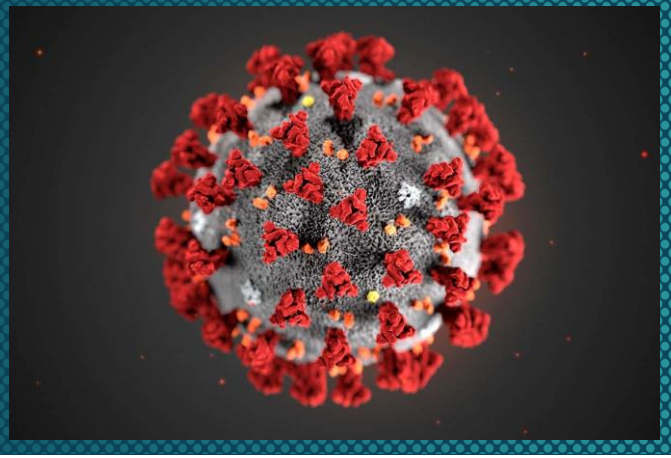


Last Updated: March 15, 2021

I-TECH
International Training and Education Center for Health

Overview

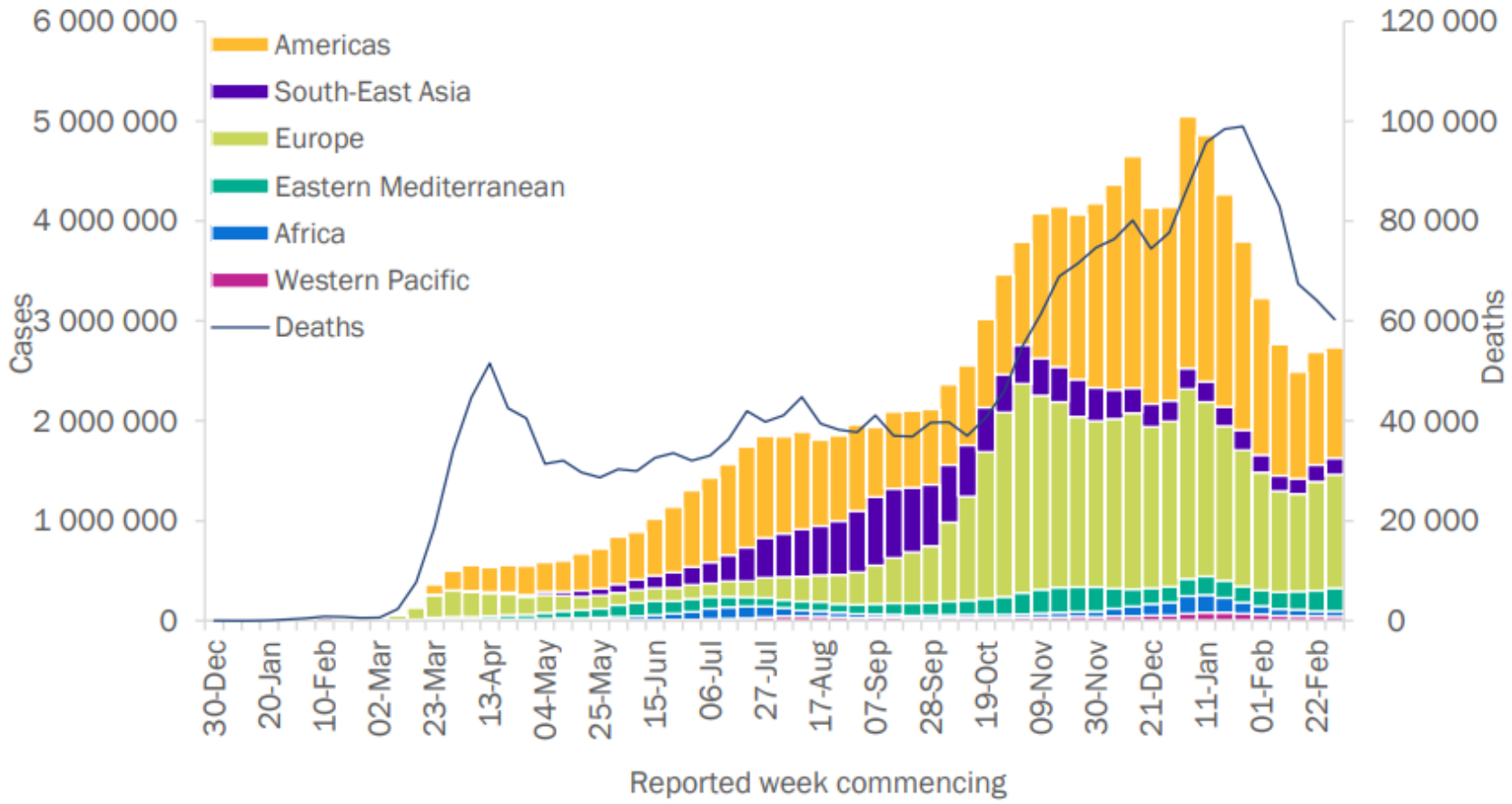
- Epidemiology
- SARS-CoV-2 Variants
- Vaccines
- Treatment

Global Trends in COVID-19 Diagnoses & Deaths

>116 Million Confirmed Cases
2.7 million cases/week

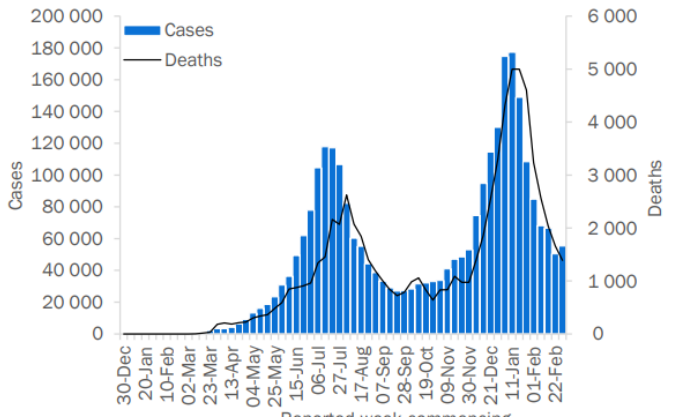
>2.5 Million Confirmed Deaths
60,323 deaths/week

Figure 1. COVID-19 cases reported weekly by WHO Region, and global deaths, as of 7 March 2021**

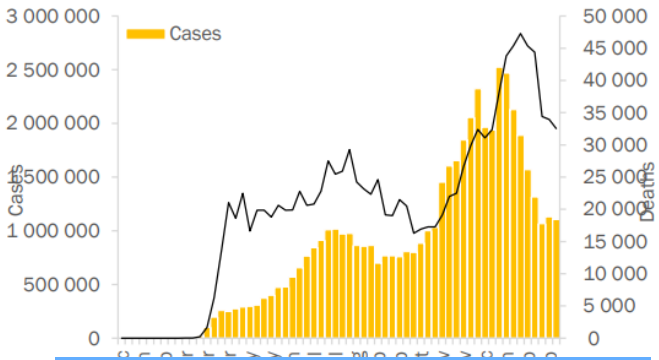


Global Trends in COVID-19 Diagnoses & Deaths

Africa

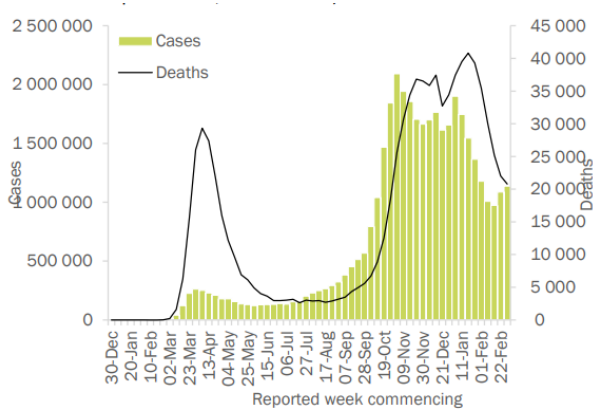


Americas

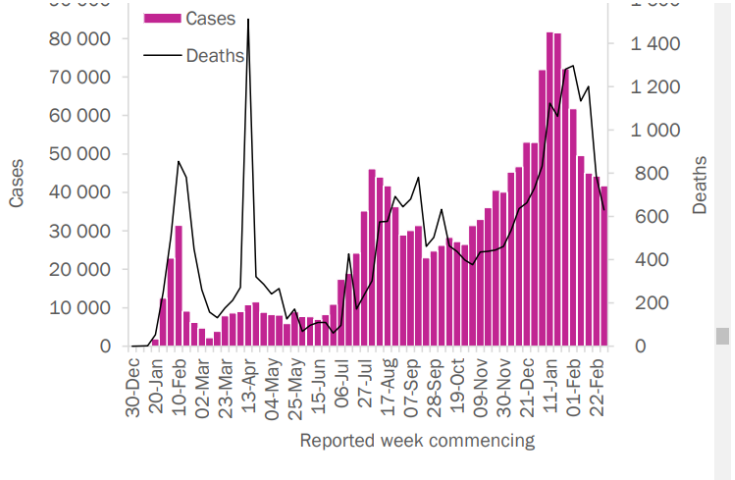


Increases in Brazil

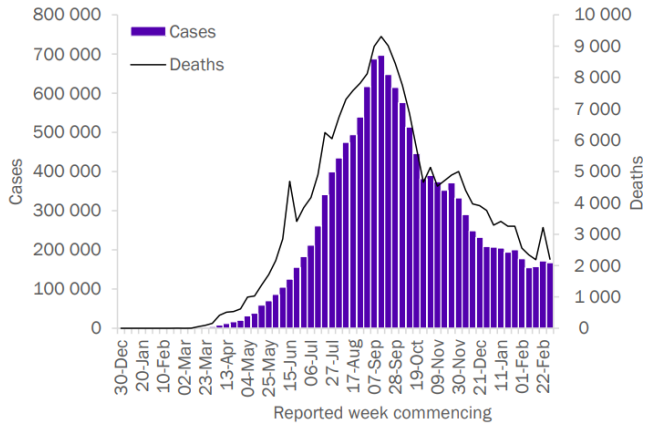
Europe



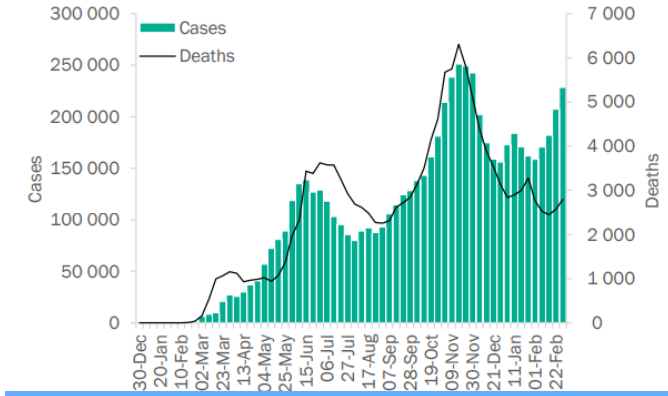
Western Pacific



South-East Asia



Eastern Mediterranean



Increases in Pakistan, Iran

Variant of Concerns

	Mutations	Epidemiology	Impacts
UK – B.1.1.7	N501Y (increases viral binding affinity for ACE), 69/70 deletion (viral escape), D614G	Described UK – 111 countries in all regions	~56% More transmissible - **More severe** - **? Decreased Novavax & J&J efficacy**
South Africa - B.1.351	N501Y, D614G, E484K, K417N/T,	Described South Africa – 52 countries in 4 WHO regions (none in South America)	- Higher viral load - More transmissible - Possible immune escape - Decreased neutralization by sera from convalescent sera and sera from Moderna vaccine recipients (not seen with B.1.1.7) - **? Decreased Novavax, J&J and AZ efficacy**
Brazil – P1	N501Y, D614G, E484K, K417T,	Brazil – 32 countries (Americas, Europe, India)	- Reinfections - **Resurgent epidemic**

Impact of B.1.1.7 on Mortality

- **Background**: Impact of SARS-CoV-2 variants on mortality uncertain
- **Design**: Matched cohort study – matching on time and geography
- **Population**: Sample 109,812 persons age >30 testing SARS-CoV-2+ 10/1/20-1/29/21 in a testing center in UK
  - 50% sample S gene negative (B.1.1.7)
  - 42% of cases during period were B.1.1.17
- **Outcome**: Death within 28 days of positive test

Mortality 0.4% in B.1.1.7 and 0.3% in non-B.1.1.17
Absolute Risk of Death is Low

Survival Curve S gene negative (B.1.1.7) & positive COVID-19

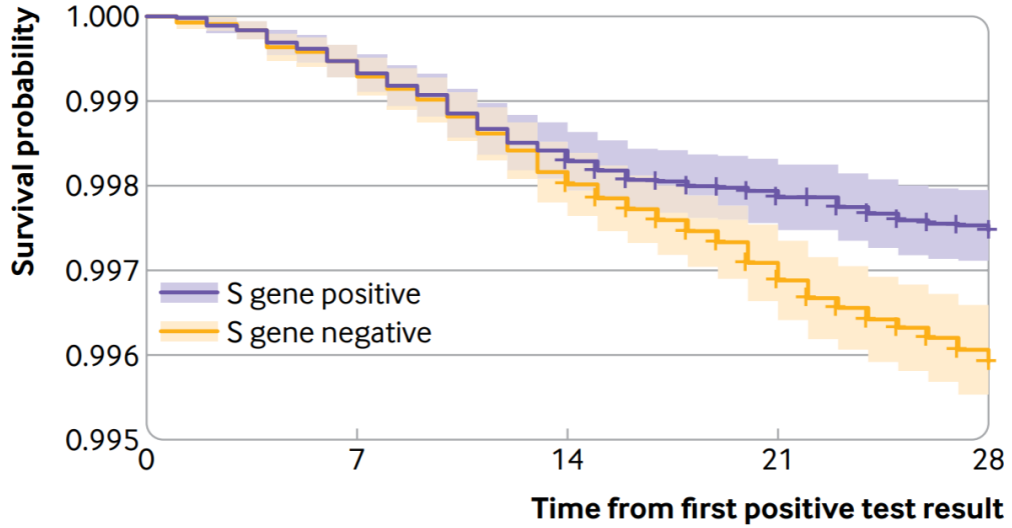


Table 2 | Risk of death in S gene negative compared with S gene positive (reference category) participants

Model, predictor, value	Hazard ratio (95% CI)	P value
S gene+age		
S gene status:		
Positive (ref)	—	—
Negative	1.64 (1.32 to 2.04)	<0.001
Age (per decade)	3.55 (3.28 to 3.84)	<0.001
S gene+N gene cycle threshold+age		
S gene status:		
Positive (ref)	—	—
Negative	1.37 (1.09 to 1.72)	0.004
Age (per decade)	3.51 (3.24 to 3.80)	<0.001
N gene cycle threshold (per 10 units)	0.50 (0.39 to 0.65)	<0.001

Hazard ratios >1 are indicative of an increased rate of death in people with infections compatible with VOC-202012/01. In the first model the S gene status is assessed as an indicator with age as a covariate, in the second model variability is included in the N gene cycle threshold value measured in the original specimen as a continuous predictor.

Variant of Concerns – 501Y Lineages

- 3 primary variants – B.1.1.7 (UK - V1), B.1.351 (South Africa, V2), P1 (Brazil, V3)
- Changes mostly affect spike protein – binds ACE
- Phenotypic effects
  - Increased binding affinity for ACE2 receptor (V1, V2, V3)
  - Increased transmissibility (V1 and V2)
  - Increased capacity to overcome prior infection and/or vaccine induced immunity (V2, V3)
  - Increased virulence (V1)

Mutation	Variants	Impact
Deletion 11288 & 11296	V1, V2, V3	• Affects nonstructural protein • Decreases cellular response to type 1 interferon – autophagosome
501Y	V1, V2, V3	• Increase affinity spike protein for ACE2 receptor 3.5-fold
E484K	V2, V3, some V1	• In presence of 501Y increases affinity for ACE2 receptor 12.7-fold (epistasis) • Decreased neutralization by convalescent sera, vaccine elicited antibody, monoclonal antibody
S/417	V2 (K417N), V3 (K417T)	• Reduce affinity for ACE2 • Increase spike expression – decreased antibody neutralization
L18F	Some V2, V3	• Some decreased antibody neutralization

Variant of Concerns – 501Y Lineages

Figure

- Size circles indicates statistical significance of tests for positive selection
- Redder means larger percent of isolates have mutations

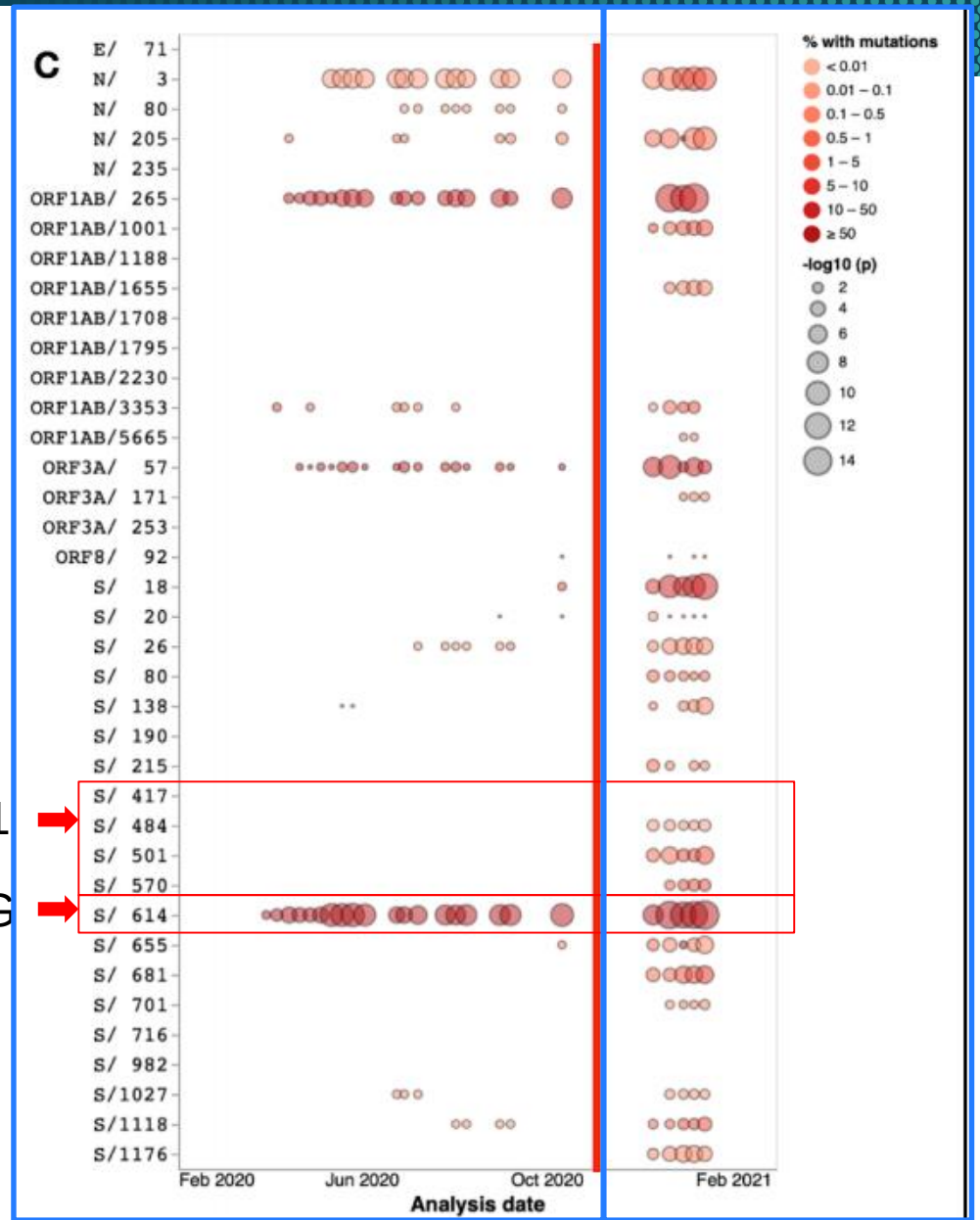
Why the shift?

- Change in the global fitness landscape
  - Evasion of preexisting immunity hypothesis (doesn't fit for V1)
- Chronic-illness emergence hypothesis
  - Mutations accumulate in immunocompromised persons with longer duration of infection – selection occurs within individuals
  - It took time to have enough people with infections lasting months to select for multiple mutations

Martin D. Medrxiv 2020

417, 484, 501

D614G



Variant of Concerns: B.1.429

B.1.429

- Initially identified in June in California
- Mutations facilitate strong binding to ACE (L452R)
- Some evidence this is more transmissible and causes more severe disease
- May at least partially escape immune control

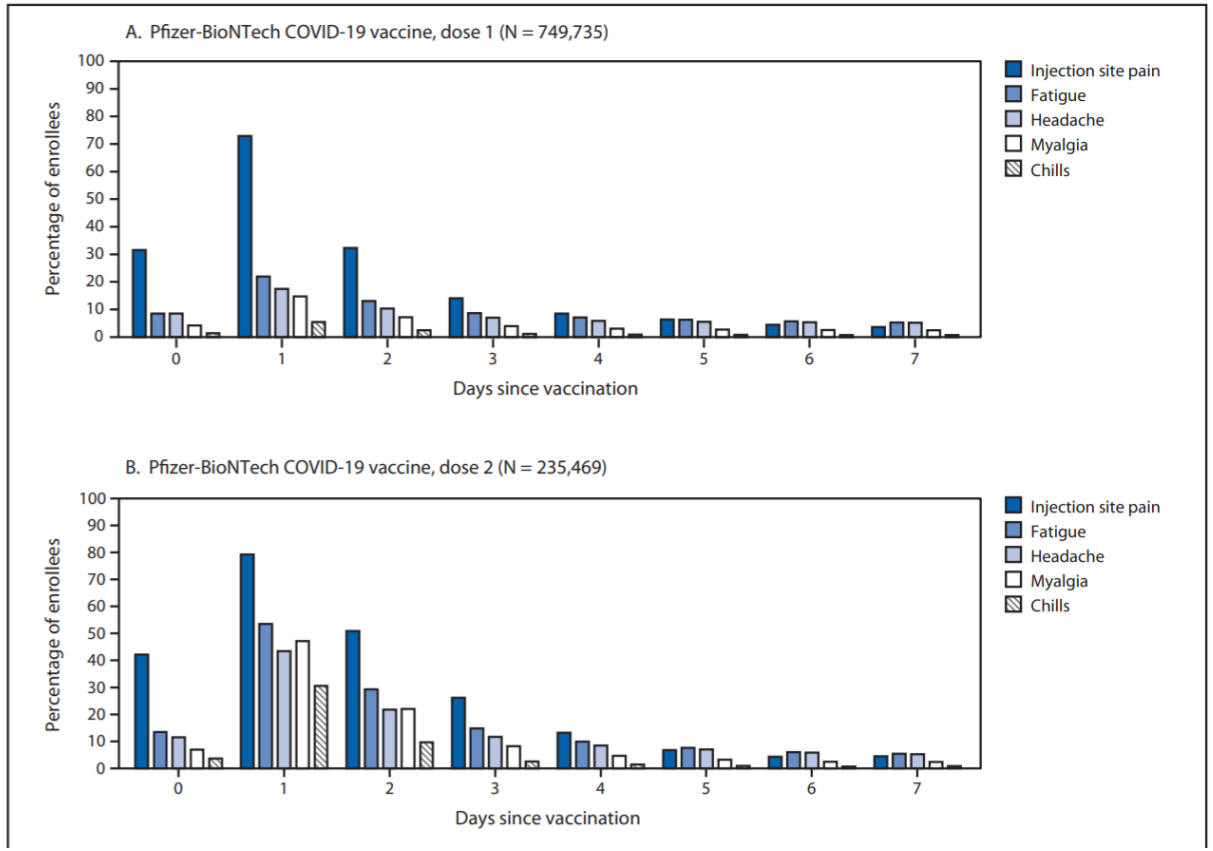
B.1.526

- Identified in New York – now 14-28% isolates
- E484K (South Africa & Brazil) + S477N (affecting binding ACE)

Trends in B.1.429 in California

Vaccine Safety

- Vaccine safety data 12/140/20-1/13/21 – 13,794,904 vaccines administered
- Vaccine adverse event reporting system (VAERS) – Passive surveillance
  - 6,994 events – 91% nonserious (headache, fatigue, dizziness)
  - 640 serious - 113 deaths - 78 in long term care facilities
    - No suggestion that vaccine was a cause of death
  - 62 cases anaphylaxis (no deaths) – 4.5 cases per million doses
    - Higher than flu vaccine (1.4) and lower than shingles vaccine (9.6).
    - Food induced anaphylaxis in US = 50-160 per 1 million person years
- V-Safe – Active surveillance – 1,603,065



Gee J. MMWR 2021

Novavax Vaccine: Update from January

Vaccine: Protein-based vaccine – spike protein in nanoparticle
Design: Two placebo controlled, double blind RCTs
Administration: 2 doses
Storage: 2-8ºC (refrigeration)
Population:
- UK study - >15,000 subjects – 106 events
- South Africa – 2665 subjects -147 events
Outcome: PCR confirmed COVID-19 >7 after 2nd dose – seronegative at baseline

Results

- UK Study
  - 96.4% effective again original strain
  - 86.3% effective against B.1.1.7 (UK variant)
  - **5 cases severe disease – 4 B.1.1.7 – all in placebo group**
- South Africa – >90% of infections with B.1.135
  - 48.6% effective overall
  - **All 5 severe cases in placebo group**
  - Prior infection was partially protective in placebo group
    - 90 day illness – 7.9% seronegatives vs. 4.4% seropositives

Novavax press release March 11, 2021

Vaccines: Janssen Ad26.COV2.S

Vaccine: replication incompetent adenovirus vector S protein vaccine
Design: Two placebo controlled, double blind RCTs
Administration: **1 dose**
Storage: 2-8ºC (refrigeration)
Population: 39,321 enrolled and eligible for analysis – 47% in US, 41% Latin Am, 13% South Africa – 35% >60years
- **Outcome**: PCR confirmed Moderate to Severe COVID-19 >14 & >28 after vaccine – seronegative at baseline

Results

	>14 Days			>28 Days		
	Vaccine Cases	Placebo	Efficacy	Vaccine Cases	Placebo	Efficacy
All	116	348	66.9%	66	193	66.1%
Severe	14	60	76.7%	5	34	85.4%

- Suggestion of efficacy against **asymptomatic infection** based on N-specific antibody (not spike) at day 71 – 74% after day 29 (small numbers)
- Some variation by site: US (72%), Brazil (68%) South Africa (64%) – 95% cases in South Africa were B.1.521 and 69% in Brazil were P.2.

Source: FDA briefing document 2021

Efficacy mRNA Vaccines Against Asymptomatic Infections

Background: Prevention impact of mRNA vaccines on asymptomatic infection – not just disease – uncertain.
- 80% ↓ PCR+ asymptomatic infection 28 days after 1st dose
Design: Retrospective cohort study 39,156 adults undergoing pre-procedure asymptomatic SARS-CoV-2 PCR testing at Mayo Clinic System 12/17/20-2/8/21
Exposure: ≥1 dose mRNA vaccine (94% Pfizer)
Outcome: Relative risk PCR+ asymptomatic infection
- Adjusted – age, race, place residence, local vs. referred

Results

	Percent Positive	Unadjusted RR (95% CI)
Unvaccinated	3.1%	Ref
1 dose prior to screening	1.6%	0.49 (0.36-0.69)
2 doses prior to screening*	0.9%	0.27 (0.12-0.60)
Unvaccinated	3.1%	Ref
Screening 0-10 days after 1st dose	2.6%	0.81 (0.54-1.2)
Screening >10 days after 1st dose	0.9%	0.28 (0.16-0.49)
Screening >0 days after 2nd dose*	0.9%	0.27 (0.12-0.60)

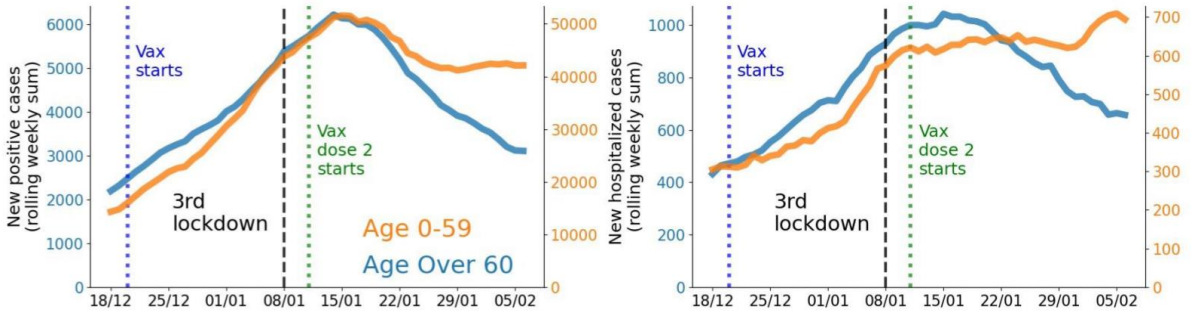
Adjust RR >10 days after 1st dose 0.21 (0.12-0.37) and >0 days after 2nd dose 0.20 (0.09-0.44)
*36% of tests done <7 days following 2nd dose

Tande AJ. CID 2021

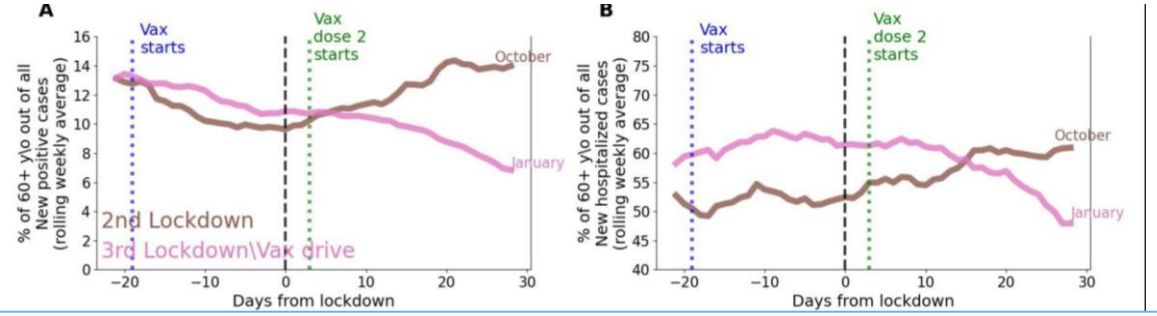
Vaccines: Real World Effectiveness

- Israel has achieved very high levels of immunization
- Feb 6 – 45% and 30% of population had received 1st and 2nd doses of Pfizer vaccine (90% and 80% persons >6 years)
- Nationalized healthcare with good data system
- Observational analysis of trends
  - Age – older people vaccinated 1st
  - Lockdown effect?
  - Early vs. late vaccine areas

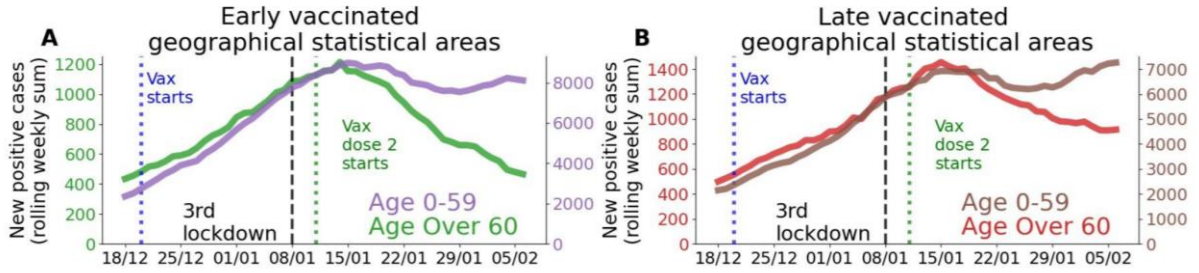
Trends in New Cases and Hospitalizations by Age



Trends Cases & Hospitalizations, 2nd vs. 3rd Lockdown



Trends Early vs. Late Vaccination Areas



Rossman H. MedRxiv 2021

Impact COVID-19 Vaccination on Social Distancing: CDC Guidelines

What's stayed the same - Everyone

- Public mask wearing and social distancing – 6 feet apart, avoid crowds and poorly ventilated spaces
- Delay travel when possible

What's new – People >2 weeks after final dose of vaccine

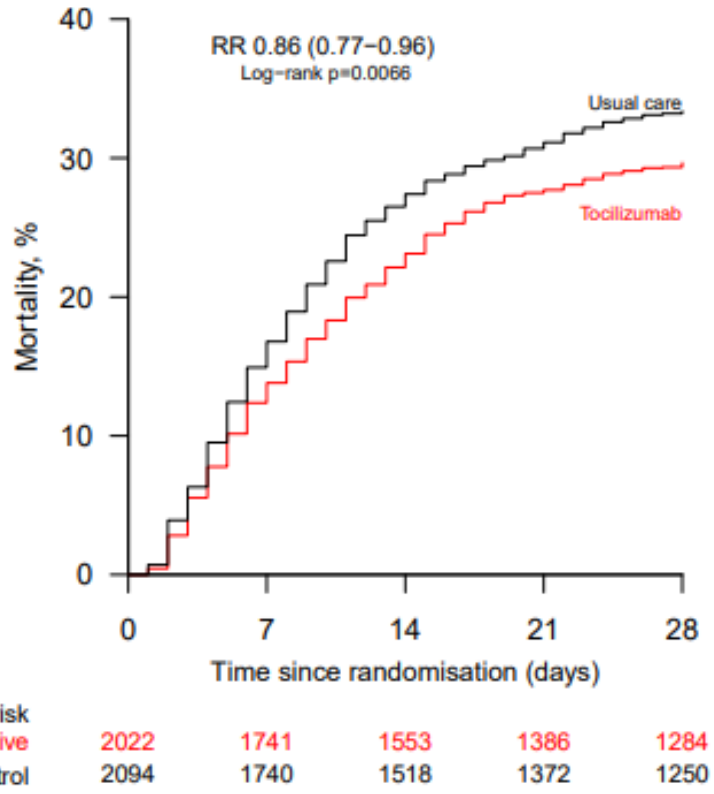
- OK gather indoors with fully vaccinated people without wearing a mask.
- OK gather indoors with unvaccinated people from one other household (for example, visiting with relatives who all live together) without masks, unless any of those people or anyone they live with has an increased risk for severe illness from COVID-19.
- Exposure COVID-19
  - No routine quarantine of asymptomatic persons outside of group settings (e.g. jails, group homes)
  - Symptom monitoring – quarantine if symptomatic

https://www.cdc.gov/coronavirus/2019-ncov/vaccines/fully-vaccinated.html

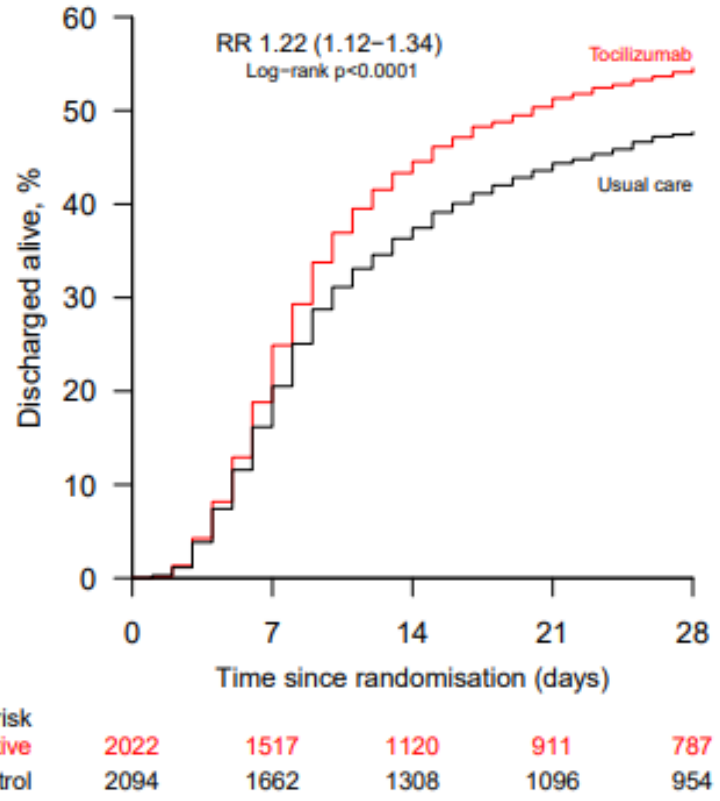
Anti IL-6 Monoclonal Ab: Tocilizumab

- **Background**: Small RCTs suggest that mAb against IL-6 receptor may confer a mortality benefit. In January (last I-TECH review on IL-6 mAb) were not yet integrated into guidelines.
- **Design**: Open-label RCT – adaptive trial
- **Population**: 4116 patients hospitalized in UK with hypoxia and elevated CRP
- **Intervention**: Tocilizumab 400-800mg IV (+/- 2nd dose)
- **Outcome**: 28 day mortality

Mortality at 28 days



Discharge from Hospital at 28 days



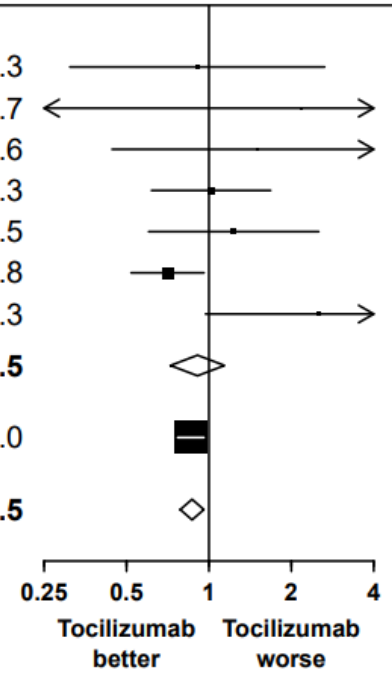
Source: Recovery Collaborative Group. Medrxiv 2021

Anti IL-6 Monoclonal Ab: Tocilizumab

Figure 4: Tocilizumab vs usual care in patients hospitalised with COVID − Meta−analysis of mortality in RECOVERY and other trials

	Deaths / Patients randomised (%)		Observed−Expected		Ratio of death rates, RR (95% CI)
	Tocilizumab	Usual care	(O−E)*	Var(O−E)	
COR−IMUNO TOCI	7/64 (10.9)	8/67 (11.9)	−0.3	3.3	0.91 (0.31−2.65)
RCT−TCZ−COVID−19	2/60 (3.3)	1/66 (1.5)	0.6	0.7	2.17 (0.22−21.3)
BACC Bay	9/161 (5.6)	(3/82) x2† (3.7)	1.0	2.6	1.51 (0.44−5.13)
COVACTA	58/294 (19.7)	(28/144) x2† (19.4)	0.3	15.3	1.02 (0.62−1.68)
EMPACTA	26/249 (10.4)	(11/128) x2† (8.6)	1.6	7.5	1.23 (0.60−2.52)
REMAP−CAP	98/353 (27.8)	142/402 (35.3)	−14.2	40.8	0.71 (0.52−0.96)
TOCIBRAS	14/65 (21.5)	6/64 (9.4)	3.9	4.3	2.51 (0.97−6.50)
Subtotal: 7 trials	**214/1246 (17.2)**	**241/1307 (18.4)**	**−7.2**	**74.5**	**0.91 (0.72−1.14)**
RECOVERY	596/2022 (29.5)	694/2094 (33.1)	−48.2	316.0	0.86 (0.77−0.96)
All trials	**810/3268 (24.8)**	**935/3401 (27.5)**	**−55.4**	**390.5**	**0.87 (0.79−0.96) p=0.005**

Heterogeneity between RECOVERY and previous trials: χ^2_1=0.2



Source: Recovery Collaborative Group. Medrxiv 2021

NIH Guideline Revision 3/5/21

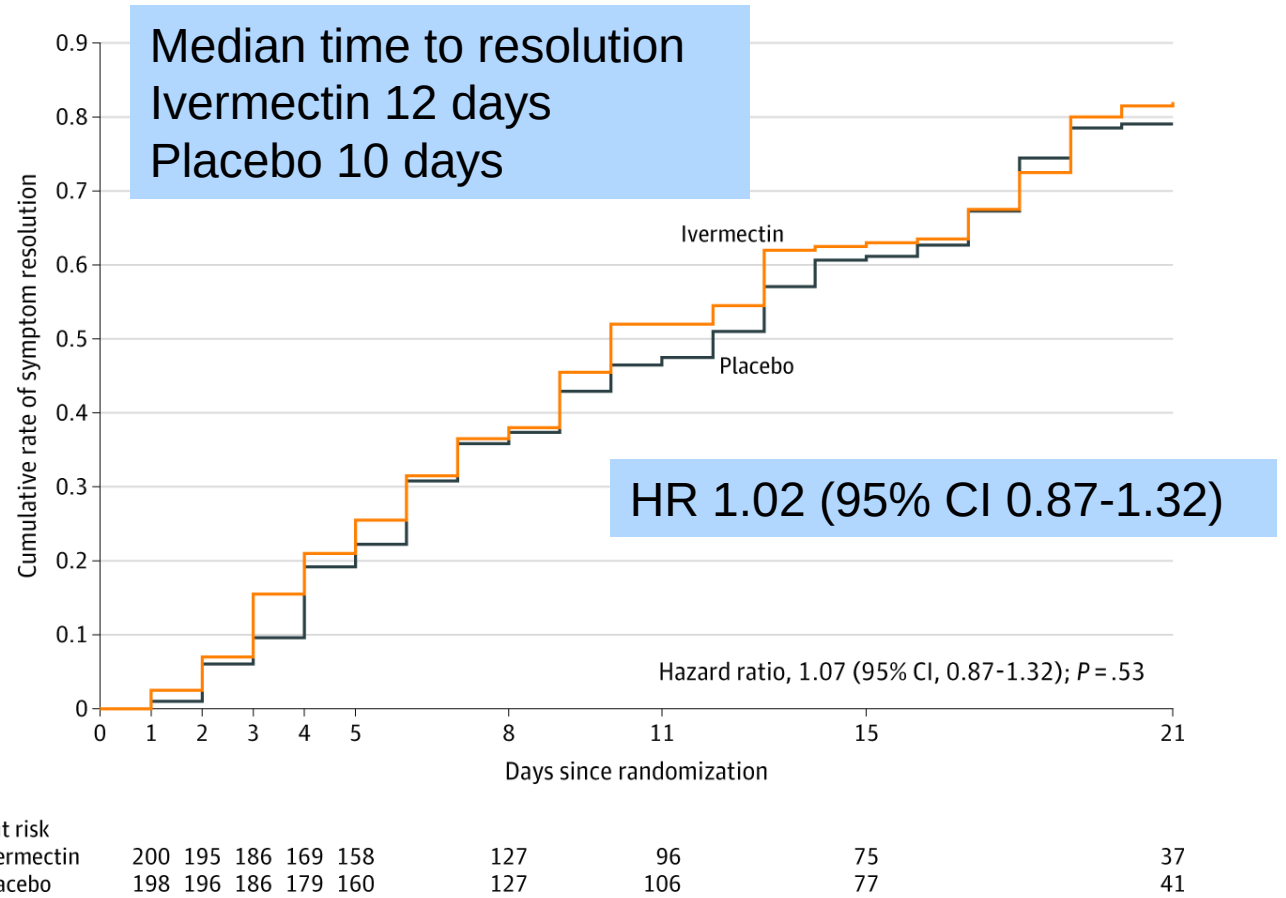
- Use of **tocilizumab** (single intravenous dose of 8 mg/kg of actual body weight, up to 800 mg) **in combination with dexamethasone** (6 mg daily for up to 10 days) in hospitalized patients exhibiting rapid respiratory decompensation due to COVID-19. These patients are:
  - Recently hospitalized patients admitted to an ICU within 24 hours who require invasive mechanical ventilation, noninvasive mechanical ventilation (NIV) or high-flow nasal canula (HFNC) oxygen (>0.4 FiO_2/30 L/min of oxygen flow) **(BIIa)**; *or*
  - Recently hospitalized patients (not in an ICU) with rapidly increasing oxygen needs who require NIV or HFNC and have significantly increased markers of inflammation **(BIIa)**.
- In hospitalized patients with hypoxemia who require conventional oxygen therapy, the Panel recommends using one of the following options: **remdesivir (BIIa)**, **dexamethasone plus remdesivir (BIII)**, or **dexamethasone alone (BI)**
  - There is insufficient evidence to specify which of these patients would benefit from the addition of tocilizumab. Some Panel members would also give tocilizumab to patients who are exhibiting rapidly increasing oxygen needs while on dexamethasone and have a CRP ≥75 mg/L, but who do not yet require NIV or HFNC, as described above.

https://www.covid19treatmentguidelines.nih.gov/whats-new/

Ivermectin for COVID-19

- **Background**: Ivermectin has in vitro activity against SARS-CoV-2 and is widely used to treat COVID-19. Clinical trials have generally been small, and data demonstrating its efficacy is lacking.
- **Design**: Double blind placebo controlled RCT
- **Population**: 476 patients with mild COVID-19 diagnosed in prior 7 days in Colombia (median 5 days)
- **Intervention**: Ivermectin 300ug/kg qd x 5 days
- **Outcome**: Time to resolution of symptoms within 21 days

Time To Resolution of Symptoms



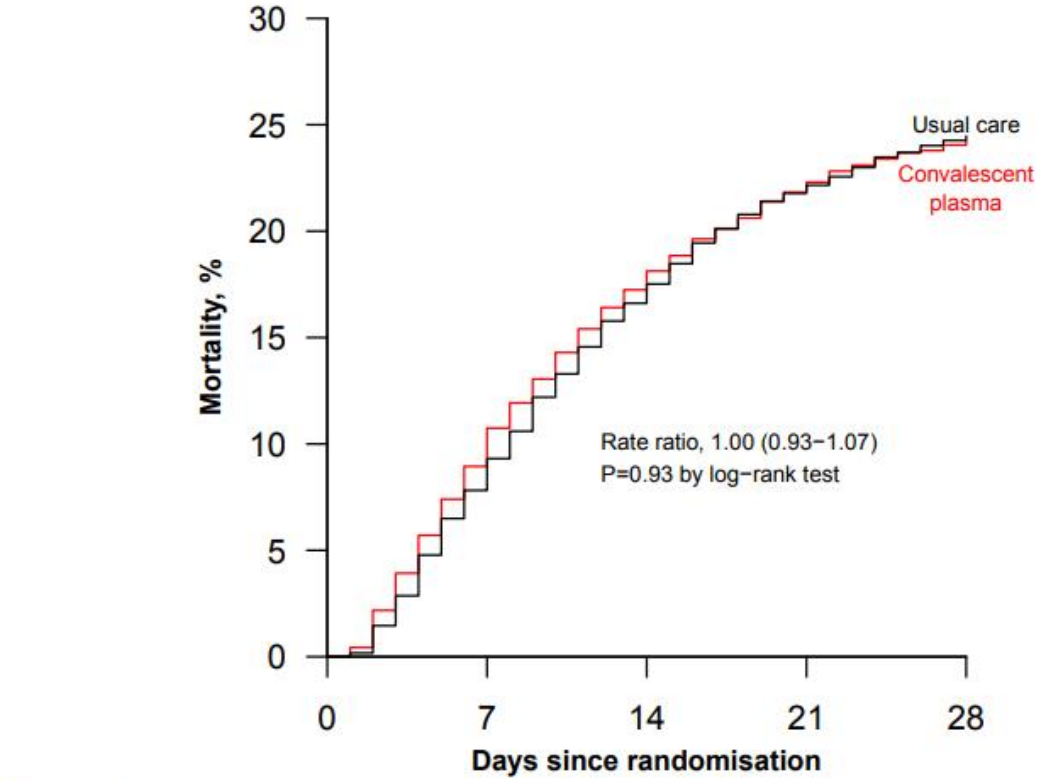
Source: Lopez-Medina E. JAMA 2021

NIH Guideline 2/11/21: Prior Columbian Study

There are insufficient data for the COVID-19 Treatment Guidelines Panel (the Panel) to recommend either for or against the use of ivermectin for the treatment of COVID-19. Results from adequately powered, well-designed, and well-conducted clinical trials are needed to provide more specific, evidence-based guidance on the role of ivermectin in the treatment of COVID-19.

Convalescent Plasma; RECOVERY Trial

- **Background**: Convalescent plasma has been widely use to treat COVID-19. One observational study suggested benefit, but small RCTs have not. NIH guidelines do not recommend it's use.
- **Design**: Open-label RCT – adaptive trial of multiple interventions
- **Population**: 11,558 patients hospitalized in UK
- **Intervention**: High titer convalescent plasma – most 2 units
- **Outcome**: 28 day mortality – post-hoc analysis looking at before 12/20 to assess if B.1.1.9 might affect outcome



- No benefit in any subgroup analysis
- Mortality higher in antibody negative persons (34% vs. 19%, but no different in intervention effect.

Source: RECOVERY Collaborative Group Medrxiv 2021

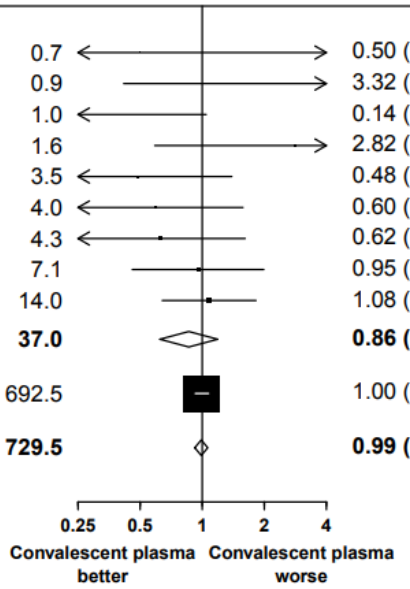
Convalescent Plasma; RECOVERY Trial

- No benefit in meta-analysis with other trials

Figure 4: Convalescent plasma vs usual care in patients hospitalised with COVID – Meta-analysis of mortality in RECOVERY and other trials

	Deaths / Patients randomised (%)		Observed-Expected		
	Convalescent plasma	Usual care	(O-E)*	Var(O-E)	Ratio of death rates, RR (95% CI)
AlQahtani	1/20 (5.0)	2/20 (10.0)	-0.5	0.7	0.50 (0.05-5.06)
Bajpai	3/14 (21.4)	1/15 (6.7)	1.1	0.9	3.32 (0.42-26.4)
Avendano-Sola	0/38 (0.0)	4/43 (9.3)	-1.9	1.0	0.14 (0.02-1.05)
Balcells	5/28 (17.9)	2/30 (6.7)	1.6	1.6	2.82 (0.59-13.5)
Gharbharan	6/43 (14.0)	11/43 (25.6)	-2.5	3.5	0.48 (0.17-1.39)
Li	8/51 (15.7)	12/50 (24.0)	-2.1	4.0	0.60 (0.22-1.58)
Ray	10/40 (25.0)	14/40 (35.0)	-2.0	4.3	0.62 (0.24-1.62)
Simonovich	25/228 (11.0)	(12/105) x2† (11.4)	-0.3	7.1	0.95 (0.46-1.99)
Agarwal	34/235 (14.5)	31/229 (13.5)	1.1	14.0	1.08 (0.64-1.82)
Subtotal: 9 trials	**92/697 (13.2)**	**101/680 (14.9)**	**-5.5**	**37.0**	**0.86 (0.62-1.19)**
RECOVERY	1398/5795 (24.1)	1408/5763 (24.4)	-2.3	692.5	1.00 (0.93-1.07)
All trials	**1490/6492 (23.0)**	**1509/6443 (23.4)**	**-7.8**	**729.5**	**0.99 (0.92-1.06) p=0.77**

Heterogeneity between RECOVERY and previous trials: χ^2_1=0.8



* Log-rank O-E for RECOVERY, O-E from 2x2 tables for the other trials. RR is calculated by taking ln RR to be (O-E)/V with Normal variance 1/V. Subtotals or totals of (O-E) and of V yield inverse-variance-weighted averages of the ln RR values.

† For balance, controls in the 2:1 study by Simonovich count twice in the control totals and subtotals.

Source: RECOVERY Collaborative Group Medrxiv 2021

Questions and Comments