COVID-19 Grand Round

COVID EBM Committee. April 5, 2021

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COVID-19 Pandemic: One Year Later
What do we know and where have we been?

Evidence-Based-Medicine (EBM) Committee

Renown Health

April 5, 2021

Renown EBM Committee

- Co-Chair: Farah Madhani-Lovely, Pulmonary and Critical Care
- Co-Chair: Kevin Kuriakose, MD, Infectious Disease
- Rudy Tedja, DO, Infectious Disease and Critical Care
- Natalie Crawford, MD, Infectious Disease
- Sara Healy, MD, Pediatric Infectious Disease
- Chris Rowan, MD, Cardiology
- Jessica Thompson, PharmD, Infectious Disease
- Kiya Mohadjer, PharmD, Infectious Disease
- David Lemak, MD, Primary Care/Urgent Care
- Mike Miller, MD, Critical Care
- Evan Cherry, MD, Hospital Medicine
- Asem Mutasher, MD, Hospital Medicine

Disclaimer and conflict of interest

- **Many of us are involved in multiple COVID-19 clinical trials**

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Learning Objectives

1. To describe the epidemiology of COVID-19 including the new COVID-19 variants
2. To understand the different types, efficacy, and adverse effects of available COVID-19 vaccines in US
3. To understand and describe the different methods of diagnosis of COVID-19
4. To explain the clinical manifestations of COVID-19 in both adults and pediatrics population
5. To describe the most updated guidelines on anticoagulation and pharmacological therapies for COVID-19

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Epidemiology

Rudy Tedja, DO
Infectious Disease/Critical Care

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COVID-19 Data as of 4/5/2021 at 8am

World: 131

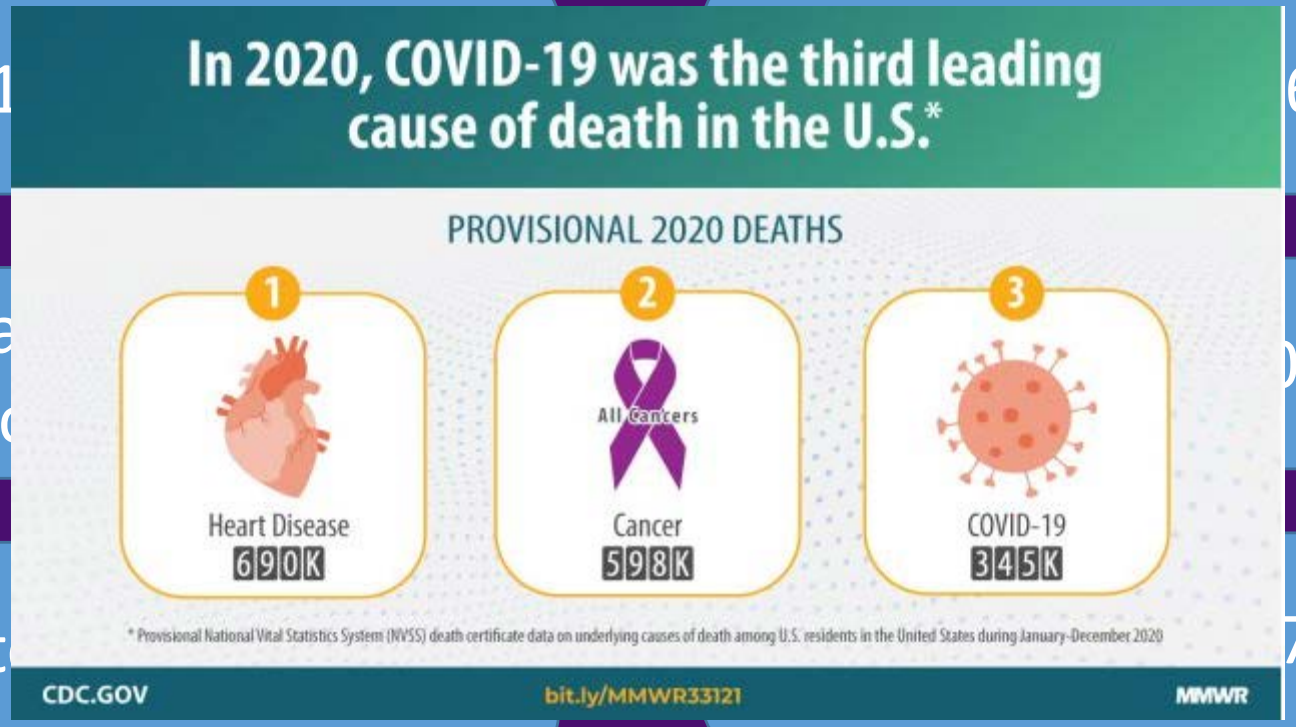
6 cases

World Dea

002 cases

Nevada stat

74 cases



https://coronavirus.jhu.edu/map.html; https://covid.cdc.gov/covid-data-tracker; nvhealthresponse.nv.gov

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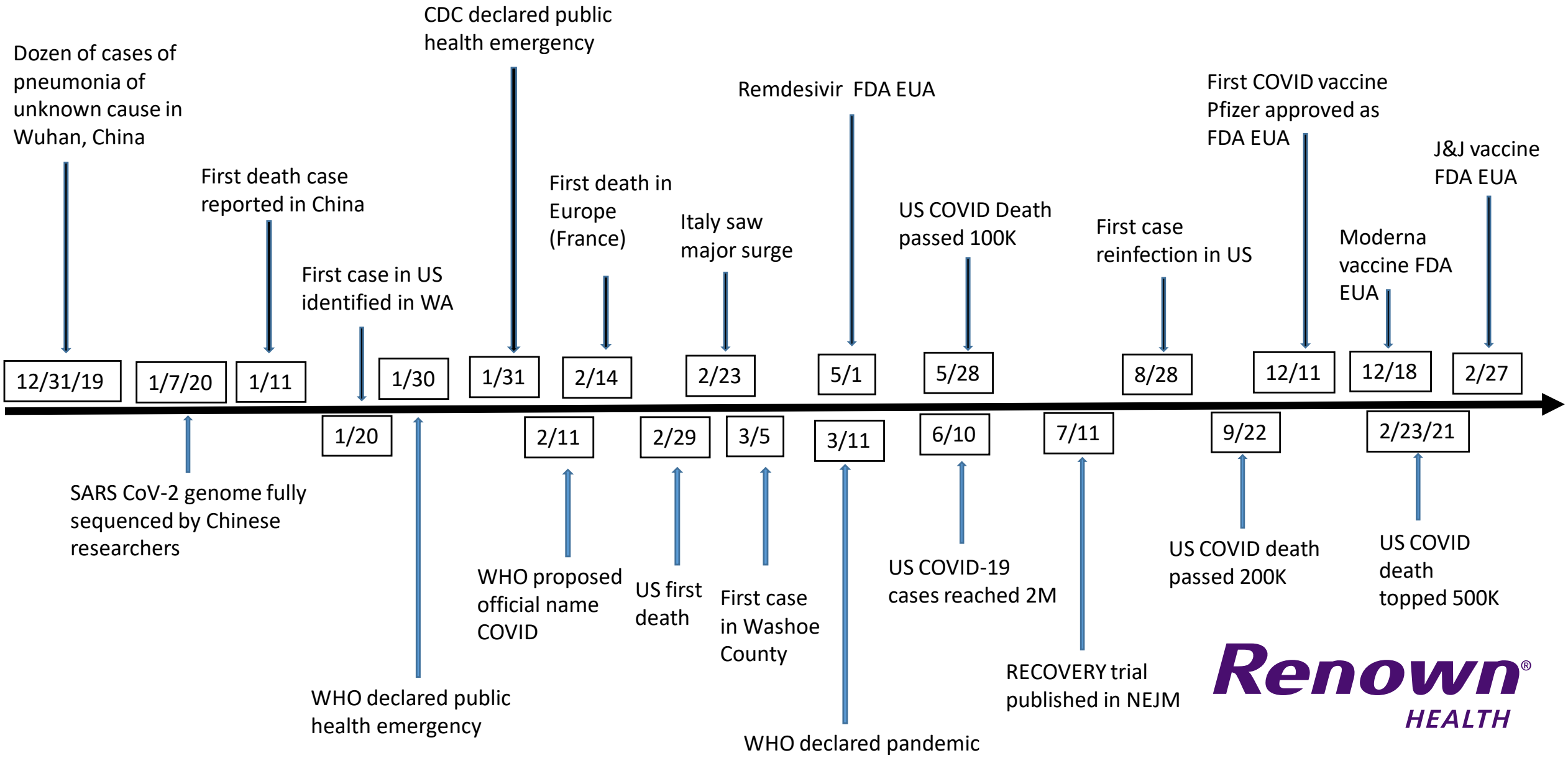
HIGHLIGHTS OF COVID PANDEMIC



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Highlights of COVID Pandemic – Renown Health

- HICS was formed
- Multiple committees were formed to address the pandemic
  - Crisis Standard of Care
  - Provider Task Force
  - EBM
  - Capacity, PPE, others
- Alternate Care Site (ACS) was created
- Shortage of PPE, diagnostic tests, beds, oxygen device and more
- Donning/Doffing PAPR/CAPR
- Numerous changes in protocols of patient triage, admission, discharge
- All departments were involved
  - Emergency Department
  - Inpatient (ICU and nonICU)
  - Surgery/Anesthesia
  - Outpatient/Urgent Care
  - MD, RN, RT, IP, Pharmacy, EVS, Security, etc

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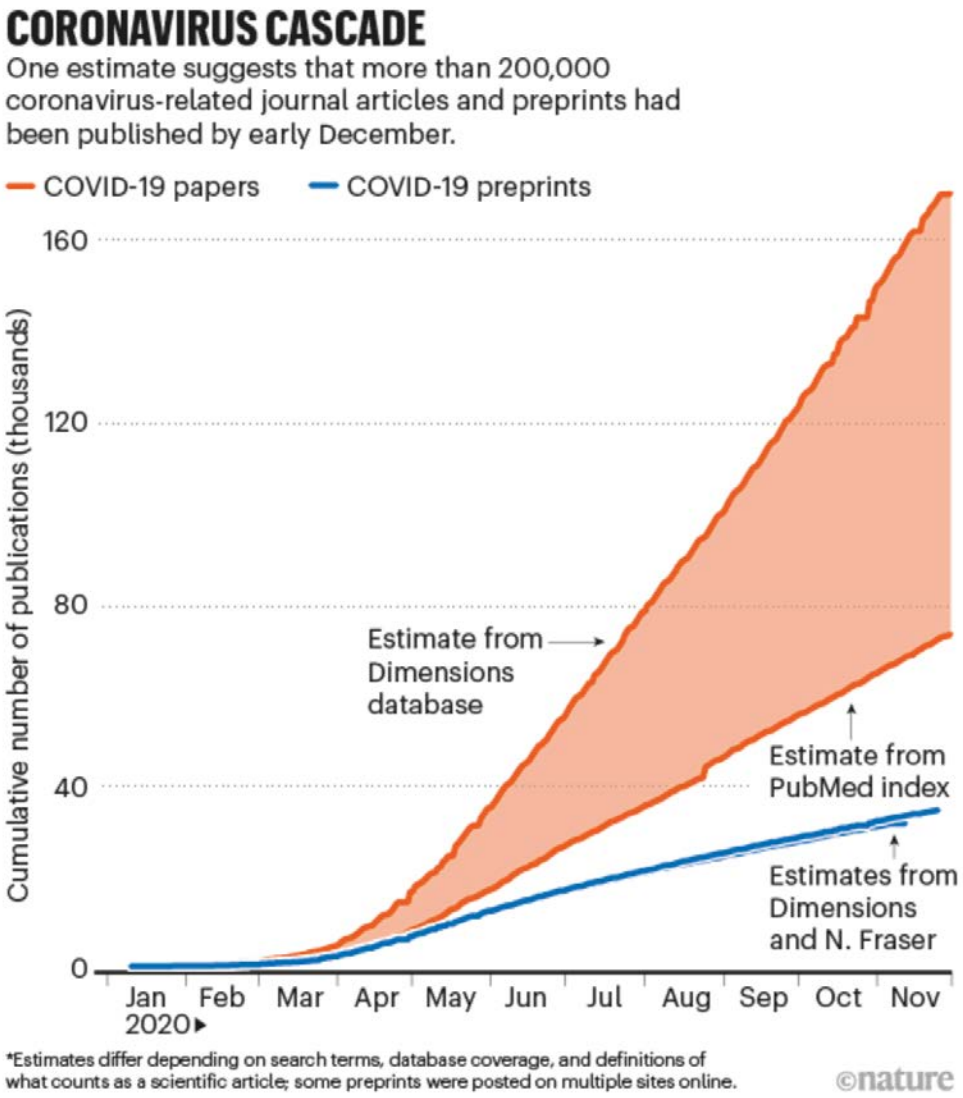
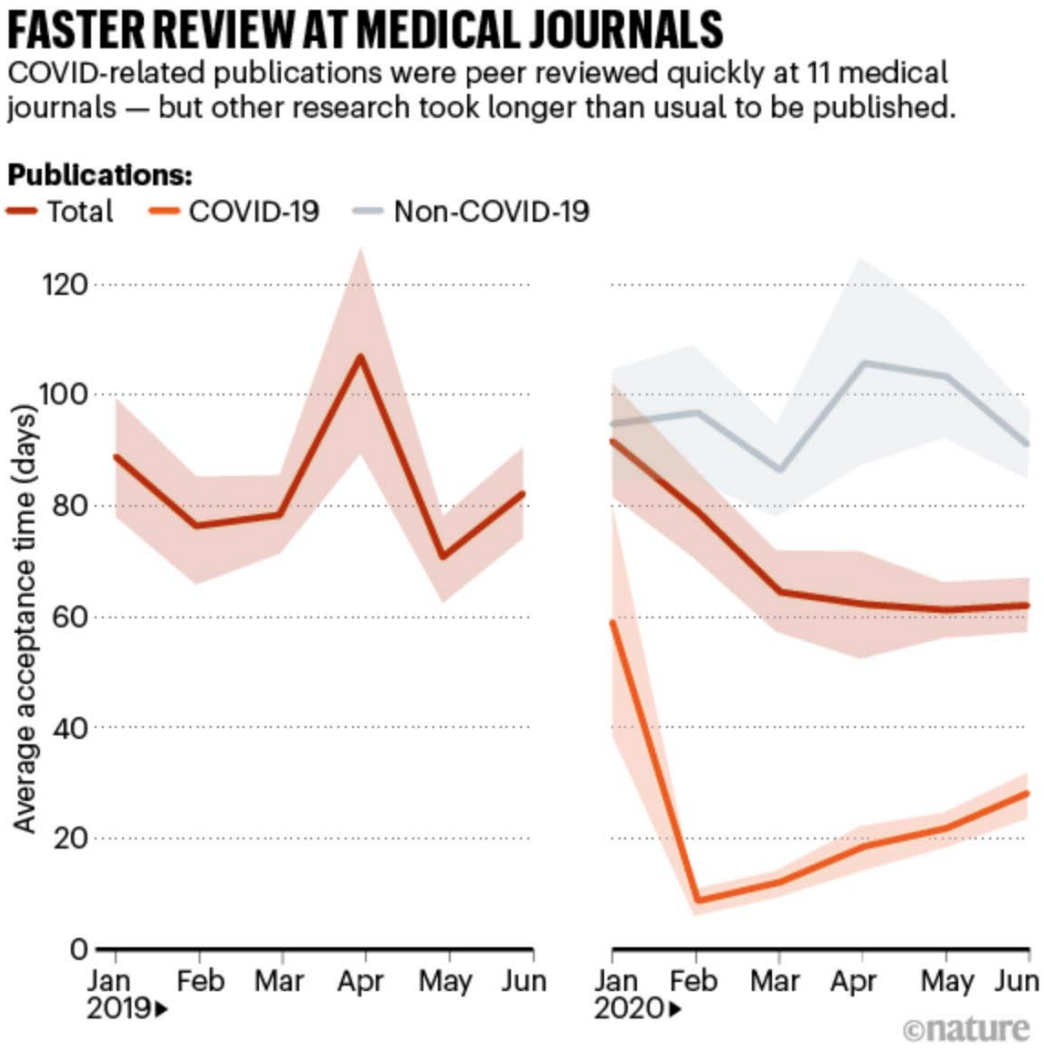
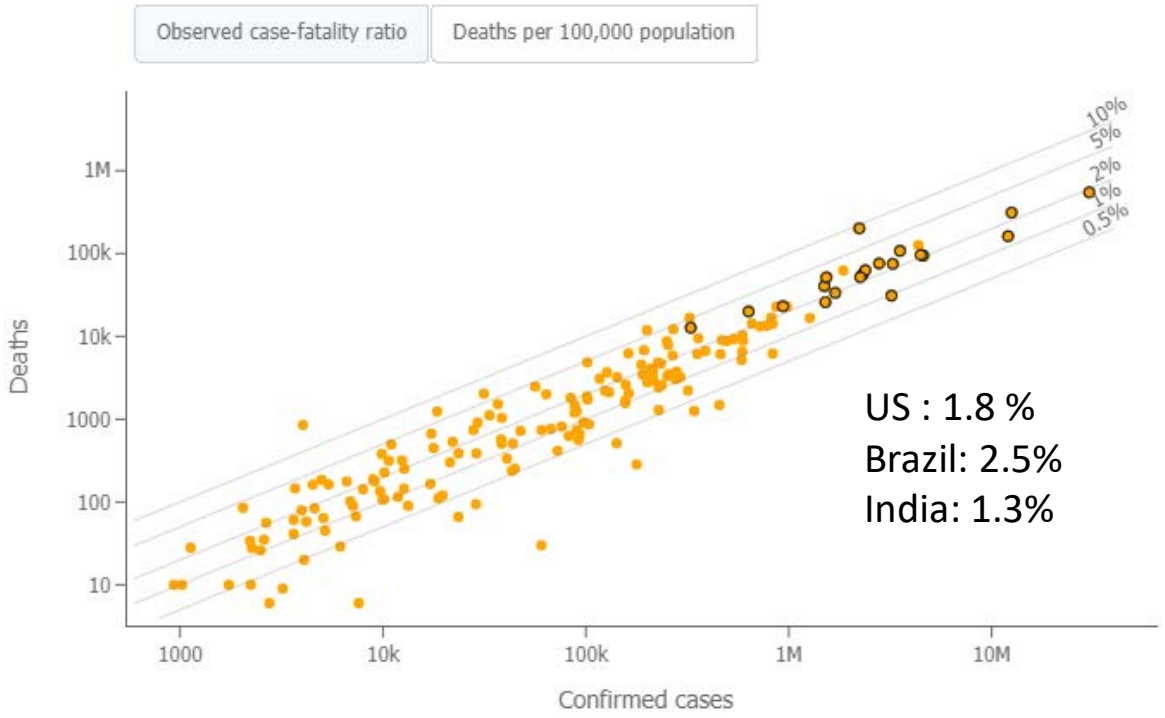
Rise of publications and pre-print studies

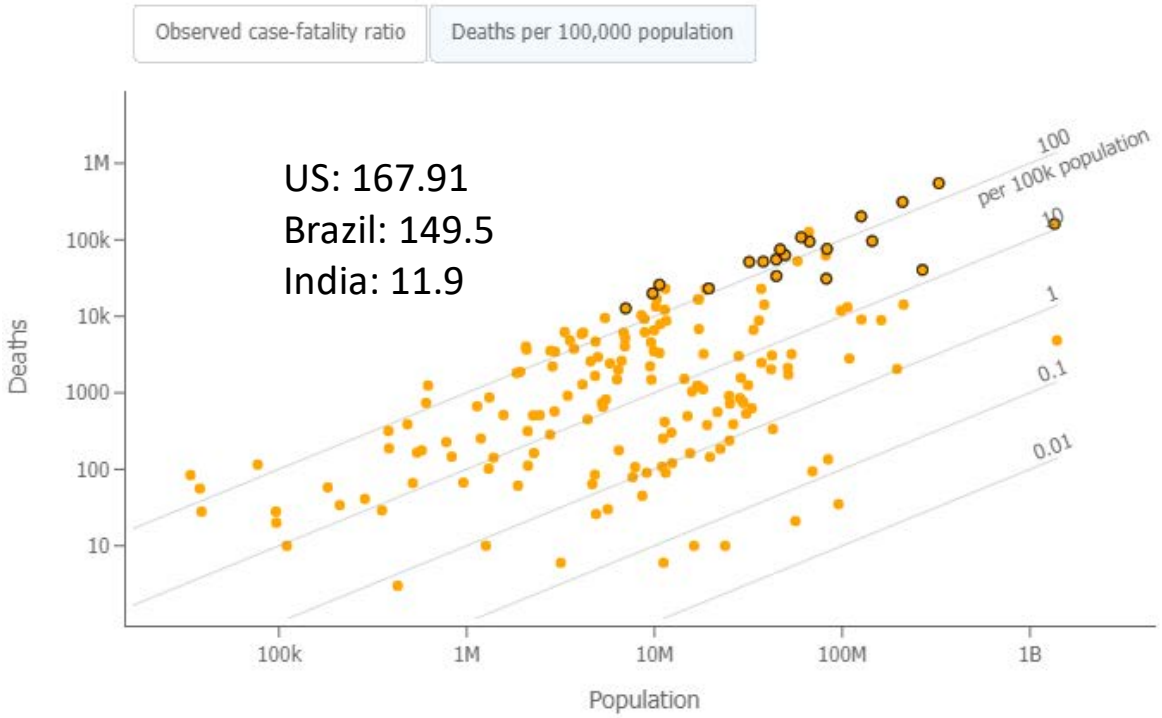




https://www.nature.com/articles/d41586-020-03564-y

Case-fatality ratio and death per 100K worldwide





Observed case-fatality ratio = # deaths/100 confirmed cases
Per 100,000 population represents both confirmed cases and healthy people

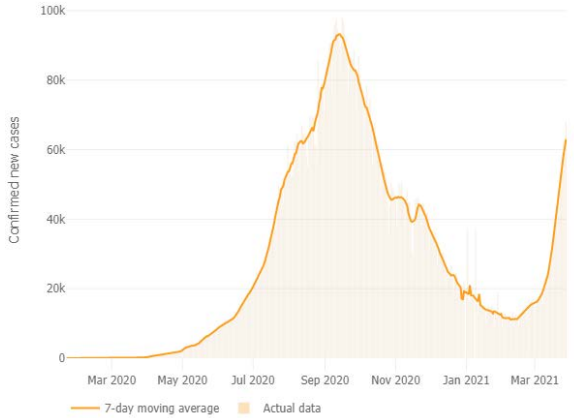
Data: as of 3/29/2021

https://coronavirus.jhu.edu/data/mortality

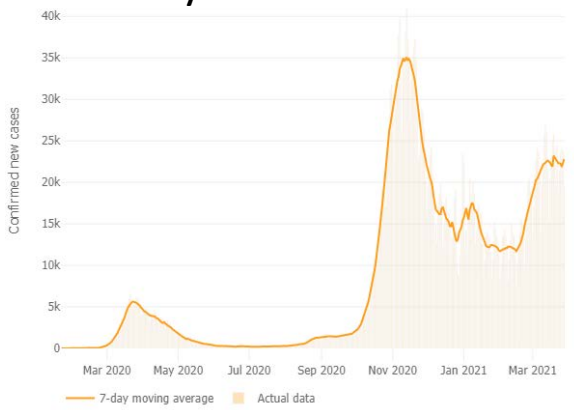
Cases are rising worldwide – 7-day moving average

Brazil

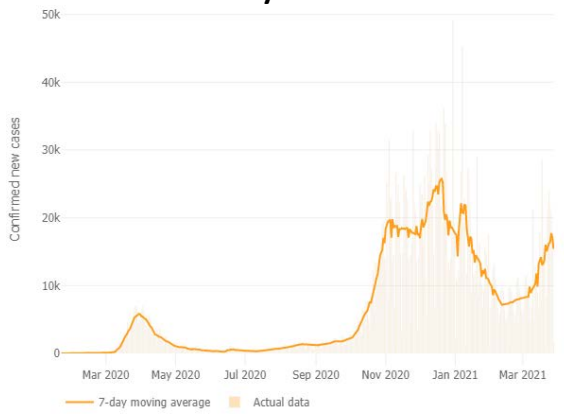
India



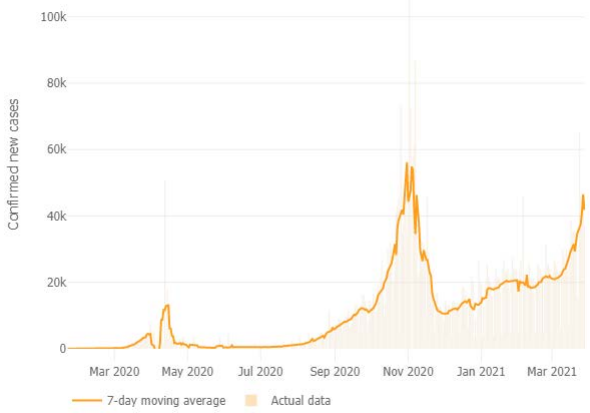
Italy



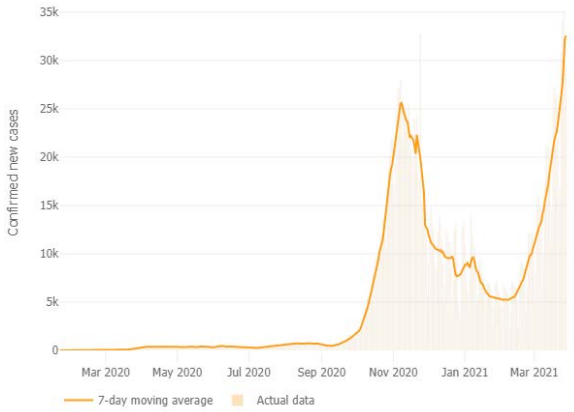
Germany



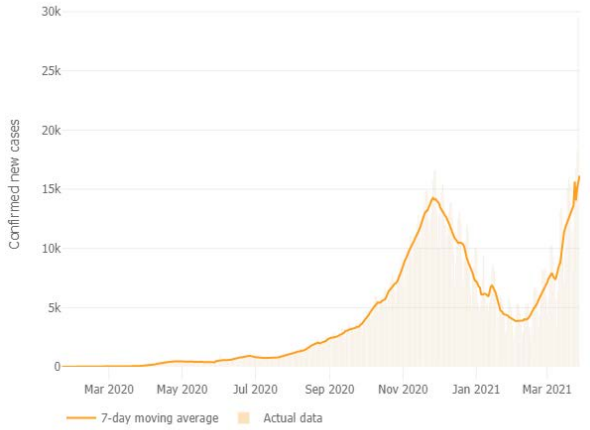
France



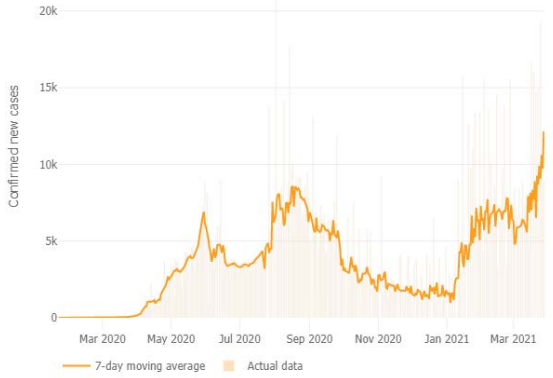
Poland



Ukraine



Peru



Data: as of 3/29/2021

https://coronavirus.jhu.edu/data/new-cases

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Which states have increasing COVID cases?

https://coronavirus.jhu.edu/data/new-cases-50-states

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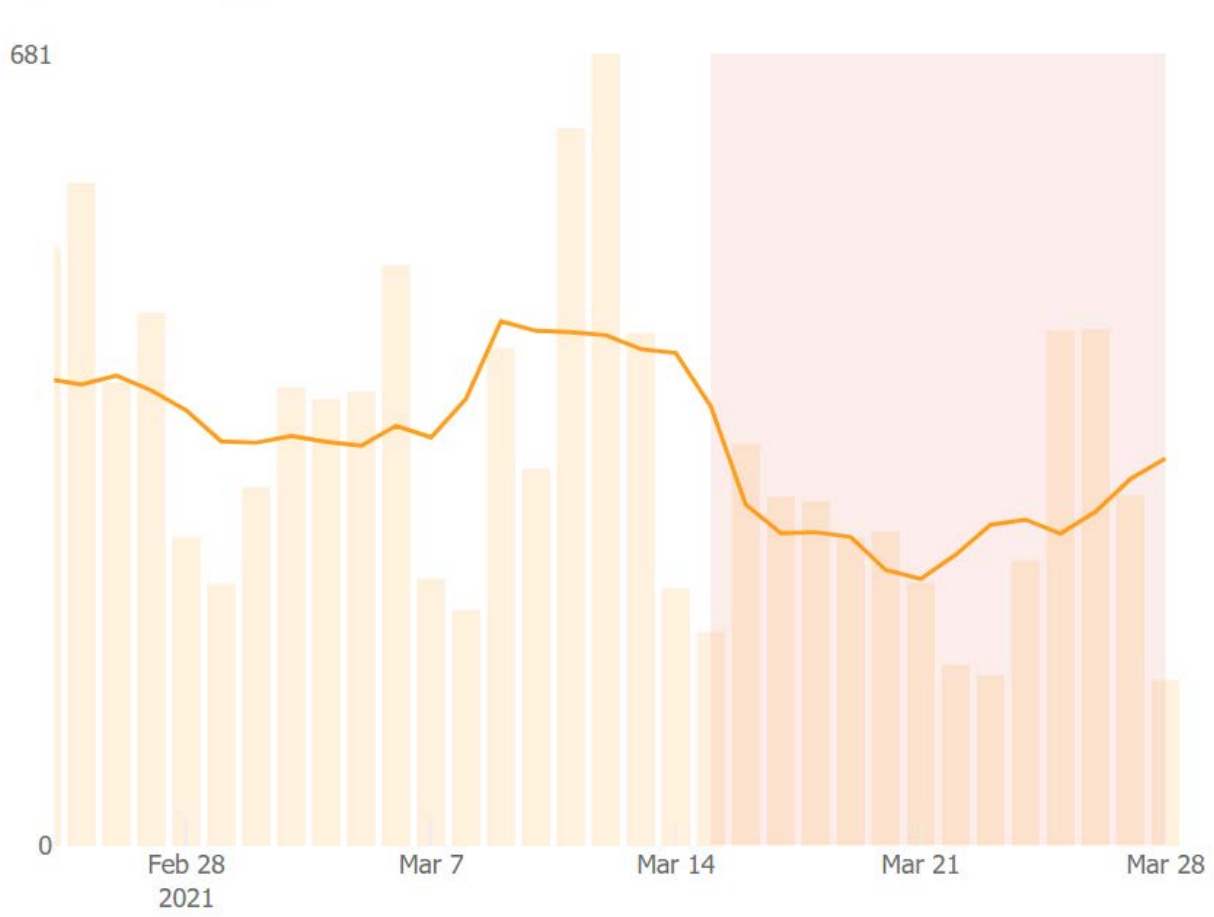
Daily confirmed new cases (7-day moving average) - Nevada



Data: as of 3/29/2021

https://coronavirus.jhu.edu/data/new-cases-50-states/nevada

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COVID-19 Variants

Natalie Crawford, MD
Infectious Disease

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CDC

- **Variants of Interest: (sort of like a person of interest) bears watching (3)**
- **Variants of Concern: evidence of increased transmissibility, more severe disease or reduction in neutralization by antibodies, reduced effectiveness of treatments of hard to detect. (5)**
- **Variant of High Consequence: clear evidence that prevention measures or medical countermeasures (MCMs) have significantly reduced effectiveness relative to previously circulating variants. (NONE)**

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Variants of Interest

- **B.1.526 - New York 11/2020**
- **B.1.525 – New York 11/2020**
- **P-2 - Brazil 4/2020**
- **Potential reduction in neutralization by monoclonal antibody treatments**
- **Potential reduction in neutralization by convalescent and post-vaccination sera**

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Variants of Concern: B.1.1.7

- **United Kingdom**
- **~50% increased transmission**
- **Likely increased severity based on hospitalizations and case fatality rates**
- **Minimal impact on neutralization by EUA monoclonal antibody therapeutics**
- **Minimal impact on neutralization by convalescent and post-vaccination sera (Natural/Vaccine immunity effective)**

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Variants of Concern: P.1

- **Japan (travelers from Brazil) / Brazil**
- **Moderate impact on neutralization by EUA monoclonal antibody therapeutics**
- **Reduced neutralization by convalescent and post-vaccination sera**
- **Manaus, city in the Amazon region, ~75% of the population had been infected with COVID in October. Despite this the area is experiencing a surge of infection – concern for increase in transmissibility and re-infection.**

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Variants of Concern: **B.1.351**

- **South Africa**
- **~50% increased transmission**
- **Moderate impact on neutralization by EUA monoclonal antibody therapeutics**
- **Moderate reduction on neutralization by convalescent and post-vaccination sera**

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Variants of Concern: **B.1.427 & B.1.429**

- **California**
- **~20% increased transmissibility**
- **Significant impact on neutralization by some, but not all, EUA therapeutics**
- **Moderate reduction in neutralization using convalescent and post-vaccination sera**

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Variants in Nevada (3/29/21)

- **B.1.427/B.1.429 (California) ~30% of all cases statewide**
- **B.1.1.7 (UK) 91 in NV (57 are in WCHD)**
- **B.1.351 (South Africa) 1 in NV (Renown)**
- **P.1 (Brazil) 0 cases in WCHD, 1 in NV (UMC)**

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- Dr. Mark Pandori, Director Nevada State Public Health Laboratory

Nevada

- **B.1.427 & B.1.429 are circulating in high numbers so the monoclonal antibody therapy Bamlanivimab is not recommended as a stand alone therapy by the US Dep HHS (affects CA, AZ & NV)**

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B.1.427 & B.1.429 (Ca) progression

SARS-CoV-2 Lineage Weekly Report, 29 March 2019,
Nevada State Public Health Laboratory

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B.1.1.7 (UK) Progression Jan-March

SARS-CoV-2 Lineage Weekly Report, 29 March 2019, Nevada State Public Health Laboratory

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Vaccines

Rudy Tedja, DO
Infectious Disease/Critical Care

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March 17, 2021

Governor Sisolak announces all Nevadans aged 16 and older will be eligible for the COVID-19 vaccine on April 5

Nevadans aged 16 and over with underlying conditions eligible for vaccine on March 22 through the Retail Pharmacy Program

BRIEFING ROOM

FACT SHEET: President Biden Announces 90% of the Adult U.S. Population will be Eligible for Vaccination and 90% will have a Vaccination Site Within 5 Miles of Home by April 19

MARCH 29, 2021 • STATEMENTS AND RELEASES

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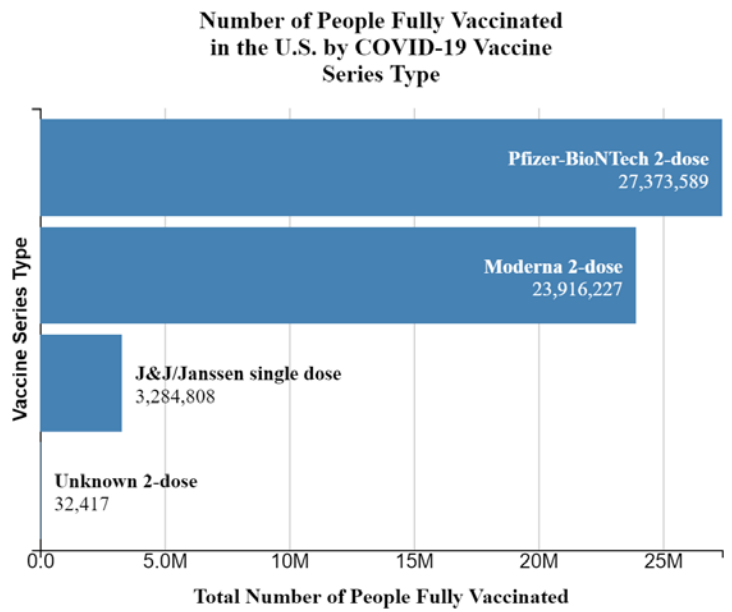
People Vaccinated	At Least One Dose	Fully Vaccinated
Total	97,593,290	54,607,041
% of Total Population	29.4%	16.4%
Population ≥ 18 Years of Age	97,226,718	54,514,865
% of Population ≥ 18 Years of Age	37.7%	21.1%
Population ≥ 65 Years of Age	40,218,262	27,762,018
% of Population ≥ 65 Years of Age	73.5%	50.8%

CDC | Data as of: Mar 31 2021 6:00am ET | Posted: Mar 31 2021 12:39PM ET

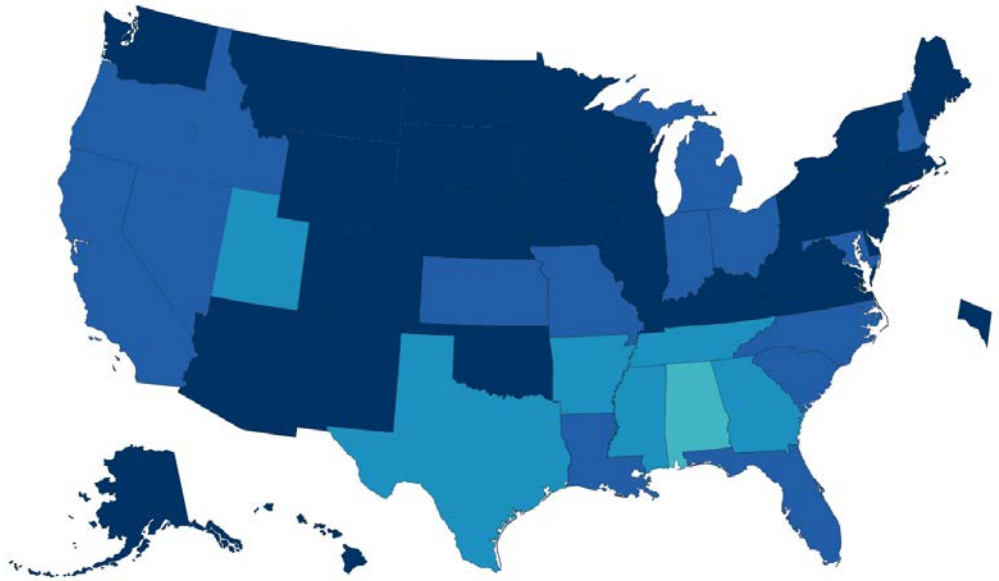
As of 3/31/2021

https://covid.cdc.gov/covid-data-tracker/#vaccinatio

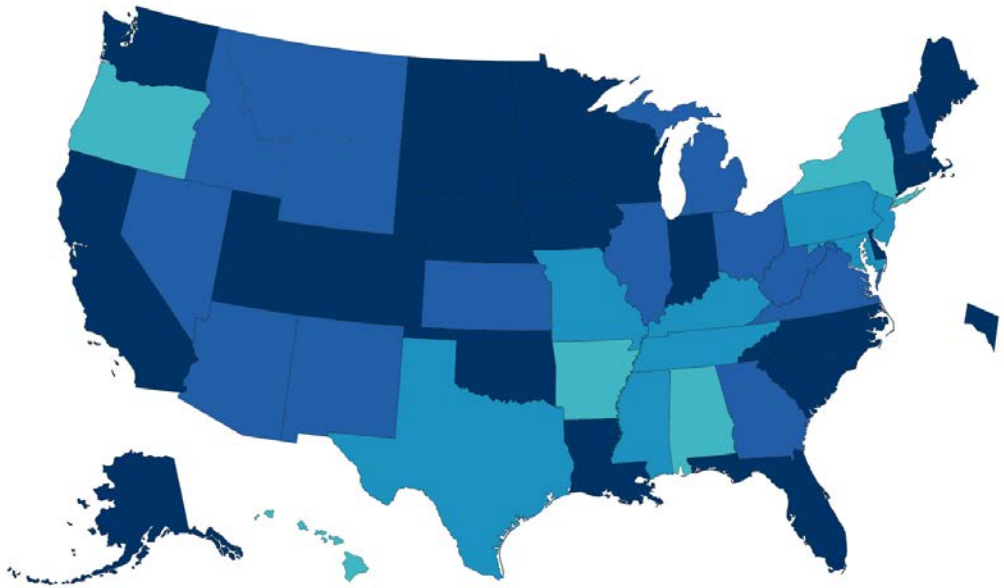


Total vaccine doses administered per 100,000 population

TOTAL POPULATION



POPULATION ≥ 65 YO



No Data | 0 | 1 - 30,000 | 30,001 - 35,000 | 35,001 - 40,000 | 40,001 - 45,000 | 45,001+

As of 3/31/2021

https://covid.cdc.gov/covid-data-tracker/#vaccinations

Total Doses Administered in Washoe County

KEY METRICS

203,019 Total Doses Reported as Administered

42,354 Doses Reported as Administered per 100K

126,773 Total Vaccinations Reported as Initiated+ (includes completed vaccinations)

26,448 Vaccinations Reported as Initiated per 100K

26.45 % % of Population that Initiated Vaccination

33.11 % % of Population 16 Years and Older that Initiated Vaccination

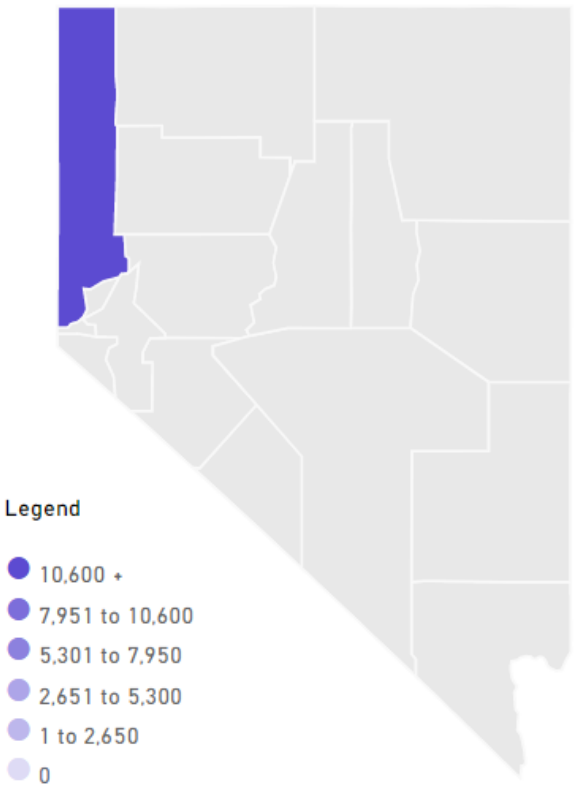
80,163 Total Vaccinations Reported as Completed

16,724 Vaccinations Reported as Completed per 100K

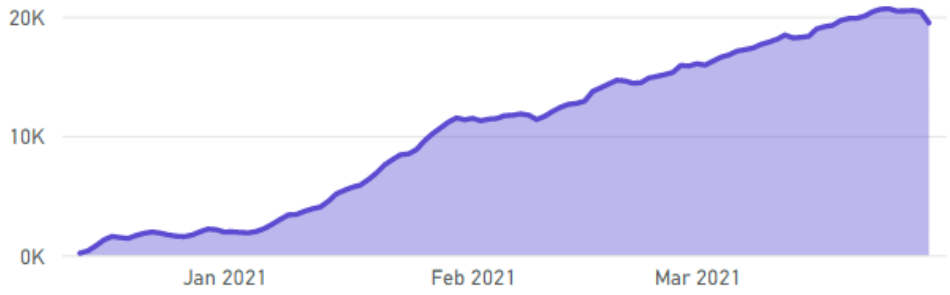
16.72 % % of Population Vaccinated

20.94 % % of Population 16 Years and Older Vaccinated

VACCINATION DOSES ADMINISTERED PER 100K



DAILY VACCINATIONS ADMINISTERED (14-day moving avg.) STATEWIDE ONLY



RESIDENT COUNTY	POPULATION	TOTAL DOSES ADMINISTERED	TOTAL VACCINATIONS INITIATED	TOTAL VACCINATIONS COMPLETED
Washoe	479,336	203,019	126,773	80,163
Total	**479,336**	**203,019**	**126,773**	**80,163**

As of 3/31/2021

https://nvhealthresponse.nv.gov/#covid-data-tracker

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COVID-19 Vaccines

- **Safe and effective**
- **Very effective against hospitalization and death**
- **Takes two weeks after fully vaccinated**

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What we don’t know yet

- **How well vaccines prevent you from spreading the virus, even if asymptomatic**
- **How long the acquired immunity after vaccines last**
- **How effective the vaccines are against new variants**
- **The unknown vaccine safety profile and effectiveness in immunocompromised individuals**

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Press releases – Pfizer-BioNTech vaccine

- **Safe and effective in adolescents (12-15yo) – 3/31/2021**
- **High efficacy up to 6 months – 4/1/2021**
- **100% effective in preventing COVID-19 cases in South Africa, where B.1.351 lineage is prevalent – 4/1/2021**

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https://www.pfizer.com/news/press-release/press-release-detail/pfizer-biontech-announce-positive-topline-results-pivotal. Accessed 4/4/2021
https://www.pfizer.com/news/press-release/press-release-detail/pfizer-and-biontech-confirm-high-efficacy-and-no-serious. Accessed 4/4/2021

Overview of COVID vaccines in US

Name	Type	Doses	FDA EUA	Age	Encode	Immune Response	Storage
Pfizer – BioNTech	mRNA	Two	12/11/2020	≥ 16 yo	Spike (S) protein	Neutralizing Abs; Th1 CD4+, CD8+	-70°C
Moderna	mRNA	Two	12/18/2020	≥ 18 yo	Spike (S) protein	Neutralizing Abs; Th1 CD4+	35°F-46°F (2-8°C)
Janssen (Johnson & Johnson)	Human Adenovirus vector (Ad26) DNA	One	2/27/2021	≥ 18 yo	Recombinant replication-incompetent S protein	Neutralizing Abs; Th1 CD4+, CD8+	36°F-46°F (2 -8°C)

Baden. NEJM. Feb 4, 2021; Polack NEJM. Dec 31, 2020

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Overview of Vaccine efficacy

	Demographics	Efficacy* for mild – mod disease (%)	Efficacy for severe disease (%)	COVID-hospitalization /death (%)
Pfizer - BioNTech	49% female 28% Hispanics 35% obesity >21% >65yo	95.0% (90.3 – 97.6)	100%	100%
Moderna	47% female 25% >65yo	94.1% (89.3 – 96.8)	97%	100%
Janssen (Johnson & Johnson)	45% female 34% >60yo 41% comorb 28% obesity	66.3% (59.9, 71.8) US -72% Latin America – 66% South Africa – 57%	85.4% all 3 SA: 95% B1.1.351 Brazil: 69% P.1/P.2	100%

Oliver et al. MMWR. December 18, 2020; March 2, 2021

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Overview of Vaccine Safety

- **No death that can be linked to the vaccine**
- **Anaphylaxis rate: 3-5 per million cases**
- **Majority of adverse effects are mild and last for 2-3 days post vaccine dose**

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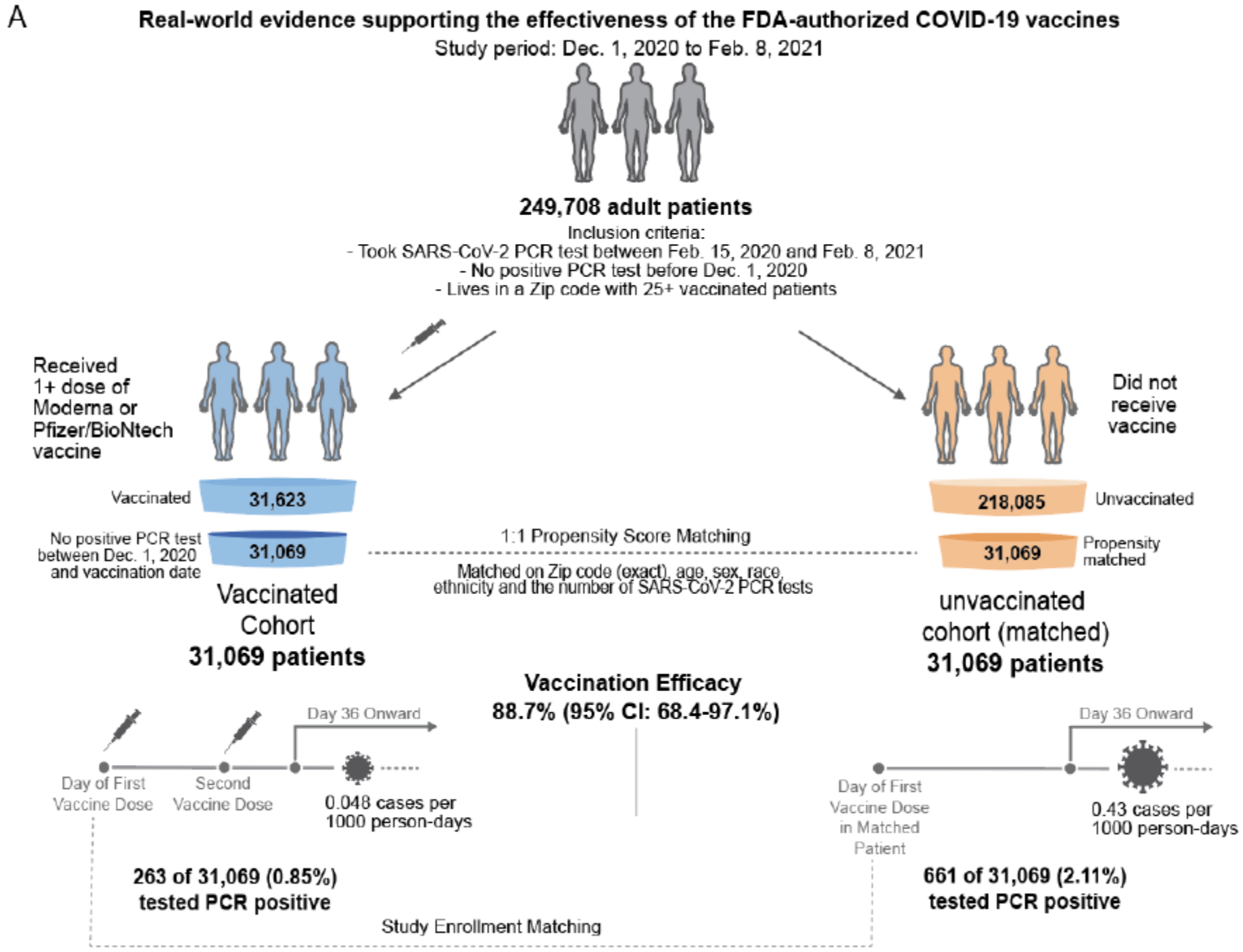
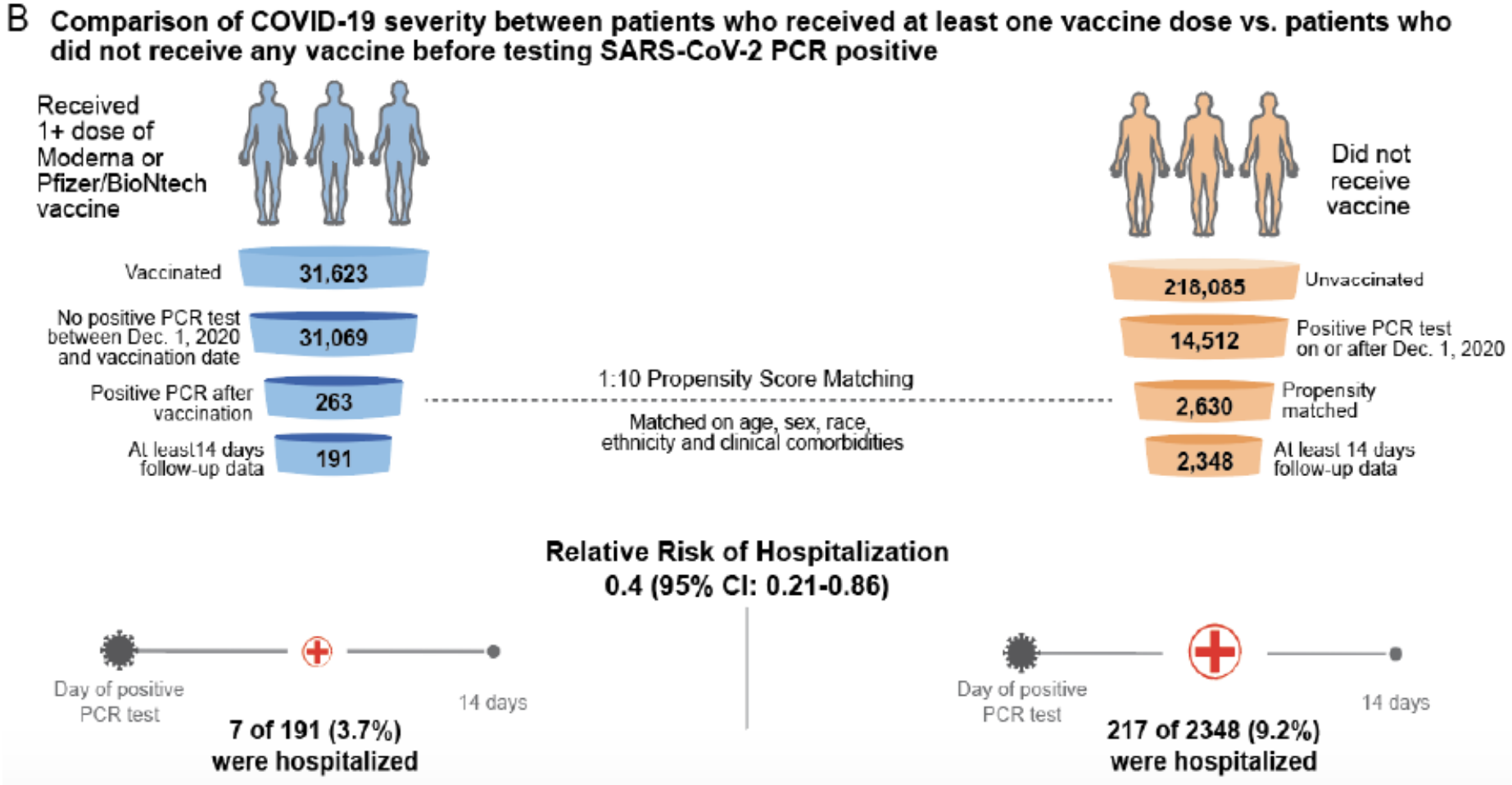
Real-world vaccine effectiveness



Pawlowski et al. medRxiv. Febuary 21, 2021



Pawlowski et al. medRxiv. Febuary 21, 2021

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Centers for Disease Control and Prevention
MMWR
Morbidity and Mortality Weekly Report
Early Release / Vol. 70
March 29, 2021

Interim Estimates of Vaccine Effectiveness of BNT162b2 and mRNA-1273 COVID-19 Vaccines in Preventing SARS-CoV-2 Infection Among Health Care Personnel, First Responders, and Other Essential and Frontline Workers — Eight U.S. Locations, December 2020–March 2021

TABLE 2. Person-days, SARS-CoV-2 infections, and vaccine effectiveness among health care personnel, first responders, and other essential and frontline workers, by messenger RNA immunization status — eight U.S. locations, December 14, 2020–March 13, 2021

		SARS-CoV-2 infections		Unadjusted vaccine effectiveness*	Adjusted vaccine effectiveness*,†
COVID-19 immunization status	Person-days	No.	Incidence rate per 1,000 person-days	% (95% CI)	% (95% CI)
Unvaccinated	116,657	161	1.38	N/A	N/A
Partially immunized	41,856	8	0.19	82 (62–91)	80 (59–90)
≥14 days after receiving first dose only§	15,868	5	0.32		
≥14 days after first dose through receipt of second dose	25,988	3	0.12		
Fully immunized					
≥14 days after second dose	78,902	3	0.04	91 (73–97)	90 (68–97)

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Thompson et al. MMWR. March 29, 2021

Real-world vaccine effectiveness in UK

- **Pfizer-BioNTech vaccine**
- **86% effective against UK Healthcare personnel**
- **85% effective in ≥ 80yo adults with multiple underlying multiple conditions**

Bernal et al. medRxiv. March 2, 2021
Hall et al. Lancet. February 2021

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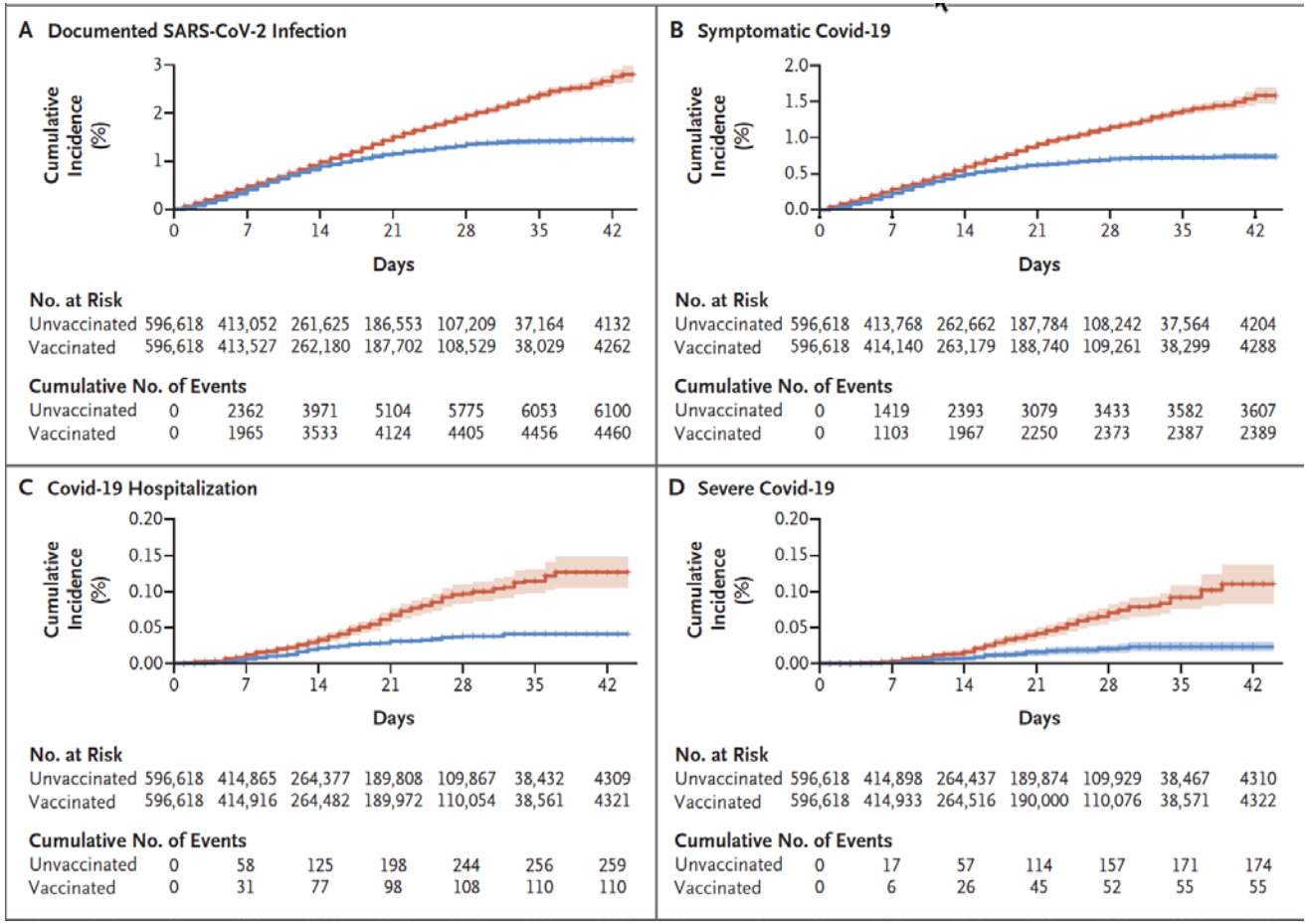
Large observational study in Israel



- **Pfizer-BioNTech vaccine**
- **90-94% effective against a spectrum of illness**

Dagan et al. NEJM. Feb 24, 2021

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Most commonly asked questions

1. **Should I not get the J&J vaccine since it’s not as effective as Pfizer or Moderna vaccines?**
2. **Do vaccines provide protection against asymptomatic infection?**
3. **Do vaccines prevent transmission to others?**
4. **How long does the vaccine work?**
5. **Should we relax COVID restrictions as we get more people vaccinated?**

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1. Should I not get the J&J vaccine since it's not as effective as Pfizer or Moderna vaccines?

NO

- **All vaccines are highly effective against severe disease, COVID-related hospitalizations and death**
- **Get whichever vaccine you can get first!**

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2. Do vaccines provide protection against asymptomatic infection?

YES

- In Moderna trial, 2/3 reduction of asymptomatic persons who tested positive at 2nd dose appointment
- In J&J trial, efficacy against asymptomatic seroconversion was 74% in a subset of participants
- Evidence of biological plausibility

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3. Do vaccines prevent transmission to others?

YES

- **Evidence of biological plausibility**
  - ↑ IgG antibodies in nasal passage
  - ↑ IgA mucosal immunoglobulins[1]
  - Monoclonal antibodies increase viral clearance in airways[2]
- **Real-world vaccine effectiveness[3,4,5]**
- **Decreased viral load after vaccination[6,7]**
- **Individual and community-level prevention**

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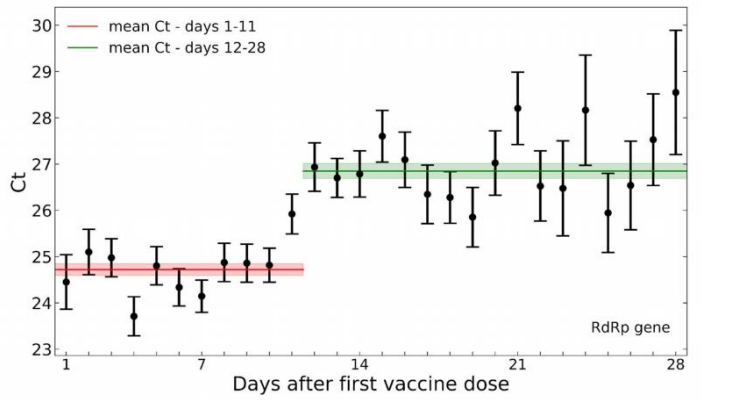
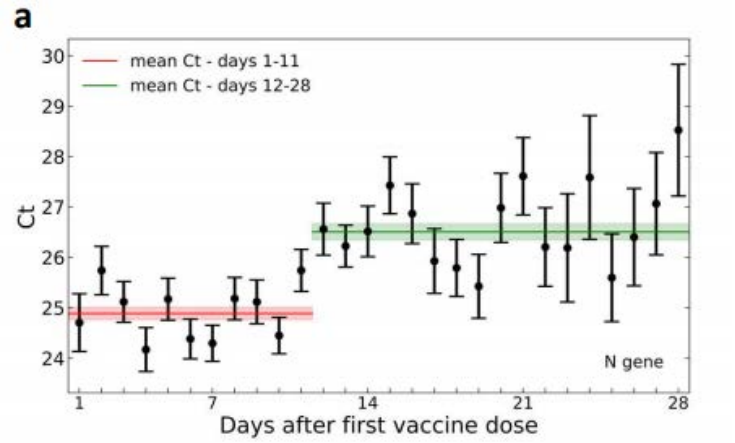
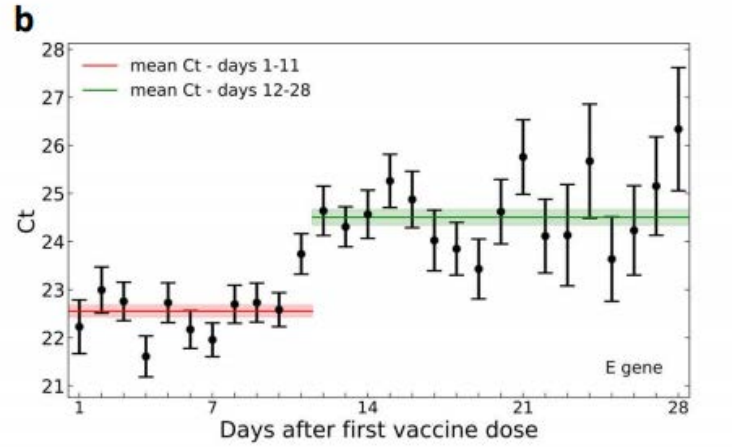
[1]Pasetti et al. Immuno Rev. Jan 2021; [2]Chen et al. NEJM. Jan 21, 2021
[3]Pawlowski. medRxiv. Feb, 2021; [4]Dagan. NEJM Feb, 2021; [5]Bernal. medRiv. March 2021
[6]Petter et al. NEJM. Feb 7, 2021; [7]Levine-Tiefenburn et al. medRxiv. Feb 8, 2021







Decreased SARS CoV-2 viral load after vaccination

- **Ct threshold against RdRp gene, N gene and E gene**
- **4 fold reduction of viral load 12-28 days after first dose of vaccine**
- **Reduced transmissibility?**

Levine-Tiefenburn. medRxiv Feb 8, 2021

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4. How long will the vaccines work?

- **Still learning**
- **Pfizer is effective for 6 months (press release 4/1)**
- **Data from phase 1 trial of Moderna vaccines suggested neutralizing antibodies persisted nearly for 4 months, with titers slightly declining overtime**
- **No specific recommendation yet for booster doses**

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5. Should we relax COVID restrictions as we get more people vaccinated?

ABSOLUTELY NO!

- **Premature**
- **We are still learning how many people are needed to achieve herd immunity**

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Diagnostic Testing

Evan Cherry, MD
Hospital Medicine

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Renown COVID Testing Platforms

1. Cepheid PCR
2. Thermo Fisher PCR
3. Quidel Fluorescent ImmunoAssay (FIA)
4. Roche Antibody Test

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Cepheid GeneXpert Xpress SARS-COV-2 RT-PCR

- **Nasopharyngeal Sample**
- **GeneXpert Infinity Automated System**
- **Cartridges include SARS-CoV2, Influenza A/B, and RSV**
- **“On-Demand” tests run immediately after sample is received**
- **March 2021:**
  - 773 Cepheid PCR Tests
  - Average Turnaround 1.3-2.04 hours

Renown® HEALTH

Thermo Fisher TaqPath COVID-19 SARS-CoV-2 RT-PCR

- **Nasopharyngeal Sample**
- **Roche Cobas 6800 automated system**
- **Thermofisher Thermocycler manual system**
- **Requires approximately 3 hours after preparing plate for a batch**
- **Guaranteed results within 24 hours, Inpatient prioritization**
- **March 2021:**
  - 4,377 Thermo Fisher PCR Tests
  - Average Turnaround 13.8-18.36 hours

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Quidel Fluorescent Immunoassay (FIA)

- **Nasopharyngeal Sample**
- **Sofia Fluorescent Immunoassay Analyzer**
- **Assay requires approximately 1 hour of preparation**
- **Samples are run every 15 minutes**
- **March 2021:**
  - 103 FIA Tests
  - Average Turnaround 3.67-6.47 hours

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Roche Elecsys Anti-SARS-CoV-2 Antibody Test

- **Serum Sample**
- **Run on standard Roche chemistry machine**
- **Detects a different epitope than the vaccine**
- **March 2021:**
  - 14 Total Ab Tests
  - Average Turnaround 10.92-14.67 hours

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Addressing SARS-CoV-2 Variants

- **Tests have multiple targets (e.g. 3 targets for Thermo Fisher test).**
- **If one target is negative while remainders are positive, the sample is flagged as a potential variant.**
- **Potential variants are sent to the state laboratory for sequencing and determination of variant.**
- **Assay manufacturers have informed our lab committee that standard assays are expected to detect variants (not expected false-negative).**
- **Laboratory committee reviews accuracy of test when new variants are discovered.**

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Clinical Manifestations

Farah Madhani-Lovely, MD
Pulmonary/Critical Care

Sarah Healy, MD
Pediatric Infectious Disease

Renown HEALTH

Clinical Manifestations

Table 2 Frequency of COVID-19 symptoms in the general population. 2020

Symptoms	Total number of studies					Studies with *n* of patients ≥ 10					Studies with *n* of patients ≥ 100				
	Studies (*n*)	Total Population	Presenting symptoms	%	Min–Max	Studies (*n*)	Total Population	Presenting symptoms	%	Min–Max	Studies (*n*)	Total Population	Presenting symptoms	%	Min–Max
Fever	144	40,674	23,858	58.66	4.3–100.0	129	40608	23,809	58.63	4.3–100	57	37,712	21,845	57.93	30.4–98.9
Cough	139	34,318	18,711	54.52	6.7–100.0	123	34,249	18,675	54.53	6.7–90.9	56	31,620	17,140	54.21	10.2–81.6
Malaise	5	316	94	29.75	29.2–100.0	4	315	93	29.52	29.2–90.9	1	244	65	26.64	–
Dyspnea	99	29,116	8973	30.82	1.3–100.0	88	29,068	8952	30.80	1.3–87.5	49	27,291	8363	30.64	1.3–77.0
Fatigue	78	15,061	4241	28.16	1.3–100.0	72	15,068	1238	8.18	1.3–81.4	37	13,492	3732	27.66	1.3–75.0
Sputum/secretion	57	14,835	3757	25.33	1.8–100.0	55	14,826	3752	25.31	1.8–100.0	34	13,855	3486	25.16	1.8–72.0
Dermatological manifestations	1	88	18	20.45	20.4	1	88	18	20.45	20.4	–	–	–	–	–
Anorexia	18	2621	531	20.26	1.2–39.9	17	262	530	202.29	1.3–39.9	11	2258	506	22.41	2.5–39.9
Sneeze	3	374	55	14.71	14.2–60.0	3	374	55	14.71	14.2–60.0	2	364	49	13.46	14.2
Neurological symptoms	7	2099	437	20.82	9.9–36.4	6	2091	435	20.80	9.9–36.4	5	2044	405	19.81	9.9–36.4
Rhinitis	3	224	32	14.29	16.3	3	224	32	14.29	16.3	1	100	15	15.00	–
Myalgia	69	15,037	2542	16.90	1.5–100.0	64	15,014	2533	16.87	1.5–62.7	34	13,571	2158	15.90	1.5–47.5
Goosebumps	4	1260	170	13.49	6.7–95.7	4	1260	170	13.49	6.7–95.7	1	1099	126	11.46	11.5
Sore throat	62	24,000	3459	14.41	2.2–100.0	59	23,986	3455	14.40	2.2–81.2	31	22,728	3239	14.25	2.2–89.8
Headache	76	17,367	2113	12.17	1.9–100.0	72	17,352	2108	12.15	1.9–66.1	34	15,609	1795	11.50	1.9–25.2
Diarrhea	85	11,841	1136	9.59	0.8–80.0	78	11,838	2415	20.40	0.8–80.0	41	22,599	2235	9.89	0.8–40.0
Chest pain	27	8287	952	11.49	0.6–43.9	27	8287	952	11.49	0.6–43.9	17	3467	883	25.47	0.6–86.7
Rhinorrhea	32	5634	433	7.69	1.4–100.0	27	5618	427	7.60	1.4–36.4	8	4820	334	6.93	1.4–15.9
Palpitation	7	1040	80	7.69	3.7–100.0	7	1040	80	7.69	3.7–100.0	5	904	69	7.63	3.7–10.7
Dizziness	14	2473	152	6.15	1.5–100.0	12	2468	149	6.04	2.0–15.7	6	2165	130	6.00	2.0–10.2
Nausea or vomiting	60	13,215	969	7.33	1.0–100.0	55	13,189	961	7.29	1.0–50.0	28	2965	869	29.31	1.3–20.0
Shivering	3	671	40	5.96	3.3–10.5	3	671	40	5.96	3.3–10.5	2	611	38	6.22	5.0–10.3
Confusion	7	3193	184	5.76	4.3–16.2	7	3193	184	5.76	4.3–16.2	3	2927	127	4.34	3.1
Nasal congestion	19	7957	435	5.47	0.7–100.0	17	7952	433	5.45	0.7–47.5	8	7599	375	4.93	0.7–6.8
Abdominal pain	16	4355	221	5.07	1.7–33.3	15	4352	220	5.06	1.7–20.0	11	4224	215	5.09	2.0–6.6
Hemoptysis	17	7580	125	1.65	0.9–7.3	17	7580	125	1.65	0.9–7.3	14	7433	122	1.64	0.9–7.3

Wien Klin Wochenschr
https://doi.org/10.1007/s00508-020-01760-4

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Clinical Manifestations

Table 1

Characteristic comparison of SARS-CoV, SARS-CoV-2, and MERS-CoV

	SARS-CoV-2	SARS-CoV	MERS-CoV
Start time	December 2019	November 2002	June 2012
Initial area	Wuhan, China	Guangdong, China	Jedda, Saudi Arabia
Confirmed patients	214 894	8096	2494
Mean age (range)	47-56 (0.5-92)	39.9 (1-91)	56
Male	58%-75%	44%	76.70%
HCWs	2%-29%	23.10%	9.80%
Symptoms			
Fever	83%-98%	99%-100%	98%
Dry cough	59%-78%	29%-75%	47%
Dyspnea	19%-55%	40%-42%	72%
Diarrhea	2%-10%	20%-25%	...
Sore throat	5%-17%	13%-25%	...
Ventilator support	2%-12%	14%-20%	80%
ARDS	3%-29%	20%-30%	Case reports
Mortality	690 953 (3.8%)	744 (10%)	858 (37%)

ARDS = adult respiratory distress syndrome; HCWs = healthcare workers; MERS-CoV = Middle East respiratory syndrome coronavirus; SARS-CoV = severe acute respiratory syndrome coronavirus.

<zdoi: 10.1097/JCMA.0000000000000463>

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TABLE 1

COVID-19 Pneumonia Imaging Classification	Rationale[6–11]	CT Findings*	Suggested Reporting Language
Routine Screening CT for Diagnosis or Exclusion of COVID-19 is Currently not Recommended by Most Professional Organizations or the US Centers for Disease Control and Prevention			
Typical appearance	Commonly reported imaging features of greater specificity for COVID-19 pneumonia	Peripheral, bilateral, GGO with or without consolidation or visible intralobular lines ("crazy-paving") Multifocal GGO of rounded morphology with or without consolidation or visible intralobular lines ("crazy-paving") Reverse halo sign or other findings of organizing pneumonia (seen later in the disease)	"Commonly reported imaging features of (COVID-19) pneumonia are present. Other processes such as influenza pneumonia and organizing pneumonia, as can be seen with drug toxicity and connective tissue disease, can cause a similar imaging pattern." [Cov19Typ]†
Indeterminate appearance	Nonspecific imaging features of COVID-19 pneumonia	Absence of typical features and presence of: Multifocal, diffuse, perihilar, or unilateral GGO with or without consolidation lacking a specific distribution and are non-rounded or non-peripheral Few very small GGO with a non-rounded and non-peripheral distribution	"Imaging features can be seen with (COVID-19) pneumonia, though are nonspecific and can occur with a variety of infectious and noninfectious processes." [Cov19Ind]†
Atypical appearance	Uncommonly *or* not reported features of COVID-19 pneumonia	Absence of typical or indeterminate features and presence of: Isolated lobar or segmental consolidation without GGO Discrete small nodules (centrilobular, "tree-in-bud") Lung cavitation Smooth interlobular septal thickening with pleural effusion	"Imaging features are atypical or uncommonly reported for (COVID-19) pneumonia. Alternative diagnoses should be considered." [Cov19Aty]†
Negative for pneumonia	No features of pneumonia	No CT features to suggest pneumonia.	No CT findings present to indicate pneumonia. (Note: CT may be negative in the early stages of COVID-19.) [Cov19Neg]†

*Please see[35] for specific definitions of CT findings.
†Suggested coding for future data mining.
Suggested reporting language includes coding of CT findings for data mining. Associated CT findings for each category are based upon available literature at the time of writing in March 2020, noting the retrospective nature of many reports, including biases related to patient selection in cohort studies, examination timing, and other potential confounders.
Notes: 1. Inclusion in a report of items noted in parenthesis in the Suggested Reporting Language column may depend upon clinical suspicion, local prevalence, patient status as a PUI, and local procedures regarding reporting; 2. CT is not a substitute for RT-PCR, consider testing according to local recommendations and procedures for and availability of RT-PCR.
GGO indicates ground glass opacity.

[Radiological Society of North America Expert Consensus Statement on Reporting Chest CT Findings Related to COVID-19. Endorsed by the Society of Thoracic Radiology, the American College of Radiology, and RSNA - Secondary Publication]

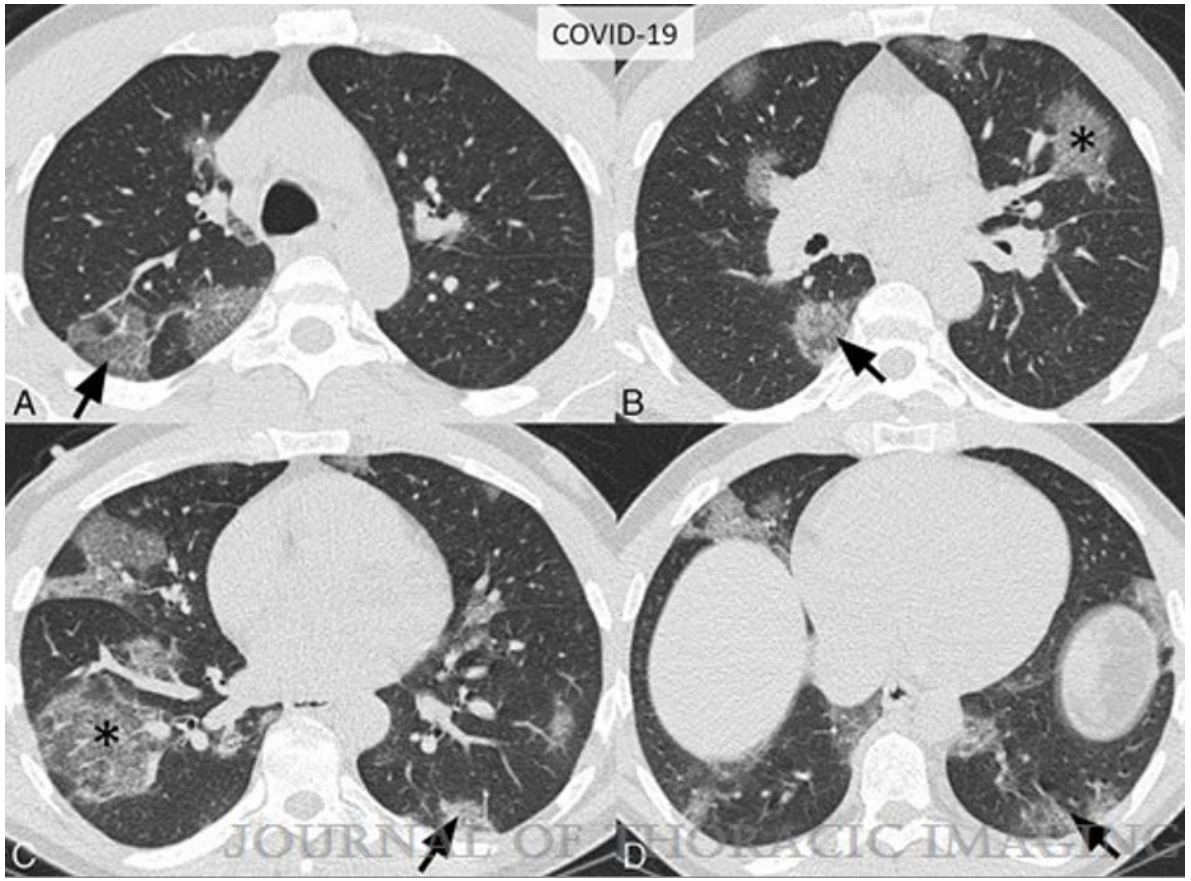
Simpson, Scott; Kay, Fernando U.; Abbara, Suhny; Bhalla, Sanjeev; Chung, Jonathan H.; Chung, Michael; Henry, Travis S.; Kanne, Jeffrey P.; Kligerman, Seth; Ko, Jane P.; Litt, Harold

Journal of Thoracic Imaging35(4):219-227, July 2020.

doi: 10.1097/RTI.0000000000000524

Proposed Reporting Language for CT Findings Related to COVID-19, Including Rationale, CT Findings and Suggested Reporting Language for each Category

FIGURE 1



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Typical CT imaging features for COVID-19. Unenhanced, thin-section axial images of the lungs in a 52-year-old man with a positive RT-PCR (A–D) show bilateral, multifocal rounded (asterisks) and peripheral GGO (arrows) with superimposed interlobular septal thickening and visible intralobular lines (“crazy-paving”). Routine screening CT for diagnosis or exclusion of COVID-19 is currently not recommended by most professional organizations or the US Centers for Disease Control and Prevention.

Extrapulmonary Clinical Manifestations

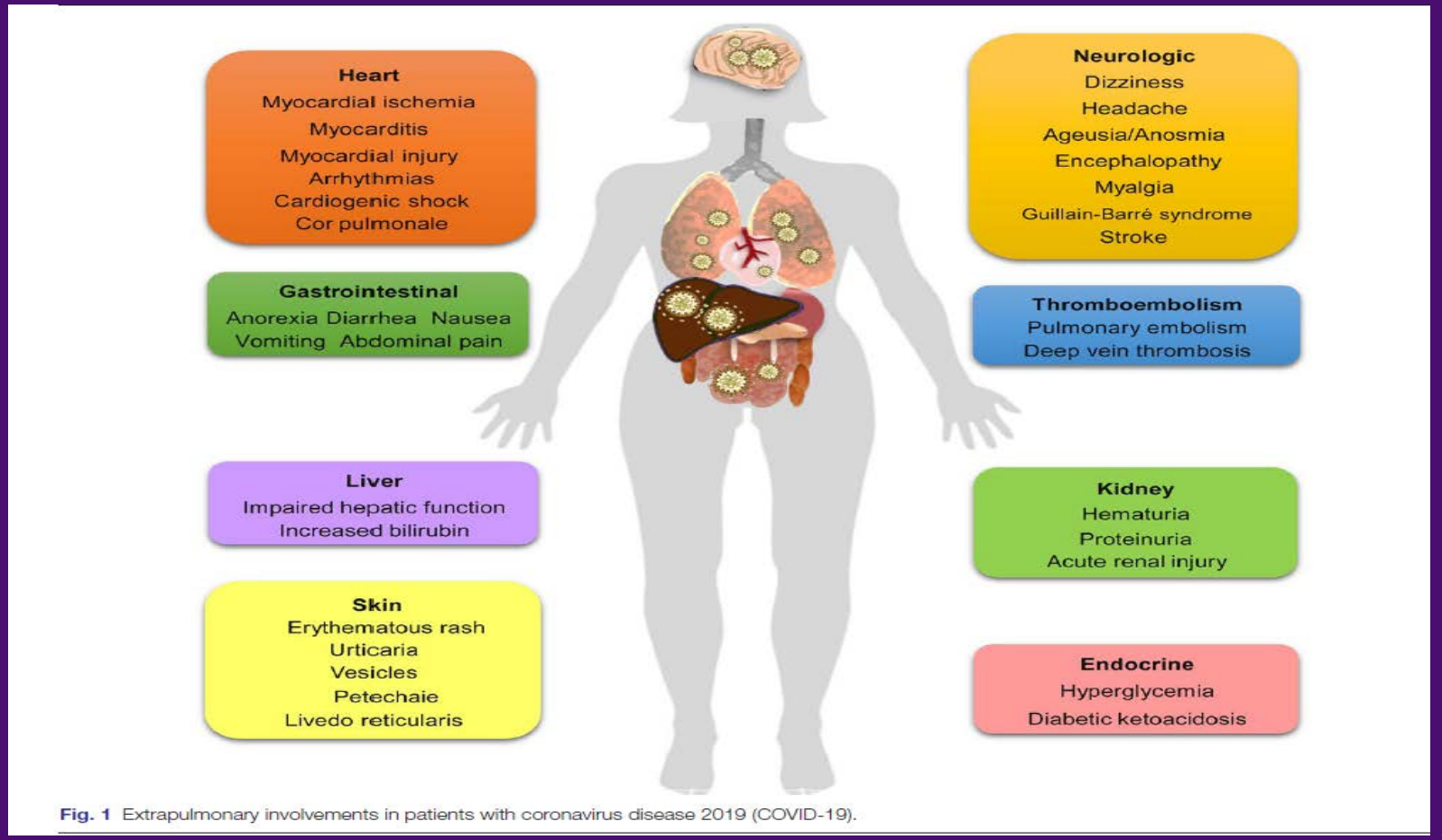

Fig. 1 Extrapulmonary involvements in patients with coronavirus disease 2019 (COVID-19).

https://doi.org/10.1038/s41591-021-01283-z

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Table 2 Summary results of the meta-analysis of mean values of each Biomarker in severe vs non-severe cases

Anomalies	SMD (95% CI)	P-value	Heterogeneity I2 (%)	Number of studies	Sample size for severe	Sample size for Non-severe
Inflammation						
Procalcitonin	0.72 (0.34;1,11)	< 0.001	87	6	467	1042
CRP	1.34 (0.83;1.86)	< 0.001	95	9	670	1304
IL-6	0.93 (0.25;1.61)	0.007	93	3	369	506
ESR	0.27 (−0.16;0.70)	0.22	90	4	435	1029
Blood routine						
Lymphocytes count	-0.57 (−0.71; −0.42)	< 0.001	61	12	888	2449
Lymphocytes %	-0.81 (−1.12; −0.49)	< 0.001	62	3	367	306
Thrombocytes	-0.26 (− 0.48; − 0.04)	0.02	72	7	445	1619
Eosinophils	−0.28 (− 0.50; − 0.06)	0.01	0	2	114	322
Neutrophils	0.52 (0.28;0.76)	< 0.001	80	9	646	1510
Haemoglobin	−0.20 (− 0.37; − 0.03)	0.02	0	4	165	678
Monocytes	−0.09(− 0.27;0.08)	0.30	14	4	372	426
White Blood Cells	0.13 (−0.14;0.39)	0.35	90	11	1133	2566
CD3+T	−0.77(−0.95; −0.59)	< 0.001	0	2	307	437
Cardiac injury biomarkers						
CK-MB	0.68(0.48;0.87)	< 0.001	30	4	185	965
Troponin I	0.71(0.42;1.00)	< 0.001	0	2	57	373
Biochemestry						
CK	0.48(0.10;0.87)	0.01	89	7	343	1317
Myoglobin	1.14(0.81;1.47)	< 0.001	66	3	149	863
ALAT	0.53(0.34;0,71)	< 0.001	68	10	507	1785
ASAT	0.96(0.58;1.34)	< 0.001	91	9	453	1650
Albumin	−1.67(−2.40; −0.94)	< 0.001	93	4	185	855
Creatinemia	0.18(0.01;0.35)	0.04	49	8	368	1417
Blood urea nitrogen	0.58(0.23;0.93)	0.001	83	5	277	920
Total bilirubin	0.32(0.18;0.47)	< 0.001	28	7	344	1253
LDH	1.36(0.75;1.98)	< 0.001	95	7	343	1317
Potassium	−0.10(−0.43;0.23)	0.55	79	3	248	1061
Sodium	−0.19(− 0.72;0.34)	0.49	91	3	231	983
γ-GT	1.03(0.83;1.22)	< 0.001	0	2	143	473
Blood clothing						
PT	0.48(0.23;0.73)	< 0.001	16	3	111	246
D-dimer	0.54(0.31;0.77)	< 0.001	69	7	348	1235
aPT	0.17(−0.23;0.57)	0.40	74	4	164	274
Fibrinogen	0.09(−0.56;0.74)	0.78	77	2	56	320

SMD Standardized mean difference; *CRP* C-reactive protein; *CK* Creatine kinase; *IL-6* interleukin-6; *ALAT* alanine amino-transferase; *ASAT* aspartate amino-transferase; *LDH* Lactate dehydrogeneses; *PT* prothrombin time; *aPT* activated partial thromboplastin;

Covid Long Hauler

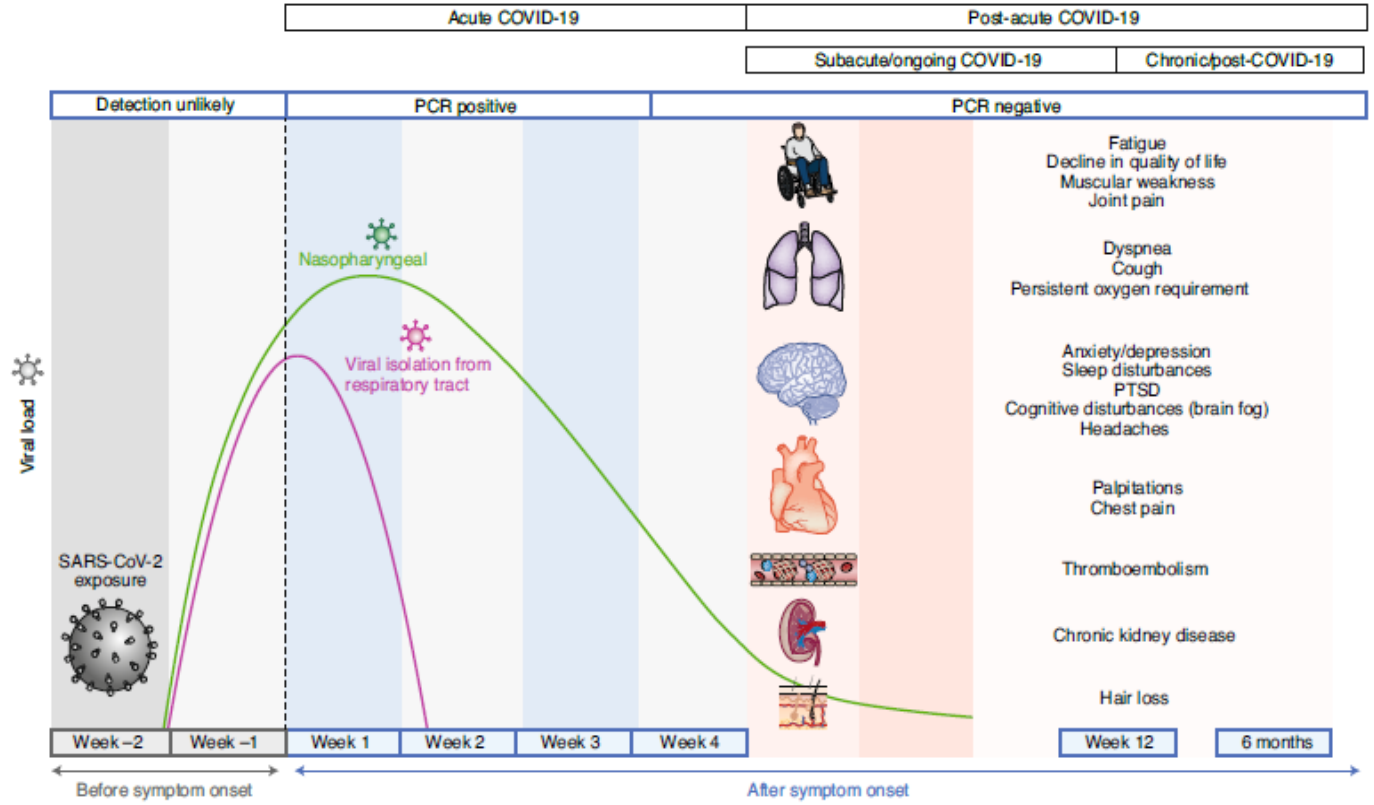

Fig. 1 | Timeline of post-acute COVID-19. Acute COVID-19 usually lasts until 4 weeks from the onset of symptoms, beyond which replication-competent SARS-CoV-2 has not been isolated. Post-acute COVID-19 is defined as persistent symptoms and/or delayed or long-term complications beyond 4 weeks from the onset of symptoms. The common symptoms observed in post-acute COVID-19 are summarized

https://doi.org/10.1038/s41591-021-01283-z

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Multidisciplinary Approach

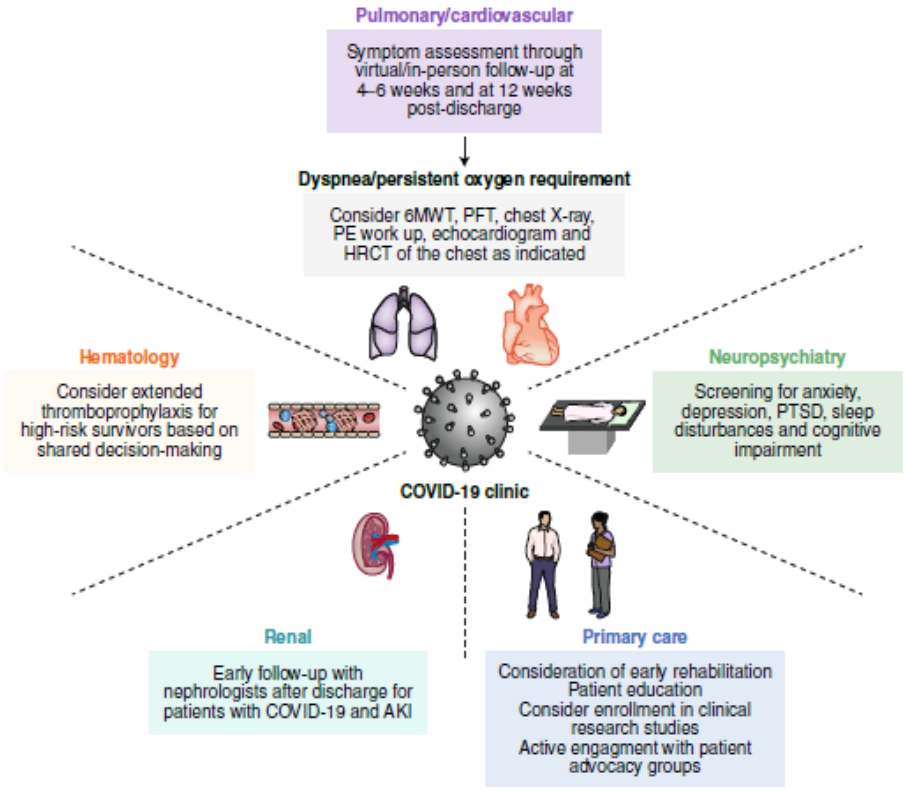

Fig. 2 | Interdisciplinary management in COVID-19 clinics. Multidisciplinary collaboration is essential to provide integrated outpatient care to survivors of acute COVID-19 in COVID-19 clinics. Depending on resources, prioritization may be considered for those at high risk for post-acute COVID-19, defined as those with severe illness during acute COVID-19 and/or requirement for care in an ICU, advanced age and the presence of organ comorbidities (pre-existing respiratory disease, obesity, diabetes, hypertension, chronic cardiovascular disease, chronic kidney disease, post-organ transplant or active cancer). The pulmonary/cardiovascular management plan was adapted from a guidance document for patients hospitalized with COVID-19 pneumonia[76]. HRCT, high-resolution computed tomography; PE, pulmonary embolism.

https://doi.org/10.1038/s41591-021-01283-z

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Research trials – answer questions

Table 2 | Active research studies and questions pertaining to post-acute COVID-19

Question	Study name and/or ID*
General	
What are the long-term sequelae of COVID-19?	COVIDOM (NCT04679584) CO-Qo-ICU (NCT04401111) MOIST (NCT04525404) LIINC (NCT04362150) NCT04411147 NCT04573062 NCT04605757
What are the immunologic, enzymatic, metabolic and radiographic predictors of post-acute COVID-19?	BIOMARK-COVID (NCT04664023) MOIST (NCT04525404)
What are the long-term effects of COVID-19 on health-related quality of life?	COVIDOM (NCT04679584) RECOVER-19 (NCT04456036) CO-Qo-ICU (NCT04401111) COREG Extension (NCT04602260) NCT04586413 NCT04632355
What are the long-term effects of COVID-19 on functional exercise capacity?	CO-Qo-ICU (NCT04401111) COREG Extension (NCT04602260)
Pulmonary	
Is there a role for antifibrotic therapy for the prevention of development of pulmonary fibrosis and other respiratory complications in COVID-19 survivors?	NCT04652518 NCT04282902 NCT04541680 NCT04527354
Does pulmonary rehabilitation improve pulmonary outcomes in post-acute COVID-19?	NCT04649918 NCT04365738 NCT04406532 NCT04642040
Hematologic	
Does extended thromboprophylaxis lead to clinically meaningful benefit with regards to post-hospital discharge VTE in patients with COVID-19?	NCT04508439 COVID-PREVENT (NCT04416048)
Does prolonged thromboprophylaxis lead to clinically meaningful benefit with regards to venous thromboembolic events in outpatients with COVID-19?	ACTIV4 (NCT04498273) PREVENT-HD (NCT04508023)
Do anti-platelets such as aspirin have a role in primary thromboprophylaxis in patients with COVID-19 managed as outpatients?	ACTIV4 (NCT04498273)
Cardiovascular	
What are the medium- and long-term effects of COVID-19 on biventricular cardiac function?	CO-Qo-ICU (NCT04401111) MOIST (NCT04525404)
Neuropsychiatric	
What are the physical examination and brain-imaging characteristics in those with persistent neurological symptoms in post-acute COVID-19?	NCT04564287
What are the long-term psychiatric sequelae of COVID-19?	CO-Qo-ICU (NCT04401111) NCT04632355 MIND/COVID-19 (NCT04556565)
Renal	
What are the short- and long-term renal outcomes and their predictors in COVID-19 survivors?	NCT04353583 CO-Qo-ICU (NCT04401111) MOIST (NCT04525404)
Gastrointestinal and hepatobiliary	
What are the long-term consequences of COVID-19 on gastrointestinal symptoms, post-infection irritable bowel syndrome and dyspepsia?	NCT04691895

*Study IDs are for ClinicalTrials.gov.

https://doi.org/10.1038/s41591-021-01283-z

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Pediatric COVID-19

- **Sara Healy, MD MPH; Pediatric Infectious Diseases**

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COVID-19 + Pediatrics

Figure 1. Timeline of the Impact of the COVID-19 Pandemic on Pediatric Patients[8,9]

Dec. 18 2019 — First COVID-19 case identified in China

Dec. 31 — Cases reported to the WHO

Jan. 12 2020 — Genetic sequence of SARS-CoV-2 is shared

Jan. 20 — First pediatric case reported in China

Jan. 30 — WHO declares a public health emergency of international concern

Feb. 19 — First pediatric case reported in Korea

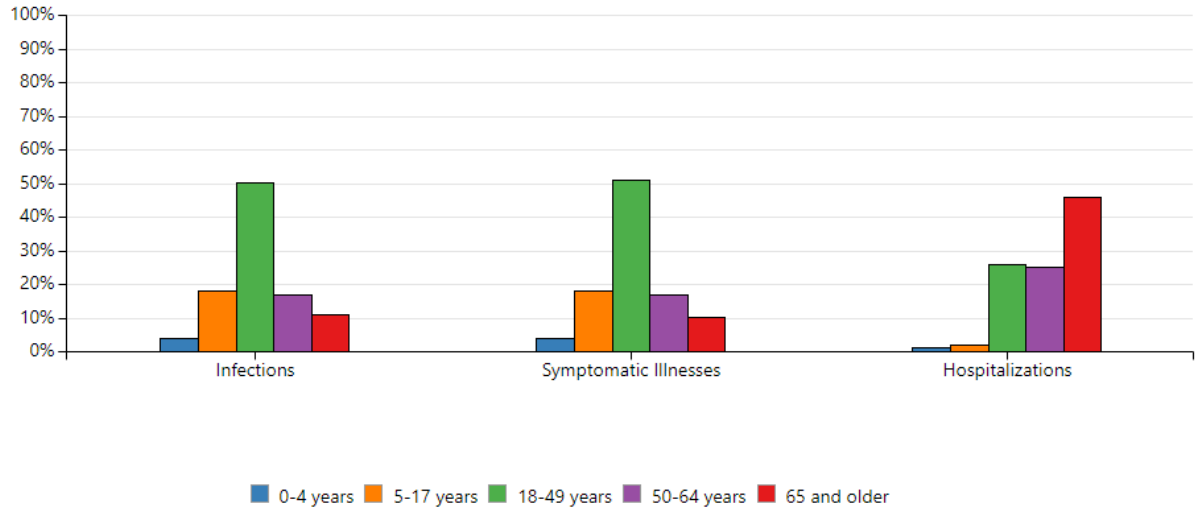
Mar. 02 — First pediatric case reported in the United States

Mar. 11 — Global pandemic declared by WHO

Mar. 13 — United States declares national state of emergency

Mar. 24 — First pediatric death reported in the United States

Percentage of COVID-19 infections, symptomatic illness, and hospitalizations by age group



Data Table

	Infections	Symptomatic Illnesses	Hospitalizations
0-4 years	4%	4%	1%
5-17 years	18%	18%	2%
18-49 years	50%	51%	26%
50-64 years	17%	17%	25%
65 and older	11%	10%	46%

Feldstein LR et al. NEJM. June 2020.

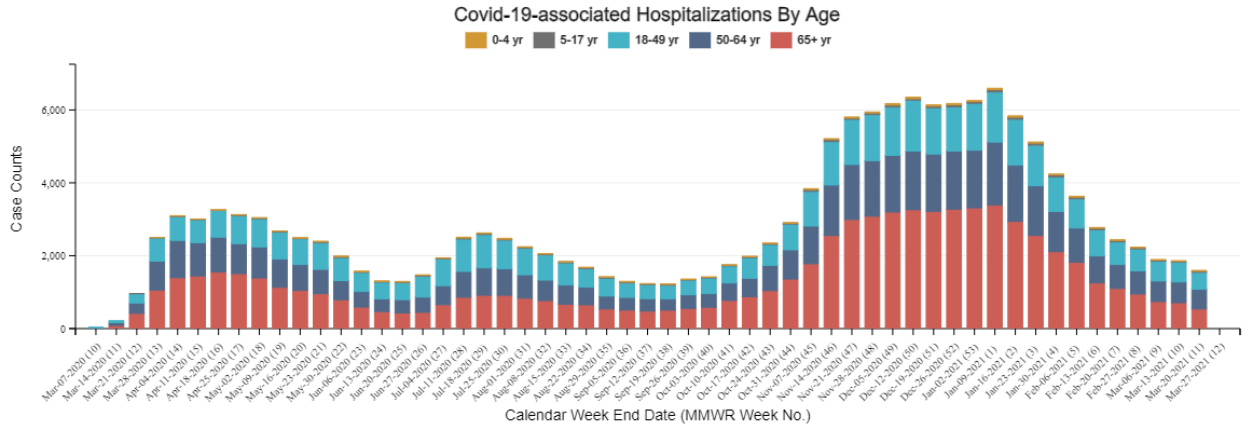
COVID-19 + Pediatrics

Figure 1. Timeline of the Impact of the COVID-19 Pandemic on Pediatric Patients[8,9]

Dec. 18 2019	**Dec. 31**	**Jan. 12 2020**	**Jan. 20**
First COVID-19 case identified in China	Cases reported to the WHO	Genetic sequence of SARS-CoV-2 is shared	First pediatric case reported in China
Jan. 30	**Feb. 19**	**Mar. 02**	**Mar. 11**
WHO declares a public health emergency of international concern	First pediatric case reported in Korea	First pediatric case reported in the United States	Global pandemic declared by WHO
Mar. 13	**Mar. 24**		
United States declares national state of emergency	First pediatric death reported in the United States		

COVID-NET | A Weekly Summary of U.S. COVID-19 Hospitalization Data

Laboratory-Confirmed COVID-19-Associated Hospitalizations



Cumulative case count by age group

	0-4 yr	5-17 yr	18-49 yr	50-64 yr	65+ yr	Total
2020	931	1528	40181	43251	73048	158939

The Coronavirus Disease 2019 (COVID-19)-Associated Hospitalization Surveillance Network (COVID-NET) hospitalization data are preliminary and subject to change as more data become available. In particular, case counts and rates for recent hospital admissions are subject to lag. As data are received each week, prior case counts and rates are updated accordingly.

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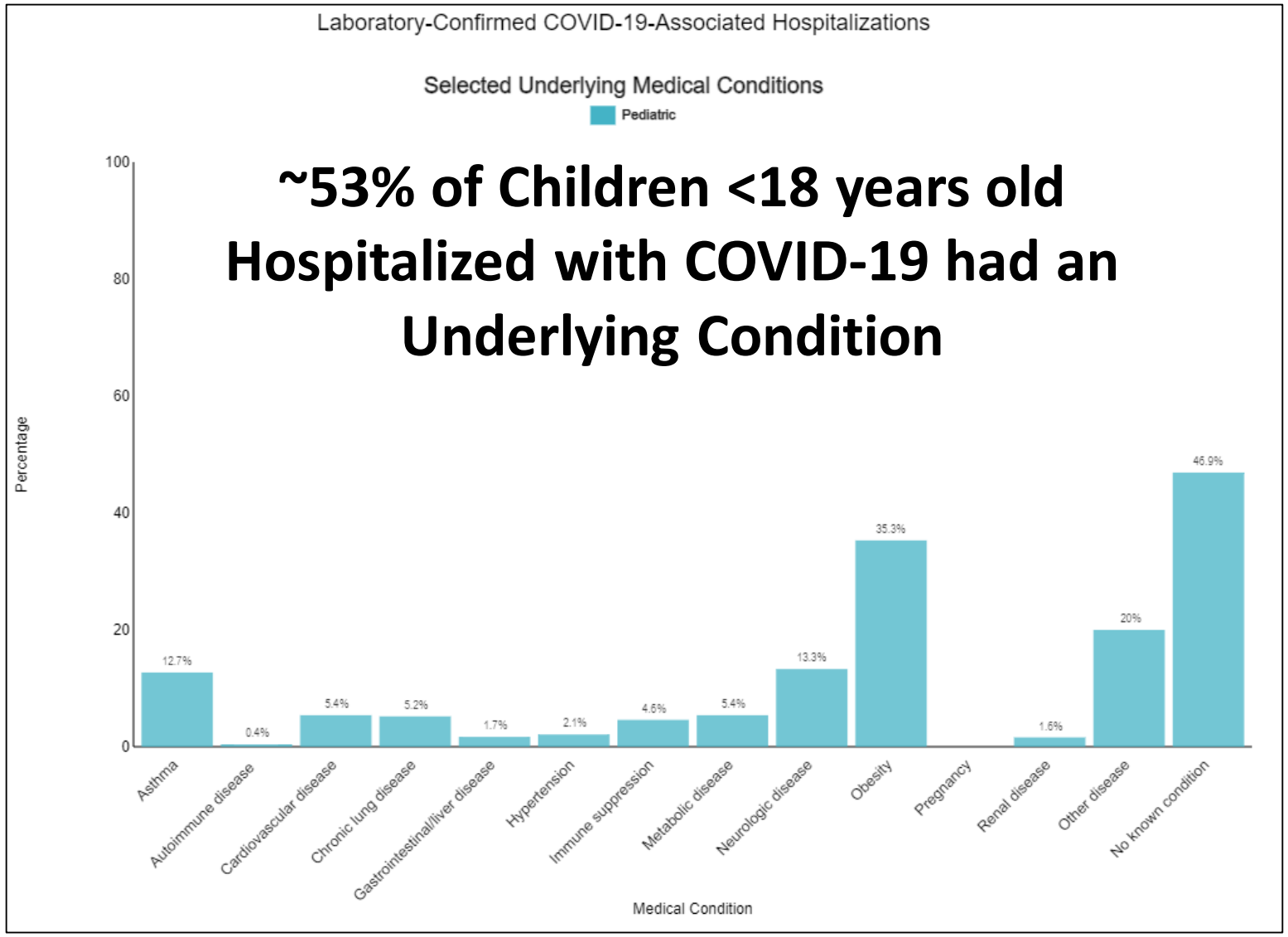
CDC. COVID-NET. 2020

COVID-19 + Pediatrics



- **Treatment**
  - Supportive care
  - Remdesivir
  - Steroids

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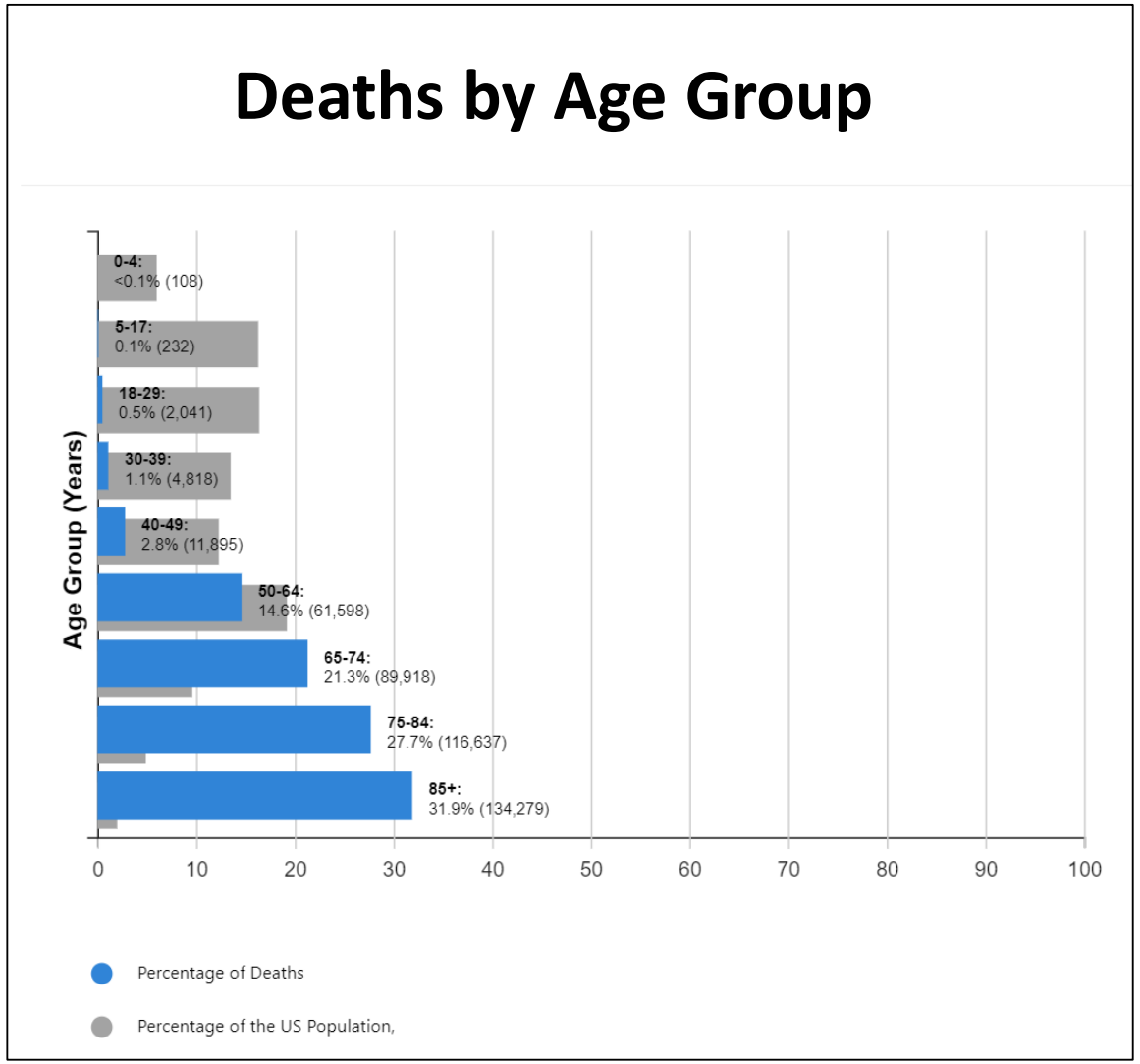
CDC. COVID-NET. 2020; Bhimraj A et al. IDSA. 2021.

COVID-19 + Pediatrics



- **Treatment**
  - Supportive care
  - Remdesivir
  - Steroids

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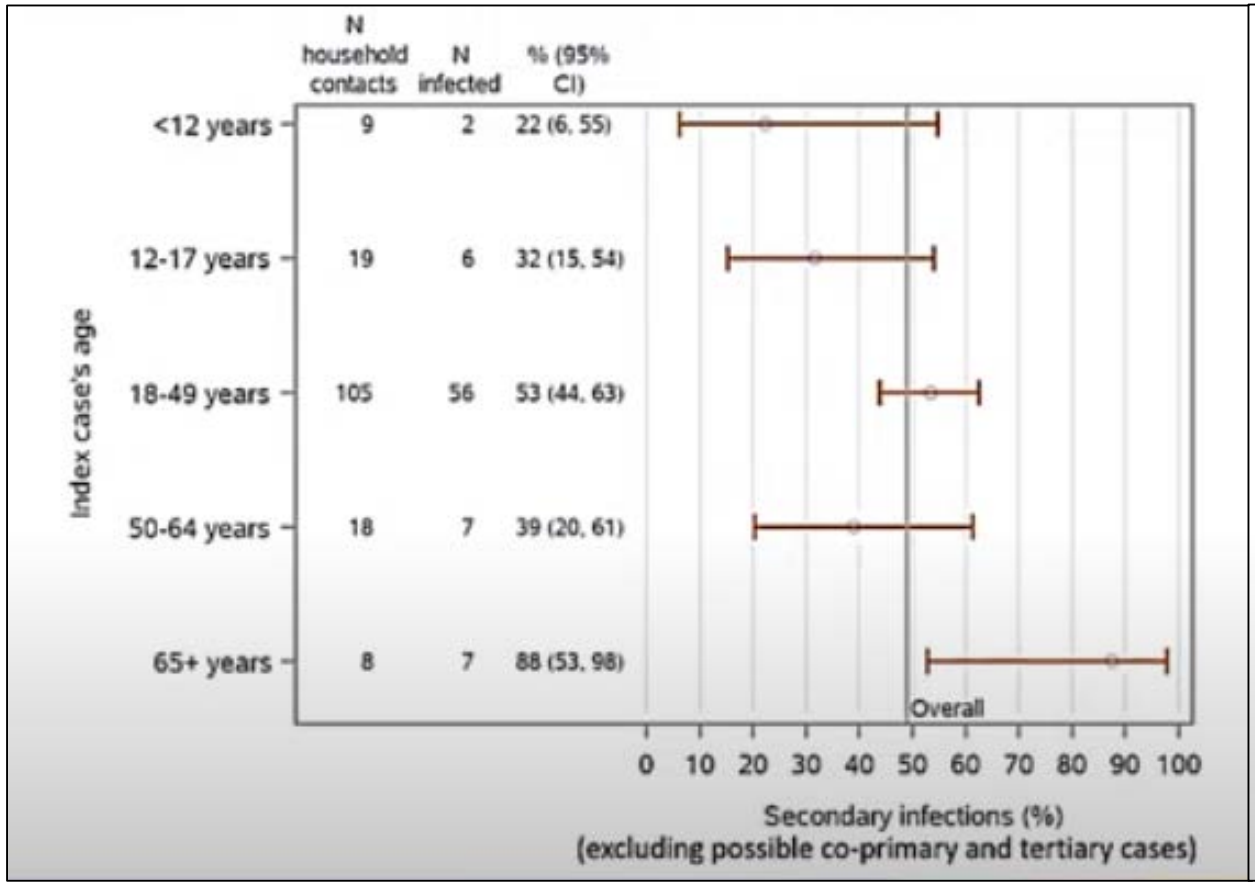
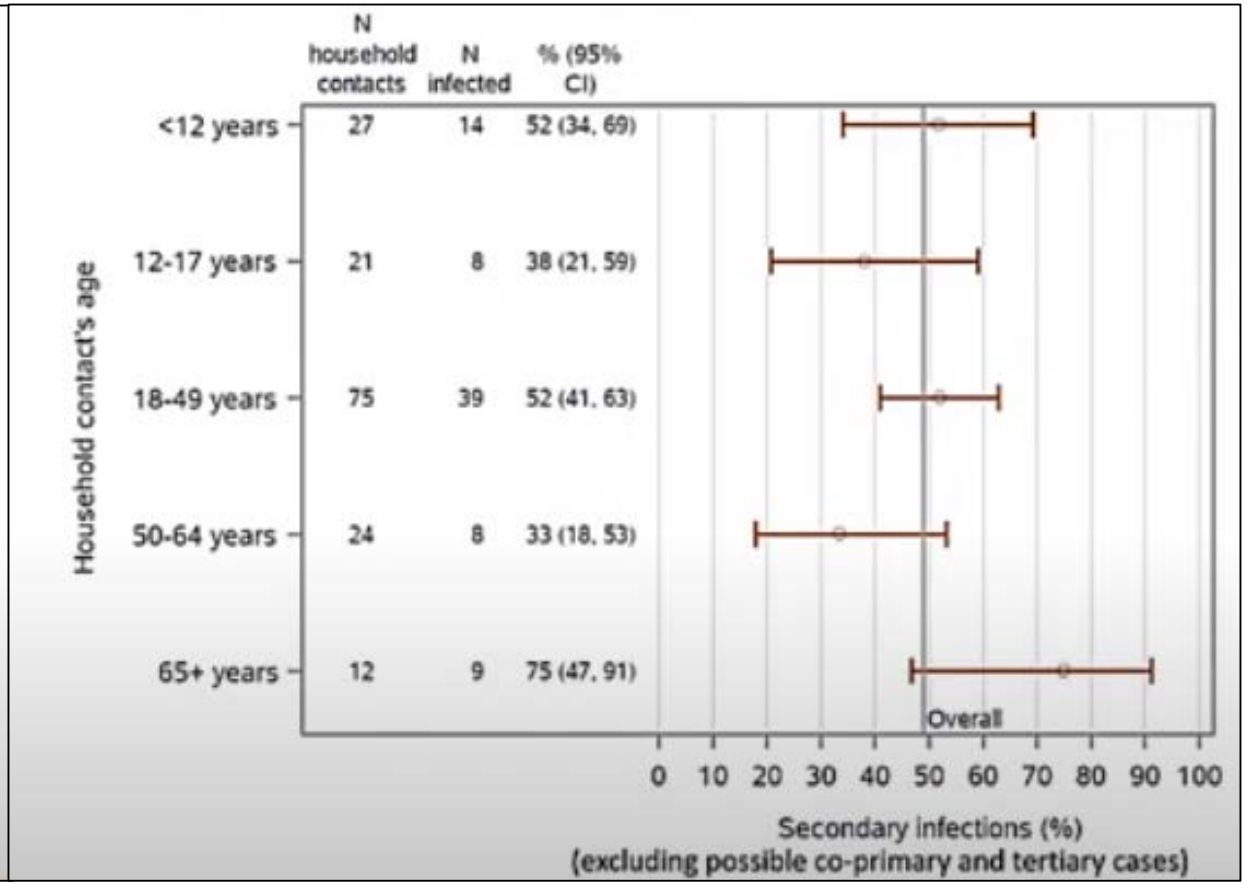
CDC. COVID-NET. 2020; Bhimraj A et al. IDSA. 2021.

COVID-19 + Pediatrics

Secondary Infection Rates: Symptomatic Children Seem to Transmit SARS-CoV-2 Less than Adults



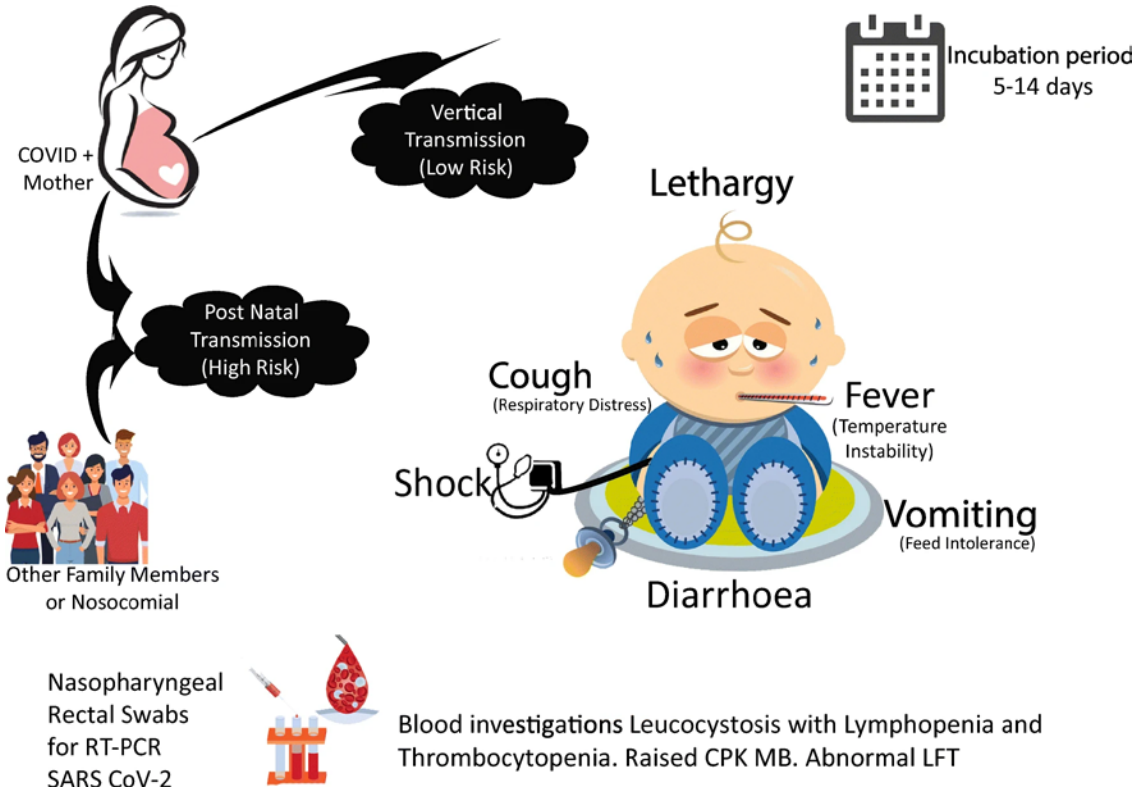
Children Exposed in the Household had Similar Risk of SARS-CoV-2 Infection as Adults



Laws RL et al. Pediatrics. 2020

COVID-19 + Neonates

- **In-utero vertical transmission is possible, but rare**
- **Post-delivery transmission**
  - ~2% neonates infected post-delivery (24-96 hrs)
  - Highest risk = closer onset of COVID-19 infection in mom to delivery
  - Hospitalization/NICU needs occur but are rare
- **Evolution from separation to room-in**
  - Same rate of a positive PCR when simple infection prevention steps taken
- **Infant testing**
  - 24 hrs of life and repeat at 48-72 hrs if still hospitalized



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Perinatal COVID-19 Registry, AAP. 2021; Vardhelli V et al. Euro J Peds. 2021.

COVID-19 + Pediatrics

Figure 1. Timeline of the Impact of the COVID-19 Pandemic on Pediatric Patients[8,9]

Dec. 18 2019 — First COVID-19 case identified in China

Dec. 31 — Cases reported to the WHO

Jan. 12 2020 — Genetic sequence of SARS-CoV-2 is shared

Jan. 20 — First pediatric case reported in China

Jan. 30 — WHO declares a public health emergency of international concern

Feb. 19 — First pediatric case reported in Korea

Mar. 02 — First pediatric case reported in the United States

Mar. 11 — Global pandemic declared by WHO

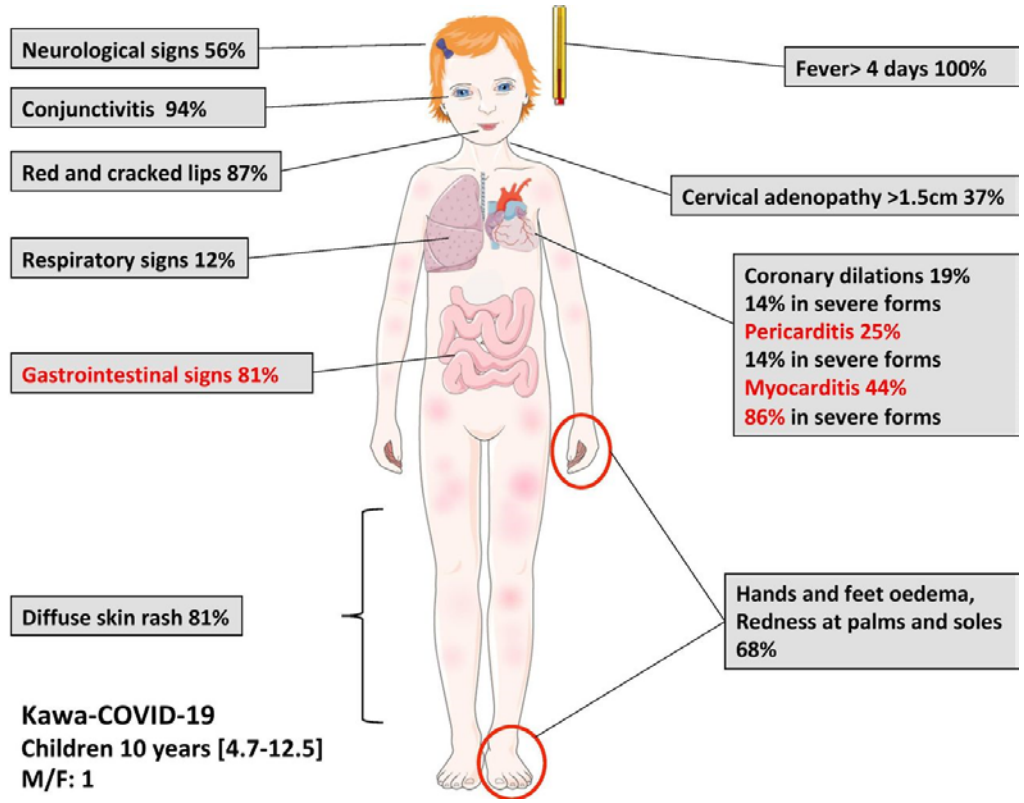
Mar. 13 — United States declares national state of emergency

Mar. 24 — First pediatric death reported in the United States

Apr. 26 — Alert released by National Health Service (NHS) in the United Kingdom regarding a rise in cases of critically ill children with overlapping features of toxic shock syndrome and atypical Kawasaki disease, potentially related to COVID-19

May 08 — First reported pediatric death from this syndrome

May 14 — CDC Health Alert Network releases an official health advisory for multisystem inflammatory syndrome in children (MIS-C) associated with COVID-19



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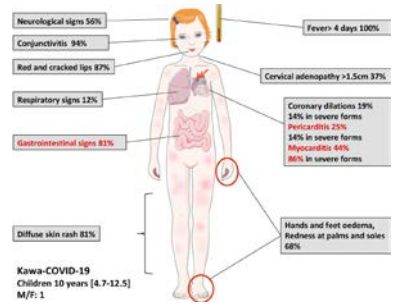
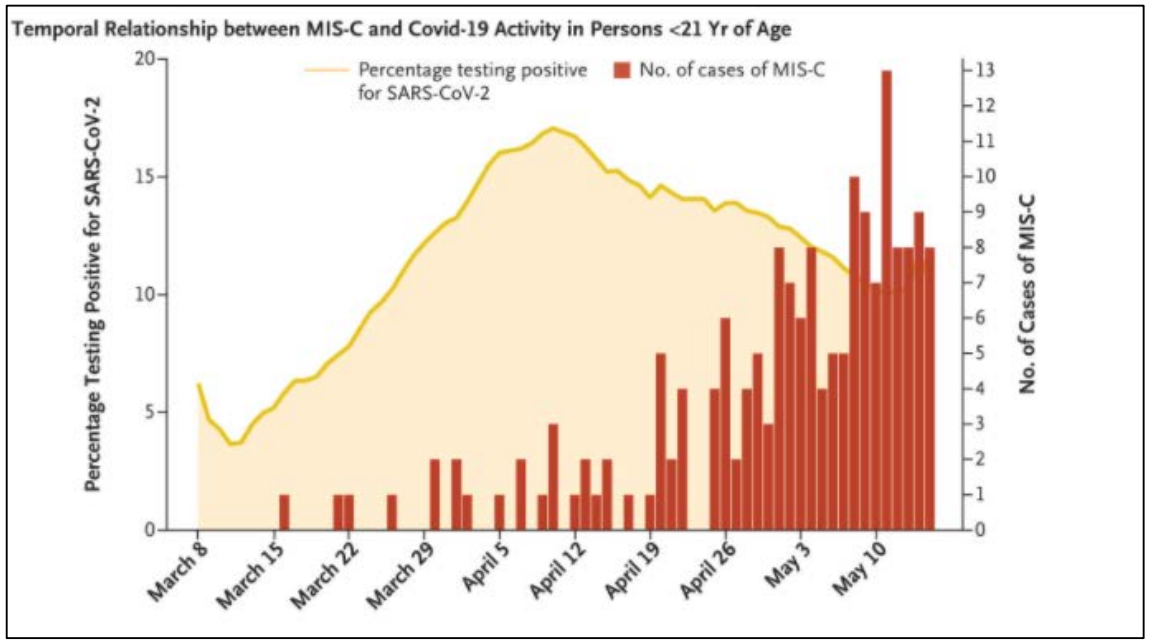
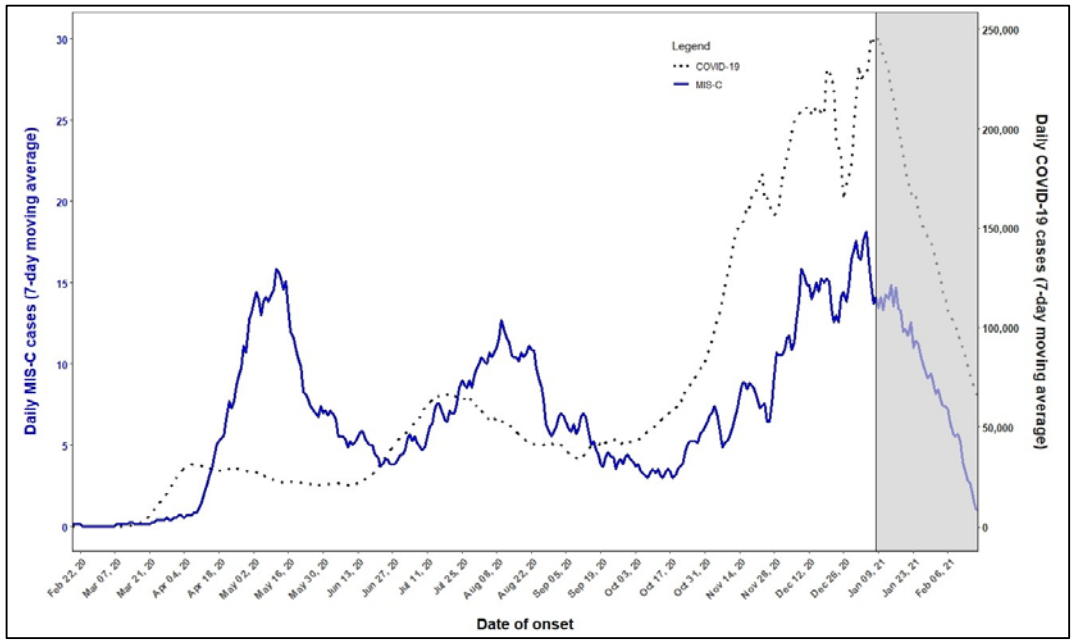
Feldstein LR et al. NEJM. June 2020.

Multisystem inflammatory syndrome in children (MIS-C)







Summary

- Most cases were in children and adolescents between the ages of 1 and 14 years, with a median age of 9 years.
- Cases have occurred in children and adolescents from <1 year old to 20 years old.
- 66% of reported cases have occurred in children who are Hispanic or Latino (842 cases) or Black, Non-Hispanic (746 cases).
- 99% of cases (2,591) tested positive for SARS CoV-2, the virus that causes COVID-19. The remaining 1% were around someone with COVID-19.
- More than half (59%) of reported cases were male.

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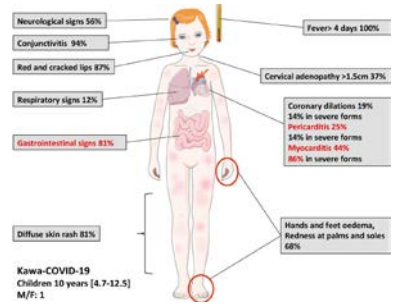
Pouletty M et al. Annals of the Rheumatic Diseases. 2020. Feldstein LR et al. NEJM. 2020. CDC. MIS-C. 2021

Multisystem inflammatory syndrome children (MIS-C)



Case Definition for Multisystem Inflammatory Syndrome in Children (MIS-C)

- An individual aged <21 years presenting with fever[i], laboratory evidence of inflammation[ii], and evidence of clinically severe illness requiring hospitalization, with multisystem (≥2) organ involvement (cardiac, renal, respiratory, hematologic, gastrointestinal, dermatologic or neurological); **AND**
- No alternative plausible diagnoses; **AND**
- Positive for current or recent SARS-CoV-2 infection by RT-PCR, serology, or antigen test; or COVID-19 exposure within the 4 weeks prior to the onset of symptoms

[i]Fever ≥38.0°C for ≥24 hours, or report of subjective fever lasting ≥24 hours
[ii]Including, but not limited to, one or more of the following: an elevated C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), fibrinogen, procalcitonin, d-dimer, ferritin, lactic acid dehydrogenase (LDH), or interleukin 6 (IL-6), elevated neutrophils, reduced lymphocytes and low albumin

Additional comments

- Some individuals may fulfill full or partial criteria for Kawasaki disease but should be reported if they meet the case definition for MIS-C
- Consider MIS-C in any pediatric death with evidence of SARS-CoV-2 infection

- **Class 1 (n=203): "typical" MIS-C**
  - 98% serology positive
  - 100% CV + 98% GI manifestations
  - Markedly elevated lab markers of inflammation
  - 84% admitted to ICU
- **Class 2 (n=169): acute COVID-19/MIS-C combo**
  - 16% serology positive + 100% RT-PCR positive
  - More respiratory involvement
  - 62% admitted to ICU
- **Class 3 (n=198): milder illness**
  - 97% serology positive + 36% RT-PCR positive
  - Younger (median age ~6 years)
  - Higher frequency of rash, mucocutaneous lesions
  - 44% admitted to ICU

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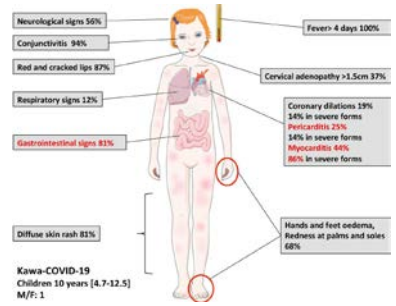
CDC. CDC Health Alert Network. 2020. ACR MIS-C Task Force. ACR. 2020. Godfred-Cato et al. MMWR. 2020

Multisystem inflammatory syndrome children (MIS-C)



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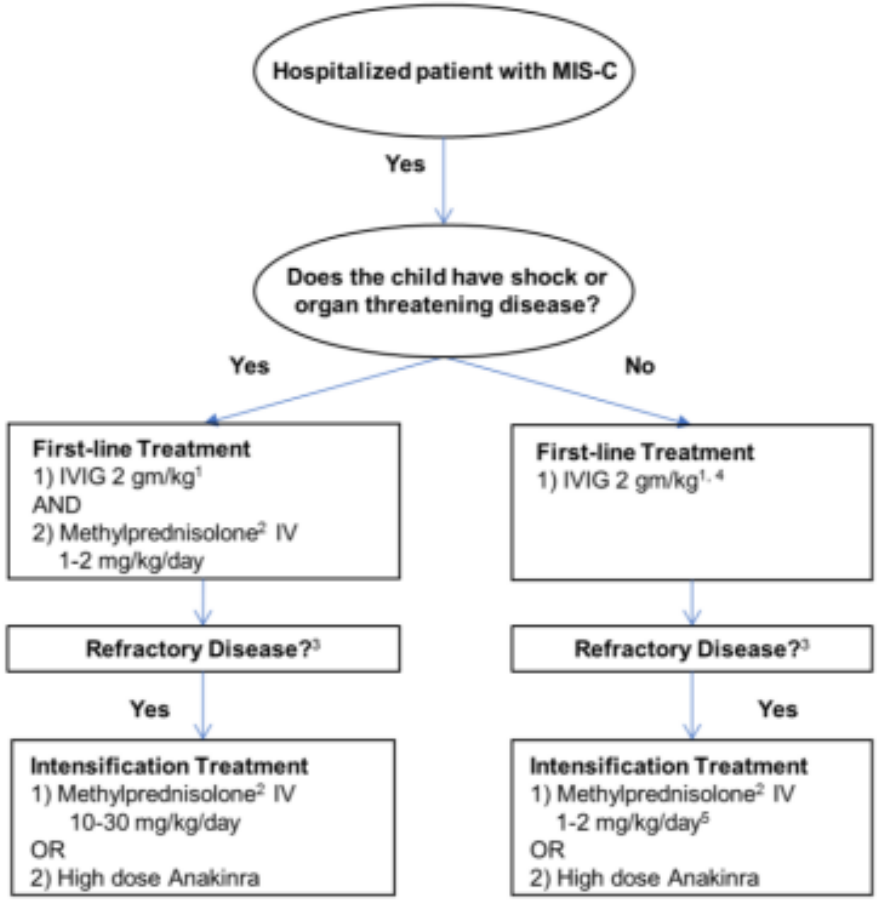

CDC. CDC Health Alert Network. 2020. ACR MIS-C Task Force. ACR. 2020.

Anticoagulation

Chris Rowan, MD
Cardiology

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COVID Management

Cardiac Manifestations, Thrombosis and Statins

CHRIS ROWAN, MD, FACC

Thrombosis

- **Objectives**
- **Basic Understanding and Biology**
  - Historical Perspective of Thrombosis in COVID
  - WUHAN Data
  - Initial US Data
  - Itialian and new York Data
- **Rationale**
- **Treatment Algorithm**

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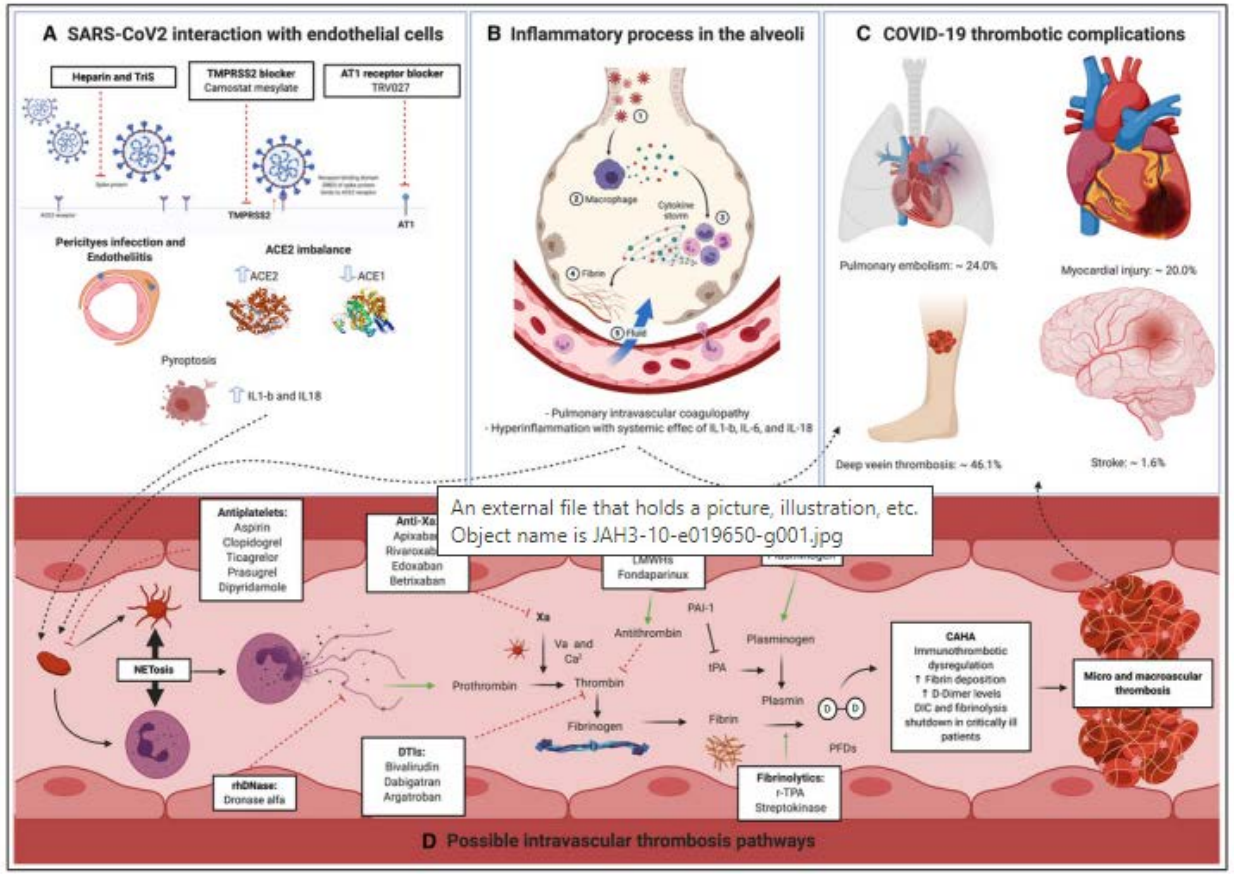

[J Am Heart Assoc.](#) 2021 Feb 2; 10(3): e019650.

A, The interaction of the severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) with endothelial cells (type II pneumocytes, glomerular capillary loops, and small intestine capillaries). Angiotensin-converting enzyme 2 (ACE2) imbalance may promote susceptibility to the SARS-CoV-2 infection of these cell types. Furthermore, cell infection and induced inflammation in pericytes and endothelial cells may promote local apoptosis and potent inflammatory cytokines. **B**, Inflammatory process in the pulmonary alveoli, leading to pulmonary tissue edema and intravascular coagulopathy. **C**, Selection of thrombotic complications in COVID-19 and their approximate frequency. **D**, Proposed intravascular thrombosis pathways leading to microvascular and macrovascular thrombosis complications. Because of the potent local and systemic cytokine production, the platelets are activated and interact with neutrophils. The neutrophil extracellular trap (NET)osis process may also stimulate thrombin production and fibrin deposition. The excess of fibrin deposition and fibrinolysis shutdown lead to intravascular thrombosis and, finally, to clinical thromboembolic complications. The pointed black and continued black lines denote pathway connections, pointed red lines denote inhibition, and green arrows denote agonism. ACE-I indicates angiotensin-converting enzyme inhibitor; anti-Xa, anti–factor Xa; AT1, angiotensin II receptor type 1; CAHA, COVID-19–associated hemostatic abnormalities; D-D, D-dimer; DTI, direct thrombin inhibitor; IL, interleukin; LMWH, low-molecular-weight heparin; PAI-1, plasminogen activator inhibitor I; PFD, fibrin degradation product; r-tPA, recombinant tPA; TMPRSS2, transmembrane protease serine 2; tPA, tissue-type plasminogen activator; TriS, synthesized trisulfated heparin; and UFH, unfractionated heparin. Data derived and visual presentation modeled from Bikdeli et al. [14](#)

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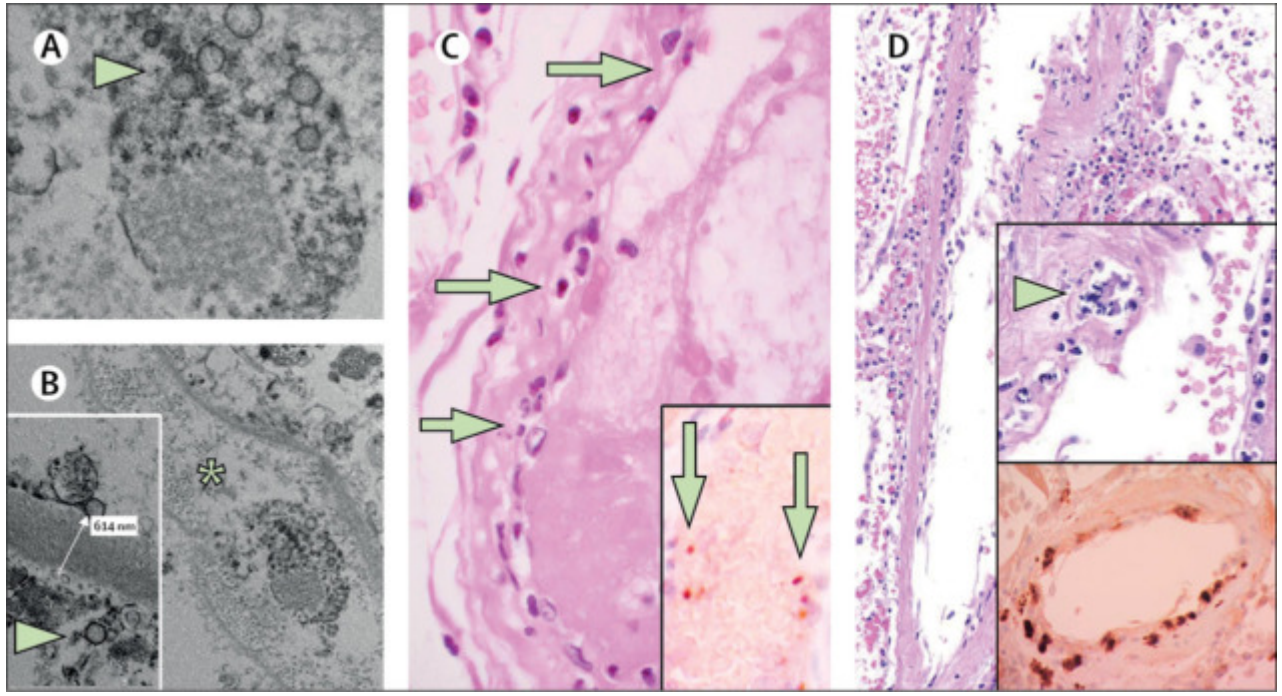
Basic Biology of COVID as it relates to thrombosis

- **COVID S-protein attaches to ACE2 receptor**
  - Ziegler et al, Cell: DOI: 10.1016/j.cell.2020.04.035
- **Highly expressed throughout the blood vessel walls**
- ***Varga, Z,. Et al. Endothelial cell infection and endotheliitis in COVID-19 The Lancet*, March 20, 20202**
  - **DOI: 10.1016/S0140-6736(20)30937-5**



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The ACE-2 Connection

- **ACES converts angiotensin II into angiotensin (1-7)**
- **Angiotensin**
  - Potent vasoconstrictor
  - Profibrotic
  - Pro-inflammatory
- **Angiotensin (1-7)**
  - Potent vasodilator
  - Antiapototic
  - Antiproliferative
- **Patients with CV disease have a dysregulated ACE/ACE2 balance**
  - Leads to downregulation of ACE2

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ACE2

- **ACE2 highly expressed in pulmonary and CV tissue**
- **Cells die by a highly inflammatory mechanism call pyroptosis**
- **Leads to high levels of IL-1b and IL-18**
- **Leads to endotheliitis**

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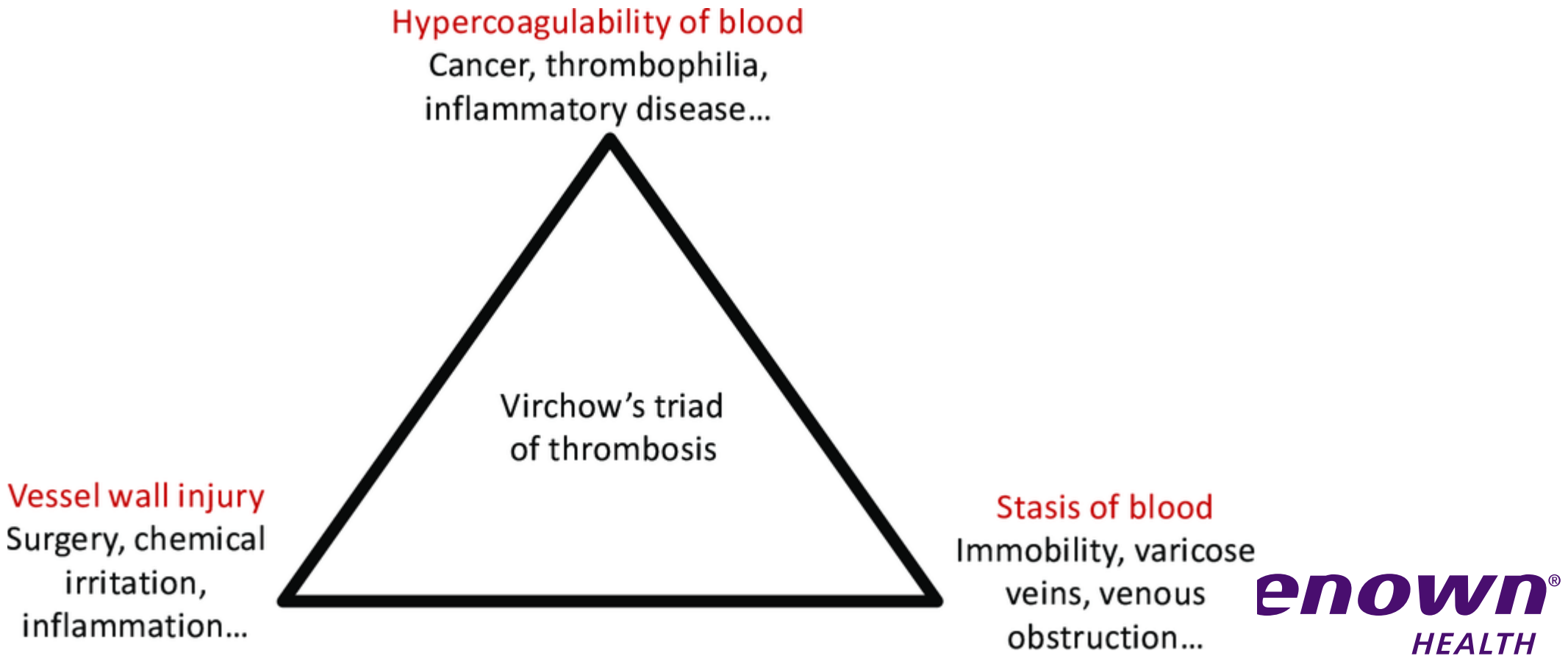
Thrombosis – Virchow's Triad



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Effect on Coagulation and Fibrinolysis

- **COVID induces a state of CAHA (COVID associated hemostatic abnormalities)**
- **Most commonly leads to elevated d-dimer**
- **TEG studies**
  - Decrease time to fibrin formation
  - Decrease in time clot formation
  - Increase in clot strength
  - Low lysis at 30 minutes → pathway of fibrinolysis is turned off

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International Society on Thrombosis and haemostasis

- **Consider hospitalization for:**
  - D-dimer over 3-4 times higher
  - Prolonged PT
  - Platelet count under 100
  - Fibrinogen < 2.0 g/L

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Table 1

Distinguishing Laboratory Features of SIC, DIC, Thrombotic Microangiopathy, and CAHA

Variable	SIC [49]	DIC [38]	Microangiopathy [38]	CAHA [38],*
Prothrombin time	↑	↑↑	↔	↑↑
Activated partial thromboplastin time	↑↑	↑↑↔↑	↔	↑
Fibrinogen	↓	↓	↔	↑↑
Fibrin(ogen) degradation products	↑	↑↑	↔	↑↑
D-dimer	↑	↑↔	↔	↑↑ or ↑+
Platelet count	↓	↓↓	↓	↑ or ↔
Peripheral blood smear + +	+	+	++	+
von Willebrand factor	↑	↑↑	↔	↑↑
ADAMTS13	↔	↔	↓	↔
Antithrombin	↓	↓	↓	↑
Anticardiolipin antibodies	↔	↔	↔	+
Protein C	↓	↓	↔	+
Protein S	↓	↓	NA	↓
Factor VIII	↑	↑	NA	↑
Plasminogen	↓	↓	NA	↑

+ indicates ≥6 times the upper limit of normal; ++, peripheral blood smear containing fragmented red blood cells; ADAMTS13, a disintegrin-like and metalloprotease with thrombospondin type 1 motif 13; CAHA, coronavirus disease 2019–associated hemostatic abnormalities; DIC, disseminated intravascular coagulation; NA, not available; and SIC, sepsis-induced coagulopathy.

*Some laboratory features can change significantly, depending on the stage of the CAHA.

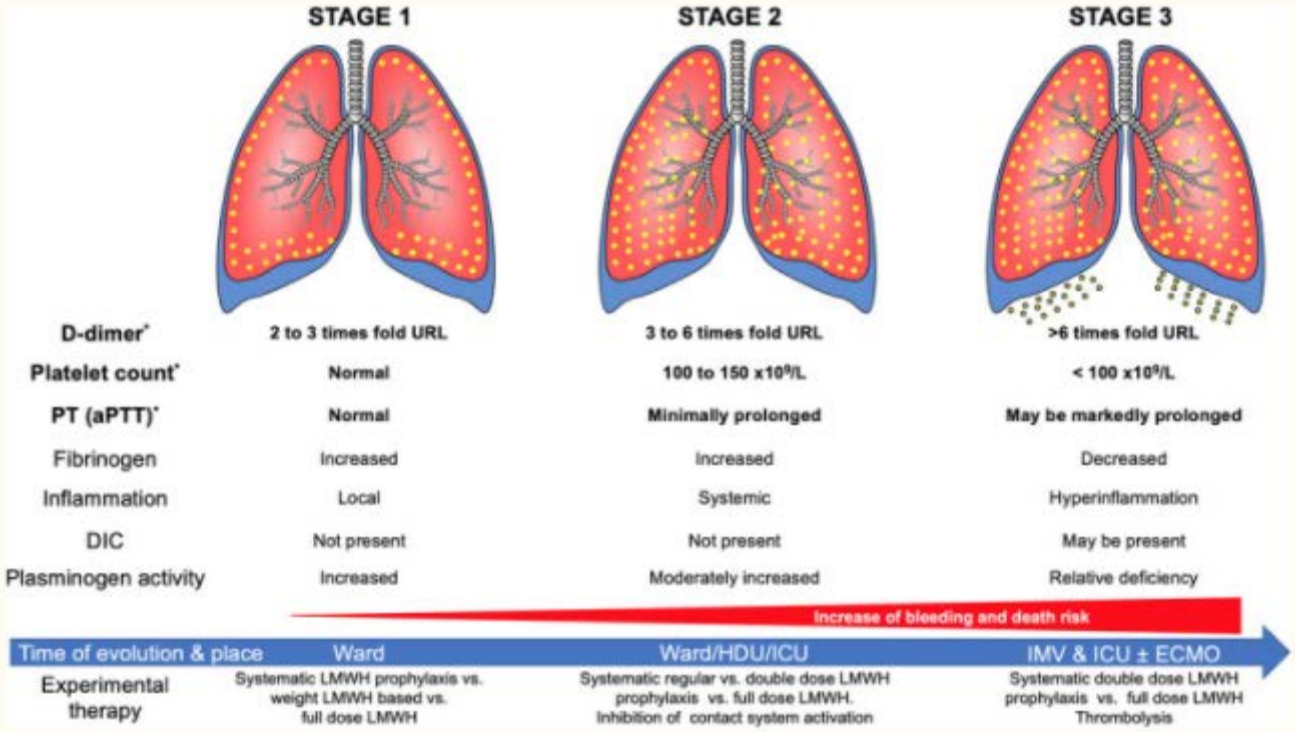

Figure 3

Stages of coronavirus disease 2019 (COVID-19)–associated hemostatic abnormalities.

*Laboratory parameters included in the COVID-19–associated hemostatic abnormality stages described by Thachil et al. 46 aPTT indicates activated partial thromboplastin time; DIC, disseminated intravascular coagulation; ECMO, extracorporeal membrane oxygenation; HDU, high-dependency unit; ICU, intensive care unit; IMV, invasive mechanical ventilation; LWMH, low-molecular-weight heparin; PT, prothrombin time; and URL, upper reference level.

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Thrombosis – The Wuhan Experience

- **Observation of NICU in Tongji Hospital** ***https://doi.org/10.1111/jth.14830***
- **81 patients with COVID**
- **At one week 20(25%) had a DVT, of which 8 died**

Table 2 Characteristics between the VTE and non-VTE groups (n = 81).

Characteristics	Normal range	VTE (n=20)	Non-VTE (n=61)	P-value
Age (years)	-	68.4±9.1	57.1±14.3	<0.001
Leucocytes ($\times 10^9$/L)	3.5-9.5	7.8±3.1	6.6±2.6	0.120
Lymphocytes ($\times 10^9$/L)	1.1-3.2	0.8±0.4	1.3±0.6	<0.001
Platelets ($\times 10^9$/L)	125.0-350.0	246.6±110.6	248.8±111.7	0.938

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Wuhan data

- **Criticism**
- **Use of prophylaxis for DVT was not reported and is generally not high**
- **Protect Study showed an 8-10% risk of DVT in ICU patients**
  - N Engl J Med 2011; 364:1305-1314
    DOI: 10.1056/NEJMoa1014475

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Data from Wuhan

D-Dimer		ICU	Non-ICU
Huang, Lancet 2020 (n=41)	D-dimer	2.4 µg/ml	0.5 µg/ml
Wang, JAMA 2020 (n=138)	D-dimer	414 mg/l	166 mg/L

D-Dimer		Non-survivor	Survivor
Tang, JTH 2020 (n=183)	D-dimer	2.12 µg/ml	0.66 µg/ml
	PT	15.5 sec	13.6 sec
	FDP	7.6 µg/ml	4.0 ug/ml

- Cui S. Brief report. JTH 2020 (n=81)
- 25% of patients (20/81) had VTE; 8 out of 20 patients died
- D-dimer 1.5 µg/ml – sensititivy 85% and specificity 85%
- Higher D-dimer in non-survivors (5.2 vs. 0.8)

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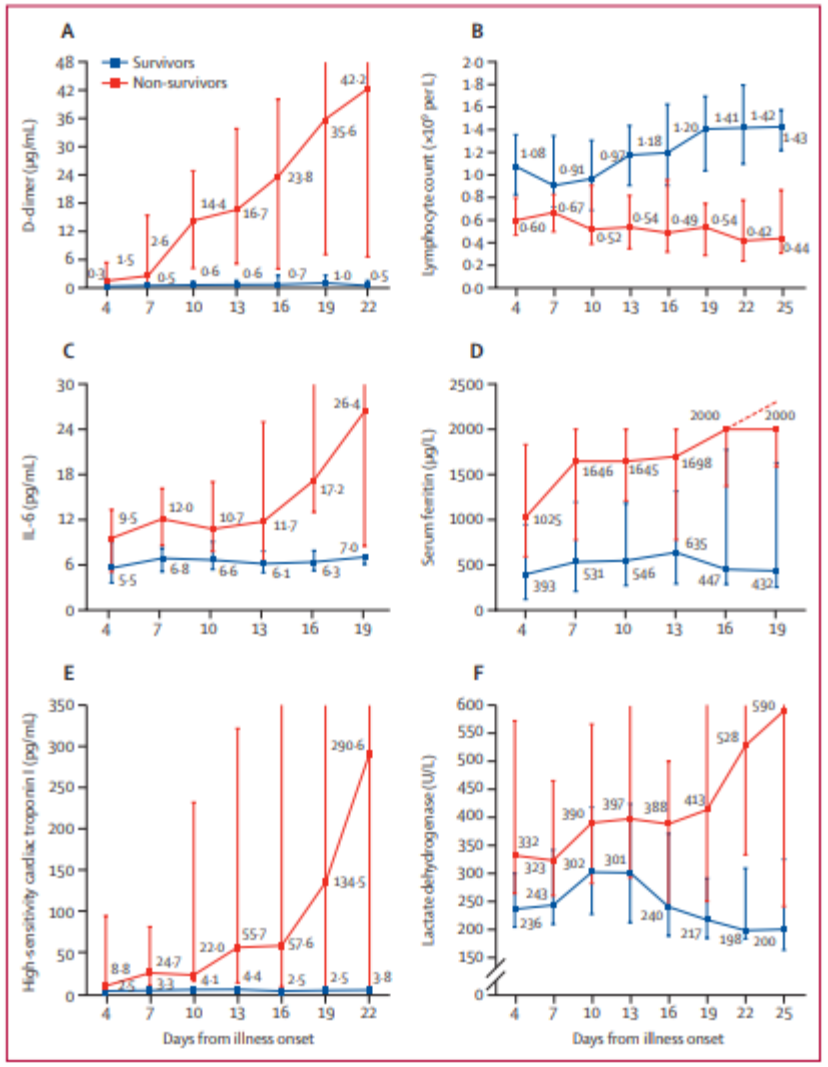

Figure 2: **Temporal changes in laboratory markers from illness onset in patients hospitalised with COVID-19**
Figure shows temporal changes in d-dimer (A), lymphocytes (B), IL-6 (C), serum ferritin (D), high-sensitivity cardiac troponin I (E), and lactate dehydrogenase (F). Differences between survivors and non-survivors were significant for all timepoints shown, except for day 4 after illness onset for d-dimer, IL-6, and high-sensitivity cardiac troponin I. For serum ferritin (D), the median values after day 16 exceeded the upper limit of detection, as indicated by the dashed line. COVID-19=coronavirus disease 2019. IL-6=interleukin-6.

Zhou. The Lancet 2020 395: 1054-1062

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On to the Netherlands

Klok, et al. Incidence of thrombotic complications in critically ill ICU patients with COVID-19 Thrombosis Research https://doi.org/10.1016/j.thromres.2020.04.013

- **184 ICU COVID Positive Patients**
- **All patients received standard dose prophylaxis**
- **US Confirmed VTE noted in 31%**

Table 3
Description of thrombotic complications.

Type of event	Number of cases	Relevant details
Pulmonary embolism	25	– 18 cases with at least PE in segmental arteries, 7 cases PE limited to subsegmental arteries
Other venous thromboembolic events	3	– 1 proximal deep-vein thrombosis of the leg – 2 catheter related upper extremity thrombosis
Arterial thrombotic events	3	– All ischemic strokes

Note: acute pulmonary embolism was diagnosed with CT-pulmonary angiography, deep vein thrombosis/upper extremity vein thrombosis was diagnosed with ultrasonography, strokes were diagnosed with CT.

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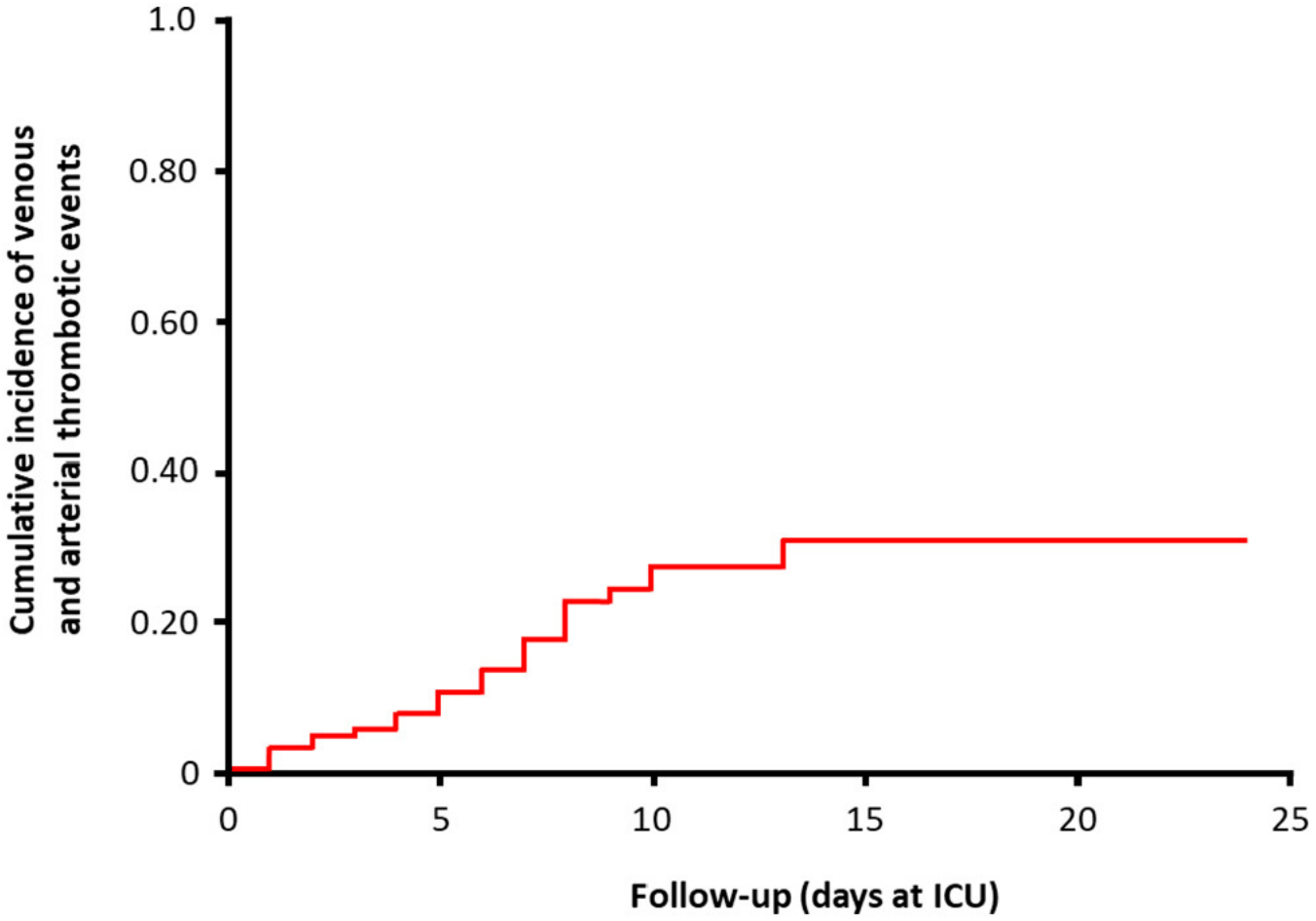
On to the Netherlands



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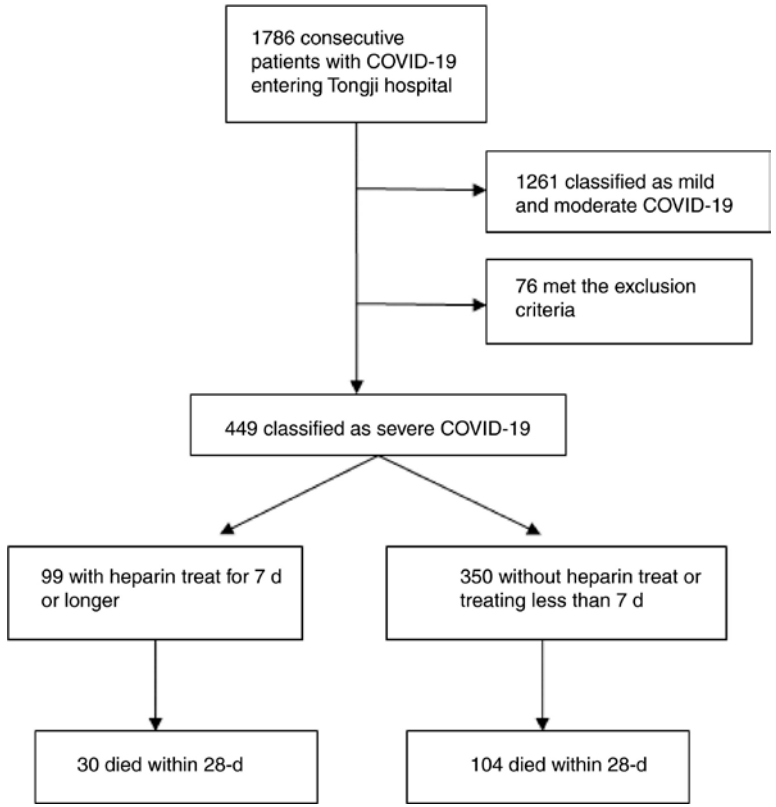
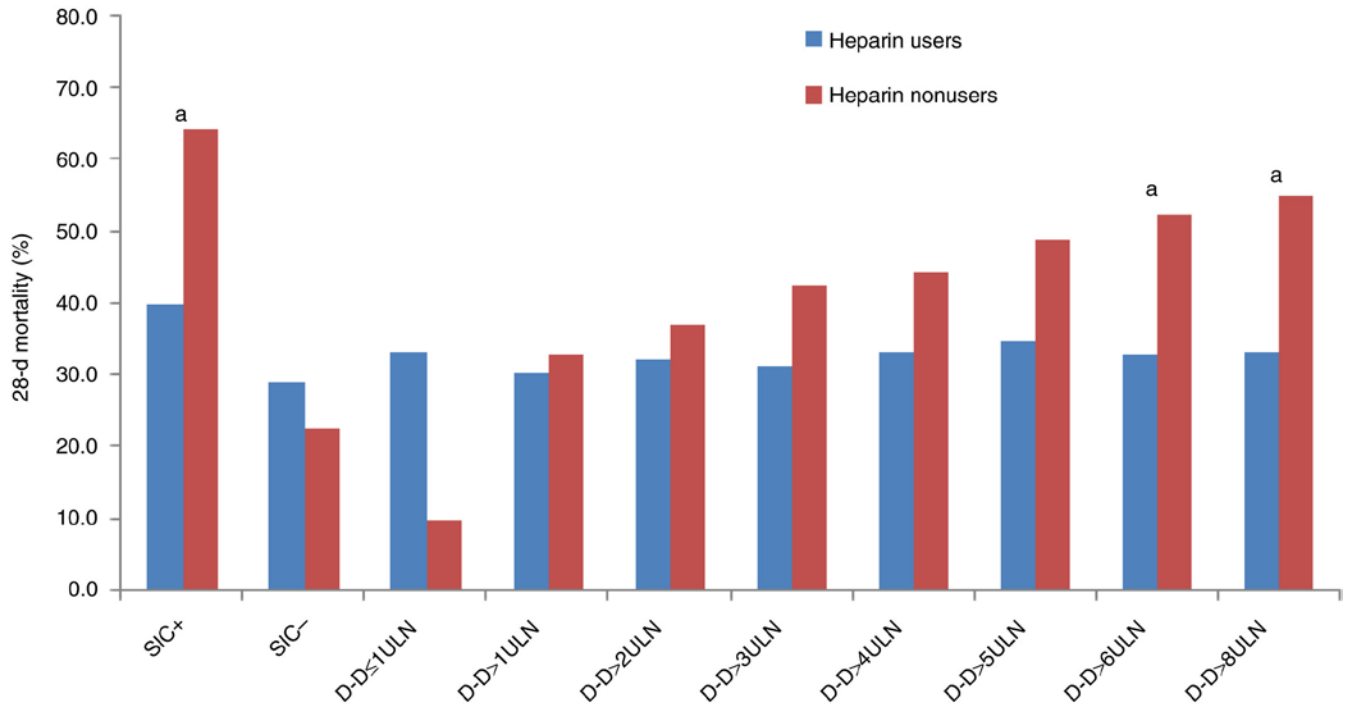


Journal of Thrombosis and Haemostasis, First published: 27 March 2020, DOI: (10.1111/jth.14817)



Journal of Thrombosis and Haemostasis, First published: 27 March 2020, DOI: (10.1111/jth.14817)

- **Heparin products have been shown to bind to the COVID-19 spike proteins.**
- **Additionally, treatment with heparin products has been shown to downregulate IL-6 activity.**
- **Direct Oral Anticoagulants (DOAC) do not have this additional mechanism.**
- **The risk of DVT/PE/Death continues after discharge.**

Cohen at el. NEJM 368;6. 513
Tang, N., JTH 202. Doi:10.111?JTH.14817
Belouzard et al., PNAS, 2009 106(14), 5871-6.
De HAAN et al., J. Virol. 2005 Nov 79(22): 14451-14456.
Mummery et al. J. Immunol, 2000. 165(10), 5671-9.
Alexander, C., and the Magellan Investigators, NEJM 2013;368:513-23.

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Recommendations

J Thromb Haemost. 2020;18:1859–1865

Treatment

- Patients with COVID-19 who experience an incident thromboembolic event or who are highly suspected of having a thromboembolic disease at a time when imaging is not possible should be managed with therapeutic doses of anticoagulant therapy, as per the standard of care for patients without COVID-19 (NIH grade AIII). 92
- In patients taking treatment-dose DOACs or vitamin K antagonists, consider switching to LMWH, especially for those in critical care settings or taking relevant concomitant medications. 8 , 93
- The anticoagulation with LMWHs may be preferred in an inpatient setting, whereas DOACs may be preferred in an outpatient setting. 8 , 93
- In patients taking treatment-dose DOACs or vitamin K antagonists, consider switching to LMWH, especially for those in critical care settings or taking relevant concomitant medications. 8 , 93
- Duration of treatment is ≥3 mo. 8 , 93
- Patients with COVID-19 who require extracorporeal membrane oxygenation or continuous renal replacement therapy or who have thrombosis of catheters or extracorporeal filters should be treated with antithrombotic therapy, per the standard institutional protocols for those without COVID-19 (NIH grade AIII). 92

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Extended prophylaxis	• The routine discharge of patients on VTE prophylaxis is not generally recommended (NIH grade AIII). 92 • In patients at high risk of VTE, if bleeding risk is low, extended prophylaxis can be considered with either LMWH or DOACs (rivaroxaban or betrixaban). 93 • The patients at risk for postdischarge VTE include those with reduced mobility and those with coexisting conditions, such as cancer, previous VTE event, D-dimer level >2 times the upper level of normal, older age (≥75 years), ICU admission, or thrombophilia (NIH grade AIII). 92 • The duration of postdischarge prophylaxis should be ≥14 d and up to 30 d. 93

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Previous indication of antithrombotic treatment (eg, CAD or NVAF)	• Patients who are receiving anticoagulant or antiplatelet therapies for underlying conditions should continue these medications if they receive a diagnosis of COVID-19 (NIH grade AIII). 92 • Drug-drug interactions should be considered between investigational COVID-19 therapies and antithrombotic agents. 14 • Patients who take low-dose aspirin should continue the treatment. 14 • In patients who take $P2Y_{12}$ inhibitors, clopidogrel and ticagrelor have a potentially dangerous drug-drug interaction and are contraindicated. Prasugrel can be used, taking into account its contraindications and precautions. 94 • In patients using anticoagulant therapy and who have the concomitant need for specific COVID-19 treatment, baseline anticoagulant therapy could be changed to LMWH. After COVID-19 treatment is completed, the baseline treatment can be reinitiated. 8

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Arterial thrombosis events		
	Acute ischemic stroke	• If COVID-19–associated coagulopathy is severe, it may contraindicate the use of intravenous thrombolysis. Even if intravenous thrombolysis is not contraindicated, increased inflammation and hypercoagulability may increase postthrombolysis mortality and morbidity. 96 • In patients treated with thrombolysis or endovascular therapy, antiplatelet therapy should be avoided until a complete risk assessment is well defined. In patients not treated with thrombolysis or endovascular treatment, SAPT or DAPT could be considered. 96
	Acute limb ischemia	• In patients with COVID-19 who presented with acute limb ischemia, prolonged UFH might be warranted for both limb salvage and improved survival. 97

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Coagulopathy

Diagnosis

- In patients with significantly elevated D-dimer level (3- to 4-fold increase), prolonged PT, platelet count <100×10^9/L, or fibrinogen <2 g/L: consider hospital admission (regardless of other condition) and monitor once or twice a day. Patients with impaired renal function may require a closer follow-up. 45

Prophylaxis

- Consider prophylaxis with LMWH in all patients, if not contraindicated (eg, active bleeding or platelet count <25×10^9/L). 45

Treatment

- The management of DIC is focused on the treatment of the underlying condition. 98
- Without bleeding: blood products should be administered to maintain platelet count >25×10^9/L. 45
- With bleeding: blood products should be administered to maintain platelet count >50×10^9/L, fibrinogen >1.5 g/L, and PT ratio <1.5. 45
- In patients with DIC, antifibrinolytics are not recommended. 98

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Pharmacological Therapy

Jessica Thompson, PharmD
Pharmacy Infectious Disease

Kevin Kuriakose, MD
Infectious Disease

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Overview of IDSA COVID-19 Treatment Guidelines (v4.1.0)

	Ambulatory Care	Hospitalized: No Suppl O_2	Hospitalized: spO_2 < 94% on room air	Hospitalized: Critical Disease
Hydroxychloroquine (HCQ)	NA	+++	+++	+++
HCQ + Azithromycin	NA	++	++	++
Lopinavir + ritonavir	NA	+++	+++	+++
Corticosteroids	NA	+	+++	+++
Tocilizumab	NA	NA	+	+
Convalescent Plasma	NA	Clinical Trial	Clinical Trial	Clinical Trial
Remdesivir	NA	+	++	++
Famotidine	NA	+	+	+
Bamlanivimab + Etesevimab	++	NA	NA	NA
Bamlanivimab	NA	NA	+++	NA
Baricitinib + Remdesivir	NA	NA	++ (if steroids contraindicated)	
Baricitinib + Remdesivir + Steroids	Clinical Trial	NA	NA	NA
Ivermectin	+	NA	+	NA

Certainty of Evidence: + to ++++

Recommend Against Use	Suggest Against Use	Suggest Use	Recommend Use

HEALTH

Recommended Treatments

Medications	FDA Approval Status	Proposed Mechanism of Benefit in COVID-19
Corticosteroids	Approved for other indications	Immunomodulator that addresses the **hyperinflammatory state** (i.e. ARDS, systemic inflammation)
Tocilizumab	Approved for other indications	A monoclonal anti-IL-6-receptor blocking antibody that may **mitigate hyperinflammation**
Remdesivir	Approved for COVID-19	Antiviral that causes premature termination of RNA transcription (i.e. **decreases viral replication**)
Bamlanivimab + Etesevimab*	Not FDA approved; available via FDA Emergency Use Authorization (EUA)	Monoclonal neutralizing antibodies that may **rapidly reduce viral load** in the upper and lower airways and confer protection more rapidly than vaccine-induced immune response

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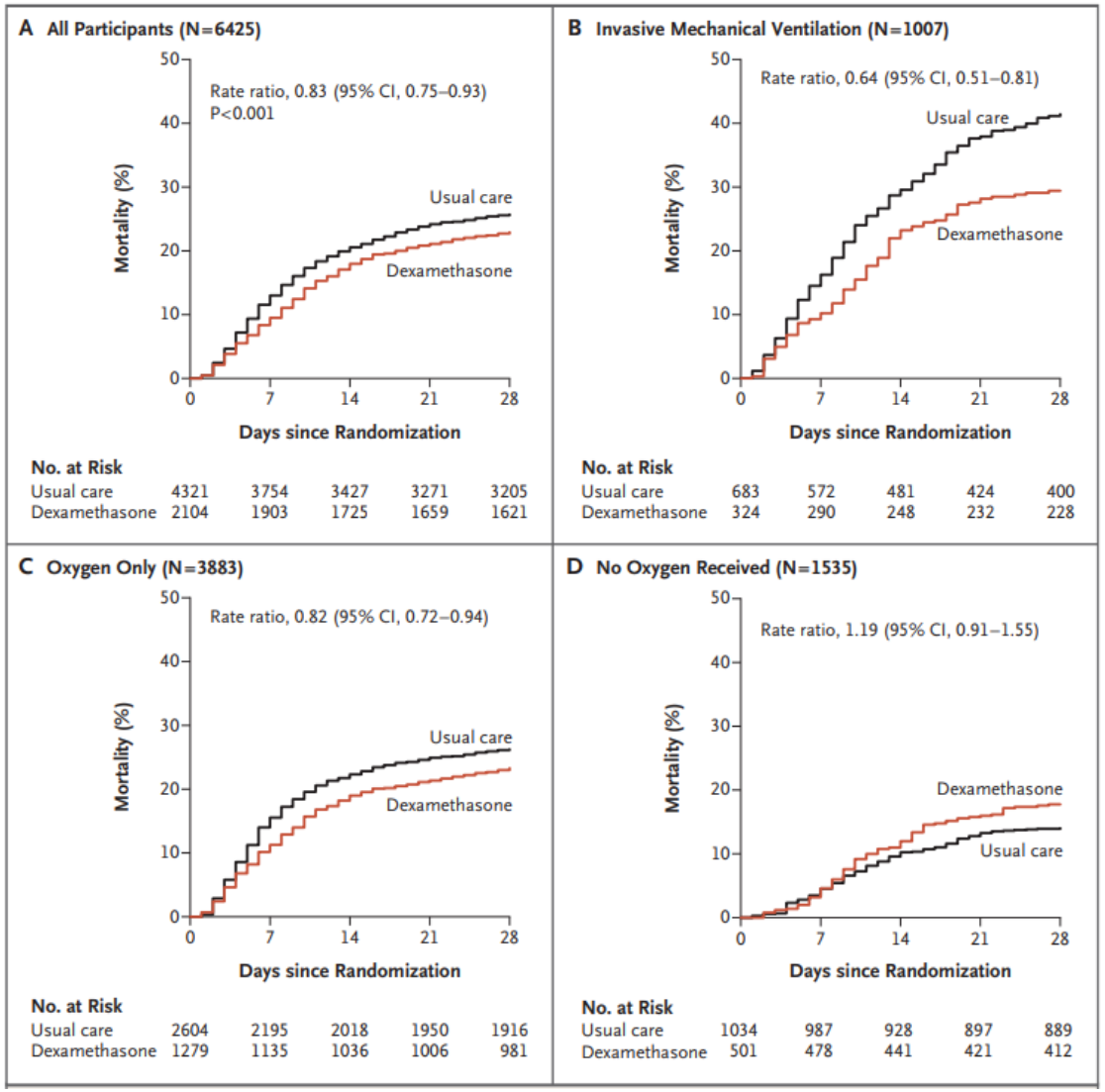
Corticosteroids: RECOVERY (NEJM 2020)



- Randomized, open-label, multicenter UK study of 6,425 hospitalized pts
- Dexamethasone 6 mg IV or PO x 10 d vs usual care
- **Results**: Dexamethasone **reduced 28-day mortality** in patients requiring mechanical ventilation or oxygen
  - No benefit if not requiring respiratory support

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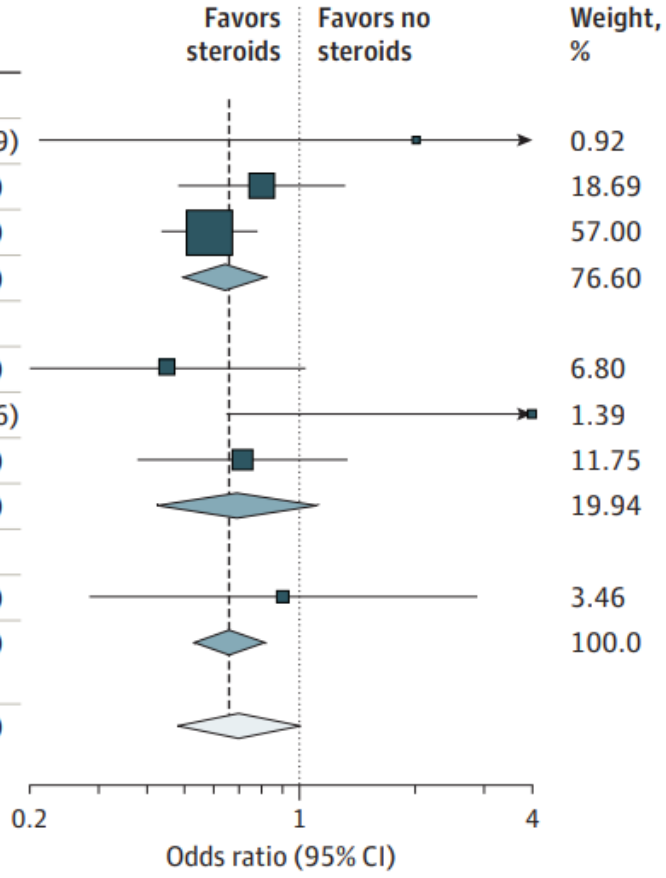
Corticosteroids: REACT (JAMA 2020)

Figure 2. Association Between Corticosteroids and 28-Day All-Cause Mortality in Each Trial, Overall, and According to Corticosteroid Drug

Drug and trial	ClinicalTrials.gov identifier	Initial dose and administration	No. of deaths/total No. of patients		Odds ratio (95% CI)
			Steroids	No steroids	
Dexamethasone					
DEXA-COVID 19	NCT04325061	High: 20 mg/d intravenously	2/7	2/12	2.00 (0.21-18.69)
CoDEX	NCT04327401	High: 20 mg/d intravenously	69/128	76/128	0.80 (0.49-1.31)
RECOVERY	NCT04381936	Low: 6 mg/d orally or intravenously	95/324	283/683	0.59 (0.44-0.78)
Subgroup fixed effect			166/459	361/823	0.64 (0.50-0.82)
Hydrocortisone					
CAPE COVID	NCT02517489	Low: 200 mg/d intravenously	11/75	20/73	0.46 (0.20-1.04)
COVID STEROID	NCT04348305	Low: 200 mg/d intravenously	6/15	2/14	4.00 (0.65-24.66)
REMAP-CAP	NCT02735707	Low: 50 mg every 6 h intravenously	26/105	29/92	0.71 (0.38-1.33)
Subgroup fixed effect			43/195	51/179	0.69 (0.43-1.12)
Methylprednisolone					
Steroids-SARI	NCT04244591	High: 40 mg every 12 h intravenously	13/24	13/23	0.91 (0.29-2.87)
Overall (fixed effect) $P = .31$ for heterogeneity; $I^2 = 15.6\%$			222/678	425/1025	0.66 (0.53-0.82)
Overall (random effects[a])			222/678	425/1025	0.70 (0.48-1.01)



Tocilizumab

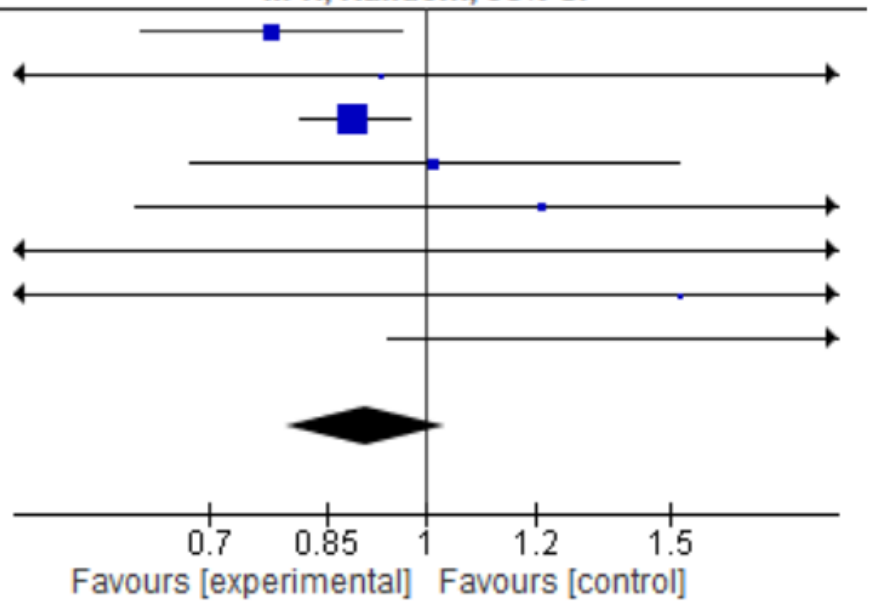
- 8 randomized clinical trials
  - 2 showed a mortality benefit; 6 showed no benefit

Figure s4a. Forest plot for the outcome of mortality for tocilizumab vs. no tocilizumab

Study or Subgroup	Tocilizumab Events	Tocilizumab Total	No tocilizumab Events	No tocilizumab Total	Weight	Risk Ratio M-H, Random, 95% CI
Gordon 2021 REMAP-CAP	98	366	142	412	25.4%	0.78 [0.63, 0.96]
Hermine 2020	7	63	8	67	1.9%	0.93 [0.36, 2.42]
Horby 2021 RECOVERY	596	2022	694	2094	55.8%	0.89 [0.81, 0.97]
Rosas 2020	58	294	28	144	9.5%	1.01 [0.68, 1.52]
Salama 2020	26	249	11	128	3.8%	1.22 [0.62, 2.38]
Salvarani 2020	2	60	1	63	0.3%	2.10 [0.20, 22.56]
Stone 2020	9	161	3	82	1.1%	1.53 [0.43, 5.49]
Veiga 2021	14	65	6	64	2.2%	2.30 [0.94, 5.61]
Total (95% CI)		**3280**		**3054**	**100.0%**	**0.91 [0.79, 1.04]**
Total events	810		893			

Heterogeneity: $Tau^2 = 0.01$; $Chi^2 = 8.32$, $df = 7$ ($P = 0.31$); $I^2 = 16\%$

Test for overall effect: $Z = 1.43$ ($P = 0.15$)



IDSA Guidelines 4.1.1

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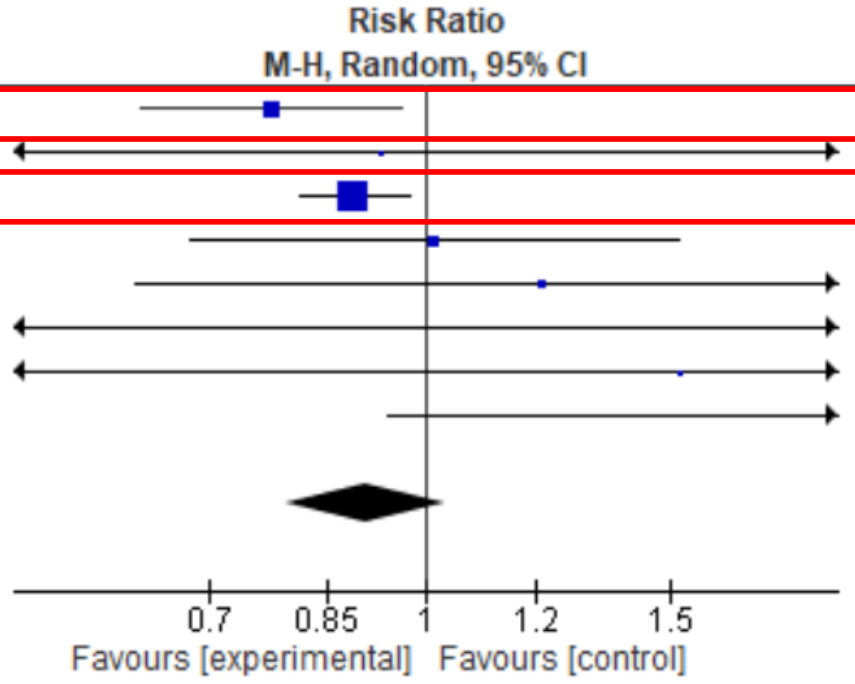

IDSA Guidelines 4.1.1

Tocilizumab: RECOVERY (medRxiv preprint)

- Randomized, open-label, multicenter study in the UK
- 4,116 hospitalized patients with clinical evidence of progressive disease (hypoxia and CRP ≥ 7.5 mg/dL)
- Tocilizumab 8 mg/kg IV vs usual care
- Results:
  - Decreased 28-day mortality with tocilizumab (29 vs 33%, RR 0.86 [0.77-0.96], p = 0.0066)
    - Time from initial hospitalization to randomization: 2 days (IQR: 1-5)
    - Time patients initially met criteria to randomization is unclear

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Tocilizumab: REMAP-CAP (NEJM 2021)

- Randomized, open-label multicenter trial
- 803 adults patients within 24 hours of requiring organ support in the ICU
  - Organ support was high-flow O_2, mechanical ventilation, or vasopressors)
- Results: Tocilizumab 8 mg/kg IV vs usual care
  - More organ support-free days (adjOR 1.64 [95%CI 1.25-2.14])
  - Higher in-hospital survival (adjOR 1.64 [95%CI 1.14-2.35]
  - Median CRP at baseline was 13.6 mg/dL (IQR 79-208)
  - Median time to enrollment 1.2 days (IQR 0.2-2.8)

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Tocilizumab

- Studies that demonstrated a benefit
  - Elevated CRP > 7.5 mg/dL plus oxygen support
  - Early administration in patients that met inclusion criteria

- Studies that did not demonstrate a benefit
  - Small sample sizes
  - Extended time from hospital admission to administration
  - Excluded patients on high-flow O2 or mechanical ventilation

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Tocilizumab: Toxicities & Contraindications

- Known Toxicities
  - Elevated liver enzymes
  - Serious infections (e.g. TB, bacterial, and fungal infections)
  - Bowel perforation
  - Neutropenia and thrombocytopenia
- Contraindications (NIH)
  - Recent biologic use
  - AST > 5xULN
  - High risk of GI perforation
  - Uncontrolled infection
  - ANC < 500
  - Platelet < 50,000

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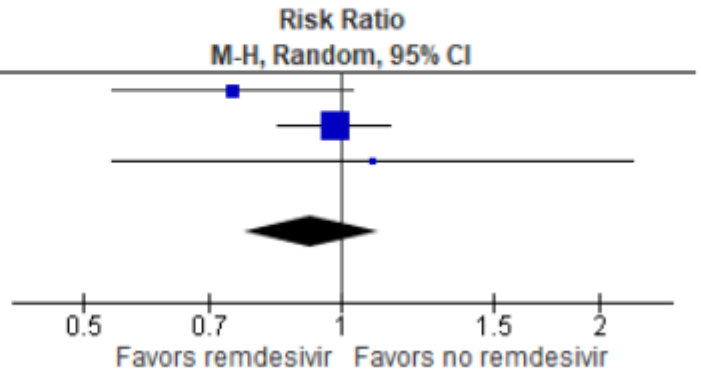
Remdesivir

- 3 randomized clinical trials
  - No RCT has demonstrated a mortality benefit

Figure s5c. Forest plot for the outcome of mortality for remdesivir vs. no remdesivir in hospitalized patients with severe disease

	Remdesivir		No remdesivir			Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI
Beigel 2020	57	486	74	471	25.2%	0.75 [0.54, 1.03]
Pan 2020	290	2082	290	2044	68.5%	0.98 [0.84, 1.14]
Wang 2020	22	158	10	78	6.3%	1.09 [0.54, 2.18]
Total (95% CI)		**2726**		**2593**	**100.0%**	**0.92 [0.77, 1.10]**
Total events	369		374			

Heterogeneity: Tau² = 0.01; Chi² = 2.46, df = 2 (P = 0.29); I² = 19%
Test for overall effect: Z = 0.89 (P = 0.37)



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Remdesivir: ACTT-1 (NEJM 2020)

- RCT remdesivir vs placebo (N = 1,062)
- Primary outcome was time to recovery
- Results:
  - Remdesivir **improved time to recovery** (10 vs 15 day [rate ratio for recovery, 1.29; 95%CI 1.12-1.49; p <0.001)]
  - Subgroup analysis
    - Benefit was more pronounced in patients requiring supplemental oxygen
    - No observed benefit in patients not receiving oxygen or patieints on high-flow oxygen, non-invasive mechanical ventilation, mechanical ventilation, or ECMO

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Bamlanivimab+Etesevimab: BLAZE-1 (FDA fact sheet)

- Phase 3, randomized, multicenter trial of 1,035 ambulatory patients with mild COVID-19 symptoms not requiring supplemental oxygen
- Bamlanivimab + etesevimab vs placebo
- Results
  - Primary outcome: **reduced COVID-19 related hospitalizations** by day 29 (2% vs 7%, p <0.001)
  - Secondary outcome: **decreased mortality** (0 vs 10 deaths, p <0.001)

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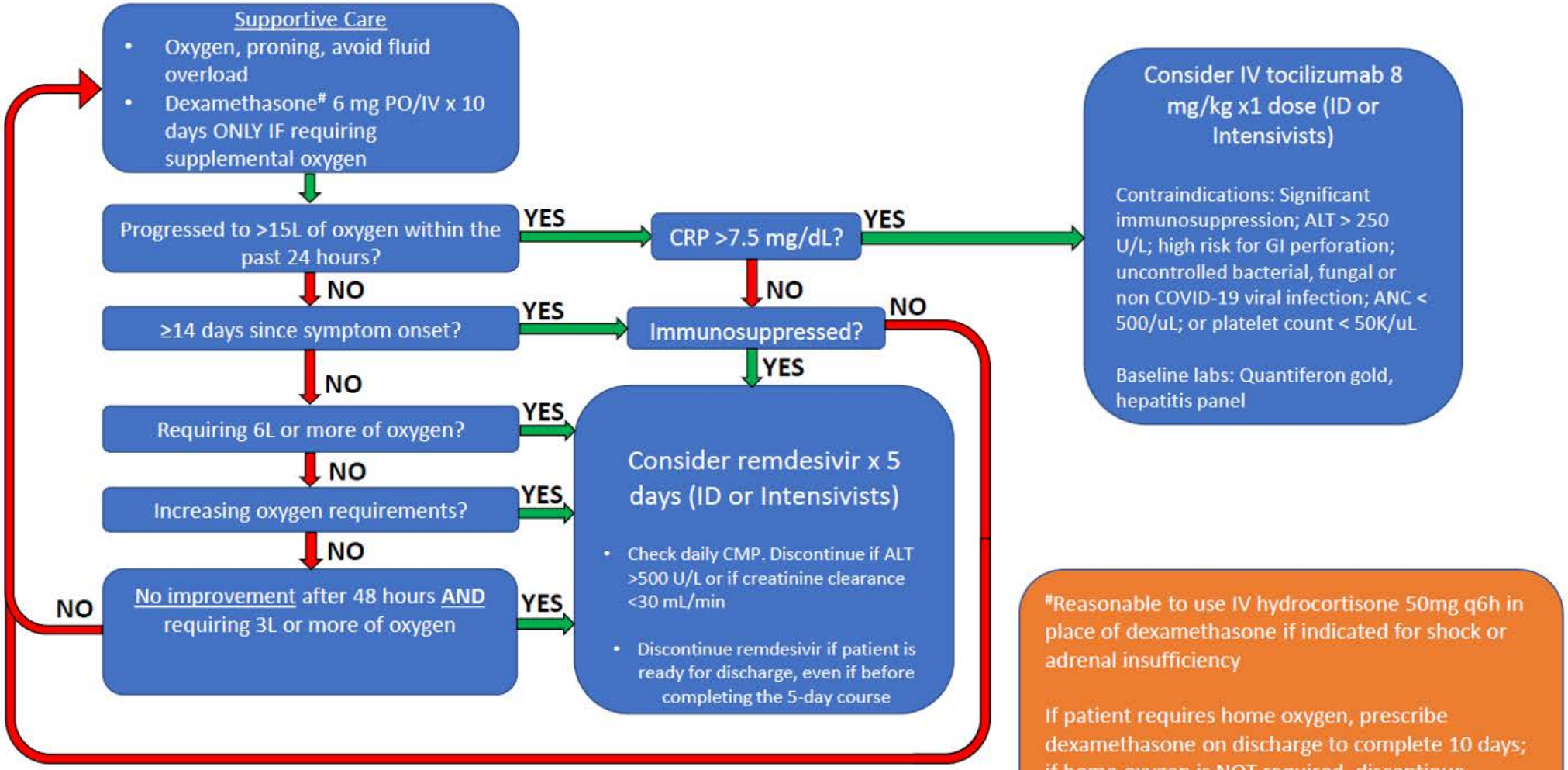
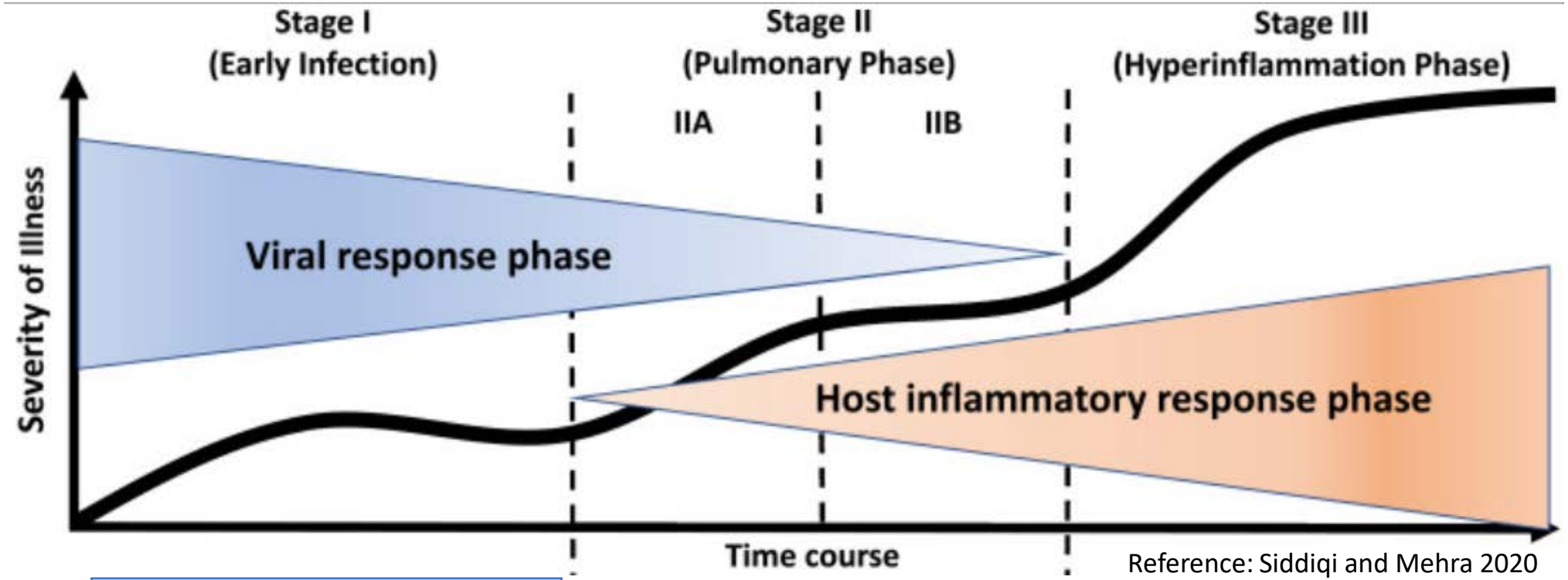
Renown's Inpatient Treatment Algorithm



LTH

Corticosteroids

Tocilizumab



Reference: Siddiqi and Mehra 2020

Bamlanivimab + Etesevimab

Remdesivir

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(some) Ongoing US outpatient studies

- **Fluvoxamine (Washington University)**
  - https://stopcovidtrial.wustl.edu/
- **Metformin (University of Minnesota)**
  - https://covidout.umn.edu/
- **Vitamin D (Brigham and Women's)**
  - https://www.vividtrial.org/
- **Ivermectin and doxycycline (Max Health, FL)**
  - (NCT number): NCT04729140

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Take Home Message

- **The war against SARS CoV-2 is not over. It is FAR from over**
- **We are still learning and the information are constantly changing**
- **We should not be complacent on COVID restrictions**
- **Get VACCINATED!**

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