RAOM COVID-19 ARCHIVE

July - December 2020

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THE VIRUS

Wajnberg A, Mansour M, Leven E et al. **Humoral immune response and prolonged PCR positivity in a cohort of 1343 SARS-CoV 2 patients in the New York City region. region**. medRxiv 2020..
https://doi.org/10.1101/2020.04.30.20085613

- Individuals with confirmed or suspected SARS-CoV-2 infection were screened via PCR for presence of viral genome and via enzyme-linked immunosorbent assay for presence of 21 anti SARS-CoV-2 spike antibodies.
- Of the 1,343 total participants, almost all were outpatients who had experienced mild to moderate symptoms; only 3% were seen in the ED or hospital
- 57% of participants in the total sample were antibody positive, 5% were weakly positive, 39% were negative.
- 47% had confirmed SARS-CoV-2 diagnosis by prior PCR testing. All but three of these confirmed SARS-CoV-2 patients seroconverted to the SARS-CoV-2 spike
- Only 37.4% of suspected SARS-CoV-2 patients had seroconverted.
- PCR- throat culture positivity was detected up to 28 days from symptom resolution but it is unclear whether this represents infectious virus.

Zhang L, Jackson CB, Mou H et al. **The D614G mutation in the SARS-CoV-2 spike protein reduces S1 shedding and increases infectivity.** BioRxiv: 6/2020
https://doi.org/10.1101/2020.06.12.148726

- In SARS-C0V-2, the spike (S) protein mediates receptor binding and fusion of the viral and host cellular membrane via 2 domains: S1 which mediates receptor binding & S2 which mediates downstream membrane fusion.
- Over time, SARS-CoV-2 isolates encoding a D614**G** mutation in the viral spike (S) protein were found to predominate, implying that this change enhanced viral transmission. The G614 genotype was not detected in February and observed at low frequency in March (26%) but increased rapidly by April (65%) and May (70%).

- Researchers studying both versions of the gene using a proxy virus in a petri dish of human cells showed that G variant viruses had more & more stable spike proteins.
- Retroviruses pseudo-typed with SG614 infected ACE2-expressing cells 9X more efficiently than those with SD614 & this greater infectivity was correlated with less S1 shedding and greater incorporation of the S protein into the pseudo-virion.
- → SG614 is more stable than SD614, consistent with epidemiological data suggesting that viruses with SG614 transmit more efficiently.
- The pseudo-viruses containing these S proteins were neutralized with comparable efficiencies by convalescent plasma suggesting that vaccines based on the original version of the virus will be effective against the new strain.

Ibarrondo FJ, Fulcher JA, Goodman-Meza D et al. **Rapid Decay of Anti–SARS-CoV-2 Antibodies in Persons with Mild Covid-19.** N Engl J Med 2020; Published July 21, 2020. **DOI: 10.1056/NEJMc2025179**

- Antibody evaluation of 34 persons who had recovered from Covid-19 infection confirmed by PCR assay in 30/34; typical symptoms of Covid-19 + cohabitation with Covid-19 (+) individuals in remaining 4.
- Most had mild illness; 2 received low flow O2 + leronlimab (a CCR5 antagonist).
- Mean age: 43 years (range, 21 to 68); 20 women/14 men.
- Samples were analyzed by ELISA to detect anti–SARS-CoV-2 spike receptor-binding domain IgG + modified ELISA to quantify serum anti–receptor-binding domain activity relative to control anti–receptor-binding domain monoclonal IgG.
- 31/34 participants had 2 serial measurements of IgG levels, 3 participants had 3.
- The first measurement was obtained a mean of 37 days after the onset of symptoms (range, 18 to 65), and the last measurement was obtained at a mean of 86 days after the onset of symptoms (range, 44 to 119).
- On the basis of a linear regression model, the antibody half-life averaged 36 days.
- Antibody loss was faster than that reported for SARS-CoV-1
- Findings raise concern that humoral immunity against SARS-CoV-2 may not be long lasting in persons with mild illness.

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Griffoni A, Weiskopf D, Ramirez SI et al. **Targets of T cell responses to SARS-CoV-2 in humans with COVID-19 and unexposed individuals.** Cell 2020; 181(7). July,2020. DOI:https://doi.org/10.1016/j.cell.2020.05.015

- Measuring immunity to SARS-CoV-2 is key for understanding COVID-19 and vaccine development
- Epitope pools detect CD4+ and CD8+ T cells in 100% and 70% of convalescent COVID patients
- T cell responses are focused not only on spike but also on M, N, and other proteins.
- T cell reactivity to SARS-CoV-2 epitopes is also detected in non-exposed individuals suggesting prior, unrecognized exposure to other CoVs.

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Braun, J., Loyal, L., Frentsch, M. *et al.* **SARS-CoV-2-reactive T cells in healthy donors and patients with COVID-19.** *Nature* (July 2020). **https://doi.org/10.1038/s41586-020-2598-9**

- SARS-CoV-2 spike glycoprotein (S)-reactive CD4+ T cells assessed in peripheral blood of COVID-19 pts & SARS-CoV-2-unexposed healthy blood donors (HD).
- SARS-CoV-2 S-reactive CD4+ T cells were detected in 83% of pts with COVID-19 but also in 35% of HD.
- S-reactive T cell lines generated from SARS-CoV-2-naive HD responded similarly to C-terminal S of human endemic coronaviruses 229E and OC43 and to SARS-CoV-2, demonstrating the presence of S-cross-reactive T cells, probably generated during past encounters with endemic coronaviruses.
- The role of pre-existing SARS-CoV-2 cross-reactive T cells for clinical outcomes remains to be determined in larger cohorts. However, the presence of S-cross-reactive T cells in a sizable fraction of the general population may affect the dynamics of the current pandemic, and has important implications for the design and analysis of upcoming COVID-19 vaccine trials.
- CONCLUSION: 83% of pts with COVID-19 were found to have CD4+ T cells reactive against SARS-CoV-2; 35% of unexposed healthy donors were also found to possess these immune cells.

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Chen M, Shen W, Rowan NR, et al. **Elevated ACE2 expression in the olfactory neuroepithelium: implications for anosmia and upper respiratory SARS-CoV-2 entry and replication.** Eur Respir J 2020; in press (**https://doi.org/10.1183/13993003.01948-2020**).

- SARS-CoV-2 infection often presents with olfactory loss without nasal inflammatory symptoms, suggesting direct targeting of the olfactory system.
- The cellular location of ACE2 protein in the olfactory epithelium has not been previously demonstrated.
- In this study, we performed immunohistological analyses to determine the location of ACE2 protein in human nasal and tracheal specimens in 23 pts undergoing biopsy for non-SARS-C0V-2 problems.
- Results: ACE2 protein is expressed at high levels in the human olfactory epithelium relative to upper airway epithelial cells, evidence that the upper, rather than the lower, airway is the initial site of SARS-CoV-2 infection.
- Findings may explain COVID-19-associated olfactory dysfunction, while suggesting a SARS-CoV-2 reservoir site and potential intranasal therapy.

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Lemieux J, Siddle KJ, Shaw BM et al. **Phylogenetic analysis of SARS-CoV-2 in the Boston area highlights the role of recurrent importation and superspreading events.** medRxiv 2020.08.23.20178236; **https://doi.org/10.1101/2020.08.23.20178236**

- Detailed viral genome sequencing & phylogenetic analysis of a Boston area SARS-CoV-2 epidemic using NP samples collected from 1/29/2020 – 5/9/2020.
- Phylogenetic tree constructed from this dataset in the context of a global set of 4,011 genomes from the Global Initiative on Sharing All Influenza Data (GISAID).
- Root-to-tip regression showed a clear, temporal signal in our dataset, with the fitted regression model accounting for 17% of the variance in the root-to-tip distance. The presence of a temporal signal means that a molecular clock can be fitted to infer the timing of ancestral branching based on SARS-CoV-2 genomes.
- First large cluster of cases was recognized in the context of an international business conference held in Boston from 2/26 – 27 with >90 cases diagnosed in conference attendees or their contacts, raising suspicion of a superspreading event.
- Dataset containing SARS-CoV-2 genomes from 28 of these cases, allowed search for genetic evidence of superspreading in the form of phylogenetic clustering of identical/highly similar viruses in a narrow time window → all 28 genomes formed a well-supported monophyletic cluster marked by the presence of the SNP C2416T, first seen in the GISAID database in 2 French pts on 2/29/2020 →all 27 US C2416T-containing viruses collected before 3/10 were from conference exposures.
- This strongly suggests there was low-level community transmission of C2416T in Europe in 2/2020 before the allele was introduced to Boston via a single introduction and amplified by superspreading at the conference.
- SARS-CoV-2 containing C2416T allele subsequently spread extensively in the Boston area, representing 35.1% of our dataset. Beginning in early March, C2416T appeared in multiple other US states & other countries & increased steeply in frequency, comprising 2.7% of domestic & 1.7% of global SARS-CoV-2 genomes in GISAID through 6/28 → ultimately, >20,000 cases spread from this 1 conference.
- Single introduction had an outsize effect because it was amplified by superspreading in a highly mobile population very early in the outbreak, before precautions were in place & when its effects were amplified by exponential growth.
- This is direct evidence that superspreading events may profoundly alter the course of an epidemic & implies that prevention, detection & mitigation of such events should be a public health priority.

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Bunyavanich S, Grant C, Vicencio A. **Racial/Ethnic Variation in Nasal Gene Expression of Transmembrane Serine Protease 2 (TMPRSS2).** JAMA. Published online September 10, 2020. **doi:10.1001/jama.2020.17386**

- SARS-CoV-2) is spread by airway contact & uses TMPRSS2 to facilitate viral entry and spread. Host-expressed TMPRSS2 on nasal and bronchial epithelium activates the SARS-CoV-2 spike protein & cleaves the ACE-2 receptor to which the virus binds, enabling SARS-CoV-2 to enter the body
- Nasal epithelium collected by nasal brushing from healthy individuals & individuals with asthma aged 4-60 yrs from 2015-2018 were analyzed for TMPRSS2 by self-identified race/ethnicity.
- RNA isolation of brushings followed by RNA sequencing, sequence alignment, and normalization were performed.
- The cohort (n = 305) was 8.2% Asian, 15.4% Black, 26.6% Latino, 9.5% mixed race/ethnicity, & 40.3% White. 48.9% were male and 49.8% had asthma.

- Nasal gene expression of TMPRSS2 in log2 counts per million was highest in Blacks (n = 47; mean, 8.64 [95% CI, 8.41-8.86]) compared with Asians (n = 25; mean, 8.07 [95% CI, 7.74-8.40]), Latinos (n = 81; mean, 8.02 [95% CI, 7.90-8.14]), individuals of mixed race/ethnicity (n = 29; mean, 7.97 [95% CI, 7.77-8.16]), and Whites (n = 123; mean, 8.04 [95% CI, 7.94-8.15]) .
- CONCLUSION: By linear regression, TMPRSS2 expression was significantly higher in Black individuals compared with Asian, Latino, mixed race/ethnicity & Whites (all P < .001). There were no significant associations between TMPRSS2 expression & sex, age, or asthma.

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Zhang T, Wu Q, Zhang Z. **Probable Pangolin Origin of SARS-CoV-2 Associated with the COVID-19 Outbreak.** Current Biology 2020; 30:1346-1351.e2. https://doi.org/10.1016/j.cub.2020.03.022

- Genomic and evolutionary evidence of the occurrence of a SARS-CoV-2-like CoV (named Pangolin-CoV) was identified in dead Malayan pangolins.
- Pangolin-CoV is 91.02% identical to SARS-CoV-2 at the whole-genome level
- Pangolin-CoV is the second closest relative of SARS-CoV-2 behind RaTG13 – the bat coronavirus thought to be the origin of SARS-CoV-2
- The S1 protein of Pangolin-CoV is much more closely related to SARS-CoV-2 than to RaTG13.
- Five key amino acids involved in the interaction with human ACE2 are completely consistent between Pangolin-CoV and SARS-CoV-2, but 4 amino acid mutations are present in RaTG13.
- Only SARS-CoV-2 contains a potential cleavage site for furin proteases – this is lost in both Pangolin-CoV and bat RaTG13.
- Conclusively, this study suggests that pangolin species are a natural reservoir of SARS-CoV-2-like CoVs.

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Meltzer DO, Best TJ, Zhang H, Vokes T, Arora V, Solway J. **Association of Vitamin D Status and Other Clinical Characteristics With COVID-19 Test Results.** JAMA Netw Open. 2020;3(9):e2019722. **doi:10.1001/jamanetworkopen.2020.19722**

- Vitamin D treatment has been found to decrease the incidence of viral respiratory tract infection, especially in pts with vitamin D deficiency. This study examines whether the last vitamin D status before COVID-19 testing is associated with COVID-19 test results.
- This retrospective cohort study at an urban academic medical center included all pts with a 25-hydroxycholecalciferol or 1,25-dihydroxycholecalciferol level measured within 1 year before being tested for COVID-19 from March 3 to April 10, 2020.
- Vitamin D deficiency was defined by the last measurement of 25-hydroxychole- calciferol less than 20 ng/mL or 1,25-dihydroxycholecalciferol less than 18 pg/mL before COVID-19 testing. Treatment changes were defined by changes in vitamin D type and dose between the date of the last vitamin D level measurement and the date of COVID-19 testing. Vitamin D deficiency and treatment changes were combined to categorize the most recent vitamin D status before COVID-19 testing as likely deficient (last level deficient and treatment not increased), likely sufficient (last level not deficient and treatment not decreased), and 2

groups with uncertain deficiency (last level deficient and treatment increased, and last level not deficient and treatment decreased).

- RESULTS A total of 489 patients (mean [SD] age, 49.2 [18.4] years; 366 [75%] women; and 331 [68%] race other than White) had a vitamin D level measured in the year before COVID-19 testing. Vitamin D status before COVID-19 testing was categorized as likely deficient for 124 participants (25%), likely sufficient for 287 (59%), and uncertain for 78 (16%).
- Overall, 71 participants (15%) tested positive for COVID-19. In multivariate analysis, testing positive for COVID-19 was associated with increasing age up to age 50 years (relative risk, 1.06; 95% CI, 1.01-1.09; P = .02); non-White race (relative risk, 2.54; 95% CI, 1.26-5.12; P = .009), and likely deficient vitamin D status (relative risk, 1.77; 95% CI, 1.12-2.81; P = .02) compared with likely sufficient vitamin D status.
- Predicted COVID-19 rates in the deficient group were 21.6% (95% CI, 14.0%-29.2%) vs 12.2%(95% CI, 8.9%-15.4%) in the sufficient group.
- In this single-center, retrospective cohort study, likely deficient vitamin D status was associated with increased COVID-19 risk.

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Popkin BM, Du S, Green WD et al. **Individuals with obesity and COVID-19: A global perspective on the epidemiology and biological relationships.** Obesity Review. First published: 26 August 2020.
https://doi.org/10.1111/obr.13128

- A systematic search of the Chinese & English language literature on COVID-19 identified 75 studies used to conduct a series of meta-analyses on the relationship of individuals with obesity–COVID-19 over the full spectrum from risk to mortality.
- Pooled analysis shows that individuals with obesity were more at risk for COVID-19 infection, >46.0% higher (OR = 1.46; 95% CI, 1.30–1.65; p < 0.0001); for hospitalization, 113% higher (OR = 2.13; 95% CI, 1.74–2.60; p < 0.0001); for ICU admission, 74% higher (OR = 1.74; 95% CI, 1.46–2.08); and for mortality, 48% increase in deaths (OR = 1.48; 95% CI, 1.22–1.80; p < 0.001).
- Mechanistic pathways for COVID-19 infection and increased disease severity in individuals with obesity include associated metabolic dysfunction, impaired immune function & chronic inflammation.
- CONCLUSION: Individuals with obesity are linked to large significant increases in morbidity and mortality from COVID-19.

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Y. J. Hou, Chiba S, Halfmann P et al. et al. **SARS-CoV-2 D614G variant exhibits efficient replication ex vivo and transmission in vivo**. Science 2020. First release: 12 November 2020 www.sciencemag.org. **DOI:10.1126/science.abe8499**

- Recent reports have identified an emergent D614G substitution in the spike glycoprotein of SARS-CoV-2 strains that is now the most prevalent form globally.
- Patients infected with the D614G variant have higher upper respiratory tract viral loads than seen with the ancestral strain, but not altered disease severity.
- SARS-CoV-2 S pseudotyped viruses encoding the D614G substitution were reported to exhibit increased infectivity in continuous cell lines and increased sensitivity to neutralization

- To examine whether the D614G substitution enhances authentic SARS-CoV-2 entry, four susceptible cell lines were infected with the ancestral wild-type (WT)-nLuc and D614G-nLuc viruses. The D614G-nLuc infection resulted in a 3.7 to 8.2-fold higher transgene expression as compared with WT-nLuc virus in different cell lines.
- Growth curves comparing WT and D614G viruses were performed in those cell lines. Although the D614G variant showed similar or slightly higher titers at 8 hrs, its peak titers were ~0.5 logs lower than the ancestral WT virus.
- With multi-step growth kinetics (MOI = 0.1) of the WT and D614G viruses in ex vivo primary human nasal epithelial (HNE) cells, large proximal airway epithelial cells from SARS-CoV-2 D614G variant exhibited efficient replication ex vivo and transmission in vivo.

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Meinhardt, J., Radke, J., Dittmayer, C. et al. **Olfactory transmucosal SARS-CoV-2 invasion as a port of central nervous system entry in individuals with COVID-19.** Nat Neurosci (2020). https://doi.org/10.1038/s41593-020-00758-5

- Neurological symptoms such as loss of smell and taste, headache, fatigue, nausea and vomiting are present in more than one-third of individuals with COVID-19., investigators performed a systematic analysis of autopsy brains and peripheral tissues aimed at understanding the port of entry and distribution for SARS-CoV-2 within the CNS.
- To investigate SARS-CoV-2 penetrance of the CNS, investigators analyzed the cellular mucosal–nervous micromilieu as a first site of viral infection and replication, followed by thorough regional mapping of the consecutive olfactory nervous tracts and defined CNS regions, in autopsy material from 33 individuals with COVID-19.
- Analysis visualized viral RNA and protein using ISH and immunohistochemical staining techniques and showed SARS-CoV-2 can enter the nervous system by crossing the neural–mucosal interface in olfactory mucosa in the nasopharynx, exploiting the close vicinity of olfactory mucosal, endothelial and nervous tissue, including delicate olfactory and sensory nerve endings.
- Morphological changes such as thromboembolic ischemic infarction of the CNS & present evidence of SARS-CoV-2 neurotropism were shown to follow neuroanatomical structures in defined neuro- anatomical areas including the primary respiratory & CV control center in the medulla oblongata.
- Presence of intact CoV particles & SARS-CoV-2 RNA in the olfactory mucosa and in neuro-anatomical areas receiving olfactory tract projections suggests SARS-CoV-2 neuro-invasion via axonal transport.

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Çevik M, et al. **SARS-CoV-2, SARS-CoV, and MERS-CoV viral load dynamics, duration of viral shedding, and infectiousness: a systematic review and meta-analysis.** Lancet Microbe 2020; **DOI: 10.1016/S2666-5247(20)30172-5.**

- To characterize viral load dynamics, duration of viral RNA shedding, and viable virus shedding of SARS-CoV-2, and to compare SARS-CoV-2, SARS-CoV, and Middle East respiratory syndrome coronavirus (MERS-CoV) viral dynamics, a systematic review and

meta-analysis of research articles published between Jan 1, 2003, and June 6, 2020 was performed.

- Findings: 79 studies (5340 individuals) on SARS-CoV-2, 8 studies (1858 individuals) on SARS-CoV, and 11 studies (799 individuals) on MERS-CoV were included.
- Mean duration of SARS-CoV-2 RNA shedding was 17·0 days (95% CI 15·5–18·6) in upper respiratory tract, 14·6 days (9·3–20·0) in lower respiratory tract, 17·2 days (14·4–20·1) in stool, and 16·6 days (3·6–29·7) in serum samples.
- Pooled mean SARS-CoV-2 shedding duration was positively associated with age (slope 0·304 [95% CI 0·115–0·493]; p=0·0016).
- No study detected live virus beyond day 9 of illness, despite persistently high viral loads, which were inferred from cycle threshold values. SARS-CoV-2 viral load in the upper respiratory tract appeared to peak in the first week of illness, whereas that of SARS-CoV peaked at days 10–14 and that of MERS-CoV peaked at days 7–10.

→ Although SARS-CoV-2 RNA shedding in respiratory and stool samples can be prolonged, duration of viable virus is relatively short-lived.

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Mengfei Chen, Wenjuan Shen, Nicholas R. Rowan et al. **Elevated ACE2 expression in the olfactory neuroepithelium: implications for anosmia and upper respiratory SARS-CoV-2 entry and replication.** European Respiratory Journal, 2020; 2001948
DOI: 10.1183/13993003.01948-2020

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Peckham, H., de Gruijter, N.M., Raine, C. et al. **Male sex identified by global COVID-19 meta-analysis as a risk factor for death and ITU admission.** Nat Commun 11, 6317 (2020). https://doi.org/10.1038/s41467-020-19741-6

- To address whether the reported sex-bias is validated by large-scale statistical analysis of global data, we have collected available case data from 90 reports including 46 different countries and 44 US states totalling 3,111,714 infected cases, and present a meta-analysis to investigate sex as a risk factor for SARS-CoV-2 infection, and COVID-19 morbidity and mortality.
- The proportion of male cases with COVID-19 in these reports was exactly half at 0.50 (95% confidence interval (CI) = 0.48,0.51; p = 0.56; n = 3,111,714), demonstrating that males and females have similar numbers of infections.
- Male sex was associated with increased odds of ITU admission (odds ratio (OR) = 2.84; 95% CI = 2.06, 3.92; p = 1.86 × 10−10; n = 341,571), and increased odds of death (OR = 1.39; 95% CI = 1.31,1.47; p = 5.00 × 10−30; n = 2,751,115).

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Emerging SARS-CoV-2 Variants. MMWR Dec. 20, 2020.
DOI: http://dx.doi.org/10.15585/mmwr.mm7003e2

- Multiple SARS-CoV-2 variants are circulating globally with several new variants emerging in the fall of 2020.

- In the United Kingdom, a Variant of Concern (VOC) 202012/01, a.k.a. B.1.1.7, has a mutation in the receptor binding domain (RBD) of the spike protein at position 501, where amino acid asparagine (N) has been replaced with tyrosine (Y). The shorthand for this mutation is N501Y. There are several other associated, identified mutations.
- This variant is estimated to have first emerged in the UK during September 2020.
- Since December 20, 2020, 33 countries have reported cases of B.1.1.7, including the US and Canada.
- Preliminary epidemiologic indicators suggest that this variant is associated with increased transmissibility.
- In South Africa, another variant of SARS-CoV-2 (501Y.V2 or B.1.351) has emerged independently although the 2 variants share some mutations.
- In Nigeria, another distinct variant strain of SARS-CoV-2 also emerged.
- Currently there is no evidence to suggest that these variants have any impact on the severity of disease or vaccine efficacy.

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Volz E, Ferguson N, Mishra S et al. **Transmission of SARS-CoV-2 Lineage B.1.1.7 in England: Insights from linking epidemiological and genetic data**. medRxiv 2020. MRC Centre for Global Infectious Disease. Analysis of COVID-19: Report 42 - Dec. **https://doi.org/10.1101/2020.12.30.20249034**

- The SARS-CoV-2 lineage B.1.1.7 originated in the UK in late Summer to early Autumn 2020. British investigators examined epidemiological evidence for a transmission advantage of B.1.1.7.
- Whole genome sequence data collected from community-based diagnostic testing reveals an increased prevalence of the B.1.1.7 variant over time. Phylodynamic modelling additionally indicates that genetic diversity of this lineage has changed consistent with exponential growth.
- Changes in B.1.1.7 frequency inferred from genetic data correspond closely to changes inferred by S-gene target failures (SGTF) in community-based diagnostic PCR testing.
- Growth trends in SGTF and non-SGTF case numbers at local area level across England show that B.1.1.7 has higher transmissibility than non-B.1.1.7 lineages, even if B.1.1.7 has a different latent period or generation time.
- B.1.1.7 has a substantial transmission advantage with its reproduction numbers varying from 1.4 to 1.8. (For context, prior research found seasonal influenza had a median reproduction number of 1.28, while the median reproduction number for the 1918 flu pandemic was 1.80.)

THE DISEASE

Arons MM, Hatfield KM, Reddy SC, et al. Presymptomatic SARS-CoV-2 infections and transmission in a skilled nursing facility. N Engl J Med.2020. 5/28/2020. **DOI: 10.1056/NEJMoa2008457.**

- After 1 resident in a skilled nursing facility tested (+) for SARS-CoV-2, all residents underwent 2 assessments of symptoms and NP/OP testing including real-time RT-PCR, viral culture, and sequencing.
- Asymptomatic residents who tested positive were reassessed 7 days later.
- 23 days after the first (+) test result, 57/89 residents(64%) tested (+) for SARS-CoV2.
- In 76 residents who participated in 2 surveys, 27/48 tested (+) and were asymptomatic at the time of testing; 24/27 developed symptoms within 4 days.
- Among 64%(+) for SARS-CoV-2, 11 hospitalized &15 died (mortality, 26%).
- Rapid, widespread transmission of SARS-CoV-2 was demonstrated with more than half of culture (+) residents asymptomatic at the time of testing.

→ Infection-control strategies focused solely on symptomatic individuals are not sufficient to prevent transmission of this very highly contagious virus after SARS-CoV-2 introduction into this kind of facility.

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Ackermann M, Verleden SE, Kuehnel M. **Pulmonary Vascular Endothelialitis, Thrombosis, and Angiogenesis in Covid-19**. New Engl J Med 2020; May 21, 2020
DOI: 10.1056/NEJMoa2015432

- 7 lungs obtained at autopsy from COVID-19 pts were compared with 7 lungs obtained at autopsy from pts who died from ARDS secondary to influenza A(H1N1) and 10 age-matched, uninfected control lungs.
- Lungs studied with 7-color immunohistochemical analysis, micro-CT imaging, scanning EM, corrosion casting & direct multiplexed measurement of gene expression.
- RESULTS: In both COVID-19 pts and pts who died from influenza-associated respiratory failure, the histologic pattern in the peripheral lung was diffuse alveolar damage with perivascular T-cell infiltration.
- Only COVID-19 lungs also showed distinctive vascular features of severe endothelial injury associated with presence of intracellular virus and disrupted cell membranes.
- Histologic analysis of pulmonary vessels in COVID-19 pts showed widespread thrombosis with microangiopathy. Alveolar capillary microthrombi were 9X as prevalent in COVID-19 pts as in influenza pts($P<0.001$).
- In lungs from COVID-19 pts, the amount of new vessel growth - predominantly through a mechanism of intussusceptive angiogenesis - was 2.7X as high as that in the lungs from influenza pts ($P<0.001$).

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Toubiana J, Poirault C, Corsia A et al. **Kawasaki-like multisystem inflammatory syndrome in children during the covid-19 pandemic in Paris, France: prospective observational study.** BMJ 2020;369:m2094. Published online, 6/2/2020. **http://dx.doi.org/10.1136 bmj.m2094**

- Case series of 21 children and adolescents with features suggestive of Kawasaki disease admitted to hospital between 27 April and 11 May 2020
- Median age 7.9 yrs (range 3.7-16.6); 12 (57%) of African ancestry.
- 21/21 had GI symptoms; 12 (57%) presented in shock and 16 (76%) had myocarditis; 17 (81%) required intensive care support.
- Moderate coronary artery dilations detected in 5 pts (24%) but none had coronary aneurysms.
- 21/21 had high levels of inflammatory markers; 19 (90%) had evidence of recent SARS-CoV-2 infection ([+] RT-PCR result in 8/21, [+] IgG antibody in 19/21).
- All 21 patients received intravenous immunoglobulin and 10 (48%) also received corticosteroids.
- The clinical outcome was favorable in all pts.
- Delay between the peak of SARS-CoV-2 infections and presentation of PIMS raises the possibility that this is a post-infectious, immunologically mediated phenomenon.

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McGuinness G, Zhan C, Rosenberg N et al. **High Incidence of Barotrauma in Patients with COVID-19 Infection on Invasive Mechanical Ventilation.** Radiology 2020; Published Online: Jul 2 2020. **https://doi.org/10.1148/radiol.2020202352**

- Retrospective review of clinical and imaging data of COVID-19 pts seen between 3/1/2020 & 4/6/2020 who experienced barotrauma (extrapulmonary air) during invasive mechanical ventilation were compared to pts without COVID-19 infection ventilated during the same period.
- Historical comparison also made to barotrauma rates of ARDS ptsfrom 02/01/2016 to 02/01/2020 at our institution.
- Of 601 ventilated COVID-19 pts (63 ± 15 years, 71% men), 89/601 (15%) had >/= 1 barotrauma events, 145 total barotrauma events (24% overall events) (95% CI 21-28%). Of 196 ventilated pts without COVID-19 infection (64 ± 19 years, 52% male) only 1 had a single barotrauma event (.5% 95% CI, 0-3%, p<.001).
- Of 285 ventilated ARDS pts over the prior 4 years (68 ± 17 years, 60% men), 28 patients (10%) had 31 barotrauma events, with overall barotrauma rate of 11% (95% CI 8-15%, p<.001 vs. the group with COVID-19 infection).
- Barotrauma was an independent risk factor for death in COVID-19 (OR=2.2, p=.03), and was associated with longer hospital length of stay (OR=.92, p<.001).

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Davies, N.G., Klepac, P., Liu, Y et al. **Age-dependent effects in the transmission and control of COVID-19 epidemics.** *Nat Med* (2020). Published 6/16/2020. https://doi.org/10.1038/s41591-020-0962-9

- To evaluate age disparities in observed COVID-19 cases, an age-structured mathematical model to data from China, Italy, Japan, Singapore, Canada and South Korea was constructed.
- Results indicate susceptibility to infection in individuals </= 20 yrs of age is half that of adults >20 yrs
- Clinical symptoms were manifest in 21% (95% credible interval: 12–31%) of infections in 10-19-yr-olds, rising to 69% (57–82%) in people > 70 yrs.

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Nicolai L, Leunig A, Brambs S, et al. **Immunothrombotic Dysregulation in COVID-19 Pneumonia is Associated with Respiratory Failure and Coagulopathy.** Circulation. 2020 Jul 28. doi: 10.1161/CIRCULATIONAHA.120.048488. Online ahead of print. **https://www.ahajournals.org/doi/10.1161/CIRCULATIONAHA.120.048488**

- 38 pts with RT-PCR confirmed COVID-19 and 24 controls underwent histo-pathological assessment of autopsy specimens, surface-marker based phenotyping of neutrophils & platelets & functional assays for platelet, neutrophil function & coagulation.
- In COVID-19. inflammatory microvascular thrombi are present in the lung, kidney& heart, containing neutrophil extracellular traps associated with platelets and fibrin.
- COVID-19 pts also present with neutrophil-platelet aggregates & a distinct neutrophil/ platelet activation pattern in blood, changing with disease severity: cases of intermediate severity show an exhausted platelet & hyporeactive neutrophil phenotype, severely affected COVID-19 pts are characterized by excessive platelet & neutrophil activation vs healthy controls & non-COVID pneumonia.
- Dysregulated immunothrombosis in SARS-CoV-2 pneumonia is linked to both ARDS and systemic hypercoagulability suggesting that this is a key marker of disease severity in COVID-19.

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Yonker LM, Neilan AM, Bartsch Y et al. **Pediatric SARS-CoV-2: Clinical Presentation, Infectivity, and Immune Responses.** The Journal of Pediatrics (2020). **https://doi.org/10.1016/j.jpeds.2020.08.037.**

- Children ages 0-22 years with suspected SARS-CoV-2 infection presenting to urgent care clinics or being hospitalized for confirmed/suspected SARS-CoV-2 infection or multisystem inflammatory syndrome in children (MIS-C) were evaluated.
- A total of 192 children (mean age 10.2 +/- 7 years) were enrolled: 49 (26%) with acute SARS-CoV-2 infection; an additional 18 children (9%) met criteria for MIS-C.
- Only 25 (51%) children with acute SARS-CoV-2 infection presented with fever; symptoms of SARS-CoV-2 infection, if present, were non-specific.
- Nasopharyngeal viral load was highest in the first 2 days of symptoms, significantly higher than hospitalized adults with severe disease (P = .002).
- Age did not impact viral load, but younger children had lower ACE2 expression (P=0.004).
- IgM and IgG to the receptor binding domain (RBD) of the SARS-CoV-2 spike protein were increased in severe MIS-C (P<0.001), with dysregulated humoral responses observed.
- Children may be a potential source of contagion in the SARS-CoV-2 pandemic in spite of milder disease or lack of symptoms, and immune dysregulation is implicated in severe post-infectious MIS-C.

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Del Valle, D.M., Kim-Schulze, S., Huang, H. et al. **An inflammatory cytokine signature predicts COVID-19 severity and survival.** Nat Med (2020). Aug. 24,2020. **https://doi.org/10.1038/s41591-020-1051-9**

- A hyper-inflammatory response induced by SARS-CoV-2 is a major cause of disease severity and death.
- A rapid multiplex cytokine assay was used to measure serum interleukin (IL)-6, IL-8, tumor necrosis factor (TNF)-α and IL-1β in 1484 hospitalized patients with COVID-19 on admission to the Mount Sinai Health System in New York from 3/21-4/28/2020.
- Pts (n = 1,484) were followed up to 41 d after admission (median, 8 d), and clinical information, laboratory test results and patient outcomes were collected.
- Cutoffs chosen for further statistical analyses were >70 pg ml−1 for IL-6, >50 pg ml−1 for IL-8, >35 pg ml−1 for TNF-α and >0.5 pg ml−1 for IL-1β.
- Men had significantly higher levels of IL-6 than women ($P < 0.0001$), but no sex differences were observed for the other three cytokines.
- With increasing age brackets (<50, 50–70 and >70 years old), levels of IL-6, IL-8 and TNF-α increased.
- CKD was the only other comorbidity significantly associated with elevated cytokine levels
- RESULTS: High serum IL-6, IL-8 and TNF-α levels at hospitalization were strong and independent negative predictors of patient survival by Cox regression analysis. ($P < 0.0001$, $P = 0.0205$ and $P = 0.0140$, respectively).
- After adjustment for demographics and comorbidities, only age (50–70 versus <70 years, hazard ratio (HR) = 2.09 (1.25–3.49); >70 versus <50 years, HR = 3.76 (2.24–6.33)), IL-6 (HR = 2.23 (1.61–3.09)), IL-8 (HR = 1.41 (1.05–1.89)) and TNF-α (HR = 1.50 (1.09–2.07)) remained significantly associated with decreased survival ($P = 0.0049$, $P < 0.0001$, $P = 0.0205$ and $P = 0.0140$, respectively).
- CONCLUSION: After adjusting for disease severity, common laboratory inflammation markers, hypoxia and other vitals, demographics, and a range of comorbidities, IL-6 and TNF-α serum levels remained independent and significant predictors of disease severity and death.

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Bixler D, Miller AD, Mattison CP, et al. **SARS-CoV-2-Associated Deaths Among Persons Aged <21 Years - United States, February 12-July 31, 2020**. MMWR. Morb Mortal Wkly Rep. ePub: 15 September 2020. **http://dx.doi.org/10.15585/mmwr.mm6937e4external icon**.

- This report describes characteristics of 121 U.S. persons <21 yrs who died in association with SARS-CoV-2 infection between 2/12-7/31/2020, as reported to the CDC. Persons aged <21 yrs constitute 26% of the U.S. population
- 63% of deaths occurred in males, 10% were aged <1 year, 20% were aged 1–9 years, 70% were aged 10–20 years; 50 deaths (41%) occurred in 18-20 yr olds.
- 45% were Hispanic, 29% were non-Hispanic Black (Black) persons, and 4% were non-Hispanic American Indian or Alaska Native (AI/AN) persons.
- Among these 121 decedents, 91 (75%) had an underlying medical condition,*
- 120 (99.2) had COVID-19; 15 (12.4) had MIS-C.
- 79 (65%) died after admission to a hospital, 39 (32%) died at home or in the ED.
- CONCLUSION: Nearly three quarters of SARS-CoV-2–associated deaths among infants, children, adolescents, & young adults have occurred in persons aged 10–20 yrs, with a disproportionate percentage among young adults aged 18–20 yrs and among Hispanics, Blacks, AI/ANs, and persons with underlying medical conditions.

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Dennis J, McGovern A, Vollmer S et al. **Improving COVID-19 critical care mortality over time in England: A national cohort study, March to June 2020.** MedRxiv 2020; Preprint, 10/20/2020.
https://doi.org/10.1101/2020.07.30.20165134

- To determine mortality trend in pts with severe COVID-19 requiring critical care (high intensive unit [HDU] or intensive care unit [ICU]management), national English data on all 14,958 adult COVID-19 specific critical care admissions from 3/1/2020-5/30/2020 was accessed from a national surveillance system.
- Primary outcome was in-hospital 30-day all-cause mortality. Cox proportional hazards model adjusted for age, sex, ethnicity, comorbidities & geographical region.
- Results: 30-day mortality peaked for people admitted to critical care in early April (peak 29.1% for HDU, 41.5% for ICU). There was subsequently a sustained decrease in mortality risk until the end of the study period.
- Adjusted mortality risk decreased by 11.2% (adjusted HR 0.89 [95% CI 0.87 - 0.91]) per week in HDU, and 9.0% (adjusted HR 0.91 [95% CI 0.88 - 0.94]) in ICU.
- Conclusions: There has been a substantial mortality improvement in COVID-19 pts admitted to critical care in England, with markedly lower mortality in people admitted in mid-April and May compared to earlier in the pandemic.
- Trend remains after adjustment for patient demographics and comorbidities, suggesting this improvement is not due to changing patient characteristics.

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Horwitz L, Jones SA, Cerfolio RJ et al. **Trends in Covid-19 risk-adjusted mortality rates in a single health system**. medRxiv 2020.08.11.20172775. October, 2020.
doi: https://doi.org/10.1101/2020.08.11.20172775

- COVID-19 outcomes over time were assessed in a single health system, accounting for changes in demographics and clinical factors.
- METHOD: Biweekly mortality rates for admissions between March 1 and June 20, 2020 were analyzed in a single health system in New York City. Outcomes were obtained as of July 14, 2020. All hospitalizations with laboratory-confirmed Covid-19 disease were included. Mortality was defined as in-hospital death or discharge to hospice care.
- A multivariable logistic regression model was created to generate expected risk of death, adjusting for age; sex; self-reported race and ethnicity; body mass index; smoking history; presence of hypertension, heart failure, hyperlipidemia, coronary artery disease, diabetes, cancer, chronic kidney disease, or pulmonary disease individually as dummy variables; and admission oxygen saturation, D-dimer, C reactive protein, ferritin, and cycle threshold for RNA detection. All data were obtained from the electronic health record.
- Observed and expected deaths in each two-week period were added and multiplied by each period's observed/expected (O/E) risk by the overall average crude mortality to generate biweekly adjusted rates.
- RESULTS; We included 4,689 hospitalizations, of which 4,661 (99.4%) had died or been discharged. The median age decreased from 67 years in the first two weeks to 49 in the last two; the proportion male or with any comorbidity decreased over time.
- Unadjusted mortality dropped each period, from 30.2% in the first two weeks to 3% in the last two weeks, with the last eight weeks being lower than the 95% control limits.
- Risk adjustment partially attenuated the mortality decline, but adjusted mortality rates in the second-to-last two weeks remained outside the control limits. The O/E risk of mortality

decreased from 1.07 (0.64-1.67) in the first two weeks to 0.39 (0.08-1.12) in the last two weeks.
- In this 16-week study of Covid-19 mortality at a single health system, we found a significant decrease in unadjusted mortality; changes in demographics and severity of illness at presentation accounted for some, but not all, of the decrease in unadjusted mortality. Even after risk adjustment for multiple clinical and demographic factors, mortality was significantly lower at the end of the study period.

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Nadkarni GN, Lala A, Bagiella E et al. **Anticoagulation, Bleeding, Mortality, and Pathology in Hospitalized Patients With COVID-19**. J Am Coll Cardiol. 2020 Aug, 76(16): 1815–1826. **doi: 10.1016/j.jacc.2020.08.041**

- To evaluate the association of thromboembolic disease and anticoagulation in pts with COVID-19 with outcomes and postmortem findings, consecutive cases were evaluated retrospectively for therapeutic versus prophylactic AC initiated ≤48 h from admission and mortality, intubation and major bleeding.
- Thromboembolic disease was contextualized by premortem AC among consecutive autopsies.
- RESULTS: Among 4,389 patients, median age was 65 yrs, 44% women. Compared with no AC (n = 1,530; 34.9%), therapeutic AC (n = 900; 20.5%) and prophylactic AC (n = 1,959; 44.6%) were associated with lower in-hospital mortality (adjusted hazard ratio [aHR]: 0.53(CI: 0.45 to 0.62); aHR: 0.50 (CI: 0.45 to 0.57), and intubation (aHR: 0.69 (CI: 0.51 to 0.94); aHR: 0.72 (CI: 0.58 to 0.89).
- Overall, 89 patients (2%) had major bleeding adjudicated by clinician review, with 27 of 900 (3.0%) on therapeutic, 33 of 1,959 (1.7%) on prophylactic, and 29 of 1,530 (1.9%) on no AC.
- Of 26 autopsies, 11 (42%) had thromboembolic disease not clinically suspected and 3 of 11 (27%) were on therapeutic AC.
- CONCLUSIONS: AC was associated with lower mortality and intubation among hospitalized COVID-19 patients. Compared with prophylactic AC, therapeutic AC was associated with lower mortality, although not statistically significant. Autopsies revealed frequent thromboembolic disease.

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Anup A, Aparna M, Kumar Gunjan K et al. **Convalescent plasma in the management of moderate covid-19 in adults in India: open label phase II multicentre randomised controlled trial (PLACID Trial)** BMJ 2020; 371 :m3939 **https://doi.org/10.1136/bmj.m3939** (Published 22 October 2020)

- To investigate the effectiveness of using convalescent plasma to treat moderate coronavirus disease 2019 (covid-19) in adults in India, an open label, parallel arm, phase II, multi-centre, randomised controlled trial was performed in 39 public and private hospitals across India.
- 464 adults admitted to hospital between 22 April & 14 July 2020 with confirmed moderate covid-19 (partial pressure of oxygen in arterial blood/fraction of inspired oxygen (PaO2/FiO2) ratio between 200 mm Hg and 300 mm Hg or a respiratory rate of more than 24/min with oxygen saturation 93% or less on room air): 235 were assigned to convalescent plasma with best standard of care (intervention arm) and 229 to best standard of care only (control arm).

- Participants in the intervention arm received two doses of 200 mL convalescent plasma, transfused 24 hours apart. The presence and levels of neutralising antibodies were not measured a priori; stored samples were assayed at the end of the study.
- Main outcome measure as a composite of progression to severe disease (PaO2/FiO2 <100 mm Hg) or all cause mortality at 28 days post-enrolment.
- Results: Progression to severe disease or all cause mortality at 28 days after enrolment occurred in 44 (19%) participants in the intervention arm and 41 (18%) in the control arm (risk difference 0.008 (95% confidence interval −0.062 to 0.078); risk ratio 1.04, 95% confidence interval 0.71 to 1.54).
- Convalescent plasma was **not** associated with a reduction in progression to severe covid-19 or all cause mortality.
- This trial has high generalizability and approximates convalescent plasma use in real life settings with limited laboratory capacity.

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Giustino G, Croft LB, Stefanini GG et al. **Characterization of Myocardial Injury in Patients With COVID-19.** J Am Coll Cardiol. 2020 October; 76 (18) 2043–2055.
doi: 10.1016/j.jacc.2020.08.069.

- To characterize the echocardiographic abnormalities associated with myocardial injury and their prognostic impact in hospitalized pts with COVID-19, a combined multicenter study evaluated all pts with elevated cardiac troponin at any point during hospitalization plus recorded ECG and trans-thoracic echocardiographic assessment (TTE).
- Of 305 pts, myocardial injury was observed in 190 patients (62.3%). Compared with patients without myocardial injury, those with myocardial injury had more ECG abnormalities, higher inflammatory biomarkers and an increased prevalence of major
- TTE abnormalities. included LV wall motion abnormalities, global LV,dysfunction, LV diastolic dysfunction grade II or III, RV dysfunction and pericardial effusions.
- In-hospital mortality rates were 5.2%, 18.6%, & 31.7% in pts without myocardial injury, with myocardial injury without TTE abnormalities & with myocardial injury and TTE abnormalities.
- With MVA, myocardial injury with TTE abnormalities was associated with higher risk of death but not myocardial injury without TTE abnormalities.

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Gold JA, Rossen LM, Ahmad FB et al. **Race, Ethnicity, and Age Trends in Persons Who Died from COVID-19 — United States, May–August 2020.** MMWR; October 23, 2020; 69:1517–1521**.**
DOI: http://dx.doi.org/10.15585/mmwr.mm6942e1

- Updated COVID-19 mortality data reported from the CDC for May to August 2020.,
- Of 114,411 deaths across the US during this time, a disproportionate percentage were black (18.7% of overall deaths despite representing 12.5% of the US population) and Hispanic (24.2% of overall deaths despite representing 18.5% of the US population) decedents.
- The Hispanic percentage of overall COVID-19 deaths increased from 14% in May to 25% in August.
- The report highlights geographic trends, including a dramatic increase in the % distribution of COVID-19–associated deaths in the South from 23.4% in May to 62.7% in August.

- →The COVID-19 pandemic continues to expose and exacerbate pre-existing health disparities in the US. By highlighting racial and geographic trends, this updated report provides sobering evidence to direct ongoing public health efforts.

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Perry RJ, Smith CJ, Roffe C et al. **Characteristics and outcomes of COVID-19-associated stroke: a UK multicentre case-control study.** J Neurol Neurosurg Psychiatry 2020. October, 2020.
http://dx.doi.org/10.1136/jnnp-2020-324927

- To determine characteristics and outcomes of stroke associated with COVID19, this case-control study included all patients admitted with stroke to 13 hospitals in England and Scotland between 9th March and 5th July 2020.
- There were 86 strokes (81 ischaemic strokes & 5 intracerebral hemorrhages) in pts with evidence of COVID-19 at the time of stroke onset; they were compared with 1384 strokes (1193 ischaemic strokes & 191 intracerebral haemorrhages) in pts admitted during the same time period who never had evidence of COVID19 (Controls).
- The whole group of stroke admissions, plus another 37 in pts who appeared to have developed COVID-19 after their stroke, were included in two logistic regression analyses examining which features were independently associated with COVID-19 status and with inpatient mortality.
- RESULTS: Cases with ischaemic stroke were more likely than ischaemic controls to occur in Asians (18.8% vs 6.7%, p<0.0002), were more likely to involve multiple large vessel occlusions (17·9% vs 8.1%,p<0·03), were more severe (median NIHSS 8 vs 5, p<0·002), were associated with higher D-dimer levels (p<0·01) and were associated with more severe disability on discharge (median mRS 4 vs 3,p<0·0001) and inpatient death (19.8% vs9·6%, p<0·0001).
- Data suggest that COVID-19 may be an important modifier of the onset, characteristics and outcome of acute ischaemic stroke.

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Dam JM, Mateus J, Kato Y et al. **Immunological memory to SARS-CoV-2 assessed for greater than six months after infection** bioRxiv. November 17, 2020.
https://doi.org/10.1101/2020.11.15.383323

We analyzed multiple compartments of circulating immune memory to SARS-CoV-2 in 185 COVID-19 cases, including 41 cases at > 6 months post-infection. Spike IgG was relatively stable over 6+ months. Spike-specific memory B cells were more abundant at 6 months than at 1 month. SARS-CoV-2-specific CD4+ T cells and CD8+ T cells declined with a half-life of 3-5 months. By studying antibody, memory B cell, CD4+ T cell, and CD8+ T cell memory to SARS-CoV-2 in an integrated manner, we observed that each component of SARS-CoV-2 immune memory exhibited distinct kinetics. Eight months after infection, most people who have recovered still have enough immune cells to fend off the virus and prevent illness, the new data show. A slow rate of decline in the short term suggests, happily, that these cells may persist in the body for a very, very long time to come.

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Levin AT, Hanage WP, Owasu-Boaitey N et al. **Assessing the Age Specificity of Infection Fatality Rates for COVID-19: Systematic Review, Meta-Analysis, and Public Policy Implications.** medRxiv. Nov, 2020 **doi: https://doi.org/10.1101/2020.07.23.20160895**

- To determine age-specific infection fatality rates for COVID-19, studies of COVID-19 prevalence were collected and 17 studies satisfied the inclusion criteria and were included in the meta-analysis.
- Age-specific IFRs were computed using the prevalence data in conjunction with reported fatalities 4 weeks after the midpoint date of the study, reflecting typical lags in fatalities and reporting. Meta-regression procedures in Stata were used to analyze the infection fatality rate (IFR) by age.
- Results: There is an exponential relationship between age and IFR for COVID-19. The estimated age-specific IFR is very low for children (0.002% at age 10) and younger adults (0.01% at age 25) but increases progressively to 0.4% at age 55, 1.4% at age 65, 4.6% at age 75, and 15% at age 85.
- 90% of the variation in population IFR across geographical locations reflects differences in the age composition of the population.

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Piazza G, Campia U, Hurwitz S et al. **Registry of Arterial and Venous Thromboembolic Complications in Patients With COVID-19.** J Amer Coll Cardiol 2020; 76(18):2060-2072. November, 2020. **doi: 10.1016/j.jacc.2020.08.070.**

- To assess the frequency of arterial and venous thromboembolic disease, risk factors, prevention and management patterns, and outcomes in patients with COVID-19, a multicenter, observational cohort study assessed 1114 pts.
- Analysis was by site: ICU (n = 170); hospitalized non-ICU (n = 229); Out Pt (n = 715). Primary study outcome was a composite of adjudicated major arterial or venous thromboembolic events.
- Patients with COVID-19 were 22.3% Hispanic/Latinx and 44.2% non-White. Hypertension (35.8%), hyperlipidemia (28.6%), and DM (18.0%) were common.
- Prophylactic anticoagulation was prescribed in 89.4% of patients in the ICU cohort and 84.7% of those in the hospitalized non-ICU setting.
- Major arterial or venous thromboembolism, major CV adverse events, and symptomatic venous thromboembolism were highest in the ICU cohort (35.3%, 45.9%, and 27.0 %, respectively) followed by the hospitalized non=ICU cohort (2.6%, 6.1%, and 2.2%, respectively). No outpts had any TE event.
- CONCLUSION: Despite high utilization of thromboprophylaxis, major arterial or venous thrombo- embolism, major CV events, and symptomatic venous thromboembolism occurred with high frequency in patients with COVID-19, especially in the ICU setting.

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Bailey LC, Razzaghi H, Burrows EK, et al. **Assessment of 135 794 Pediatric Patients Tested for Severe Acute Respiratory Syndrome Coronavirus 2 Across the United States.** JAMA Pediatr. Published online November 23, 2020. **doi:10.1001/jamapediatrics.2020.5052**

- To describe SARS-CoV-2 testing & the epidemiology of infected pts, a retrospective cohort study was conducted using EHR data from all pts <25 yrs tested for SARS-CoV-2 from 1/1 – 9/8, 2020 in PEDSnet, a network of 7 US pediatric health systems, comprising 6,500,000 pts from 11 states.
- Results: Of 135 794 pediatric pts, 53% were male; mean [SD] age, 8.8 [6.7] years; 3% Asian, 15% Black, 11% Hispanic, and 59% White.
- 290 per 10 000 population were tested for SARS-CoV-2, and 5374 (4%) were infected with the virus (12 per 10 000 population [range, 7-16 per 10 000 population]).
- Compared with White pts, those of Black, Hispanic, and Asian race/ethnicity had lower rates of testing (Black: odds ratio [OR], 0.70 [95% CI, 0.68-0.72]; Hispanic: OR, 0.65 [95% CI, 0.63-0.67]; Asian: OR, 0.60 [95% CI, 0.57-0.63]); however, they were significantly more likely to have (+) test results (Black: OR, 2.66 [95% CI, 2.43-2.90]; Hispanic: OR, 3.75 [95% CI, 3.39-4.15]; Asian: OR, 2.04 [95% CI, 1.69-2.48]).
- Older age (5-11 years: OR, 1.25 [95% CI, 1.13-1.38]; 12-17 years: OR, 1.92 [95% CI, 1.73-2.12]; 18-24 years: OR, 3.51 [95% CI, 3.11-3.97]), public payer (OR, 1.43 [95% CI, 1.31-1.57]), outpatient testing (OR, 2.13 [1.86-2.44]), & ED testing (OR, 3.16 [95% CI, 2.72-3.67]) were associated with increased risk of infection.
- In univariate analyses, nonmalignant chronic disease was associated with lower likelihood of testing, and preexisting respiratory conditions were associated with lower risk of (+) test results (standardized ratio [SR], 0.78 [95% CI, 0.73-0.84]). Every other diagnosis group was associated with a higher risk of (+) test results.
- Among the 5374 pts with (+) test results, 359 (7%) were hospitalized for respiratory, hypotensive, or COVID-19–specific illness. Of these, 99 (28%) required ICU services, and 33 (9%) required mechanical ventilation. The case fatality rate was 0.2% (8 of 5374).
- Conclusions/ Relevance: In this large cohort study of US pediatric patients, SARS-CoV-2 infection rates were low & clinical manifestations were typically mild. Black, Hispanic & Asian race/ethnicity; adolescence & young adulthood; & non-respiratory chronic medical conditions were associated with identified infection.

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Bajema KL, Wiegand RE, Cuffe K, et al. **Estimated SARS-CoV-2 Seroprevalence in the US as of September 2020. JAMA Intern Med.** Published online November 24, 2020. **doi:10.1001/jamainternmed.2020.7976**

- To estimate the prevalence of SARS-CoV-2 antibodies, this repeated, cross-sectional study conducted across all 50 states, DC and Puerto Rico used a convenience sample of residual serum specimens originally submitted for routine screening/clinical management from 2 private commercial labs.
- Samples were obtained during 4 collection periods: July 27 to August 13, August 10 to August 27, August 24 to September 10, and September 7 to September 24, 2020.
- MAIN OUTCOME: The proportion of persons previously infected with SARS-CoV-2 as measured by the presence of antibodies to SARS-CoV-2 by 1 of 3 chemiluminescent immunoassays.
- RESULTS: Of 177 919 serum samples tested, 58.3% were from women, 15% from persons <17 yrs, 26.7% from persons > 65 yrs, & 14.8% from individuals living in nonmetropolitan areas.

- Seroprevalence over 4 collection periods ranged from < 1% to 23%. In 42/49 jurisdictions, <10% of people had detectable SARS-CoV-2 antibodies. Seroprevalence varied between sexes, across age groups, and between metropolitan/nonmetropolitan areas.
- Changes from period 1 to 4 were less than 7 %age points in all jurisdictions and across sites.
- Seroprevalence ranged from 0.0% (95% bootstrap CI, 0.0%-4.4%) in South Dakota in period 2 to 23.3% (95% bootstrap CI, 20.1%-26.3%) in NY in period 1.
- Changes from period 1 to 4 varied across sites. The largest absolute decreases occurred in NY (6.3%) and North Dakota (6.1%), while large increases occurred in Georgia (6.2%) and Minnesota (4.5%).
- CONCLUSIONS: As of September 2020, most persons in the US did not have serologic evidence of previous SARS-CoV-2 infection.

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Giustino G, Croft LB, Stefanini GG et al. **Characterization of Myocardial Injury in Patients With COVID-19. J Am Coll Cardiol**. 2020 Oct, 76 (18) 2043–2055.
doi: 10.1016/j.jacc.2020.08.069.

- To characterize the echocardiographic abnormalities associated with myocardial injury and their prognostic impact in pts with COVID-19, investigators reviewed ERs of all inpts from 7 hospitals with confirmed COVID-19 who had undergone transthoracic echocardiographic (TTE) and ECG evaluation during their index hospitalization.
- Myocardial injury was defined as any elevation in cardiac troponin at the time of clinical presentation or during the hospitalization.
- RESULTS: A total of 305 pts were included, 67.2% male. Overall, myocardial injury was observed in 62.3%. Compared with pts without myocardial injury, those with myocardial injury had significantly more ECG abnormalities, higher inflammatory biomarkers and an increased prevalence of major echocardiographic abnormalities.
- Pts with myocardial injury also had significantly more baseline HT, pre-existing cardiac problems and renal failure.
- TTE abnormalities included LV wall motion abnormalities, global LV dysfunction, LV diastolic dysfunction grade II or III, RV dysfunction and pericardial effusions.
- Rates of in-hospital mortality were 5.2% in patients without myocardial injury, 18.6% with myocardial injury without TTE abnormalities, and 31.7% with myocardial injury and TTE abnormalities. By MVA, myocardial injury with TTE abnormalities was associated with higher risk of death.

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Meltzer DO, Best TJ, Zhang H et al. **Association of Vitamin D Status and Other Clinical Characteristics With COVID-19 Test Results.** JAMA Network Open. 2020;3(9):e2019722.
doi:10.1001/jamanetworkopen.2020.19722

- Vitamin D treatment decreases the incidence of viral respiratory tract infection, especially with vitamin D deficiency. To examine association of vitamin D status with COVID-19 test results, this retrospective cohort study at an urban academic medical center included all pts with a 25-hydroxycholecalciferol/ 1,25-dihydroxycholecalciferol level measured within 1 yr before COVID-19 testing, from 3/3 -4/10/2020.

- Vitamin D deficiency was defined by the last measurement of 25-hydroxycholecalciferol less than 20 ng/mL or 1,25-dihydroxycholecalciferol less than 18 pg/mL before COVID-19 testing. Vitamin D deficiency and treatment changes were combined to categorize the most recent vitamin D status before COVID-19 testing as likely deficient (last level deficient and treatment not increased), likely sufficient (last level not deficient and treatment not decreased), and 2 groups with uncertain deficiency (last level deficient and treatment increased, and last level not deficient and treatment decreased).
- RESULTS: 489 pts (mean age, 49.2 [18.4] years; 75% women; 68% race other than White) had a vitamin D level measured in the year before COVID-19 testing. Vitamin D status was categorized as likely deficient for 124 pts (25%), likely sufficient for 287 (59%), and uncertain for 78 (16%).
- Overall, 71 pts (15%) tested positive for COVID-19. In MVA, (+) COVID-19 test was associated with increasing age up to age 50 yrs (RR 1.06; 95% CI, 1.01-1.09; P = .02); non-White race (RR 2.54; 95% CI, 1.26-5.12; P = .009), and likely deficient vitamin D status (RR 1.77; 95% CI, 1.12-2.81; P = .02).
- Predicted COVID-19 rates in the deficient group were 21.6% (95% CI, 14.0%-29.2%) vs 12.2%(95% CI, 8.9%-15.4%) in the sufficient group.
- →In this single-center, retrospective cohort study, likely deficient vitamin D status was associated with increased COVID-19 risk.

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Woolf SH, Chapman DA, Lee JH. **COVID-19 as the Leading Cause of Death in the United States.** JAMA. Published online December 17, 2020. **doi:10.1001/jama.2020.24865**

- COVID-19–related mortality rates were compared with the leading causes of death that, under ordinary circumstances, would pose the greatest threat to different age groups.
- The 3 leading causes of death in each of the 10 age groups from infancy to old age were compared during the period of March through October 2018(the most recent year for which detailed cause-of-death data are available) with COVID-19 mortality rates during March through October 2020
- By October 2020 COVID-19 had become the third leading cause of death for persons aged 45 through 84 yrs and the second leading cause of death for those aged >/= 85 yrs.
- Adults >/= 45 yrs were more likely to die from COVID-19 during those months than from chronic lower respiratory disease, transport accidents (eg, MVAs), drug overdoses, suicide, or homicide.
- In contrast, for individuals younger <45 yrs, other causes of death, such as drug overdoses, suicide, transport accidents, cancer, and homicide exceeded those from COVID-19.
- These numbers are an underestimate because they represent aggregate data. In fact, between 11/1/2020 & 12/13/2020, the 7-day moving average for daily COVID-19 deaths tripled, so that as occurred in the spring, COVID-19 has become the leading cause of death in the United States.
- Daily mortality rates for heart disease and cancer, which for decades have been the 2 leading causes of death, are approximately 1700 and 1600 deaths per day, respectively. COVID-19 mortality rates now exceed these thresholds so that this infectious disease has become the leading cause of mortality in the USA, deadlier than heart disease and cancer.

TREATMENT

Gharbharan A, Jordans CCE, Geurtsvan-Kessel C et al. **Convalescent Plasma for COVID-19. A randomized clinical trial**. medRxiv 2020.07.01.20139857. **https://doi.org/10.1101/2020.07.01.20139857**

- RCT comparing convalescent plasma with standard of care therapy in pts hospitalized for COVID-19 in the Netherlands.
- Pts were randomized 1:1 and received 300ml of plasma with anti-SARS-CoV-2 neutralizing antibody titers of at least 1:80.
- Primary endpoint was day-60 mortality and key secondary endpoints were hospital stay and WHO 8-point disease severity scale improvement on day 15.
- Results: The trial was halted prematurely after 86 patients were enrolled. Although symptomatic for only 10 days (IQR 6-15) at the time of inclusion, 53 of 66 patients tested had anti-SARS-CoV-2 antibodies at baseline.
- A SARS-CoV-2 plaque reduction neutralization test showed neutralizing antibodies in 44 of the 56 (79%) pts tested with median titers comparable to the 115 donors (1:160 vs 1:160, p=0.40).
- No difference in mortality (p=0.95), hospital stay (p=0.68) or day-15 disease severity (p=0.58) was observed between plasma treated pts and pts on standard of care.
- Conclusion Most COVID-19 pts already have high neutralizing antibody titers at hospital admission. Screening for antibodies and prioritizing convalescent plasma to risk groups with recent symptom onset will be key to identify patients that may benefit from convalescent plasma.

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Mather JF, et al. **Impact of famotidine use on clinical outcomes of hospitalized COVID-19 patients.** Am J Gastroenterol; August 14, 2020.

- Famotidine, a histamine-2 receptor antagonist used to treat heartburn, is postulated to be effective against SARS-C0V-2 infection since that process is thought to be at least partially mediated by pathological histamine release.
- Retrospective, propensity-matched observational study of consecutive COVID-19 positive pts between 2/24/2020 and 5/13/2020.
- 878 pts, 83 received famotidine; FAM pts were slightly younger but did not differ with respect to baseline demographics or pre-existing comorbidities.
- FAM use was associated with a significantly decreased risk of in-hospital mortality (OR 0.37, 95%CI 0.16-0.86; p=.021) as well as combined death or intubation.(OR 0.47. 95% CI 0.23-0.96; p=0.04)
- Adjusting for age difference did not change results.
- FAM pts had lower serum markers for severe disease including CRP & pro-calcitonin.
- By logistic regression, FAM was an independent predictor of lower mortality and death/intubation while older age, BMI>30 kg/m^2, CKD & higher neutrophil/lymphocyte ratio were all predictors of both adverse outcomes.

The Writing Committee for the REMAP-CAP Investigators. **Effect of hydrocortisone on mortality and organ support in patients with severe COVID-19: the REMAP-CAP COVID-19 Corticosteroid Domain randomized clinical trial**. *JAMA*. Published online September 2, 2020. doi:10.1001/jama.2020.17022

Tomazini BM, Maia IS, Cavalcanti AB, et al; COALITION COVID-19 Brazil III Investigators. **Effect of dexamethasone on days alive and ventilator-free in patients with moderate or severe acute respiratory distress syndrome and COVID-19: the CoDEX randomized clinical trial.** *JAMA*. Published online September 2, 2020. doi:10.1001/jama.2020.17021

Dequin PF, Heming N, Meziani F, et al; CAPE COVID Trial Group and the CRICS-TriGGERSep Network. **Effect of hydrocortisone on 21-day mortality or respiratory support among critically ill patients with COVID-19: a randomized clinical trial.** *JAMA*. Published online September 2, 2020. doi:10.1001/jama.2020.16761

The WHO Rapid Evidence Appraisal for COVID-19 Therapies (REACT) Working Group. **Association between administration of systemic corticosteroids and mortality among critically ill patients with COVID-19: a meta-analysis.** *JAMA*. Published online September 2, 2020. doi:10.1001/jama.2020.17023

- On Sept. 2, JAMA published the results of 3 multicenter RCTs that assessed corticosteroid therapy in critically ill patients with COVID-19 and a WHO-sponsored prospective M/A.
- Results show conclusive benefit for steroid treatment best appreciated in the prospective M/A which included the results of these 3 RCTs, the RECOVERY trial of dexamethiasone published in the NEJM in 6/2020 & 3 additional trials, totaling 1703 patients (678 had been randomized to corticosteroids and 1025 to usual care or placebo. 28-day mortality was significantly lower in pts randomized to corticosteroids: 222 deaths among 678 pts vs. 425 deaths among 1025 pts (summary odds ratio, 0.66 [95% CI, 0.53,-0.82]; $P < .001$).
- The association between administration of corticosteroids and reduced mortality was similar for dexamethasone and hydrocortisone, suggesting the benefit is a general class effect; was similar with lower- vs higher-dose steroid regimens; and was similar among pts with fewer vs greater than 7 days of symptoms at randomization.
- Corticosteroids also appear to be associated with benefit among critically ill pts with COVID-19 whether they are receiving mechanical ventilation or O2 alone.
- The launch and conduct of these high-quality trials in the midst of a pandemic is an important accomplishment, as is the agreement to share unpublished data with WHO, exemplifying how science can advance even in the context of numerous underpowered RCTs.

➢ **Corticosteroids are inexpensive, readily available, and based on these data, are associated with reduced mortality in critically ill patients with COVID-19.**

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Beigel JH, Tomashek KM, Dodd LE et al. **Remdesivir for the Treatment of Covid-19 — Final Report. NEJM 2020;** Published online October 8, 2020.
DOI: 10.1056/NEJMoa2007764

- Double-blind RCT of intravenous remdesivir in adults hospitalized with Covid-19 who had evidence of lower respiratory tract infection.

- 1062 pts were randomly assigned to receive either remdesivir (200 mg loading dose on day 1, followed by 100 mg daily for up to 9 additional days) or placebo for up to 10 days.
- RESULTS Remdesivir pts had a median recovery time of 10 days (95% confidence interval [CI], 9 to 11) vs 15 days (95% CI, 13 to 18) (rate ratio for recovery, 1.29; 95% CI, 1.12 to 1.49; P<0.001, by a log-rank test).
- Patients who received remdesivir were more likely than those who received placebo to have clinical improvement at day 15 (odds ratio, 1.5; 95% CI, 1.2 to 1.9, after adjustment for actual disease severity).
- Kaplan–Meier estimates of mortality were 6.7% with remdesivir and 11.9% with placebo by day 15 and 11.4% with remdesivir and 15.2% with placebo by day 29 (hazard ratio, 0.73; 95% CI, 0.52 to 1.03).
- Serious AEs were reported in 131 of the 532 patients who received remdesivir (24.6%) and in 163 of the 516 patients who received placebo (31.6%).
- CONCLUSIONS Remdesivir was superior to placebo in shortening time to recovery in adults who were hospitalized with Covid-19 and had evidence of lower respiratory tract infection.

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Lernze EJ, Mattar C, Zorumski CF et al. **Fluvoxamine vs Placebo and Clinical Deterioration in Outpatients with Symptomatic COVID-19: A Randomized Clinical Trial**. JAMA. Published online November 12, 2020. **doi:10.1001/jama.2020.22760**

- COVID-19 may lead to serious illness as a result of an excessive immune response. Fluvoxamine may prevent clinical deterioration by stimulating the σ-1 receptor, which regulates cytokine production.
- To determine whether fluvoxamine, given during mild COVID-19 illness, prevents clinical deterioration and decreases the severity of disease.
- Double-blind RCT of fluvoxamine vs placebo. 152 participants were community-living, non-hospitalized adults with confirmed severe ARDS acute respiratory syndrome & COVID-19 with symptom onset within 7 days and oxygen saturation of 92% or greater.
- Participants were randomly assigned to receive 100 mg of fluvoxamine (n = 80) or placebo (n = 72) 3 times daily for 15 days
- Primary outcome was clinical deterioration within 15 days defined by meeting both criteria of (1) shortness of breath or hospitalization for shortness of breath or pneumonia and (2) O2 saturation less than 92% on room air or need for supplemental O2 to achieve saturation of >/=92%.
- Results: 115 pts completed the trial. Clinical deterioration occurred in 0 of 80 patients in the fluvoxamine group and in 6 of 72 patients in the placebo group (8.7% [95% CI, 1.8%-16.4%]; P = .009. The fluvoxamine group had 1 serious adverse event and 11 other adverse events, whereas the placebo group had 6 serious adverse events and 12 other adverse events.
- In this preliminary study of adult outpatients with symptomatic COVID-19, pts treated with fluvoxamine had a lower likelihood of clinical deterioration over 15 days.

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Chen P, Nirula A, Heller B, et al. **SARS-CoV-2 neutralizing antibody LY-CoV555 in outpatients with COVID-19**. N Engl J Med. 2020; Published online ahead of print. Available at: **https://www.ncbi.nlm.nih.gov/pubmed/33113295.**

- Background: Virus-neutralizing monoclonal antibodies are predicted to reduce viral load, ameliorate symptoms, and prevent hospitalization.
- Methods: 452 outpatients with recently diagnosed mild/moderate Covid-19 were randomly assigned to receive a single IV infusion of neutralizing antibody LY-CoV555 in one of three doses (700 mg, 2800 mg, or 7000 mg) or placebo. Quantitative virologic end points and clinical outcomes were analyzed.
- Results: Mean decrease from baseline in the log viral load for the entire population was -3.81, for an elimination of more than 99.97% of viral RNA. For patients who received the 2800-mg dose of LY-CoV555, the difference from placebo in the decrease from baseline was -0.53 (95% confidence interval [CI], -0.98 to -0.08; P = 0.02), lower by a factor of 3.4. Smaller differences in change from baseline were observed among the pts who received the 700-mg doseor the 7000 mg dose.
  On days 2 to 6, the patients who received LY-CoV555 had a slightly lower severity of symptoms than those who received placebo. The percentage of patients who had a Covid-19-related hospitalization or visit to an emergency department was 1.6% in the LY-CoV555 group and 6.3% in the placebo group.

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Simonovich VA, Pratx LDB, Scibona P et al. **A Randomized Trial of Convalescent Plasma in Covid-19 Severe Pneumonia.** NEJM: November 24, 2020. **DOI: 10.1056/NEJMoa2031304**

- To assess potential benefit of convalescent plasma, hospitalized adult pts with severe Covid-19 pneumonia were randomized in a 2:1 ratio to receive convalescent plasma or placebo. Primary outcome was clinical status 30 days post intervention, measured on a 6-point ordinal scale ranging from total recovery to death.
- RESULTS 228 pts were assigned to receive convalescent plasma and 105 to receive placebo. The median time from the onset of symptoms to enrollment in the trial was 8 days (interquartile range, 5 to 10), and hypoxemia was the most frequent severity criterion for enrollment.
- At day 30 day, no significant difference was noted between the convalescent plasma group and the placebo group in the distribution of clinical outcomes according to the ordinal scale (odds ratio, 0.83 (95% confidence interval [CI], 0.52 to 1.35; P=0.46).
- Overall mortality was 10.96% in the convalescent plasma group and 11.43% in the placebo group, for a risk difference of −0.46 percentage points (95% CI, −7.8 to 6.8). Adverse events were similar in the two groups.

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Kalil AC, Patterson TF, Mehta AK et al. **Baricitinib plus Remdesivir for Hospitalized Adults with Covid-19**. New Engl J Med; December 11, 2020.
DOI: 10.1056/NEJMoa2031994

- Double-blind, randomized, placebo-controlled trial evaluating baricitinib (anti-inflammatory arthritis drug) plus remdesivir in hospitalized adults with Covid-19. All pts received remdesivir (≤10 days) and either baricitinib (≤14 days) or placebo (control).
- Primary outcome was time to recovery. Key secondary outcome was clinical status at day 15.
- 515 pts assigned to combination treatment and 518 to control.
- Baricitinib pts had a median time to recovery of 7 days (95% confidence interval [CI], 6 to 8), vs 8 days (95% CI, 7 to 9) with control; (rate ratio for recovery, 1.16; 95% CI, 1.01 to 1.32; P=0.03), and a 30% higher odds of improvement in clinical status at day 15 (odds ratio, 1.3; 95% CI, 1.0 to 1.6).
- Pts receiving high-flow O2 or noninvasive ventilation at enrollment had a time to recovery of 10 days with combination Rx and 18 days with control (rate ratio for recovery, 1.51; 95% CI, 1.10 to 2.08).
- 28-day mortality was 5.1% in the combination group & 7.8% in the control group (hazard ratio for death, 0.65; 95% CI, 0.39 to 1.09).
- Serious adverse events were less frequent in the combination group than in the control group (16.0% vs. 21.0%; difference, −5.0 percentage points; 95% CI, −9.8 to −0.3; P=0.03)

→ Baricitinib plus remdesivir was superior to remdesivir alone in reducing recovery time and accelerating improvement in clinical status in pts with Covid-19.

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Hranjec T, Estreicher M, Rogrs B et al. **Platelet Mapping to Guide Appropriate Treatment, Avoid Complications, and Improve Survival of Patients with Coronavirus Disease 2019–Related Coagulopathy**. Critical Care Explorations: December 2020 - Volume 2 - Issue 12 - p e0287 **doi: 10.1097/CCE.0000000000000287**

- To evaluate if algorithm-guided thromboelastography (TEG) with platelet mapping could better characterize COVID-19-related coagulopathic state & improve outcomes, 100 pts receiving TEG with platelet mapping assay upon admission were followed prospectively by a hospital-based TEG team.
- Treating clinicians were provided with the option of using a pre-established algorithm for anticoagulation, including follow-up TEG with platelet mapping → 2 groups evolved: 1) patients managed by algorithm-guided TEG; and 2) those treated without algorithm-guided TEG.
- RESULTS: Elevated d-dimer, C-reactive protein, and ferritin in critically ill pts did not distinguish between coagulopathic and noncoagulopathic patients.
- Platelet hyperactivity (maximum amplitude-arachidonic acid/adenosine diphosphate > 50 min), with or without thrombocytosis, was associated with thrombotic/ischemic complications, whereas severe thrombocytopenia (platelet count < 100,000/μL) was uniformly fatal.
- Hemorrhagic complications were observed with decreased factor activity (reaction time > 8 min).
- Non-algorithm-guided patients had increased risk for subsequent mechanical ventilation (relative risk = 10.9; p < 0.0001), acute kidney injury (relative risk = 2.3; p = 0.0017), dialysis (relative risk = 7.8; p < 0.0001), and death (relative risk = 7.7; p < 0.0001), with 17 of 28 non-

algorithm-guided patients (60.7%) dying versus four algorithm-guided-thromboelastography patients (5.6%) ($p < 0.0001$).

- TEG with platelet mapping–guided antiplatelet treatment decreased mortality 82% ($p = 0.0002$), whereas non-algorithm-guided use of antifactor therapy (heparin/enoxaparin) resulted in 10.3-fold increased mortality risk ($p = 0.0001$).
- CONCLUSION: TEG with platelet mapping better characterizes the spectrum of COVID-19 coagulation-related abnormalities and guides more tailored, pt-specific therapies in these pts.

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PREVENTION/ MITIGATION

Jackson LA, Anderson EJ, Rouphae NG et al. **An mRNA Vaccine against SARS-CoV-2 — Preliminary Report.** NEJM 2020. Published online, 7/14/2020.
DOI: 10.1056/NEJMoa2022483

- NIAID and Moderna have developed a candidate vaccine against SARS-CoV-2, mRNA-1273, a lipid nanoparticle-encapsulated, nucleoside-modified mRNA–based vaccine that encodes the SARS-CoV-2 spike.
- Phase 1, dose-escalation, open-label clinical trial designed to determine the safety, reactogenicity, and immunogenicity of mRNA1273 enrolled 45 adults 3 months ago
- Eligible participants were healthy adults 18 to 55 yrs who received two injections of trial vaccine 28 days apart at a dose of 25 µg,100 µg, or 250 µg.
- After the first vaccination, Ab responses were dose-related and this difference increased after the second dose
- After the second vaccination, serum neutralizing activity was detected by two methods in all participants evaluated, with values similar to those in the upper half of the distribution of a panel of control convalescent serum specimens.
- Solicited AEs that occurred in >50% of participants included fatigue, chills, headache, myalgia, and injection site pain with no serious patterns of concern.
- Durability and clinical utility of Ab response could not be assessed.

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Chan JF-W, Yuan DS, Zhang AJ et al. **Surgical mask partition reduces the risk of non-contact transmission in a golden Syrian hamster model for Coronavirus Disease 2019** (COVID-19). Clinical Infectious Diseases: Published: 30 May 2020
https://doi.org/10.1093/cid/ciaa644

- Investigation of SARS-CoV-2-challenged & naïve hamsters in closed system units separated by a polyvinyl chloride air porous partition with unidirectional airflow within the isolator +/- a surgical mask partition placed in between the cages.
- Hamsters tested for viral load, histopathology & viral nucleocapsid Ag expression.
- Non-contact transmission was found in 66.7% (10/15) of exposed naïve hamsters.
- Surgical mask partition for challenged index or naïve hamsters reduced transmission to 25% (6/24, P=0.018). Surgical mask partition for challenged index hamsters reduced transmission to only 16.7% (2/12, P=0.019) of exposed naïve hamsters.
- Unlike the severe COVID-19 manifestations of challenged hamsters, infected naïve hamsters had lower clinical scores, milder histopathological changes, and lower viral nucleocapsid antigen expression in respiratory tract tissues.

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Shen y, Li C, Dong H et al. **Community Outbreak Investigation of SARS-CoV-2 Transmission Among Bus Riders in Eastern China.** JAMA Intern Med. Published online September 1, 2020. **doi:10.1001/jamainternmed.2020.5225**

- Background: Evidence supporting airborne transmission of SARS-CoV-2 is emerging with an experimental study demonstrating SARS-CoV-2 viability in aerosols for ≥3 hrs & evidence of SARS-CoV-2 transmission between ferrets via the air connection established between them.
- To investigate airborne transmission between humans in a community setting, an outbreak of COVID-19 among lay Buddhists in Zhejiang province was investigated.
- On January 19, 2020, 128 individuals took 2 buses (60 in bus 1, 68 in bus 2) on a 100-min round trip to attend a 150-min worship event. One passenger on bus 2 was SARS-C0V-2 positive. In both buses, central A/Cs were in indoor recirculation mode.
- Results: 24 of 68 individuals (35.3%) on bus 2, received a diagnosis of COVID-19 after the event vs. none of the 60 individuals in bus 1. Among the other 172 individuals at the event, 7 (4.1%) subsequently received a COVID-19 diagnosis.
- Individuals in bus 2 had a 34.3% (95% CI, 24.1%-46.3%) higher risk of getting COVID-19 vs. those in bus 1 and were 11.4 times (95% CI, 5.1-25.4) more likely to have COVID-19 compared with all other individuals attending the event.
- On bus 2, individuals in high-risk zones had moderately, but not significantly, higher risk for COVID-19 compared with those in low-risk zones. Absence of a significantly increased infection risk in locations closer to the index case suggests that airborne spread at least partially explains the extremely high attack rate.

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Anand S, Montez-Rath M, Han J et al. **Prevalence of SARS-CoV-2 antibodies in a large nationwide sample of patients on dialysis in the USA: a cross-sectional study.** Lancet 2020. Published online September 25, 2020
https://doi.org/10.1016/S0140-6736(20)32009-2

- Cross-sectional study of SARS-CoV-2 spike protein receptor binding domain total antibody in 28,503 randomly selected adult pts who received dialysis in 7/2020
- Data on age, sex, race and ethnicity, residence and facility ZIP codes were extracted from EHRs, linking pt-level residence data with cumulative and daily cases, deaths per 100 000 population and with nasal swab test positivity rates.
- Prevalence estimates were standardized according to the overall US dialysis and adult population, and present estimates for 4 strata: age, sex, region, R/E.
- RESULTS: Seroprevalence was 9·3% (8·8–9·9) when standardised to the US adult population.
- When standardised to the US dialysis population, seroprevalence ranged from 3·5%(3·1–3·9) in the west to 27·2% (25·9–28·5) in the northeast.
- Comparing seroprevalent and case counts per 100000 population, 9·2% (8·7–9·8) of seropositive patients were diagnosed.
- Seroprevalence correlated best with deaths per 100 000 population (Spearman's ρ=0·77).
- Residents of non-Hispanic Black and Hispanic neighborhoods experienced higher odds of seropositivity (OR 3·9 [95% CI 3·4–4·6] & 2·3 [1·9–2·6], respectively) vs residents of predominantly non-Hispanic white neighborhoods.
- Residents of neighborhoods in the highest population density quintile experienced increased odds of seropositivity (10·3 [8·7–12·2]) vs lowest density quintile residents.

- INTERPRETATION: During the first wave of the COVID-19 pandemic, fewer than 10% of the US adult population formed antibodies against SARS-CoV-2, and fewer than 10% of those with antibodies were diagnosed.

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Meltzer DO, Best TJ, Zhang H et al. **Association of Vitamin D Status and Other Clinical Characteristics With COVID-19 Test Results.** JAMA Network Open 2020; 3(9): e2019722. Online 9/3/2020. **doi:10.1001/jamanetworkopen.2020.19722**

- Retrospective study of all pts at an urban academic medical ctr with vitamin D level (25-hydroxycholecalciferol or 1,25-dihydroxycholecalciferol) measured within 1 yr before COVID-19 testing, from 3/3 to 4/19/2020.
- Vitamin D deficiency defined by the last 25-hydroxycholecalciferol <20 ng/mL. or 1,25-dihydroxycholecalciferol <18 pg/mL before COVID-19 testing.
- Vitamin D deficiency & Rx changes combined to categorize vitamin D status as likely deficient (last level deficient/ Rx not increased); likely sufficient (last level not deficient/ Rx not decreased), and 2 groups with uncertain deficiency.
- RESULTS: 489 pts, mean age 49.2+/-18.4 yrs, 75% women, 68% nonwhite; vit D likely deficient for 25%, sufficient for 59%, uncertain for 16%
- 71 pts (15%) tested (+) for COVID-19. In MVA, testing (+) for COVID-19 was associated with increasing age up to age 50 yrs (RR 1.06; CI, 1.01-1.09; P = .02); non-White race (RR 2.54; CI 1.26-5.12; P = .009), likely deficient vitamin D status (RR 1.77; CI, 1.12-2.81; P = .02) vs, likely sufficient vitamin D status. Predicted COVID-19 rates in the deficient group were 21.6% (95% CI, 14.0%-29.2%) vs 12.2%(95% CI, 8.9%-15.4%) in the sufficient group.
- → In this single-center, retrospective cohort study, likely deficient vitamin D status was associated with increased risk of COVID-19 infection.

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Hoiland RL, Fergusson NA, Mitra AR et al. **The association of ABO blood group with indices of disease severity and multiorgan dysfunction in COVID-19.** Blood Adv 2020; 4 (20): 4981–4989. October, 2020. https://doi.org/10.1182/bloodadvances.2020002623

- Multicenter retrospective analysis and nested prospective observational substudy of 95 critically ill patients with COVID-19.
- ABO blood group distributions did not differ from national standards
- Higher proportion of COVID-19 pts with blood group A or AB required mechanical ventilation (P = .02) and dialysis (P = .004) and had a longer ICU stay (P = .03)
- Blood group A or AB also had an increased probability of requiring mechanical ventilation and CRRT after adjusting for age, sex, and presence of ≥1 comorbidity.
- CONCLUSION: COVID-19 pts with blood group A or AB are at increased risk for requiring mechanical ventilation and exhibit greater disease severity than patients with blood group O or B.

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Viner RM, Mytton OT, Bonell C et al. **Susceptibility to SARS-CoV-2 Infection Among Children and Adolescents Compared with Adults: A Systematic Review and Meta-**

analysis. JAMA Pediatr. Published online September 25, 2020. **doi:10.1001/jamapediatrics.2020.4573**

- To systematically review the susceptibility to and transmission of SARS-CoV-2 among children and adolescents compared with adults, PubMed and medRxiv were searched & a total of 13 926 studies were identified..
- Main Outcomes and Measures: Secondary infection rate (contact-tracing studies) or prevalence or seroprevalence (population screening studies) among children and adolescents compared with adults.
- Results: A total of 32 studies comprising 41 640 children and adolescents and 268 945 adults met inclusion criteria (18 contact-tracing studies;14 population screening studies). Pooled odds ratio of being an infected contact in children compared with adults was 0.56 (95% CI, 0.37-0.85), with substantial heterogeneity.
- Three school-based contact-tracing studies found minimal transmission from child or teacher index cases. Findings from population screening studies were heterogenous and were not suitable for meta-analysis.
- → There is preliminary evidence that children and adolescents have lower susceptibility to SARS-CoV-2, with an odds ratio of 0.56 for being an infected contact compared with adults. There is weak evidence that children and adolescents play a lesser role than adults in transmission of SARS-CoV-2 at a population level.

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Chang, S., Pierson, E., Koh, P.W. et al. **Mobility network models of COVID-19 explain inequities and inform reopening.** Nature; November, 2020. https://doi.org/10.1038/s41586-020-2923-3.

- Analysis of mobile-phone records from 3/2 to 5/1, 2020 for 98 million US people provided anonymized location information, comprising more than 5 billion time points.
- Cell phone data allowed creation of acquired mobility networks mapping the hourly movements of all 98 million people from neighborhoods (census blocks[CBGs]) to points of interest (POIs) such as restaurants and religious establishments, connecting 57k CBGs to 553k POIs with 5.4 billion hourly edges.
- For a given venue, the mobile phone data gives detailed estimates of how many people visit/hr, average length of stay and neighborhood of origin.
- Hypothesis is that the rate at which people in a population are likely to become infected depends on which venues they visit and how long they stay. Venues at which people stay longer and that are more densely occupied carry a higher risk than less crowded settings where people stay for less time.
- Cell phone data was used as parameters in a mathematical metapopulation SEIR model to simulate the spread of SARS-CoV-2 in 10 large US cities.
- By capturing information about individual POIs (e.g., hourly number of visitors, median visit duration), the model can estimate the impacts of specific reopening strategies, such as only reopening certain POI categories or restricting maximum occupancy at each POI.
- RSULTS: Restaurants, gyms, cafes and other crowded indoor venues accounted for 8 in 10 new coronavirus infections in large cities in the early months of the epidemic.

- Low-income neighborhoods were hardest hit because public venues in those communities were more crowded than in more affluent ones, and residents were more mobile on average, likely because of work demands.
- → Capping the maximum occupancy of venues — a strategy that implicitly reduces the number of person-hours spent in risky, high-occupancy settings — was predicted to result in a decreased number of new infections compared with a strategy of less-targeted, overall activity reduction.

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de Vries RD, Schmitz KS, Bovier FT et al. **Intranasal fusion inhibitory lipopeptide prevents direct contact SARS-CoV-2 transmission in ferrets**. Med Rx iv. Nov. 5, 2020. **doi: https://doi.org/10.1101/2020.11.04.361154**

- SARS-CoV-2 infection is initiated by membrane fusion between the virus and host nasal membrane cells, mediated by the viral spike protein.
- A nasal spray containing a dimeric lipopeptide fusion inhibitor that blocks this critical first step of infection was developed.
- Daily intranasal administration to ferrets completely prevented SARS-CoV-2 direct-contact transmission during 24-hour co-housing with infected animals, under stringent conditions that resulted in infection of 100% of untreated animals.
- These lipopeptides are highly stable and non-toxic and could translate into a safe & effective intranasal prophylactic approach to reduce transmission of SARS-CoV-2.
- Studies in humans are underway.

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Polack FP, Thomas SJ, Kitchin N et al. **Safety and Efficacy of the BNT162b2 mRNA Covid-19 Vaccine.** New Engl J Med; December 10, 2020.
DOI: 10.1056/NEJMoa2034577

- BNT162b2 vaccine is a lipid nanoparticle–formulated, nucleoside-modified RNA vaccine that encodes a prefusion stabilized, membrane-anchored SARS-CoV-2 full-length spike protein.
- 43,538 persons 16 years of age or older were randomized in a 1:1 ratio to receive two doses, 21 days apart, of either placebo or the BNT162b2 vaccine candidate (30 μg per dose)
- Primary end points were efficacy of the vaccine against laboratory-confirmed Covid-19 and safety.
- RESULTS: There were 8 cases of Covid-19 with onset at least 7 days after the second dose among participants assigned to receive BNT162b2 and 162 cases among those assigned to placebo → BNT162b2 was 95% effective in preventing Covid-19 (95% credible interval, 90.3 to 97.6).
- Vaccine efficacy was observed across subgroups defined by age, sex, race, ethnicity, baseline body-mass index, and the presence of coexisting conditions.
- Among 10 cases of severe Covid-19 with onset after the first dose, 9 occurred in placebo recipients and 1 in a BNT162b2 recipient.
- The safety profile of BNT162b2 was characterized by short-term, mild-to-moderate pain at the injection site, fatigue, and headache. The incidence of serious adverse events was low and was similar in the vaccine and placebo groups.

→A two-dose regimen of BNT162b2 conferred 95% protection against Covid-19 in persons 16 years of age or older. Safety over a median of 2 months was similar to that of other viral vaccines.

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Clapp PW, Sickbert-Bennett EE, Samet JM, et al. **Evaluation of Cloth Masks and Modified Procedure Masks as Personal Protective Equipment for the Public During the COVID-19 Pandemic.** JAMA Intern Med. Published online December 10, 2020. **doi:10.1001/jamainternmed.2020.8168**

- The Occupational Safety and Health Administration (OSHA) Fit Test was used to determine the fitted filtration efficiency (FFE) of various consumer-grade and improvised face masks and popular modifications of medical procedure masks.
- a TSI 8026 Particle Generator was used to supplement the chamber with sodium chloride (NaCl) particles that had a count median diameter of 0.05 μm (range, 0.02-0.60 μm) as measured by a scanning mobility particle sizer. The test atmosphere reflects typical indoor conditions, with exposure to particles that are slightly smaller than individual SARS-CoV-2 virions (reported to range between 0.06 μm and 0.14 μm).
- All masks were fitted on a non-obese man with no beard. A pair of TSI 3775 Condensation Particle Counters were run in single-particle analysis mode to continuously monitor ambient particles (0.02 μm-3 μm) in the chamber just outside the face mask and particles in the breathing space behind the face mask at a sampling rate of 1 second.
- The FFE corresponds to the concentration of particles behind the mask expressed as a percentage of the particle concentration in the chamber air, and was measured for the duration of each test during multiple changes in position.
- Two categories of products were tested for this study: consumer-grade face masks and medical procedure masks with and without enhancements.
- RESULTS:

→ Simple modifications to improve medical mask fit can substantially improve filtration efficiency. However, when FFE is considered (combined fit and material filtration), we demonstrated the practical effectiveness of consumer-grade masks is nearly equivalent to or better than their non-respirator medical mask counterparts.

Table. Face Mask FFE Against Submicron Particle Penetration

Consumer-grade face masks	Condition	% FFE (SD)[a]
2-Layer woven nylon mask with ear loops		
Without aluminum nose bridge	New	44.7 (6.4)
With aluminum nose bridge	New	56.3 (6.5)
With aluminum nose bridge and 1 nonwoven insert	New	74.4 (4.8)
With aluminum nose bridge, washed (no insert)	Washed 1 time	79.0 (4.3)
Cotton bandana		
Folded surgeon general style	New	49.9 (5.8)
Folded "bandit" style	New	49.0 (6.2)
Single-layer woven polyester gaiter/ neck cover (balaclava bandana)	New	37.8 (5.2)
Single-layer woven polyester/nylon mask with ties	New	39.3 (7.2)
Nonwoven polypropylene mask with fixed ear loops	New	28.6 (13.9)
3-Layer woven cotton mask with ear loops	New	26.5 (10.5)
Medical face masks and modifications		
3M 9210 NIOSH-approved N95 respirator	New	98.4 (0.5)
Surgical mask with ties	New	71.5 (5.5)
Procedure mask with ear loops	New	38.5 (11.2)
Procedure mask with ear loops		
Loops tied and corners tucked in	New	60.3 (11.1)
Ear guard	New	61.7 (6.5)
23-mm Claw hair clip	New	64.8 (5.1)
Fix-the-mask (3 rubber bands)	New	78.2 (3.3)
Nylon hosiery sleeve	New	80.2 (3.1)

Abbreviations: FFE, fitted filtration efficiency; NIOSH, National Institute for Occupational Safety and Health.

[a] The percentage of FFE corresponds to 100 × (1 − behind the mask particle concentration / ambient particle concentration). Overall FFE percentage and SD were calculated across the length of the test.