

The Weekly Covid-19 Literature Round-Up

Edition 2: March 25, 2020

Collated by Emory ID and Medical Microbiology Fellows

“What’s natural is the microbe. All the rest—health, integrity, purity (if you like)—is a product of the human will, of a vigilance that must never falter. The good man, the man who infects hardly anyone, is the man who has the fewest lapses of attention.” -Albert Camus

Get your facts first, then you can distort them as you please. -Mark Twain

Epidemiology

Brought to you by: Jessica Howard-Anderson, MD

**Onder G et al. “Case-Fatality Rate and Characteristics of Patients Dying in Relation to COVID-19 in Italy”
JAMA 3/23/2020 doi:10.1001/jama.2020.4683**

And

Livingston E et al. Coronavirus Disease 2019 (COVID-19) in Italy. JAMA 3/17/2020 doi 10.1001/jama.2020.4344

- The Italian National Institute of Health performs surveillance of all COVID-19 cases
- Italy’s case fatality rate (CFR) as of 3/17/20 was 7.2%
(<https://jamanetwork.com/journals/jama/fullarticle/2763401>) which is higher than other countries (CFR 2.3% in China, 1.0% in Republic of Korea)
- 3 reasons why Italy’s CFR may be higher:
 - Older demographic in Italy (23% > 65) and 37.6% of cases in Italy are in people > 70
 - Italian CFR uses death from any cause, not limited to “COVID-19-related deaths”
 - Stringent testing policy (only hospitalized, high risk patients), may have decreased denominator and therefore increased CFR

Ran et al. “Risk Factors of Healthcare Workers with Corona Virus Disease 2019: A Retrospective Cohort Study in a Designated Hospital of Wuhan in China.” CID 3/17/20. Doi <https://doi.org/10.1093/cid/ciaa287>

- Retrospective cohort of 72 clinicians and nurses (HCW) **with acute respiratory symptoms** that worked in a large tertiary hospital in China
- Median age 31, 53% clinicians, median hours of daily work was 8
- 28 HCWs with acute resp symptoms were diagnosed with COVID-19 (PCR confirmed)
- Risk of COVID-19 was higher in HCWs with a diagnosed family member (RR 2.8, CI 2.0– 3.8) but lower in HCW with diagnosed patient (RR 0.4, CI 0.2 – 0.6)
- Inadequate (self-reported) hand hygiene (RR ranges 2.4- 3.1) and improper PPE (RR 2.8 CI 1.1 – 7.2) as well as work in high risk departments (respiratory, infectious disease, critical care and surgery) (crude RR 2.13 CI 1.5-4) were associated with COVID-19 infection
- Study limited by small sample size, recall bias, and likely uncontrolled confounding factors

Transmission/Infection Control

Brought to you by: Lauren Collins, MD

Kucharski, Adam J. et al. "Early Dynamics of Transmission and Control of COVID-19: A Mathematical Modelling Study." *The Lancet Infectious Diseases* 0, no. 0 (March 11, 2020). [https://doi.org/10.1016/S1473-3099\(20\)30144-4](https://doi.org/10.1016/S1473-3099(20)30144-4).

- Study goal = to understand early transmission dynamics of SARS-CoV-2 and to evaluate the effectiveness of control measures in mitigating sustained transmission in new areas
- Combined stochastic transmission modeling with four datasets comprised of COVID-19 cases in Wuhan and those internationally exported from Wuhan
 - After implementation of large-scale control measures, the estimated median daily reproduction number (R_t) in Wuhan decreased from 2.35 to 1.05 (1 wk before/after travel restrictions implemented)
- Model estimates for international cases in top 20 most at-risk countries were broadly consistent with number of subsequently confirmed exported cases outside of Wuhan (except higher for France, USA, Australia)
- Model estimated that once 4 or more infections have been introduced into a new location, there is >50% chance that an outbreak will occur
 - Of note, if transmission is more "homogeneous" (i.e. all infectious individuals generating a similar number of secondary cases), it is more likely that an outbreak will be established
- **Strength:** model was fit to multiple existing clinical datasets to infer parameters
- **Weakness:** assumed individuals become infectious and symptomatic at the same time and that all infected individuals will become symptomatic, which we believe is unlikely the case (however sensitivity analysis on this did not change main findings)

Wang, Yanrong et al. "Clinical Outcome of 55 Asymptomatic Cases at the Time of Hospital Admission Infected with SARS-Coronavirus-2 in Shenzhen, China." *The Journal of Infectious Diseases*. Accessed March 25, 2020. <https://doi.org/10.1093/infdis/jiaa119>.

- Retrospective analysis of cases that were asymptomatic at time of hospitalization but laboratory-confirmed +SARS-CoV-2 by pharyngeal NAAT after known +family contact (admitted for isolation/observation)
- N=55; 22 male, 33 female; median age 49yrs; >50% native to Hubei Province
- Of the 55, 14 developed mild, 39 ordinary and 2 severe COVID-19 (none were critical)
- Time from hospitalization to illness onset was 1 to 7 days
- All 55 had CT chest on admission with 37/55 (67%) showing evidence of PNA
- Take home: Family contacts at-risk of developing +PCR preceding symptom onset and middle-aged individuals may significantly contribute to asymptomatic carriage

Clinical Syndrome

Brought to you by: Daniel Graciaa, MD, MPH

Arentz et al. Characteristics and Outcomes of 21 Critically Ill Patients With COVID-19 in Washington State. JAMA. 19 March 2020. <https://jamanetwork.com/journals/jama/fullarticle/2763485>

- 21 ICU pts: cough (48%) or fever (52%) only present in half of patients on admission, almost all (95%) had abnormal CXR
- 15/21 (71%) required mechanical ventilation, all 15 developed ARDS
- Cardiomyopathy (reduced LVEF + signs of cardiogenic shock, elevated CK or troponin, or ScvO₂ <70%) developed in 7 (33%) and 11 (52%) died, with 8 remaining critically ill at time of publication
- Limitations: small case series from single center, majority linked to skilled nursing facility

Severe Outcomes Among Patients with Coronavirus Disease 2019 (COVID-19) — United States, February 12–March 16, 2020. MMWR. 18 March 2020.

https://www.cdc.gov/mmwr/volumes/69/wr/mm6912e2.htm?s_cid=mm6912e2_w

- 2449 cases in US from Feb 12-Mar 16: estimated CFR 1.8-3.4%
- Adults age 65+ accounted for 31% of cases, 53% of ICU admissions, 80% of deaths
- Estimated mortality highest over age 85 (10-27%) and decreased by age category: 3-11% age 65-84, 1-3% age 55-64, <1% age 20-54, no deaths reported <20 years of age.
- Range of estimates due to high proportion missing data on hospitalization (35%), ICU admission (53%), death (47%), and no information on underlying health conditions

Wu, et al. Risk Factors Associated With Acute Respiratory Distress Syndrome and Death in Patients With Coronavirus Disease 2019 Pneumonia in Wuhan, China. JAMA Internal Medicine. 13 March 2020. doi:10.1001/jamainternmed.2020.0994

- Retrospective cohort of 201 patients with COVID-19 PNA admitted Dec 25-Jan 26, follow up through Feb 13. 84 (41.8%) developed ARDS: 44 of these (52%) died
- Factors associated with ARDS and progression from ARDS to death: age 65+ (HR 3.26 and 6.17, respectively), neutrophilia (HR 1.14 and 1.08), markers of organ dysfunction including elevated LDH (HR 1.61 and 1.3). Other markers such as d-dimer (1.03 and 1.02) and IL-6 (1.02 and 1.03) with small point estimates and narrow confidence intervals.
- Fever >39C associated with ARDS (HR 1.77, 1.11-2.84) but lower hazard rate of death (HR 0.41, 0.21-0.82). Those receiving methylprednisolone had lower hazard rate of death (HR 0.38, 0.20-0.72)
- Major limitations: unadjusted analysis from a single center with mostly severe illness

Diagnosics

Brought to you by: Ahmed Babiker, MBBS

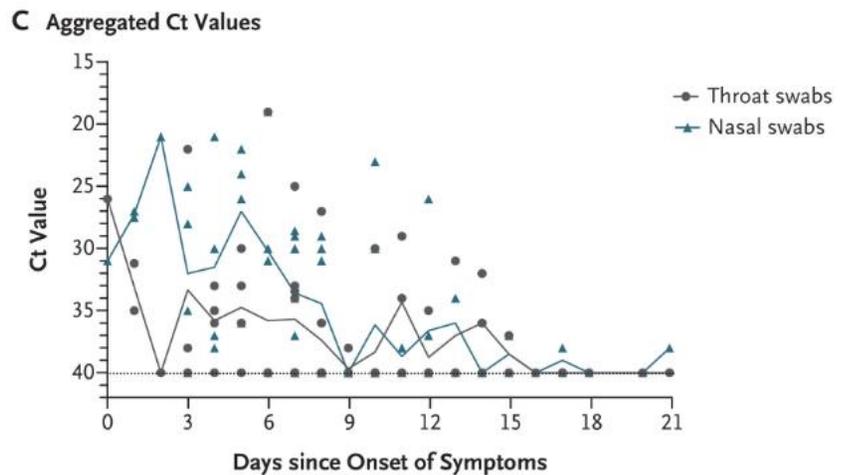
As we the face a critical shortage of swabs and testing consumables, the question of which site to sample for highest yield is imperative. Below are some studies examining this question:

SARS-CoV-2 Viral Load in Upper Respiratory Specimens of Infected Patients

Lirong Zou et al. NEJM

Link: <https://www.nejm.org/doi/full/10.1056/NEJMc2001737>

- In a letter to editor in NEJM; 17 patients had both nasopharyngeal (NP) and throat swabs collected
- Overall a total of 72 nasal swabs and 72 throat swabs (Figure 1B) were analyzed.
- Each patient had 1 to 9 sequential samples obtained
- Results revealed higher found lower CT (cycle threshold) values (i.e higher viral load) in NP vs throat swabs.



Clinical presentation and virologic assessment of hospitalized cases of coronavirus disease 2019 in a travel-associated transmission cluster

Roman Wölfel et al.

Link: <https://www.medrxiv.org/content/10.1101/2020.03.05.20030502v1.full.pdf>

- In this preprint from Germany authors examined paired oro- or nasopharyngeal
- All patients were initially diagnosed by RT-PCR from oro- or nasopharyngeal swabs
 - Both specimen types were collected over the whole clinical course in all patients
- All swabs from all patients taken between days 1 and 5 tested positive. The average virus RNA load was 6.76×10^5 copies per whole swab until day 5
- Swab samples taken after day 5 had an overall decrease in average viral load to 5.13×10^3 copies per swab and a detection rate of 46%
- The authors concluded "There was **no discernable difference** in viral load or detection rates when comparing NP vs OP"
- However, the small sample size precludes a reliable assessment

Detection of SARS-CoV-2 in Different Types of Clinical Specimens

Wenling Wang et al. JAMA

Link: <https://jamanetwork.com/journals/jama/fullarticle/2762997>

- All patients were diagnosed based on symptoms and radiology and confirmed by SARS-CoV-2 detection.

- There were 1070 specimens collected from 205 patients:
 - Pharyngeal swabs were collected from most patients 1-3 days after admission
 - Blood, sputum, feces, urine, and nasal samples were collected throughout the illness.
 - Bronchoalveolar lavage fluid (BAL) and fibrobronchoscope brush biopsy were sampled from patients with severe illness or undergoing mechanical ventilation

- Results of percent positivity per sample types were as follows
 - BAL: 93% (14/516)
 - Sputum: 72% (72/104; 72%),
 - Nasal swabs: 63% (5/8),
 - Fibrobronchoscope brush biopsy: 46% (6/13)
 - Pharyngeal swabs: 32% (126/398)
 - Feces 29% (44/153)
 - blood 1%/(3/307)
 - Urine: 0% (0/72)

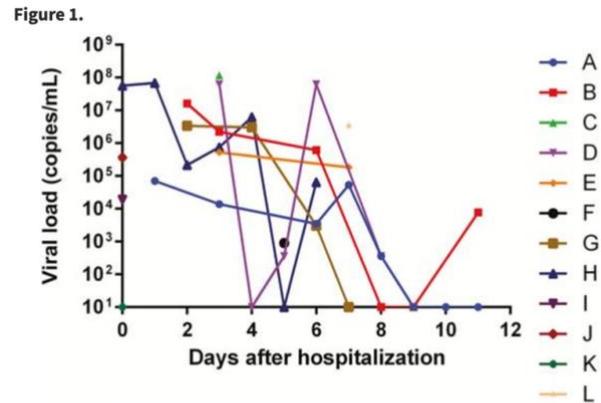


Figure 1. Saliva viral load in patients with 2019 novel coronavirus infection. For this figure, specimens with undetected viral load were assigned a value of 10^1 .

- Mean cycle threshold values of all specimen types were more than 30 ($<2.6 \times 10^4$ copies/mL) except for nasal swabs with a mean cycle threshold value of 24.3 (1.4×10^6 copies/mL)
- This paper has received the most attention. However, we must be clear that this data provides percent agreement by body site and these numbers should not be interpreted as sensitivity of body sites.
- More data (especially paired samples from the same patient) is needed to determine optimal testing sites. All the above must be taken with the caveat of sampling technique are critical for yield

Table. Detection Results of Clinical Specimens by Real-Time Reverse Transcriptase-Polymerase Chain Reaction

| Specimens and values | Bronchoalveolar lavage fluid (n = 15) | Fibrobronchoscope brush biopsy (n = 13) | Sputum (n = 104) | Nasal swabs (n = 8) | Pharyngeal swabs (n = 398) | Feces (n = 153) | Blood (n = 307) | Urine (n = 72) |
|-------------------------------|---------------------------------------|---|------------------|---------------------|----------------------------|-----------------|-----------------|----------------|
| Positive test result, No. (%) | 14 (93) | 6 (46) | 75 (72) | 5 (63) | 126 (32) | 44 (29) | 3 (1) | 0 |
| Cycle threshold, mean (SD) | 31.1 (3.0) | 33.8 (3.9) | 31.1 (5.2) | 24.3 (8.6) | 32.1 (4.2) | 31.4 (5.1) | 34.6 (0.7) | ND |
| Range | 26.4-36.2 | 26.9-36.8 | 18.4-38.8 | 16.9-38.4 | 20.8-38.6 | 22.3-38.4 | 34.1-35.4 | |
| 95% CI | 28.9-33.2 | 29.8-37.9 | 29.3-33.0 | 13.7-35.0 | 31.2-33.1 | 29.4-33.5 | 0.0-36.4 | |

Abbreviation: ND, no data.

Two papers from the same group examine the question of testing saliva for COVID-19

[Consistent detection of 2019 novel coronavirus in saliva.](#)

Kelvin Kai-Wang To et al. Consistent Detection of 2019 Novel Coronavirus in Saliva, *Clinical Infectious Diseases*. <https://academic.oup.com/cid/advance-article/doi/10.1093/cid/ciaa149/5734265>

- A total of 12 patients with laboratory-confirmed 2019-nCoV infection in Hong Kong
- Saliva specimens were mixed with lysis buffer and underwent RT-qPCR targeting the S gene of 2019-nCoV
- Saliva specimens were collected at a median of 2 days after hospitalization (range, 0–7 days).
- The 2019-nCoV was detected in the initial saliva specimens of 11/12 patients (91.7%).
- In 33 patients whose nasopharyngeal specimens tested negative for 2019-nCoV, all saliva specimens also tested negative.

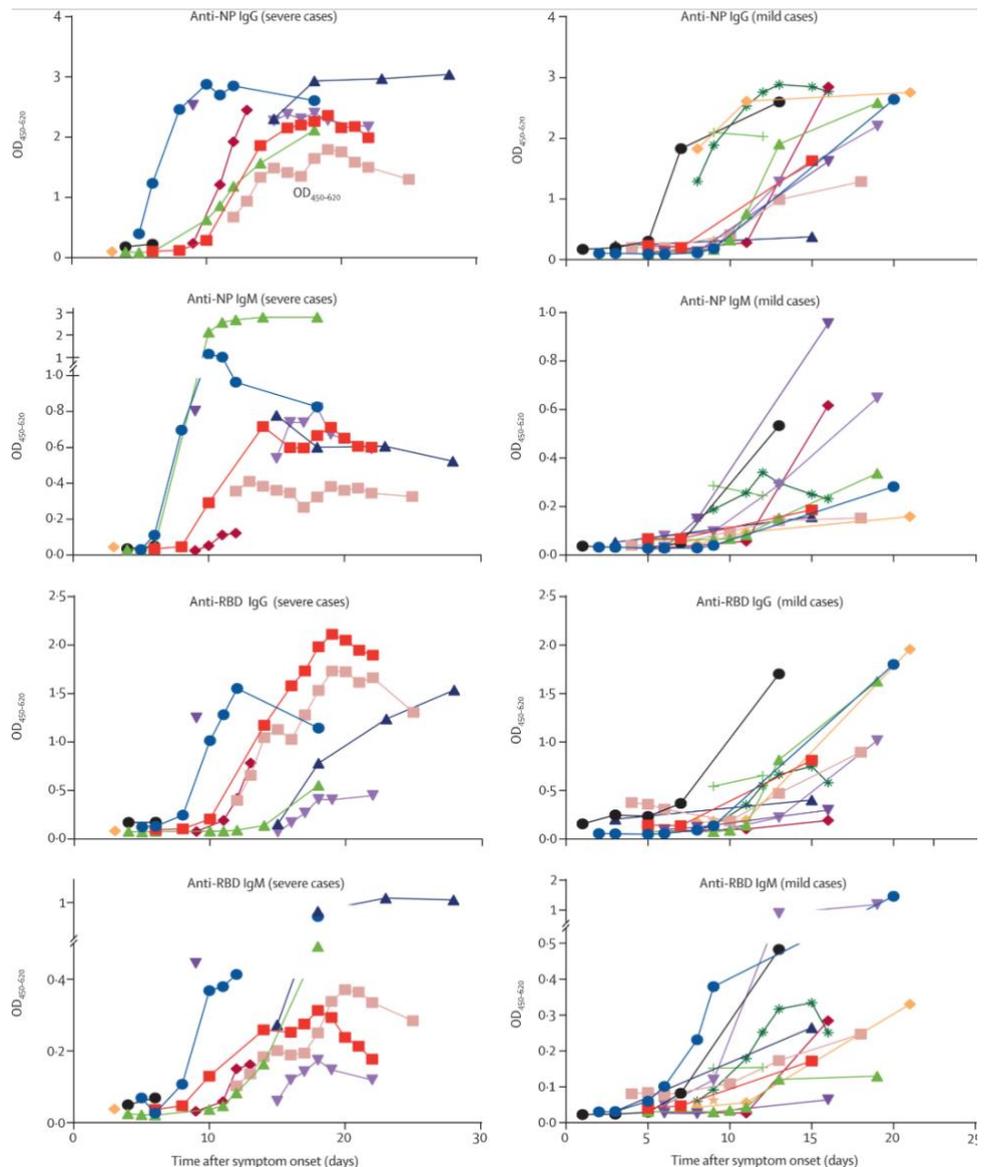
- Viral load declined in the majority of patients in whom repeat samples were collected, although follow up was limited to 11 days, with one patient having continued evidence of viral shedding in saliva on day 11

Temporal profiles of viral load in posterior oropharyngeal saliva samples and serum antibody responses during infection by SARS-CoV-2: an observational cohort study. Lancet ID

Kelvin Ka-Wang et al. Lancet Infectious Diseases

Link: [https://www.thelancet.com/journals/laninf/article/PIIS1473-3099\(20\)30196-1/fulltext](https://www.thelancet.com/journals/laninf/article/PIIS1473-3099(20)30196-1/fulltext)

- Cohort study at two hospitals in Hong Kong
- Recombinant NP (anti-P) and spike protein RBD (anti-RBD) of SARS-CoV-2 were used for the EIAs for serological testing in serum. RT PCR was performed from early morning saliva specimens.
 - 23 patients were included (median age 62 years [range 37–75]).
- SARS-CoV-2 RNA was not detected in the saliva of three (13%) patients.
- Salivary viral load was highest during the first week after symptom onset and subsequently declined with time
- Of the 21 patients who survived, seven (33%) had viral RNA detected for 20 days or longer after symptom onset
- Older age was correlated with higher viral load (Spearman's $\rho=0.48$, 95% CI 0.074–0.75; $p=0.020$)
- An increase was noted in IgG or IgM antibody levels against NP or RBD for most patients at 10 days or later after symptom onset
- Onset of seropositivity was earlier for anti-RBD vs. anti-NP, for both IgG and IgM. In general earlier seroconversion was seen for IgG vs. IgM for both anti-RBD and anti-NP
- Nanopore sequencing was successful for paired samples from four patients. The interval between the first and second specimens was 1–3 days. No viral mutations were identified between paired samples from individual patients.



Therapeutics

Brought to you by: Amy Sherman, MD

Xu, Xiaoling et al. Effective Treatment of Severe COVID-19 Patients with Tocilizumab. March 5, 2020. [ChinaXiv:202003.00026]

- **Background:** In patients diagnosed with severe COVID-19, higher plasma levels of cytokines (e.g. IL-6, IL-2, IL-7, IL-10, G-CSF, TNF-alpha) were recovered, suggesting cytokine storm. Hypothesized that this cytokine storm (leading to increased alveolar-capillary blood-gas exchange dysfunction) is related to disease severity and poor prognosis.
 - IL-6 is a key cytokine leading to inflammatory/cytokine storm.
- A single-arm trial was conducted in China to evaluate the role of tocilizumab, a recombinant humanized anti human IL-6 receptor monoclonal antibody.
 - 21 patients met inclusion criteria: 17 patients categorized as severe and 4 as critical.
 - All received “standard care” including lopinavir, methylprednisolone, and O2 therapy, as well as 400mg IV tocilizumab x1 dose (18 patients) or x2 doses (3 patients).
- **Results:** All 21 patients had resolution of fever on Day 1 after tocilizumab, 15 patients (75%) had reduced O2 requirements and 1 patient was extubated Day 1 after tocilizumab. 1 patient remained on the ventilator, but had decreased parameters of ventilator needs and was expected to be extubated imminently.
 - Lymphocytes in 10 patients returned to normal. CRP decreased and returned to normal in 16 patients after Day 5.
 - Mean hospitalization time (for 19 patients discharged) was 13.5 days (SD 3.1) after treatment. At time this was published, 2 patients remained hospitalized.
- While this study has promising results, it was a small sample size and other treatments given may have biased the results. Randomized controlled trials are needed. Sanofi and Regeneron have started recruitment for a [US Phase 2/3 trial for sarilumab](#), a monoclonal antibody that inhibits the IL-6 pathway.

Gautret, Philippe et al. “Hydroxychloroquine and Azithromycin as a Treatment of COVID-19: Results of an Open-Label Non-Randomized Clinical Trial.” *International Journal of Antimicrobial Agents*, March 20, 2020, 105949. <https://doi.org/10.1016/j.ijantimicag.2020.105949>.

- Single-arm study conducted in Marseille, France of hospitalized patients with confirmed COVID-19 (positive PCR from NP swab), age >12 yo.
- 36 patients were enrolled: 26 received hydroxychloroquine (HCQ), 16 were control patients.
 - 6 patients in the HCQ arm were lost in follow-up (early cessation of therapy).
 - 3/6 transferred to ICU, 1/6 patient died on day 3, 1/6 patient left the hospital on day 3, 1/6 patient stopped therapy because of nausea on day 3
 - Thus only 20 patients included in analysis for hydroxychloroquine group.
 - Of the patients in the HCQ group, 6 received azithromycin as well (500mg day 1, followed by 250mg daily for 4 days).
- **Results:** Day 1 post-inclusion, number of negative NP PCR (HCQ 10/20 patients; control 1/16). Day 6, number of negative NP PCR (HCQ 14/20; control 2/16).
 - At Day 6, negative NP PCR for HCQ were 8/14 patients v. HCQ+azithro 6/6 patients.
- Limitations: 6 in HCQ arm were not included in results and 4 of these patients had severe outcomes (3 transfer to ICU, 1 death); study does NOT account that HCQ may have been implicated in these

outcomes. Day 6 was primary endpoint for viral clearance, however control group did not have daily NP swabs collected. The endpoint evaluated viral clearance—will be interesting to see a study that assesses clinical outcome as well.

Cao, Wei et al. “High-Dose Intravenous Immunoglobulin as a Therapeutic Option for Deteriorating Patients with Coronavirus Disease 2019.” *Open Forum Infectious Diseases*. March 21, 2020.

<https://doi.org/10.1093/ofid/ofaa102>.

- Report of 3 patients with severe COVID-19 who received high-dose intravenous immunoglobulin (IVIg) at 0.3-0.5 g/kg body weight for 5 days.
 - Patient 1: Severe respiratory deterioration on hospital day 7, with high-dose IVIg given daily for 5 days. By the time of treatment completion, he was afebrile, and O2 saturation returned to normal, with recovery of lymphocyte count. End of therapy OP swabs negative for SARS-CoV-2, discharged home.
 - Patient 2: Decreased O2 saturation to 90%, lymphopenia, and b/l opacities on CT chest on admission. Started on IVIg. Afebrile by day 2 of treatment, with gradual respiratory improvement. At the end of treatment, nasal PCR was negative for SARS-CoV-2, and he was discharged two days later.
 - Patient 3: Initially admitted with mild symptoms, and was receiving lopinavir/ritonavir. Hospital day 6, she desaturated to 92% RA, with worsening CT chest findings, lymphopenia, and elevation of CRP. IVIg was initiated for 5 days. Fever resolved after first dose, and O2 improved to 98% on day 2 of therapy. End of therapy PCR was negative for SARS-CoV-2, and CT chest opacities were improved. She was discharged 7 days later.
- Limitations: Confounding factors for these patients; different antivirals also being administered, and one patient received steroids. Only 3 patients and their clinical courses were reported.
- Conclusions: All 3 patients survived and had clinical improvement of fever and respiratory symptoms, although difficult to conclude if these effects were due to IVIg alone. Further trials are needed to evaluate the efficacy; one is underway ([NCT NCT04261426](https://clinicaltrials.gov/ct2/show/study/NCT04261426)). Note: IVIg is already on critical shortage in the United States.

Pediatrics

Brought to you by: Madeleine Goldstein, MD

Dong Y, Mo X, Hu Y, et al. Epidemiological Characteristics of 2,143 Pediatric Patients with 2019 Coronavirus Disease in China. *Pediatrics*. 2020; doi: 10.1542/peds.2020-0702

- Retrospective analysis of 2,143 pediatric patients < 18 years old with confirmed or suspected COVID-19 in China from January 16 to February 8, 2020.
 - 731 (34.1%) laboratory-confirmed cases and 1412 (65.9%) suspected cases
 - ~94% of cases were considered asymptomatic, mild, or moderate.
 - Patients less than 1 years old had more severe or critical illness (10.6%), consisting of hypoxia, dyspnea, central cyanosis, ARDS, respiratory failure, or multiorgan dysfunction.
- At the time of analysis, 1 patient had died (14 years old)
- The more severe or critical illnesses were seen in the suspected cases vs the confirmed cases

- Conclusion: Children of all ages were susceptible to COVID-19, with more severe/critical illness seen in young children. No discussion of co-infection or co-morbidities in these patients.

Liu W, Zhang Q, Chen J, et al. Detection of Covid-19 in Children in Early January 2002 in Wuhan, China. N Engl J Med. March 12, 2020. DOI: 10.1056/NEJMc2003717

- Retrospective analysis of children < 16 years old admitted to Tongji Hospital in Wuhan, China from January 7 to 15th, 2020 with respiratory infections, of which 6 had confirmed Covid-19 (1.6%)
 - Age range: 1 year to 7 years old.
 - All children had previously been completely healthy
- Common clinical findings: high fever (>39°C) and cough (6 patients), vomiting (4 patients), pneumonia (4 patients).
- One patient required supplemental oxygen and admission to the PICU.
- All children recovered and were discharged from the hospital
- During the early stages of the pandemic, Covid-19 was causing moderate-severe respiratory illness in children

Lu X, Zhang L, Du H, et al. SARS-CoV-2 Infection in Children. N Eng J Med. March 18, 2020. DOI: 10.1056/NEJMc2005073

- Observational study of 171 children < 16 years old admitted to Wuhan Children’s Hospital from January 28 to February 26, 2020 with confirmed SARS-CoV-2 infection
 - Median age: 6.7 years (ranged from 1 day to 15 years old)
 - Common clinical characteristics: fever (41.5%), cough (48.5%), and pharyngeal erythema (46.2%). The most common radiologic finding was bilateral ground-glass opacity (32.7%).
- A total of 27 patients (15.8%) were asymptomatic and had no radiologic features of pneumonia.
 - 3 patients required ICU and vents; all had coexisting conditions (hydronephrosis, leukemia, and intussusception). The 10-month-old child with intussusception had multiorgan failure and died 4 weeks after admission.
- SARS-CoV-2 causes a spectrum of illness in children, with majority causing mild or asymptomatic illness in children less than 16 years old.

Basic Science/Virology

Brought to you by: Sam Stampfer, MD, PhD

Li, Xiaojun et al. “Emergence of SARS-CoV-2 through Recombination and Strong Purifying Selection.” BioRxiv, March 24, 2020, 2020.03.20.000885. <https://doi.org/10.1101/2020.03.20.000885>.

- A phylogenetic analysis of 43 genomes of sarbecovirus group (Betacoronavirus lineage b) was done- this includes close SARS-related viruses but not MERS, a more distant betacoronavirus
- Analysis at the genome level was difficult because this family of viruses showed extensive recombination
- They used SimPlot analysis to note that, while the whole genome was most similar to RaTG13 overall (bat origin), there were two regions where it switched.

- A critical region was at the receptor binding domain on Spike protein, which is most similar to a pangolin group of coronaviruses Pan_SL-Cov_GD. This allows much better contact with the SARS-CoV-2 receptor human ACE2 based on structural analysis, which RaTG13 is unlikely to be able to bind.
- Two more recombination hotspots in the sarbecovirus group were noted- at ORF1a (encoding replicase subunits) and ORF8 (unknown function, possibly a replication enhancer).
- Overall, they conclude that recombination of at least three bat coronaviruses was required to form SARS-CoV-2

Disclaimer: The above references were selected and summarized by amazing Emory ID fellows. We have tried to put together an accurate list and summary, but please know that this is not intended to be 100% comprehensive! Also impossible to keep completely up-to-date!