

The Weekly Covid-19 Literature Round-Up

Edition 1: March 18, 2020
Collated by Emory ID Fellows

“There have been as many plagues as wars in history, yet always plagues and wars take people equally by surprise.” -Albert Camus, [The Plague](#)

“We work in the dark - we do what we can - we give what we have. Our doubt is our passion, and our passion is our task. The rest is the madness of art.” -Henry James

Epidemiology/Transmission/Infection Control

Brought to you by: Jessica Howard-Anderson

Guan, Wei-jie et al. “Clinical Characteristics of Coronavirus Disease 2019 in China.” *New England Journal of Medicine*(February 28, 2020). <https://doi.org/10.1056/NEJMoa2002032>.

- 1099 patients with lab-confirmed Covid-19 from 30 provinces in China who were hospitalized. "Cohort randomly selected, so descriptive stats only presented"
- Median age 47, 42% female, 3.5% HCW. Comorbid conditions more common in severe disease
- Incubation period 4 d (IQR 2-7 d)
- Symptoms: fever (44% on admission, 89% during hospital), cough (68%), diarrhea (4%)
- Signs: GGOs (56%), lymphocytopenia (83%)
- Outcomes: 5% admitted to ICU; 2.3% needed mechanical ventilation; 1.4% died
- Conclusion: Varying degrees of illness in HOSPITALIZED patients, including many w/out fever or abnormal imaging on admission

Cheng, Vincent C. C. et al. “Escalating Infection Control Response to the Rapidly Evolving Epidemiology of the Coronavirus Disease 2019 (COVID-19) Due to SARS-CoV-2 in Hong Kong.” *Infection Control and Hospital Epidemiology*, March 5, 2020, 1–24. <https://doi.org/10.1017/ice.2020.58>.

- Describes infection control practices in Hong Kong in the first 42 days after the announcement of COVID-19 outbreak in China
- Proactive Infection control measures were activated by the governing body of all 43 public hospitals (90% of beds in Hong Kong)
- Infection prevention “bundle” included: enhanced active surveillance (criteria broadened over the 42 days), airborne isolation, rapid molecular diagnostic testing (4-8 hr run around time) and contact tracing for HCWs with exposures. Also had open staff forums, PPE training, hand hygiene compliance assessments
- 1275 patients screened. 42 cases of confirmed COVID-19 infection
- 11 HCW had exposure with inadequate PPE, **but NO HCW were infected, NO nosocomial transmission documented**
- Conclusion: Aggressive hospital infection control measures can prevent nosocomial transmission of SARS-CoV-2

“Aerosol and Surface Stability of SARS-CoV-2 as Compared with SARS-CoV-1 | NEJM.” *New England Journal of Medicine*. <http://www.nejm.org/doi/10.1056/NEJMc2004973>.

- Compared viability of SARS-CoV-2 and SARS-CoV-1 after being aerosolized (generated using a nebulizer and fed into a Goldberg drum) or on common surfaces
- SARS-CoV-2 was viable in aerosols (after being aerosolized in drum) for 3 hours (median half-life 1.1 hrs); reduction similar to SARS-CoV-1
- SARS-CoV-2 was more stable on plastic and stainless steel compared to copper and cardboard
- Viable SARS-CoV-2 was detected up to 72 hrs after application on plastic (median half-life 6.8 hrs) and steel (median half-life 5.6 hrs). Similar to SARS-CoV-1
- “Aerosol and fomite transmission of SARS-CoV-2 is plausible, depending on the inoculum shed” and importantly, the procedure being performed

Clinical Syndrome

Brought to you by: Amy Sherman

Zhou, Fei et al. “Clinical Course and Risk Factors for Mortality of Adult Inpatients with COVID-19 in Wuhan, China: A Retrospective Cohort Study.” *The Lancet* 0, no. 0 (March 11, 2020). [https://doi.org/10.1016/S0140-6736\(20\)30566-3](https://doi.org/10.1016/S0140-6736(20)30566-3).

- Retrospective cohort study of adult inpatients at 2 hospitals in Wuhan of confirmed COVID-19 cases.
 - Total 191 patients: 137 discharged, 54 died in the hospital.
- Comorbidities reported in 48% of the patients
 - HTN being the most common (30% of patients) > DM2 (19%) > CAD (8%)
- Multivariable regression showed increasing odds of in-hosp death associated with older age, higher SOFA score, and d-dimer greater than 1 µg/mL.
- Median duration of viral shedding was 20 days in survivors.
 - Longest duration of viral shedding in survivors was 37 days.
- SARS-CoV-2 was detectable until death in non-survivors.

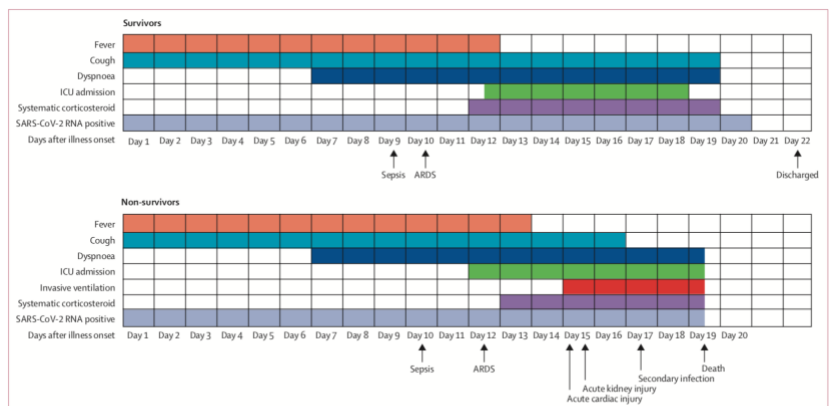


Figure 1: Clinical courses of major symptoms and outcomes and duration of viral shedding from illness onset in patients hospitalised with COVID-19
 Figure shows median duration of symptoms and onset of complications and outcomes. ICU=intensive care unit. SARS-CoV-2=severe acute respiratory syndrome coronavirus 2. ARDS=acute respiratory distress syndrome. COVID-19=coronavirus disease 2019.

Fang, Lei et al. "Are Patients with Hypertension and Diabetes Mellitus at Increased Risk for COVID-19 Infection?" *The Lancet Respiratory Medicine* 0, no. 0 (March 11, 2020). [https://doi.org/10.1016/S2213-2600\(20\)30116-8](https://doi.org/10.1016/S2213-2600(20)30116-8).

- HTN treated with ACEi/ARBs upregulates ACE2 ([Li XC](#)). ACE2 may also be increased by thiazolidinediones and ibuprofen.
- Increased expression of ACE2 could facilitate infection with SARS-CoV-2, and thus ACE2-stimulating drugs may increase the risk of developing severe and fatal COVID-19.
 - Can consider changing patients to calcium channel blockers instead of ACEi/ARBs for this hypothetical reason.
- However, in a recent retrospective analysis in China by [Peng YD et al](#), ACEi/ARB therapy did NOT affect the morbidity and mortality of cardiovascular patients with COVID-19 (although severe group had n=16 only).

"The Incubation Period of Coronavirus Disease 2019 (COVID-19) From Publicly Reported Confirmed Cases: Estimation and Application." *Annals of Internal Medicine*. March 10, 2020. doi: <https://doi.org/10.7326/M20-0504>

- Retrospective pooled analysis of confirmed COVID-19 cases reported between Jan 4 – Feb 24, 2020 in provinces outside of Hubei – cases with no known community transmission.
 - Data collected from 181 cases
- Time to possible exposure, symptom onset, fever onset, and case detection were collected.
- Incubation time was estimated using a previously described parametric accelerated failure time model, and assumed that incubation time follows a log-normal distribution (as it does for other acute respiratory viral infections).
- Median incubation period = 5.1 days (95% CI, 4.5-5.8 days).
- 97.5% of individuals who develop symptoms do so within 11.5 days of infection.
 - Thus active monitoring recommended by CDC of 14 days is supported by these findings.
 - However, since transmission can occur from mildly symptomatic people, the time from exposure to onset of infectiousness (latent period) may be shorter than the estimated incubation period...which would have important implications for transmission dynamics.

Diagnostics

Brought to you by: Alfonso Hernandez

COVID-19 IgM-IgG Rapid Test Clinical Study, Li et al. Development and Clinical Application of A Rapid IgM-IgG Combined Antibody Test for SARS-CoV-2 Infection Diagnosis. *J Clin Virology*, 27 Feb 2018
<https://www.biomedomics.com/documents/?sub-field=infectious-disease>

Point-of-care lateral flow immunoassay (LFIA)

- Can detect IgM and IgG simultaneously within 15 minutes
- Tested in 8 hospitals and the Chinese CDC
- Recombinant antigen is the receptor binding domains of SARS-CoV-2 spike protein
- Mouse anti-human IgG/IgM, and rabbit IgG (control) were used
- 397 clinical positive (+PCR) and 128 negative blood samples

- Sample 10-15uL and use of a dilution buffer
- 352 positives among 397 infected patients – Sensitivity 88.7%
 - 256 had both IgM and IgG antibodies (64.5%)
 - 72 had IgM only (20.1%)
 - 24 had IgG only (6.7%)
 - 12 positives among 128 positives uninfected patients – Specificity 90.6%
 - PPV 96.7%, NPV 72%
- No data on date of symptom onset
 - From 58 patients who did have this data tests were performed between day 8 and 33 after symptoms appeared
- Tested fingerstick blood only in 7 positive and 3 negative patients: results were consistent with serum
- Did not check cross-reactivity with other viruses

Antibody responses to SARS-CoV-2 in patients of novel coronavirus disease 2019

<https://www.medrxiv.org/content/10.1101/2020.03.02.20030189v1>

- Goal to study the dynamics of total Ab, IgM, and IgG antibodies against SARS-CoV-2
 - Serial blood samples from 173 confirmed COVID-19 patients
 - Antibodies were tested with ELISA
- All patients enrolled had acute respiratory infection syndromes +/- chest CT abnormalities and +PCR, 18.5% were critically ill
- 535 plasma samples collected on 173 patients
- Seroconversion rates were 93.1% for total Ab, 8.27% for IgM, and 64.7% for IgG
- Twelve patients remained seronegative: all specimens collected <15 days after onset of symptoms
- Median time to total Ab, IgM, and IgG was 11, 12, and 14 days – not different between critically ill and non-critically ill patients
 - Quicker seroconversion possibly related to sandwich assay used for total Ab versus capture assay (IgM) and indirect assay (IgG)
- Cumulative seroconversion reached 100% ~1 month after start of illness
- Compared to RNA PCR (throat/nasal swab sample)
 - Se 66.7% for PCR vs 38.3% for Ab in the first 7 days since symptom onset
 - Higher sensitivity of Ab after day 8 compared to RNA PCR
 - 89.6% Ab, 73.3% IgM, 54.1%, RNA PCR 54.0% at days 8-14
 - 100% Ab, 94.3% IgM, 79.8% IgG, 45.5% RNA PCR days 15-39
- Among patients with negative PCR in respiratory tract samples
 - 28.6% (2/7), 53.6% (15/28), 98.2% (56/57) and 100% (30/30) had detectable total Ab at days 1-3, 4-7, 8-14, and 15-39 since symptom onset respectively
- Combining Ab and RNA PCR significantly improved Se
 - Adding Ab test to PCR increase Se from 66.7% to 78.7% in days 1-7 of symptom onset
- Unable to assess cross-reactivity with other viruses
- Did not study how long antibodies were present

Therapeutics

Brought to you by: Amy Sherman

Wang, M et al. "Remdesivir and Chloroquine Effectively Inhibit the Recently Emerged Novel Coronavirus (2019-NCoV) in Vitro." *Cell Research* 30, no. 3 (March 2020): 269–71. <https://doi.org/10.1038/s41422-020-0282-0>.

- Several pre-existing antivirals were tested against a clinical isolate of SARS-CoV-2 *in vitro*: ribavirin, penciclovir, nitazoxanide, nafamostat, chloroquine (all FDA-approved drugs), and remdesivir (GS-5734) and favipiravir (T-705).
- The effects of the compounds were measured based on cytotoxicity, virus yield, and infection rates.
- Remdesivir and chloroquine were found to potently block virus infection at low-micromolar concentration, and both showed high SI (selectivity index).
 - Remdesivir: acted at a stage post virus entry
 - Chloroquine: (proposed mechanism), blocks virus infection by increasing endosomal pH required for the virus and cell fusion, also interferes with glycosylation of cellular receptors of SARS-CoV-2.

Gao, Jianjun et al. "Breakthrough: Chloroquine Phosphate Has Shown Apparent Efficacy in Treatment of COVID-19 Associated Pneumonia in Clinical Studies." *BioScience Trends* 14, no. 1 (2020): 72–73. <https://doi.org/10.5582/bst.2020.01047>.

- This article highlights numerous trials testing chloroquine in clinical trials in China, after *in vitro* studies showed efficacy.
- Prelim results in more than 100 patients demonstrate that chloroquine phosphate (as compared to various "control treatments") has reduced exacerbations of pneumonia, improved lung imaging findings, shorten disease course.
- Anti-inflammatory properties, in addition to anti-viral properties, may be responsible for potent efficacy seen in these patients.
- While this seems promising, [Touret et al](#) caution that the outcomes have NOT been fully elucidated (unable to see trial data/info from Chinese studies), and thus further peer review and robust trials are needed to determine efficacy and safety of chloroquine.

[Yao X et al.](#) "In Vitro Antiviral Activity and Projection of Optimized Dosing Design of Hydroxychloroquine for the Treatment of Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2)." Published by Oxford University Press for the Infectious Diseases Society of America, Advance article, CID March 17, 2020.

- *In vitro* model evaluating chloroquine v hydroxychloroquine for treatment of SARS-CoV-2.
- PBPK (Physiologically based pharmacokinetic) models for chloroquine and hydroxychloroquine were created and validated, and then used to predict lung concentrations for different doses (see Table 1).
- Both drugs found to decrease viral replication in a concentration-dependent manner.
 - Hydroxychloroquine had better *in vitro* anti SARS-CoV-2 activity than chloroquine (EC50 values for hydroxychloroquine smaller than EC50 values for chloroquine).

This is an excellent reference for drug targets and list of R&D for therapies: [Research and Development on Therapeutic Agents and Vaccines for COVID-19 and Related Human Coronavirus Diseases \(C Liu\)](#)

Virology/Basic Science

Brought to you by: Max Adelman

Reinfection could not occur in SARS-CoV-2 infected rhesus macaques. Bao et al, <https://www.biorxiv.org/content/10.1101/2020.03.13.990226v1.full.pdf> (preprint).

- *In vivo* study of macaques to determine if reinfection with SARS-CoV-2 can occur 28d post initial infection
- At day=7 post infection, wide viral dissemination (PCR+ nasopharynx, lung, gut, spinal cord, heart, muscle) on necropsy
- NP/OP/rectal RCR remained positive until day=14 post infection
- Anti-spike IgG abs became elevated day=14 post initial infection
- Of 4 macaques initially infected (who had recovered), 2 were re-challenged and had negative NP/OP/rectal PCR and no evidence of viral dissemination on necropsy
- In the short-term (<=28 days), immune response was protective against subsequent re-infection in a small (N=2) cohort of macaques

"Structure, Function, and Antigenicity of the SARS-CoV-2 Spike Glycoprotein". Walls et al <https://doi.org/10.1016/j.cell.2020.02.058>

- Compared to other coronaviruses, SARS-CoV-2 has a novel cleavage site between S1 and S2 subunits of the spike (S) glycoprotein (the surface glycoprotein that binds ACE2 and facilitates membrane fusion)
- Proteins that cleave at similar sites in other viruses are ubiquitous, which may partially explain transmissibility and pathogenicity (authors suppose)
- SARS-CoV-2 and SARS-CoV bind ACE2 with similar kinetics, likely because many key contact residues of S protein are conserved
- Abs from mice immunized with SARS-CoV S protein were protective against *in vitro* viral entry and replication

"SARS-CoV-2 Cell Entry Depends on ACE2 and TMPRSS2 and Is Blocked by a Clinically Proven Protease Inhibitor." Hoffman et al. <https://doi.org/10.1016/j.cell.2020.02.052>

- Similar to the above study, these authors show that conserved regions in the S protein between SARS-CoV and SARS-CoV-2 facilitate binding to ACE2 (but not other receptors used by other coronaviruses including MERS)
- S protein requires "priming" (ie, cleavage via proteases) prior to binding ACE2 in SARS-CoV
- SARS-CoV uses proteases cathepsin B/L and TMPRSS2 for priming
- In this study, the authors show that these proteases are required for SARS-CoV-2 infection *in vitro*
- The clinically used TMPRSS2 inhibitor camostat mesylate blocked *in vitro* SARS-CoV-2 infection, providing a novel therapeutic target