COVID-19 Literature Review

Summary of selected papers considered recent, rigorous, and reflecting the current state of science surrounding the outbreak

Not all studies have been peer-reviewed

(last updated 05/19/2020; new papers added are marked as NEW)

<u>**To go to a topic directly**</u>**: Ctrl+Click on the topic name from table to contents**

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GENERAL

Link to NIH iSearch COVID-19 portfolio: https://icite.od.nih.gov/covid19/search/

Link to Spectrum Health Literature Review Site (searchable): http://covidlit.spectrumhealth.org/

Up-To-Date Coronavirus disease 2019 (COVID-19)

Date: 03/30/2020

Link - https://www.uptodate.com/contents/coronavirus-disease-2019-covid-19#H4014462337

- Provides a general overview of COVID-19
- Excellent quick reference to all COVID-19 relevant topics

PERSONAL PROTECTIVE EQUIPMENT

NEW: The Airborne Lifetime of Small Speech Droplets and Their Potential Importance In SARS-CoV-2 Transmission

Date: 05/13/2020

Link: https://doi.org/10.1073/pnas.2006874117

- Used laser light scattering to visualize droplets produced during repeated spoken phrases by volunteers.
- Distance droplets traveled from the mouth of the speaker affected by amount and velocity of air exhaled.
    - Velocity is influenced by volume or loudness.
    - In environments with little ventilation, droplets persist in a slowly descending cloud.
- Volunteers spoke "stay healthy" into an enclosure for 25 seconds.
    - Movie clips were analyzed frame by frame to determine the number of particles.
    - Largest particles settled out of air quicker than smaller particles.
    - Counted average of ~2600 small droplets are generated per second of speaking.
        - Estimated viral load from 1 minute of loud talking generates 1000 infectious virus particles which could remain airborne for longer than 8 minutes.

NEW: Transmission of Aerosols Through Pristine and Reprocessed N95 Respirators

Date: 05/18/2020

Link: https://doi.org/10.1101/202.05.14.20094821

- Tested treated masks (3M 1860S, 8210, 9210) vs pristine masks under experimental conditions that simulated
    airflow of infectious particles found in healthcare settings.
    - Conditions simulated size, density, and airflow properties of infectious aerosols that would be encountered
        in healthcare.
    - Used polydispersed challenge of negatively charged spherical latex polystyrene beads (0.1 - 1 um) passed

through a nebulizer.
- Force-air dry heat and humid heat maintained acceptable particle transmission for up to 3 cycles, while vaporized hydrogen peroxides up to 10 cycles.
  - Autoclaving physically deformed masks thereby preventing fit test approval.
  - UV irradiation maintained acceptable particle transmission for up to 3 cycles, but caused slight dose
  dependent photochemical damage.
- Less than 1.5% of particle size known to carry infectious aerosols were measured to penetrate reprocessed masks.
  - Different treatments maintained mask functioning for different number of cycles.
  - Critical to be alert to degradation of filter charge, strap aging, and mask deformation when Reprocessing masks.

Validation of N95 Filtering Facepiece Respirator Decontamination Methods Available at a Large University Hospital

Date: 04/30/2020

Link –https://doi.org/10.1101/2020.04.28.20084038

- Current CDC/FDA guidelines for decontamination methods are in need of additional data on viricidal and bactericidal efficiency of different methods.
- Evaluated different methods of decontamination for FFR using vaporized hydrogen peroxide, pulsed xenon UV, and dry versus moist heat.
  - Organisms used included MS2 (non-enveloped phage), Phi6 (enveloped phage), influenza A, murine hepatitis virus (CoV), E. Coli, S. Aureus, G. stearothermophilus(spores), Aspergillus niger.
  - Fit testing on decontaminated masks followed current OSHA guidelines.
- Observed pulsed xenon UV coupled with moderate relative humidity inactivated all viruses.
  - Poorly inactivated bacterial spores and bacteria.
  - Vaporized hydrogen peroxide inactivated all viruses and bacterial spores.
    - Incomplete S. Aureus inactivation, as previously reported.
  - Observed that the media viruses are grown in could affect inactivation.

N95 Respirators vs Medical Masks for Preventing Influenza Among Health Care Personnel

Date: 09/03/2019

Link – https://doi.org/10.1001/jama.2019.11645

- Inpatient respiratory protection studies indicate adherence rates between 10 – 84% for health care personnel.
- Four-year multicenter outpatient study compared effectiveness of N95 masks vs surgical masks in preventing viral respiratory infection in health care workers.
  - Nasal swabs obtained from participants within 24 hours of reporting symptoms.
  - Samples analyzed for viral RNA using reverse transcriptase PCR.
    - Also used seroconversion to detect participants that were asymptomatic.
    - Tested for 4-fold rise in titer using hemaglutination inhibition assay in pre and post influenza season serum.
- Both masks equally effective in decreasing the number of participants infected with Influenza.

Assessment of Fabric Mask as Alternatives to Standard Surgical Masks in Terms Of Particle Filtration Efficiency

Date: 04/17/2020

Link –https://doi.org/10.1101/2020.04.17.20069567

- Examination of the effectiveness of sewn fabric masks vs standard surgical mask in protection of wearer from airborne particle sizes in range known to transport viruses.
  - Fabric masks included cotton batting, sterilization wrap, and sections from HEPA vacuum bags.
  - Particles were generated using TSI particle generator and measured using a Porta Count particle counter.
    - Instruments were calibrated daily prior to use.
    - Particle counts were measured outside and inside mask every second for 1 minute.
    - Participant breathed normally through nose with mouth closed.
- Average particle removal efficiency was >99% for standard N95 mask.
  - Standard surgical mask mean particle removal efficiency was 75%.
    - Other fabric masks measured <60% mean particle removal efficiency.
- Standard commercial medical mask had mean particle removal efficiency of 75%.
  - Most other fabric masks had a mean particle removal efficiency between 30-60%.
  - Addition of nylon stocking overlay increased particle removal efficiency by additional 15-50%.

Assessment of N95 Respirator Decontamination and Re-Use for SARS-CoV-2

Date: 04/15/2020

Link - https://doi.org/10.1101/2020.04.11.20062018.

- 4 different methods of decontamination of N95 masks were evaluated for ability to ability to reduce contamination of SARS-CoV-2.
- Vaporized hydrogen peroxide exhibited best combination of rapid virus inactivation and preservation of mask integrity.
  - UV irradiation inactivated virus more slowly and preserved mask function.
  - Dry heat (70°C) inactivated virus similar to UV and masks retained function for 2 rounds.
  - Ethanol treatment failed to maintain mask integrity and not recommended.
- Vaporized hydrogen peroxide and UV treated N95 masks retained filtration and performance masks retained fil

Aerodynamic Characteristics and RNA Concentration of SARS-CoV-2 Aerosol in Wuhan Hospitals During COVID-19 Outbreak

Date: 03/10/2020

Link –https://doi.org/10.1101/2020.03.08.982637

- Examined airborne SARS-CoV-2 at different sites in 2 separate hospitals in Wuhan, China.
  - Measured amounts of virus RNA inside and outside hospitals.
- Collected 3 sample types -
  - Air without segregating particles by size.
  - Air with particle size segregated.

- ○ Samples from surfaces.
- ICU and CCU samples had very low detectable viral RNA, by RTPCR.
  - ○ Higher levels of viral RNA detected in patient toilets.
  - ○ Elevated virus from area where protective clothing is doffed.
  - ○ Increased levels of virus RNA detected outside hospitals in areas of high pedestrian traffic.

Absence of Contamination of Personal Protective Equipment (PPE) by Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2)

Date – 03/26/2020

Link - https://doi.org/10.1017/ice.2020.91

- Examined contamination of health care workers providing care for 15 COVID-19 patients.
  - No patients were on ventilators or had aerosol generating procedures performed prior or during sampling.
- 90 samples tested negative for viral RNA using real time PCR.
  - Samples were obtained from PPE using pre moistened sterile swabs.
  - Tested goggles, fronts of N95 respirators, and front surfaces of shoes.
  - Gloves and gowns not tested since disposed of after each use.
- Limits of study included -
  - Entrapped virus could have been missed by swabbing PPE.
  - All patients were in isolation rooms.
  - No samples were collected from environment.

Air, Surface Environmental and Personal Protective Equipment Contamination by Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) From a Symptomatic Patient

Date – March 4, 2020

Link - https://doi.org/10.1001/jama.2020.3227

- Sampled 26 sites from 3 patient rooms in SARS-CoV-2 outbreak center.
  - Examined samples for viral RNA by real time PCR.
- Sampled 2 rooms while patient symptomatic after cleaning and all results were negative for virus.
  - Third patient room tested prior to cleaning was positive for viral RNA.
    - ○ Contaminated sites included toilet and room sites.
    - ○ Possible that patient shed greater amounts of virus.
    - ○ Post cleaning samples were negative indicating cleaning was sufficient to remove virus.
- Air samples were negative, but air exhaust outlets were positive for virus.
  - Suggests virus containing droplets deposited on room vents.

Effectiveness of Surgical and Cotton Masks in Blocking SARS-CoV-2: A Comparison Controlled Comparison in 4 Patients

Date – 04/06/2020

Link - https://doi.org/10.7326/M20-1342

- Utilized 4 COVID-19 patients to determine if surgical &/or cotton masks could prevent virus transmission by coughing.

- Patients coughed into sterile petri dishes containing viral transport media before donning a mask, while wearing a surgical mask, while wearing a cotton mask, and after removal of all masks.
- Masks were also swabbed on the outer surface and inner surfaces.
- Viral RNA was measured by real time PCR.
- Viral RNA detectable in viral media from all patients regardless of if a mask was worn.
  - Outer and inner surfaces of masks also had detectable levels of viral RNA.
- Indicates virus present in particles small enough to penetrate surgical masks.
  - Reported that 0.04 to 0.2 um sized particles can penetrate surgical masks.
    - SARS-CoV-2 estimated at 0.08 to 0.14 um in size.
  - Demonstrates importance of proper hand hygiene if mask surfaces are touched.

N95 Mask Decontamination Using Standard Hospital Sterilization Technologies

Date – 04/08/2020

Link - https://doi.org/10.1101/2020.04.05.20049346.

- N95 masks from different manufacturers (3M, Pleats Plus, Aearo Co.) were decontaminated using standard autoclaving, ethylene oxide, ionizing hydrogen peroxide, or vaporized hydrogen peroxide.
  - Each mask was contaminated at 3 different points with either vesicular stomatitis virus or SARS-CoV-2.
  - After treatment virus from masks was tested for viability in cell culture.
- Vaporized hydrogen peroxide was most effective method across all mask types allowing for 10 cycles of decontamination without affecting mask function.
- Ionized hydrogen peroxide was effective for 1 cycle, but after 5 cycles masks failed fit test.
- Autoclaving inactivated virus, but rigid masks (3M – model 1860) demonstrated loss of function after 1 cycle.

Disposable N95 Masks Pass Qualitative Fit-Test But Have Decreased Filtration Efficiency After Cobalt-60 Gamma Irradiation

Date – 03/30/2020

Link - https://doi.org/10.1101/2020.03.28.20043471

- Cobalt-60 gamma irradiation tested as a sterilization method for N95 masks.
  - Sets of 5 N95 masks (3M) were irradiated at 10kGy and 50kGy.
  - After treatment masks were fit tested using OSHA approved protocol.
- All masks, after irradiation passed fit testing, except for one that was improperly fitted.
  - Masks were tested using special air duct to measure particulate matter filtration.
  - All masks irradiated had comprised ability to filter particulate matter in the size range of 0.3um - 0.5um.
- Believed small particle filtration due to electrostatic charge and ionizing radiation discharges masks.
  - Demonstrates that fit testing alone is an insufficient test to judge sterilization processes of N95 masks.

Aerosol Emission and Super emission During Human Speech Increase with Voice Loudness

Date – March 27, 2020

Link - https://www.facs.org/covid-19/clinical-guidance/surgeon-protection

- Airborne particles released with vocalization.
    - Alternating between vocalization and nose breathing demonstrated the greatest release of particles during vocalization.
- Loudest voice generated the greatest number of particles.
    - Linear correlation of voice loudness and number of particles emitted.
    - Some study participants released more particles than other participants.
    - No difference observed in size of particles.
    - No trends observed in relation to gender, age, or BMI.
    - Study did not include elderly participants.
- Reading out loud, in English, generated particles
    - 10-fold increase in particle emission vs whispering.
    - No relationship to size of particles and loudness.
    - No correlation to language spoken and particle emission rate.
    - Temperature and humidity did not impact rate of particle emission.
- Some participants emitted more particles than other participants.
    - Called speech super emitters.
        - May super spread infectious airborne particles more readily.
        - Super spreaders documented in SARS and MERS outbreaks.
    - Particle emission highest for speech than for breathing.
    - Diameter of particles larger, on average, from speaking than those from breathing.

Rapid Evidence Summary on SARS-CoV-2 Survivorship and Disinfection, and Reusable PPE Protocol Using a Double-Hit Process.

Date: 04/06/2020.

Link - https://doi.org/10.1101/2020.04.02.20051409

- Extensive review of PPT decontamination for reuse.
    - Focused on UV irradiation, heat treatment, and chemical disinfection.
- Based on literature review recommended the following.
    - Gowns and surgical masks heated at 60oC for 90 minutes.
    - Face shield decontamination using UV irradiation.
        - Repeated treatment can lead to fogging and therefore disposal.
    - Goggles and eyewear should be immersed for a minimum of 10 minutes.
        - Either in 5000 mg/L solution.
        - Alternatively, immersion in $\geq$ 80% alcohol for 30 seconds.
        - After disinfection rinse in warm water to remove disinfectant.
        - Must be checked for fogging.
- Agree with CDC guidelines, in absence of manufacturer, N95 FFRs should not be re used > 5 times.
    - Masks and respirators should never be sprayed with alcohol.
        - Eliminates electrostatic charge of filter thereby reducing ability to filter.
    - Never re use visibly soiled PPE.
- Authors recommend the following steps for PPE reuse -
    - Inspect and sort PPE for damage or soiling.

- Store intact unsoiled PPE for at least 4 days in designated area.
  - Recommend 20oC with 40-50% relative humidity.
- After storage, N95 masks and plastic face shields treated using UV chamber at dose 2000mJ/cm2.
  - Outer side and face fitting side must be treated.
- After storage, gowns and surgical masks heat treated at 60oC for 90 minutes, preferably at 40-50% humidity.
- After storage, eyewear disinfected by soaking for indicated times.
- Post disinfection all PPE re-inspected and damaged items discarded.
- Fit test all PPE to insure proper fit.

Rational Use of Personal Protective Equipment for Coronavirus Disease 2019 (COVID-19)

Date: 02/27/2020

Link: https://apps.who.int/iris/bitstream/handle/10665/331215/WHO-2019-nCov-IPCPPE_use-2020.1-eng.pdf

- Guidelines for use of personal protective equipment in different settings.
- Includes tables covering the following areas -
  - Inpatient/Outpatient facilities
  - Community at large
  - Points of entry
    - Screening areas
    - Temporary isolation areas
    - Ambulance staff

Transmission of SARS-CoV-2 in Viral shedding Observed at The University of Nebraska Medical Center

Date: 03/26/2020

Link - https://doi.org/10.1101/2020.03.23.20039446

- Numerous samples obtained from multiple surfaces and air samples from patient isolation rooms and hallways.
- Samples were analyzed for viral RNA using rtPCR.
  - 76.5% personal items (+) for viral RNA (IPads, reading glasses, personal computers).
    - 83.3% cell phones (+)
    - 64.7% TV remotes (+)
    - 81% room toilets (+)
  - 80% room surfaces (+).
    - 75% bedside tables and bed rails (+)
    - 81.8% window ledges (+)
  - Although viral RNA was present on most objects the genomic copy number was very low: <1 copy/ul for all items, except air handling grates (1.5-2.0 copies/uL)
  - Room air samples (63.2%) and hallway air samples (66.7%) were positive.
    - Positive air samples cultured in cell line to detect viable virus
      - All cultures were negative for cytopathic cell effects
        - Negative by immunofluorescence for cells positive for virus
        - Negative by Western blotting for viral proteins
- Data suggests infected patients generate viral aerosols even in the absence of cough.
- All air samplers worn by sampling personnel were (+) for viral RNA in spite of patients not coughing while present.

- Small to non-significant relationship between patient body temperature *vs* (+) environmental samples.
- Observed significant environmental contamination regardless of symptoms or degree of illness.

COVID 19: Considerations for Optimum Surgeon Protection

Date: 03/27/2020

Link - https://www.facs.org/covid-19/clinical-guidance/surgeon-protection

- Guidelines for use of personal protective equipment before, during, and after operations.
- Includes a table outlining use of PPE for different patient populations.

Hydrogen Peroxide Vapor sterilization of N95 respirators for reuse

Date: 03/27/2020

Link - https://www.medrxiv.org/content/10.1101/2020.03.24.20041087v1

- Authors evaluated viricidal activity of Hydrogen Peroxide vapor using a BQ-50 system.
    - Inoculated 3 different aerosolized bacteriophages onto 3M 1870 N95 respirators.
    - Concentrations used approximated viral titers necessary for 50% tissue culture infectious dose of SARS-CoV-2.
- Viricidal activity measures using standard plaque assay prior and post sterilization.
    - 1 cycle of HP vapor completely eradicated phage from masks.
    - After 5 cycles of HP vapor, respirators did not demonstrate any deformities.
- Biquell HP vapor demonstrated high viricidal activity for N95 respirators.

GUIDELINES FOR RECOVERED CASES

Disposition of Hospitalized Patients with COVID-19

Date: 03/23/2020

Link- https://www.cdc.gov/coronavirus/2019-ncov/hcp/disposition-hospitalized-patients.html

- Provides guidance on when COVID-19 patients can leave quarantine
- Guidance for test and no-test approaches

EPIDEMIOLOGY

Clinical characteristics of asymptomatic and symptomatic patients with mild COVID-19

Date: 05/01/2020

Link: https://www.sciencedirect.com/science/article/pii/S1198743X20302688?via%3Dihub

- The purpose of this article is to determine prevalence of asymptomatic cases and the clinical characteristics of asymptomatic and symptomatic cases.

- 213 patients were diagnosed with COVID-19, and 19.2% were asymptomatic to admission.

- The most common symptoms were cough (40.1%), hyposmia (39.5%), and sputum (39.5%). Fever was only observed in 11.6% of cases.

- One-fifth of patients were asymptomatic from exposure to admission.

Epidemiological characteristics and incubation period of 7,015 confirmed cases with Coronavirus Disease 2019 outside Hubei Province in China

Date: 04/27/2020

Link: https://academic.oup.com/jid/advance-article/doi/10.1093/infdis/jiaa211/5825699

- This article examined epidemiological characteristics of cases of COVID-19 outside of Hubei Province in China to evaluate the effect of traffic restrictions.

- 7,015 cases were confirmed between January 19 and February 8, 2020.

- Median incubation period of the disease in these cases was 5 days.

- The greatest number of cases were seen in young to middle-aged adults.

Presenting Characteristics, Comorbidities, and Outcomes Among 5700 Patients Hospitalized with COVID-19 in the New York City Area

Date: 04/22/2020

Link: https://jamanetwork.com/journals/jama/fullarticle/2765184

- 5700 patients from 12 hospitals in New York City, Long Island, and Westchester County, New York were included in the study.

- The median age of patients was 63 years (IQR: 52 – 75 years) and 39.7% were female

- Comorbidities of hospitalized patients included hypertension (56.6% of patients), obesity (41.7% of patients), and diabetes (33.8%)

- 2.2% of patients who were discharged were readmitted later in the study period. The median time for readmission was 3 days (IQR: 1.0 - 4.5 days)

Epidemiology and Clinical Features of COVID-19: A Review of Current Literature

Date: 04/20/2020

Link: https://www.sciencedirect.com/science/article/pii/S1386653220300998?via%3Dihub

- This article provides an overview of the COVID-19 virus, transmission, clinical features of the virus, symptoms, laboratory findings, X-ray and other image findings, complications of the virus, disease severity, and prognosis

- The article notes that COVID-19 is rapidly changing, but summarizes key features of the virus at the time of the article

Epidemiological and Clinical Features of 125 Hospitalized Patients with COVID-19 in Fuyang, Anhui, China

Date: 04/11/2020

Link: https://www.sciencedirect.com/science/article/pii/S1201971220302034?via%3Dihub

- 125 patients were confirmed to have COVID-19 with real-time RT-PCR between January 20 and February 9, 2020

- Mean age of patients was 38.76 years (standard deviation of 13.799 years), 56.8% were male

- The most common symptom was fever (92.8%), followed by cough (81.6%) and shortness of breath (45.6%)

- Median length of stay was 14.8 days (standard deviation of 4.16 days)

- Old age, chronic underlying conditions, and smoking history may be a risk factor for worse conditions

Spread of SARS-CoV-2 in the Icelandic Population

Date: 04/14/2020

Link: https://www.nejm.org/doi/full/10.1056/NEJMoa2006100?query=featured_coronavirus

- Icelandic health officials conducted robust testing of the Icelandic population after the first case of COVID-19 was detected in the population.

- High risk patients, those who were symptomatic, had recently traveled to a high-risk country, or had contact with an infected person, were tested for COVID-19. Population screening then followed by random invitation and open invitation.

- 13.3% of the high-risk patients tested positive, and 0.8% and 0.6% of those patients from random invitation and open invitation tested positive.

- Children under 10 years of age and females had lower incidence of COVID-19 than adolescents or adults and males.

Baseline Characteristics and Outcomes of 1591 Patients Infected with SARS-CoV-2 Admitted to ICUs of the Lombardy Region, Italy

Date: 04/06/2020

Link: https://jamanetwork.com/journals/jama/fullarticle/2764365?guestAccessKey=b31f5704-e073-4df7-bc2f-165927e428e8&utm_source=silverchair&utm_medium=email&utm_campaign=article_alert-jama&utm_content=olf&utm_term=040620

- Characterizes patients admitted to ICU in Lombardy, Italy region with positive COVID-19 test.

- Median age of admitted patients was 63 (IQR: 56-70), 82% were male, and ICU mortality was 26%.

- Provides comorbidities, respiratory data, other clinical characteristics, and outcomes data of patients.

Epidemiology of Covid-19 in a Long-Term Care Facility in King County, Washington

Date: 03/27/2020

Link: https://www.nejm.org/doi/full/10.1056/NEJMoa2005412

- Includes data linking subsequent cases of COVID-19 from initial cases in a long-term care facility in Washington state.

- Provides demographics, symptoms, and statistics on epidemiologically linked cases from the facility.

- Outcomes: Between the first case on February 28 and March 18, there were 167 cases of COVID-19, of which 101 were residents of the facility, 50 were health care workers, and 16 were visitors; case fatality

rate among residents 33.7%; hospitalization rates were 54.5% for residents, 50.0% for visitors, and 6.0% for health care workers.

Interventions to mitigate early spread of SARS-CoV-2 in Singapore: a modelling study

Date: 3/23/3030

Link: https://www.sciencedirect.com/science/article/pii/S1473309920301626?via%3Dihub

- Used an existing model for influenza to estimate the number of cases in Singapore using four containment strategies:
  - Isolation of ill and quarantine of contacts
  - Isolation of ill, quarantine of contacts, and school closings
  - Isolation of ill, quarantine of contacts, and work closures
  - A combined method including all the above
- They ran the model for separate infectivity scenarios (basic reproduction number [R0] of 1.5, 2.0, or 2.5) using a 7.5% asymptomatic rate.
- The combined method was best at reducing the number of infections.
- Workplace closures should be prioritized over school closings if necessary, since symptomatic children have higher withdrawal rates than symptomatic employees.

Clinical Characteristics, Laboratory Findings, Radiographic Signs and Outcomes of 52,251 Patients with Confirmed COVID-19 Infection: A Systematic Review and Meta-analysis

Date: 03/16/2020

Link: https://www.preprints.org/manuscript/202003.0252/v1

- Includes data from 20 studies of patients from China
- Outcomes: Hospitalization 85.4% of cases (range 68-94%); ICU/Critical condition 20.6% (rage 6.7-48%); Death 5.6% (range 2.5-12.5%)

Report on the Epidemiological Features of Coronavirus Disease 2019 (COVID-19) Outbreak in the Republic of Korea from January 19 to March 2, 2020

Date: 03/16/2020

Link: https://www.jkms.org/Synapse/Data/PDFData/0063JKMS/jkms-35-e112.pdf

- Includes data on 4,212 cases in Korea (0.082 confirmed cases per 1,000 people; range 0.002 to 1.26 confirmed cases per 1,000 people)
- In contrast to other reports, nationwide more women (62%) then men (38%) with confirmed cases
- In Korea, two predominant age peaks of confirmed cases: 20-29 year olds (largest group) and 50-59 year olds
- Mortality: 22 out of 4,212 confirmed cases died (0.5%); Death rate ranged from 0.2% in those 30-39 and 40-49, increased slightly in those 50-59 (0.6%), greater increase at 60-69 (1.1%), and was largest in the oldest age groups: 3.1% in those 70-79 years and 3.7% in those ≥80 years

Analysis of factors associated with disease outcomes in hospitalized patients with 2019 novel coronavirus disease

Date: 02/28/2020

Link:https://journals.lww.com/cmj/Abstract/publishahead/Analysis_of_factors_associated_with_disease.99363.aspx

- 78 patients with confirmed COVID-19 induced pneumonia in China; 67 (85.9% improved/stabilized) and 11 (14.1%) progressed
- Older age, history of smoking, higher maximum body temperature at admission, presence of respiratory failure and faster respiratory rate all associated with being in the progression group
- Lower albumin and higher C-reactive protein associated with being in the progression group (with lower lymphocyte levels and higher neutrophil levels also associated with higher risk of being in the progression group)

Clinical Progression of patients with COVID-19 in Shanghai, China

Date: 03/19/2020

Link: https://www.sciencedirect.com/science/article/abs/pii/S0163445320301195

- 249 confirmed cases from Shanghai Public Health Clinical Center (median age 51, 50.6% male)
- 22 (8.8%) patients admitted to ICU
- Older age increased risk of ICU admission whereas higher CD4 T cell counts decreased risk of ICU admission; suggestive evidence that higher lymphocyte count and higher lactate dehydrogenase level also increased risk of ICU admission
- Median time from symptom initiation to viral clearance (2 repeat PCR negative tests) was 11 days; shorter in asymptomatic patients (median time to viral clearance 2 days after admission) and longer in ICU admitted patients (median not reported; some patients still shedding virus at time of study end)

Estimating unobserved SARS-CoV-2 infections in the United States

Date: 03/22/2020

Link: https://www.medrxiv.org/content/10.1101/2020.03.15.20036582v1

- As of March 12th, there are likely tens of thousands of cases in the US, and quite possibly more than 100,000
- Number of deaths will increase despite mitigation efforts due to survival time being weeks from time of infection
- The US is well past feasible containment periods

Incubation Period and Other Epidemiological Characteristics of 2019 Novel Coronavirus Infections with Right Truncation: A Statistical Analysis of Publicly Available Case Data

Date: 02/17/2020

Link: https://www.mdpi.com/2077-0383/9/2/538

- Incubation period has a mean of 5 days
- Number of days from onset of symptoms to death has median 13 days

Clinical course and outcomes of critically ill patients with SARS-CoV-2 pneumonia in Wuhan, China: a single-centered retrospective, observational study

Date: 02/21/2020

Link: https://doi.org/10.1016/S2213-2600(20)30079-5

- Geographic location/Country-Wuhan/China
- Lymphopenia hallmark of severe COVID-19
- Observed 80% of critically ill study participants
- Speculate drop in lymphocytes due to apoptosis or necrosis of lymphocytes

Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China

Date: 01/24/2020

Link: https://doi.org/10.1016/So140-6736(20)30183-5

- Geographic location/Country - Wuhan/China
- Patients on admission had leukopenia and lymphopenia
- Patients had elevated cytokines (IL1B, IFNg, IP10, MCP-1)
- Most severe cases of Covid-19 (ICU admission) characterized by elevated GCSF, IP10, MCP-1, MIP1a, TNFa

BIOINFORMATICS/PHYLOGENETICS

Transmission dynamics and evolutionary history of 2019-nCoV

Date: 04/08/2020

Link: https://onlinelibrary.wiley.com/doi/epdf/10.1002/jmv.25701

- The final dataset ("dataset_32") included 32 genomes of 2019-nCoV from China (n = 25), Thailand (n = 2), and USA (n = 5) with sampling dates between 24 December 2019 and 23 January 2020.
- pairwise homoplasy index (PHI) test did not find statistically significant evidence for recombination (P = 1.0).
- Likelihood-mapping analysis of "dataset_14" revealed that 100% of the quartets were distributed in the center of the triangle, indicating a strong star-like topology signal reflecting a novel virus, which may be due to exponential epidemic spread.
- Basis of the likelihood-mapping analysis, the increasing tree-like signals over time may be indicative of increasing genetic diversity of 2019-nCoV in human hosts.
- Beginning of the virus outbreak suggests that 2019-nCoV initially exhibited low genetic divergence, with recent and rapid human-to- human transmission
- Authors predict that one or more mutations may be selected and sustained during the 2019-nCoV outbreak as the virus adapts to human hosts and possibly reduces its virulence, as reported in the previous study.

The role of phylogenetic analysis in clarifying the infection source of a COVID-19 patient

Date: 04/08/2020

Link: https://www.sciencedirect.com/science/article/pii/S0163445320301596?via%3Dihub
- To clearly clarify the infection source in order to initiate an efficient and successful contact tracing.
- 66-year-old Taiwanese woman travelled to Dubai & Egypt and participated in a Nile cruise boat. Returned to Taiwan and showed symptoms.
- Possible she contacted the infection while in Taiwan or while she was travelling.

- Phylogenetic analysis and whole genome sequencing of SARS-CoV-2 isolate (NTU03) from her throat swab collected show belongs to clade A2a, in which all other of the reported patients were currently either from Europe or travelled to Europe recently and in contrast, none of the viruses isolated from Taiwan were assigned to clade A2a or A2.

Phylogenetic network analysis of SARS-CoV-2 genomes

Date- 03/30/2020

Link: https://www.pnas.org/content/early/2020/04/07/2004999117

- Phylogenetic analysis of largely complete 160 SARS-Cov-2 genomes analyzed provides 3 clusters, node A, B, C.
- Closely related bat coronavirus, with 96.2% sequence similarity to the human virus was placed in root cluster designated by A.
- Two sub-clusters of A by synonymous mutation T29095C, T-allele subcluster, four Chinese individuals (from the southern coastal Chinese province of Guangdong, the C-allele subcluster sports relatively long mutational branches and includes five individuals from Wuhan, two of which are represented in the ancestral node, and eight other East Asians from China and adjacent countries
- Node B is derived from A by two mutations: the synonymous mutation T8782C and the nonsynonymous mutation C28144T changing a leucine to a serine.
- B type is monopolized by East Asians.
- Type C differs from its parent type B by the nonsynonymous mutation G26144T which changes a glycine to a valine. Mainly found in European type with representatives in France, Italy, Sweden, and England, and in California and Brazil. It is absent in the mainland Chinese sample, but evident in Singapore and also found in Hong Kong, Taiwan, and South Korea.
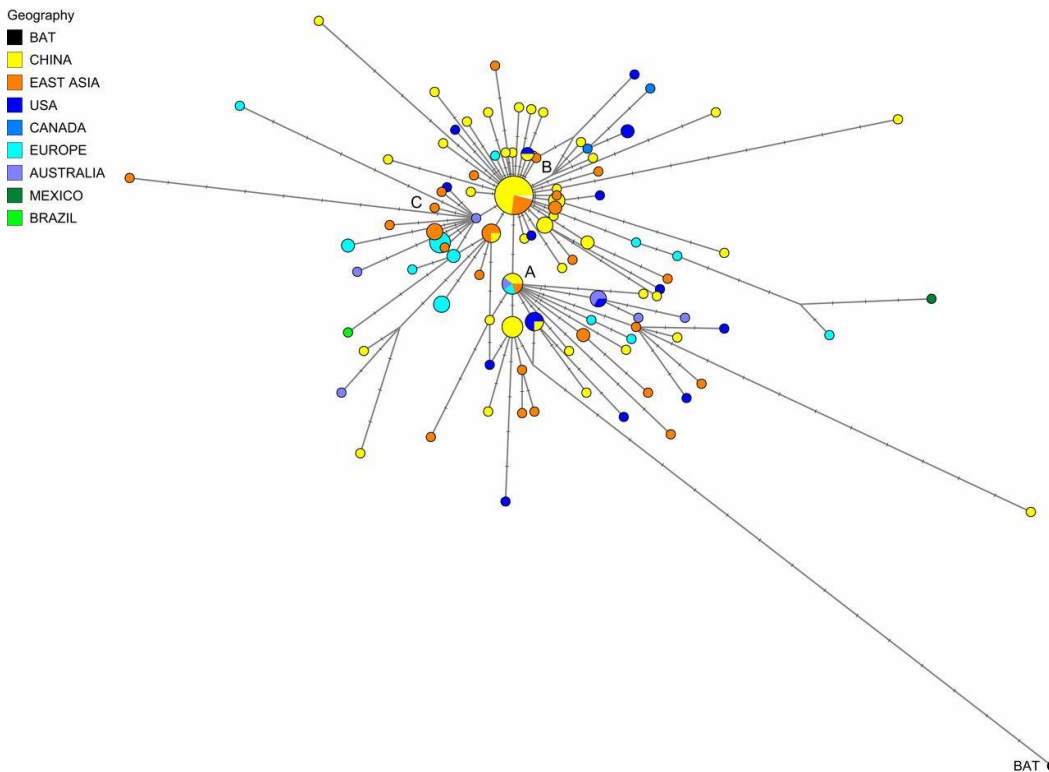
Computational inference of selection underlying the evolution of the novel coronavirus, SARS-CoV-2

Date: 04/01/2020

Link:https://jvi.asm.org/content/jvi/early/2020/03/27/JVI.00411-20.full.pdf

- Based on the alignment of forty-four SARS-CoV-2 genomes and the BatCoV RaTG13 sequence, 147 amino acid replacements, unevenly distributed along the genome, were found to separate SARS-CoV-2 from its closest relative. Forty-one amino acid changes are polymorphic in the SARS127 CoV-2 population.
- The M protein (M ORF) interacts with other structural viral proteins and plays an important role in virion morphogenesis. Importantly, the M protein is a dominant immunogen for both the humoral and the cellular immune responses.
- Based on estimates on codon-wise posterior probabilities for each selection coefficient, very strong evidence (defined as a posterior probability > 0.80 of $\gamma \geq 1$) of positive selection was detected for seven sites, six in the S1 region of the spike protein and one in N.
- The N protein is the most abundant protein in coronavirus-infected cells. Its primary function is to package the viral genome into a ribonucleoprotein complex.

Structural modeling of 2019-novel coronavirus (nCoV) spike protein reveals a proteolytically sensitive activation loop as a distinguishing feature compared to SARS-CoV and related SARS like coronaviruses

Date: 02/10/2020

Link:https://www.biorxiv.org/content/10.1101/2020.02.10.942185v1.full.pdf

- The coronavirus spike protein (S), a glycoprotein composed of S1 & S2 domains, is the primary determinant of viral tropism and is responsible for receptor binding and membrane fusion.
- This study identifies a small structural loop at the S1/S2 interface that contains a short insert containing two arginine residues for 2019-nCoV S. These features are missing from all other SARS-CoV-related viruses.
- Protein sequence alignment between Wuhan-Hu-1 strain of the novel coronavirus with that of the closely related human SARSCoV S strain Tor2 sequence was 76%.
- 2019-nCoV genomic sequences revealed that it clustered closely with sequences originating from SARS-like sequences from bats, within lineage B of the Betacoronavirus genus.

Full-genome evolutionary analysis of the novel corona virus (2019-nCoV) rejects the hypothesis of emergence as a result of a recent recombination event

Date: 01/26/2020

Link: https://www.biorxiv.org/content/10.1101/2020.01.26.920249v1.full.pdf

- Viral genetic sequence comparison reveals the most closely related sequence to the 2019-nCoV throughout the genome was with BatCoV RaTG13. The genetic similarity between the 2019-nCoV and RaTG13 was 96.3%.
- Discordant phylogenetic relationships between 2019-nCoV and RaTG13 clade with their closest partners, the Bat_SARS-like coronavirus sequences rejects the hypothesis of emergence as a result of a recent recombination event.
- It is divergent from the SARS-CoV and MERS-CoV that caused epidemics in the past.

Genomic characterization and epidemiology of 2019 novel coronavirus: implications for virus origins and receptor binding

Date: 01/19/2020

Link: https://www.thelancet.com/action/showPdf?pii=S0140-6736%2820%2930251-8

- 2019-nCov was closely related (with 88% identity) to two bat-derived (SARS)-like coronaviruses (bat-SL-CoVZC45 and bat-SL-CoVZXC21) but were more distant from SARS-CoV (about 79%) and MERS-CoV (about 50%).
- 2019-nCov had a similar receptor-binding domain in structure to that of SARS-CoV with some amino-acid variations at key residues.
- Bats might be the original host of this virus; animals sold at Wuhan seafood markets might be intermediate host.

Evidence of the Recombinant Origin and Ongoing Mutations in Severe Acute Respiratory Syndrome 2 (SARS-COV-2)

Date: 03/19/2020

Link: https://www.biorxiv.org/content/10.1101/2020.03.16.993816v2

- Researchers used phylogenetic classification to identify the source of SARS-CoV-2 and found it likely originated from a recombination event from bat and pangolin coronavirus
- SARS-CoV-2 is actively mutating in human populations to increase adaptability

VIRAL PROPERTIES

NEW: Growth factor receptor signaling inhibition prevents SARS-CoV-2 replication

Date: 05/14/2020

Link: https://doi.org/10.1101/2020.05.14.095661

- Measured differences in cell signaling proteins of permissive human colon epithelial cell line infected with SARS-CoV-2.
  - Analyzed 7150 cellular and viral proteins for increases or decreases in phosphorylation.
    - Observed requirement of viral nucleocapsid protein phosphorylation critical for binding to viral RNA.
  - Majority of proteins were phosphoryated on serine residues.
- Three groups of proteins impacted by virus infection including those critical for signaling, cell cycle, and splicing.
- Since growth factor receptor signaling was observed to be important, tested GFR inhibitors on virus replication in human colon cell line.
  - PI3 kinase inhibitors interfered with viral replication as demonstrated by cytopathic effect and synthesis of viral RNA.
  - Virus replication also reduced using MAP2K2 and RAF inhibitors.
  - Previous reports indicate GFR signaling critical for SARS-CoV-1 replication.

NEW: <mark>Unveiling diffusion pattern and structural impact of the most invasive SARS-CoV-2 spike mutation</mark>

Date: 05/15/2020

Link: https://doi.org/10.1101/2020.14.095620

- Determined effects of aspartic acid replacement with glycine at position 614 of the SARS-CoV-2 spike protein in a natural mutant.
  - Detected increased prevalence of mutant not due to genetic drift or virus migration across various countries.
  - Observed only 1 country demonstrated a decrease in prevalence of spike mutant and also Reporting lowest fatality rates, Iceland.
- Determined that enhanced transmission not due to increased pathogenesis of the mutant.
- Using molecular dynamic simulations analyzed examined selective advantage of mutation.
  - Measured an increase in mobility of the furin cleavage site.
  - Allows easier access for cleavage.
  - Increases rate of spike mediated membrane fusion and virus entry into host cell.
- The observed natural mutation creates a spike protein facilitates interaction with the ACE2 receptor and viral entry via membrane fusion.

NEW: <mark>Virological assessment of hospitalized patients with COVID-2019</mark>

Date: 04/01/2020

Link: https://doi.org/10.1038/s41586-020-2196-x

- Studied 9 mildly ill patients with acquired infections from a known index case, all treated at the same hospital.
  - All samples tested for viral RNA from a panel of respiratory viruses and were only positive for SARS-CoV-2.
    - Samples included oro/nasopharyngeal swabs, sputum, urine and stool specimens.
  - Culturable virus only isolated from swab and sputum samples from first week of symptoms.
- Measured viral replication, in vivo, by identification of subgenomic mRNAs in clinical specimens.
  - Subgenomic mRNA only found in infected cells as evidence of viral replication.
  - Highest levels were consistently found in throat samples during first 5 days of symptoms.
- Viral RNA load consistently higher in initial samples versus later samples.
  - Observed declining levels of virus in throat samples from first specimens.
    - Levels observed to decline slower in sputums.
    - Virus loads in stool samples paralleled observations in sputum samples.
- Throat swabs observed to provide sufficient sensitivity for virus detection at early stage of infection.
  - Virus peak reached earlier, 5 days post symptom onset, and 1000 X higher than that reported for SARS-CoV-1.
  - Isolation of culturable virus from throat swabs more common than with SARS-CoV-1.
  - Most participants were beyond peak shedding when first tested which suggests more efficient transmission of virus early in disease when symptoms are still mild.

High frequency of SARS-CoV-2 RNAemia and association with severe disease

Date: 05/01/2020

Link: https://doi.org/10.1101/2020.04.26.20080101

- Examined link between detectable SARS-CoV-2 RNA in nasal swabs vs whole blood plasma samples.
  - Collected EDTA whole blood samples from patients with SARS-CoV-2 positive nasal swabs.
    - Blood samples were collected within 72 hours of nasal sample.
  - Tested blood sample for viral RNA using RT-PCR targeting "S" gene.
    - All positive blood samples were confirmed before being reported as positive.
- Study included 85 patients with paired nasal and blood samples.
  - Samples with viral RNA were from significantly older cases.
  - Viral RNA detectable in 32.9% of study participants.
    - Determined that +RNAemia patients were more frequently transferred to ICU.
      - More frequently needed mechanical ventilation.
    - No association in viral loads between nasal samples and blood samples.
- In a group of 85 patients with nasal samples positive for virus RNA could also detect viral RNA from blood samples.
  - Unsure if viral RNA represented infectious virus since viral cultures were not performed.

Viral load of SARS-CoV-2 in clinical samples

Date: 02/24/2020

Link: https://doi.org/10.1016/S1473-3099(20)30113-4

- Analyzed samples from 82 infected individuals by throat swab, sputum, urine, or stool specimens.
  - Examined samples using RT-PCR.
- Viral RNA levels peaked in throat and sputum samples 5 – 6 days post onset of symptoms.
  - Earlier than peak observed with SARS which was 10 post symptoms.
  - Sputum samples exhibited higher loads of viral RNA vs throat samples.
- Virus load in early post symptom onset was high ($>1\text{x}10^6$ copies/ml)
  - Sputum samples could have very high viral loads ($1.34 \text{ x } 10^{11}$ copies/ml).

Potential pre-symptomatic transmission of SARS-CoV-2

Date: 05/2020

Link: https://doi.org/10.3201/eid2605.200198

- Examined 2 family clusters of individuals infected with SARS-CoV-2 from contact with an asymptomatic individual from Wuhan.
  - Attended dinner with 2 individuals and became symptomatic shortly after return to Wuhan.
- 4 days after dinner one attendee became symptomatic.
  - SARS-CoV-2 diagnosis 9 days later.
  - Wife became positive for virus but remained asymptomatic.
  - Additional roommate remained negative for virus.
- 6 days post dinner second attendee became symptomatic
  - Wife and son both tested positive for SARS-CoV-2.
    - Both remained asymptomatic.

How fast does SARS-CoV-2 virus really mutate in heterogeneous populations

Date: 04/27/2020

Link: https://doi.org/10.1101/2020.04.23.20076075

- Genomic mutation rate for SARS-CoV-2 estimated at 2 to 3 mutations/month.
    - European isolates have 3X more mutations in the ORF1b gene than isolates from North America.
    - Virus isolates from Asia have undergone more mutations in the ORF1a gene than isolates from North America.
    - Both genes encode proteins critical in viral replication efficiency.
- Nucleocapsid gene demonstrates more mutations than predicted in models.
    - Potentially problematic since often used as target in PCR studies.
- Largest differences in ORF1a gene exists between isolates from Europe and North America.
    - Largest differences in ORF1b gene occur between isolates from Asia vs North America.

SARS-CoV-2 productively infects human gut enterocytes

Date: 05/01/2020

Link: https://doi.org/10.1126/science.abc1669

- SARS- CoV-2 replicates in tissue cultures of human airway epithelium.
    - Observed viral nucleocapsid staining by immunofluorescence in ciliated vs goblet cells.
- Human small intestinal organoids could be infected with SARS-CoV-2.
    - Examination of mRNA measured upregulation of ACE2 induced by SARS-CoV-2 infection.
- SARS-CoV-2 infection increased mRNA of immune modulating proteins.
    - IP10 (CXCL-10) known to induce chemotaxis, apoptosis, and cell growth.
    - ISG15 (Interferon stimulated gene 15), a ubiquitin like protein with anti-viral activity.

SARS-CoV-2 viral load in upper respiratory of infected patients

Date: 03/19/2020

Link: https://doi.org/10.1056/NEJMc2001737

- Monitored SARS-CoV-2 viral loads from upper respiratory
    - Collected 72 nasal and throat swabs.
    - Viral loads determined using reverse transcriptase PCR.
- Higher viral loads identified soon after symptom onset in 17 symptomatic patients.
    - Highest load from was from nasal samples.
    - Pattern of virus shedding similar to that seen with influenza, not SARS-CoV
- Virus transmission occurs early in infection.
    - Modest levels of viral RNA detectable in nasal samples from patients with few or no symptoms.

SARS-CoV-2 detection in patients with influenza-like illness

Date: 04/07/2020

Link: https://doi.org/10.1038/s41564-020-0713-1.

- Retrospectively examined 640 throat swab samples from patients from 2 different hospitals.
  - Diagnosed with influenza like illness, sudden onset of fever, cough, or sore throat.
  - Swabs collected over 16-week period between October 6, 2019 and January 21, 2020.
  - Ages of patients ranged from 9 months to 87 years of age.
- Detected SARS-CoV-2 viral RNA from 9 patient specimens.
  - Collected in January 2020.
  - All of the patients ranged between ages of 35 – 71.
- SARS-CoV-2 was present in January.
  - Earliest sample was from January 4.
  - 9 positive patients were from six different districts in Wuhan metro area.
  - Indicates community spread had begun by early January.

Aerodynamic characteristics and RNA concentration of SARS-CoV-2 aerosol in Wuhan hospitals during COVID-19 outbreak

Date: 03/10/2020

Link: https://doi.org/10.1101/2020.03.08.982637

- Examined airborne SARS-CoV-2 at different sites in 2 separate hospitals in Wuhan, China.
  - Measured amounts of virus RNA inside and outside hospitals.
- Collected 3 sample types -
  - Air without segregating particles by size.
  - Air with particle size segregated.
  - Samples from surfaces.
- ICU and CCU samples had very low detectable viral RNA, by RTPCR.
  - Higher levels of viral RNA detected in patient toilets.
  - Elevated virus from area where protective clothing is doffed.
  - Increased levels of virus RNA detected outside hospitals in areas of high pedestrian traffic.

Attenuated SARS-CoV-19 variants with deletions at S1/S2 junctions

Date: 04/17/2020

Link: https://doi.org/10.1101/2020.03.08.982637

- Virus purified from clinical specimens using plaque assay.
  - Observed large and small plaques.
- Viral genomes sequenced by rtPCR.
  - Large plaques exhibited sequences homologous to wild type SARS-CoV-2.
  - Small plaques demonstrated an in-frame deletion located in the spike encoding region of the genome.
  - Unable to directly identify any deletion mutants in clinical specimens.
- Hamsters were infected with each type of virus.
  - Deletion mutants produced a less pathogenic form of disease.

- No weight loss.
- Less pathology in lung histology.
- Much lower viral titers compared with wild type.
- Although deletion mutants undetectable in a few clinical specimens examined, results suggest changes to virus may help explain variation of disease observed across populations.

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

Date – 03/28/2020

Link: https://doi.org/10.1093/cid/ciaa344

- Examined dynamic of IgM and IgG antibody to SARS-CoV-2 in serial blood samples from 173 COVID-19 patients.
- Reported increasing titer of antibody did not always correlate with viral RNA clearance.
- High titer of antibody could serve as surrogate for worse prognosis.

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

Date– 03/23/2020

Link: https://doi.org/10.1016/S1473-3099(20)30196-1

- 23 patients, 13 males and 10 females, were examined for antibody and viral RNA presence.
  - Collected 174 respiratory samples for detection of viral RNA.
  - Virus load highest in posterior oropharyngeal saliva samples during 1st week of symptoms.
  - No association between disease severity and prolonged detection of viral RNA.
- Detected increase in antibody to viral nucleocapsid (N) and receptor binding domain (RBD) of viral spike protein in most patients 10 days or later after symptom onset.
  - Antibody to RBD came up earlier than antibody to N in most patients.
  - Viral RNA still detectable even when antibody was detectable.
- Elevated viral load detected in COVID-19 patients shortly after onset of symptoms.
  - Older patients exhibited higher peak viral antibody titers.
  - Elevated initial viral load indicates ease of virus transmission when symptoms are mildest.
  - Virus could be potentially shed at low levels even in spite of clinical recovery.

Identifying SARS-CoV-2 related coronaviruses in Malayan pangolins

Date – 03/26/2020

Link: https://doi.org/10.1038/s41586-020-2169-0

- Tissue specimens from 18 Malayan pangolins, from anti-smuggling program were tested for coronavirus.
  - Identified virus in 6/18 animals.
- Compared genomic sequence to SARS-CoV-2 and all were organized similarly to SARS-CoV-2.
  - Genomic sequence of 1 isolate exhibited 99.9% homology with SARS-CoV-2
  - Samples from an additional 12 animals were tested and 3 identified as positive for coronavirus.
- Bat coronavirus (RaTg12) demonstrates high degree of genetic homology with SARS-CoV-2

- ○ 97.4% genetic homology in the receptor binding domain with Guangdong pangolin coronavirus.
- ○ Consistent with report of ACE2 genetic sequence being slightly higher between humans and pangolins rather than bats.
- ○ But, to date, no report of pangolin coronaviruses containing a furin cleavage site.

Detection of SARS-CoV-2 in different types of clinical specimens

Date – 03/11/2020

Link: https://doi.org/10.1001./jama.2020.378

- Examined clinical samples for viral RNA by rtPCR.
- Total of 1070 samples from 205 patients.
  - ○ BALs 95% positive, sputums 72% positive, nasal swabs 63% positive, brush biopsies 46% positive, pharyngeal swabs 32% positive, feces 29% positive, blood 1% positive, urine positive
- Viral RNA in stool sample
- Positive blood samples may demonstrate that some infections could become systemic.

Antibodies to coronaviruses are higher in older compared with younger adults and binding antibodies are more sensitive than neutralizing antibodies in identifying coronavirus-associated illness

Date of article – February 2020

Link: https://doi.org/10.1002/jmv.25

- Antibody titers in two groups of patients, (>60; 99 patients or 21-40; 101 participants) to 4 different coronaviruses was examined over a 2-year period.
- Preexisting antibodies to coronaviruses were not found to protect from infection with subsequent coronavirus infections.
  - ○ Could affect amount of virus shed.
- Neutralizing antibodies recognized viral spike protein while non neutralizing antibodies bound other viral proteins such as the nucleocapsid.
- Patients with detectable antibody from earlier coronavirus infections demonstrated a greater increase in titer of non-neutralizing antibodies than neutralizing antibodies.
  - ○ More frequently observed in younger vs older patients.

Neutralizing antibody responses to SARS-CoV-2 in a COVID-19 recovered patient cohort and their implications.

Date: 03/30/2020

Link: https://doi.org/10.1101/2020.03.30.20047365

- Cohort of 175 COVID-19 patients that had recovered and been discharged.
  - ○ Characterized by mild symptoms, none had been in ICU.
- 5 patient samples collected at discharge were used for virus neutralization assay.
  - ○ Each sample exhibited high titers of neutralizing antibody vs SARS-CoV-2, in vitro.
  - ○ Did not cross neutralize, in vitro, SARS-CoV infection.
- Antibody titer lowest before day 10, after disease onset, but peaked between days 10 and 14.
  - ○ Recognized receptor binding domain and S2 subunit of virus spike.

Approximately 30% of recovered patients had undetectable levels of neutralizing antibody.
- ▪ Measurement of samples collected later lacked detectable levels of neutralizing antibody.
- ▪ Some patients able to recover without making neutralizing antibody.
- ▪ Neutralizing antibodies higher in older patients.
  - Blood lymphocyte counts negatively associated with antibody titers.

The emergence of a novel coronavirus (SARS-CoV-2), their biology and therapeutic options

Date: 03/11/2020

Link: https://doi.org/10.1128/JCM.00187-20

- Coronaviruses contain a lipid envelope.
  - ○ Genome consists of (+) single stranded RNA.
- Consist of 4 genera, alpha, beta, gamma, and delta.
- Only alpha and beta known to infect animals and humans.
  - ○ SARS-CoV, MERS, and SARS-CoV-2 are all beta coronaviruses.

SARS-CoV-2 infects T lymphocytes through its spike protein-mediated membrane fusion

Date: 04/07/2020

Link: https://doi.org/10.1038/s41423-020-0424-9

- Examined susceptibility of T lymphocytes to infection with SARS-CoV-2 using T cell lines.
  - ○ Both cell lines expressed very low levels of ACE2 receptor.
  - ○ Pseudotyped virus reported to infect both cell lines.
- Virus entry into cell lines was inhibited by treatment with fusion inhibitor, EK1.
- Could detect viral protein in cells 24 hours after infection.
  - ○ No evidence of replication in cell lines as determined by measurement of viral genome.

Structure, function, and antigenicity of the SARS-CoV-2 glycoprotein

Date: 03/19/2020

Link: https://doi.org/10.1016/j.cell.2020.02.058

- SARS-CoV-2 spike protein contains 4 amino acids inserted between S1 and S2, furin cleavage site.
  - ○ Could explain tropism and disease severity.
- Recognition of ACE2 from other animals could have allowed for easier jump to humans.
- SARS-CoV spike murine polyclonal antibodies significantly inhibit infection of cell ACE2 expressing cell line.

Cryo-EM structure of the 2019-nCoV spike in the prefusion conformation

Date of article – 03/13/2020

Link: https://doi.org/10.1126/science.abb2507

- S protein trimeric class I fusion protein
  - ○ "prefusion" conformation undergoes rearrangement after binding host cell receptor

- 98% genomic homology with Spike protein of bat coronavirus RaTG13
    - Mutation generated furin recognition site in SARS-CoV-2 spike protein
    - Common mutation observed in highly virulent avian and human influenza viruses
- ACE2 receptor binds SARS-CoV-2 spike with 10-20 fold greater affinity than SARS-CoV spike
- High degree structural homology between SARS-CoV & SARS-CoV-2
    - No cross reactivity of SARS-CoV monoclonal antibodies and SARS-CoV-2 spike protein

Characterization of the receptor-binding domain (RBD) of 2019 novel coronavirus implication for development of RBD protein as a viral attachment inhibitor and vaccine.

Date: 03/19/2020

Link: https://doi.org/10.1038/s41423-020-0400-4

- Polyclonal antibodies against receptor binding domain (RBD) of SARS-CoV bind RBD of SARS-CoV-2
- SARS-CoV-2 RBD specifically bound cells engineered to express bat ACE2 receptor
    - RBD of SARS-CoV-2 more tightly binds bat or human ACE2
    - May explain high transmission rate

Remdesivir and chloroquine effectively inhibit the recently emerged novel coronavirus (2019-nCoV) in vitro

Date: 02/04/2020

Link: https://doi.org/10.1038/s41422-020-0282-0

- Virus infection of African green monkey cell line blocked at low levels of Remdesivir and Chloroquine
    - Remdesivir adenosine analog
    - Incorporated into new viral genome
        - Causes premature termination of chain elongation
        - Post viral entry activity
        - Demonstrated to inhibit infection of human cell lines too
- Chloroquine blocks infection by virus
    - Increases endosomal pH
        - Inhibits fusion of virus and host cell membranes
    - Also interferes glycosylation of ACE2 receptor
        - Observed with SARS-CoV

A pneumonia outbreak associated with a new coronavirus of probable bat origin

Date: 02/03/2020

Link: https://doi.org/10.1038/s41586-020-2012-7

- SARs-CoV-19 cell entry mediated by angiotensin converting enzyme II (ACE2) receptor (same receptor used by SARS CoV)
- Receptor expressed on type 2 alveolar cells and small number of lung resident monocytes/macrophages
- Virus specific IgM peaked 9 days post symptom onset (1 patient)
- 2 weeks post onset virus specific IgG detectable
- Antibody from SARS-CoV-2 patients neutralize SARS-CoV-2, in vitro

- Genome exhibits 96% homology with whole genome of known bat coronovirus RaTG13

Reinfection could not occur in SARS-CoV-2 infected rhesus macaques

Date: 03/14/2020

Link: https://www.biorxiv.org/content/10.1101/2020.03.13.990226v1

- Primary infection from SARS-CoV-2 could protect against subsequent exposure
- Reports of reinfection are likely due to false negatives on subsequent testing, suggesting tests need to be refined

Aerosol and surface stability of HCoV-19 (SARS-CoV-2) compared to SARS-CoV-1

Date: 03/14/2020

Link: https://www.nejm.org/doi/10.1056/NEJMc2004973

- SARS-CoV-2 viable in aerosols for 3 hours
- SARS-CoV-2 detected on plastic and stainless steel for up to 72 hours
- No viable virus on copper after 4 hours
- No viable virus on cardboard after 24 hours

RAPIDLY EVOLVING ALTERNATIVE DIAGNOSTIC TESTS FOR THE VIRUS

Note: As of 5/19/2020, the FDA has issued Emergency Use Authorizations (EUA) for 75 tests. Fifty-eight are RT-PCR for viral RNA in respiratory specimens, most requiring nasopharyngeal (NP) swabs. Three utilize an isothermal nucleic acid amplification method to detect viral RNA in respiratory samples. One is a test utilizing CRISPR technology. Twelve are various types to detect antibodies in blood samples. One identifies SARS-CoV-2 nucleocapsid protein antigen in NP/nasal swabs. Five are point-of-care tests, and 4 offer at-home collection options.

Lab Test Quick Reference Guide (This link provides a summary of laboratory testing)

A Droplet Digital PCR Assay to Detect SARS-CoV-2 RNA

Date: 05/06/2020

Link: https://www.medrxiv.org/content/10.1101/2020.05.06.20090449v1.full.pdf

- Describes a droplet digital PCR assay using the FDA approved SARS CoV-2 RTPCR reactions but with improved detection limits
- The technique was able to achieve Lower Limit of Quantification/LLOQ (though defined as LOD in the EUA guidance document) of 0.25 copies/µL of viral N1 in the final ddPCR, or 4 copies/µL of viral RNA in the total RNA extract (75.8% accuracy, 19.0% CV) with 19/20 individually spiked replicates demonstrating reactivity.
- There was no cross-reactivity with other respiratory pathogens that was tested.

FACT- Frankfurt adjusted COVID-19 testing- a novel method enables high-throughput SARS-CoV-2 screening without loss of sensitivity

Date – 04/28/2020

Link:https://www.medrxiv.org/content/10.1101/2020.04.28.20074187v1.full.pdf

- Simultaneous incubation of multiple respiratory swabs in a single tube for high-throughput testing of SARS-CoV-2.
- The analytics validity of this concept was demonstrated in a five-sample mini pool set-up and applied for testing of symptomatic and asymptomatic patients without any significant loss in analytic or diagnostic sensitivity compared to single sample testing in multiple setups.
- It reduced the amount of reagents needed by up to 40%, and also reduced hands-on time. This method could enhance testing efficiency, especially in groups with a low pretest-probability, such as systemically relevant professional groups.

Development and Multicenter Performance Evaluation of The First Fully Automated SARS-CoV-2 IgM and IgG Immunoassays

Date – 04/16/2020

Link: https://www.medrxiv.org/content/10.1101/2020.04.16.20067231v1.full.pdf

- Developed fully automated chemiluminescent immunoassays for SARS-CoV-2 IgM and IgG antibodies in human serum and tested on hospitalized patients and normal population
- clinical sensitivity for IgM and IgG - 85.58% and 96.62% for confirmed cases, 73.08% and 86.54% for suspected cases
- Clinical specificity for IgM and IgG – 97.33% and 99.49% for confirmed hospitalized patients and 97.43% and 99.15% for normal population

CRISPR–Cas12-based detection of SARS-CoV-2

Date- 04/16/2020

Link: https://www.nature.com/articles/s41587-020-0513-4?

- Reports development of a rapid (<40 min), easy-to-implement and accurate CRISPR–Cas12-based DETECTR lateral flow assay for detection of SARS-CoV-2 from respiratory swab RNA extracts compared to the existing CDC RT-PCR assays.
- Validated on clinical samples from patients in the United States, including 36 patients with COVID-19 infection and 42 patients with other viral respiratory infections.
- Faster visual detection compared to RT-PCR assays with 95% Positive predictive agreement and 100% negative predictive agreement.

A novel high specificity COVID-19 screening method based on simple blood exams and artificial intelligence

Date: 04/10/2020

Link: https://www.medrxiv.org/content/10.1101/2020.04.10.20061036v1.full.pdf

- Developed an artificial intelligence framework based initial screening tool that for suspect COVID-19 cases using simple blood exams as input to predict positive (having SARS-CoV-2) or negative (not

having SARS-CoV-2). The positive cases can then be referred for further highly sensitive testing (e.g. CT scan, or specific antibodies).

- All code for the AI model, called ER-CoV is publicly available at https://github.com/soares-f/ER-CoV .
- The framework achieved an average specificity of 92.16% and negative predictive value (NPV) of 95.29%. Not very good for severe cases but a good add on when resources are limited and is helpful especially for patient triage of milder or early stages of infection.

LAMP-Seq: Population-Scale COVID-19 Diagnostics Using a Compressed Barcode Space

Date of Article – 04/06/2020

Link: https://www.biorxiv.org/content/10.1101/2020.04.06.025635v1.full.pdf

- AMP-seq is a barcoded RT-LAMP protocol developed by Broad Institute for COVID-19 detection with reduced cost (<7 USD/ sample) and complexity
- Individual samples are processed after a single heating step, followed by creation of sample-specific barcoded amplicons (the barcode is inserted in forward or backward inner primer of the LAMP reaction)which are then pooled with multiple samples for pooled processing, deep sequencing and analysis. Sample pooling allows for scaling the diagnostic pipeline, resource and time optimization. Unique tracking of tens of millions of samples with asynchronous testing logistics is achieved using a compressed barcode space.
- This protocol has not been validated with clinical samples. To facilitate collaborations with interested parties to jointly advance the fight against the current coronavirus pandemic, the authors have set up a public forum on www.LAMP-Seq.org.

Loss of smell and taste in combination with other symptoms is a strong predictor of COVID-19 infection

Date of Article – 04/05/2020

Link: https://www.medrxiv.org/content/10.1101/2020.04.05.20048421v1.full.pdf

- Authors describe the use of a COVID-19 app that has helped detect infections and isolate individuals based on symptom tracking
- Within a few days 1.5 million individuals in UK signed up for the app
- Loss of smell and taste was predominant symptom in 59% of COVID-19 positive patients.
- The app can be downloaded on any mobile device. For more details visit https://covid.joinzoe.com/us

Rapid and accurate identification of COVID-19 infection through machine learning based on clinical available blood test results

Date: 04/02/2020

Link:https://www.medrxiv.org/content/10.1101/2020.04.02.20051136v1

- Developed an "assistant discrimination tool" using machine learning to screen patients based on their clinically available blood indices.
- This would complement the nucleic acid diagnostic test but is helpful to isolate patients before these test results are confirmed.

- A user-friendly website service available to test the assistant tool online at http://lishuyan.lzu.edu.cn/COVID2019_2/ which provides 11 clinical parameters to classify COVID-19 patient along with the probability of prediction.

One-step RNA extraction for RT-qPCR detection of 2019-nCoV

Date: 04/02/2020

Link:https://www.biorxiv.org/content/10.1101/2020.04.02.022384v1.full.pdf

- One Step RNA extraction during times with limited RNA extraction kit availability
- Direct lysis of respiratory samples for 20 mins (without using the column purification) to replace RNA extraction steps to run CDC 2019-nCoV diagnostic tests
- Lysis buffer is easy to obtain and does not require use of a centrifuge or manifold unlike when using column purification.

Potential false-negative nucleic acid testing results for Severe Acute Respiratory Syndrome Coronavirus 2 from thermal inactivation of samples with low viral loads.

Date: 04/04/2020

Link:https://academic.oup.com/clinchem/advance-article/doi/10.1093/clinchem/hvaa091/5815979

- Thermal inactivation of SARS-CoV-2 at 56 deg Celsius before nucleic acid testing could increase the false negative in RT-PCR, especially in conditions of low-viral load.
- Chemical inactivation using Guanidinium-based lysis is recommended to preserve the viral specimen.

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

Date: 03/28/2020

Link:https://academic.oup.com/cid/advance-article/doi/10.1093/cid/ciaa344/5812996

- Combining RNA and antibody detection can improve diagnosis of COVID-19 in the early stages of the disease.
- In the early stages (within 1-week), some patients with undetectable RNA could be screened out through Ab testing.
- The presence of antibodies in the serum was <40% among patients within 1-week since onset, and rapidly increased to 100.0% (total Antibody), 94.3% (IgM) and 79.8% (IgG) since day-15 after onset.
- Strong positive correlation between clinical severity and Ab titer since 2-week after illness onset. The results suggested that a high Ab titer may be considered as a risk factor of critical illness, independent from older age, male gender and comorbidities

Reverse transcription loop-mediated isothermal amplification combined with nanoparticles-based biosensor for diagnosis of COVID-19
Date: 03/17/2020

Link: https://www.medrxiv.org/content/10.1101/2020.03.17.20037796v1.full.pdf

- Geographic location/Country - Hainan/China
- RT-LAMP combined with NBS (nanoparticles-based biosensor that can be constructed in house as a dipstick) without need for special equipment

- Sample collection to result indication in approximately 60 mins. Steps – respiratory sample collection (3mins) + rapid RNA extraction (15 min) + RT-LAMP reaction at 63degrees(40 mins) + results on NBS interpretation (2min)
- Two target sequences are detected – F1ab (Open reading frame 1a/b) and np (nucleoprotein gene). Addition of np increases the specificity of SARS-Cov-2 detection with a sensitivity of 12 copies of F1ab and np-plasmid

All-in-One Dual CRISPR-Cas12a (AIOD-CRISPR) Assay: A Case for Rapid, Ultrasensitive and Visual Detection of Novel Coronavirus SARS-CoV-2 and HIV virus

Date: 03/19/2020

Link: https://www.biorxiv.org/content/10.1101/2020.03.19.998724v1

- Geographic location/Country - CT/USA
- New CRISPR assay (AIOD-CRISPR) allows incubation of all components in a single tube as a single step at one single temp without separate preamplification steps
- Able to detect SARS-COV-2 in 40 min incubation
- High specificity – the SARS-CoV-2 DNA detection using AIOD-CRISPR was not detecting other virus such as SARS-CoV and MERS-CoV
- Real-time RT-PCR assay (RT-AIOD-CRISPR) able to detect 4.6 copies of SARS-CoV-2 RNA targets in 40 min

Serological diagnostic kit of SARS-CoV-2 antibodies using CHO-expressed full-length SARS-CoV-2 S1 proteins

Date: 03/26/2020

Link: https://www.medrxiv.org/content/10.1101/2020.03.26.20042184v1

- Geographic location/Country - Beijing/China
- ELISA based method to detect SARS-CoV-2-S1 antibodies (expression of the S1 protein significantly improved using CHO cells for protein expression)
- Specificity and sensitivity at 97.5% from human sera
- Able to capture cases that were ruled negative by nucleic acid tests
- Key protocol points - 1) 1.5µg/mL SARS-CoV2 S1-His 266 for plate coating, 2) 1:20 dilution of human sera using 20% CS-PBS as sample and 267 enzyme diluent, 3) incubation with constant rotation using a temperature controlled 268 micro-plate shaker.

TRANSMISSION DYNAMICS

Aerosol and Surface Distribution of Severe Acute Respiratory Syndrome Coronavirus 2 in Hospital Wards

Date: 4/10/2020

Link: https://wwwnc.cdc.gov/eid/article/26/7/20-0885_article#suggestedcitation

- SARS-CoV-2 was found widely distributed in the air and on surfaces, implying high risk of infection for hospital workers
- ICU has greater levels of air and surface contamination

- Transmission might be greater than 4 meters
- Virus was found on shoes of hospital workers, spreading to where they walk

Time-varying transmission dynamics of Novel Coronavirus Pneumonia in China

Date: 02/13/2020

Link: https://www.biorxiv.org/content/10.1101/2020.01.25.919787v2

- Rate of infection of virus (R_0= the average number of new infections generated by an infectious person in a totally naïve population) has increased from 2.2 infections/infected person from early studies to 4.5 infections/infected person in later studies with longer follow up periods, but with measures such as social distancing, the rate of infection is decreasing.
- Time from onset of symptoms to isolation of virus is mean 2.9 days

The reproductive number of COVID-19 is higher compared to SARS coronavirus

Date: 02/13/2020

Link: https://www.ncbi.nlm.nih.gov/pubmed/32052846

- Summary of the different estimates of R_0 (the average number of new infections generated by an infectious person in a totally naïve population) from different studies using different methods.
- R_0 from China was estimated from 12 studies
- The average estimate of 3.28 (median 2.79) exceed the WHO estimate range (1.4-2.5)
- Stochastic methods produced less varying estimates than mathematical models

TESTING OF ASYMPTOMATIC PEOPLE

Covid-19: four fifths of cases are asymptomatic, China figures indicate

Date: 04/02/2020

Link – https://www.bmj.com/content/bmj/369/bmj.m1375.full.pdf

- Unnoticed, asymptomatic cases of coronavirus infection are an important source of contagion.
- New evidence has emerged from China indicating that the large majority of coronavirus infections do not result in symptoms.
- In a 24-hour period on April 1st, a total of 130 of the 166 new infections (78%) were asymptomatic, according to China's National Health Commission.

Estimation of the asymptomatic ratio of novel coronavirus infections (COVID-19)

Date: 02/17/2020

Link: https://www.medrxiv.org/content/10.1101/2020.02.03.20020248v2

- Estimated the asymptomatic ratio (the percentage of those infected with no symptoms) using information on 565 Japanese nationals evacuated from Wuhan, China on chartered flights.
- The asymptomatic ratio was estimated to be 30.8% (95% CI=(7.7%, 53.8%)).

- Other numbers of note: 502 (89%) were asymptomatic. Among these 502 asymptomatic individuals, 4 (0.8%) tested positive for COVID-19.

Estimating the asymptomatic proportion of coronavirus disease 2019 (COVID-19) cases on board the Diamond Princess cruise ship, Yokohama, Japan, 2020

Date: 03/12/2020

Link: https://www.eurosurveillance.org/content/10.2807/1560-7917.ES.2020.25.10.2000180

- COVID-19 cases on the Diamond Princess cruise ship, which underwent a 2-week quarantine of 3,711 people starting on February 5th, 2020 in Yokohama, Japan, after a former passenger tested positive for COVID-19 after disembarking.
- As of February 20th, 3,063 passengers were tested, 634 (20.7%) of which tested positive for COVID-19. The delay-adjusted asymptomatic proportion of infection was estimated to be 17.9% (95% credible interval (CrI): 15.5%–20.2%).
- Most infections occurred before quarantine start.

PREVENTION STRATEGIES

From Containment to Mitigation of COVID-19 in the US

Date: 03/13/2020

Link: https://jamanetwork.com/journals/jama/fullarticle/2763187

- Argues that strategy for slowing spread of the COVID-19 pandemic should change from containment to mitigation.
- Mitigation approaches seek to: (1) slow the further spread of the virus, (2) reduce the anticipated surge in health care use, (3) provide patients with the right level of care to maximize the likelihood that the majority of patients will only require time-limited home isolation, (4) expand testing capability to increase available hospital capacity, and (5) tailor isolation to minimize transmission.
- Without rapid uptake of these approaches across hospitals, COVID-19 will pose a critical risk to an already strained health care system.
- Discusses the COVID-19 mitigation program developed at Kaiser Permanente by their emergency management and preparedness teams, based on good clinical practice, available evidence, and experience.

Impact of non-pharmaceutical interventions (NPIs) to reduce COVID19 mortality and healthcare demand

Date: 03/16/2020

Link: https://www.imperial.ac.uk/media/imperial-college/medicine/sph/ide/gida-fellowships/Imperial-College-COVID19-NPI-modelling-16-03-2020.pdf

- Performed epidemiological modelling which was used to inform policymaking in the UK and other countries in recent weeks.
- Multiple interventions that are combined needed to have a substantial impact on transmission.
- Suppression (which aims to reverse epidemic growth, reducing case numbers to low levels) will at minimum require a combination of social distancing of the entire population, home isolation of cases,

and household quarantine of their family members. This may need to be supplemented by school and university closures, though it should be recognized that such closures may have negative impacts on health systems due to increased absenteeism.

- These measures will need to be maintained until a vaccine becomes available (potentially 18 months or more) – given that we predict that transmission will quickly rebound if interventions are relaxed.

PREDICTION OF HEALTH CARE SYSTEM BURDEN

Critical Care Utilization for the COVID-19 Outbreak in Lombardy, Italy

Date: 03/13/2020

Link: https://jamanetwork.com/journals/jama/fullarticle/2763188

- In Italy, proportion of ICU admissions represents 12% of total positive cases and 16% of all hospitalized patients
- Significantly higher than 5% ICU rate for all total positive cases reported in China
- Collaborative health care network (ICU networks) necessary for health care systems to handle burden of patients

RAPIDLY EMERGING CLINICAL TRIALS/OFF LABEL USE OF PHARMACOLOGIC AGENTS

Federally Funded Clinical Trials Summary_18May2020 (CTRL+CLICK to access a PDF file that provides a summary of federally funded clinical trials)

Clinical Trials Summary_18May2020 (CTRL+CLICK to access an excel file that provides a summary of clinical trials)

Number of Clinical Trials Posted on ClinicalTrials.gov
Data was obtained on May 18, 2020

First posted date on ClinicalTrials.gov
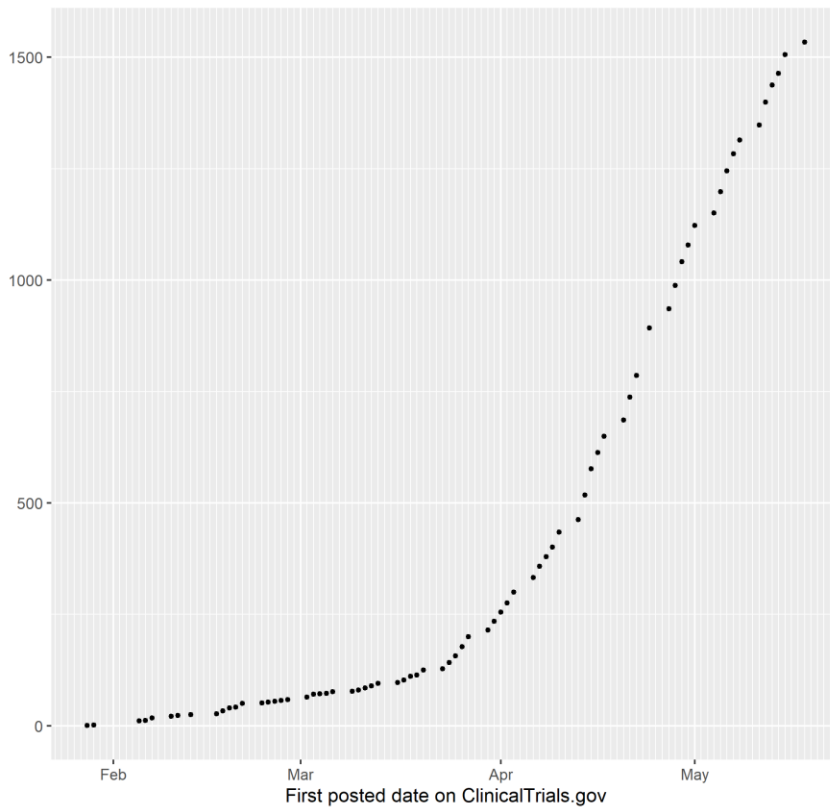
Pie Chart by Study Types
Data was obtained on May 18, 2020
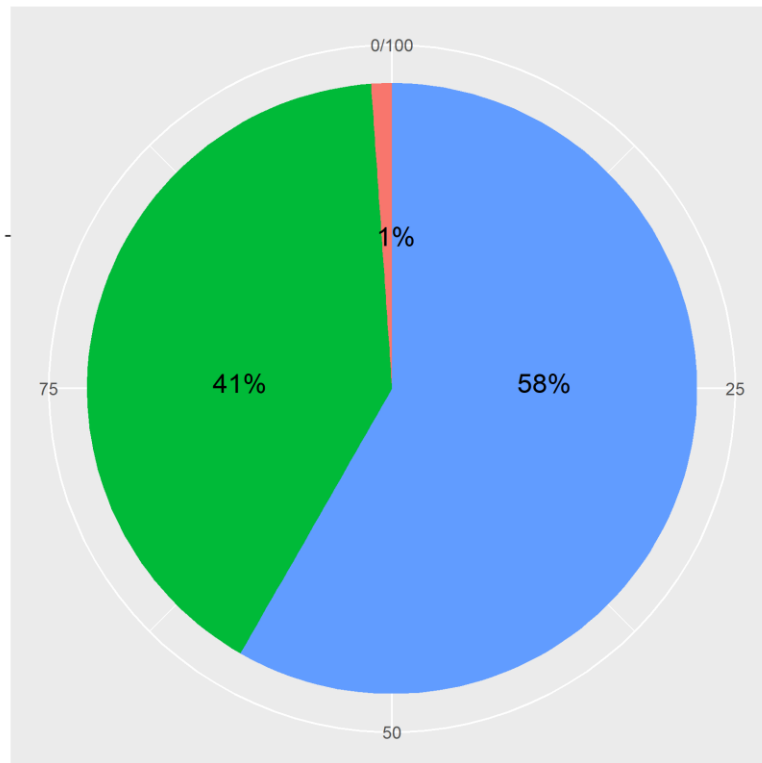
Interventional Observational Expanded Access
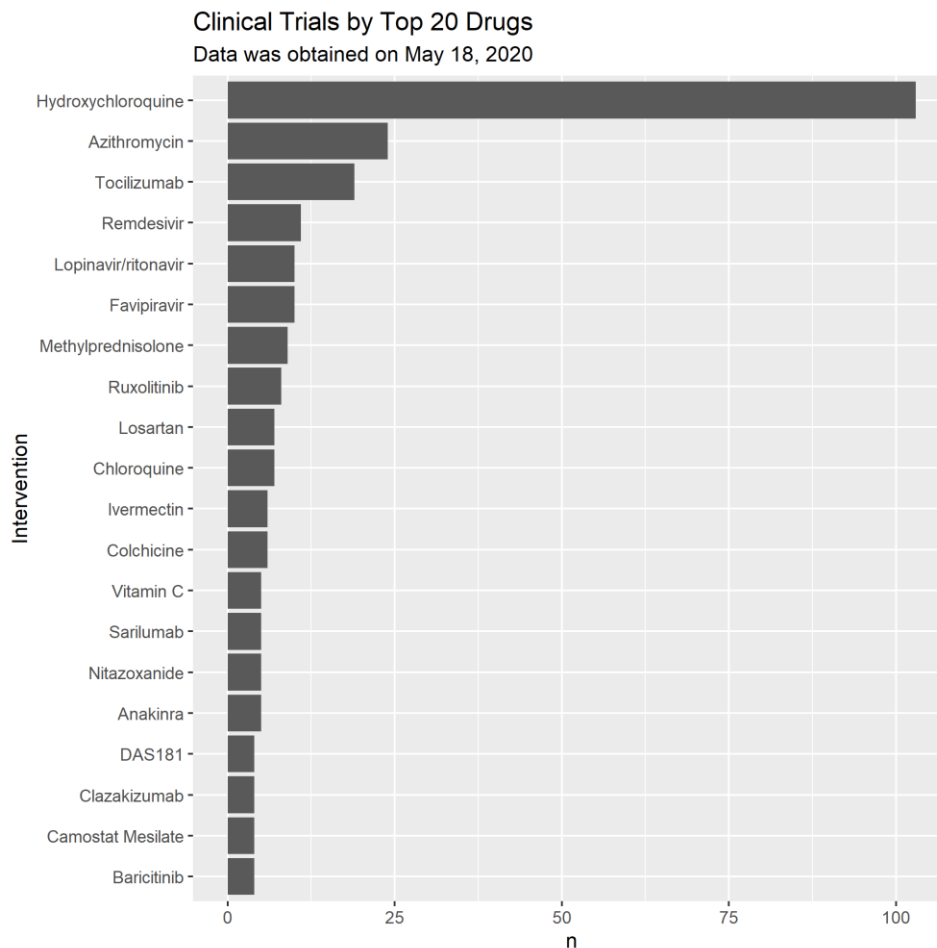
Pie Chart by Phase among Interventional Studies
Data was obtained on May 18, 2020

Legend:
- Early Phase 1
- Phase 1|Phase 2
- Phase 2|Phase 3
- Phase 4
- Phase 1
- Phase 2
- Phase 3
- Not Applicable
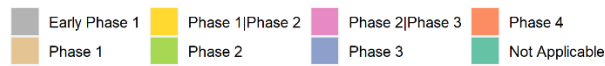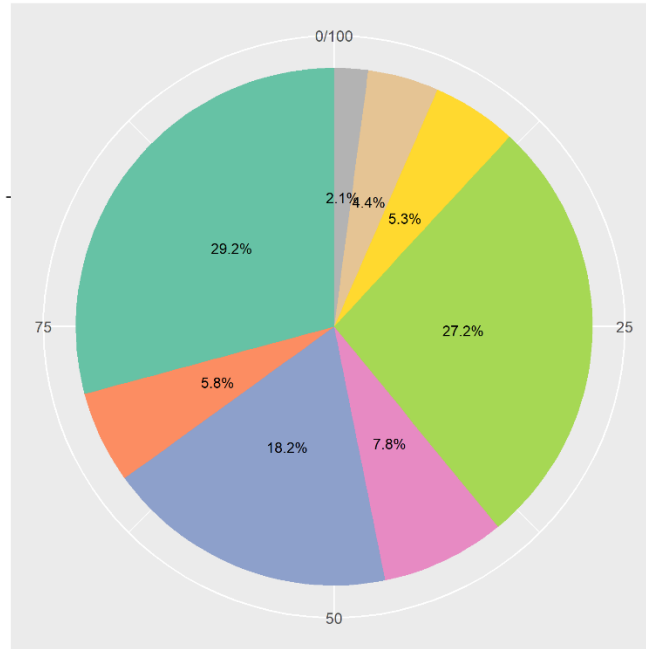
Number of Treatment Types
Data was obtained on May 18, 2020

Clinical Trials by Top 20 Drugs
Data was obtained on May 18, 2020
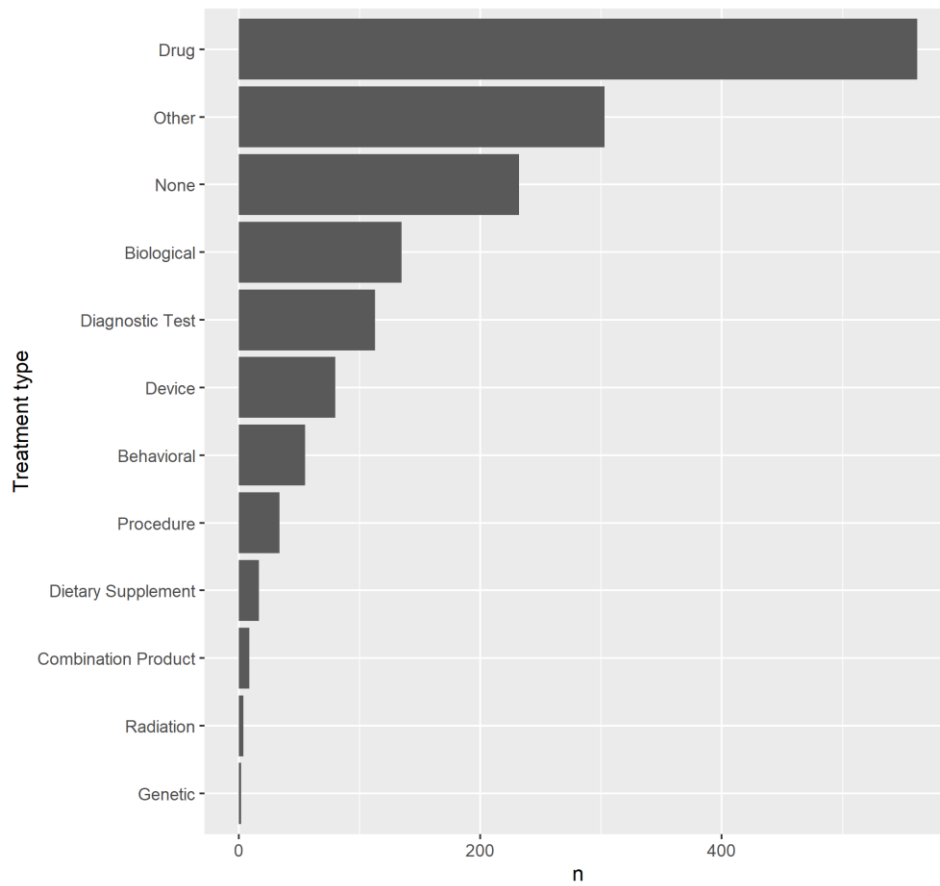
The COVID-19 vaccine development landscape

Date of article – April 04, 2020

Link – https://www.nature.com/articles/d41573-020-00073-5

- As of 8 April 2020, the global COVID-19 vaccine R&D landscape includes 115 vaccine candidates, of which 78 are confirmed as active and 37 are unconfirmed (development status cannot be determined from publicly available or proprietary information sources).

- Of the 78 confirmed active projects, 73 are currently at exploratory or preclinical stages. The most advanced candidates have recently moved into clinical development, including mRNA-1273 from Moderna, Ad5-nCoV from CanSino Biologicals, INO-4800 from Inovio, LV-SMENP-DC and pathogen-specific aAPC from Shenzhen Geno-Immune Medical Institute.

- The range of technology platforms being evaluated is diverse, including nucleic acid (DNA and RNA), virus-like particle, peptide, viral vector (replicating and non-replicating), recombinant protein, live attenuated virus and inactivated virus approaches.

Compassionate Use of Remdesivir for Patients with Severe Covid-19

Date: 04/10/ 2020

Link – https://www.nejm.org/doi/full/10.1056/NEJMoa2007016

- Researchers provided remdesivir on a compassionate-use basis to patients hospitalized with Covid-19, the illness caused by infection with SARS-CoV-2. Patients were those with confirmed SARS-CoV-2 infection who had an oxygen saturation of 94% or less while they were breathing ambient air or who were receiving oxygen support. Patients received a 10-day course of remdesivir, consisting of 200 mg administered intravenously on day 1, followed by 100 mg daily for the remaining 9 days of treatment.

- At baseline, 30 patients (57%) were receiving mechanical ventilation and 4 (8%) were receiving extracorporeal membrane oxygenation. During a median follow-up of 18 days, 36 patients (68%) had an improvement in oxygen-support class, including 17 of 30 patients (57%) receiving mechanical ventilation who were extubated. A total of 25 patients (47%) were discharged, and 7 patients (13%) died; mortality was 18% (6 of 34) among patients receiving invasive ventilation and 5% (1 of 19) among those not receiving invasive ventilation.

- In this cohort of patients hospitalized for severe Covid-19 who were treated with compassionate-use remdesivir, clinical improvement was observed in 36 of 53 patients (68%). Measurement of efficacy will require ongoing randomized, placebo-controlled trials of remdesivir therapy.

Treatment of 5 Critically Ill Patients With COVID-19 With Convalescent Plasma

Date: 03/27/2020

Link – https://jamanetwork.com/journals/jama/fullarticle/2763983

- Case series of 5 critically ill patients with laboratory-confirmed COVID-19 and acute respiratory distress syndrome (ARDS) who met the following criteria: severe pneumonia with rapid progression and continuously high viral load despite antiviral treatment; Pao_2/Fio_2 <300; and mechanical ventilation. All 5 were treated with convalescent plasma transfusion.

- All 5 patients (age range, 36-65 years; 2 women) were receiving mechanical ventilation at the time of treatment and all had received antiviral agents and methylprednisolone. Following plasma transfusion, body temperature normalized within 3 days in 4 of 5 patients, the SOFA score decreased, and Pao_2/Fio_2 increased within 12 days (range, 172-276 before and 284-366 after). Viral loads also decreased and became negative within 12 days after the transfusion, and SARS-CoV-2–specific ELISA and neutralizing antibody titers increased following the transfusion (range, 40-60 before and 80-320 on day 7). ARDS resolved in 4 patients at 12 days after transfusion, and 3 patients were weaned from mechanical ventilation within 2 weeks of treatment. Of the 5 patients, 3 have been discharged from the hospital (length of stay: 53, 51, and 55 days), and 2 are in stable condition at 37 days after transfusion.

Remdesivir and chloroquine effectively inhibit the recently emerged novel coronavirus (2019-nCoV) in vitro

Date: 03/27/2020

Link: https://www.nature.com/articles/s41422-020-0282-0

- Researchers evaluated the antiviral efficiency of five FDA-approved including ribavirin, penciclovir, nitazoxanide, nafamostat, chloroquine and remdesivir (GS-5734) and favipiravir (T-705) against a clinical isolate of 2019-nCoV in vitro.
- Remdesivir and chloroquine are highly effective in the control of 2019-nCoV infection in vitro

Hydroxychloroquine and azithromycin as a treatment of COVID-19: results of an open-label non-randomized clinical trial

Date: 03/20/2020 (In press, pre proof)

Link: https://www.sciencedirect.com/science/article/pii/S0924857920300996#ecom0001

- French Confirmed COVID-19 patients were included in a single arm protocol from early March to March 16th, to receive 600mg of hydroxychloroquine daily and their viral load in nasopharyngeal swabs was tested daily in a hospital setting. Depending on their clinical presentation, azithromycin was added to the treatment
- A total of 26 patients received hydroxychloroquine and 16 were control patients. Hydroxychloroquine treatment is significantly associated with viral load reduction/disappearance in COVID-19 patients and its effect is reinforced by azithromycin.
- Limited by small sample size, dropout of 6 patients.

Race to find COVID-19 treatments accelerates

Date: 03/27/2020

Link: https://science.sciencemag.org/content/367/6485/1412

- At least 12 potential COVID-19 treatments are being tested, including drugs already in use for HIV and malaria, experimental compounds that work against an array of viruses in animal experiments, and antibody-rich plasma from people who have recovered from COVID-19
- On March 20, WHO announced the launch of SOLIDARITY, choosing an experimental antiviral remdesivir; the malaria medication chloroquine (or hydroxychloroquine); a combination of the HIV drugs lopinavir and ritonavir; and that combination plus interferon-beta, an immune system messenger that can help cripple viruses.

A Trial of Lopinavir-Ritonavir in Adults Hospitalized with Severe Covid-19

Date: 03/18/2020

Link: https://www.nejm.org/doi/10.1056/NEJMoa2001282

- Hospitalized adult patients with confirmed SARS-CoV-2 infection, oxygen saturation (Sao2) $\leq$ 94% while they were breathing ambient air or Pao2/Fio2 < 300 mm Hg were randomized 1:1 ratio to receive either lopinavir–ritonavir (400 mg and 100 mg, respectively) twice a day for 14 days, in addition to standard care, or standard care alone
- primary end point: the time to clinical improvement (the time from randomization to either an improvement of two points on a seven-category ordinal scale or discharge from the hospital, whichever came first)
- Treatment with lopinavir–ritonavir was not associated with a difference from standard care in the time to clinical improvement (hazard ratio for clinical improvement, 1.24; 95% confidence interval [CI], 0.90 to 1.72)

A systematic review on the efficacy and safety of chloroquine for the treatment of COVID-19

Date: 03/17/2020

Link: https://www.sciencedirect.com/science/article/pii/S0883944120303907?via%3Dihub

- Chloroquine is widely used, safe, cheap, and effective in viral infections in pre-clinical studies
- Chloroquine seems to be effective in limiting replication of SARS-CoV-2 (virus causing COVID-19) in vitro
- 23 clinical trials studying the efficacy and safety of Chloroquine or related formulation in patients with COVID-19

More than 80 clinical trials launch to test coronavirus treatments

Date: 02/15/2020

Link: https://www.nature.com/articles/d41586-020-00444-3

- China has more than 80 running or pending clinical trials on potential treatments for COVID-19
- WHO is working with Chinese scientists to set standards to ensure the trials are well designed
- A few trials test chloroquine, a malaria drug that killed the new coronavirus (recently named SARS-CoV-2) in cell culture
- A 300-person controlled trial will test serum from COVID-19 survivors
- A stem-cell trial will infuse 28 people with stem cells derived from menstrual blood, and compare results with those from people who did not receive the infusions
- About 15 trials listed in China's registry expect to enroll a total of more than 2,000 people in studies on a variety of traditional Chinese medicines

Safety and Immunogenicity Study of 2019-nCoV Vaccine (mRNA-1273) to Prevent SARS-CoV-2 Infection

Date: 03/20/2020

Link: https://clinicaltrials.gov/ct2/show/NCT04283461

- Phase I, open-label, dose ranging clinical trial in males and non-pregnant females, 18 to 55 years of age, in good health designed to assess the safety, reactogenicity and immunogenicity of mRNA-1273 manufactured by ModernaTX, Inc.
- mRNA-1273 is a novel lipid nanoparticle (LNP)-encapsulated mRNA-based vaccine that encodes for a full-length, prefusion stabilized spike (S) protein of 2019-novel coronavirus (nCoV).
- Forty-five subjects will be enrolled into one of three cohorts and will receive an intramuscular (IM) injection of mRNA-1273 on Days 1 and 29 in the deltoid muscle. Subjects will be followed through 12 months post second vaccination (Day 394).
- primary objective is to evaluate the safety and reactogenicity of a 2-dose vaccination schedule of mRNA-1273, given 28 days apart, across 3 dosages in healthy adults.
- Results: Pending. Estimated Study Completion Date: June 1, 2021

IMPACT ON HEALTH CARE WORKERS

Safety Recommendations for Evaluation and Surgery of the Head and Neck During the COVID-19 Pandemic

Date- 03/31/2020

Link- <https://jamanetwork.com/journals/jamaotolaryngology/fullarticle/2764032>

- Article prepared with otolaryngologist across US, Asia and Europe
- Guidelines will be modified as more information becomes available
- Per CMS, following factors should be considered to determine if planned or surgical procedure should proceed-
    - Current and projected COVID-19 cases in facility
    - PPE, beds, ventilators and staff availability
    - Health and age of patients
    - Risk of SARS-CoV-2 infection during recovery
    - Urgency of procedure
- Summary table below

Table. Summary of Head and Neck Examination and Procedure Recommendations[a]

Risk and definition	Patient wears	Clinician/staff wear
Nonprocedure encounters in non-immune-compromised patients		
High risk to clinician: any examination in: • Patients with active SARS-CoV-2 infection • Patients with influenzalike symptoms • Patients under evaluation for SARS-CoV-2 infection	Surgical mask	• Single-use N95 mask • Goggles or face shield • Gown • Gloves
Moderate risk to clinician: examination of ear, nose, mouth, or throat in asymptomatic patients	Nothing[b]	• Surgical mask with face shield to allow for reuse of mask • Gloves
Low risk to clinician: other examination in asymptomatic patients	Nothing[b]	• Mask optional • Gloves
Aerosol-generating interventional procedures		
Procedures including but not limited to the following: Intubation, extubation, office-based nasal and laryngeal endoscopy, bronchoscopy, gastrointestinal endoscopy, drainage of peritonsillar abscess, placement of nasal packing, foreign body management in the nose or airway, tracheostomy, tracheostomy care, powered instrumentation in mucosal head and neck surgery, possibly laparoscopic surgery		
High risk to clinician: consider delaying or discussing the following: • Patients with active SARS-CoV-2 infection • Patients with influenzalike symptoms • Patients under evaluation for SARS-CoV-2 infection	Surgical mask	• PAPR or single-use N95 mask and goggles or face shield • Gown • Double gloves
Low risk to clinician: • Patients who are asymptomatic and untested or SARS-CoV-2 negative in 48 h preceding surgery • If possible, test patients within 48 h of procedure	Nothing[b]	• N95 mask and eye protection (may be appropriate to reuse; must use face shield to allow reuse) • If unavailable, surgical mask with goggles or face shield • Gown • Double gloves
Non-aerosol-generating interventional procedures		
Soft tissue surgery exposes blood, which can have a viral count, but unless the blood is aerosolized by the use of energy devices, it would be expected to be lower risk. Suctioning away smoke and aerosolized tissue is recommended. To our knowledge, the infectiousness of aerosolized blood with SARS-CoV-2 is not yet known.		
High risk to clinician: consider delaying or discussing in: • Patients with active SARS-CoV-2 infection • Patients with influenzalike symptoms • Patients under evaluation for SARS-CoV-2 infection	Surgical mask	• Single-use N95 mask • Goggles or face shield • Gown • Gloves
Low risk to clinician: patients who are asymptomatic or SARS-CoV-2 negative in last 48 h	Nothing[b]	• Surgical mask • Goggles or face shield • Gown • Gloves

Abbreviations: PAPR, powered air-purifying respirator; SARS, severe acute respiratory syndrome; SARS-CoV-2, SARS coronavirus 2.

[a] Adapted and updated with permission from Stanford Health Care. Recommendations are subject to change as more data become available.

[b] If the patient is immune compromised (receiving active chemotherapy, radiotherapy, or immunotherapy; <1 y after solid organ transplant; receiving chronic immunosuppression therapy; pregnant), both the patient and clinician should wear a surgical mask unless the patient is high risk. Clinicians and staff should wear a face shield over a surgical mask to allow reuse of the mask.

Environmental contamination of the SARS-CoV-2 in healthcare premises: An urgent call for protection for healthcare workers

Date: 03/16/2020

Link: https://www.medrxiv.org/content/10.1101/2020.03.11.20034546v1

- The most contaminated zones were the intensive care unit specialized for taking care of novel coronavirus pneumonia (NCP) (31.9%), Obstetric Isolation Ward specialized for pregnant women with NCP (28.1%), and Isolation Ward for NCP (19.6%).

- The most contaminated objects are self-service printers (20.0%), desktop/keyboard (16.8%), and doorknob (16.0%). Both hand sanitizer dispensers (20.3%) and gloves (15.4%) were most contaminated PPE.

Impact of viral epidemic outbreaks on mental health of healthcare workers: a rapid systematic review

Date- 04/06/2020

Link: https://www.medrxiv.org/content/10.1101/2020.04.02.20048892v1

- 61 studies were included (56 examining impact on mental health and five about interventions to reduce such impact). Most were conducted in Asia (59%), examined the impact of the SARS epidemic (69%), and took place in the hospital setting (79%).
- The pooled prevalence was higher for anxiety (45%, 95% CI 21 to 69%; 6 studies, 3,373 participants), followed by depression (38%, 95% CI 15 to 60%; 7 studies, 3,636 participants), acute stress disorder (31%, 95% CI 0 to 82%, 3 studies , 2,587 participants), burnout (29%, 95% CI 25 to 32%; 3 studies; 1,168 participants) and post-traumatic stress disorder (19%, 95% CI 11 to 26%, 10 studies, 3,121 participants).
- Based on 37 studies, a broad number of risk factors were identified for these conditions, including sociodemographic: younger age and female gender; social factors: lack of social support, social rejection or isolation, stigmatization; and occupational: working in a high risk environment (frontline staff), specific occupational roles (e.g., nurse), and lower levels of specialized training, preparedness and job experience.
- One multifaceted intervention (based on training and organizational changes) targeted at hospital nurses during the SARS epidemic produced statistically significant improvements in anxiety, depression, and sleep quality (very low certainty).

Long-Term Persistence of IgG Antibodies in SARS-CoV Infected Healthcare Workers

Date: 02/14/2020

Link: https://www.medrxiv.org/content/10.1101/2020.02.12.20021386v1

- A long-term prospective cohort study followed 34 SARS-CoV-infected healthcare workers from a hospital with clustered infected cases during the 2002-2003 SARS outbreak in Guangzhou, China, with a 13-year follow-up. Serum samples were collected annually from 2003-2015.
- Anti SARS-CoV IgG was found to persist for up to 12 years. IgG titers typically peaked in 2004, declining rapidly from 2004-2006, and then continued to decline at a slower rate. IgG titers in SARS-CoV-infected healthcare workers remained at a significantly high level until 2015.

Geo-temporal distribution of 1,688 Chinese healthcare workers infected with COVID-19 in severe conditions – a secondary data analysis

Date: 03/23/2020

Link: https://www.medrxiv.org/content/10.1101/2020.03.19.20032532v1.full.pdf

- 1,688 infected Chinese medical workers
- Case fatality rate lower in medical workers (0.3%) compared to similar aged cases who were not medical workers (0.65%)

Novel Coronavirus (COVID-19) Knowledge and Perceptions: A Survey of Healthcare Workers

Date: 03/16/2020

Link: https://www.medrxiv.org/content/10.1101/2020.03.09.20033381v2

- Health care worker survey distributed globally first week of March, 2020 to estimate COVID-19 knowledge
- 529 participants; 30% doctors, 29% medical students; 68% from Asia
- Poor knowledge of COVID-19 symptoms and transmission
- Significant number of health care workers used social media to obtain information about COVID-19
- Educational interventions of health care workers about COVID-19 may be needed

MATERNAL AND CHILD HEALTH

Second-Trimester Miscarriage in a Pregnant Woman With SARS-CoV-2 Infection

Date of article – April 30th, 2020

Link – https://jamanetwork.com/journals/jama/fullarticle/2765616

- No data exist regarding the effect on fetuses of maternal SARS-CoV-2 infection during the first or second trimester, and data are limited regarding infections that occur during the third trimester.
- However, reports of newborns with fetal distress or requiring admission to the ICU and a stillbirth after maternal COVID-19 in the third trimester suggest the possibility of COVID-19–induced placental pathology.
- The authors present a case of miscarriage during the second trimester in a woman with COVID-19, which appears to relate to placental infection with SARS-CoV-2, supported by virological findings in the placenta. Contamination at the time of delivery, sampling, or laboratory evaluation is unlikely, as all other swabs were negative for SARS-CoV-2. No other cause of fetal demise was identified.
- Whether SARS-CoV-2 crosses the placental barrier warrants further investigation.

Possible Vertical Transmission of SARS-CoV-2 From an Infected Mother to Her Newborn

Date: 03/26/2020

Link: https://jamanetwork.com/journals/jama/fullarticle/2763853

- Controversy exists regarding whether SARS-CoV-2 can be transmitted *in utero* from an infected mother to her infant before birth.
- The authors report a newborn with elevated IgM antibodies to SARS-CoV-2 born to a mother with COVID-19.
- Following cesarean delivery, the neonate had no symptoms and was immediately quarantined in the NICU. At 2 hours of age, the SARS-CoV-2 IgG level was 140.32 AU/mL and the IgM level was 45.83

AU/mL (normal values<10 AU/mL for both). Cytokines were elevated (IL-6, 28.26 pg/mL; IL-10, 153.60 pg/mL), as well as a white blood cell count of 18.08×109 /L. Chest CT was normal. Results from 5 RT-PCR tests on nasopharyngeal swabs taken from 2 hours to 16 days of age were negative.

- These results suggest that the neonate was infected *in utero*, although infection at delivery cannot be ruled out.

Antibodies in Infants Born to Mothers With COVID-19 Pneumonia

Date: 03/26/2020

Link: https://jamanetwork.com/journals/jama/fullarticle/2763854

- Neonatal throat swabs and blood samples all had negative RT-PCR test results. All 6 infants had antibodies detected in their serum. Two infants had IgG and IgM concentrations higher than the normal level (<10 AU/mL). One infant had an IgG level of 125.5 and IgM level of 39.6 AU/mL; the second infant had an IgG level of 113.91 AU/mL and IgM level of 16.25 AU/mL. Three infants had elevated IgG levels (75.49, 73.19, 51.38 AU/mL) but normal IgM levels. Inflammatory cytokine IL-6 was significantly increased in all infants. None of the infants presented any symptoms as of March 8, 2020.
- IgG (which was elevated in 5 of the 6 infants) is passively transferred across the placenta from mother to fetus beginning at the end of the second trimester and reaches high levels at the time of birth. However, IgM, which was detected in 2 infants, is not usually transferred from mother to fetus because of its larger macromolecular structure.

Can SARS-CoV-2 Infection Be Acquired In Utero? More Definitive Evidence Is Needed

Date: 03/26/2020

Link: https://jamanetwork.com/journals/jama/fullarticle/2763851?guestAccessKey=f64eb0a0-2f35-418c-b2db-127c8d5c7aac&utm_source=silverchair&utm_medium=email&utm_campaign=article_alert-jama&utm_content=olf&utm_term=032620

- This is a JAMA editorial discussing two recent manuscripts (Dong et al. 2020; Zeng et al. 2020) on potential vertical transmission of SARS-CoV-2 *in utero*.
- The authors argue that at this time, these data are not conclusive and do not prove *in utero* transmission. More definitive evidence is needed before these findings can be used to counsel pregnant women that their fetuses are at risk from congenital infection with SARS-CoV-2.
- The suggestion of *in utero* transmission rests on IgM detection, and IgM is a challenging way to diagnose many congenital infections. IgM antibodies are too large to cross the placenta and so detection in a newborn reasonably could be assumed to reflect fetal production following in utero infection. However, most congenital infections are not diagnosed based on IgM detection because IgM assays can be prone to false-positive and false-negative results, along with cross-reactivity and testing challenges.

Clinical characteristics of novel coronavirus disease 2019 (COVID-19) in newborns, infants and children

Date: 03/10/2020

Link: https://www.sciencedirect.com/science/article/pii/S1875957220300267?via%3Dihub
- Children with COVID-19 infection may be asymptomatic or have fever, dry cough, and fatigue, with a few upper respiratory symptoms, including nasal congestion and runny nose; some patients have gastrointestinal symptoms, including abdominal discomfort, nausea, vomiting, abdominal pain, and diarrhea. Most infected children have mild clinical manifestations, and good prognosis.

- Although COVID-19 cases were rare in infants and newborns, nine hospitalized infants diagnosed with COVID-19 in China from December 8, 2019, to February 6, 2020 were reported. The minimum age was 1 month and the maximum 11 months. Of the nine infants, four had fever, two mild upper respiratory symptoms, one asymptomatic, and two no information on symptoms. All nine babies had at least one infected family member, and the baby's infection usually occurred after the family member's infection. All nine infants did not require intensive care or mechanical ventilation and had no serious complications.
- All possible or laboratory-confirmed neonatal SARS-CoV-2 infections should be admitted to the neonatal intensive care unit. The efficacy of antiviral drugs is uncertain in children, and antimicrobial agents are only applicable to patients with possible or proven bacterial infections. If newborns also present with respiratory distress syndrome, administration of high-dose pulmonary surfactant, nitric oxide inhalation, and high-frequency oscillatory ventilation should be considered. In critically ill newborns, intravenous administration of glucocorticoids or immunoglobulins, sustainable kidney replacement, and extracorporeal membrane oxygenation may also be considered.

Guidelines for pregnant women with suspected SARS-CoV-2 infection

Date: 03/03/2020

Link: https://www.sciencedirect.com/science/article/pii/S1473309920301572?via%3Dihub

- Consequences of infection with SARS-CoV-2 for pregnancies are uncertain. However, the possibility should be considered: coronaviruses responsible for severe acute respiratory syndrome (SARS) and Middle East respiratory syndrome (MERS) can cause severe adverse pregnancy outcomes, such as miscarriage, premature delivery, intrauterine growth restriction, and maternal death. Recommendations are therefore urgently needed.
- The authors provide a detailed management algorithm for health-care providers (see appendix in link above). Recommendations are broken down by SARS-CoV-2 exposure, travel history, and presentation of symptoms.

ANESTHESIA, OPERATING ROOM AND ICU

NEW: COVID-19: Obstetric anesthesia care considerations

Date: 05/2020

Link: https://www.sciencedirect.com/science/article/pii/S0952818020308710?via%3Dihub#!

- Pre-hospital COVID-19 screening should be implemented for all pregnant patients.
- Limit the number of staff in a delivery room or operating room when feasible
- Encourage the use of video messaging with other members of the patient's support system
- An experienced provider should perform neuraxial procedures and intubations, whenever possible.

Pediatric Airway Management in COVID-19 patients – Consensus Guidelines from the Society for Pediatric Anesthesia's Pediatric Difficult Intubation Collaborative and the Canadian Pediatric Anesthesia Society

Date: 04/13/2020

Link: https://journals.lww.com/anesthesia-analgesia/Abstract/9000/Pediatric_Airway_Management_in_COVID_19_patients__.95683.aspx

- The Pediatric Difficult Intubation Collaborative (PeDI-C) group, which currently includes 35 hospitals from six countries, generated consensus guidelines on airway management in pediatric anesthesia.
- Recommendations include administering anxiolytic medications, intravenous anesthetic inductions, tracheal intubation using video laryngoscopes and cuffed tracheal tubes, use of in-line suction catheters, and modifying workflow to recover patients from anesthesia in the operating room.
- In addition, PeDI-C recommends that anesthesiologists consider using appropriate personal protective equipment when performing aerosol-generating medical procedures in asymptomatic children, in addition to known or suspected children with COVID-19.

- Airway procedures should be done in negative pressure rooms when available. Adequate time should be allowed for operating room cleaning and air filtration between surgical cases. Research using rigorous study designs is urgently needed to inform safe practices during the COVID-19 pandemic.
- Until further information is available, the PeDI-C advises that clinicians consider these guidelines to enhance the safety of health care workers during airway management when performing aerosol-generating medical procedures.

Anesthesia Considerations and Infection Precautions for Trauma and Acute Care Cases During the COVID-19 Pandemic

Date: 04/24/2020

Link: :https://journals.lww.com/anesthesia-analgesia/Abstract/9000/Anesthesia_Considerations_and_Infection.95652.aspx

- Personal protective equipment (PPE) for different levels of professional protection during COVID-19 Epidemic

Table 1. Personal protective equipment (PPE) for different levels of professional protection during COVID-19 Epidemic

Level of protection	Applicable settings	Applicable procedures	Work clothes	Disposable hair cover	Surgical masks	Latex gloves	N95 respirators or higher level masks	Fluid resistant gown	Protective coverall	Goggles/ Face shield	Disposable shoe covers	Positive pressure breathing headgears
Level-one protection	General clinics and ward	General diagnosis and treatment	√	√	√	If needed						
Level-two protection	Fever clinics	General diagnosis and treatment	√	√		√	√	√	If needed	√	√	
Level-three protection	Isolation ward, fever clinic, isolation area, operating room, and laboratory	Sputum aspiration, lower respiratory tract sampling, endotracheal intubation and tracheotomy, and other procedures involving airway intervention for COVID-19 related patients. Test-running for COVID-19 samples	√	√		√ Double	√	√	√	√	√	Recommended

- Workflow of COVID-19 triage for emergency surgery and infection precautions for healthcare workers (HCWs) during the epidemic
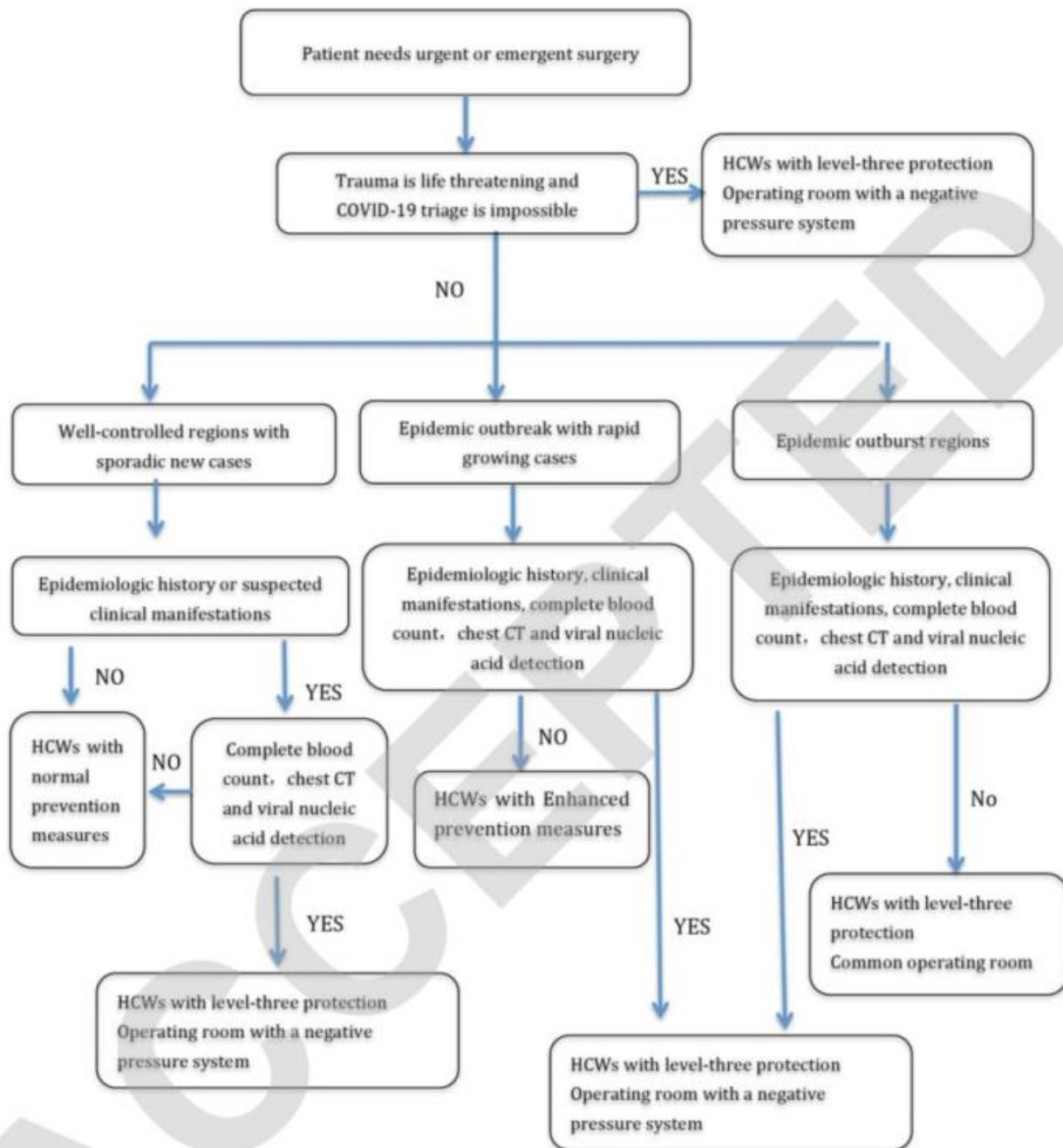
Fair Allocation of Scarce Medical Resources in the Time of Covid-19

Date: 03/23/2020

Link: https://www.nejm.org/doi/full/10.1056/NEJMsb2005114?cid=DM89089_NEJM_COVID-19_Newsletter&bid=172963038

- The Covid-19 pandemic is likely to cause a shortage of hospital beds, ICU beds, and ventilators. It is also likely to affect the availability of the medical workforce, since doctors and nurses are already becoming ill or quarantined.

- Maximizing benefits, treating equally, promoting and rewarding instrumental value, and giving priority to the worst off —yield six specific recommendations for allocating medical resources in the Covid-19 pandemic.

Table 2. Ethical Values to Guide Rationing of Absolutely Scarce Health Care Resources in a Covid-19 Pandemic.

Ethical Values and Guiding Principles	Application to COVID-19 Pandemic
Maximize benefits	
Save the most lives	Receives the highest priority
Save the most life-years — maximize prognosis	Receives the highest priority
Treat people equally	
First-come, first-served	Should not be used
Random selection	Used for selecting among patients with similar prognosis
Promote and reward instrumental value (benefit to others)	
Retrospective — priority to those who have made relevant contributions	Gives priority to research participants and health care workers when other factors such as maximizing benefits are equal
Prospective — priority to those who are likely to make relevant contributions	Gives priority to health care workers
Give priority to the worst off	
Sickest first	Used when it aligns with maximizing benefits
Youngest first	Used when it aligns with maximizing benefits such as preventing spread of the virus

Perioperative COVID-19 Defense: An Evidence-Based Approach for Optimization of Infection Control and Operating Room Management

Date: 03/26/2020

Link: : https://journals.lww.com/anesthesia-analgesia/Abstract/publishahead/Perioperative_COVID_19_Defense__An_Evidence_Based.95734.aspx

- Researchers described an evidence-based approach for optimization of infection control and operating room management during the COVID-19 pandemic, which involved involve a combination of deep cleaning with surface disinfectants and ultraviolet light (UV-C)
- Place alcohol-based hand rubs on the IV pole to the left of the provider.
- Place a wire basket lined with a zip closure plastic bag, on the IV pole to the right of the provider. Place all contaminated instruments in the bag and close. Designate and maintain clean and dirty areas. After induction of anesthesia, wipe down all equipment and surfaces with disinfection wipes that contain a quaternary ammonium compound and alcohol. Use a top down cleaning sequence adequate to reduce bioburden. Treat operating rooms using UV-C
- Decolonize patients using preprocedural chlorhexidine wipes, 2 doses of nasal povidone iodine within one hour of incision, and chlorhexidine mouth rinse.
- Create a closed lumen IV system and use hub disinfection.
- Provide data feedback by surveillance of ESKAPE transmission

- Use relatively long (e.g., 12-hour) to reduce the use of surgical masks and to reduce potential COVID-19 exposure
- Do 1 case in each operating room daily, with terminal cleaning after each case
- Do not have patients go into a large, pooled phase I post-anesthesia care unit

What we do when a COVID-19 patient needs an operation: operating room preparation and guidance

Date: 03/26/2020

Link: https://link.springer.com/article/10.1007%2Fs12630-020-01617-4

- Complete operating room workflow for a COVID-19 case (see figure below). CD = controlled drugs; ICU = intensive care unit; NM = nurse manager; OR = operating room; PAPR = powered air-purifying respirator; PC = personal computer; PPE = personal protection equipment; pre-op = preoperative
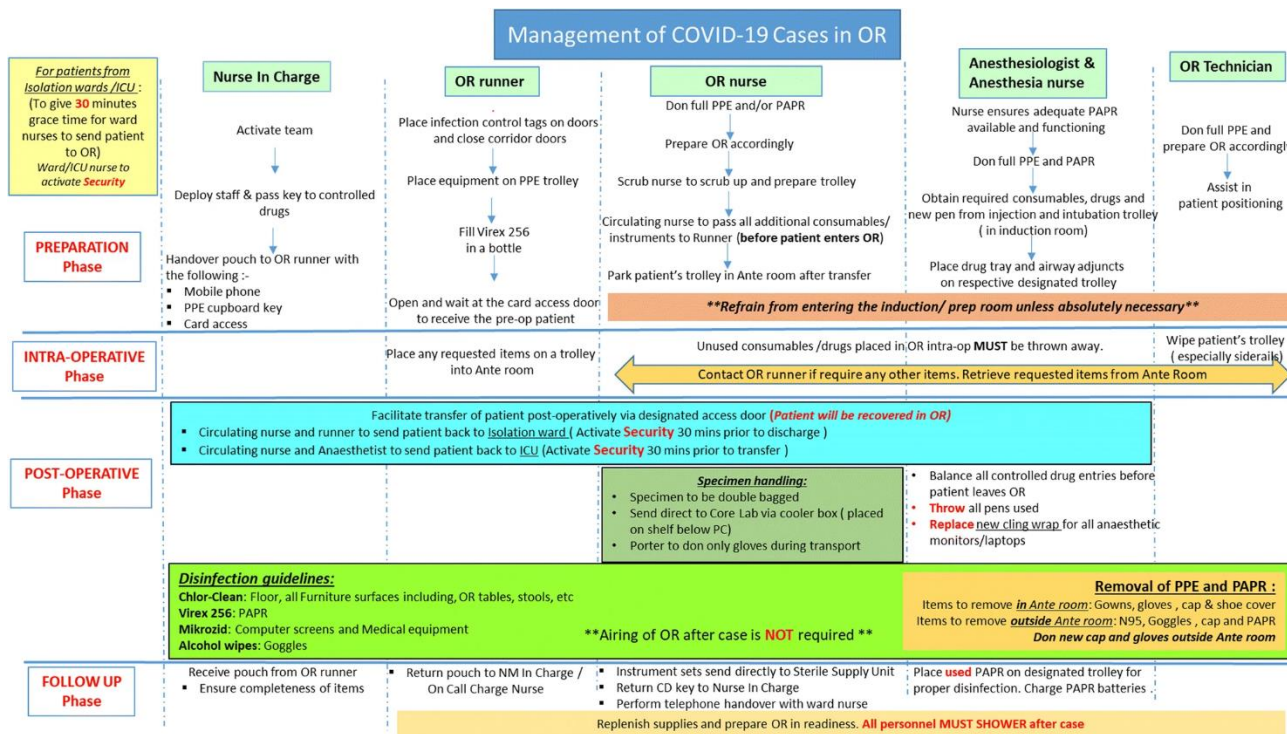
EFFECTIVENESS OF QUARANTINE

Interventions to mitigate early spread of SARS-CoV-2 in Singapore: a modelling study

Date: 3/23/3030

Link: https://www.sciencedirect.com/science/article/pii/S1473309920301626?via%3Dihub
- Used an existing model for influenza to estimate the number of cases in Singapore using four containment strategies:
  - Isolation of ill and quarantine of contacts
  - Isolation of ill, quarantine of contacts, and school closings

- - Isolation of ill, quarantine of contacts, and work closures
  - A combined method including all the above
- They ran the model for separate infectivity scenarios (basic reproduction number [R0] of 1.5, 2.0, or 2.5) using a 7.5% asymptomatic rate.
- The combined method was best at reducing the number of infections.
- Workplace closures should be prioritized over school closings if necessary, since symptomatic children have higher withdrawal rates than symptomatic employees.

Detection of SARS-CoV-2 Among Residents and Staff Members of an Independent and Assisted Living Community for Older Adults — Seattle, Washington, 2020

Date: 4/3/2020

Link:
https://www.cdc.gov/mmwr/volumes/69/wr/mm6914e2.htm?s_cid=mm6914e2_e&deliveryName=USCDC_921-DM24955

- Real-world example of how social distancing/isolation measures prevented an outbreak in a joint independent and assisted living facility.
- Two patients were hospitalized with COVID-19 in early March. Within one day, the entire facility was in isolation.
- All residents and staff were tested using RT-PCR on NP swabs.
- Three residents tested positive at that time; only one was showing mild symptoms. Two staff members tested positive; both reported symptoms.
- One week later, all residents were re-tested. Two of the previous three patients were still positive; there was also one new positive resident at that time.
- All residents remain in isolation and are clinically stable as of March 31.

IMMUNE RESPONSE

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

Date: 03/28/2020

Link: https://www.ncbi.nlm.nih.gov/pubmed/32221519

- 137 patients in China with SARS-CoV-2 (COVID-19) infections.
- Seroconversion rates for antibodies (Ab), IgM and IgG were 93.1%, 82.7% and 64.7% respectively.
- Median conversion times for antibodies, IgM and IgG were 11, 12 and 14 days respectively
- Ab was <40% at 1 week following onset but Ab were 100%, IgM 94.3% and IgG 79.8% at day 15 post symptom onset.
- RNA detection decreased from 66.7% to 45.5% from days <7 to >=15 days.
- Higher antibody titer independently associated with worse clinical classification (p=0.006)

Profiling Early Humoral Response to Diagnose Novel Coronavirus Disease (COVID-19)

Date: 03/21/2020

Link: https://academic.oup.com/cid/advance-article/doi/10.1093/cid/ciaa310/5810754

- 82 confirmed and 58 probable COVID-19 cases in China. 208 plasma samples collected and assayed by ELISA using recombinant viral nucleocapsid protein for IgA, IgM and IgG.
- Median time to IgM and IgA detection was 5 days (IQR 3-6), IgG detected at 14 days (IQR 10-18). Positive rate of 85.4%, 92.7% and 77.8%, respectively.
- In confirmed and probable cases the positive rates of IgM were 75.6% and 93.1%, respectively.
- Detection efficiency of IgM ELISA significantly better than qPCR after 5.5 days of symptoms.
- Positive detection increased to 98.6% for IgM + qPCR compared to qPCR alone of 51.9%.

Viral Shedding and Antibody Response in 37 Patients with Middle East Respiratory Syndrome Coronavirus Infection

Date: 02/15/2020

Link: https://www.ncbi.nlm.nih.gov/pubmed/26565003

- 37 patients with MERS. 199 lower respiratory tract (LRT) samples during 3 weeks of illness tested with PCR for viral load (93% were positive). 84 upper respiratory tract (URT) samples tested. 33% of 108 serum samples positive for viral RNA.
- IgM testing offered no advantage of IgG testing
- All surviving patients but only ~half of fatal cases had detectable IgG and neutralizing antibodies
- Levels of IgG and neutralizing antibodies weakly inversely correlated with LRT viral loads
- Presence of antibodies did not eliminate virus from LRT

COVID-19 AND CANCER

Determinants of Severity in Cancer Patients with COVID-19 Illness

Date: 05/04/2020

Link: https://www.medrxiv.org/content/10.1101/2020.05.04.20086322v1.full.pdf

- COVID-19 illness is associated with higher rates of hospitalization and severe outcomes in patients with cancer
- 40% (out of 423) patients with cancer were hospitalized for COVID-19 illness, 20% developed severe respiratory illness, including 9% that required mechanical ventilation, and 9% that died.
- Age ≥ 65 years and treatment with immune checkpoint inhibitors (ICI) within 90 days were predictors for hospitalization and severe disease, while receipt of chemotherapy within 30 days and major surgery were not.

Systematic investigations of COVID-19 in 283 cancer patients

Date: 04/28/2020

Link: https://www.medrxiv.org/content/10.1101/2020.04.28.20083246v1.full.pdf

- Systematic review of Covid-19 in a large cancer cohort in China
- Current cancer patients exhibited worse outcomes versus former cancer patients (overall survival, HR=2.45, 95% CI 1.10 to 5.44, p=0.02; mortality rate, 21% vs 9%).
- Higher mortality rate in patients with lymphohematopoietic malignancies (LHM) (53%, 9/17). LHM (p=0.001) was one of the independent factors associating with critical illness or death.