

RAOM COVID-19 ARCHIVE

December, 2019 - July, 2020

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THE VIRUS

(Coronaviruses are enveloped non-segmented positive-sense RNA viruses belonging to the family Coronaviridae and the order Nidovirales and are broadly distributed in humans and other mammals. Coronaviruses are ecologically diverse with the greatest variety seen in bats, the suggested reservoir for these viruses. An important CoV factor is their ability to expand their genetic diversity through ongoing recombination and mutation events. Four CoVs are endemic globally and cause 10% to 30% of mild upper respiratory tract infections in adults. Although most human coronavirus infections are mild, the two most recent major CoVs-- SARS-CoV and MERS-CoV -- have caused more than 10 000 cumulative cases of severe respiratory disease in the past two decades, with mortality rates of 10% for SARS and 37% for MERS.)

Tan W, Zhao X, Ma X, et al. **A novel coronavirus genome identified in a cluster of pneumonia cases—Wuhan, China 2019–2020.** *China CDC Weekly* 2020; 2: 61–62.

Zhu N, Zhang D, Wang W, et al. **A novel coronavirus from patients with pneumonia in China, 2019.** *N Engl J Med* 2020; 382:727-33. Published online Jan 24.

DOI:10.1056/NEJMoa2001017

- Researchers at the China Center for Disease Control investigating the cause of infection in 3 adults with pneumonia of unknown etiology definitively identified a novel coronavirus from broncho-alveolar lavage specimens using whole-genome sequencing, direct polymerase chain reaction (PCR), and culture on January 7, 2020.
- The 2019-nCoV virus -- now officially known as SARS-CoV-2 -- is physically large among viruses, measuring 125 nanometers in diameter, covered with spiky projections -- the surface spike glycoprotein is critical for binding to host cell receptors and is believed to represent a key determinant of host range restriction.
- By phylogenetic analysis, the previously unknown virus fell into the betacoronavirus genus, which includes SARS-CoV, MERS-CoV, and a bat SARS-like coronavirus.

- Novel coronavirus was named 2019-nCoV and formed another clade within the subgenus sarbecovirus, Orthocoronavirinae subfamily.

Roujian Lu, Xiang Zhao, Juan Li et al. **Genomic characterization & epidemiology of 2019 novel coronavirus: implications for virus origins and receptor binding.** Lancet 2020; 395: 565–74. [doi.org/10.1016/S0140-6736\(20\)30251-8](https://doi.org/10.1016/S0140-6736(20)30251-8)

- Next-generation sequencing of samples from bronchoalveolar lavage fluid from 9 pts with SARS-CoV-2 infection; 8/9 had visited the Huanan seafood market in Wuhan
- Genome sequences were extremely similar, exhibiting >99.98% sequence identity.
- By phylogenetic analysis, 2019-nCoV was most closely related (88% identity) to 2 bat-derived SARS-like coronaviruses, bat-SL-CoVZC45 & bat-SL-CoVZXC21, collected in 2018 in Zhoushan, eastern China; virus is more distant from SARS-CoV (~79%) and MERS-CoV (~ 50%).
- Homology modelling revealed that 2019-nCoV had a similar receptor-binding domain structure to that of SARS-CoV, despite amino acid variation at some key residues.
- Bats might be the original host of this virus with an animal from the seafood market representing an intermediate host facilitating the emergence of the virus in humans.
- Structural analysis suggests that 2019-nCoV may bind to the angiotensin converting enzyme 2 receptor in humans.

South China Agricultural University finds pangolin as a potential intermediate host for new coronavirus. Published Jan. 20,2020. Available at: flutrackers.com › - 2019-ncov-new-coronavirus › china-2019-ncov.

- The chief suspect for intermediate host between bats and humans for SARS-COV-2 is the pangolin, a small ant-eating creature.
- Pangolins are prized in Asia as food and medicine and were being sold in the Wuhan Huanan seafood and wild animal market, linked to early cases of 2019-nCoV
- The genome sequence of the novel coronavirus strain derived from pangolins is 99% identical to SARS-CoV-2.

Paraskevisa D, Kostakia G, Magiorkinisa G et al. **Full-genome evolutionary analysis of the novel coronavirus (2019-nCoV) rejects the hypothesis of emergence as a result of a recent recombination event.** Infection, Genetics and Evolution 2020; 79. April 20, 2020. doi.org/10.1016/j.meegid.2020.104212

- Full-genomic sequence analysis of the novel coronavirus (2019-nCoV).
- Phylogenetic and recombination analysis within the subgenus of sarbecovirus.

- Evidence that the 2019-nCoV shows discordant clustering with the BatSARS-like coronavirus sequences.
- No evidence that 2019-CoV 2 emerged as a result of a recent recombination event.

vanDorp L, Acman M, Richard D et al. **Emergence of genomic diversity and recurrent mutations in SARS-CoV-2.** Infection, Genetics and Evolution (2019). doi.org/10.1016/j.meegid.2020.

- Curating a dataset of 7666 public genome SARS-CoV-2 assemblies allowed analysis of the emergence of genomic diversity over time.
- Results point to all sequences sharing a common ancestor towards the end of 2019, supporting this as the period when SARS-CoV-2 jumped to its human host.
- Due to extensive transmission, the genetic diversity of the virus in several countries recapitulates a large fraction of its worldwide genetic diversity.
- By focusing on mutations which have emerged independently multiple times, 198 filtered recurrent mutations in the SARS-CoV-2 genome were identified.
- Nearly 80% of recurrent mutations produced non-synonymous changes at the protein level, suggesting possible ongoing adaptation of SARS-CoV-2.

Zheng S, Fan J, Yu F et al. **Viral load dynamics and disease severity in patients infected with SARS-CoV-2 in Zhejiang province, China, January-March 2020: retrospective cohort study.** BMJ. 2020 Apr 21;369:m1443. [doi: 10.1136/bmj.m1443.](https://doi.org/10.1136/bmj.m1443)

- Serial respiratory, stool, serum, and urine samples for RNA viral load collected from 96 consecutive pts with SARS-CoV-2 during hospital course in Zhejiang, China.
- RNA virus detected in sputum and saliva samples in all pts, 55% in stool, 41% in serum.
- Median virus duration in stool (22 days, IQR:17-31) was significantly longer than in respiratory (18 days, IQR:13-29) & serum samples (16 days, IQR:11-21).
- Viral load was higher in pts with severe disease than in those with mild disease.
- Virus duration was longer in patients older than 60 years and in male patients.

Wölfel R, Corman VM, Guggemos W et al. **Virologic assessment of hospitalized patients with COVID-2019.** Nature. 2020 Apr 1. [doi: 10.1038/s41586-020-2196-x](https://doi.org/10.1038/s41586-020-2196-x)

Detailed virologic analysis of nine cases of COVID-19 showed active replication of the SARS-CoV-2 virus in tissues of the throat /upper respiratory tract → Confirmation of early contagious state due to active pharyngeal viral shedding.

Wajnberg A, Mansour M, Leven E et al. **Humoral immune response and prolonged PCR positivity in a cohort of 1343 SARS-CoV 2 patients in the New York City region.** medRxiv 2020. May 5, 2020.

doi: doi.org/10.1101/2020.04.30.20085613

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

Zhang L, Jackson CB, Mou H et al. **The D614G mutation in the SARS-CoV-2 spike protein reduces S1 shedding and increases infectivity.** BioRxiv: Posted 6/12/2020. doi.org/10.1101/2020.06.12.148726

- In SARS-CoV-2, the spike (S) protein mediates receptor binding and fusion of the viral and host cellular membrane via 2 domains: S1 which mediates receptor binding & S2 which mediates downstream membrane fusion.
- Over time, SARS-CoV-2 isolates encoding a D614G mutation in the viral spike (S) protein were found to predominate, implying that this change enhanced viral transmission. The G614 genotype was not detected in February and observed at low frequency in March (26%) but increased rapidly by April (65%) and May (70%).
- Researchers studying both versions of the gene using a proxy virus in a petri dish of human cells showed that viruses with the G variant had more and more stable spike proteins.
- Retroviruses pseudo-typed with SG614 infected ACE2-expressing cells 9X more efficiently than those with SD614 & this greater infectivity was correlated with less S1 shedding and greater incorporation of the S protein into the pseudo-virion.
- → SG614 is more stable than SD614, consistent with epidemiological data suggesting that viruses with SG614 transmit more efficiently.
- The pseudo-viruses containing these S proteins were neutralized with comparable efficiencies by convalescent plasma suggesting that vaccines based on the original version of the virus will be effective against the new strain.

THE DISEASE

CHINA

Huang C, Wang Y, Li X et al. **Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China.** Lancet 2020. Published online on Jan. 24, 2020. doi:10.1016/S0140-6736(20)30183-5.

Case series of the first 41 hospitalized pts infected with 2019-nCoV by Jan 2, 2020:

- Prodromal phase included fever, dry cough, and malaise.
- Two-thirds of pts had worked or shopped at a local fish and wild animal market, the Huanan Seafood Wholesale Market suggesting a possible origin for the virus.
- Upper respiratory and GI symptoms were notably infrequent.
- Common laboratory findings on admission included lymphopenia and bilateral ground-glass opacity on CXR &/or consolidation in chest CT scans.
- 22/41 pts (55%) developed severe dyspnea and 13 (32%) required ICU admission;
- 6 pts died → case-fatality rate of 14.6%. (With true number of infections unknown, fatality rate is likely much lower.)

Chan JF-W, Yuan S, Kok K-H et al. **A familial cluster of pneumonia associated with the 2019 novel coronavirus indicating person-to-person transmission: A study of a family cluster.** Lancet 2020 Jan 24; [e-pub].
[https://doi.org/10.1016/S0140-6736\(20\)30154-9](https://doi.org/10.1016/S0140-6736(20)30154-9).

Confirmation of person-to-person transmission.

WHO. Daily media briefing on #2019-nCoV. Feb. 7, 2020. Available at: [www.who.int/ Coronavirus disease 2019](http://www.who.int/Coronavirus-disease-2019) › Media resources.

In clinical series of culture (+) pts from China, 82% have had mild symptoms, 15% severe, 3% critical.

Li Q, Guan X, Wu P et al. **Early Transmission Dynamics in Wuhan, China, of Novel Coronavirus–Infected Pneumonia.** N Engl J Med. Published January 29, 2020. doi/full/10.1056/NEJMoa2001316

Chen N, Zhou M, Dong X et al. **Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China: a descriptive study.** Lancet 2020. Published January 30,2020. doi.org/10.1016/S0140-6736(20)30211-7.

Wang D, Hu B, Hu C et al. **Clinical Characteristics of 138 Hospitalized Patients With 2019 Novel Coronavirus–Infected Pneumonia in Wuhan, China.** JAMA. Published online February 7, 2020.

doi:10.1001/jama.2020.1585.

3 early published series of laboratory-confirmed, hospitalized cases from Wuhan →

- Median age: 55-59 yrs with male predominance; no pt <15 yrs.
- Pts with earlier presentation much more likely had exposure to the Huanan Market.
- Increasing proportion of cases acquired in hospital by pts or hospital personnel over time, to maximum of 40% in one series.
- Mean incubation period: 5.2 days, 95th%ile at 12.5 days → resulted in 14 day standard quarantine period
- Most common clinical symptoms: fever(80%); dry cough(70%), sob(30%); myalgias(10%).
- On CXR &/or CT scan, bilateral pneumonia present in 75% of pts with multiple areas of consolidation and ground-glass opacifications.
- Median time from 1st symptom to sob was 5 days and to hospital admission was 7 days; ~60% developed ARDS at a median of 8 days S/P first symptom.
- Mortality ranged from 4 to 17%, predominantly in older patients, due to progressive respiratory and multi-organ failure.
- Overall, mean mortality estimated at ~2%.

To KK, Tsang OT, Leung WS et al. **Temporal profiles of viral load in posterior oropharyngeal saliva samples and serum antibody responses during infection by SARS-CoV-2: an observational cohort study.** Lancet Infect Dis. 2020 Mar 23. pii: S1473-3099(20)30196-1. doi:10.1016/S1473-3099(20)30196-1.

Serial respiratory viral load of SARS-CoV-2 in posterior oropharynx saliva samples and serum antibody responses from 23 patients with COVID-19 showed highest viral load at presentation and during the first week of illness with subsequent decline over time.

Zheng S, Fan J, Yu F et al. **Viral load dynamics and disease severity in patients infected with SARS-CoV-2 in Zhejiang province, China, January-March 2020: retrospective cohort study.** BMJ. 2020 Apr 21;369:m1443. **doi:10.1136/bmj.m1443.**

- Serial respiratory, stool, serum & urine samples for RNA viral load collected from 96 consecutive pts with SARS-CoV-2 during hospital course in Zhejiang province, China
- RNA virus detected in sputum and saliva samples in all pts, in 55% in stool, in 41% in serum.

- Median duration of virus in stool (22 days, IQR:17-31) was significantly longer than in respiratory (18 days, IQR:13-29) and serum samples (16 days, IQR:11-21).
- Viral load was higher in pts with severe disease than in those with mild disease.
- Virus duration was longer in patients >60 years and in males.

USA

Holshue ML, DeBolt C, Lindquist S et al. **First Case of 2019 Novel Coronavirus in the United States.** N Engl J Med 2020; 382; 10: 929-936.

DOI: 10.1056/NEJMoa2001191

- 41 yr old previously healthy male resident of Snohamish county, Washington who returned from a visit to Wuhan, China on January 14,2020, presented to an urgent care center on Jan. 21, 2020 with 4 d hx of fever, cough
- Because of pt.'s travel and awareness of the new coronavirus, SARS-CoV-2 cultures were obtained and were positive
- Illness was relatively benign with minimal O2 requirement, no critical events
- Pt was normally active in the community before presentation and sat in the waiting room for some time before he was seen
- On Feb.28, the virus in another case in that community was found to be very likely descended from that first case based on phylogenetic analysis. → These genetic findings suggest that SARS-CoV-2 had been spreading through the community for close to six weeks.
- Snohamish county is close to Everett, Washington where major early COVID-19 outbreak occurred → local disease spread was occurring in the US beginning in the third week of January.

Wölfel R, Corman VM, Guggemos W et al. **Virologic assessment of hospitalized patients with COVID-2019.** Nature. 2020 Apr 1.

doi: 10.1038/s41586-020-2196-x

Detailed virologic analysis of nine cases of COVID-19 showed active replication of the SARS-CoV-2 virus in tissues of the throat /upper respiratory tract → Confirmation of early contagious state due to active pharyngeal viral shedding.

Sutton D, Fuchs K, D'Alton M, Goffman D. **Universal screening for SARS-CoV-2 in women admitted for delivery.** N Engl J Med April 13, 2020.

DOI: 10.1056/NEJMc2009316

- Case series: 215 pregnant women who delivered infants at NY-Presbyterian MC screened for COVID-19
- 4 women had fever, all tested (+) for SARS-CoV-2

- Of 211 women without symptoms, 29(13.7%) tested (+) for SARS-CoV-2 on N/P culture → 87.9% of culture (+) women were asymptomatic
- Overall, 15% of women presenting for delivery were SARS-CoV-2 (+)
- Universal testing in asymptomatic women presenting for delivery allows protection of mothers, babies and hospital staff.

Eliezer M, Hautefort C, Hamel A-L et al. **Sudden and Complete Olfactory Loss Function as a Possible Symptom of COVID-19.** JAMA Otolaryngol Head Neck Surg. Published online April 8, 2020. [doi:10.1001/jamaoto.2020.0832](https://doi.org/10.1001/jamaoto.2020.0832)

Case report of sudden loss of olfactory function due to COVID-19 infection with bilateral obstructive inflammation of olfactory clefts on imaging, which severely impaired the olfactory function by preventing odorant molecules from reaching the olfactory epithelium.

Oxley TJ, Mocco J, Majidi S et al. **Large-Vessel Stroke as a Presenting Feature of Covid-19 in the Young. Correspondence.** N Engl J Med: April 28, 2020
[DOI: 10.1056/NEJMc2009787](https://doi.org/10.1056/NEJMc2009787)

Case series of 5 COVID-19 pts < 60 yrs whose initial disease presentation was a large vessel ischemic stroke. All presented in NYC in March and early April. Mixed picture of coagulopathy in the group. 5% of Wuhan pts experienced stroke as part of their illness. Further knowledge pending.

FRANCE

Poissy J, Goutay J, Caplan M et al. **Pulmonary Embolism in COVID-19 Patients: Awareness of an Increased Prevalence.** Circulation 2020. Originally published 24 Apr 2020. <https://doi.org/10.1161/CIRCULATIONAHA.120.047430>

Case-series of 107 consecutive COVID-19 ICU pts with pneumonia admitted to a tertiary care center in northern France. 22/107(20.6%) developed a pulmonary embolus (PE) within a median of 6 days (range 1 to 18 days) from ICU admission. Frequency of PE in COVID-19 series was twice as high as comparison group of ICU pts with pneumonia (20.6% vs 6.1%; absolute increase risk of 14.4%, 95%CI 6.1 to 22.8%). At PE diagnosis, 20/22 patients were receiving prophylactic antithrombotic treatment. Of note, median BMI of PE pts was 30 (range:22-53). No additional information provided.

USA – NYC

Richardson S, Hirsch JS, Narasimhan M et al. **Presenting Characteristics, Comorbidities, and Outcomes Among 5700 Patients Hospitalized With COVID-19 in the New York City Area.** JAMA. Published online April 22, 2020.
[doi:10.1001/jama.2020.6775](https://doi.org/10.1001/jama.2020.6775)

- Case series of 5700 consecutive pts with culture-proven SARS-CoV-2 infection admitted to 12 hospitals in New York City & environs (in the Northwell Health system) from 3/1/2020 through 4/4/2020.
- Median age, 63 years [IQR, 52-75; range, 0-107 years]; 39.7% female.
- At triage, 30.7% of patients were febrile, 17.3% had RR>24 breaths/min, and 27.8% on supplemental oxygen. Rate of respiratory virus co-infection was 2.1%.
- Most common comorbidities were hypertension (3026; 56.6%), obesity (1737; 41.7%) & diabetes (1808; 33.8%). Pulmonary diagnoses were not significant co-morbidities.
- Outcomes assessed for pts who were discharged or died by study end point.
 - ➔ During hospitalization, 373 patients (14.2%) (median age, 68 yrs [IQR, 56-78]; 33.5% female) were treated in ICU, 320 (12.2%) received invasive mechanical ventilation, 81 (3.2%) received dialysis, and 553 (21%) died.
- For pts requiring mechanical ventilation (n = 1151, 20.2%), 38 (3.3%) were discharged alive, 282 (24.5%) died, & 831 (72.2%) remained in hospital.
- Mortality was 0% (0/20) for male and female patients younger than 20 years.
- Mortality rates were higher for male vs female pts at every 10-yr age interval.
- Mortality rates for those who received mechanical ventilation in the 18-to-65 vs > 65 age groups were 76.4% and 97.2%, respectively.
- Mortality rates for those in the 18-to-65 and older-than-65 age groups who did not receive mechanical ventilation were 19.8% and 26.6%, respectively.

Petrelli CM, Jones SA, Yang J et al. **Factors associated with hospitalization and critical illness among 4,103 patients with COVID-19 disease in New York City.** medRxiv 2020. doi.org/10.1101/2020.04.08.20057794

- Cross-sectional analysis of all patients with laboratory-confirmed Covid-19 treated at a single academic health system in New York City between March 1, 2020 and April 2, 2020, with follow up through April 7, 2020.
- Primary outcomes were hospitalization and critical illness (intensive care, mechanical ventilation, hospice and/or death).
- Among 4,103 Covid-19 patients, 1,999 (48.7%) were hospitalized, of whom 981/1,999 (49.1%) have been discharged home, and 292/1,999 (14.6%) have died or were discharged to hospice.
- Of 445 patients requiring mechanical ventilation, 162/445 (36.4%) have died.
- Strongest hospitalization risks were age ≥75 years (OR 66.8, 95% CI, 44.7-102.6), age 65-74 (OR 10.9, 95% CI, 8.35-14.34), BMI>40 (OR 6.2, 95% CI, 4.2-9.3), and heart failure (OR 4.3 95% CI, 1.9-11.2).
- Strongest critical illness risks were admission oxygen saturation <88% (OR 6.99, 95% CI 4.5-11.0) and elevated inflammatory markers: d-dimer>2500 (OR 6.9, 95% CI, 3.2-15.2), ferritin >2500 (OR 6.9, 95% CI, 3.2-15.2), and C-reactive protein (CRP) >200 (OR 5.78, 95% CI, 2.6-13.8).
- In the decision tree for admission, most important features were age >65 and obesity; for critical illness, the most important was SpO2<88, followed by procalcitonin >0.5, troponin <0.1 (protective), age >64 and CRP>200.

- **Conclusions:** Age and comorbidities are powerful predictors of hospitalization; however, admission oxygen impairment and markers of inflammation are most strongly associated with critical illness.

ITALY

Grasselli G, Zangrillo A, Zanella A et al. **Baseline Characteristics and Outcomes of 1591 Patients Infected With SARS-CoV-2 Admitted to ICUs of the Lombardy Region, Italy.** JAMA. 2020;323(16):1574-1581. [doi:10.1001/jama.2020.5394](https://doi.org/10.1001/jama.2020.5394)

Retrospective case series of all 1591 consecutive patients with laboratory-confirmed COVID-19 referred for ICU admission to the COVID-19 Lombardy ICU Network and treated at one of the 72 ICUs in this network between 2/2/2020 3/18/2020. and March 18, 2020. Median (IQR) age was 63 (56-70) years, 82% male. 68% had > comorbidity & 49% had hypertension. 99% (1287/1300 patients) required respiratory support, including endotracheal intubation in 88% and noninvasive ventilation in 11%; ICU mortality was 26%.

To KK, Tsang OT, Leung WS et al. **Temporal profiles of viral load in posterior oropharyngeal saliva samples and serum antibody responses during infection by SARS-CoV-2: an observational cohort study.** Lancet Infect Dis. 2020 Mar 23. pii: S1473-3099(20)30196-1. [doi: 10.1016/S1473-3099\(20\)30196-1](https://doi.org/10.1016/S1473-3099(20)30196-1).

Serial respiratory viral load of SARS-CoV-2 in posterior oropharynx saliva samples and serum antibody responses from 23 patients with COVID-19 showed highest viral load at presentation and during the first week of illness with subsequent decline over time.

Arons MM, Hatfield KM, Reddy SC, et al. Presymptomatic SARS-CoV-2 infections and transmission in a skilled nursing facility. N Engl J Med.2020. [DOI: 10.1056/NEJMoa2008457](https://doi.org/10.1056/NEJMoa2008457).

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

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

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

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

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

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

- Delay between the peak of SARS-CoV-2 infections and presentation of PIMS [pediatric multisystem inflammatory syndrome temporally associated with COVID-19] raises the possibility that this is a post-infectious, immunologically mediated phenomenon

Preliminary Estimates of the Prevalence of Selected Underlying Health Conditions Among Patients with Coronavirus Disease 2019 — United States, February 12–March 28, 2020. MMWR Morb Mortal Wkly Rep 2020; 69:382–386. [doi.org/10.15585/mmwr.mm6913e2external icon](https://doi.org/10.15585/mmwr.mm6913e2external_icon). April 3, 2020.

- Data from laboratory-confirmed COVID-19 cases reported to CDC from 50 states, four U.S. territories and affiliated islands, the District of Columbia, and New York City with February 12–March 28, 2020 onset dates were analyzed.
- Of 122,653 laboratory-confirmed COVID-19 cases with 2,112 deaths, data on presence or absence of underlying health conditions (lung disease, heart disease, diabetes) and other recognized risk factors for severe outcomes from respiratory infections (i.e., smoking and pregnancy) were available for 7,162 (5.8%) patients.
- **RESULTS:** Percentage of non-ICU hospitalizations was higher among those with underlying health conditions (27.3%–29.8%) than among those without underlying health conditions (7.2%–7.8%); the percentage of cases that resulted in an ICU admission was also higher for those with underlying health conditions (13.3%–14.5%) than those without these conditions (2.2%–2.4%)
- Among all COVID-19 patients with complete information on underlying conditions or risk factors, **94%** of all 184 deaths occurred among patients aged ≥ 19 years with at least one underlying condition.

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

- Retrospective review of clinical and imaging data of COVID-19 pts seen between 3/1/2020 & 4/6/2020 who experienced barotrauma (extrapulmonary air) during invasive mechanical ventilation were compared to pts without COVID-19 infection ventilated during the same period.
- Historical comparison also made to barotrauma rates of ARDS pts from 02/01/2016 to 02/01/2020 at our institution.
- Of 601 ventilated COVID-19 pts (63 \pm 15 years, 71% men), 89/601 (15%) had ≥ 1 barotrauma events, 145 total barotrauma events (24% overall events) (95% CI 21–28%). Of 196 ventilated pts without COVID-19 infection (64 \pm 19 years, 52% male) only 1 had a single barotrauma event (.5% 95% CI, 0–3%, $p < .001$).

- Of 285 ventilated ARDS pts over the prior 4 years (68 ± 17 years, 60% men), 28 patients (10%) had 31 barotrauma events, with overall barotrauma rate of 11% (95% CI 8-15%, $p < .001$ vs. the group with COVID-19 infection).
- Barotrauma was an independent risk factor for death in COVID-19 (OR=2.2, $p = .03$), and was associated with longer hospital length of stay (OR=.92, $p < .001$).

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

Age disparities in observed cases could be explained by children having lower susceptibility to infection, lower propensity to show clinical symptoms or both. We evaluate these possibilities by fitting an age-structured mathematical model to epidemic data from China, Italy, Japan, Singapore, Canada and South Korea. We estimate that susceptibility to infection in individuals under 20 years of age is approximately half that of adults aged over 20 years, and that clinical symptoms manifest in 21% (95% credible interval: 12–31%) of infections in 10- to 19-year-olds, rising to 69% (57–82%) of infections in people aged over 70 years. Accordingly, we find that interventions aimed at children might have a relatively small impact on reducing SARS-CoV-2 transmission, particularly if the transmissibility of subclinical infections is low. Our age-specific clinical fraction and susceptibility estimates have implications for the expected global burden of COVID-19, as a result of demographic differences across settings. In countries with younger population structures—such as many low-income countries—the expected per capita incidence of clinical cases would be lower than in countries with older population structures, although it is likely that comorbidities in low-income countries will also influence disease severity. Without effective control measures, regions with relatively older populations could see disproportionately more cases of COVID-19, particularly in the later stages of an unmitigated epidemic.

EPIDEMIOLOGY / TRANSMISSION DYNAMICS

Huang C, Wang Y, Li X et al. **Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China.** Lancet 2020. Published online on Jan. 24, 2020. [doi:10.1016/S0140-6736\(20\)30183-5](https://doi.org/10.1016/S0140-6736(20)30183-5).

Case series of the first 41 hospitalized pts infected with 2019-nCoV by Jan 2, 2020

→ Two-thirds of patients had worked or shopped at a local fish and wild animal market, the Huanan Seafood Wholesale Market suggesting a possible origin for the virus.

Progress continues in coronavirus trace: Wuhan Market Cultures. By Wang Xiaodong | chinadaily.com.cn Updated: 2020-01-26 14:26.

China Center for Disease Control reported on January 26th that of 585 collected samples from the Huanan market, 33 tested positive for the virus. The 33 samples came from 22 stalls and a garbage vehicle in the market, most in the area where wild animals were traded. Further public results of this investigation are still pending.

Chan JF-W, Yuan S, Kok K-H, et al. **A familial cluster of pneumonia associated with the 2019 novel coronavirus indicating person-to-person transmission: a study of a family cluster.** Lancet 2020 January 24 (Epub ahead of print)
DOI: [doi/10.1093/infdis/jiaa077/5739751](https://doi.org/10.1093/infdis/jiaa077/5739751)

First formal report of person-to-person transmissibility in China.

Zhao S, Lin Q, Ran J et al. **Preliminary estimation of the basic reproduction number of novel coronavirus (2019-nCoV) in China, from 2019 to 2020: A data-driven analysis in the early phase of the outbreak.** Inter J Inf Dis 2020. Published online 30 January 2020. doi.org/10.1016/j.ijid.2020.01.050.

Early estimates of the basic reproduction number or R0 for SARS-CoV-2 ranged from 2.2 to 3.6.

Li Q, Guan X, Wu P et al. **Early Transmission Dynamics in Wuhan, China, of Novel Coronavirus–Infected Pneumonia.** N Engl J Med. Published January 29, 2020. [doi/full/10.1056/NEJMoa2001316](https://doi.org/10.1056/NEJMoa2001316)

Chen N, Zhou M, Dong X et al. **Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China: a descriptive study.** Lancet 2020. Published January 30, 2020. [doi.org/10.1016/S0140-6736\(20\)30211-7](https://doi.org/10.1016/S0140-6736(20)30211-7)

- Median age: 55-59 yrs with male predominance; no pt <15 yrs.
- Pts with earlier presentation much more likely to report exposure to the Huanan Mkt.
- Increasing proportion of cases acquired in hospital by pts or hospital personnel over time, to maximum of 40% in one series → increasing evidence of importance of person-to-person transmission.

Holshue ML, DeBolt C, Lindquist S et al. **First Case of 2019 Novel Coronavirus in the United States.** N Engl J Med 2020; 382; 10: 929-936.

DOI: 10.1056/NEJMoa2001191

- 41 yr old previously healthy male resident of Snohamish county, Washington who returned from a visit to Wuhan, China on January 14, 2020, presented to an urgent care center on Jan. 21, 2020 with 4 d hx of fever, cough
- Because of pt.'s travel and awareness of the new coronavirus, SARS-CoV-2 cultures were obtained and were positive
- Illness was relatively benign with minimal O2 requirement, no critical events
- Pt was normally active in the community before presentation and sat in the waiting room for some time before he was seen
- On Feb.28, the virus in another case in that community was found to be descended from that first case based on phylogenetic analysis. → These genetic findings suggest that SARS-CoV-2 had been spreading through the community for close to six weeks, beginning in mid-January.
- Snohamish county is close to Everett, Washington where the major early COVID-19 outbreak occurred → proof that local disease spread was occurring in the US beginning in the third week of January.

Gonzalez-Reiche AS, Hernandez MM, Sullivan M et al. **Introductions and early spread of SARS-CoV-2 in the New York City area.** medRxiv 2020.

doi.org/10.1101/2020.04.08.20056929

- To identify the early events underlying the rapid spread of the virus in the NYC metropolitan area, investigators sequenced the virus causing COVID19 in 90 patients
- Phylogenetic analysis of 84 distinct SARS-CoV2 genomes indicates multiple, independent but isolated introductions mainly from Europe and other parts of the United States with limited evidence of direct introductions from China.
- As early as February 20 (90%CI: January 29 to February 26) (Table 1), an identified virus was inferred to be of domestic origin based on its close relationship with US isolates, including those from the main community transmission in Washington state

- The earliest sequences include isolates from Italy, Finland, Spain, France, the UK, and other European countries from late February plus a few North American isolates (Canada and US) from the first week of March 2020.
- The sequenced isolates were spatially distributed throughout all NYC boroughs and 21 neighborhoods providing evidence for community transmission of SARS-CoV2 suggested by clusters of related viruses found in patients living in different neighborhoods of the city.

Fauver JR, Petrone ME, Hodcraft EB et al. **Coast-to-Coast Spread of SARS-CoV-2 during the Early Epidemic in the United States.** Cell 2020 May 28; 181(5): 990–996.e5. Published online 2020 May 7. doi:10.1016/j.cell.2020.04.021

- To uncover the sources of SARS-CoV-2 introductions & patterns of spread, viral genomes from early COVID-19 cases in Connecticut were sequenced – because of its proximity to multiple high-volume airports, Connecticut cases could theoretically be used to analyze the US pattern.
- By comparing SARS-CoV-2 sequences from local cases to genome sequences from other areas, ‘genomic epidemiology’ allowed identification of the likely virus sources for the Connecticut cases. Analysis was supplemented with airline travel data.
- RESULTS: Combined genomic epidemiology and travel pattern analysis indicates the spread of SARS-CoV-2 from coast-to-coast was a combination of international and domestic travel beginning in late January, with domestic spread becoming dominant by the beginning of March.

Millett GA, Jones AT, Benkeser D et al. **Assessing Differential Impacts of COVID-19 on Black Communities.** Manuscript under review - JAMA.

- Discrete state and city data sources show Black Americans to be at elevated risk for COVID-19 infection and death but the race/ethnicity of 78% of current diagnoses nationally is unknown.
- Investigators compared COVID-19 cases and deaths in above average (i.e. > 13% of the population) black counties versus all other US counties.
- Roughly one in five counties nationally is disproportionately black, representing 22% of all U.S. counties but these counties accounted for 52% of coronavirus cases and 58% of COVID-19 deaths.
- Structural factors including health care access, density of households, unemployment +/- pervasive discrimination and others drive these disparities, not intrinsic characteristics of black communities or individual-level factors.

Sadoughi S, Saltz R. **Pediatric multisystem inflammatory syndrome.** NEJM Journal Watch. May 5, 2020.

At least 64 children in New York state, primarily in NYC and on Long Island, New York, have developed a multisystem inflammatory syndrome related to COVID-19, the New York Times reports. The cases first emerged about a month after a surge in COVID-19 in the region, suggesting "it's a post-infectious immune response," one pediatrician said. Most cases have tested positive either for SARS-CoV-2 or for antibodies to the virus. The syndrome includes persistent fever and features of Kawasaki disease or toxic shock but it is definitively not KD. Many of the children have been admitted to intensive care, where they've received cardiac or respiratory support. None have died. U.K. health officials last week warned clinicians to be on the lookout for this syndrome. The Times notes that cases have also been reported elsewhere in the U.S.

van Doremalen N, Bushmaker T, Hamilton, MT et al. **Aerosol and Surface Stability of SARS-CoV-2 as Compared with SARS-CoV-1.** NEJM 2020. 382:1564-1567. DOI.org/10.1056/NEJMc2004973.

- Evaluation of the stability of SARS-CoV-2 and SARS-CoV-1 in aerosols and in five environmental conditions (aerosols, plastic, stainless steel, copper, and cardboard)
- Artificially aerosolized SARS-CoV-2 remained viable in air samples for 3 hours with a gradual decrease in virus titer over time
- On plastic and stainless steel, SARS-CoV-2 was detected up to 72 hours with greatly reduced virus titer over time
- On copper, no viable SARS-CoV-2 was measured after 4 hours
- On cardboard, no viable SARS-CoV-2 was measured after 24 hours
- Results indicate that aerosol and fomite transmission of SARS-CoV-2 is plausible, since the virus can remain viable and infectious in aerosols for hours and on surfaces up to days

Stadnytskyi V, Bax CF, Bax A, Anfinrud P. **The airborne lifetime of small speech droplets and their potential importance in SARS-CoV-2 transmission.** PNAS. First published, May 13, 2020.

doi.org/10.1073/pnas.2006874117

- Highly sensitive laser light scattering observations revealed that loud speech can emit thousands of oral fluid droplets per second.
- In a closed, stagnant air environment, droplets disappear from the window of view with time constants in the range of 8 to 14 min, which corresponds to droplet nuclei of ~ 4 µm diameter, or 12- to 21-µm droplets prior to dehydration.

Ellinghaus D, Degenhardt F, Bujanda L et al. **The ABO blood group locus and a chromosome 3 gene cluster associate with SARS-CoV-2 respiratory failure in an Italian-Spanish genome-wide association analysis.** MedRxiv. Preprint published 6/2/2020. doi.org/10.1101/2020.05.31.20114991

- To assess genetic risk for respiratory failure with COVID-19, investigators performed genome-wide association analysis of 835 pts with COVID-19 respiratory failure & 1,255 population-derived controls from Italy + 775 pts & 950 controls from Spain.
- In total, investigators analyzed 8,582,968 single-nucleotide polymorphisms (SNPs) and conducted a meta-analysis of both case-control panels.
- **RESULTS:** Study detected cross-replicating associations with rs11385942 at chromosome 3p21.31 and rs657152 at 9q34, which were genome-wide significant in the meta-analysis of both study panels.
- Among six genes at 3p21.31, SLC6A20 encodes a known interaction partner with angiotensin converting enzyme 2 (ACE2) – further analysis pending.
- The association signal at 9q34 was located at the ABO blood group locus and a blood-group-specific analysis showed higher risk for A-positive individuals (OR=1.45, 95% CI, 1.20 to 1.75, P=1.48×10⁻⁴) and a protective effect for blood group O (OR=0.65, 95% CI, 0.53 to 0.79, P=1.06×10⁻⁵).

Zhang R, Li Y, Zhang AL et al. **Identifying airborne transmission as the dominant route for the spread of COVID-19.** PNAS 2020; first published June 11, 2020. <https://doi.org/10.1073/pnas.2009637117>

- Investigators analyzed the trend in new cases with various mitigation measures in Wuhan, China, Italy, and New York City, from January 23 to May 9, 2020.
- Analysis reveals that the difference with and without mandated face covering represents the major determinant in shaping pandemic trends in the three epicenters.
- This protective measure alone significantly reduced the number of new infections, by over 78,000 in Italy from April 6 to May 9 and by over 66,000 in NYC
- Findings confirm airborne transmission as the dominant route for COVID-19 spread
- Wearing face masks in public is the most effective means to prevent interhuman transmission.

Zhoua C, Xua Z, Castiglionea GM et al. **ACE2 and TMPRSS2 are expressed on the human ocular surface, suggesting susceptibility to SARS-CoV-2 infection.** bioRxiv preprint. Posted May 9, 2020. doi.org/10.1101/2020.05.09.086165.

- To determine whether ocular surface cells possess the factors required for cellular susceptibility to SARS-CoV-2 entry/infection, investigators analyzed human post-mortem eyes & surgical specimens for the expression of ACE2 (the receptor for

SARS-CoV-2) and TMPRSS2, a cell surface-associated protease that facilitates viral entry following binding of the viral spike protein to ACE2.

- Results: Across all eye specimens, immunohistochemical analysis revealed expression of ACE2 in the conjunctiva, limbus, and cornea, with especially prominent staining in the superficial conjunctival and corneal epithelial surface. Surgical conjunctival specimens also showed expression of ACE2 in the conjunctival epithelium, especially prominent in the superficial epithelium, as well as the substantia propria. All eye and conjunctival specimens also expressed TMPRSS2. Finally, western blot analysis of protein lysates from human corneal epithelium obtained during refractive surgery confirmed expression of ACE2 and TMPRSS2.
- Conclusions: Results indicate that ocular surface cells including conjunctiva are susceptible to infection by SARS-CoV-2, and could serve as a portal of entry as well as a reservoir for person-to-person transmission of this virus.

He X, Lau EH, Wu P et al. **Temporal dynamics in viral shedding and transmissibility of COVID-19.** *Nature Medicine* 2020; 26: 672–675. Published 4/15/220. <https://doi.org/10.1038/s41591-020-0869-5>

We report temporal patterns of viral shedding in 94 patients with laboratory-confirmed COVID-19 and modeled COVID-19 infectiousness profiles from a separate sample of 77 infector–infectee transmission pairs. We observed the highest viral load in throat swabs at the time of symptom onset, and inferred that infectiousness peaked on or before symptom onset. We estimated that 44% (95% confidence interval, 25–69%) of secondary cases were infected during the index cases' pre-symptomatic stage, in settings with substantial household clustering, active case finding and quarantine outside the home. Disease control measures should be adjusted to account for probable substantial pre-symptomatic transmission.

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

- Investigators fitted an age-structured mathematical model to epidemic data from China, Italy, Japan, Singapore, Canada and South Korea.
- Results estimate that susceptibility to infection in individuals under 20 yrs of age is approximately half that of adults aged over 20 yrs.
- Clinical symptoms are manifest in 21% (95% CI: 12–31%) of infections in 10- to 19-year-olds, rising to 69% (CI: 57–82%) in people aged over 70 yrs.

Bunyavanich S, Do A, Vicencio A. **Nasal Gene Expression of Angiotensin-Converting Enzyme 2 in Children and Adults.** JAMA. 2020;323(23):2427-2429. doi:10.1001/jama.2020.8707.

- Retrospective examination of nasal epithelium from individuals aged 4 to 60 years in the Mount Sinai Health System, NY, NY, during 2015-2018.
- Given the role of ACE2 in SARS-CoV-2 host entry, ACE2 gene expression was analyzed by age group.
- ACE2 gene expression was lowest (mean log₂ counts per million, 2.40; 95% CI, 2.07-2.72) in younger children (n = 45) & increased with age, with mean log₂ counts per million of 2.77 (95% CI, 2.64-2.90) for older children (n = 185), 3.02 (95% CI, 2.78-3.26) for young adults (n = 46), and 3.09 (95% CI, 2.83-3.35) for adults (n = 29).
- Linear regression showed that compared with younger children, ACE2 gene expression was significantly higher in older children (P = .01), young adults (P < .001), and adults (P = .001)
- Age-dependent expression of ACE2 in nasal epithelium, the first point of contact for SARS-CoV-2 and the human body may help explain why COVID-19 is less prevalent in children.

Qian H, Miao T, Liu L et al. **Indoor transmission of SARS-CoV-2.** MedRxiv preprint, posted 4/7/2020. doi: <https://doi.org/10.1101/2020.04.04.20053058>.

- Using case reports from the local Municipal Health Commissions of 320 prefectural cities (municipalities) in China, not including Hubei province, from 1/4 - 2/11, 2020, investigators identified 318 outbreaks involving ≥ 3 cases
- Characteristics of the enclosed spaces in which the outbreaks were reported and associated indoor environmental issues were recorded
- RESULTS: There were 1245 confirmed cases in 120 prefectural cities: 53.8% involved 3 cases, 26.4% involved 4 cases, and only 1.6% involved ≥ 10 cases.
- 254 of 318 outbreaks; 79.9% occurred in the home; 108/318 (34%) occurred in transport settings; many outbreaks involved >1 potential venue category.
- **Only a single outbreak involving 2 cases occurred in an outdoor environment.**
- → Sharing indoor space is a major SARS-CoV-2 infection risk.

Long QX, et al. **Clinical and immunological assessment of asymptomatic SARS-CoV-2 infections.** Nat Med 2020; DOI: 10.1038/s41591-020-0965-6. Published 6/18/2020.

- 37 SARS-CoV-2 infected, asymptomatic individuals identified during contact tracing were evaluated and serologic results compared to 37 sex-, age-frequency- and comorbidity-matched mildly symptomatic pts.

- 21/37 asymptomatic pts had abnormal chest CT findings including ground-glass opacities and stripe shadows and/or diffuse consolidation.
- Median duration of viral shedding in the asymptomatic pts was 19 d (IQR, 15–26 d) vs 14 d (IQR, 9–22 d) in pts with mild symptoms.
- IgG levels in the symptomatic group were significantly higher than those in the asymptomatic group in the acute phase.
- ~80% of both groups tested (+) for IgG 3–4 weeks after exposure but >90% of both groups had significantly decreased IgG levels by 8 wk F/U.
- 62.2% (23/37) of the asymptomatic group were positive for IgM vs 78.4% (29/37) of the symptomatic group
- Asymptomatic individuals had a reduced inflammatory response characterized by low circulating concentrations of cytokines and chemokines.
- **IgG levels and neutralizing antibodies in a high proportion of individuals who recovered from SARS-CoV-2 infection decrease significantly within 2–3 months after infection suggesting a short duration of immunity.**

Kissler SM, Tedijanto C, Goldstein E, et al. Projecting the transmission dynamics of SARS-CoV-2 through the post-pandemic period. Science. 2020 Apr 14. doi: 10.1126/science.abb5793. [Epub ahead of print.]

Theoretical transmission dynamics based on modelling including possible contributions of seasonality, duration of immunity, and cross-protection from prior infection with other beta-coronaviruses in common circulation (HKU1 and OC43). Scenarios assess the effects of the length (4 weeks to indefinite) & strength (0–60% reductions in R_0) of social distancing.

Baseline seasonality and immunity info:

- Seasonal coronaviruses circulate from autumn to early spring in temperate regions
- High levels of seasonality → smaller initial peak, but larger wintertime outbreaks
- Immunity to these viruses (HKU1 and OC43) wanes rapidly, over ~1 year
- Some cross-protection exists between these 2 viruses → ? also SARS-CoV-2
- SARS-CoV-2 can proliferate at any time of the year (as we are seeing now)
- If immunity is not permanent, SARS-CoV-2 will eventually enter regular circulation as a fifth seasonal coronavirus
- If immunity permanent, SARS-CoV-2 will disappear in a few yrs 2° to herd immunity.

Modeling results:

Social distancing without seasonality:

→ Short durations of social distancing displace cases into the near future

- Longer durations of higher-intensity social distancing reduce case burden in the near term, but result in significant outbreaks during autumn and winter
- Permanent social distancing of moderate to high intensity works well to keep SARS-CoV-2 at bay but difficult & unpleasant to sustain

Social distancing + seasonality:

- Short durations of social distancing slightly delay peaks of COVID-19, but result in high overall infection rates
- Longer durations of social distancing push the peaks into the winter months and increase the overall infection rate
- Intermittent social distancing, based on good surveillance, may be needed to keep case load in check until vaccines are available or herd immunity is achieved

Pei S, Kandula S, Shaman J. **Differential Effects of Intervention Timing on COVID-19 Spread in the United States**. medRxiv. May 20, 2020. Preprint.

doi: <https://doi.org/10.1101/2020.05.15.20103655>

- Epidemiologic analysis of county-level observations of reported infections and deaths, human mobility data and a metapopulation transmission model combined to quantify disease transmission rates in US counties from 3/15 to 5/3/2020.
- Results show significant reductions of R_0 in major metropolitan areas in association with social distancing and other control measures.
- Counterfactual simulations indicate that, had these same control measures been implemented just 1 week earlier, nationwide, 61.6% [54.6%-67.7%] of reported infections and 55.0% [46.1%-62.2%] of reported deaths could have been avoided.
- If the country had begun locking down cities and limiting social contact on 3/1, the vast majority of the nation's deaths — about 83% — would have been avoided.

TREATMENT

Shen C, Wang Z, Zhao F et al. **Treatment of 5 Critically Ill Patients With COVID-19 With Convalescent Plasma: Preliminary Communication.** JAMA 2020;323(16): 1582-1589.
doi:10.1001/jama.2020.4783.

Uncontrolled case series of 5 critically ill patients with COVID-19 and acute respiratory distress syndrome (ARDS) with multiple indicators of disease severity received donor convalescent plasma containing neutralizing antibody. Clinical status and all measures of disease severity improved beginning within 3 days and 3 pats were extubated between 2 and 9 days post infusion.

→ Promising preliminary findings require RCT evaluation.

News Release. NIH – NIAID. April 29, 2020.

NIH Clinical Trial Shows Remdesivir Accelerates Recovery from Advanced COVID-19.

Wang Y, Zhang D, Du G et al. **Remdesivir in Adults With Severe COVID-19: A Randomised, Double-Blind, Placebo-Controlled, Multicentre Trial.** Lancet 2020 Apr 29. **doi.org/10.1016/S0140-6736(20)31022-9**

Hospitalized patients with advanced COVID-19 and lung involvement who received remdesivir recovered faster than similar patients who received placebo, according to preliminary data analysis from a RCT involving 1063 pts, which began on 2/21/20. Pts who received remdesivir had a 31% faster time to recovery than those who received placebo ($p < 0.001$). Specifically, the median time to recovery was 11 days for pts treated with remdesivir compared with 15 days for those who received placebo. Results also suggested a survival benefit, with a mortality rate of 8.0% for the group receiving remdesivir versus 11.6% for the placebo group ($p = 0.059$). More detailed trial results are forthcoming. The trial known as the Adaptive COVID-19 Treatment Trial, or ACTT involved 68 sites, 47 in the U.S. and 21 in countries in Europe and Asia. Remdesivir, developed by Gilead Sciences Inc., is an investigational broad-spectrum antiviral treatment administered via daily infusion for 10 days.

→ Results confirmed in final report published in NEJM: **Remdesivir for the Treatment of Covid-19.** Beigel JH, Tomashek KM, Dodd LE et al. NEJM. Published online, May 22, 2020.

DOI: 10.1056/NEJMoa2007764

Magagnoli J, Narendran S, Pereira F et al. **Outcomes of hydroxychloroquine usage in United States veterans hospitalized with COVID-19.** medRxiv 2020.
https://doi.org/10.1101/2020.04.16.20065920

- Retrospective analysis of data of all pts hospitalized with confirmed SARS-CoV-2 infection in all U.S. VA medical centers until April 11, 2020.
- Patients were categorized based on exposure to hydroxychloroquine alone (HC) or with azithromycin (HC+AZ) as treatments in addition to standard COVID-19 management. Primary outcomes were death and need for mechanical ventilation.
- RESULTS: 368 patients were evaluated (HC: n=97; HC+AZ: n=113; No HC: n=158). Rates of death in the HC, HC+AZ, and no HC groups were 27.8%, 22.1%, 11.4%, respectively. Rates of ventilation in the HC, HC+AZ, and no HC groups were 13.3%, 6.9%, 14.1%, respectively.
- → Compared to the no HC group, the risk of death from any cause was higher in the HC group (adjusted HR, 2.61; 95% CI, 1.10 to 6.17; P=0.03) but not in the HC+AZ group (adjusted HR, 1.14; 95% CI, 0.56 to 2.32; P=0.72).
- → No evidence that use of HC, either with or without AZ reduced the risk of mechanical ventilation in patients hospitalized with COVID-19.

Chloroquine, Hydroxychloroquine Likely Ineffective For COVID-19. CONTAGION Review: Rachel Lutz. April 30, 2020. ([Publication pending](#))

Chloroquine and hydroxychloroquine likely are not effective against the novel coronavirus, according to a paper published in the May issue of The FASEB Journal. Investigators from Harvard Medical School and Mass General conducted a comprehensive literature review of clinical experiences with chloroquine and hydroxychloroquine. Data through April 22 showed that these drugs reduced viral uptake by cells cultured in a lab but not in patients. The drugs prevent the immune system from completing its vital response to viruses, investigators wrote. The drugs also disrupt the cell-mediated immunity that is critical to controlling a viral outbreak such as the one the world is currently facing. There is a need for caution if using these therapies to treat the coronavirus based solely on the results of lab studies and not human trials. "Current trial results involving chloroquine and hydroxychloroquine are leading to a rapidly diminishing view of their utility for COVID-19."

Borba MGS, Almeida-Val FF, Sampaio VS et al. **Effect of High vs Low Doses of Chloroquine Diphosphate as Adjunctive Therapy for Patients Hospitalized With Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) Infection: A Randomized Clinical Trial.** JAMA Network Open 2020;3(4):e208857. April 24, 2020. doi:10.1001/jamanetworkopen.2020.8857

In this phase IIb randomized clinical trial of 81 pts with COVID-19, an unplanned interim analysis by an independent data safety and monitoring board found that the higher dosage of chloroquine diphosphate was associated with more toxic effects and lethality, particularly affecting QTc interval prolongation. The limited sample size did not show any benefit regarding treatment efficacy. The preliminary findings from the CloroCovid-

19 trial suggest that higher dosage of chloroquine should not be used for treatment of severe COVID-19 because of safety concerns regarding QTc interval prolongation and increased lethality.

Mehra MR, Desai SS, Ruschitzka F, Patel AN, **Hydroxychloroquine or chloroquine with or without a macrolide for treatment of COVID-19: a multinational registry analysis.** Lancet 2020; Published online, May 22, 2020.
[https://doi.org/10.1016/S0140-6736\(20\)31180-6](https://doi.org/10.1016/S0140-6736(20)31180-6)

- Multinational registry analysis of the use of hydroxychloroquine or chloroquine with or without a macrolide for treatment of COVID-19.
- Data from 671 hospitals in 6 continents included pts hospitalized from 12/20/2019-4/14/2020 with positive diagnosis of SARS-CoV-2.
- Five groups: Chloroquine alone, chloroquine + macrolide, hydroxychloroquine alone, hydroxychloroquine + macrolide; none of these treatments = controls.
- Exclusions: Treatment initiated >48 h after diagnosis; pt on mechanical ventilation; pts received remdesivir.
- Total n= 96032 patients, mean age 53.8 years, 46.3% women.
- Chloroquine alone=1868; chloroquine + macrolide=3783; hydroxychloroquine alone=3016; hydroxychloroquine + macrolide period=6221; control=81,144.
- Overall, 10698 (11.1%) patients died in hospital.
- Analysis controlled for multiple confounding factors (age, sex, race/ethnicity, BMI, underlying CVD, diabetes or lung disease, smoking, immunosuppressed condition, and baseline disease severity),
- →When compared with mortality in the control group (9.3%), hydroxychloroquine (18.0%; hazard ratio 1.335), hydroxychloroquine+macrolide (23.8%; HR=1.447), chloroquine (16.4%; HR=1.365) & chloroquine+macrolide (22.2%; HR=1.368) were each independently associated with increased risk of in-hospital mortality.
- Compared with the control group (0.3%),hydroxychloroquine (6.1%; HR=2.369), hydroxychloroquine+macrolide (8.1%; HR=5.106),chloroquine (4.3%; HR=3.561), and chloroquine+macrolide (6.5%; HR=4.011) were independently associated with increased risk of de-novo ventricular arrhythmia during hospitalization.
- Each of these drug regimens was associated with significantly decreased in-hospital survival and increased frequency of ventricular arrhythmias when used for treatment of COVID-1

Richardson P, Griffin I Tucker C et al. **Baricitinib as potential treatment for 2019-nCoV acute respiratory disease.** Lancet 2020; 395:e30-e31. February 3, 2020.
[https://doi.org/10.1016/S0140-6736\(20\)30304-4.](https://doi.org/10.1016/S0140-6736(20)30304-4)

Application of a proprietary, AI-derived knowledge graph queried by a suite of 2019-CoV derived algorithms enabled identification of a potential therapeutic agent. Baracitinib is an already approved anti-arthritic drug with known antiviral and anti-inflammatory properties which has the potential to inhibit the cellular processes used by the virus in cell infection and to inhibit potential cytokine storm. Investigator-led studies have been underway since March with a large randomized trial beginning on April 14 in conjunction with Eli Lilly and NIH-USAID. Results anticipated within 2 months.

Paranjpe I, Fuster V, Lala A et al. **Association of Treatment Dose Anticoagulation with In-Hospital Survival Among Hospitalized Patients with COVID-19.** J Amer Coll Cardiol 2020. May 2020.

DOI: 10.1016/j.jacc.2020.05.001

- Increased thromboembolic events and anecdotal observations of improved outcomes with systemic anticoagulation(AC) have been reported in hospitalized COVID-19 pts
- →Retrospective analysis of association between administration of in-hospital AC and survival in a cohort of 2773 COVID-19 pts hospitalized in NYC
- 786/2773 pts (28%) received AC a median of 2 days post admission; median AC duration was 3 days.
- Pts who received AC had significantly more B/L coagulation abnormalities
- Overall, in-hospital mortality for AC pts was 22.5% with median survival of 21 days vs. mortality of 22.8% and median survival of 14 days for non-AC group.
- In patients who required mechanical ventilation (n = 395), in-hospital mortality was 29.1% with a median survival of 21 days for those treated with AC as compared to 62.7% with a median survival of 9 days in patients who did not receive treatment-dose AC.
- In a multivariable proportional hazards model, longer duration of AC was associated with reduced mortality risk.
- No increased incidence of bleeding events with AC
- RCT of systemic AC needed.

Hung If-N, Lung K-C, Tso EY-K et al. **Triple combination of interferon beta-1b, lopinavir–ritonavir, and ribavirin in the treatment of patients admitted to hospital with COVID-19: an open-label, randomised, phase 2 trial.** The Lancet, 2020.

Published: May 08, 2020. [https://doi.org/10.1016/S0140-6736\(20\)31042-4](https://doi.org/10.1016/S0140-6736(20)31042-4)

- Multicenter, prospective, open-label, randomized, phase 2 trial in adults with COVID-19 who were admitted to six hospitals in Hong Kong.
- 86 pts randomly assigned (2:1) to a 14-day combination of lopinavir 400 mg/ ritonavir 100 mg every 12 h, ribavirin 400 mg every 12 h, and three doses of 8 million IU of

interferon beta-1b on alternate days (combination group); vs 41 pts in control group receiving 14 days of lopinavir 400 mg & ritonavir 100 mg every 12 h

- Pts had mild-mod disease: 17 required O2 therapy, 6 were in ICU, none intubated.
- Primary endpoint was time to negative RT-PCR N/P swab for SARS-CoV-2.
- RESULTS: The combination group had a significantly shorter median time from start of study treatment to negative N/P swab (7 days [IQR 5–11]) than the control group (12 days [8–15]; hazard ratio 4.37 [95% CI 1.86–10.24], p=0.0010).
- No major safety issues or AEs.

The RECOVERY Collaborative Group. **Dexamethasone in hospitalized patients with Covid-19** - Preliminary report. N Engl J Med 2020; Online, June 16, 2020.
DOI: 10.1056/NEJM0a2021436.

- Randomized clinical trial to test a range of potential treatments for COVID-19, including low-dose dexamethasone.
- Over 11,500 patients enrolled from over 175 NHS hospitals in the UK.
- 2104 pts randomized to receive dexamethasone 6 mg 1X/day X 10 days were compared with 4321 pts randomized to usual care (UC) alone.
- Among pts who received UC alone, 28-day mortality was highest in those who required ventilation (41%), intermediate in those who required oxygen only (25%), and lowest among those who did not require any respiratory intervention (13%).
- Dexamethasone reduced deaths by one-third in ventilated patients (rate ratio 0.65 [95% confidence interval 0.48 to 0.88]; p=0.0003) and by one fifth in pts receiving O2 only (0.80 [0.67 to 0.96]; p=0.0021). There was no benefit in pts who did not require respiratory support (1.22 [0.86 to 1.75]; p=0.14).

Thompson AE, Ranard BL, Wei Y et al. **Prone Positioning in Awake, Nonintubated Patients With COVID-19 Hypoxemic Respiratory Failure.** JAMA Intern Med. 2020;180(11):1537-1539. Published online, 6/17/2020.
doi:10.1001/jamainternmed.2020.3030

- Case series of 29 consecutive COVID-19 pts with severe hypoxemic respiratory failure defined as respiratory rate \geq 30 breaths/min & Spo2 \leq 93% on O2 6 L/min via nasal cannula and 15 L/min via nonrebreather face mask
- Pts were asked to lie on their stomach for as long as tolerated up to 24 hours daily.
- Primary outcome was change in Spo2 before & 1 hr after initiation of prone position
- RESULTS: In this small single-center cohort study, use of the prone position for awake, spontaneously breathing patients with COVID-19 severe hypoxemic respiratory failure was associated with significantly improved oxygenation.
- In addition, patients with an Spo2 of 95% or greater after 1 hour of the prone position had a lower rate of intubation.

Liang W. Liang H, Ou L et al. **Development and Validation of a Clinical Risk Score to Predict the Occurrence of Critical Illness in Hospitalized Patients With COVID-19.** JAMA Int Med. Published online, May 12, 2020.
doi:10.1001/jamainternmed.2020.2033

- To develop a clinical score at hospital admission for predicting which patients with COVID-19 will develop critical illness defined as invasive ventilation, ICU admission or death based on a nationwide cohort in China.
- Retrospective cohort of 1590 pts with COVID-19 from 575 hospitals in China as of January 31, 2020. Epidemiological, clinical, laboratory, and imaging variables at hospital admission were used to construct a predictive risk score (COVID-GRAM).
- Data from 710 additional pts hospitalized with COVID-19 were used to validate the score.
- From 72 potential predictors, 10 variables were independent predictive factors & were included in the risk score: chest radiographic abnormality (OR, 3.39; 95% CI, 2.14-5.38), age (OR, 1.03; 95% CI, 1.01-1.05), hemoptysis (OR, 4.53; 95% CI, 1.36-15.15), dyspnea (OR, 1.88; 95% CI, 1.18-3.01), unconsciousness (OR, 4.71; 95% CI, 1.39-15.98), # of comorbidities (OR, 1.60; 95% CI, 1.27-2.00), cancer hx (OR, 4.07; 95% CI, 1.23-13.43), neutrophil-to-lymphocyte ratio (OR, 1.06; 95% CI, 1.02-1.10), LDH (OR, 1.002; 95% CI, 1.001-1.004), direct bilirubin (OR, 1.15; 95% CI, 1.06-1.24).
- The mean AUC in the development cohort was 0.88 (95% CI, 0.85-0.91) and the AUC in the validation cohort was 0.88 (95% CI, 0.84-0.93).
- The outcome predictor score is available as an online risk calculator:
(<http://118.126.104.170/>)

Gordon, D. E. et al. **A SARS-CoV-2 protein interaction map reveals targets for drug repurposing.** Nature 2020; E-published ahead of print, April 30, 2020.
<https://doi.org/10.1038/s41586-020-2286-9>.

- Investigators cloned, tagged & expressed 26 SARS-CoV-2 proteins in human cells & identified physically associated proteins using affinity-purification mass spectrometry
- 332 high-confidence SARS-CoV-2-human protein-protein interactions were identified with 66 druggable human proteins or host factors targeted by 69 compounds (29 FDA-approved drugs, 12 drugs in clinical trials, 28 preclinical compounds).
- Screening these in multiple viral assays identified 2 sets of pharmacological agents that displayed antiviral activity: inhibitors of mRNA translation and predicted regulators of the Sigma1 and Sigma2 receptors.
- Further studies of these host factor targeting agents, including their combination with drugs that directly target viral enzymes, could lead to a therapeutic regimen to treat COVID-19.

AHJ Danser, M Epstein, D Batlle. **Renin-angiotensin system blockers and the COVID-19 pandemic: At present there is no evidence to abandon renin-angiotensin system blockers.** Hypertension 2020 Mar 25;[EPub Ahead of Print], **DOI: 10.1161/HYPERTENSIONAHA.120.15082**

The angiotensin-converting enzyme 2 (ACE2) protein facilitates the entry of coronavirus-2 into cells. ACE inhibitors do not impact ACE2 as ACE and ACE2 are distinct enzymes. There are no data to support the hypothesis that ACE inhibitors or angiotensin II type 1 receptor blockers increase ACE2 expression and hence increase coronavirus entry. Current evidence does not support the discontinuation of ACE inhibitor treatment due to concerns regarding coronavirus infection.

PREVENTION: VACCINE DEVELOPMENT

(There are at least 108 vaccines in development as of 5/8/2020, 8 in clinical trials)

Lane R. **Carving a path towards a COVID-19 vaccine.** Lancet April 18, 2020; 395:1247.

DOI: [https://doi.org/10.1016/S0140-6736\(20\)30796-0](https://doi.org/10.1016/S0140-6736(20)30796-0)

- Post SARS-CoV-2 genome sequence availability, Oxford University team used recombinant DNA techniques to create a vaccine with SARS-CoV-2 antigen embedded in a primate adenovirus vector.
- The vaccine includes Spike glycoproteins genetic material, a surface protein from SARS-CoV-2 responsible for virus binding to host cell ACE2 inhibitors.
- Investigators hope to engender an immune response to the Spike protein that will prevent SARS-CoV-2 from entering human cells and causing infection.
- ChAdOx1-derived vaccines have already been given to >320 people to date, with consistent reports of safety and tolerability and no major adverse events.
- RCT of the potential vaccine -- ChAdOx1 nCoV-19 -- in 1100 volunteers has begun with results anticipated in 2-6 months. Participants are randomized to the trial vaccine or a control meningitis vaccine.
- Main outcome is assessment of effectiveness, safety, and immune responses to the vaccine. COVID-19 cases in the 2 groups will be compared.
- The Serum Institute of India—the world’s largest producer of vaccines—announced plans to make 40 million doses of hAdOx1 nCov-19 beginning prior to trial results.

Gao Q, Bao L, Mao H et al. **Rapid development of an inactivated vaccine for SARS-CoV-2.** bioRxiv 2020.

<https://doi.org/10.1101/2020.04.17.046375>

- Researchers from Sinovac Biotech, a privately held Beijing-based company, gave two different doses of their COVID-19 vaccine to a total of eight rhesus macaques.
- Three weeks later, the group introduced SARS-CoV-2 directly into the monkeys’ lungs → none developed a full-blown infection.
- The purified inactivated SARS-CoV-2 virus vaccine candidate (PiCoVacc) conferred complete protection in these non-human primates against multiple SARS-CoV-2 strains circulating worldwide by eliciting potent humoral responses devoid of immunopathology. Phase 1-2 studies underway.

[To quickly obtain phase 2 & 3 data, investigators may ask regulatory agencies in multiple countries for emergency authorization to give the vaccine to high risk individuals. The DRC in 2018 began to widely use an experimental Ebola vaccine under that status and evidence suggests it significantly helped curb that epidemic.]

Chu DK, Aki EA, Duda S et al. **Physical distancing, face masks, and eye protection to prevent person-to-person transmission of SARS-CoV-2 and COVID-19: a systematic review and meta-analysis.** Lancet 2020; Published: June 01, 2020
DOI:[https://doi.org/10.1016/S0140-6736\(20\)31142-9](https://doi.org/10.1016/S0140-6736(20)31142-9)

- Purpose: To determine the distance from a patient that SARS-CoV-2 is infective, and the optimum person-to-person physical distance to prevent infection.
- Method: SR & MA of all studies of pts with confirmed/ probable COVID-19, SARS, or MERS, and people in close contact with them, comparing distances between people and infected pts of ≥ 1 m vs < 1 m, w/without a face mask on the pt, or w/without face mask, eye protection, or both on the exposed individual.
- 172 studies from 16 countries & 6 continents in SR; 44 studies in comparative M/A.
- Results: Virus transmission was lower with physical distancing of ≥ 1 m vs < 1 m (aOR= 0.18, 95% CI 0.09 to 0.38); protection increased as distance lengthened (change in relative risk [RR] 2.02 per m).
- Face mask use resulted in a large reduction in risk (aOR 0.15, 95% CI 0.07 to 0.34), with stronger associations with N95 vs disposable surgical masks.
- Eye protection was associated with less infection (aOR 0.22, 95% CI 0.12 to 0.39).

Lindsley WG, Noti JD, Blachere FM et al. **Efficacy of Face Shields Against Cough Aerosol Droplets from a Cough Simulator.** Occup Environ Hyg 2014;11(8):509-18.
doi: [10.1080/15459624.2013.877591](https://doi.org/10.1080/15459624.2013.877591).

- Study used a coughing patient simulator and a breathing worker simulator to investigate the exposure of health care workers to cough aerosol droplets, and to examine the efficacy of face shields in reducing this exposure
- Face shields reduced immediate viral exposure by 96% when worn by a simulated health care worker within 18" of a cough.
- Even after 30 minutes, protective effect exceeded 80% and face shields blocked 68% of small particle aerosols, not thought to be a dominant mode of transmission of SARS-CoV-2
- When the study was repeated at the currently recommended physical distancing distance of 6', face shields reduced inhaled virus by 92%, similar to distancing alone, reinforcing the importance of physical distancing in preventing SARS-CoV-2 infection
- No studies have evaluated the effects of face shields on source control, ie, containing a sneeze or cough, when worn by asymptomatic or symptomatic infected persons.
- Article referenced in support of face shields as community protection against SARS-CoV-2 [**Moving Personal Protective Equipment Into the Community:Face Shields and Containment of COVID-19.** Perencevich EN, Diekema,DJ, Edmond MB. JAMA 2020;323(22):2252-2253. doi:[10.1001/jama.2020.7477](https://doi.org/10.1001/jama.2020.7477)]

Zhang R, Li Y, Zhang AL et al. **Identifying airborne transmission as the dominant route for the spread of COVID-19.** PNAS 2020; first published June 11, 2020.
<https://doi.org/10.1073/pnas.2009637117>

- Investigators analyzed the trend in new cases with various mitigation measures in Wuhan, China, Italy, and New York City, from January 23 to May 9, 2020.
- Analysis reveals that the difference with and without mandated face covering represents the major determinant in shaping pandemic trends in the three epicenters.
- This protective measure alone significantly reduced the number of new infections, by over 78,000 in Italy from April 6 to May 9 and by over 66,000 in NYC
- Findings confirm airborne transmission as the dominant route for the spread of COVID-19.
- Wearing face masks in public corresponds to the most effective means to prevent interhuman transmission.

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

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