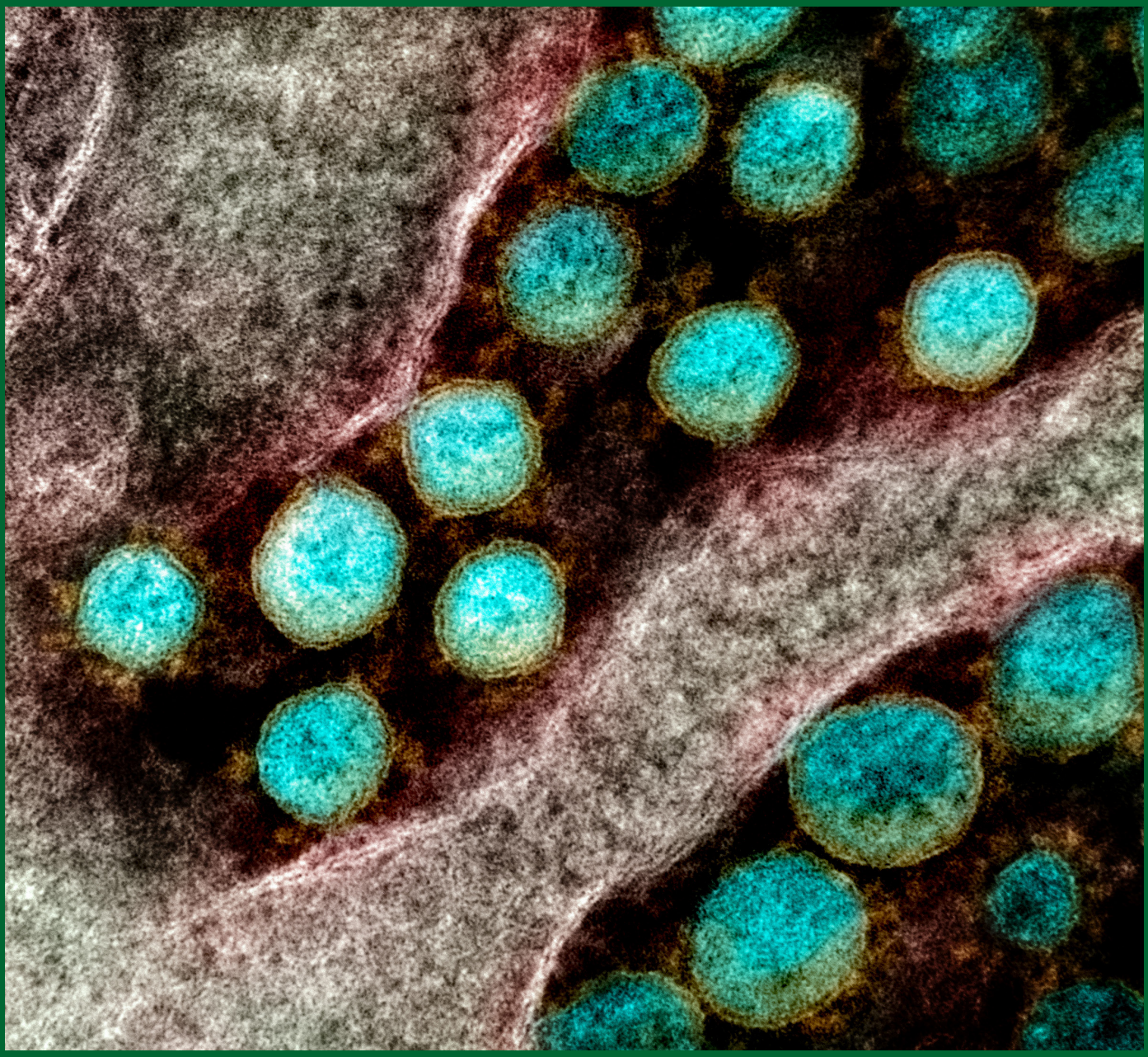
COVID-19 Rush Journal Club: Biology and Epidemiology



NOVEL CORONAVIRUS SARS-COV-2. Transmission electron micrograph of SARS-CoV-2 virus particles, isolated from a patient. Image captured and color-enhanced at the NIAID Integrated Research Facility (IRF) in Fort Detrick, Maryland. Credit: NIAID Available at: https://www.flickr.com/photos/niaid/49597768397/in/album-72157712914621487/. Accessed April 19, 2020.

This document is a collection of efforts from students of Rush University. It provides brief reviews of research articles regarding COVID-19. We hope that this will be helpful to clinicians, students, community leaders, and the general public. This document, however, does not act as a replacement of the original source documents. Please use the DOI on each page to read more.

Is there a study you'd like us to review? Do you have questions or feedback?
Please email: Joseph_b_deBettencourt@rush.edu

Reviews are provided by students at Rush University and edited by Rush faculty. Level of evidence in each study, if applicable, was assessed using the Oxford guidelines as presented below. More information can be found at http://www.cebm.net/2016/05/ocebm-levels-of-evidence/

Oxford Centre for Evidence-Based Medicine 2011 Levels of Evidence

Question	Step 1 (Level 1*)	Step 2 (Level 2*)	Step 3 (Level 3*)	Step 4 (Level 4*)	Step 5 (Level 5)
How common is the problem?	Local and current random sample surveys (or censuses)	Systematic review of surveys that allow matching to local circumstances**	Local non-random sample**	Case-series**	n/a
Is this diagnostic or monitoring test accurate? (Diagnosis)	Systematic review of cross sectional studies with consistently applied reference standard and blinding	Individual cross sectional studies with consistently applied reference standard and blinding	Non-consecutive studies, or studies without consistently applied reference standards**	Case-control studies, or "poor or non-independent reference standard**	Mechanism-based reasoning
What will happen if we do not add a therapy? (Prognosis)	Systematic review of inception cohort studies	Inception cohort studies	Cohort study or control arm of randomized trial*	Case-series or case-control studies, or poor quality prognostic cohort study**	n/a
Does this intervention help? (Treatment Benefits)	Systematic review of randomized trials or *n*-of-1 trials	Randomized trial or observational study with dramatic effect	Non-randomized controlled cohort/follow-up study**	Case-series, case-control studies, or historically controlled studies**	Mechanism-based reasoning
What are the COMMON harms? (Treatment Harms)	Systematic review of randomized trials, systematic review of nested case-control studies, *n*-of-1 trial with the patient you are raising the question about, or observational study with dramatic effect	Individual randomized trial or (exceptionally) observational study with dramatic effect	Non-randomized controlled cohort/follow-up study (post-marketing surveillance) provided there are sufficient numbers to rule out a common harm. (For long-term harms the duration of follow-up must be sufficient.)**	Case-series, case-control, or historically controlled studies**	Mechanism-based reasoning
What are the RARE harms? (Treatment Harms)	Systematic review of randomized trials or *n*-of-1 trial	Randomized trial or (exceptionally) observational study with dramatic effect			
Is this (early detection) test worthwhile? (Screening)	Systematic review of randomized trials	Randomized trial	Non -randomized controlled cohort/follow-up study**	Case-series, case-control, or historically controlled studies**	Mechanism-based reasoning

*** Level may be graded down on the basis of study quality, imprecision, indirectness (study PICO does not match questions PICO), because of inconsistency between studies, or because the absolute effect size is very small; Level may be graded up if there is a large or very large effect size.**

**** As always, a systematic review is generally better than an individual study.**

How to cite the Levels of Evidence Table

OCEBM Levels of Evidence Working Group*. "The Oxford 2011 Levels of Evidence".

Oxford Centre for Evidence-Based Medicine. http://www.cebm.net/index.aspx?o=5653

** OCEBM Table of Evidence Working Group = Jeremy Howick, Iain Chalmers (James Lind Library), Paul Glasziou, Trish Greenhalgh, Carl Heneghan, Alessandro Liberati, Ivan Moschetti, Bob Phillips, Hazel Thornton, Olive Goddard and Mary Hodgkinson*

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Section	*Manuscript*	*Reviewer (Date Posted)*
Epidemiology	*Frieden TR et al. Identifying and interrupting superspreading events—implications for control of severe acute respiratory syndrome coronavirus 2. Emerg Infect Dis. 2020 Jun [5/12/2020]. https://doi.org/10.3201/eid2606.200495*	*Natalie Maltby (5/12)*
	Richardson S 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	*Elena Perkins (5/12)*
	Ghinai I et al. Community transmission of SARS-CoV-2 at two family gatherings - Chicago, Illinois, February-March 2020. MMWR Morb Mortal Wkly Rep 69(15):446-450, 2020.	*Natalie Maltby (5/16)*
	Wynants L et al. Prediction models for diagnosis and prognosis of covid-19 infection: systematic review and critical appraisal. BMJ 369:m1328, 2020.	*Steven Heidt (5/16)*
	Lau H et al. The association between international and domestic air traffic and the coronavirus (COVID-19) outbreak. J Microbiol Immunol Infect 2020 [Epub ahead of print].	*Elena Perkins (5/16)*
	Randhawa AK et al. "Changes in SARS-CoV-2 positivity rate in outpatients in Seattle and Washington state, March 1-April 16, 2020." JAMA 2020 [Epub ahead of print].	*Antonios Skondras (5/19)*
	Haffajee, Rebecca L., and Michelle M. Mello. "Thinking Globally, Acting Locally—The US Response to Covid-19." New England Journal of Medicine (2020).	*Ritika Dhawan (5/19)*
	Park SY et al. "Coronavirus disease outbreak in call center, South Korea." Emerg Infect Dis 2020.	*Antonios Skondras (5/19)*
	Pongpirul WA et al. Clinical characteristics of patients hospitalized with coronavirus disease, Thailand. Emerg Infect Dis. 2020. https://doi.org/10.3201/eid2607.200598	*Natalie Maltby (5/21)*
	Lyu W et al. Comparison of Estimated Rates of Coronavirus Disease 2019 (COVID-19) in Border Counties in Iowa Without a Stay-at-Home Order and Border Counties in Illinois With a Stay-at-Home Order. JAMA Netw Open. 2020;3(5):e2011102. doi:10.1001/jamanetworkopen.2020.11102	*Antonios Skondras (5/30)*
	Anirban Basu. Estimating the Infection Fatality Rate Among Symptomatic COVID-19 Cases in the United States. Health Affairs May 7, 2020. https://doi.org/10.1377/hlthaff.2020.00455	*Alexandria Taphorn (6/8)*
	Rogers JP. et al. "Psychiatric and neuropsychiatric presentations associated with severe coronavirus infections: a systematic review and meta-analysis with comparison to the COVID-19 pandemic" Lancet Psychiatry. 2020;7(7):611-627. doi:10.1016/S2215-0366(20)30203-0	*Javier Paulino (8/28)*

Table of Contents: Epidemiology (4/4)

BIOLOGY

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

Roujian Lu et al.

Lancet

January 20, 2020

DOI: https://doi.org/10.1016/S0140-6736(20)30251-8

Purpose	To sequence and characterize the genome of 2019 novel coronavirus (2019-nCov).
Study design	Case Series (n = 9 patients)
Level of evidence	Not applicable
Methods	Isolates collected from nine inpatients of three area hospitals in Wuhan, China presenting with viral pneumonia of unknown origin. Researchers studied eight complete and two partial genomes obtained from the nine study patients.
Findings	Novel coronavirus 19 belongs to subgenus Sarbecovirus. The virus is more similar to two bat-derived coronavirus strains (88% identity) than to known human-infecting coronaviruses (SARS-CoV: 79% identity, MERS-CoV: 50% identity). However, there was **greater similarity in S1 domain of the spike protein of the novel coronavirus and SARS-CoV**, possibly suggesting the novel coronavirus might also use angiotensin-converting enzyme 2 (ACE-2) as a cell receptor (as SARS-CoV is known to do). There is **likely an intermediate host, currently unknown, between bats and humans for novel coronavirus.**
Clinical Implications	The **genomes of the virus across all patient samples were remarkably similar, indicating a common source of infection.** Not all patients had visited the Huanan wet market, also supporting hypothesized human-to-human transmission via droplets. Identification of the 2019-nCov intermediate host could facilitate further understanding of disease control during this pandemic. **Like SARS-CoV, the 2019-nCoV uses ACE2 as a receptor, although there were key variances in the receptor-binding domains of SARS-CoV and 2019-nCoV**. Further research is necessary to determine the significance of this similarity, and how it could affect the diagnosis and treatment of the virus, as well as vaccine development.
Limitations	While likely due to the urgency surrounding the health crisis of this novel coronavirus, this study only analyzed sequences from isolates of a small number of patients. Future research is needed to map the changes in genome sequencing of this virus as it spreads throughout the world.

Comparative replication and immune activation profiles of SARS-CoV-2 and SARS-CoV in human lungs: an ex vivo study with implications for the pathogenesis of COVID-19.

Hin Chu et al.

Clinical Infectious Diseases
April 9, 2020
DOI: https://doi.org/10.1093/cid/ciaa410

Purpose	To compare viral kinetics, cell tropism, and immune response profiles of SARS-CoV-2 and SARS-CoV to understand the mechanism behind transmission and presentation of COVID-19.
Study design	Case Series (n = 6 patients)
Level of evidence	Level 4
Methods	Six patients undergoing wedge resection or lobectomy for lung tumor donated tissue to be inoculated with SARS-CoV-2 and SARS-CoV. Virus titers measured at 2, 24, and 48 hours, and tissues underwent panel of representative IFNs and pro-inflammatory cytokines/chemokines.
Findings	SARS-CoV-2 antigens detected in significantly higher amount and in more areas of the lung tissues than SARS-CoV antigens. **SARS-CoV-2 generated 3.20 folds more infectious virus particles in 48 hours than SARS-CoV (P<0.024).** Both SARS-CoV-2 and SARS-CoV infected type I pneumocytes, type II pneumocytes, and alveolar macrophages. SARS-CoV-2 infection did not significantly trigger the expression of any IFN, compared to SARS-CoV. SARS-CoV-2 infection only significantly upregulated 5 of 13 inflammatory mediators, compared to 8 of 13 in SARS-CoV.
Clinical Implications	The **high degree of replication and viral particles of SARS-CoV-2 may explain high viral loads in COVID-19 patients presenting early in the disease course, and possibly during intubation.** The **SARS-CoV-2 triggers fewer pro-inflammatory markers than SARS-CoV**, potentially explaining why many patients remain asymptomatic or with mild symptoms throughout their disease course. Future research should explore how the mechanism of how SARS-CoV-2 suppresses the IFN and cytokine/chemokine response.
Limitations	Ex-vivo human lung tissue explant culture doesn't represent the effect of host systemic inflammatory response and the adaptive immune response. Human tissue supply is limited, and is not a viable option to investigate the characteristics of SARS-CoV-2. This study used a small sample size, and all lung tissue donators were diagnosed with lung cancer, as such the results might not be generalizable to the larger population.

Structural and Functional Basis of SARS-CoV-2 Entry by Using Human ACE2

Qihui Wang et al.

Cell

April 7, 2020

DOI: https://doi.org/10.1016/j.cell.2020.03.045

Purpose	To analyze the human angiotensin-converting enzyme 2 (hACE2) entry receptor as a binding site for SARS-CoV-2 compared to SARS-CoV and MERS-CoV.
Study design	Descriptive Study
Level of evidence	Not applicable
Methods	Immunostaining and flow cytometry were used to identify the spike (S) glycoprotein subunits of SARS-CoV-2 which interact with the hACE2 receptor. SARS-CoV-2/hACE2 complexes were analyzed in-vitro via size exclusion chromatography to study virus-receptor interaction and complex formation. Surface plasmon resonance (SPR) assay was used to demonstrate virus-receptor binding affinity of SARS-CoV-2 compared to SARS-CoV and MERS-CoV. The epitope features of SARS-CoV-2 were assessed using murine monoclonal antibodies against SARS-CoV and MERS-CoV S proteins.
Findings	Entry of coronaviruses into host cells is mediated by the S glycoprotein. Immunostaining and flow cytometry with SARS-CoV-2 S protein preparations revealed a strong affinity for hACE2 binding, and **the complex was largely similar to the structure of the SARS-CoV/hACE2 complex.** SARS-CoV-2-CTD binding interface displayed significantly stronger interactions with hACE2 compared to SARS-CoV, with more amino acid residues that directly bind the hACE2 receptor, more hydrogen bonds, and larger buried surface areas resulting in overall increased atomic interactions. **SARS-CoV-2 demonstrated a 4-fold higher binding affinity for the hACE2 receptor when compared with SARS-CoV and MERS-CoV.**
Clinical Implications	Monoclonal and polyclonal antibodies directed against both SARS-CoV and MERS-CoV were unable to bind the SARS-CoV-2 S protein, despite the shared characteristic of these three coronaviruses to engage the hACE2 receptor for entry into host cells. **This lack of monoclonal antibody binding indicates distinct antigenic features of the novel coronavirus, SARS-CoV-2, that reduce the effectiveness of potential vaccine therapies utilized in previous coronavirus outbreaks.**
Limitations	Additional research is needed to determine the efficacy of vaccines and their role in targeting S proteins for SARS-CoV-2 as a means of prophylaxis.

Composition and divergence of coronavirus spike proteins and host ACE2 receptors predict potential intermediate hosts of SARS-CoV-2

Zhixin Liu et al.

Journal of Medical Virology
February 26, 2020
DOI: https://doi.org/10.1002/jmv.25726

Purpose	To identify potential intermediate hosts transmitting SARS-CoV-2 to humans by characterizing various species' coronavirus spike protein and its interaction with angiotensin-converting enzyme 2 (ACE2).
Study design	Observational study
Level of evidence	Not applicable
Methods	Protein sequences of ACE2 and spike glycoproteins of SARS-CoV-2, SARS-CoV, and bat SARS-like CoV were obtained in addition to the bat SARS-like CoV RaTG13 sequence and the pangolin metagenome. Protein sequence alignment and phylogenetic analysis was accomplished using Molecular Evolutionary Genetics Analysis (MEGA-X) software, and multiple comparisons were done by ClustalW. Structure and binding models of the spike receptor were accomplished using I-TASSER, PRISM 2.0, and PyMOL softwares.
Findings	SARS-CoV-2 receptor-binding domain (RBD) sequence has 93% similarity when compared to pangolin SARS-like CoV SRR10168377, which has 89% similarity with bat SARS-like CoV RaTG13. SARS-CoV and CoV-2 enter the respiratory tract by the receptor ACE2 and were found to have good alignment. An interaction model from the PRISM 2.0 database indicated that SARS-CoV-2 spike protein may bind to ACE2 through Leu455, Phe486, Gln493, Asn501, and Tyr505. CoV spike – ACE2 binding in turtles and pangolins more resemble humans than bats. ACE2 site 41 residue is tyrosine in pangolin, turtle, and human, but histidine in bat; tyrosine may possess higher affinity for RBD than histidine.
Clinical Implications	Studying the evolutionary relationship of the RBD of the spike protein of SARS-CoV-2 **is useful in determining possible intermediate hosts**. This method may facilitate finding reservoirs of SARS-CoV2 and future viral pandemics.
Limitations	The authors noted that the spike protein crystallization of SARS-CoV-2 was analyzed urgently. Further studies need to confirm its structure, and the interactions between SARS-CoV-2 spike protein RBD and ACE2 in other possible intermediate hosts.

Characterization of spike glycoprotein of SARS-CoV-2 on virus entry and its immune cross-reactivity with SARS-CoV

Xiuyuan Ou et al.

Nature Communications
March 27, 2020
DOI: https://doi.org/10.1038/s41467-020-15562-9

Purpose	To determine cell type susceptibility, entry receptor, entry pathway, protease priming mechanisms, and serological specificity of SARS-CoV-2.
Study design	Observational study
Level of evidence	Not applicable
Methods	Pseudovirions produced by co-transfection 293T cells with plasmids encoding SARS-CoV-2 S. HEK 293 cells stably expressing hACE2 (293/hACE2) were pretreated with lysosomotropic agents or cathepsin inhibitors, then inoculated with pseudovirions. Cells were lysed, and luciferase activity measured to determine entry into the cell. SARS-CoV S, SARS-CoV-2 S, and VSV G pseudovirons (control) were pre-incubated with rabbit anti-SARS S1 antibodies T62 or patient sera. Mixture was added onto 293/hACD2 cells. Cells were lysed and pseudovirus transduction was measured.
Findings	293/hACE2 cells were highly transduced by SARS-CoV-2 S pseudovirions, indicating that hACE2 is the receptor for SARS-CoV-2. Phosphatidylinositol 3-phosphate 5-kinase (PIKfyve) inhibitors, apilimod, and YM201636 inhibited entry of SARS-CoV-2 S pseudovirions via endocytosis to 293/hACE2 cells. Cathepsin L inhibitors decreased entry of SARS-CoV-2 S pseudovirions by over 76%, suggesting it is essential for SARS-CoV-2 S priming. Type II membrane serine proteases-mediated cleavage activated fusion potential of SARS-CoV-2 S protein in 293/hACE2 cells. Trypsin could activate SARS-CoV-2 S protein efficiently but was not necessary for SARS-CoV-2 S protein to trigger syncytium formation. SARS-CoV-2 S protein was less stable than SARS-CoV-S protein, requiring shorter time and lower temperature to be inactivated. Anti-SARS S1 antibodies T62 recognized SARS-CoV-2 S protein. A low-level binding of SARS-CoV-2 S protein to rabbit anti-SARS S1 antibody T62 was detected. Substitution of SARS-CoV-2 receptor binding domain (RBD) with SARS-CoV RBD increased the affinity of S protein to polyclonal antibodies T62 suggesting differences between SARS-CoV and SARS-CoV-2 RBDs. Serum from recovered SARS patient demonstrated strong inhibition on transduction by SARS-CoV S pseudovirions and modest neutralization activity against SARS-CoV-2 S pseudovirions. Sera from all five COVID-19 patients neutralized SARS-CoV-2 S pseudovirions but had no effect on transduction by SARS-CoV S pseudovirions.
Clinical Implications	Entry of SARS-CoV-2 S pseudovirions into 293/hACE2 cells was reduced by preincubation of soluble hACE2; **soluble hACE2 may be a viable therapeutic inhibitor against SARS-CoV-2 infection**. Inhibition of SARS-CoV-2 S pseudovirion entry by lysosomotropic agents suggested that **PIKfyve should be considered as a potential drug target**. Due to only moderate cross-neutralization between covalescent sera of SARS and COVID-19 patients, **those previously recovered from SARS-CoV infection may not be protected against SARS-CoV-2 infection.**
Limitations	Involvement of additional endogenous proteases in HEK293T cell syncytium formation and mechanism of entry into other cell types requires further research. Further characterization of the differences between the SARS-CoV-2 RBD and SARS-CoV RBD should be pursued.

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

Daniel Wrapp et al.

Science
March 13, 2020
DOI: 10.1126/science.abb2507

Purpose	To facilitate vaccine formulation and identification of drug targets against COVID-19 (2019-nCoV), the CoV spike (S) glycoprotein was characterized and compared to the S glycoprotein of various other coronaviruses including SARS-CoV.
Study design	Observational study
Level of evidence	Not applicable
Methods	2019-nCoV S protein was compared to several other coronaviruses, including SARS-CoV S, in protein sequence, orientation of receptor binding domains (RBD) by cryo-electron microscopy (cryo-EM), binding affinity for angiotensin-converting enzyme 2 (ACE2), and cross reactivity of four published anti-SARS-CoV S protein antibodies against 2019-nCoV S protein by biolayer interferometry (BLI).
Findings	Cryo-Em demonstrated that structure, orientation, and binding movement of 2019-nCoV S protein overlapped strongly with SARS and MERS-CoV S protein. Amino acid sequence of 2019-nCoV S protein was 98% shared between bat coronavirus RaTG13 (SARS-CoV S protein shared sequence was not reported). Of note, a gain of function mutation in 2019-nCoV S protein leads to RRAR furin recognition site, allowing protease cleavage and potentially enhanced virulence. Similar mutations are seen in hemagglutinin of highly virulent strains of influenza. Binding orientation of S protein to ACE2 was preserved across the viruses and revealed a 10-20-fold higher affinity in 2019-nCoV S protein compared to SARS. To investigate if immunity to SARS-CoV could contribute to immunity to COVID-19, authors assessed binding of four published anti-SARS S protein antibodies to 2019-nCoV S protein. No binding was detected between anti-SARS antibodies and COVID-19 antigens.
Clinical Implications	Enhanced affinity for fusion and entry may contribute to COVID-19 virus's capacity to spread rapidly and make S protein-ACE2 binding a potential pharmacologic target. **Previous infection with SARS-CoV does not necessarily confer immunity to Covid-19.**
Limitations	Analysis of additional antigens and population-level epidemiological studies are needed to assess the shared immunity of various coronaviruses, such as SARS and MERS, with COVID-19.

Structure of Mpro from COVID-19 virus and discovery of its inhibitors.

Zhenming Jin et al.

Nature
April 9, 2020
DOI: https://doi.org/10.1038/s41586-020-2223-y

Purpose	To characterize COVID-19 protease (Mpro) and develop screening strategy revolving around in-silico (computer-modeled) and in-vitro analysis of Mpro inhibition by pre-approved drugs to facilitate pharmacotherapy development.
Study design	Observational study
Level of evidence	Not applicable
Methods	COVID-19 protease Mpro underwent Fluorescence Resonance Energy Transfer (FRET) assay to determine efficiency. Kinetic analysis was used to assess the binding affinity of Mpro inhibitor "N3", showing inhibition and antiviral activity in animal models against MERS-CoV and SARS-CoV, to COVID-19 Mpro. Structure analysis of the N3-Mpro complex identified binding characteristics of N3, identifying potential coronavirus drug targets that may bind and inhibit Mpro in a similar manner. Measured effects of various compounds on COVID-19 Mpro enzyme kinetics.
Findings	**COVID-19 Mpro had slightly increased efficiency compared to SARS-CoV Mpro.** Potent, irreversible inhibition of COVID-19 Mpro was achieved with coronavirus Mpro inhibitor "N3", to which other potential drug candidates were compared. Virtual screening of potential Mpro inhibitors that also bind to the substrate binding pocket identified Cinanserin, a serotonin antagonist from the 1960's, with potential for optimizing as an anti-viral drug. **Screening of ~10,000 compounds using FRET yielded six FDA-approved or clinical trial/preclinical trial candidates: Ebselen, Disulfiram, Tideglusib, Carmofur, Shikonin, and PX-12.**
Clinical Implications	**This methodology provides a framework for systematically identifying potential drug candidates targeting COVID-19 Mpro** that already underwent clinical trials for safety. This same framework can be applied in future pandemics needing rapid and novel drug development.
Limitations	While this methodology rapidly provides potential pharmacological therapies with well-theorized anti-microbial mechanisms, it lacks in-vivo data that animal models may provide.

Structure of the RNA-dependent RNA Polymerase from COVID-19 Virus

Yan Gao et al.

Science
April 10, 2020
DOI: 10.1126/science.abb7498

Purpose	To determine the molecular structure of the COVID-19 RNA-dependent RNA polymerase (RdRp or nsp12) and nonstructural proteins nsp7 and nsp8.
Study design	Structural analysis comparison
Level of evidence	Not applicable
Methods	COVID-19 RdRp gene was cloned into a plasmid vector and then transformed into Escherichia coli. Proteins were purified via nickel-nitrilotriacetic acid chromatography and again via Hitrap Q ion-exchange column. RdRp-nsp7-nsp-8 complex was stabilized and assembled at a molar ratio of 1:2:2.The architecture of the COVID-19 virus RdRp-nsp7-nsp8 complex was elucidated via cryogenic electron microscopy.
Findings	The structure of the COVID-19 virus RdRp-nsp7-nsp8 complex is similar to SARS-CoV with a root-mean-square deviation (rmsd) value of 0.82 for 1,078 C-alpha atoms. Key distinguishing features of COVID-19 include additional residues A4-R118 in the NiRAN domain, and residues N215-D218 form a β-strand in COVID-19 virus RdRp providing additional conformational stability. COVID-19 virus RdRp has the highest similarity with the Apo state of hepatitis C virus (HCV) ns5b, providing context to comparative analysis between the potential mechanism of remdesivir and the known mechanism of sofosbuvir. COVID-19 RdRp domain adopts the conserved architecture of the viral polymerase family consisting of a finger (residues L366-A581 and K621-G679), palm (residues T582-P620 and T680-Q815), and thumb (residues H816-E920) domain. The active site of the COVID-19 virus RdRp is in the finger domain via motifs A-F.
Clinical Implications	**COVID-19 RdRp is considered a primary target for chain terminating nucleotide analog antiviral inhibitors including remdesivir.** Such findings serve to inform pharmaceutical design in efforts to produce effective drugs and vaccines against COVID-19.
Limitations	Cryogenic electron microscopy failed to map the S1-D3 and G897-D901 residues of COVID-19 virus RdRp. The study models a potential molecular interaction of COVID-19 motifs and remdesivir after the molecular interactions of HCV and sofosbuvir. While there are similarities between the mechanisms of the chain terminating nucleotide analog antiviral inhibitors, and while the model is theoretical in nature, there are limitations to what can be extrapolated from comparative analysis.

Is low alveolar type II cell SOD3 in the lungs of elderly linked to the observed severity of COVID-19?

Ahmed Abouhashem et al.

Antioxidants and Redox Signaling
April 23, 2020
DOI: https://doi.org/10.1089/ars.2020.8111

Purpose	To compare type II alveolar cell RNA sequencing data between elderly and young healthy subjects to further understand age differences in COVID-19 presentations.
Study design	Case series (n = 4)
Level of evidence	Level 4
Methods	Human lung single cell RNA sequencing (scRNA-seq) data from 4 healthy donors were divided into the "old-age group" (57 and 63 years-old) and the "young-age group" (22 and 29-years-old). Using expression atlas of human primary cells, alveolar type II pneumocytes were isolated from the mixed cell populations. Genes of this alveolar type II cell cluster were assessed for differential expression as a function of aging.
Findings	Expression of angiotensin-converting enzyme 2 (ACE2) and transmembrane serine protease 2 (TMPRSS2), colocalization of which enables SARS-CoV-2 to enter cells, in the alveolar type II cells were comparable between old and young donors. Superoxide dismutase 3 (SOD3) was the most downregulated in the old-age group, along with downregulation of other redox-based genes including activating transcription factor 4 (ATF4), metallothionein 2A (M2TA) and glutathione peroxidase 1 (GPX1). 21 of the 24 ATF4 downstream factors were significantly downregulated in alveolar type II cells of the elderly. Gene regulator database analysis suggested older patients' ability to respond to heme deficiency and the ATF4-dependent ability to respond to ER oxidative stress is significantly compromised.
Clinical Implications	COVID-19 produces oxidative stress within the lungs, and older patients displayed reduced redox gene expression relative to two younger patients. This data, in combination with evidence that superoxide dismutase (SOD) can decrease severity of respiratory illnesses, warrants **further investigation of therapies focused on reducing the oxidative stress on type II pneumocytes both in vitro and in vivo.**
Limitations	A small sample, low powered case series with 4 COVID19-free participants.

Visualizing speech-generated oral fluid droplets with laser light scattering.

Philip Anfinrud et al.

New England Journal of Medicine
April 15, 2020
DOI: 10.1056/NEJMc2007800

Purpose	To demonstrate aerosol expulsion of normal speech with and without a face cover.
Study design	Observational study
Level of evidence	Level 5
Methods	A laser source was set up in order to visualize droplets from people speaking the phrase "stay healthy". The speaker was given a slightly damp cloth face mask, and repeated the phrase with the mask and without, at three different volumes each time. The aerosol spray was recorded with a camera and analyzed.
Findings	The act of speaking generates oral droplets and **most droplets were visualized when the voiceless dental fricative ("th" sound) was made.** The droplets ranged from 20-500 µm in size. Large droplets fall quickly to the ground whereas small droplets behave like an aerosol, which further expands the distance and spread of infectious particles. The presence of a slightly damp face mask significantly reduced the number of droplets emitted by the speaker.
Clinical Implications	Viral agents transmit from human to human through speech and **viral aerosol spread can be mitigated by mask usage**.
Limitations	The study was limited by its small sample size (6 different conditions, with a limited number of repetitions per trial). Furthermore, this is not a true laser-light scattering experiment, despite the title—the analysis of the light scattering data was not described, and there was no mention of how they arrived at the 20-500 µm size-scale of the droplets. Studies of light scattering are often impeded by dust, and the HEPA filter may not have adequately filtered the air within the cardboard box in which they made their measurements. Some of the flashes representing speech droplets were streaked suggesting that the rate of 60 frames per second was insufficient to freeze the motion of the droplets. The size detection limit for observed particles was not stated, and if particles <10µm evaded their image analysis scheme, it could have detrimental implications for the applicability of their study, since the lung passageways most readily absorb particles smaller than that threshold. Additionally, it was unclear why authors didn't test a dry facemask, or why they didn't test more phrases corresponding to a broader range of the phonemes in the English language.

A highly conserved cryptic epitope in the receptor-binding domains of SARS-CoV-2 and SARS-CoV

Men Yuan et al.

Science
April 3, 2020
DOI: 10.1126/science.abb7269

Purpose	To analyze the ACE2 receptor binding domain (RBD) of SARS-CoV and SARS-CoV-2 S-spike protein, and the cross-reactivity of an anti- SARS-CoV S-protein antibody with SARS-CoV-2.
Study design	Original molecular biology investigation
Level of evidence	Level 5
Methods	CR3022, a neutralizing antibody targeting RBD of SARS-CoV, was exposed to SARS-CoV-2 S-protein RBD. Authors assessed this complex's structure and binding affinity to find out conserved vs divergent RBD sequences affecting binding of CR3022 on these S-proteins. Ability of CR3022 to neutralize SARS-CoV-2 was assessed via in vitro by microneutralization assay. ELISA assessed interaction of CR3022 and m396, another SARS-CoV antibody, with SARS-CoV-2 RBD.
Findings	As revealed by structural studies, CR3022 targets a highly conserved epitope that enables cross-reactive binding between SARS-CoV-2 and SARS-CoV. Despite cross-reactivity of CR3022 and CoV-2 and 86% conserved residues between CoV and CoV-2 RBDs, CR3022 binds to CoV RBD (Kd=1 nM) with significantly more affinity than CoV-2 RBD (Kd=115 nM). Authors attributed this to an additional N-glycosylation site on CoV-2 RBD. While CR3022 does not block ACE2 binding of RBD, its epitope is only exposed when RBDs are in their "up" conformation allowing them to bind to ACE2. This suggests a different mechanism of suppression besides blocking cell entry via ACE2. In-vitro microneutralization assay failed to show any neutralization of CoV-2 at the highest concentration CR3022 tested (400 µg/ml). ELISA confirmed CR3022 does interact with CoV-2 and demonstrated a higher binding signal compared to m396 antibody.
Clinical Implications	Despite binding both CoV and CoV-2, **immunity conferred by anti-SARS-CoV RBD antibodies is not robust.** Other targets should be considered for vaccine and drug development against coronaviruses broadly and COVID-19 specifically.
Limitations	This study did not assess possible synergistic effects of CR3022 with other known anti-RBD antibodies in-vitro, nor did they investigate in-vivo effects against CoV-2. Authors cite numerous examples of antibodies against coronaviruses, influenza A, herpesvirus, cytomegalovirus, dengue virus and others which confer in-vivo protection while failing in-vitro neutralization. Additionally, further investigation of other conserved CoV epitopes are needed for coronavirus vaccine development.

High expression of ACE2 receptor of 2019-nCoV on the epithelial cells of oral mucosa.

Hao Xu et al.

International Journal of Oral Science
February 24, 2020
DOI: https://doi.org/10.1038/s41368-020-0074-x

Purpose	To determine angiotensin-converting enzyme II (ACE2) receptor expression and its composition in various tissues.
Study design	Basic/Molecular
Level of evidence	N/A
Methods	Bulk RNA-sequence data of para-carcinoma normal tissues were downloaded from The Cancer Genome Atlas (TCGA) and the Functional Annotation of The Mammalian Genome Cap Analysis of Gene Expression (FANTOM5 CAGE) dataset. To specifically assess distribution of ACE2 in the oral cavity, four tissue specimens from patients' oral mucosa were obtained from a previous study. All patients were diagnosed with hyperkeratosis without dysplasia or cellular atypia, rendering genetic profiles closer to normal tissue than malignant.
Findings	Analysis of bulk RNA-sequence data from TCGA showed ACE2 expression in various organs. Among these tissues, **the oral cavity had the sixth highest mean ACE2 expression** (following intestine, kidney, stomach, bile duct and liver). Expression of ACE2 in the oral cavity was highest in the tongue (95.86% ACE2-positive cells) compared to the floor of the mouth and base of the tongue. Assessment of cell type specific expression of ACE2 in the oral cavity showed expression in B cells, endothelial cells, epithelial cells, fibroblasts, macrophages, mast cells, and T cells.
Clinical Implications	Although COVID-19 infections hardly present with oral symptoms, ACE2 expression in the oral cavity indicates that **the oral infection route of COVID-19 cannot be excluded as a significant means of transmission**.
Limitations	This study relies heavily on secondary analysis of existing data. Because publicly available datasets usually delete identifying variables about subjects, variables that may be important, there is potential to create residual confounders when the omitted variables are crucial covariates to control for. The small sample size poses difficulties in interpretation of results, specifically confidence intervals and P-values. Furthermore, all subjects from which the specimens were collected were diagnosed with hyperkeratosis, representing a specific subpopulation that most likely is not be representative of target populations.

Phylogenetic network analysis of SARS-CoV-2 genomes.

Peter Forster et al.

PNAS

April 8, 2020

DOI: https://doi.org/10.1073/pnas.2004999117

Purpose	To understand the evolution of the coronavirus within humans by analyzing 160 complete viral genomes to be sequenced from human patients in the midst of the current pandemic.
Study design	Basic/experimental research study, genetic analysis
Level of evidence	N/A
Methods	Phylogenetic network analysis was utilized to study 160 complete SARS-CoV-2 genomes contributed by researchers around the world since December 2019. Viral genomes were provided by the Global Initiative on Sharing Avian Influenza Data (GISAID), a database for global collaboration since 2006.
Findings	A bat coronavirus (BatCoVRaTG13) from Yunnan Province (China) with 96.2% sequence similarity to that found in humans, was used as an outgroup to determine the root of the phylogeny within the network. Phylogenetic network analysis identified three major variants of SARS-CoV-2: A, B, and C, types distinguished by amino acid changes. Type A was most closely related to the virus found in both bats and pangolins and represents the ancestral type. Types A and C genomes are primarily found outside of East Asia, particularly in Europe and the Americas. Type C differs from type B by a G26144T mutation which changes a glycine to a valine. This variant is the major genome identified in Europe, California, and Brazil. Type B was found to be derived from type A by two mutations. The ancestral B-type genome is clustered in East Asia. All B-type genomes found outside of East Asia have mutated.
Clinical Implications	Identification of viral genome mutations by genetic networking techniques allows for the reconstruction of infection paths. An understanding of the SARS-CoV-2 mutational variants poses significant implications for the development of a vaccine and may play a role in the range of clinical presentations and spread of the disease.
Limitations	Given the pandemic-level spread of SARS-CoV-2, phylogenetic network analysis is less useful as significant migration and mutation of the virus has taken place. The first viral genome sampled in late December 2019 was found to be evolutionarily distant from the root type in comparison to the bat coronavirus outgroup.

Circulating plasma concentrations of angiotensin-converting enzyme 2 in men and women with heart failure and effects of renin-angiotensin-aldosterone inhibitors

Iziah E Sama et al.

European Heart Journal
May 10, 2020
DOI: https://doi.org/10.1093/eurheartj/ehaa373

Purpose	To examine plasma angiotensin-converting enzyme 2 (ACE-2) levels in heart failure (HF) patients and impact of renin-angiotensin-aldosterone system (RAAS) inhibitors on ACE-2 levels.
Study design	Non-randomized cohort study with index (n = 2022; 1485 male, 537 female) and validation cohorts (n = 1698; 1123 male, 575 female)
Level of evidence	Level 3
Methods	Data were obtained from the BIOlogy Study to Tailored Treatment in Chronic Heart Failure (BIOSTAT-CHF) which focused on improvement of HF management. Data were drawn from an index cohort of patients from 11 European countries and a validation cohort of patients from Scotland. Included patients had LVEF <40%, BNP > 400 pg/mL, or pro-BNP > 2000 pg/mL. Per study protocol, patients were treated with furosemide though use of goal-directed medical therapy for HF including beta-blockers, angiotensin conversion enzyme inhibitors (ACE-Is) or angiotensin receptor blockers (ARBs), and mineralocorticoid receptor antagonists (MRAs), was not standardized. ACE-2 levels were measured via immunoassay. Data for BIOSTAT-CHF were collected prior to the onset of coronavirus disease 19 (COVID-19).
Findings	**In both index and validation cohorts, mean concentration of ACE-2 was significantly higher in men than women** (5.38 vs. 5.09, p<0.001 and 5.46 vs. 5.16, p<0.001, respectively). In the index cohort, ACE-2 levels were not elevated to a statistically significant level in patients on ACE-Is, ARBs, or MRAs. **In the validation cohort, use of ACE-Is or ARBs was associated with lower ACE-2 concentrations (p=0.002 and p=0.03, respectively) while use of MRAs was associated with elevated ACE-2 concentrations (p=0.04).** These data do not definitively illustrate that ACE-2 levels are significantly altered in HF patients using RAAS inhibitors.
Clinical Implications	Elevated ACE-2 levels are associated with male sex, though ACE-2 levels are not consistently elevated in patients using ACE-Is, ARBs, or MRAs. Therefore, this study does not support stopping use of RAAS inhibitors in patients undergoing treatment of COVID-19.
Limitations	Data were not collected from CHF patients with COVID-19, so no direct inference can be made to ACE-2 levels in such a patient population. ACE-2 concentrations were measured in the plasma and therefore do not account for membrane bound ACE-2. The authors speculate that these levels are similar.

A multi-basic cleavage site in the spike protein of SARS-CoV-2 is essential for infection of human lung cells

Markus Hoffmann et al.

Molecular Cell
March 5, 2020
DOI: https://doi.org/10.1016/j.molcel.2020.04.022

Purpose	To assess the interaction of proteases with arginine multi-basic cleavage site of spike (S) protein of SARS-CoV-2. Authors manipulated this epitope to investigate its contribution to infectivity and virulence.
Study design	Original Biomolecular Investigation.
Level of evidence	Level 4
Methods	Authors used a pseudotype particle system to generate multiple viruses harboring different spike protein variations with alterations in the multi-basic S1/ S2 cleavage site. These variants included analogous cleavage sites from SARS and RaTG (bat-born coronavirus), the addition of basic arginine residues, and the deletion of basic residues. The cleavage of the spike protein from SARS-Cov, SARS-Cov-2 and RatG viruses were directly compared. This study assessed the contribution of the S1/S2 site to TMPRSS2-dependent cleavage of the spike protein (known mechanism of SARS-2 entry into pneumocytes) and the efficacy of furin protease inhibitor on spike protein cleavage. Viral entry and infectivity by cell-cell fusion/spread (syncytia formation) was assessed using cultured cell lines from human and non-human primate sources.
Findings	Cleavage of the SARS-Cov-2 spike protein was enhanced by and dependent on the multi-basic S1/S2 motif but was not enhanced by additional arginine resides. Treatment with furin protease inhibitor resulted in a dose-dependent reduction in cleavage at the SARS-2-S and MERS-S S1/S2 site. No cleavage was seen in SARS-S. Vero cell syncytia formation was also dependent on the multi-basic SARS-2 S1/ S2 site. Synctia formation was enhanced with induced TMPRSS2 expression, and insertion of additional arginine residues. Mutations of SARS-2-S multi-basic site prevented entry into TMPRSS2+ cells, but these mutants were able to enter TMPRSS2- cells, likely via an alternative cleavage pathway.
Clinical Implications	The multi-basic SARS-2-S S1/S2 site appears to facilitate efficient SARS-2-S cleavage, entry into cells and cell-to-cell transmission. This proteolytic activation is not preserved across all coronavirus strains. Pharmacotherapy development may find targets in this pathway (furin, TMPRSS2) to reduce virulence of SARS-2 specifically. Mutations of monobasic cleavage sites in SARS-CoV-2-related zoonotic viruses may be key in their ability to infect humans.
Limitations	This study assessed recombinant protein as a proof of principle but investigating this S1/ S2 motif with patient-derived SARS-CoV-2, and primary human pneumocytes would bolster these findings and open potential targets for pharmacology.

SARS-CoV-2 infection protects against rechallenge in rhesus macaques

Abishek Chandrashekar et al.

Science
May 20, 2020
DOI: 10.1126/science.abc4776

Purpose	To determine if SARS-CoV-2 infection induces natural immunity that provides protective efficacy against re-exposure in rhesus macaques.
Study design	Animal Model
Level of evidence	N/A
Methods	Nine adult rhesus macaques were placed into three groups and inoculated with three different concentrations of SARS-CoV-2. Subsequently, viral RNA levels were assessed by RT-PCR in bronchoalveolar lavage (BAL), nasal swab (NS) and plasma. SARS-CoV-2-specific humoral and cellular immune responses were evaluated via ELISA, pseudovirus neutralization assay and live virus neutralization assay. On day 35 following initial viral infection, the nine macaques were rechallenged with the same doses utilized for primary infection, with the addition of three naïve animals for a positive control group. Following rechallenge, viral RNA levels were assessed by RT-PCR with subgenomic mRNA (sgmRNA) levels as well as plaque assays in BAL and NS samples. Immune responses were characterized by ELISA, pseudovirus neutralizing antibody (NAb) and live virus NAb titers.
Findings	Throughout primary infection of the nine macaques, high levels of viral RNA were observed in BAL and NS. Viral load peaked on day two and resolved by day 10-14 in BAL and day 21-28 in NS. All nine macaques had developed antibody responses to the SARS-CoV-2 S protein and neutralizing antibody responses. Cellular immune responses were lower in the lower dose groups. On day one following viral rechallenge, very limited viral RNA was observed in BAL and NS in previously exposed macaques, and no viral RNA was detected at subsequent timepoints. High levels of viral RNA were observed in the naïve control animals, as expected. By the seventh day following re-exposure, rapid anamnestic immune responses were observed in all animals, including increased SARS-CoV-2-specific ELISA titers, pseudovirus NAb titers and live virus NAb titers. **Following rechallenge, there was little to no clinical disease observed.**
Clinical Implications	Primary SARS-CoV-2 infection provided protection against re-exposure in rhesus macaques via humoral and cellular immune responses mediated by immunologic control. This provides evidence that immunologic approaches to the prevention and treatment of SARS-CoV-2 infection may be effective.
Limitations	Though the rhesus macaques model of SARS-CoV-2 infection encompasses many aspects of human disease, this model did not produce respiratory failure or mortality, so further research will be required to develop a nonhuman primate model of severe disease. Additionally, further research will be required to determine immune correlates of protection and to define the durability of natural immunity. Clinical studies will be required to determine whether primary SARS-CoV-2 infection provides protective efficacy against reinfection in humans.

Cell type-specific expression of the putative SARS-CoV-2 receptor ACE2 in human hearts.

Luka Nicin et al.

European Heart Journal
March 23, 2020
DOI: https://doi.org/10.1093/eurheartj/ehaa311

Purpose	To ascertain the expression of ACE and ACE2 in the numerous cell types of the human heart, further characterizing SARS-CoV-2 disease risk and possible treatment contraindications.
Study design	Case-control (n=7)
Level of evidence	Level 4
Methods	Single nuclei RNA sequencing was utilized to determine the expression of ACE and ACE2 in cardiomyocytes, fibroblasts, endothelial cells, leukocytes, and pericytes. Gene expression was determined in five participants with a diagnosis of aortic stenosis (AS), two participants with a diagnosis of heart failure with reduced ejection fraction (HFrEF), and one healthy donor heart that was utilized as a control. Immunostaining was utilized to confirm ACE2 expression in cardiomyocytes.
Findings	ACE2 was found to be prominently expressed in cardiomyocytes and pericytes. ACE2 was expressed to a lower degree in fibroblasts, endothelial cells and leukocytes. Comparison of ACE2 expression amongst the participants found an elevated level of ACE2 expression in the cardiomyocytes of participants with heart disease, when compared to the healthy control. ACE2 expression appeared to be elevated in the cardiomyocytes of patients with AS. Additionally, ACE expression was elevated in the cardiomyocytes of participants with heart disease (AS and HFrEF). Interestingly, participants on ACE-inhibitor therapy showed a significantly higher ACE2 expression when compared with participants on Angiotensin II Receptor Blocker (ARB) therapy; participants on ACE-inhibitor therapy demonstrated at least a 4x higher ACE/ACE2 ratio when compared with healthy controls.
Clinical Implications	ACE2 has been identified as the main receptor for SARS-CoV-2 and is expressed at high levels in both lung and heart tissue. It has been previously established that SARS-CoV-2 infects alveolar epithelial cells and is thought to cause myocardial injury as evidenced by increased troponin T and NT-proBNP levels in COVID-19 patients. Patients with heart disease demonstrate augmented cardiac expression of ACE2 levels, particularly in cardiomyocytes. This alteration of expression may present a significant risk in patients with heart disease who are infected with SARS-CoV-2. Though it is not clear whether these effects are secondary to viral infection of cardiac tissue or the cardiac damage is due to systemic inflammation and resulting hypoxia, these patients may need to be monitored for cardiac complications. Additionally, ACE/ACE2 ratios appear to be correlated with ACE-inhibitor and ARB therapies and, as such, further characterization of the impact of these therapies should be undertaken.
Limitations	Small sample size limits the impact and external validity of the results.

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

Peng Zhou et al.

Nature

February 3, 2020

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

Purpose	To provide a detailed report on SARS-CoV-2 describing the identification and characterization of a novel coronavirus.
Study design	Case Series with molecular analysis
Level of evidence	Level 4
Methods	Samples of seven patients admitted to the ICU of Wuhan Jin Yin-Tan Hospital with severe pneumonia were sent to the Wuhan Institute of Virology for determination of the causative pathogen. Anti-SARSr-CoV Rp3 N antibody was used to determine the presence of the virus. Virus neutralization tests were carried out with diluted serum samples and diluted horse anti-SARS-CoV serum; serum samples from healthy humans were used as controls. ACE2 receptor testing was completed using HeLa cells and isolated virus. ACE2 expression was detected by mouse anti-S tag monoclonal antibody and a FITC-labelled goat anti-mouse IgG.
Findings	Assembly and PCR identified a 29,891-base-pair CoV genome that shared 79.6% sequence identity to SARS-CoV, a human coronavirus. The amino acid sequences of the conserved replicase domains are 94.4% identical between SARS-CoV and SARS-CoV-2, suggesting that they belong to the same species. **A short region of RNA polymerase from bat coronavirus RaTG13 demonstrated 96.2% genome sequence identity to SARS-CoV-2 and a similar spike protein gene, indicating that RaTG13 is the closest relative of SARS-CoV-2. The close phylogenetic relationship to RaTG13 provides evidence that SARS-CoV-2 may have originated in bats.** A second analysis tested samples from five of the seven virus-positive patients 20 days following disease onset – all patient samples tested strongly positive for viral IgG. Additionally, it was determined that the virus could be cross-neutralized by horse anti-SARS-CoV serum. Finally, receptor testing determined that SARS-CoV-2 is able to use ACE2 proteins from Chinese horseshoe bats, civets, and pigs, but not mouse ACE2, as an entry receptor to ACE2-expressing cells, but not cells that did not express ACE2.
Clinical Implications	Characterization and origination of SARS-CoV-2 provides valuable epidemiological information and may inform therapeutic approaches. Neutralization assays indicated that serum neutralization of the virus was successful ex vivo and may have therapeutic potential. Considering the wide spread of SARSr-CoV in natural reservoirs, future research should focus on active surveillance of coronaviruses. Furthermore, broad-spectrum antiviral drugs and vaccines should be prepared for emerging infectious diseases caused by coronaviruses.
Limitations	This study is limited by a small sample size. Additionally, at the time of publication, transmission route was not yet established, though it appeared that the virus was transmissible between humans, and that airborne transmission could also be possible.

Cardiovascular Implications of Fatal Outcomes of Patients with Coronavirus Disease 2019 (COVID-19)

Tao Guo et al.

JAMA Cardiology
March 27, 2020
DOI: https://doi.org/10.1001/jamacardio.2020.1017

Purpose	To evaluate the association of underlying cardiovascular disease (CVD) and myocardial injury with fatal outcomes in patients with COVID-19.
Study design	Retrospective Case Series
Level of evidence	Level 2
Methods	Retrospective analysis of 187 COVID-19 patients hospitalized at the Seventh Hospital of Wuhan City, China from January 23, 2020 to February 23, 2020, including 144 discharged individuals and 43 individuals who died. Primary endpoint was incidence of COVID-19-associated death. Patient data included demographics, medical history, clinical lab values, comorbidities, complications, treatment measures, and outcomes.
Findings	**A total of 66 patients (35.3%) had underlying CVD** including hypertension, coronary heart disease, and cardiomyopathy, whereas **52 patients (27.8%) exhibited myocardial injury** as indicated by elevated Troponin T (TnT) levels. **Mortality was markedly increased in patients with elevated plasma TnT than in patients with normal TnT (31 [59.6%] vs 12 [8.9%]). Mortality was decreased in patients with underlying CVD and normal plasma TnT (13.33%, 4 of 30) when compared to patients with elevated TnT but no underlying CVD (37.5%, 6 of 16).** Patients with elevated TnT had significantly higher rates of common comorbidities, including hypertension, coronary heart disease, cardiomyopathy, diabetes, COPD, and CKD. Common inflammatory biomarkers (CRP, procalcitonin, and globulin) were all significantly higher in patients with elevated TnT. Patients with elevated TnT had significantly different indices of organ dysfunction as compared to patients with normal TnT**: elevated cardiac (CK-MB, myoglobin, NT-proBNP), kidney (creatinine), and liver (AST) biomarkers as well as decreased respiratory function (PaO2, FiO2).**
Clinical Implications	Myocardial injury is significantly associated with increased mortality in COVID-19. Myocardial biomarkers should be evaluated in patients with CVD who develop COVID-19 infection to best determine care plans and possible early and aggressive intervention.
Limitations	Those are early data from hospitalized patients at the epicenter of the coronavirus pandemic and the complete cardiac data (such as electrocardiography, echocardiography, coronary angiography, and magnetic resonance imaging) are missing due to the urgency of containing COVID-19. A larger cohort study is necessary in order to verify the conclusions from this project. Data was incomplete for portions of the study given the increased threshold of testing in the COVID-19 isolation ward. The impact of myocardial injury on mortality could be exaggerated as COVID-19 patient deaths may be caused by multiple organ dysfunctions.

Receptor binding and priming of the spike protein of SARS-CoV-2 for membrane fusion

Donald J. Benton et al.

Nature

September 17, 2020

DOI: https://doi.org/10.1038/s41586-020-2772-0

Purpose	To examine the binding mechanism between ACE2 and the SARS-CoV-2 spike glycoprotein (S) using cryo-electron microscopy (Cryo-EM) and provide a new insight into the mechanism of Covid-19 infection.
Study design	Basic Science Findings
Level of evidence	Level 5
Methods	Ectodomains of ACE2 and stabilized '2P' mutant of SARS-CoV-2 Spike glycoprotein with intact furin cleavage sites were expressed on Expi293F cells and purified with affinity chromatography followed by gel filtration. Purified Spike glycoprotein was then incubated with endogenous furin to induce S cleavage. Furin-treated SARS-CoV-2 Spike was mixed with ACE2 (final concentration of Spike = 0.5 mg/mL) for 45-60 s then treated with octyl glucoside and plunge frozen in ethanol for Cryo-EM.
Findings	The S glycoprotein is a trimeric protein cleaved and activated by furin resulting in three homotrimers containing an S1 subunit, with a receptor-binding domain (RBD) and N-terminal domain (NTD), that promote binding between the virion and host cell, and an S2 fusion subunit that promotes membrane fusion. Upon binding with the ACE2 domain, the S1 subunit undergoes conformational changes that facilitate opening and exposure of the S2 trimeric protein core, responsible for membrane fusion. Binding of S1 to ACE2 further facilitates S1:ACE-2 binding events, which helps the virus to fuse to the cell membrane and permits the infection.
Clinical Implications	Researchers analyzed the structure of spikes of SARS-CoV-2 and ACE2 binding events to unravel the mechanism of the earliest stages of infection. Such characterization of spikes that are unique to SARS-CoV-2 will help clinicians to focus on new targets and vaccines for anti-viral treatments.
Limitations	CryoEM allows the researchers to make suggestions regarding possible mechanisms based on the specimens they obtain, however, cannot definitively account for the transitional rearrangements of the Spike glycoprotein

EPIDEMIOLOGY

Epidemiology and clinical features of coronavirus disease 2019 in children

Soo-Han Choi et al.

Clinical and Experimental Pediatrics
April 6, 2020
DOI: https://doi.org/10.3345/cep.2020.00535

Purpose	To summarize the incidence and most common presenting symptoms in children/adolescents with COVID-19, and to discuss the potentialof 2019-nCoV transmission in pregnant mothers and newborns.
Study design	Systematic Review
Level of evidence	Level 2
Methods	This paper reviewed selected pediatric cases of 2019-nCoV worldwide, summarizing findings from prospective and retrospective studies of pediatric cohorts.
Findings	The limited data on the infection rate of 2019-nCoV in children, due to the lack of pediatric testing, shows that **children's symptoms are often mild, but some cases may progress to severe disease.** Of all COVID-19 cases in the studied populations, pediatric cases comprise 0.6-5.2%. The clinical manifestations of 2019-nCoV in children are **most commonly fever, cough, and fatigue along with rhinorrhea, diarrhea, and headache.** In studies of 31 COVID-19 positive pregnant women, 29 had C-sections, 11 infants experienced fetal distress, 1 infant was stillborn, and 1 infant died after birth. To date, there have been no reports of the vertical transmission of COVID-19. **However, a small number of neonatal COVID-19 diagnoses have been reported independent of maternal infections.**
Clinical Implications	**Transmission of 2019-nCoV in children primarily occurs through contact with adult patients, mainly through household exposure.** Prolonged detection of viral RNA in throat swabs and feces suggests that children may transmit the virus to others in the community. While infected neonates had mild symptoms, **special precautions including hand hygiene must be taken by individuals in close contact with newborns.**
Limitations	This study only included data through March 12th. Due to lack of testing capability, it is unclear how long infected children are contagious. Studies of pregnant mothers and newborns had small sample sizes, only observed third trimester mothers, and were disproportionately C-section cases. Further research is needed to assess the possibility of vertical transmission.

Comparison of Hospitalized Patients with Acute Respiratory Distress Syndrome Caused by COVID-19 and H1N1

Xiao Tang et al.

Chest

March 26, 2020

DOI: https://doi.org/10.1016/j.chest.2020.03.032

Purpose	To compare clinical presentation of acute respiratory distress syndrome (ARDS) in COVID-19 and H1N1 patients
Study design	Retrospective case-control (n = 148)
Level of evidence	Level 3
Methods	Retrospective case-control study of COVID-19 positive patients with ARDS (n=73, Wuhan Pulmonary Hospital, 12/2019-02/2020) compared with H1N1 (n=75, Beijing Chao-Yang Hospital, 03/2016-12/2019).
Findings	All differences in patient characteristics listed below were statistically significant. • Median age is higher in COVID-19 (67 years) vs H1N1 (52 years) • Septic shock more prevalent in COVID-19 (31.5%) vs H1N1 (13.3%) • Lower Sequential Organ Failure Assessment (SOFA) score and Acute Physiology And Chronic Health Evaluation II (APACHE II) score in COVID-19 (2, 11) vs H1N1 (5, 14) • Median PaO2/FIO2 in COVID-19 was higher (198.2 mm Hg) vs H1N1 (107.0 mm Hg) • Greater proportion of patients with PMHx of cardiovascular disease in COVID-19 (31.5%) vs H1N1 (10.7%) • SOFA adjusted mortality greater in H1N1 than COVID-19 (rate ratio=2.009)
Clinical implications	**COVID-19 patients were more likely to exhibit constitutional symptoms such as fatigue and diarrhea.** Ground-glass opacities on imaging were more common in COVID-19 patients compared to consolidation in H1N1 patients. ARDS is accompanied by fibromyxoid exudates in COVID-19, whereas H1N1 is accompanied by necrotizing bronchiolitis and extensive hemorrhage. Prior data suggest that glucocorticoid use in treating MERS-CoV and SARS-CoV has increased morbidity and mortality. **Steroid use in COVID-19 patients should be carefully considered**.
Limitations	Retrospective study including data from two independent single-center cohorts may introduce bias. The patients of the H1N1 cohort were more clinically ill than the COVID-19 cohort. A large proportion of the COVID-19 cohort (35.6%) were still hospitalized at time of manuscript writing, possibly leading to underestimation of COVID-19 mortality rate. Data from H1N1 cohort was gathered from a longer time period than COVID-19 cohort, which may have affected results and analysis. Therefore, continued follow-up on this cohort and studies conducting longer follow-up are necessary.

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

Yuanyuan Liu et al.

Journal of Travel Medicine
February 13, 2020
DOI: https://doi.org/10.1093/jtm/taaa021

Purpose	To compare the basic reproduction number (R0) of the COVID 19 virus to the SARS coronavirus.
Study design	Systematic Review
Level of evidence	Level 3
Methods	PubMed, bioRxiv and Google Scholar were searched for eligible studies between January 1st 2020 to February 7th 2020 with the search terms "coronavirus & basic reproduction number". The basic reproduction number is a tool used to gauge the transmissibility of a virus and is expressed as a positive number. An R0 > 1 will indicate that a virus is spreading and will likely increase in transmission, whereas a R0 < 1indicated that the virus is decreasing transmission and will likely die out.
Findings	The search results found 12 studies that qualified by reporting a calculated basic reproduction number. The authors found that **the calculated R0 in these 12 studies ranged from 1.40 to 6.49, with a mean of 3.28 and a median of 2.79**. The authors note that there was a temporal change in the estimated R0 value, ith lower levels in early January and increasing as the disease spread.
Clinical Implications	**The R0 calculated in this study was considerably higher than the WHO estimates, indicating that the disease may transmit at a faster rate than previously estimated**. The estimated COVID-19 R0 from these studies falls between the published R0 for SARS (between 2 and 5). However, COVID-19 is already more widespread than SARS, suggesting that it is more transmissible than these estimations would suggest.
Limitations	The studies reviewed used three distinct modeling techniques that yielded different calculated basic reproduction numbers, though the differences were not statistically significant. Future studies will need to track this value using standardized assumptions to better understand transmissibility. Additionally, future studies need to assess the WHO estimation of the basic reproduction number relative to these new results to resolve this discrepancy.

Are patients with hypertension and diabetes mellitus at increased risk for COVID-19 infection?

Lei Fang et al.

Lancet: Respiratory Medicine
March 11, 2020
DOI: https://doi.org/10.1016/S2213-2600(20)30116-8

Purpose	To explore the theory that comorbidities, specifically hypertension and diabetes, put individuals at greater risk of severe COVID-19 infection.
Study design	Systematic Review
Level of evidence	Level 4
Methods	The authors reviewed three studies demonstrating increased incidence among severe COVID-19 disease in patients with hypertension (HTN) and diabetes mellitus (DM).
Findings	The first study found that of 32 non-survivors from a group of 52 intensive care unit patients, 22% had cerebrovascular disease and 22% had diabetes (RR 1.34 and 1.78, respectively). In the second study, 173 patients with severe disease were found to have comorbidities of HTN (23.7%), DM (16.2%), coronary heart diseases (5.8%), and cerebrovascular disease (2.3%). By contrast, the third study observed comorbidities in all hospitalized patients (total of 140), regardless of COVID severity, with HTN and DM being the most prevalent at 30% and 12% respectively.
Clinical Implications	**Human pathogenic coronaviruses bind to membrane bound angiotensin-converting enzyme 2 (ACE2) on endothelial cells expressed in epithelial cells of the lung, intestine, kidney, and blood vessels.** So far, evidence suggests COVID-19 uses the same mechanism. Individuals with hypertension and diabetes are commonly treated with ACE-inhibitors and angiotensin receptor blockers (ARBs), which lead to the upregulation of ACE2 receptors. ACE2 receptor polymorphisms have been linked to diabetes and hypertension. With this understanding, the article proposes a hypothesis for the increase risk of severe disease in this patient population.
Limitations	Only three studies were reviewed. It was not noted whether patients with severe disease and comorbid hypertension or diabetes were being treated with ACE-inhibitors or ARBs. Future research could address patient medications in addition to comorbid conditions, as well as genetic testing to determine the existence of a possible link between polymorphisms of ACE2 receptor and severe disease.

First-wave COVID-19 transmissibility and severity in China outside Hubei after control measures, and second-wave scenario planning: A modelling impact assessment.

Kathy Leung et al.

Lancet

April 8, 2020

DOI: https://doi.org/10.1016/S0140-6736(20)30746-7

Purpose	To review the impact and transmissibility of COVID-19 during the early cases of Hubei province (original epicenter) in China.
Study design	Retrospective analysis
Level of evidence	Level 4
Methods	The authors used publicly available data from four major cities (Beijing, Shanghai, Shenzhem, and Wenzhou) to determine reproduction number (Rt) and confirmed case fatality rate (cCFR). Furthermore, they also incorporated susceptible-infectious-recovery models to assess what role relaxing intervention (social distancing, community shutdowns, etc.) had on spread of virus.
Findings	Estimates of instantaneous reproduction number (Rt) on weekly intervals were reported between early January and later February 2020. **In most provinces the mean Rt decreased after aggressive control measures were implemented,** suggesting that reduction in control measures could lead to a resurgence of case numbers. The confirmed case-fatality risk (cCFR) was estimated to be 0.98% (0.82-1.16) among the provinces/cities outside Hubei. In comparison the cCFR in Hubei province was 5.91% and Wuhan was 1.4%.
Clinical Implications	**Relaxation of social control measures increased the cumulative case count exponentially** proportional to the duration of relaxation. Furthermore, the duration of aggressive control measures must be longer than the duration of attempted relaxation in order to get the Rt below 1.5. Stated differently, **allowing Rt to rise when no herd immunity is present will incur health and economic loss** even if future aggressive control measures push prevalence of infection back to the previous level during original aggressive control measures.
Limitations	This study used public data only from provinces that actively reported cases. Cases were likely under-reported due lack of testing and resources. Asymptomatic cases of COVID-19 that go undiagnosed would alter the projections of Rt and cCFR. The data obtained did not include specifics regarding exposure or travel history, which could be important to further understanding virus transmission.

Epidemiology of 2019 Novel Coronavirus Disease-19 in Gansu Province, China, 2020

Jingchun Fan et al.

Emerging Infectious Diseases
March 13, 2020
DOI: https://doi.org/10.3201/eid2606.200251

Purpose	To compare the characteristics of COVID-19 positive groups observed during two time periods: January 23 – 28 2020 (early period) and January 29 2020 - February 3 2020 (late period) in Gansu Province.
Study design	Case control study (n = 54 patients)
Level of evidence	Level 4
Methods	Demographic data and exposure history were collected for confirmed cases of COVID-19 from the Gansu Provincial Center for Disease Control and Prevention. Researchers studied 54 total confirmed cases between January 23rd and February 3rd, 2020. The authors designated cases as primary or secondary. Primary cases had recent travel to Wuhan, and secondary cases had no travel outside the Gansu Province.
Findings	Of the total cases, 35 were primary and 19 were secondary. Almost two thirds of the early period cases were primary. Early period patients were younger than the late period patients (34 vs 48 years old, p=0.014). More patients in the early period were laborers, compared to the late period where there were more retired patients (p=0.009). There were no significant differences in sex.
Clinical Implications	This research shows that social distancing practices are warranted and useful. Primary cases were 3 times greater than secondary cases in the early period compared to the late period. These younger patients were more likely to be laborers, and thus traveled more than their older, retired counterparts diagnosed in the late period. As travel bans were implemented, COVID-19 cases came from community spread. **This transition between transmission mechanism demonstrates how the virus can affect patients of any age or occupation, and underscores the importance of mandatory, strict social distancing policies.**
Limitations	This study used a relatively small number of cases observed in a relatively short period of time (i.e., 12 days). Future research in the Gansu Province should obtain information on more cases spanning a longer time frame. This will provide information about the entire epidemiology of the virus (and the effects of preventative measures) in Gansu Province.

Spread of SARS-CoV-2 in the Icelandic population.

Daniel Gudbjartsson et al.

New England Journal of Medicine
April 14, 2020
DOI: 10.1056/NEJMoa2006100

Purpose	This study was conducted in Iceland for targeted testing of persons at high risk for coronavirus and population screening/stratification of those who tested positive.
Study design	Cross sectional study
Level of evidence	Level 2
Methods	Targeted testing was provided for symptomatic persons coming from high risk areas or those who were in contact with infected persons from Jan 31-Mar 31. On March 13 through April 4, population screening was open to anyone who desired testing, whether symptomatic or asymptomatic. Nasopharnygeal and oropharyngeal samples were sent for viral RNA isolation. Persons who tested positive were required to self-quarantine and identify other persons that came into contact with the patient 24 hours prior to symptom onset. Identified close contacts were required to self-quarantine for 2 weeks.
Findings	Of the 9199 persons who were targeted for testing, 1221 (13.3%) tested positive for SARS-CoV-2. Of these people, 65% had recently traveled internationally. Through population screening, positive results were reported for 100 of 13,080 participants (0.8%), of whom 86% had reported recent travel outside the country. Positive test results were reported for 87 of 10,797 persons (0.8%) who accepted the open invitation for testing and 13 of 2283 persons (0.6%) who were invited at random.
Clinical Implications	Towards the end of the study period, the origin of infection has shifted away from international travel to close contact spread of the virus. Overall, the frequency of infection in the overall Icelandic population is currently stable, which hints at success of current containment measures implemented by the Icelandic people.
Limitations	Iceland is a country with a population just over 360,000. Population testing is appropriate, but this method lacks external validity in larger countries. In addition, testing in larger countries would not be centralized (tested in a single laboratory). The majority of SARS-CoV-2 identified in this study are of the A2 clade that originated exclusively from Europe, and its characteristics may not apply to other haplotypes of the virus. Further epidemiologic studies needs to be corroborated with the data produced by this study to characterize SARS-CoV-2.

Temporal dynamics in viral shedding and transmissibility of COVID-19.

Xi He et al.

Nature: Medicine
April 15, 2020
DOI: https://doi.org/10.1038/s41591-020-0869-5

Purpose	To evaluate the viral shedding pattern of COVID-19 and study the periods in which COVID-19 is most transmissible.
Study design	Observational, retrospective study
Level of evidence	Level 4
Methods	Two-part study with separate clinical and observational groups. In the clinical group, 94 COVID-19 positive patients from Guangzhou Hospital in Guangdong, China received a nasopharyngeal swab during each day of symptoms to evaluate temporal changes in viral load. Patients had laboratory confirmed COVID-19 by RT-PCR. In the epidemiologic group, 77 pairs of patients who developed COVID-19 were identified to determine the serial interval (time between symptom presentation in infector to symptom presentation in infectee). Case information was gathered from publicly available sources in several countries. All infector-infectee pairs were evaluated to ensure that neither party had other contacts who tested positive for COVID-19 or traveled to areas known to have a high number of COVID-19 cases.
Findings	Viral load was highest on day one of hospitalization and decreased in a linear fashion. Mean serial interval was noted to be 5.8 days, and when taken with a noted incubation period of 5.2 days, **COVID-19 infectiousness was noted to begin 2.3 days prior to symptom presentation and peak 0.7 days prior to symptom presentation.** Authors estimate that 44% of patients were infected with COVID-19 by a carrier who was asymptomatic at the time of transmission
Clinical Implications	**Viral load was highest on day of COVID-19 diagnosis** and decreased linearly. **44% of patients were suspected of contracting COVID-19 from an asymptomatic carrier.**
Limitations	Patient pair data in the epidemiologic group was collected by governmental agency reports or via media, this data is possibly inaccurate or incomplete. Cases in this group were not stratified by age, gender, country, or disease severity. Treatments for the clinical group were given according to national health guidelines, and could have affected viral load testing by RT-PCR. Recall bias was likely present in the epidemiologic group and may have altered incubation period length.

Hospitalization Rates and Characteristics of Patients Hospitalized with Laboratory-Confirmed Coronavirus Disease 2019 – COVID-NET, 14 States, March 1-30, 2020

Shikha Garg et al.

CDC: Mordibity and Mortality Weekly Report
April 17, 2020
DOI: http://dx.doi.org/10.15585/mmwr.mm6915e3

Purpose	To conduct a population-based surveillance for laboratory-confirmed COVID-19-associated hospitalizations in the US.
Study design	Retrospective cross-sectional study (n = 1482 patients)
Level of evidence	Level 3
Methods	Data included from 1482 hospitalized patients with laboratory confirmed COVID-19, representing 14 states and 90 counties. Study included only the residents of a designated COVID-NET catchment area and hospitalized within 14 days of a positive SARS-CoV-2 test.
Findings	Overall, a **high proportion of US patients hospitalized with COVID are older (74.5% were aged ≥50 years) and have underlying medical conditions** including hypertension (49.7%), obesity (48.3%), chronic lung disease (34.6%), diabetes mellitus (28.3%), and cardiovascular disease (27.8%). It is therefore imperative to implement preventative measures to especially protect elderly population and those with underlying medical conditions. Among 580 COVID-19 patients with race/ethnicity data, 45% were non-Hispanic white, 33.1% were non-Hispanic blacks, 8.1% were Hispanic, 5.5 were Asian, 0.3% were American Indian/Alaskan Native, 7.9% were unknown. No statistical analysis between groups were performed, but of note, the COVID-NET catchment general population are 59% non-Hispanic white and 18% non-Hispanic black, **suggesting the non-Hispanic black population is disproportionally affected by SARS-CoV-2.**
Clinical Implications	**Elderly patients with underlying medical conditions are most susceptible to COVID-19 disease and have the worst outcomes**
Limitations	This study included preliminary results from the first month of US surveillance of COVID-19 and are subject to change as more patients are diagnosed and evaluated. Additionally, patients in this study represented a wide variety of care facilities. Without standardization of diagnostic testing practices for SARS-CoV-2, under-identification of COVID-19 cases is likely.

Epidemiology of COVID-19 among children in China

Yuanyuan Dong et al.

Pediatrics

March 13, 2020

DOI: https://doi.org/10.1542/peds.2020-0702

Purpose	To evaluate the epidemiological characteristics and transmission trends of pediatric patients with 2019 novel coronavirus disease (COVID-19) in China.
Study design	Observational study
Level of evidence	Level 3
Methods	Researchers collected data on reported COVID-19 pediatric cases from January 16, 2020 to February 8, 2020. Cases were defined as having high, medium, or low risk based on patient exposure to a COVID-19 patient and proximity to endemic areas. Suspected cases were identified if a child at high risk had 2 of the following: clinical symptoms, elevated white blood cell count or CRP, or abnormal chest radiograph. Suspected cases were confirmed by positive RT-PCR nasal swab or blood samples, or by genetic sequencing of respiratory tract or blood samples.
Findings	Among 2135 patients, 728 (34.1%) were confirmed cases and 1407 (65.9%) were suspected cases. The median age was 7, and complete age range was 1 day to 18 years. Nearly half of total cases were from Hubei province (46.0%), and another 18.5% from surrounding provinces. Of both suspected and confirmed cases, 94 (4.4%), 1088 (51.0%), 826 (38.7%), and 125 (5.8%) cases were diagnosed as asymptomatic, mild, moderate, or severe/critical, respectively. One child died. **Compared to adults, there were less severe and critical cases in children (5.8% vs 18.5%). T**he proportions of severe and critical cases in the pediatric population was highest in infants (10.6%).
Clinical Implications	Children might be less affected by COVID-19 because the maturity and functioning of ACE-2 in children is lower than adults. They may experience coronavirus infections more frequently and develop cross reacting antibodies, or their immune systems are less developed and therefore have less severe immune responses. **The highest proportion of critical and severe pediatric COVID-19 cases was in infants less than 1 year old**.
Limitations	The study was unable to assess clinical characteristics or incubation period due to lack of data at the time of analysis. There were more severe and critical cases in the suspected than confirmed group, suggesting that some suspected cases may be due to other respiratory infections besides COVID-19. Further research containing more detailed patient information and clinical outcomes is needed.

The epidemiology and pathogenesis of coronavirus disease (COVID-19) outbreak

Hussin Rothan & Siddappa Byrareddy

Journal of Autoimmunity

February 26, 2020

DOI: https://doi.org/10.1016/j.jaut.2020.102433

Purpose	To summarize recent findings regarding the symptoms, epidemiology, transmission, pathogenesis, and future directions of treating/preventing COVID-19.
Study design	Systematic review
Level of evidence	Level 3
Methods	Reviewed information from COVID-19 case reports and cohort studies.
Findings	Viruses in the Coronaviridae family generally presents with fever, dry cough, and dyspnea. Distinct symptoms for COVID-19 include rhinorrhea, sneezing, sore throat, and diarrhea. Elevated C-reactive protein, erythrocyte sedimentation rate, D-dimer, and cytokines and chemokines are generally observed, with severe cases correlating with higher levels of pro-inflammatory cytokines. Transmission occurs primarily via direct contact of virus particles with mucus membranes. Lung epithelial cells appear to be the primary target of the virus, and binding occurs between the receptor-binding domain of the spike protein and the angiotensin-converting enzyme II (ACE2) receptor. Of note, the sequence of the receptor-binding domain of COVID-19 spike protein is similar to that of SARS-CoV, which also binds to the ACE2 receptor. Pre-existing drugs including Oseltamivir, Lopinavir, Ritonavir, and Ganciclovir could prove useful in treating COVID-19 patients, as well as Remdesivir and Chloroquine. The EIDD-2801 compound (an isopropylester prodrug of a ribonucleoside analog that has shown anti-influenza virus activity in cultured cells and mice), has potential to target seasonal and pandemic viruses.
Clinical Implications	Correlation between cytokines and disease severity can be used to predict prognosis, and hopefully prevent adverse outcomes. There is further need for investigation of alternative (fecal oral) routes of transmission, and investigation of pre-existing antiviral drugs as treatment modalities for COVID-19.
Limitations	The authors discuss the need to make more testing available in order to further understand the pathogenesis and spread; to study pediatric populations, who have been under-diagnosed; to investigate the vast range of clinical presentations, from virtually asymptomatic ranging to critical condition; and to further research potential viral targets for pharmacologic therapies.

Mathematical Model Of Infection Kinetics And Its Analysis For COVID-19, SARS And MERS.

Kaihao Liang

Infection, Genetics and Evolution
April 8, 2020
DOI: https://doi.org/10.1016/j.meegid.2020.104306

Purpose	To discuss the spread rules of the three coronavirus epidemics and pandemic: COVID-19, SARS and MERS. A propagation growth model was established using growth rate and inhibition constant of infectious diseases with the parameters of the three coronavirus transmission growth models obtained by nonlinear fitting.
Study design	Statistical analysis
Level of evidence	Not applicable
Methods	Data on COVID-19 cases were obtained from Hubei, Guangdong, Zhejiang, Henan. Data on SARS cases collected using China's National data, as well as data from Guangdong, Beijing, Hong Kong. Data from MERS cases analyzed from Saudi Arabia database on 4 distinct cycles of MERS outbreaks. Model hypothesis can be simplified as: r(N) = r0 – s*N, where N = # of infected, r(N) = the growth rate as a function of # of people, r0 = constant indicating growth in the case of no preventative measures, s = infection inhibition coefficient (reflecting control/prevention measures).
Findings	The multiplication cycles of SARS and MERS are similar, ranging from 5 to 10 days. **The multiplication cycle of COVID-19 is only two to three days**, and the number of cases of COVID-19 will increase rapidly under the effect of exponential growth. In Hubei, the infection inhibition constant of COVID-19 is 3.58 × 1e-6 , two orders of magnitude lower than in Guangdong, Zhejiang, and Henan.
Clinical Implications	The growth rate of COVID-19 is about twice that of SARS and MERS, and the COVID-19 doubling cycle is two to three days, suggesting that **the number of COVID-19 patients would double in two to three days without human intervention.** COVID-19 spread rapidly in Hubei due to the large number of patients in the early stage, as medical institutions dealt with the shortage of hospital beds, equipment, medicine, masks, and protective clothing, resulting in the inability to effectively isolate patients. This led to a lower infection inhibition constant in Hubei.
Limitations	This type of modeling seems to have the most use in retrospectively analyzing the pandemic response based on region but may be of more limited use in prospective modeling.

Universal Screening for SARS-CoV-2 in Women Admitted for Delivery

Desmond Sutton et al.

New England Journal of Medicine
April 13, 2020
DOI: 10.1056/NEJMc2009316

Purpose	To investigate the prevalence of SARS-CoV-2 amongst pregnant patients upon delivery, as a vast majority of patients are asymptomatic.
Study design	Cross-sectional study (n = 215)
Level of evidence	Level 3
Methods	Between March 22 - April 4, 2020, a total of 215 pregnant women delivered infants at the New York–Presbyterian Allen Hospital and Columbia University Irving Medical Center, and all were screened on admission for COVID-19 with quantitative PCR.
Findings	Four women (1.9%) had fever or other symptoms on admission, and all 4 women tested positive for SARS-CoV-2. Of the 211 women without symptoms, all were afebrile on admission. Nasopharyngeal swabs were obtained from 210 of the 211 women (99.5%) who did not have symptoms of Covid-19; of these women, 29 (13.7%) were positive for SARS-CoV-2. Thus, **29 of the 33 (87.9%) COVID-19-positive patients were asymptomatic at presentation.**
Clinical Implications	The use of universal SARS-CoV-2 testing in all pregnant patients presenting for delivery revealed that at this point in the pandemic in New York City, **most of the patients who were positive for SARS-CoV-2 at delivery were asymptomatic.** More than one of every eight asymptomatic patients who were admitted to the labor and delivery unit were positive for SARS-CoV-2. Although this prevalence may not apply to geographic regions with lower rates of infection, it highlights the hidden prevalence of COVID-19 among asymptomatic obstetrical patients. Universal screening for the pregnant population gives the health system the opportunity to protect mothers, babies, and health care teams as the pandemic continues.
Limitations	The true prevalence of SARS-CoV-2 infection may also be underreported because of false negative results of COVID-19 tests. Given the test's relatively weak sensitivity, future research is needed to understand how patients' COVID-19 status from RT-PCR should best be used to determine hospital isolation practices and bed assignments, inform neonatal care, and guide the use of PPE.

Duration for carrying SARS-CoV-2 in COVID-19 patients.

Xinwei Du et al.

Journal of Infection
April 10, 2020
DOI: https://doi.org/10.1016/j.jinf.2020.03.053

Purpose	To evaluate the duration of carrier status for SARS-CoV-2.
Study design	Case series (n = 161)
Level of evidence	Level 4
Methods	From January 20, 2020 to March 1, 2020, inpatients in Henan province (China) with a specific SARS-CoV-2 epidemiological history and a positive nucleic acid test were identified for data collection. The duration of carrier status was defined as the time from a close contact with the source of infection to the last positive test for nucleic acid. Then, duration of carrying SARS-CoV-2 in different ages, gender, and disease condition were compared.
Findings	Patients were contagious at all stages of disease with median carrying duration of 26 days and longest up to 50 days. **There was statistically significantly longer carrying duration based on condition and age, with longer duration seen in older age and with severe COVID-19 cases.** Duration for carrying SARS-CoV-2 has nothing to do with gender. However, it is related to the age of patients. The median duration in the ≥ 60 years-old group was 28 days vs 20 days in the 0–59 years-old group (P<0.01).
Clinical Implications	Persistent infection in elderly patients may be the initiating factor that causes organ damage, especially persistent inflammation of the alveoli, and disease progression. **The long infectious duration of SARS-CoV-2 in patients means that early, purposeful isolation and monitoring are necessary to prevent further spread.**
Limitations	Limited by sample size, as well as by single location study. Additionally, carrying duration definition could be influenced by recall bias.

Evolving epidemiology and transmission dynamics of coronavirus disease 2019 outside Hubei province, China: a descriptive and modelling study

Juanjuan Zhang et al.

The Lancet: Infectious Diseases

April 2, 2020

DOI: https://doi.org/10.1016/S1473-3099(20)30230-9

Purpose	Characterization of epidemiologic qualities of COVID-19 outside of Hubei province, China fifty days after first noted case outside of the region.
Study design	Retrospective, observational study (n = 8579)
Level of evidence	Level 4
Methods	Information on laboratory positive COVID-19 patients outside of Hubei province, China was collected from national, provincial, and municipal databases as well as from media reports. Cases were divided into two groups based on date of symptom onset: December 24-January 27 and January 28-February 17. Case grouping was based on fourth revision of COVID-19 case definition. In comparing the two groups, authors analyzed differences in case demographics and time-to-event intervals, such as time to hospitalization. Incubation period and serial interval were identified from subsets of the study sample.
Findings	As the epidemic progressed, time to hospitalization and time to first healthcare consultation decreased; specifically, time to hospitalization fell from 4.4 days in the first period to 2.6 days in the second period (P<0.0001). Incubation period was estimated at 5.2 days from 49 individuals via contact tracing. Serial interval was estimated at 5.1 days from 28 index cases and 35 secondary cases. Net reproduction number differed between provinces and cities, ranging from 1.08 to 1.71 in areas under study. Reproduction number in all studied areas fell below 1 at the end of January 2020, indicating that disease did not spread in the community anymore.
Clinical Implications	Isolation measures have an effect on healthcare ascertainment, and epidemiologic characteristics of COVID-19 are varied outside of Hubei province.
Limitations	Data were collected from governmental databases and media reports, though the authors did validate their cases by examining the official line lists for cities and provinces for which reproduction number was calculated. Study data were collected during an infectious disease outbreak and therefore are subject to non-homogenous sampling and case ascertainment bias.

The impact of nutrition on COVID-19 susceptibility and long-term consequences.

Michael Butler et al.

Brain, Behavior, and Immunity
April 18, 2020
DOI: https://doi.org/10.1016/j.bbi.2020.04.040

Purpose	To discuss the relationships between diet/nutrition, social determinants of health, and COVID-19 outcomes.
Study design	Systematic review
Level of evidence	Level 5
Methods	Reviewed and summarized findings from studies on health equity, nutrition and inflammation, obesity, and disease complications following viral illnesses.
Findings	COVID-19 mortality disproportionately affects the elderly, minorities (black and Hispanic populations), and in those with co-morbid medical conditions. Obesity and type 2 diabetes (DM), two prominent risk factors for severe COVID-19, may underlie this disproportionate effect. Minorities have higher rates of poverty and less access to health care, meaning decreased access to healthy foods and nutritional education. Additionally, DM and obesity are driven by the prevalence of the Western diet, comprised of high amounts of saturated fat, refined carbohydrates/sugars, and low levels of fiber, unsaturated fats, and antioxidants. The western diet chronically activates the innate immune system and inhibits the adaptive immune system. High amounts of saturated fat may lead to increased macrophage infiltration to lung tissue, highly relevant to COVID cases given the pneumonia many patients develop. Saturated fat-induced oxidative stress impairs T and B cell proliferation and maturation, and induces B cell apoptosis, which contributes to B cell immunosuppression. Aside from known lung damage following COVID-19, there could be a potential for persistent neuro-inflammatory responses to trigger neurodegenerative diseases, like Alzheimer's Disease and other forms of dementia. Studies show that consuming healthy foods has anti-inflammatory effects, even in the presence of obesity pathology.
Clinical Implications	**Wider access to healthy foods is crucial to protecting vulnerable populations from COVID-19.** A person's underlying health is predictive of disease susceptibility — not just to COVID-19 but to a wide variety of illnesses and infectious diseases. Physicians need to educate their elderly and minority patients on the relationship between nutrition and inflammation, and help connect them to community resources.
Limitations	More research is needed to investigate long-term effects from COVID-19, as lifestyle related co-morbidities in these patients could confer an increased risk for dementia and degenerative disease. Many studies referenced looked at the inflammatory responses in mice models as opposed to humans, limiting generalizability.

Asymptomatic SARS-CoV-2 infection in household contacts of a healthcare provider, Wuhan, China.

Yi Luo et al.

Emerging Infectious Diseases
April 24, 2020
DOI: https://doi.org/10.3201/eid2608.200282

Purpose	To evaluate the case of a physician with mildly symptomatic COVID-19 and their household contacts in Wuhan, China.
Study design	Case series (n = 6)
Level of evidence	Level 3
Methods	The patient (patient 1) was a 39-year-old nephrologist at the Central Hospital of Wuhan. The patient's five household members included were his wife (contact 1), a 37-year-old laboratory scientist, 7-year-old fraternal twins (contacts 2 & 3), a 62-year-old retired grandfather who was a current smoker (contact 4), and a retired 64-year-old grandmother in good health (contact 5). All household contacts underwent CT scans, and then daily throat swabs for qRT-PCR test for SARS-CoV-2 during the the observation period: February 11th-March 1st, 2020. Blood was taken for laboratory tests: C-reactive protein, leukocyte count, lymphocyte ratio, CD19+ absolute count, alanine aminotransferase (ALT), aspartate aminotransferase (AST), and D-Dimer.
Findings	All household contacts of patient 1 had qRT-PCR confirmed SARS-CoV-2 and were asymptomatic throughout the observation period. Stool specimens for contacts 1, 2, and 3 were positive for SARS-CoV-2. Contact 2 tested negative on 4 consecutive throat swab PCRs but had a positive stool specimen for SARS-CoV-2. Contact 1 was positive for SARS-CoV-2 on qRT-PCR tests of multiple serial throat swabs but negative on IgM and IgG tests. Contact 1 underwent 11 serial throat swabs and on 2 separate occasions, she had 2 consecutive negative results for SARS-CoV-2 only to revert to having a throat swab specimen positive for SARS-CoV-2.
Clinical Implications	Data about the incidence of asymptomatic infection in families of healthcare workers can help to construct a more informed public health response during the pandemic. **There may be underestimation of positive cases, as this study illustrated negative qRT-PCR tests that subsequently tested positive.** Studies on serial testing on asymptomatic patients with a negative test should be conducted to see if they are truly negative. More research on fecal-oral transmission of SARS-CoV-2 is necessary, as three household contacts in this study had positive stool specimens.
Limitations	This study was limited by its small sample size, as it focused on asymptomatic transmission amongst household contacts of a healthcare provider.

High contagiousness and rapid spread of severe acute respiratory syndrome coronavirus 2.

Steven Sanche et al.

Emerging Infectious Diseases
April 7, 2020
DOI: https://doi.org/10.3201/eid2607.200282

Purpose	To estimate key epidemiological parameters of the early outbreak of 2019 novel coronavirus disease (COVID-19) in Wuhan.
Study design	Case series (n= 140)
Level of evidence	Level 4
Methods	140 case reports from across China were collected from the Chinese Centers for Disease Control and Prevention (China CDC) and provincial health commissions between January 15-30, 2020. Two models were developed to estimate the growth rate of the outbreak in Wuhan. First arrival model: domestic travel data from Baidu Migration server was used to compute the likelihood of arrival times of first known cases in provinces outside of Hubei, as a function of the rate of epidemic growth in Wuhan. Case count model: a hybrid deterministic-stochastic susceptible-exposed-infectious-recovered (SEIR) model was used to account for additional persons infected in Wuhan but diagnosed in other provinces. Dates for this model were restricted to January 19-26, 2020. Both models calculated growth rate (r), and theoretical time (T0), using travel data, specifically the earliest times that an infected person arrived in each of the 26 provinces.
Findings	The incubation period was estimated to be 4.2 days. The time from symptom onset to hospitalization decreased from 5.5 days before January 18 2020, to 1.5 days after January 18 2020. The change coincides with report of human to human transmission and upgrade of the emergency response to level 1 by the Chinese CDC. The time from initial hospital admittance to discharge was 11.5 days, initial hospital admittance to death was 11.2 days, and time from symptom onset to death was 16.1 days. The growth rate in the first arrival model was 0.29/day, corresponding to a doubling time of 2.4 days. This estimate was much higher than previous estimates of 0.10-0.14/day. The case count model and first arrival model both estimated consistent exponential growth rates and theoretical times: 0.29 vs 0.30/day, and December 20 vs December 16 2019.
Clinical Implications	Results suggest that **surveillance, quarantine, and strong social distancing efforts are essential for slowing down or stopping the spread of this virus.**
Limitations	Because the reports collected were from the first few persons detected in each province, the estimations may be biased toward cases with more severe symptoms. In both models, researchers assumed perfect detection of infected cases outside of Hubei Province - however in reality, this may not be the case due to changing surveillance intensity.

A systematic review of COVID-19 epidemiology based on current evidence

Minah Park et al.

Journal of Clinical Medicine
March 31, 2020
DOI: https://doi.org/10.3390/jcm9040967

Purpose	To summarize epidemiological characteristics of SARS-CoV-2 and the effectiveness of control measures.
Study design	Systematic review
Level of evidence	Level 5
Methods	Authors used the following terms in PubMed and preprint archives to find research articles published up to February 21, 2020: "COVID-19", "SARS-CoV-2", "2019-nCoV", "n-CoV", and "coronavirus." Of 317 research articles generated from the initial search, 41 met the inclusion criteria.
Findings	Basic reproduction number (R0; expected number of cases generated from 1 case) ranged from 1.9 to 6.5 based on eight published and eight preprint papers. The estimates of R0 for SARS-CoV in the early phase of the outbreak in Hong Kong was 2.7 and in Singapore as 2.2–3.6. In the studies of SARS-CoV-2, the final attack rate would lie between 75% and 100% in a completely susceptible population assuming no intervention. Median incubation period of the included studies ranged from 4 to 6 days. This is comparable to SARS-CoV (4.4 days) and MERS-CoV (5.5 days). Serial interval (time between the start of symptoms in the infector and start of symptoms in the infectee) range from 4 to 8 days. **Pre-symptomatic infection is possible, given that the estimated serial interval is shorter than the incubation period**. An analysis of 468 infector–infectee pairs confirmed in China reported a mean serial interval of 3.96 days. The study also noted that 59 of 468 pairs (12.6%) had negative-valued serial intervals, suggesting pre-symptomatic transmission.
Clinical Implications	**Infected patients may not display symptoms for 4-6 days and have the potential to spread COVID before they demonstrate symptoms**, therefore both symptomatic and asymptomatic patients should strictly adhere to social distancing guidelines.
Limitations	Not all studies have been peer-reviewed. Additionally, the studies included did not use the same method of calculating the basic reproduction number (R0). Most of the studies included in this review are based on data collected during the early phase of the outbreak. For some of that time, there were no social distancing guidelines in effect.

Feasibility of controlling COVID-19 outbreaks by isolation of cases and contacts.

Joel Hellewell et al.

The Lancet
February 28, 2020
DOI: https://doi.org/10.1016/S2214-109X(20)30074-7

Purpose	To assess if isolation and contact tracing can control the transmission of imported cases of COVID-19 using mathematical modeling.
Study design	Mathematical model, no patients/cases under study
Level of evidence	Level 5
Methods	Simulated COVID-19 outbreak scenarios were created using mathematical models with varied parameters including number of index cases, basic reproduction number (R0), delay from symptom onset to isolation, probability of contact tracing, and proportion of disease transmission before symptom onset. Outbreaks were deemed controlled if transmission ended within 12 weeks or if there were fewer than 5,000 total cases. Index case numbers for each scenario were either 5, 20, or 40, and R0 was selected as 1.5, 2.5, or 3.5. Delay from symptom onset to isolation was divided into short- (3.43 days) and long-delay (8.09 days) categories. Contact tracing was divided into groups of 20%, from 0-100%. Transmission before symptom onset was divided into 3 categories: <1, 15, and 30%. Each parameter combination was entered as a separate outbreak scenario and simulated 1,000 times.
Findings	Highest likelihood of outbreak control occurred in scenarios with a low number of initial cases, low R0, <1% transmission before symptom onset, and high contact tracing. Outbreaks with a high R0 (2.5 or 3.5) could be controlled with contact tracing and isolation of 70 or 90%, respectively, though went uncontrolled with lower percentages. For low R0 simulations, delay from symptom onset to isolation was the largest factor in outbreak control outcome.
Clinical Implications	**Outbreak control is possible under most circumstances if the majority of contacts are promptly traced and isolated**, especially if there is a low rate of disease transmission prior to symptom presentation. Otherwise, further interventions would be required to achieve control.
Limitations	Current data regarding COVID-19 demonstrates that a significant number of cases are passed from asymptomatic carriers and this model could be updated to reflect newer data. Models under study assume isolation ends disease transmission and do not account for improper isolation or those who contract disease while caring for COVID-19 cases.

Clinical characteristics and risk assessment of newborns born to mothers with COVID-19.

Pu Yang et al.

Journal of Clinical Virology
April 5, 2020
DOI: https://doi.org/10.1016/j.jcv.2020.104356

Purpose	To report clinical outcomes of newborns delivered by SARS-CoV-2 positive pregnant women, and to determine the risk of vertical transmission of SARS-CoV-2.
Study design	Prospective cohort study
Level of evidence	Level 2
Methods	Single institutional study of newborns (n=7) delivered between January 20-29 2020 by SARS-Cov-2 infected pregnant women. Delivery history including APGAR scores, clinical features, blood tests, nuclei acid detection of amniotic fluid, umbilical cord blood, and neonatal pharyngeal swabs were collected for risk assessment analysis.
Findings	Six of 7 SARS-CoV-2 positive mothers were symptomatic 1-6 days before delivery. Symptoms included fever, cough, and other respiratory symptoms followed by abdominal pain, diarrhea and other gastrointestinal symptoms. All 7 women delivered via Cesarean section: 2 were emergency cesarean section for severe pre-eclampsia, 1 was for severely elevated aspartate aminotransferase (AST), 4 were for risk reduction of potential SARS-CoV-2 vertical transmission from mother to baby. Four newborns were delivered late preterm (36-37 weeks) and 3 newborns were delivered full term. Of 5 neonates admitted to the neonatal intensive care unit (NICU), 3 underwent chest x-ray. Eventually all 7 newborns were discharged for isolated home care within 7 days of birth. All 7 newborns tested negative for SARS-CoV-2 via qRT-PCR in amniotic fluid, cord blood, and pharyngeal swabs.
Clinical Implications	**Current data does not demonstrate that pregnant women infected with SARS-CoV-2 pose a risk of vertical transmission or other severe adverse events to their newborns.** However, newborns are still at high risk for infection once delivered, thus it is necessary to separate newborns from their mothers to avoid potential complications of infection.
Limitations	The sample size of this study was small. Not all newborns received a chest x-ray, which may have missed non-symptomatic presentations on imaging. The short length of observation in the hospital may have missed subsequent manifestations of COVID-19. All patients delivered by cesarean section, and it is unknown at this time whether elective cesarean section is required to prevent vertical transmission of SARS-CoV-2 from mother to baby.

Factors associated with prolonged viral RNA shedding in patients with COVID-19.

Kaijin Xu et al.

Clinical Infectious Diseases
April 9, 2020
DOI: https://doi.org/10.1093/cid/ciaa351

Purpose	To assess viral RNA clearance within 21 days after illness onset and to determine factors associated with prolonged viral RNA shedding in SARS-CoV-2 patients.
Study design	Retrospective cohort (n = 113)
Level of evidence	Level 3
Methods	Authors analyzed 113 patients with confirmed SARS-CoV-2 infection across 2 Wuhan hospitals who met one of three inclusion criteria: 1) disease duration >21 days without viral RNA clearance; 2) viral RNA clearance occurred within 21 days; 3) death occurred within 21 days. Duration of viral RNA shedding was considered the number of days from symptom onset viral RNA clearance using RT-PCR assay. Viral RNA clearance was defined as 3 consecutive negative respiratory tract specimens.
Findings	74.3% (84/113) of patients had viral RNA clearance within 21 days after illness onset, with median duration of viral RNA detection being 17 days. The 84 patients with viral RNA clearance within 21 days were further divided into persistent negative viral detection results <15 days after illness onset (n=37) and prolonged viral RNA shedding ≥15 days after illness onset (n=79). Prolonged viral RNA shedding was associated with male sex (P=0.009), older age (median age of group with prolonged shedding was 54.5 years old compared to 48 years old, P=0.033), and concomitant hypertension (P=0.009). Treatment with corticosteroid (P=0.025) and invasive mechanical ventilation (P=0.006) were also related to prolonged shedding. Severity of disease was related to prolonged shedding with 34.2% of patients with severe disease at admission (defined as patients with severe pneumonia, ARDS, or sepsis) having prolonged shedding compared to 16.2% of severe patients who did not (P=0.049). Multivariate analysis of the variables with statistical significance (P<0.05) showed that **time from illness onset to hospital admission (odds ratio, OR, 1.30, P=0.002) and male sex (OR, 3.24, P=0.011) were independent risk factors for prolonged viral RNA shedding.**
Clinical Implications	Further investigation into the sex-related dimorphism of COVID-19 is needed. This study recommends that **symptomatic patients should be admitted to the hospital as early as possible if SARS-CoV-2 infection is confirmed** as time from illness onset to hospital admission was found to be an independent risk factor for prolonged viral RNA shedding.
Limitations	This study was limited by small sample size. Additionally, viral RNA shedding is not the same as viral shedding. It is unclear how shedding of viral RNA correlates with shedding of infectious virus. For patients with invasive mechanical ventilation, lower respiratory tract specimens (endotracheal aspirate or bronchoalveolar lavage) were collected and viral RNA shedding may not be equivocal to specimens collected in sputum.

Cardiovascular Disease, Drug Therapy, and Mortality in COVID-19.

Mandeep Mehra et al.

New England Journal of Medicine
May 1, 2020 **[Retracted 6/4/2020]**
DOI: 10.1056/NEJMoa2007621

Purpose	To investigate relationships between COVID-19 mortality and cardiovascular disease.
Study design	Retrospective chart review (n= 8910)
Level of evidence	Level 4
Methods	Data from hospitalized patients who had been diagnosed with COVID-19 infections between December 20th, 2019 and March 15th, 2020 was extracted from Surgical Outcomes Collaborative registry. Independent t-sample testing was done for comparisons between variables (demographics, coexisting conditions, drug therapy) and outcomes (death, discharge from hospital). A multivariable logistic-regression analysis was performed to ascertain the effects of these variables on the likelihood of death prior to discharge. Additional analysis looked for unmeasured confounders and subgroup analysis to see if overall data trends held true in limited sample populations.
Findings	**Age greater than 65 years, coronary artery disease (CAD), heart failure, cardiac arrhythmias, chronic obstructive pulmonary disease and current smoking were independently associated with a higher risk of in-hospital mortality among patients with COVID-19 infections.** Female sex was shown to lower the risk of in-hospital mortality. The use of angiotensin-converting enzyme (ACE) inhibitors (OR: 0.33; 95% CI, 0.20 to 0.54) and statins (OR: 0.35; 95% CI, 0.24 to 0.52) were associated with lower risk of in-hospital death among patients with COVID-19 infections. No significant association was found for use of ARBs (OR: 1.23; 95% CI, 0.87 to 1.74). No associations were noted for antiplatelet therapy, or between in-hospital death and the presence/absence of immunocompromising conditions, diabetes, or hyperlipidemia.
Clinical Implications	**This analysis supports previous observations that older ages and certain pre-existing heart conditions** (CAD, heart failure, arrhythmias, COPD and smoking) **are associated with greater risk of death in COVID-19 infection.** The data does not support concerns that ACE inhibitor and statin therapy increase in-hospital mortality.
Limitations	**Study has been retracted.** As this is not a randomized control trial, there is a greater risk of confounding factors affecting data. Furthermore, this data only looks at patients who were on therapy for hypertension or hyperlipidemia prior to hospitalization, and can provide no insight into the safety of starting these medications in COVID-19 patients who had no prior indications.

Clinical characteristics of pregnant women with Covid-19 in Wuhan, China.

Lian Chen et al.

New England Journal of Medicine
April 17, 2020
DOI: 10.1056/NEJMc2009226

Purpose	To analyze clinical characteristics of pregnant women with COVID-19.
Study design	Case series (n=118)
Level of evidence	Level 3
Methods	Data collected from December 8, 2019 to March 20, 2020,on pregnant women in Wuhan, China that met the criteria of the Chinese Clinical Guidance for Covid-19 Pneumonia Diagnosis and Treatment was analyzed. The women were grouped as to having severe or nonsevere disease and parameters regarding symptoms and pregnancy outcome were compared . Diagnosis was based on positive PCR testing (71%) or from suggestive CT findings (29%).
Findings	In this cohort of pregnant women from Wuhan (China), 92% had non-severe disease, and 8% had severe disease with hypoxemia. 95% were symptomatic, with fever (75%) and cough (73%) being most common. Of those who delivered (58%), 93% delivered via Cesarean section due to obstetrical indications (39%) or concerns about COVID-19 (61%). 35% of patients still had ongoing pregnancy at the end of the study period, and 8% of mothers had an abortion. Median APGAR score at 1 minute was 9. No deaths were recorded amongst mothers or neonates during study period. Testing for SARS-CoV-2 performed on 8 neonatal throat swabs and 3 breast milk samples were negative.
Clinical Implications	Unlike influenza (H1N1), where pregnant women are more likely to experience severe symptoms and complications (Creanga AA, et al., Obstet Gynecol 115:717-26, 2010), **SARS-CoV-2 infection is not associated with an increased risk of severe disease among pregnant women nor adverse neonatal outcomes.**
Limitations	This analysis was limited by sample size, as well as by single location study. Future studies looking at long-term follow-up for neonates should be encouraged to evaluate any effect of maternal COVID-19 infection on the infant's development.

Association of Public Health Interventions with the Epidemiology of the COVID-19 Outbreak in Wuhan, China.

An Pan et al.

JAMA
April 10, 2020
DOI: 10.1001/jama.2020.6130

Purpose	To evaluate the impact of non-pharmaceutical public health interventions on epidemiologic variables relating to SARS-CoV-2 (COVID-19) in Wuhan, China.
Study design	Retrospective cohort study
Level of evidence	Level 4
Methods	Retrospective cohort study examining the spread of COVID-19 through Wuhan, China from December 2019 to March 2020. Data were gathered from the Notifiable Disease Report System. The primary outcome measured was confirmed cases via RT-PCR testing per day per million people, organized by sex, gender, age, geographic location, occupation, and severity of disease. Effective reproduction number of COVID-19 (Rt score), was also tracked as a measure of secondary disease transmission. The study period was divided into five sections based on implementation date of intervention: 1) 12/8/19-1/9/20: No public health interventions, normal population movement. 2) 1/10/20-1/22/20: Mass population movement secondary to Chinese New Year. 3) 1/23/20-2/1/20: Traffic restrictions, home quarantine, cordons sanitaire. 4) 2/2/20-2/16/20: Centralized quarantine and treatment. 5) 2/17/20-3/8/20: Universal symptom survey conducted in Wuhan.
Findings	32,583 cases were included in the analysis. The average age of COVID-19 patients was 56.7 years old, though 74.3% of cases occurred in patients between 40 and 79 years of age. The case rate was highest during the third period, with a total of 13,880 diagnosed cases. The case rate per million people increased between periods one and three from 2.0 to 45.9 and finally to 162.6 before falling in periods four and five to 77.9 and 17.2, respectively. Illness severity was higher in men and also increased with age. The effective reproduction number of COVID-19 was highest in the first and third periods, peaking at 3.82 during the third period. The Rt fell below 1.0 (indicating the virus stopped spreading) during the fourth period and decreased to below 0.3 during the fifth period.
Clinical Implications	In this analysis, **case rates were highest following periods of mass population movement.** The implementation of strict public health interventions and measures (including social distancing, traffic restriction, and home quarantine) have shown to be effective to decrease not only the case rate but also the effective reproduction number (Rt) of COVID-19.
Limitations	A prospective study was not possible secondary to the fast spread of the disease and ethical concerns. In some instances, several interventions were initiated at the same time, making study of the effectiveness of a single intervention impossible. Patients who were clinically diagnosed with COVID-19 were not included, which could have changed results. In addition, lack of early testing and shortage of testing kits limited sample size. Finally, as patients may be asymptomatic for up to two weeks, it is possible that cases could be acquired in one period and recorded in another.

Modified SEIR and AI prediction of the epidemics trend of COVID-19 in China under public health interventions.

Zifeng Yang et al.

Journal of Thoracic Disease
February 28, 2020
DOI: 10.21037/jtd.2020.02.64

Purpose	To evaluate effectiveness of control measures implemented in China on January 23, 2020 (including quarantines, travel limitations, closure of public spaces, and temperature monitoring) in reducing the spread of the COVID-19 epidemic.
Study design	Modified Susceptible-Exposed-Infected-Removed (SEIR) Model
Level of evidence	Level 5
Methods	Epidemiological data retrieved from the National Health Commission of China was combined with population migration data before and after January 23, 2020 (inbound/outbound rail, air, and road traffic) obtained from a web-based program. These data were applied to the SEIR model with an estimated incubation period of 7 days and estimated values for the probability of transmission, recovery, and death based on epidemic data from Hubei Provence. The predictions from this model were corroborated by artificial intelligence (AI) trained on data obtained from the 2003 SARS outbreak.
Findings	The model predicted that **a five-day delay in the implementation of China's control measures would have resulted in a three-fold increase in the number of coronavirus cases**, suggesting that the measures put in place by the Chinese government did in fact have a positive impact on the course of the pandemic. Additionally, modeling predicted that relaxing the control measures at the time of publication would lead to a second wave of infections in Hubei Provence.
Clinical Implications	This study adds to existing evidence that **social distancing, travel restrictions, and mandatory quarantines are actively working to reduce the spread of the novel coronavirus**. Most importantly, it predicts that ending restrictions too soon could result in a resurgence of the virus within the population.
Limitations	The study was limited by its reliance on data gathered by the government, as the true number of COVID-positive individuals in the population most likely exceeded what was reported based on lack of available diagnostic testing. Moreover, the model used early estimates of incubation time for the virus of 7 days, while more recent data suggests a median incubation time before symptom onset is 3 days. Also, the study did not take phase-adjusted preventive measures and time-varying parameters into consideration, which may affect the accuracy of predictions.

Estimating clinical severity of COVID-19 from the transmission dynamics in Wuhan, China.

Joseph Wu et al.

Nature: Medicine
March 19, 2020
DOI: https://doi.org/10.1038/s41591-020-0822-7

Purpose	To synthesize confirmed and published coronavirus case data from mainland China to estimate the clinical severity of COVID-19 using a transmission dynamics model.
Study design	Retrospective observational study (n = 48,557)
Level of evidence	Level 3
Methods	Collected case data from multiple Chinese studies. The prevalence of infection in travelers on flights before January 19th and on charter flights from January 19th-February 4th were used to estimate infection prevalence. Authors used the first 425 cases in Wuhan, China to estimate the growth rate of the epidemic. Clinical severity was measured by infection fatality risk (IFR; defines a case as a person who would, if tested, be counted as infected and rendered immune), symptomatic case fatality risk (sCFR; defines a case as someone who is infected and shows certain symptoms), and hospitalization fatality risk (HFR; defines a case as someone who is infected and hospitalized).
Findings	Age-specific sCFRs and susceptibility to symptomatic infection both increased substantially with age. Assuming that the probability of developing symptoms after an infection (Psym) is 0.5, the sCFR values are 0.3% in those age <30, 0.5% in those age 30-59, and 2.6% in those age >59. The overall sCFR was 1.4%, which was lower than the corresponding confirmed case fatality risk of 4.5% (2,169 deaths/48,557 confirmed cases in Wuhan). Those aged <30 or >59 years are 0.16 and 2.0 times more susceptible to symptomatic infection than their middle aged counterparts. Using the Psym=0.5 parameter, the mean reproductive number (the number of new cases generated by a single case) is 1.94. The mean time from symptom onset to death is 20 days, with a standard deviation of 10 days. The epidemic doubling time was 5.2 days before Wuhan was quarantined. In comparison to the SARS virus, whose IFR and sCFR are essentially the same as the HFR, the sCFR is substantially lower than the HFR for COVID-19. Despite a lower sCFR, COVID-19 is still likely to be the cause of more deaths than SARS and MERS due to the larger number of people infected by COVID-19.
Clinical Implications	For COVID-19, sCFR is highest in the >59 age group. Unlike previously reported pandemics (SARS and MERS) or influenza, the risk of symptomatic infection also increases with age.
Limitations	The study uses an arbitrary Psym of 0.5. If the Psym were higher, for example 0.75 or 0.95, that would yield an overall sCFR of 1.3% and 1.2%, respectively. Although age-specific sCFRs are not susceptible to changes in Psym, susceptibility to symptomatic infection is unknown. The study uses population case data collected in all of mainland China prior to Wuhan undergoing quarantine. First, the data might not be generalizable to different locations outside of China. Secondly, it is unknown whether quarantine measures, social distancing, and other precautions of infection control are effective in changing the predicted outcome measure of sCFR, which should be explored in future studies.

SARS-CoV-2 infection (COVID-19) in febrile infants without respiratory distress.

Michal Paret et al.

Clinical Infectious Diseases
April 17, 2020
DOI: https://doi.org/10.1093/cid/ciaa452

Purpose	To analyze SARS-CoV-2 infection in infants.
Study design	Case series (n= 2)
Level of evidence	Level 4
Methods	A real-time RT-PCR assay performed to detect SARS-CoV-2 RNA in infants' nasopharyngeal (NP) samples. Samples of blood, urine, and CSF were obtained for laboratory evaluation including white blood cell, platelet, neutrophil, lymphocyte and monocyte counts, hemoglobin and C-reactive protein concentrations.
Findings	SARS-CoV-2 has been detected in two young infants with fever as the only manifestation: First infant was a 25-day old full-term male. He had fever, and erythematous, papular facial rash. Empiric therapy with parenteral ampicillin and cefepime was started on admission and continued until blood, urine, and CSF cultures were negative for > 48 hours. Second infant was a 56-day old full-term male. He was presented to the hospital with fever. Empiric therapy with parenteral ceftriaxone continued until blood and urine cultures were negative for > 36 hours. Both infants were discharged home in stable condition.
Clinical Implications	**In young infants, SARS-CoV-2 can cause fever without any other manifestations, including respiratory symptoms and signs.** This suggest that children are either less likely to have been exposed to the virus (due to an un-identified receptors or co-receptors, which are differently distributed in adults and infants and binds SARS-CoV-2 more efficiently in adults) or that there is a different mechanism in child's body, which responds to the virus in a less-dramatic way (e.g., children's immune system might not be mature yet to start a cytokine storm similar to the one observed in adults).
Limitations	Limited by sample size, as well as by single center study.

Demographic science aids in understanding the spread and fatality rates of COVID-19

Jennifer Beam Dowd et al.

PNAS

April 16, 2020

DOI: https://doi.org/10.1073/pnas.2004911117

Purpose	To explain how average country population age influences COVID-19 national case fatality rate (CFR).
Study design	Disease projections from publicly available data. No patients under study.
Level of evidence	Level 5
Methods	Authors created models of population size and expected population deaths in Italy, South Korea, Brazil, Nigeria, and the United States. Direct comparison models were created for all countries aside from the USA. Head-to-head comparisons were made between Italy and South Korea as well as between Brazil and Nigeria. Projections assumed a 10% population infection rate and the age-sex specific CFR seen in Italy. Separate projections of deaths per 10-year age group were made using three countries of differing average age (Italy, USA, and Nigeria) and two separate infection rates (10 and 40%).
Findings	Head-to-head comparison of population age and expected deaths, countries with a higher proportion of older citizens had a far higher number of expected deaths. Brazil, which has a higher population percentage over 80 years of age when compared to Nigeria (2.0% vs 0.2%), also has a dramatically more COVID-19 deaths than Nigeria (452,694 vs 142,056). In evaluating deaths by ten-year age group, deaths were highest in the Italian population (highest proportion of elderly) and lowest in the Nigerian population (lowest proportion of elderly).
Clinical Implications	Demographic evaluation and population analysis aids in understanding the COVID-19 fatality rates. COVID-19 CFR is likely to be highest in countries and regions with a higher percentage of older citizens. **Social distancing guidelines, particularly avoidance of intergenerational contact, may need to be more strictly enacted in these areas.**
Limitations	Models were created using CFRs specific to Italy as of the date of publication. Extrapolation of data may inappropriately estimate the number of expected deaths related to COVID-19, as the true CFR will not be known until the end of the outbreak. Patient characteristics, such as comorbidities or social history, nor isolation characteristics, such as level of social distancing, were not included in these models and therefore expected death rate may be incorrect.

Identifying and Interrupting Superspreading Events—Implications for Control of Severe Acute Respiratory Syndrome Coronavirus 2

Thomas Frieden et al.

Emerging Infectious Diseases
March 18, 2020
DOI: 10.3201/eid2606.200495

Purpose	To identify causes of superspreading events and how to both prevent and reduce their impact.
Study design	Narrative review
Level of evidence	Level 5
Methods	Narrative review of historical pandemics and current COVID-19 research pertaining to superspreading events (SSEs). The primary endpoint of the paper was to review the factors that contribute to superspreading events and identify how they may be prevented.
Findings	Strategies exist to reduce both the number and impact of superspreading events. These strategies include preventing infection through the healthcare system and non-pharmaceutical interventions (NPIs). To prevent SSEs, it is necessary to understand the pathogen, host, environmental, and behavioral drivers of SSEs. Whole genome sequencing and acquiring more information on viral binding sites, persistence, virulence and infectious dose of SARS-CoV-2 will determine if different variants of the virus are more readily transmitted. A better understaning of host factors such as a) duration, location and burden, and symptomatology of infection, b) transmission prior to being symptomatic and c) those associated with increased infectivity are needed. As SARS-CoV-2 is found in stool samples, it necessitates adequate sanitation especially in public spaces. Important behavioral factors include perception of risk, social customs, health seeking behaviors, and adherence to public health guidance. Public health campaigns should focus on targeting these behaviors to reduce SSEs. Rapid identification of infected individuals is critical as delay of diagnosis is the most common cause of SSEs.
Clinical Implications	Identifying superspreading events is important, as they are associated with early growth and continued infection, prolonging the duration of epidemics. **There have been numerous examples of how a single index patient can be the source of multiple generations of infection, thus measures need to be taken to slow the spread of COVID-19.**
Limitations	The method of selecting studies was unknown. The authors did not address bias or the strength of the studies cited. The conclusions drawn are qualitative.

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

Safiya Richardson et al.

JAMA

April 22, 2020

DOI: 10.1001/jama.2020.6775

Purpose	To describe clinical characteristics and outcomes of patients with COVID-19 hospitalized in the US health care system.
Study design	Cohort study (n= 5700)
Level of evidence	Level 4
Methods	Subjects included all SARS-CoV-2 positive patients from hospitals in Northwell Health from March 1, 2020 to April 4, 2020. Charlson Comorbidity Index, which predicts 10-year survival in patients with multiple comorbidities, was used as a measure of total comorbidity burden. Outcomes were reported for patients who were discharged or had died at study end point.
Findings	5700 patients were included, median age 63 (range 0-107 years; 39.7% female). Most common comorbidities were hypertension (3026, 56.6%), obesity (1737, 41.7%), and diabetes (1808, 33.8%). Median Charlson Comorbidity Index was 4 (IQR, 2-6), which represents an estimated 53% 10-year survival. 2634 patients were discharged or had died at study end point. 373 (14.2%) were treated in the ICU, 320 (12.2%) received invasive mechanical ventilation, 81 (3.2%) received dialysis, 553 (21%) died. Mortality for patients on mechanical ventilation was 88.1%. 436 (16.6%) were younger than age 50 with a score of 0 on the Charlson Comorbidity Index. Mortality for this group was 2%.
Clinical Implications	This study was the largest cohort of sequentially hospitalized patients with confirmed COVID-19 in the US. It showed high mortality of mechanically ventilated patients, as well as a large percentage of hospitalized COVID-19 patients with medical comorbidities, including hypertension, obesity, and diabetes.
Limitations	Only patients within the NY metropolitan area were included. Mortality rates were calculated only for patients who were discharged alive or dead by the study end point, which biases rates toward including more patients who died early in their hospital course. Supplementary indices provided outcomes stratified by age, risk factors, and angiotensin-converting enzyme inhbitor (ACE-I) or angiotensin-II receptor blocker (ARB) use, but no statistical analysis was performed and data was not adjusted for known confounders.

Community transmission of SARS-CoV-2 at two family gatherings - Chicago, Illinois, February-March 2020.

Isaac Ghinai et al.

Morbidity and Mortality Weekly Report
April 8, 2020
DOI: http://dx.doi.org/10.15585/mmwr.mm6915e1

Purpose	To better understand non-household community transmission of COVID-19 by investigating a multifamily cluster.
Study design	Case report
Level of evidence	Level 4
Methods	The Chicago Department of Public Health (CDPH) investigated a multifamily cluster of COVID-19 cases. The CDPH performed contact tracing interviews using a structured questionnaire of confirmed COVID-19 positive patients and their contacts. The close contacts were then enrolled in active symptom monitoring using Research Electronic Data Capture software (REDCap). Patients were classified as COVID-19 positive if SARS-CoV-2 was detected by laboratory testing or as being probable COVID-19 positive if they developed fever and respiratory symptoms within 14 days of close contact. The primary endpoint of the study was to show how COVID-19 can be spread in the community among non-household contacts.
Findings	This study found 16 cases or probable COVID-19 cases (7 confirmed and 9 probable) traced back to one individual. Of the 16 cases, 3 died. The locations where transmission occurred included a funeral, birthday party, church, and while caring for a family member sick with COVID-19.
Clinical Implications	This study illustrates the importance of following CDC and state recommendations for social distancing after 16 potential COVID-19 cases and 3 deaths were linked back to one person. There is implication for concern about superspreading events which can lead to considerable morbidity, mortality, and prolong the duration of the pandemic.
Limitations	As this was a single case report, it only investigated one incidence of COVID-19 transmission; therefore, it may not be representative of how most cases are being transmitted. Of the 16 cases only 7 were confirmed. It is possible that they were sick with a different respiratory illness which would reduce the secondary attack rate. Only those who experienced symptoms were considered cases; however, COVID-19 has been found to produce asymptomatic illness in some individuals. Contact tracing requires accurate recall which could introduce recall bias. Some of the patients may not have been able to remember all the potential contacts such as those which were associated with transmission in a church. It is possible that for some of the cases, it was not the index patient who transmitted but rather from another source within the community.

Prediction models for diagnosis and prognosis of covid-19 infection: systematic review and critical appraisal.

Laure Wynants et al.

BMJ

April 7, 2020

DOI: https://doi.org/10.1136/bmj.m1328

Purpose	To evaluate currently available diagnostic and prognostic prediction models for COVID-19 infection.
Study design	Systematic review of prediction models
Level of evidence	Level 1
Methods	Articles for evaluation were collected by searching PubMed, Embase, Ovid, bioRxiv, medRxiv, and arXiv for COVID-19 research published after January 3, 2020. Studies which developed or validated a multivariable model or scoring system using individual patient level data were included. Epidemiologic studies, such as those evaluating case fatality, were excluded. Model discrimination was assessed via C-index, with 1 representing perfect discrimination between outcomes in participants. Calibration was assessed using calibration intercept and slope to determine if risks were appropriately estimated and if risks were appropriately experienced by the participant, respectively. Bias was assessed using the prediction model risk of bias assessment tool (PROBAST).
Findings	Of 2696 screened titles, 27 studies with 31 total prediction models were evaluated. Three models predicted hospital admission, 18 were diagnostic models based on symptoms or CT imaging, and 10 were prognostic for length of stay, mortality, or disease progression. Most studies (25) developed models using Chinese data, though Italian (1) and international (1) data were also used in some cases. C-indices were high in diagnostic (0.81 to 0.99), prognostic (0.85 to 0.98), and admission prediction (0.73-0.81) models, though calibration was rarely completed. Bias was classified as high for all prediction models under PROBAST criteria secondary to non-representative control patient selection, limited study size, and improper patient classification.
Clinical Implications	Current prediction models regarding hospital admission, diagnosis, and prognosis of COVID-19 show promise, particularly in terms of appropriate patient discrimination, but suffer heavily from selection bias and lack of external validation. Therefore, care must be taken before making critical decisions based on these disease models, which have not been properly tested.
Limitations	Some prediction models in this study were classified as pre-prints or under peer review at the time of this publication, and it is possible that peer review could improve discrimination, calibration, and overall instrument validity. Literature was evaluated last on March 24, 2020 and additional prediction models have likely since been created and validated.

The association between international and domestic air traffic and the coronavirus (COVID-19) outbreak.

Hien Lau et al.

Journal of Microbiology, Immunology and Infection
March 28, 2020
DOI: https://doi.org/10.1016/j.jmii.2020.03.026

Purpose	To investigate the relation between regular international flight connections with China and the spread of COVID-19 cases.
Study design	Systematic review
Level of evidence	Level 5
Methods	Data on current domestic and international passenger volume and flight routes was compared to the distribution of COVID-19 cases. Information was collected from various databases, including the Civil Aviation Administration of China (CAAC), Official Aviation Guide (OAG), and the World Health Organization (WHO). All correlation analysis was evaluated using linear regression and the goodness of fit of the model was assessed by r2 value.
Findings	There is a strong, but not statistically significant, linear correlation between domestic COVID-19 cases and passenger volume for regions within China ($r^2=0.92$, $P=0.19$). There is a strong and significant correlation between international COVID-19 cases and passenger volume ($r^2=0.98$, $P<0.01$).
Clinical Implications	**Air travel is a major facilitator in the international distribution of COVID-19 cases.** The number of international cases is directly correlated to the number of air traffic routes and passenger volume. As new epicenters develop, flight services from these secondary epicenters will play a major role in COVID-19 spread.
Limitations	The CAAC has partially restricted access to information on passenger volume, destination, and location, making acquiring exact data difficult. Domestic transportation via train and car was not considered during data analysis and likely affected the relation between domestic COVID-19 cases and domestic flight.

Changes in SARS-CoV-2 positivity rate in outpatients in Seattle and Washington state, March 1-April 16, 2020

April Kaur Randhawa et al.

JAMA
May 8, 2020
DOI: 10.1001/jama.2020.8097

Purpose	To explore the effect of social distancing measures implemented by Seattle and the state of Washington on COVID-19 positivity rates in outpatients from March 1-April 16, 2020.
Study design	Case Series
Level of evidence	Level 4
Methods	17,232 samples were collected from patients at 127 outpatient clinics and from 1,932 patients at 3 emergency departments in Seattle between March 1-April 16, 2020. Diagnostic tests for COVID-19 were done by rt-PCR of nasopharyngeal swabs. COVID-19 positivity rates were analyzed during the study period and compared across two regions (Washington State vs Seattle-area) and between two populations (ER patients vs non-ER outpatients).
Findings	COVID-19 positivity rates peaked between March 28-29 for Washington State and Seattle area outpatients and then declined for both populations. **The positivity rate at peak period was 17.6% for outpatient clinics and 14.3% in the emergency departments and declined to 3.8% at outpatient clinics and 9.8% at emergency departments by the end of the study period.** Over the course of the entire study, positivity rates for COVID-19 were 8.2% in the Washington State outpatient clinics, 8.4% in Seattle-area outpatient clinics, and 14.4% iSeattle emergency departments ($p<0.001$ for outpatient clinics vs emergency departments).
Clinical Implications	The trajectory of COVID-19 positivity rate (peaking in late March and declining the remainder of the study) was aligned with local physical distancing guidelines including closure of bars and limiting social gatherings. These results suggest that social distancing regulations, enacted in a timely manner by Washington state, changed the course of COVID-19 infections and should be considered by other states/countries based on the trends seen in COVID-19 positivity rate.
Limitations	Samples were not collected across the entire state of Washington and were collected in specific areas of Seattle, so this study is not fully representative. A potential confounding variable which was not assessed was symptom severity (or presence of symptoms at all) of tested patients. These variables may have changed throughout the study period and skewed results.

Thinking Globally, Acting Locally—The US Response to Covid-19

Rebecca Haffajee et al.

New England Journal of Medicine
April 2, 2020
DOI: 10.1056/NEJMp2006740

Purpose	To highlight weaknesses in the United States'"federalist system of public health governance, which divides powers among the federal, state and local governments".
Study design	Opinion Article
Level of evidence	N/A
Methods	N/A
Findings	States & federal government can activate emergency powers to expand their ability to act to protect human life & health – such is the case now that all 50 states & the federal government have declared a state of emergency for COVID. Typical concerns with activating emergency powers is that both state and federal government can exploit their power without checks. However, the article states that during the COVID-19 pandemic, the federal government has done too little. Limited response could be a function of initial misleading information about severity of threat, negative public sentiment about worsening economy & stock market, and pressure to create sense of calm.
Clinical Implications	The authors feel we lost the chance to contain COVID through unified action – mirroring what's happened in Italy. The article states that federal measures must strengthen, not relax over these next few weeks, with social distancing extensions, relief packages contigent on state adherence, travel restrictions, and use of the Defence Production Act.
Limitations	This article provided a nice overview of how our state and federal government structures are set up to respond to a public health crises, flaws of this system, and recommendations for how to improve. This article could have expanded a bit more on ways to improve the disconnect between the executive branch and the scientific community.

Coronavirus Disease Outbreak in Call Center, South Korea

Shin Young Park et al.

Emerging Infectious Diseases
April 23, 2020
DOI: https://doi.org/10.3201/eid2608.201274

Purpose	To describe the epidemiology of a COVID-19 outbreak in a call center in South Korea.
Study design	Case Series
Level of evidence	Level 4
Methods	The study defines a patient under investigation (PUI) as someone who worked at, lived at, or visited a 19-story building in Seoul during February 21-March 8, 2020. The study also defined the diagnosis of COVID-19 as positive through rt-PCR. A symptomatic PUI was defined as a confirmed patient with symptoms at the time of positive testing, a pre-symptomatic PUI as confirmed patient who was asymptomatic at the time of positive testing but later developed symptoms, and an asymptomatic PUI as confirmed patients without symptoms at the time of positive testing and remained asymptomatic during the 14 day period after. Information on demographic characteristics and presence of symptoms was conducted through face-to-face interviews with case patients using standardized epidemiologic investigation forms. Negative case patients were retested and followed over the 14 days as well.
Findings	**Out of the 1,143 PUIs tested for COVID-19, 97 were identified as confirmed case-patients for COVID-19 (8.5% of the total).** Most of the confirmed cases 94 out of the 97 (96.9%) were working on the 11th floor call center. The call center had 216 employees which translated to an attack rate of 43.5%. The household secondary attack rate among symptomatic case-patients was 16.2%. Of the 97 PUIs with confirmed COVID-19, only 4 (1.9%) remained asymptomatic within 14 days of quarantine. **Of those that remained asymptomatic, none of their household contacts acquired secondary infections.**
Clinical Implications	Extensive contact tracing, testing all contacts, and early quarantine can block further transmission and might be effective at containing rapid outbreaks in work settings. This can be accomplished by continuing social distancing measures once people start returning to work. Further research can be done in close contacts to patients who are asymptomatic as this study showed that there was no secondhand transmission in the patients who were asymptomatic.
Limitations	This study was not able to track these cases to another cluster, which made it difficult to identify the actual index case-patient. Not all clinical information was available for all confirmed cases, prohibiting detail description of clinical symptoms.

Clinical characteristics of patients hospitalized with coronavirus disease, Thailand.

Wannarat A. Pongpirul et al.

Emerging Infectious Diseases
April 8, 2020
DOI: https://doi.org/10.3201/eid2607.200598

Purpose	To characterize the clinical presentation, management, and laboratory findings of 11 SARS-CoV-2 positive patients in Thailand.
Study design	Case series (n = 11)
Level of evidence	Level 4
Methods	In January 2020, persons in Thailand were tested for SARS-CoV-2 if they met criteria of fever (>38o C) or respiratory illness and recent travel to Wuhan, China. Contact tracing of patients with a positive test was performed and those contacts were also tested. The 11 cases were hospitalized, had daily nasopharyngeal and oropharyngeal testing, and their clinical course was monitored.
Findings	The median age of the patients was 61 years old (28-74 years). Clinical features included symptoms of cough, malaise, and sore throat. All had radiologic evidence of pneumonia. Viral co-infections including adenovirus and influenza A were detected in 2 patients. Most patients only required supportive care, none needed mechanical ventilation. One patient remained asymptomatic despite having specimens with detectable SARS-CoV-2 and having a chest radiograph with signs of unilateral pneumonia at admission. In patients with fever, resolution took a median of 6 days (range, 4-11.5 days). **Clinical resolution took a median of 12 (range, 9-13.5) days. SARS-CoV-2 RNA was detectable for median of 14 (range, 9-26) days after symptom onset.**
Clinical Implications	Presence of another viral infection should not completely deter providers from testing for SARS-CoV-2, as this study identified the presence of viral co-infections. Screening measures may not catch all patients who present later in their clinical course as this study found fevers resolved eight days prior to resolution of viral shedding. Asymptomatic patients are a concern for continual spreading of the virus. Duration of detectable SARS-CoV-2 RNA in specimens (median 14 days) underscores the lengthy duration of infectivity and risks to healthcare providers. The length of clinical resolution (median 12 days) highlights the burden on the healthcare system.
Limitations	The study had a very small sample size (n=11) limiting its generalizability. Thailand has a smaller population and current number of infected persons compared to other countries. Their methods of screening and contact tracing are less practical for countries with a larger population and larger disease burden limiting the reproducibility of the study. The study relied on accurate recall of when symptoms began to characterize the median duration of illness. Recall bias may alter the accuracy of the results.

Comparison of estimated rates of coronavirus disease 2019 (COVID-19) in border counties in Iowa without a stay-at-home order and border counties in Illinois with a stay-at-home order

Wei Lyu et al.

Journal of the American Medical Association
May 15, 2020
DOI: 10.1001/jamanetworkopen.2020.11102

Purpose	To investigate the effect of stay-at-home orders on the spread of COVID-19 by comparing cases in counties of Iowa, which did not issue the order, and Illinois, which did issue the order.
Study design	Cross-Sectional Study (n=734,740)
Level of evidence	Level 3
Methods	Researchers used a difference-in-difference design to compare changes in COVID-19 cases per 10,000 residents of 8 Iowa counties and 7 Illinois counties bordering the Iowa-Illinois state line. The rates per 10,000 people were recorded before Illinois implemented stay-at-home orders (between March 15th-21st) and then 10, 20, and 30 days after the orders were made.
Findings	**After stay-at-home orders were placed, the cases increased more quickly in Iowa compared to Illinois**. The difference in average daily cases from 10, 20, and 30 days after the stay-at-home order in Illinois showed a rate reduction ratio of -0.51 per 10,000 residents ($p<0.01$), -1.15 per 10,000 residents ($p=0.02$), and -4.71 per 10,000 residents ($p=0.02$) for the 10-day increments, respectively
Clinical Implications	The results suggest that issuing a stay-at-home order in Iowa may have helped limit the spread of COVID-19. These findings provide evidence to support the use of stay-at-home orders in counties that see future spikes in cases.
Limitations	Compared to Iowa, Illinois had a greater increase in overall COVID-19 tests following the stay-at-home order which may be considered a confounding variable. The study also did not mention whether or not the testing was standardized across all counties. This should be considered given variable sensitivities and specificities of testing methods. Lastly, population density and poverty rates were not identified in the study and may have played a confounding role.

Estimating the Infection Fatality Rate Among Symptomatic COVID-19 Cases in the United States

Anirban Basu

Health Affairs
May 7, 2020
DOI: https://doi.org/10.1377/hlthaff.2020.00455

Purpose	To estimate the infection fatality rate (IFR) among symptomatic COVID-19 cases (IFR-S) in the United States.
Study design	Observational (ecological)
Level of evidence	N/A
Methods	The authors hold three assumptions: 1) errors in the numerator and the denominator of the infection fatality rate (IFR) lead to underreporting of true COVID-19 deaths and cases, with error in deaths being smaller than cases 2) Both these errors are declining over time 3) Errors in the denominator are declining faster than errors in the numerator. A detailed mathematical formula was created, considering these assumptions, which allowed the authors to predict the IFR. Publicly reported data in GitHub from the Johns Hopkins Repository and the New York Times on the total number of cumulative deaths and detected cases by day for each county in the US was used. Each counties' analysis began from the day of the first peak in rate variable (cumulative number of deaths divided by cumulative total detected cases), and was carried out through April 20, 2020. The model fit was assessed using posterior predictions from the model against four consecutive follow-up days per county.
Findings	Overall, 40,835 confirmed cases and 1,620 confirmed deaths until April 20 were used over 116 counties and 33 states. **The posterior mean of the IFR-S was estimated to be 1.3%** (median: 1.3%, Std. Dev: 0.4%) with a 95% central credible interval of 0.6% to 2.1%. The 95% central credible intervals from the posterior predictive distribution from the model for the four follow-up days were able to capture the true CFR rates for all counties over the four days. Bayesian posterior predictive two-sided p-values were less than 0.05 for none of the 116 counties for any of the four days.
Clinical Implications	**The infection fatality rate in symptomatic individuals (IFR-S) of 1.3% is higher than the approximate IFR-S of seasonal influenza (0.1%).** This model has potential to be used by health officials and policy makers to make accurate predictions for the epidemiology of the disease and the impact of alternative policies to contain the pandemic.
Limitations	The IFR-S of this study may be higher than the true overall IFR because the study relies on cases which are all symptomatic. The true IFR may be hard to ascertain as the number of truly asymptomatic individuals remains unknown. The IFR-S of this study may also be lower than the true overall IFR because the study doesn't take into account the number of cases who may die in the future. Data was not broken down to account for age or comorbidities. Conclusions are specific to the United States, where the policies and social distancing practices differ from those seen in other countries.

Psychiatric and neuropsychiatric presentations associated with severe coronavirus infections: a systematic review and meta-analysis with comparison to the COVID-19 pandemic

Jonathan P Rogers et al.

The Lancet Psychiatry

May 18, 2020

DOI: 10.1016/S2215-0366(20)30203-0

Purpose	To examine the psychiatric and neuropsychiatric consequences of all forms of coronavirus infection (SARS, MERS, SARS-CoV-2)
Study design	Systematic review
Level of evidence	Level 1
Methods	The authors performed a systemic review of all studies which reported psychiatric and neuropsychiatric presentations, symptom severity, diagnoses, employment, and quality of life in association with coronavirus exposure. They reviewed pre-prints and published studies from MEDLINE, Embase, PsycINFO, Cumulative Index to Nursing and Allied Health Literature, MedRxiv, PsyArXiv, and BioRxiv. After yielding 1963 articles and 87 preprints from their literature search, 72 studies met inclusion criteria. This included 12 qualitative studies, 4 case reports, 5 case series, 8 cross-sectional study, 2 randomized controlled trials, and 41 cohort studies.
Findings	The systematic review revealed that during acute illness, common symptoms among patients admitted to hospital for SARS or MERS included confusion (27.9%), depressed mood (32.6%), anxiety (35.7%), impaired memory (44%), and insomnia (41.9%). The meta-analysis indicated that in the post-illness stage for SARS or MERS, the point prevalence of post-traumatic stress disorder was 32.2%, that of depression was 14.9%, and that of anxiety disorders was 14.8%. When data for patients with SARS-CoV-2 were examined (including preprint data), there was evidence for delirium (65%), agitation (69%) and altered consciousness (21%) in intensive care unit patients.
Clinical Implications	In previous coronavirus epidemics, psychiatric sequalae during the post-illness stage was common and included depression, anxiety, fatigue, and post-traumatic stress disorder. Also, **patients that developed severe acute respiratory distress syndrome (a key feature of severe SARS-CoV-2 infection) show deficits in memory, attention, concentration, or mental processing speed at 1 year.** In the current COVID-19 pandemic, there is already evidence of delirium acutely, and clinicians should be alert to the possibility of increased rates of psychiatric conditions long term.
Limitations	This systemic review excluded non-English language articles, used preprint articles which had not been subject to peer review, and included studies with very small samples. Most studies were of low or moderate quality and use of self-report questionnaires was common. For the post-illness studies, there was also substantial variation in follow-up time that hindered comparability.

Excess Deaths From COVID-19 and Other Causes, March-July 2020

Steven H. Woolf et al.

Journal of the American Medical Association (JAMA)
October 12, 2020
DOI: 10.1001/jama.2020.19545

Purpose	To provide an updated estimate of excess deaths due to COVID-19 and reveal trends related to the reopening of states.
Study design	Research Letter
Level of evidence	Level 5
Methods	The researchers obtained death data and population counts for the 50 U.S. states from 2014 to 2020 through reputable sources. They utilized a hierarchical Poisson regression model to predict expected deaths (compared to prior years) as a whole and due to particular underlying causes. They also executed a Joinpoint regression program to confirm increased death rates as well as compare it to individual states' reopening dates and epidemic curves.
Findings	-There was a 20% increase in deaths compared to expected deaths from March 1st through August 1st 2020 (for a total of 225,530 excess deaths) -67% of those 225,530 excess deaths were connected primarily to COVID-19. -Deaths due to heart disease and Alzheimer disease/dementia increased in March-April, with Alzheimer/dementia deaths increasing again between June-July. This latter surge correlates with the COVID-19 summer surge in sunbelt states. -COVID-19 excess mortality varied by state. Wyoming, Alaska, and Hawaii reflected no excess deaths while Rhode Island revealed 104% excess deaths.
Clinical Implications	The data revealed over 225,000 excess deaths due to COVID-19 with excess deaths varying per state. Certain states had surges where it was more difficult to control COVID-19, but with no end in sight to the current pandemic, it is expected to have over 400,000 excess deaths due to COVID-19 by the end of 2020. This number of excess deaths may still be underestimated due to undocumented infections and patients delaying medical care.
Limitations	The researchers relied on data from death certificates and provisional data, which may be inaccurate or omit undocumented cases of COVID-19. Additionally, missing data from Connecticut and North Carolina may further underestimate the true number of excess deaths.

COVID-19 and Excess All-Cause Mortality in the US and 18 comparison countries

Alyssa Bilinski A and Ezekiel J. Emanuel

Journal of the American Medical Association
October 12th, 2020
DOI: 10.1001/jama.2020.20717

Purpose	The purpose of the study was to compare COVID-19 mortality and all causes of mortality from 2015-2019 between the US and comparable countries.
Study design	Case control (retrospective)
Level of evidence	Level 4
Methods	Metrics used to find comparable countries to the US were done so via Organisation for Economic Co-operation and Development (OECD) countries with two parameters: populations exceeding five million and a GDP exceeding $25,000. All countries were stratified by low, moderate, and high mortality rates of <5/100 000, 5-25/100 000, and >25/100 000, respectively. The researchers then calculated the difference in COVID-19 deaths through 09/19/2020 from three temporal situations: US vs other countries' mortality rates from the beginning of the pandemic (deemed 02/13/2020), rates between 05/10/2020 to 06/07/2020, and all-cause mortality data through 07/25/2020. Excess all-cause mortality was estimated by the difference between mortality numbers in 2020 vs corresponding weeks of 2015-2019. A Poisson regression was utilized throughout the study.
Findings	**On the final data collection day of the study (09/19/2020), the US had more deaths than the lower to moderately stratified countries, but data were comparable to high-mortality countries. However, the US would have had 187 661 fewer deaths if their mortality rate was the same as Australia** (3.3/100 000). The US had lower mortality rates in the early spring compared to the higher mortality countries, but the **US has experienced higher rates since 05/10/2020 compared to the other six countries that were stratified into the high mortality group**. From the fourteen countries that provided all-cause mortality data, **excess all-cause mortality was the highest in Spain (with a rate of 102.1/100 000 vs 71.6/100 000 observed in the US). But, the US has the greatest excess all-cause mortality than other countries since 05/10/2020.**
Clinical Implications	From the data, we see some lag time in the US numbers in the early spring (due to the fact that virus did not affect every country at the same time),, but it has been evident that the US has not only caught up and exceeded COVID-19 mortality rates of other countries, but it has been sustained. The researchers are uncertain of the causality, but the non-homogenous approach to tackling the pandemic is plausible. The researchers are unsure how these trends will progress into the fall.
Limitations	These results are only based on a limited number countries, with only six US-comparable countries. Furthermore, the study solely looked at trends, and did not dive into potential exposures or reasons why the US has increased deaths compared to other countries (i.e., differences in demographics, population densities, and public health infrastructures of those nations and the US likely had an impact on the results).

Pregnancy Outcomes Among Women With and Without Severe Acute Respiratory Syndrome Coronavirus 2 Infection

Emily H. Adhikari et al.

JAMA

November 19, 2020

DOI: 10.1001/jamanetworkopen.2020.29256

Purpose	To evaluate and describe adverse outcomes, clinical management, disease progression, and neonatal outcomes following SARS-CoV-2 infection during pregnancy.
Study design	Observational Cohort Study
Level of evidence	Level 3
Methods	Women tested for SARS-CoV-2 during pregnancy who delivered at Parkland Health and Hospital Systems in Dallas, TX from March 18 - August 22, 2020 were included. Prior to May 14, 2020, testing was performed based on presenting symptoms and/or risk factors; after May 14, 2020, universal SARS-CoV-2 testing was implemented in all labor and delivery units. Women presenting for care with an external positive test were also included. Primary outcomes evaluated a composite of preterm birth (iatrogenic or spontaneous), preeclampsia, or cesarean delivery for abnormal fetal indication.
Findings	Of the 3374 women tested, 252 tested positive for SARS-CoV-2. The average age of those tested was 27.6 years. **There was no statistically significant difference in primary outcomes based on SARS-CoV-2 infection during pregnancy**. Of the infants born with congenital anomalies, it was determined that none were related to maternal SARS-CoV-2 infection. Of the women who tested positive for COVID-19, 13 (5%) had severe illness, and 14 (6%) were hospitalized for management of COVID-19. There were no maternal deaths. Severe illness was significantly associated with pregestational/gestational diabetes, while preterm birth was significantly associated with increasing severity of maternal COVID-19 illness. Among 188 tested neonates, 6 (3%) were positive for SARS-CoV-2 infection, and all were born to women whose infection occurred in the third trimester. Transmission route of the virus was not determined, though intrauterine transmission was suspected for 1 infant following placental analysis.
Clinical Implications	Most previous studies on the relationship between SARS-CoV-2 infection and pregnancy and current data reported by the CDC do not include pregnant women who receive their diagnosis from outpatient care settings and who are never hospitalized, resulting in skewed overpredictions of COVID-19 disease-related effects on maternal and neonatal outcomes. This study is the first to include such women, as well as to clarify indication of hospitalization of women positive for COVID-19, where it was found that most women with asymptomatic or mild infection were admitted for obstetric indications, and hospitalization rates for indication of COVID-19 among pregnant women was found to be similar to that of nonpregnant women.
Limitations	This study did not have sufficient power to detect differences in individual adverse outcomes, making generalizable comparisons difficult. In addition, not all women who presented during the study period between March 18 and August 22, 2020 were tested, resulting in possible underdiagnosis of some who later developed symptoms.

Estimated SARS-CoV-2 Seroprevalence in the US as of September 2020

Kristin L Bajema et al.

JAMA Internal Medicine
November 24, 2020
DOI: https://doi.org/10.1001/jamainternmed.2020.7976

Purpose	To estimate the prevalence of persons with SARS-CoV-2 antibodies using residual sera from commercial laboratories across the US and assess changes over time
Study design	Cross-Sectional Study
Level of evidence	Level 2
Methods	Residual sera collected for routine screening or clinical management by 2 commercial laboratories across the 0 US states were analyzed over 4 collection periods, beginning in late July and ending in late September, 2020. A convenience sample was selected every two weeks from the pool available to target equal sample numbers across age groups. Each lab performed chemiluminescent immunoassay testing for SARS-CoV-2 antibodies and provided the CDC with deidentified information that included patient age, sex, state, and specimen collection date. For each 2 week testing period, researchers calculated overall seroprevalence estimates by jurisdiction, as well as site-specific age group, sex, and metropolitan status for states with sufficient samples to support precise subgroup estimates. Seroprevalence estimates were used to predict the total number of SARS-CoV-2 infections in each jurisdiction by applying the estimated seroprevalence to each site's population.
Findings	Total specimens tested were 177,919. Of the specimens collected 8.3% were female, 15%were younger than 17 years old, 26.7% were 65 and older. **In nearly all jurisdictions, less than 10% of people in US had evidence of previous SARS-CoV-2 infection.** There was no consistent difference between men and women in seroprevalence. Seroprevalence generally lower in persons 65 years or older vs. adults aged between 18 and 49. Seroprevalence varied between different jurisdictions for which there were sufficient samples to estimate by metropolitan status. Overall change in seroprevalence over 4 collection periods was modest, consistent with previously reported studies that also had small changes over time.
Clinical Implications	**There is a still a low percentage (less than 10%) of people within the United States that have detectable SARS-CoV-2 antibodies and seroprevalence varies widely based on location**. Given this low percentage, people of the United States still need to follow public health policy in order to best curtail the spread of coronavirus.
Limitations	The two laboratories used different assays and these assays were not compared to each other, which may limit the ability to compare between different locations**. The samples that were utilized were taken from patients undergoing routine screening or clinical care which may not be representative of the general United States population.**

Risk Factors Associated With All-Cause 30-Day Mortality in Nursing Home Residents With COVID-19

Orestis A. Panagiotou, MD, et al

JAMA

January 4, 2021

DOI: https://www.doi.org/10.1001/jamainternmed.2020.7968

Purpose	To identify risk factors for 30-day all-cause mortality among US nursing home residents with COVID-19.
Study design	Retrospective Cohort study
Level of evidence	Level 2
Methods	Electronic medical records, daily nursing home infection logs and resident assessments were analyzed from a large provider of postacute care and long-term care from across 25 US states. Nursing home residents underwent nursing assessments multiple times per to day to screen for new signs or symptoms of COVID-19. Physical function was measured in the population with a validated 28-point composite score of activities of daily living (ADL). Study population included nursing home residents with PCR confirmed SARS-CoV-2 infection between March 16th, 2020 and September 15th, 2020. Primary outcome was death due to any cause within 30 days of a resident"s first positive PCR test.
Findings	The total study population was 5,256. The 30-day all-cause mortality rate was 21%. Of those 61% were female, 71% were white, and median age was 79 years old. When compared with residents aged 75 to 79 years old, odds of death were increased in patient subgroups aged above 80 years old and decreased in patient subgroups aged 75 years old and below. Of those patients 78% had hypertension, 48% dementia, 40% type II diabetes mellitus, 26% chronic kidney disease (CKD). Diabetes (OR 1.21), and CKD (OR 1.33) were the strongest comorbidity risk factors for mortality. **The most common 4 symptoms at COVID-19 presentation were fever, hypoxia, tachycardia and shortness of breath. Each symptom associated with increased mortality. When compared to cognitively intact residents, odds of death among residents with moderate cognitive impairment was 2.09 times higher and odds of death among was residents with sever cognitive impairment 2.79 times higher.**
Clinical Implications	Cognitive impairment and ADL dependence are associated with mortality beyond just age, symptoms, and comorbidities. These findings can be utilized as an aid to stratify risk analysis in an already vulnerable population.
Limitations	Even in a non-pandemic world, nursing home patient population has inherently an increased mortality rate when compared to community-dwelling adults. This may artificially skew the results. The nursing homes were primarily located in the Northeastern part of the United States where there were major outbreaks. This data may not be generalizable to different locations within the US

Outcomes of COVID-19 Among Hospitalized Health Care Workers in North America

Jeong Yun Yang, MD et al.

JAMA

January 28, 2021

DOI: https://www.doi.org/10.1001/jamanetworkopen.2020.35699

Purpose	To evaluate the association between Health Care Worker status and outcomes among patients hospitalized with COVID-19.
Study design	Retrospective Cohort Study
Level of evidence	Level 2
Methods	Data was collected from 36 North American medical centers. Patients were eligible if they had received a confirmed COVID-19 diagnosis and been hospitalized for any length of time. Health Care Worker (HCW) status was defined as involving direct patient care as part of one's daily responsibilities. Confirmation of whether the acquisiton of infection was not able to be determined. Primary outcome was a composite endpoint of mechanical ventilation or death. Both whole study population and 3:1 (non-HCW:HCW) propensity match data was analyzed. Data was collected between April 15-June 5, 2020.
Findings	The total study population was 1,790. Of the total study population 127 were HCWs with mean age of 54 years. Of these patients 59.8% were female, and 71.7% never smoked. A total 1663 non-HCWs were included, with a mean age of 63 years. Of these patients 41.9% were female and 58.3% never smoked. **HCW 's were significantly less likely to require ICU admission (AOR 0.56, 95%CI 0.34-0.92) and less likely to require an admission 7 days or longer (AOR 0.53, 95% CI 0.34-0.83)**. There was no significant decrease in the propensity match data for the above. **No significant decrease in either group for primary outcomes of mechanical ventilation or death.**
Clinical Implications	**HCW hospitalized for COVID-19 did not experience worse (and in certain outcomes better) COVID-19 related outcomes compared with a matched non-HCW cohort.** This difference can possibly be attributed to meticulous PPE usage in workplace settings. It is still important to recognize different burdens of the COVID-19 disease on HCWs, including physical, psychological, social and practical effects.
Limitations	The HCW population in general has been shown in prior studies to be a healthier population than the general population in the past, potentially limiting the strength of comparison within this study. The inability to distinguish where HCWs were exposed to COVID-19 may limit one of the intended hypotheses of the study, as HCW being pre-disposed to COVID because of COVID-19 exposure intensity. Limiting the cohort within the study to hospitalized patients may limit generalizability given the different access to testing between the study groups.

All-Cause Excess Mortality and COVID-19-Related Mortality Among US Adults Aged 25-44 Years, March-July 2020

Jeremy Faust et al.

JAMA

December 16, 2020

DOI: https://www.doi.org/10.1001/jama.2020.24243

Purpose	To examine all-cause excess mortality and COVID-19-related mortality during the early pandemic period (from March to July 2020) among adults aged 25 to 44 years.
Study design	Research Letter
Level of evidence	Level 2
Methods	COVID-19 mortality and observed all-cause mortality for the study time period were drawn from provisional National Center for Health Statistics data for each of the US Department of Health and Human Services (HHS) regions. Unintentional drug overdoses are usually the leading cause of death in age 25 to 44 years. COVID-19 deaths were compared with unintentional opioid deaths in this group. Unintentional opoid overdose death counts were assembled for each HHS region. The excess mortality gap was analyzed from projected monthly expected deaths from 2020 were calculated by applying autoregressive integrated moving averages to US population and mortaility counts from 2015-2019. The study used publicly available data and was not subject to Institutional Review Board (IRB) approval.
Findings	A total of 76,088 all-cause deaths were found from March 1, 2020 to July 31, 2020 in US adults aged 25-44 years. Expected all-cause deaths was 64,189 deaths. T**he excess mortality was 11,899 deaths including 4535 COVID deaths (**38% of excess mortality). A total of 10,347 unintentional opioid deaths were found from March to July 2018**. Death due to COVID-19 exceeded or were similar to unintentional opioid overdoses in 3 HHS regions.**
Clinical Implications	From March to July of 2020, there was an increase in all-cause mortality among US adults aged 25 to 44 years. **38% of excess mortality was attributed directly to COVID-19**. It is possible with inadequate testing in the population that COVID-19-related mortality may have been underdetected in this population.
Limitations	It is not abundantly clear whether increases in excess mortality rates may have been congruent with an increase in unintentional opioid related deaths during the same time period. The excess mortaliry rates utilized provisional data to make projections so the data may not be representative of the true mortality rates.

Assessment of 135 794 Pediatric Patients Tested for Severe Acute Respiratory Syndrome Coronavirus 2 Across the United States

L. Charles Bailey et al.

JAMA Pediatrics

November 23, 2020

DOI: https://www.doi.org/10.1001/jamapediatrics.2020.5052

Purpose	To describe testing for SARS-CoV-2 and the epidemiology of infected pediatric patients across the United States.
Study design	Retrospective cohort study
Level of evidence	Level 4
Methods	A retrospective cohort study of electronic health record data from 135,794 patients younger than 25 years who were tested for SARS-CoV-2 from January 1 through September 8, 2020. Data was collected from PEDSnet, a network of 7 US pediatric health systems, comprising 6.5 million patients primarily from 11 states.
Findings	**5374 (4%) patients were infected with the virus. Compared with White patients, those of Black (odds ratio [OR] 0.70), Hispanic (0.65), and Asian (0.60) race/ethnicity had lower rates of testing; however, they were statistically significantly more (CI 95%) likley to have positive test results** (Black OR 2.66, Hispanic 3.75, Asian 2.04). In univariate analysis, nonmalignant chronic disease was associated with lower likelihood of testing, and preexisting respiratory conditions were associated with lower risk of positive test results (standardized ratio [SR] 0.78). Diagnosis groups that were associated with a higher risk of positive test results: malignant disorders (SR 1.54), endocrinologic disorders (1.52), gastrointestinal disorders (2.00), hematologic disorders (1.26), mental health disorders (1.20), and metabolic disorders (1.42). The number of patients with a diagnosis of Kawasaki disease in early 2020 was 40% lower than in 2018 or 2019 (259 vs 433 and 430).
Clinical Implications	**This study shows that SARS-CoV-2 infection rates in US pediatric patients were low. Black, Hispanic, and Asian race/ethnicity and non-respiratory chronic medical conditions were associated with higher rates of identified infection.** Patients presenting with multisystem inflammatory syndrome in children likely do not receive the diagnosis of Kawasaki disease, and therefore Kawasaki disease should not be used as a proxy for studying this new entity.
Limitations	The study used viral genome detection for SARS-CoV-2 infection, but this could exclude patients when viral testing was not readily available or those with mild cases who did not reach the current threshold for testing. Second, the study did not analyze results based on location or local population data. Geographic analysis and inclusion of social determinants of risk could increase the study's external validity to locations not represented in PEDSnet.