April 9th, 2020
Daily COVID-19 Literature Surveillance Summary

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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.**

Credit: 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

Climate

A Bold Response to the COVID-19 Pandemic: Medical Students, National Service, and Public Health.

PMID: 32267488, Apr 9, 2020
Bauchner, Howard; Sharfstein, Joshua
JAMA
Level of Evidence: Level 5- Editorial
Type of Article: Editorial
Summary: Suspend the first year of medical school this coming year and encourage those rising first years to join a national service program for public health where they can be trained in infectious disease, epidemiology and outbreak response and deployed to state/local public health departments to support needs. The author identifies 3 areas of urgent needs that medical students could be helpful. 1) Testing centers, 2)Implementation of essential preventative policies or in incident command teams to respond swiftly to infectious source, 3) community call centers to guide individuals with exposures or symptoms for COVID-19.

"We Signed Up for This!" - Student and Trainee Responses to the Covid-19 Pandemic.

PMID: 32268020, Apr 9, 2020
Gallagher, Thomas H; Schleyer, Anneliese M
N Engl J Med
Level of Evidence: Level 5- Expert opinion
Type of Article: Perspective
Summary: The results of an anonymous survey of 316 third and fourth year medical students and residents in IM and EM and critical care fellows at University of Washington reflect concerns about safety, moral distress associated with patient isolation and personal health, frustration about not being able to help, worry about inadequate training or "being rusty". "Feelings of anxiety and vulnerability among students and trainees compete internally with a desire and commitment to serve the sick."

Stop the coronavirus stigma now.

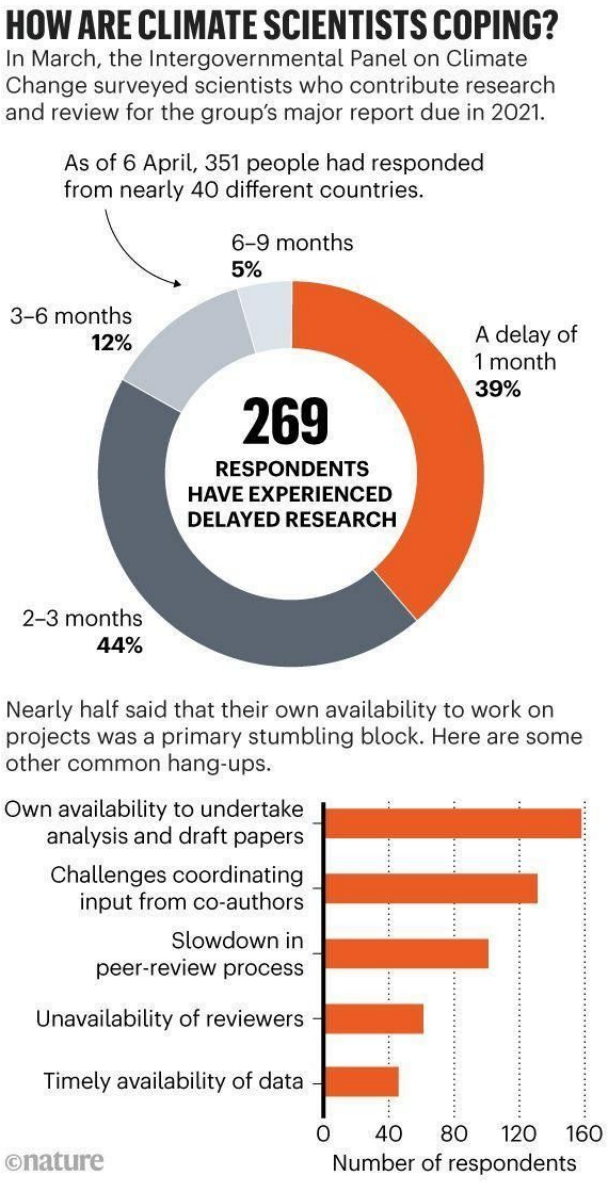
PMID: 32265571, Apr 9, 2020
No authors listed
Nature
Level of Evidence: : 5 - Expert opinion
Type of Article: News
Summary: The COVID-19 pandemic, which originated in China, has fueled "deplorable racism and discrimination, especially against Asian people. Education and research will also pay the price."

Can the world's most influential climate report carry on?

PMID: 32265540, Apr 9, 2020

Tollefson, Jeff
Nature
Level of Evidence: : 5 - Expert opinion
Type of Article: News

Summary: The Intergovernmental Panel on Climate Change (IPCC) is scheduled to release a major report next year to guide climate policies of governments around the world. However, this may be delayed due to COVID-19. Conducting science in the face of a pandemic is a challenge that may be equitable to the climate change fight itself.

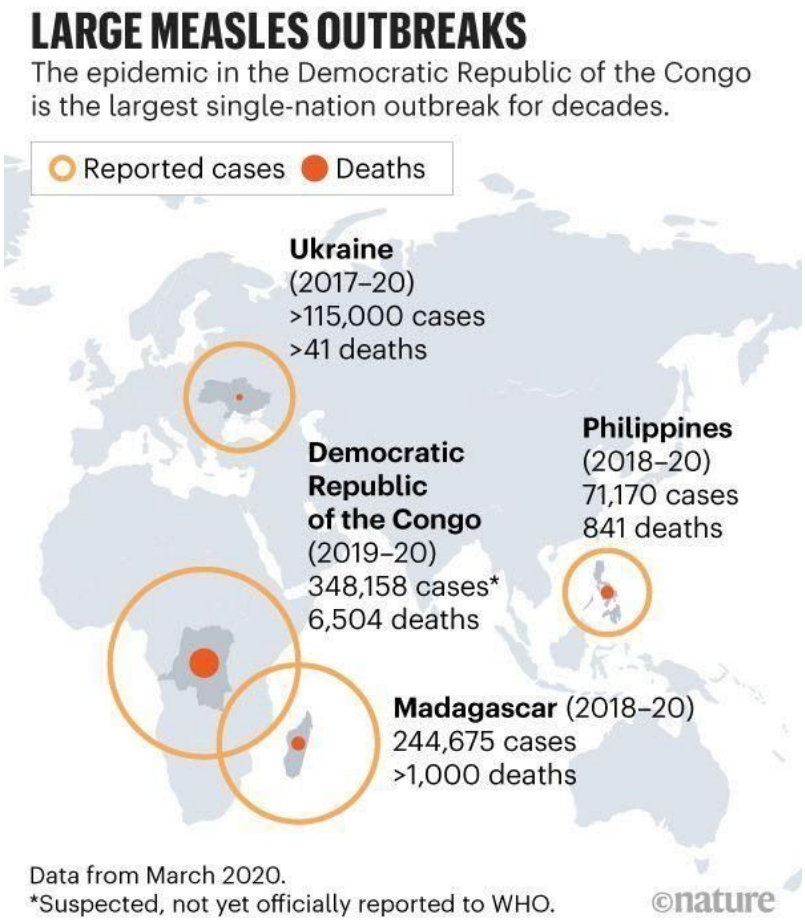


Epidemiology

Why measles deaths are surging - and coronavirus could make it worse.

PMID: 32265541, Apr 9, 2020
Roberts, Leslie
Nature
Level of Evidence: : 5 - Expert opinion
Type of Article: News

Summarizing excerpt: "The world's most contagious virus has killed thousands in the Democratic Republic of the Congo, and 23 countries have suspended measles vaccination campaigns as they cope with SARS-CoV-2... Estimates are uncertain, but the **death rate in developing countries hovers around 3–6%, and it can spike as high as 30%** in the worst outbreaks, according to the WHO... Measles tops the charts with a **reproduction number of 12–18**, which makes it the **most contagious virus** known... Because the virus is so contagious, **92–95% of a population needs to be fully immunized to ward off outbreaks**. **In the DRC, only 57% of children received even one dose of measles vaccine in 2018**, according to a UNICEF study, creating ideal conditions for the virus to explode."



COVID-19: review Indigenous peoples' data.

PMID: 32265568, Apr 9, 2020
Zavaleta, Carol

Nature
Level of Evidence: : 5 - Expert opinion
Type of Article: News
Summary: Indigenous populations in the Amazon could be particularly hard hit by COVID-19 as historically they have faced higher death rates with viral pandemics in the recent past. To better understand the effect of COVID-19 in countries with greatly varied ethnic groups, the authors propose the need to divide data by ethnicity. The authors also maintain the policy decisions of indigenous groups should be respected regarding a COVID-19 response.

Transmission & Prevention

Mask is the possible key for self-isolation in COVID-19 pandemic.

PMID: 32267002, Apr 9, 2020
Zhou, Zhi-Guo; Yue, Dong-Sheng; Mu, Chen-Lu; Zhang, Lei
Journal of Medical Virology
Level of Evidence: 5– Expert opinion
Type of Article: Comment

Summarizing Excerpt: "Ma's research shows N95 masks, medical masks, even homemade masks could block at least 90% of the virus in aerosols[1]. This study puts the debate on whether the public wear masks back on the table. Recently Science interviewed Dr. Gao, director-general of Chinese Center for Disease Control and Prevention (CDC). Dr. Gao believed that wearing a mask is an important method to prevent the rebroadcast of COVID-19 from droplets[2]. In fact, the key to effectively control the outbreak in Asian countries, especially China and South Korea, is full isolation. For individuals, the key method of adequate isolation is to wear a mask which is advised by the Chinese national healthy authority."

Analyzing Situational Awareness through Public Opinion to Predict Adoption of Social Distancing Amid Pandemic COVID-19.

PMID: 32266990, Apr 9, 2020
Qazi, Atika; Qazi, Javaria; Naseer, Khulla; Zeeshan, Muhammad; Hardaker, Glenn; Maitama, Jaafar Zubairu; Haruna, Khalid
Journal of Medical Virology
Level of Evidence: 5– Qualitative survey
Type of Article: Research

BLUF: Social distancing is highly influenced by situational awareness. Information regarding its importance in the response to the pandemic should be widely available to make the most impact.

Abstract:
COVID-19 pandemic has affected over 100 countries in a matter of weeks. People's response towards social distancing in the emerging pandemic is uncertain. In this study, we evaluated **the influence of information (formal and informal) sources on situational awareness of the public for adopting health-protective behaviors such as social distancing.** For this purpose, a questionnaire-based survey was conducted. The hypothesis proposed suggests that adoption of social distancing practices is an outcome of situational awareness which is achieved by the information sources. **Results suggest that information sources formal (p=0.001) and informal (p=0.007) were found to be significantly related to perceived understanding.** Findings also indicate that social distancing is significantly influenced by situational awareness p=0.000. It can, therefore, **be concluded that increased situational awareness in times of public health crisis using formal information sources can significantly increase the adoption of protective health behavior and in turn contain the spread of infectious diseases.**

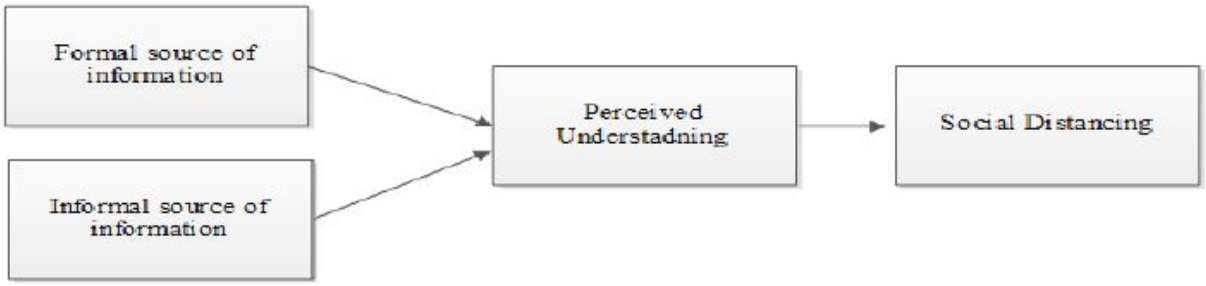


Figure 1 The proposed health care protective model This figure represents the hypothesis on which the survey was conducted. It shows that formal and informal sources of information play a significant role in developing awareness which in turn impacts the adoption of social distancing behavior.

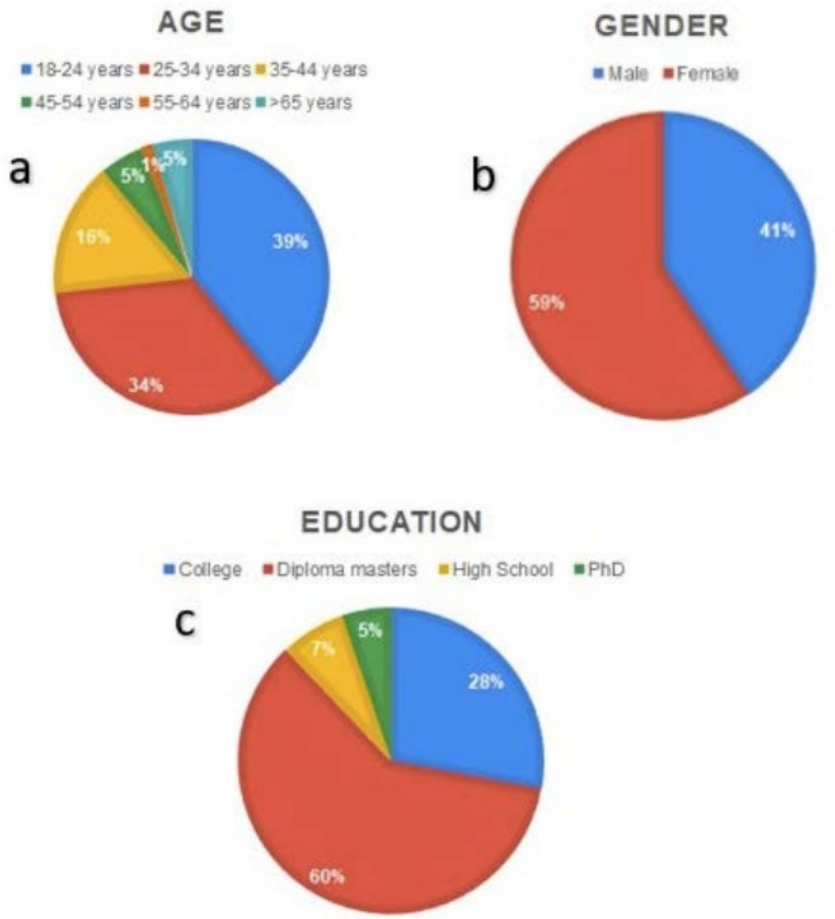


Figure 2. Demographics of Respondents The pie charts show the demographics of the respondents in terms of gender, age and education. (a) Age; 39% participants belonged to 18-24 (blue) years of age, followed by 25-34 years (red). Other age groups were 35-44 years, 45-54 years, 55-64 years and above 65. (b) Gender; 59% females (red) and 41% males (blue) participated in the study. (c) Education; majority participants i.e. 60% were diploma or masters holders (red).

Susceptibility of ferrets, cats, dogs, and other domesticated animals to SARS-coronavirus 2

PMID: 32267220, Apr 8th, 2020

Gallagher, Thomas H; Schleyer, Anneliese M

Science
Level of Evidence: Level 5- Basic Science
Type of Article: Research

BLUF: Here they evaluate the susceptibility of ferrets, cats, dogs, pigs, chickens and ducks to SARS-CoV-2. In ferrets that showed symptoms, which developed only in a minority of animals, pathological analysis showed severe lymphoplasmacytic perivasculitis, vasculitis, as well as increased inflammatory infiltrates in the alveolar spaces. Therefore ferrets are a decent model for human infection. They also detect viral RNA in various organs and in the feces of cats. Dogs showed low susceptibility to the virus. Pigs, chickens and ducks were also tested but viral RNA was undetectable in these animals.

Abstract:
Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) causes the infectious disease COVID-19, which was first reported in Wuhan, China in December, 2019. Despite the tremendous efforts to control the disease, COVID-19 has now spread to over 100 countries and caused a global pandemic. SARS-CoV-2 is thought to have originated in bats; however, the intermediate animal sources of the virus are completely unknown. Here, we investigated the susceptibility of ferrets and animals in close contact with humans to SARS-CoV-2. **We found that SARS-CoV-2 replicates poorly in dogs, pigs, chickens, and ducks, but ferrets and cats are permissive to infection.** We found experimentally that **cats are susceptible to airborne infection**. Our study provides important insights into the animal models for SARS-CoV-2 and animal management for COVID-19 control.

Diagnosis & Management

Coagulopathy and Antiphospholipid Antibodies in Patients with Covid-19.

PMID: 32268022, Apr 9, 2020

Zhang, Yan; Xiao, Meng; Zhang, Shulan; Xia, Peng; Cao, Wei; Jiang, Wei; Chen, Huan; Ding, Xin; Zhao, Hua; Zhang, Hongmin; Wang, Chunyao; Zhao, Jing; Sun, Xuefeng; Tian, Ran; Wu, Wei; Wu, Dong; Ma, Jie; Chen, Yu; Zhang, Dong; Xie, Jing; Yan, Xiaowei; Zhou, Xiang; Liu, Zhengyin; Wang, Jinglan; Du, Bin; Qin, Yan; Gao, Peng; Qin, Xuzhen; Xu, Yingchun; Zhang, Wen; Li, Taisheng; Zhang, Fengchun; Zhao, Yongqiang; Li, Yongzhe; Zhang, Shuyang

N Engl J Med
Level of Evidence: Level 4- Case study
Type of Article: Correspondence

Summary: Describe the case of 3 ICU patients with severe forms of COVID-19 had antiphospholipid antibodies and associated multifocal ischemia with leukocytosis, thrombocytopenia, elevated prothrombin time, PTT, fibrinogen and D-dimer.

Table 1. Demographic and Clinical Characteristics and Laboratory Findings.*

Characteristic	Patient 1	Patient 2	Patient 3
Demographic characteristics			
Age — yr	69	65	70
Sex	Male	Female	Male
Initial findings			
Medical history	Hypertension, diabetes, stroke	Hypertension, diabetes, coronary artery disease, no history of thrombosis	Hypertension, emphysema, nasopharyngeal carcinoma, stroke
Symptoms at disease onset	Fever, cough, dyspnea, diarrhea, headache	Fever, cough, dyspnea	Fever, fatigue, dyspnea, headache
Imaging features	Ground-glass opacity, bilateral pulmonary infiltrates	Ground-glass opacity, bilateral pulmonary infiltrates	Bilateral pulmonary infiltrates
Treatment before admission to ICU	Oseltamivir, intravenous immune globulin	Antibiotics	Antibiotics, ribavirin, rosuvastatin
Days from disease onset to thrombotic event	18	33	10
...			
Antiphospholipid antibodies	Anticardiolipin IgA, anti–β_2-glycoprotein I IgA and IgG	Anticardiolipin IgA, anti–β_2-glycoprotein I IgA and IgG	Anticardiolipin IgA, anti–β_2-glycoprotein I IgA and IgG
Imaging features	Multiple cerebral infarctions in bilateral frontal parietal occipital lobe and bilateral basal ganglia, brain stem, and bilateral cerebellar hemispheres	Multiple cerebral infarctions in right frontal and bilateral parietal lobe	Multiple cerebral infarctions in frontal lobe, right frontal parietal temporal occipital lobe, and bilateral cerebellar hemispheres

* EGFR denotes estimated glomerular filtration rate, ICU intensive care unit, and ND not determined.

Severe Acute Respiratory Syndrome Coronavirus 2-Specific Antibody Responses in Coronavirus Disease 2019 Patients.

PMID: 32267220, Apr 9, 2020
Okba, Nisreen M A; Muller, Marcel A; Li, Wentao; Wang, Chunyan; GeurtsvanKessel, Corine H; Corman, Victor M; Lamers, Mart M; Sikkema, Reina S; de Bruin, Erwin; Chandler, Felicity D; Yazdanpanah, Yazdan; Le Hingrat, Quentin; Descamps, Diane; Houhou-Fidouh, Nadhira; Reusken, Chantal B E M; Bosch, Berend-Jan; Drosten, Christian; Koopmans, Marion P G; Haagmans, Bart L
Emerg Infect Dis
Level of Evidence: Level 5- Basic science
Type of Article: Research
Summary: Using longitudinal serum samples from SARS-CoV-2 positive patients (confirmed PCR positive cases) they test commercially available serological assays (ELISAs) to examine if/when patients develop specific antibody responses. Although limited to only a few patients, they see that all patients seroconvert between days 13 and 21 post onset of symptoms. All patients had antibodies specific for the immunogenic S and N proteins of the virus, although the binding domains varied (they determine that the S1 spike subunit is most specific to SARS-CoV-2, which is important for minimizing cross reactivity for future diagnostic tests.) Importantly, all three serum samples neutralized SARS-CoV 2 infection *in vitro*. The tests seem highly specific (little to no cross reactivity with other viral proteins).

Abstract:
A new coronavirus, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), has recently emerged to cause a human pandemic. Although molecular diagnostic tests were rapidly developed, serologic assays are still lacking, yet urgently needed. **Validated serologic assays are needed for contact tracing, identifying the viral reservoir, and epidemiologic studies. We developed serologic assays for detection of SARS-CoV-2** neutralizing, spike protein–specific, and nucleocapsid-specific **antibodies**. Using serum samples from patients with PCR-confirmed SARS-CoV-2 infections, other coronaviruses, or other respiratory pathogenic infections, **we validated and tested various antigens in different in-house and commercial ELISAs. We demonstrated that most PCR-confirmed SARS-CoV-2–infected persons seroconverted by 2 weeks after disease onset.** We found that commercial S1 IgG or IgA ELISAs were of lower specificity, and sensitivity varied between the 2 assays; the IgA ELISA showed higher sensitivity. Overall, the validated assays described can be instrumental for detection of SARS-CoV-2–specific antibodies for diagnostic, seroepidemiologic, and vaccine evaluation studies.

Patterns of heart Injury in COVID - 19 and relation to outcome.

PMID: 32267000, Apr 9, 2020
Mishra, Ajay Kumar; Sahu, Kamal Kant; Lal, Amos; Sargent, Jennifer
Journal of Medical Virology
Level of Evidence: 5– Expert opinion
Type of Article: Letter
Summary: Referring to “Analysis of heart injury laboratory parameters in 273 COVID-19 patients in one hospital in Wuhan, China” by Han et al. Elevated troponin I level can be found in various types of cardiac injury and cannot be directly correlated with cytokine storm as a study measure.

Reply to Comments on 'Co-infection of SARS-CoV-2 and HIV in a patient in Wuhan city, China'.

PMID: 32266995, Apr 9, 2020
Zhu, Feng; Cao, Yang; Xu, Shuyun; Zhou, Min
Journal of Medical Virology
Level of Evidence: 5– Expert opinion
Type of Article: Letter

Summary: People living with HIV (PLWH) and receiving antiretroviral treatment have not been reported as cases of COVID-19 in Thailand, which is a country with a high prevalence of PLWH. There is a thought that antiretroviral treatment may be protective against COVID-19 and requires further exploration for validation. A recent study in China showed no benefit, and therefore the authors do not support the conclusion that PLWH may be better protected from COVID-19 than others.

PCR Assays Turned Positive in 25 Discharged COVID-19 Patients.

PMID: 32266381, Apr 9, 2020
Yuan, Jing; Kou, Shanglong; Liang, Yanhua; Zeng, JianFeng; Pan, Yanchao; Liu, Lei
Clinical Infectious Diseases
Level of Evidence: 3 – Non-randomized cohort follow-up study without controls
Type of Article: Research

Abstract:
We report the observation that **14.5% of COVID-19 patients had positive RT-PCR testing again after discharge**. We describe correlations between laboratory parameters and treatment duration (r= -0.637; p=0.002) and time to virus recrudescence (r= 0.52; p=0.008) respectively, suggesting the **need for additional measures to confirm illness resolution** in COVID-19 patients.

Therapeutics

Reporting of all cardiac medications and their outcome in COVID - 19.

PMID: 32266993, Apr 9, 2020
Mishra, Ajay Kumar; Sahu, Kamal Kant; Lal, Amos
Journal of Medical Virology
Level of Evidence: 5– Expert opinion
Type of Article: Letter
Summary: Referring to “Organ- protective effect of Angiotensin Converting Enzyme 2 and its Effect on the prognosis of COVID -19” by Cheng et al. Higher numbers of ACE2 receptors have not been established as a cause of higher organ damage in COVID-19 patients. Studies analyzing the possible harms of RAAS inhibitors have not been fully analyzed and require better reporting of drug data to establish a relationship.

Comment on "Organ-protective Effect of Angiotensin-converting Enzyme 2 and its Effect on the Prognosis of COVID-19".

PMID: 32266994, Apr 9, 2020
Cure, Erkan; Cumhur Cure, Medine
Journal of Medical Virology
Level of Evidence: 5– Expert opinion
Type of Article: Comment
Abstract: We read with great interest the article by Cheng H et al. The authors mentioned that angiotensin-converting enzyme 2 (ACE2) is protective against novel coronavirus disease 2019 (COVID-19). We would like to explain how **cytosolic pH increases the COVID-19 infection by affecting the ACE2.** In addition, we would like to mention that **amiloride, which increases the cytosolic pH, can be used in the COVID-19 treatment.**

Inquiring into Benefits of Independent Activation of Non-Classical Renin-Angiotensin System in the Clinical Prognosis and Reduction of COVID-19 mortality.

PMID: 32266375, Apr 9, 2020
Alvarez-Aragon, Luis Miguel; Cuesta-Munoz, Antonio Luis; Alvarez-Lopez, Inmaculada
Clinical Infectious Diseases
Level of Evidence: 5 – Expert opinion
Type of Article: Comment
Summary: ACE2 is implicated as a receptor for COVID-19. It is also a component in the non-classical RAS pathway, ACE2-Angiotensin(1-2)-MasR. In vitro studies of SGLT2 inhibitors used to treat diabetes have shown an increase in Angiotensin(1-7). This could possibly lead to an activation of the non-classical RAS pathway in the lungs. The authors propose questions regarding the possibility that diabetics treated with SLGT2 inhibitors might present with milder respiratory symptoms and have a better clinical prognosis.