Christian Hoffmann
Bernd Sebastian Kamps

COVID REFERENCE top10
Daily Science
COVID Reference Top 10

Daily Science
Preface

Here we publish in a single PDF the daily Top 10 scientific papers we have presented ever since COVID Reference’s first edition on 29 March 2020. There is no secret to our procedure: the daily scanning of the literature helps us to stay afloat in the never-ending waves of new publications about SARS-CoV-2 and COVID-19. Many papers discussed in the Top 10 will eventually make it into subsequent editions of COVID Reference.

We dedicate this book to our students. May this selection of approx. 1,000 fine articles and full-text links deepen their understanding of the new coronavirus and prepare them for the challenges ahead.

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15 July 2020
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COVID Reference Top 10
22 Papers

If you don’t read anything, read at least the following 22 papers.


4. Yu F, Yan L, Wang N, et al. Quantitative Detection and Viral Load Analysis of SARS-CoV-2 in Infected Patients. Clin Infect Dis. 2020 Mar 28. PubMed: https://pubmed.gov/32221523. Fulltext: https://doi.org/10.1093/cid/ciaa345 (OUTSTANDING) | Is sputum sufficient for diagnosis? In a total of 323 samples from 76 pts, the average viral load in sputum (17429 copies/test) was significantly higher than in throat swabs (2552) and nasal swabs (651). Viral load was also higher in the early and progressive stages than in the recovery stage. If these data are confirmed, collection of specimen would be much easier.

5. Wölfel R, Corman VM, Guggemos W. et al. Virological assessment of hospitalized patients with COVID-2019. Nature 2020, April 1. Full-text: https://doi.org/10.1038/s41586-020-2196-x (OUTSTANDING) | Important work, showing active virus replication in upper respiratory tract tissues (in contrast to SARS). In a detailed virological analysis of nine cases, pharyngeal virus shedding was very high during the first week of symptoms (peak at $7.11 \times 10^8$ RNA copies per throat swab, day 4), more than 1000 times higher than seen with SARS-CoV. Infectious virus was readily...
isolated from throat- and lung-derived samples, but not from stool samples, in spite of high virus RNA concentration. Blood and urine never yielded virus. Shedding of viral RNA from sputum continued after the end of symptoms.

6. Yan R, Zhang Y, Li Y, Xia L, Guo Y, Zhou Q. **Structural basis for the recognition of SARS-CoV-2 by full-length human ACE2.** Science. 2020 Mar 27;367(6485):1444-1448. PubMed: [https://pubmed.gov/32132184](https://pubmed.gov/32132184). Full-text: [https://doi.org/10.1126/science.abb2762](https://doi.org/10.1126/science.abb2762) | Using cryo–electron microscopy, it is shown how SARS-CoV-2 binds to human cells. The first step in viral entry is the binding of the viral trimeric spike protein to the human receptor angiotensin-converting enzyme 2 (ACE2). Authors present the structure of human ACE2 in complex with a membrane protein that it chaperones, B0AT1. The structures provide a basis for the development of therapeutics targeting this crucial interaction.

7. Lan J, Ge J, Yu J, et al. **Structure of the SARS-CoV-2 spike receptor-binding domain bound to the ACE2 receptor.** Nature. 2020 May;581(7807):215-220. PubMed: [https://pubmed.gov/32225176](https://pubmed.gov/32225176). Full-text: [https://doi.org/10.1038/s41586-020-2180-5](https://doi.org/10.1038/s41586-020-2180-5) | To elucidate the SARS-CoV-2 RBD and ACE2 interaction at a higher resolution/atomic level, authors used X-ray crystallography. Binding mode was very similar to SARS-CoV, arguing for convergent evolution of both viruses. The epitopes of two SARS-CoV antibodies targeting the RBD were also analysed with the SARS-CoV-2 RBD, providing insights into the future identification of cross-reactive antibodies.

8. Leung NHL, Chu DKW, Shiu EYC, et al. **Respiratory virus shedding in exhaled breath and efficacy of face masks.** Nat Med. 2020 May;26(5):676-680. PubMed: [https://pubmed.gov/32371934](https://pubmed.gov/32371934). Full-text: [https://doi.org/10.1038/s41591-020-0843-2](https://doi.org/10.1038/s41591-020-0843-2) | Do face masks work? Yes, but it depends. This important study from Hong Kong (performed 2013-16) quantified virus in respiratory droplets and aerosols in exhaled breath. In total, 111 participants (infected with seasonal coronavirus, influenza or rhinovirus) were randomized to wear (or not) a simple surgical face mask. Results suggested that masks could be used by ill people to reduce onward transmission. But note the small numbers: in respiratory droplets, seasonal coronavirus was found in 0/11 droplets
(aerosols: 0/11) from participants wearing face masks, compared to 3/10 (aerosols: 4/10) without masks. Influenza viruses were detected in 1/27 (aerosols 6/27!) with face masks, compared to 6/23 (8/23) without. For rhinovirus, there were no significant differences at all. Of note, authors also identified virus in some participants who did not cough at all during the 30-min exhaled breath collection, suggesting droplet and aerosol routes of transmission from individuals with no obvious signs or symptoms.

9. He X, Lau EHY, Wu P, et al. Temporal dynamics in viral shedding and transmissibility of COVID-19. Nat Med. 2020 Apr 15. PubMed: https://pubmed.gov/32296168. Full-text: https://doi.org/10.1038/s41591-020-0869-5 ●● (OUTSTANDING) | Important work on viral shedding: this may begin 2 to 3 days before the appearance of the first symptoms and infectiousness profile may more closely resemble that of influenza than that of SARS. Analyzing a total of 414 throat swabs in 94 patients, the highest viral load was found at the time of symptom onset. Infectiousness started from 2.3 days (95% CI, 0.8–3.0 days) before symptom onset and peaked at 0.7 days (95% CI, −0.2–2.0 days) before symptom onset. The authors estimated that 44% (95% CI 25–69%) of secondary cases were infected during the index cases’ presymptomatic stage. Infectiousness was estimated to decline quickly within 7 days.

10. Long QX, Liu BZ, Deng HJ, et al. Antibody responses to SARS-CoV-2 in patients with COVID-19. Nat Med. 2020 Jun;26(6):845-848. PubMed: https://pubmed.gov/32350462. Full-text: https://doi.org/10.1038/s41591-020-0897-1 ●● (OUTSTANDING) | One of the largest studies to date, reporting on acute antibody responses (using magnetic chemiluminescence enzyme immunoassay) in 285 patients (mostly non-severe COVID-19, 39 treated at ICU). Within 19 days after symptom onset, 100% of patients tested positive for antiviral IgG. Seroconversion for IgG and IgM occurred simultaneously or sequentially. Both IgG and IgM titers plateaued within 6 days after seroconversion. The median day of seroconversion for both IgG and IgM was 13 days post-symptom onset. No association between plateau IgG levels and clinical characteristics of the patients was found.


13. Grifoni A, Weiskopf D, Ramirez SI, et al. **Targets of T Cell Responses to SARS-CoV-2 Coronavirus in Humans with COVID-19 Disease and Unexposed Individuals.** Cell. 2020 Jun 25;181(7):1489-1501.e15. PubMed: [https://pubmed.gov/32473127](https://pubmed.gov/32473127). Full-text: [https://doi.org/10.1016/j.cell.2020.05.015](https://doi.org/10.1016/j.cell.2020.05.015) (OUTSTANDING) | Cellular response is a major knowledge gap. This important study identified circulating SARS-CoV-2-specific CD8 and CD4 T cells in around 70 and 100% of 20 COVID-19 convalescent patients, respectively. CD4 T cell responses to the spike protein were robust and correlated with the magnitude of IgG titers. Of note, the authors detected SARS-CoV-2-reactive CD4 T cells in 40-60% of unexposed individuals, suggesting cross-reactive T cell recognition between circulating seasonal coronaviruses and SARS-CoV-2.

and inappropriate inflammatory response to SARS-CoV-2 which is imbalanced with regard to controlling virus replication versus activation of the adaptive immune response. It is defined by low levels of type I and III interferons juxtaposed to elevated chemokines and high expression of IL-6. The authors propose that reduced innate antiviral defenses coupled with exuberant inflammatory cytokine production are the defining and driving features of COVID-19. Given this dynamic, treatments for COVID-19 have less to do with the IFN response and more to do with controlling inflammation.

15. Zhang X, Tan Y, Ling Y, et al. **Viral and host factors related to the clinical outcome of COVID-19.** Nature. 2020 May 20. PubMed: [https://pubmed.gov/32434211](https://pubmed.gov/32434211). Full-text: [https://doi.org/10.1038/s41586-020-2355-0](https://doi.org/10.1038/s41586-020-2355-0) | Viral variants do not affect outcome. This important study on 326 cases found at least two major lineages with differential exposure history during the early phase of the outbreak in Wuhan. Patients infected with these different clades did not exhibit significant difference in clinical features, mutation rate or transmissibility. Lymphocytopenia, especially a reduced CD4+ and CD8+ T cell counts upon admission, was predictive of disease progression. High levels of IL-6 and IL-8 during treatment were observed in patients with severe or critical disease and correlated with decreased lymphocyte count. The determinants of disease severity seemed to stem mostly from host factors such as age, lymphocytopenia, and its associated cytokine storm.

16. Docherty AB, Harrison EM, Green CA, et al. **Features of 20,133 UK patients in hospital with covid-19 using the ISARIC WHO Clinical Characterisation Protocol: prospective observational cohort study.** BMJ. 2020 May 22;369:m1985. PubMed: [https://pubmed.gov/32444460](https://pubmed.gov/32444460). Full-text: [https://doi.org/10.1136/bmj.m1985](https://doi.org/10.1136/bmj.m1985) | Clinical data from 20,133 patients, admitted to (or diagnosed in) 208 acute care hospitals in the UK until April 19. Median age was 73 years (interquartile range 58-82) and 60% were men. Comorbidities were common, namely chronic cardiac disease (31%), diabetes (21%), non-asthmatic chronic pulmonary disease (18%). Overall, 41% of patients were discharged alive, 26% died, and 34% continued to receive care. 17% required admission to high dependency or intensive care units; of these, 28% were discharged alive, 32% died, and 41% continued to receive care.
Of those receiving mechanical ventilation, 17% were discharged alive, 37% died, and 46% remained in hospital. Increasing age, male sex, and comorbidities including chronic cardiac disease, non-asthmatic chronic pulmonary disease, chronic kidney disease, liver disease and obesity were associated with higher mortality in hospital.


Doors and windows open! Important study, analyzing droplet production due to coughs and speech by measuring the droplet size distribution, travel distance and velocity, and the airborne time in relation to the level of air ventilation (no ventilation, mechanical ventilation only, and mechanical ventilation supported by the opening of an entrance door and a small window). In the best ventilated room, after 30 s the number of droplets had halved, whereas with no ventilation this took about 5 min!


In total, 821 asymptomatic participants were randomized to receive hydroxychloroquine or placebo within 4 days after exposure (88% with a high-risk exposure). Incidence of confirmed SARS-CoV-2 was 11.8% with CQ and 14.3% with placebo. Side effects were more common with hydroxychloroquine than with placebo (40.1% vs. 16.8%), but no serious adverse reactions were reported. This is bad news because after high-risk or moderate-risk exposure to Covid-19, HCQ did not prevent infection when used as post-exposure prophylaxis within 4 days after exposure.


Outstanding essay about what little is currently known about the evolution of SARS-CoV-2. At present, there is a lack of compelling evidence that any existing variants impact the progression, severity, or transmission of COVID-19 in an adaptive manner. The authors discuss
the potential evolutionary routes that SARS-CoV-2 might take and dispel some of the current misinformation that is circulating in the media.

20. Major J, Crotta S, Llorian M, et al. **Type I and III interferons disrupt lung epithelial repair during recovery from viral infection**. *Science*. 2020 Jun 11:eabc2061. PubMed: [https://pubmed.gov/32527928](https://pubmed.gov/32527928). Full-text: [https://doi.org/10.1126/science.abc2061](https://doi.org/10.1126/science.abc2061) | **Key message:** Interferon may be helpful during early infection and harmful at later stages. IFN-λ mainly signals in epithelia, inducing localized antiviral immunity, and has a key role in the reduction of epithelial proliferation and differentiation during lung repair. In animal and cell experiments, the authors show that IFN-induced p53 directly reduces epithelial proliferation and differentiation, increasing disease severity and susceptibility to bacterial superinfections. Excessive or prolonged IFN production may aggravate viral infection by impairing lung epithelial regeneration.

21. Pfeifer M, Ewig S, Voshaar T, et al. **Position Paper for the State-of-the-Art Application of Respiratory Support in Patients with COVID-19**. *Respiration*. 2020 Jun 19:1-21. PubMed: [https://pubmed.gov/32564028](https://pubmed.gov/32564028). Full-text: [https://doi.org/10.1159/000509104](https://doi.org/10.1159/000509104) | **Important statements including observations about the pathophysiology of acute respiratory failure (ARF).** Pulmonary damage in advanced COVID-19 often differs from acute respiratory distress syndrome (ARDS). Two types (type L and type H) are differentiated, corresponding to early- and late-stage lung damage. This differentiation should be taken into consideration in respiratory support. Based on current knowledge, inhalation therapy, nasal high-flow therapy (NHF), continuous positive airway pressure (CPAP), or non-invasive ventilation (NIV) can be performed without an increased risk of infection to staff if PPE is provided. In ARF, NIV should be carried out in an intensive care unit or a comparable setting by experienced staff. If the ARF progresses under CPAP/NIV, intubation should be implemented without delay in patients who do not have a “do not intubate”.

protein abundance and phosphorylation represent a powerful tool to eluci- 
date mechanisms of viral pathogenesis by providing a snapshot of how 
cellular pathways and processes are rewired upon infection. Using a 
quantitative mass spectrometry-based phosphoproteomics survey of 
SARS-CoV-2 infection in Vero E6 cells, the 78 (!) authors present the glob- 
al phosphorylation and protein abundance landscape of SARS-CoV-2 in-
fection, map phosphorylation changes to disrupted kinases and path-
ways, and use these profiles to find drugs with the potential to treat 
SARS-CoV-2 infection. In total, 87 compounds (10 FDA-approved drugs) 
were identified.
Pre-Top 10 Era
New Year 2020

30 December


This email is the first message that alerted the world to what was to become the worst health crisis in 100 years.

8 January


The first news report in a major scientific journal. A day later, an updated version reports a new coronavirus as the likely cause of the pneumonia-like illness. The virus’s genome is sequenced.

14 January


These two articles by Hui et al. and Bogoch et al. relate the questioning of researchers during the first two SARS-CoV-2 weeks of the year 2020. At that neonatal stage of the pandemic there was still “no clear evidence of human to human transmission.”

On January 14, SARS-CoV-2 was still called 2019-nCov.

The authors evaluate international travel patterns from Wuhan in order to anticipate the spread of a new coronavirus. The top 7 destination cities for passengers arriving from Wuhan (January to March 2018) were Bangkok, Hong Kong, Tokyo, Taipei, Phuket, Seoul and Singapore.

**17 January**

Imai N et al. (Imperial College London) **Estimating the potential total number of novel Coronavirus cases in Wuhan City, China.** Full-text: https://doi.org/10.25561/77149

The authors contradict official figures published by the People's Republic of China, estimating that a total of more than 1,700 cases of 2019-nCoV in Wuhan City had onset of symptoms by 12 January 2020 – while officially, less than 100 cases were reported by mid-January. How did they do the math? They analyzed the volume of international travel from Wuhan.

**24 January**


The first clinical paper about what would later be called COVID-19. The authors describe 41 patients with a median age of 49 years admitted by 2 January to Jin Yin-Tan Hospital (金银潭医院), Wuhan. Thirteen patients (32%) needed ICU care and 6 patients died (15%). The paper offers the first glimpse at laboratory prognostic markers.

The first paper on person-to-person transmission. It is also an excellent exercise: try and find your way through the intricate relationships of a family of 6 travellers from Shenzhen (two grandparents, their daughter and son-in-law and two grandchildren) and their five relatives in Wuhan.

30 January


The second clinical paper, again from Jin Yin-Tan Hospital. In this extended investigation of the previous report (see 24 January, Huang C et al.), 49 of 99 patients had a history of exposure to the Huanan seafood market. The average age of the patients was 55.5 years. Two thirds of the patients were men and 51% had previous chronic diseases. The authors identify older men with comorbidities as a special risk group.


The authors report the case of a businesswoman from Shanghai who infected at least one business partner during a trip to Germany. During her stay, she had apparently been well with no signs or symptoms of infection but had become ill on her flight back to China, where she tested positive for SARS-CoV-2 a few days after her return. The authors suggest that asymptomatic persons may be potential sources of SARS-CoV-2 infection. (And right they were! To clarify whether the index patient in question has been correctly described as asymptomatic, the authors spoke with her by telephone on 5 February 2020. Read the summary of the call.)
3 February


The authors report the identification and characterization of a new coronavirus and obtain full-length genome sequences from five patients at an early stage of the outbreak. The sequences are almost identical and share 80% sequence identity to SARS-CoV. The virus is also 96% identical at the whole-genome level to a bat coronavirus. The authors confirm that the new virus uses the same cell entry receptor—angiotensin converting enzyme II (ACE2)—as SARS-CoV.

4 February


The paper that was at the origin of the hydroxychloroquine frenzy. In human trials, hydroxychloroquine was subsequently shown to have no clinical benefit. Likewise, the clinical effect of remdesivir is, at best, modest.

5 February


The first discussion of host-directed therapies. The authors remind us that during the SARS-CoV-1 and MERS-CoV outbreaks, several unique opportunities to evaluate a range of treatment interventions were missed. The SARS-CoV-2
CoV-2 pandemic may elucidate questions about coronavirus pathogenesis that remained unanswered during the previous coronavirus epidemics.

7 February


The first Chinese consensus statement on pediatric COVID-19 informs that most infected children have mild clinical manifestations. They have no fever or symptoms of pneumonia with a good prognosis. Most of them recover within 1–2 weeks after disease onset. Only a few children progress to lower respiratory infections.

12 February


A group of physicians from the Chinese Thoracic Society propose to use corticosteroids prudently in critically ill patients with 2019-nCoV pneumonia; to be particularly cautious with patients who have hypoxemia due to underlying diseases or who regularly use corticosteroids for chronic diseases; and to use low-to-moderate doses (≤0.5 – 1 mg/kg per day methylprednisolone or equivalent) for ≤ 7 days.


The authors report 9 pregnant women with laboratory-confirmed COVID-19 pneumonia who were admitted to Zhongnan Hospital of Wuhan University. The clinical characteristics were similar to those reported for non-pregnant adult patients who developed COVID-19 pneumonia. The authors find no evidence for intrauterine SARS-CoV-2 infection in late pregnancy. A comment of

**21 February**


The authors describe a familial cluster of 5 patients with COVID-19 pneumonia in Anyang, China. Four were women, and ages ranged from 42 to 57 years. None of the patients had visited Wuhan or been in contact with any other people who had traveled to Wuhan – except an asymptomatic family member who lived in Wuhan and traveled to Anyang on January 10, 2020. The authors warn that if their findings of presumed transmission by an asymptomatic carrier are replicated, the prevention of COVID-19 infection would prove challenging.

**24 February**


A bonanza of data at a fairly early stage of the pandemic – and shocking numbers at a moment when local epidemics were taking off in Europe. A must-read for everyone.

**Spectrum of disease:**
- Mild: 81%
- Severe: 14%
- Critical: 5%

**Case-fatality rate:**
- 14.8% in patients aged ≥ 80 years
- 8.0% in patients aged 70-79 years
* Summaries of the articles from 24 February until 27 March will be added soon. *


The first description of two patients who had positive results on RT-PCR a day before symptom onset, suggesting that infected individuals can be infectious before they become symptomatic.


**25 February**


**26 February**


**27 February**


28 February


March 2020

3 March

5 March

10 March

13 March
16 March

Ferguson et al. (Imperial College COVID-19 Response Team) Impact of non-pharmaceutical interventions (NPIs) to reduce COVID-19 mortality and healthcare demand. 16 March 2020. Full-text: https://doi.org/10.25561/77482 ● (IMPORTANT)

17 March


18 March


19 March


20 March


21 March


23 March


24 March


25 March


26 March


27 March

Daily Top 10
30 March


Brief overview of current research topics from opinion leaders.

Hospital


Detailed practical recommendations, based on experiences during the Italian outbreak. Key elements of clinical management, airway management, personal protective equipment and non-technical aspects are described.


Consented principles from the UK Association of Anaesthetists for airway management, including emergency tracheal intubation, predicted or unexpected difficult tracheal intubation, cardiac arrest, anesthetic care and tracheal extubation.


Brief overview of therapeutic options for severe acute respiratory distress syndrome.
Clinical


First study on immunologic characteristics of 21 patients (retrospective). Total lymphocytes but also CD4+ and CD8+ T cells decreased in nearly all patients, and were markedly lower in severe cases (294, 178 and 89 x 10^6/L) than moderate cases (641, 382 and 254 x 10^6/L). Immunological markers may be of importance due to their correlation with disease severity in COVID-19.

Risk factors, comorbidities


Important paper that highlights the severity of COVID-19 in older people. A total of 167 confirmed cases affecting 101 residents in a long-term care facility, 50 health care personnel (HCP), and 16 visitors. The case fatality rate for residents was 33.7% (34 of 101) and 0% among HCP.


More on the role of comorbidities. 1,590 hospitalised patients from 575 hospitals across mainland China. After adjusting for age and smoking status, COPD [hazards ratio (HR) 2.681, 95% confidence interval (95%CI) 1.424-5.048], diabetes (HR 1.59, 95%CI 1.03-2.45), hypertension (HR 1.58, 95%CI 1.07-2.32) and malignancy (HR 3.50, 95%CI 1.60-7.64) were risk factors of reaching endpoints.

Interesting case report on myopericarditis with systolic dysfunction which highlights cardiac involvement as a complication, even without symptoms and signs of interstitial pneumonia.


Inspiring thoughts on treatment and care for patients with cancer. No new data.


Retrospective case series of 113 deceased patients. The median time from disease onset to death was 16 (IQR 12.0-20.0) days. Common complications observed more frequently in deceased patients included acute respiratory distress syndrome (100%), type I respiratory failure (51%), sepsis (100%), acute cardiac injury (77%), heart failure (49%), alkalosis (40%), hyperkalemia (37%), acute kidney injury (25%), and hypoxic encephalopathy (20%).


Discussion of a possible link between NSAIDs and both respiratory and cardiovascular adverse effects in COVID-19. Recommends pragmatic approach: regular NSAID use should probably not be recommended first line.

Pregnancy, pediatric patients

Updated and very detailed recommendations for the clinical management for pregnant women and their newborns with SARS-CoV-2. Experience from Wuhan. No data.


Among 6 mothers with confirmed COVID-19, SARS-CoV-2 was not detected in the serum or throat swab by RT-PCR in any of their newborns. However, virus-specific antibodies (IgG) were detected in 5 neonatal blood sera samples.

31 March

Diagnostics


Is sputum sufficient for diagnosis? In a total of 323 samples from 76 pts, the average viral load in sputum (17429 copies/test) was significantly higher than in throat swabs (2552) and nasal swabs (651). Viral load was also higher in the early and progressive stages than in the recovery stage. If these data are confirmed, collection of specimen would be much easier.


More on antibody response. Among 173 patients, the seroconversion rate (median time) for Ab, IgM and IgG was 93.1% (11 days), 82.7% (12 days) and 64.7% (14 days), respectively. A higher titer of Ab was independently associated with a worse clinical classification.

Comorbidities

Vaduganathan M, Vardeny O, Michel T, McMurray JV, Pfeffer MA, Solomon SD. Renin–Angiotensin–Aldosterone System Inhibitors in Patients with

Fantastic review of an interdisciplinary expert panel on the use, risks and benefit of RAAS inhibitors (ACE inhibitors and sartans) in the COVID-19 era. Bottom line: We don't know enough. Until further data are available, RAAS inhibitors can be continued.


A few new thoughts on HIV infection and COVID-19.


First case report of patient with undiagnosed HIV infection (low CD4 counts), recovering from a coronavirus-related pneumonia. Argues against deleterious effect of HIV.

Pregnancy


Case report on a cesarean section, suggesting that mother-to-child transmission is unlikely.

Epidemiology


Excellent work with implications for future outbreaks and the time after lockdown. Using a stochastic transmission model, contact tracing and isolation of cases was sufficient to control a new outbreak.
Clinical


More than “Ok, COVID-19 has reached the US”: this paper describes in detail the demographic characteristics, coexisting conditions, imaging findings, and outcomes among 21 critically ill patients admitted at ICUs.


An older patient with COVID-19 and non-specific symptoms is described, as well as another case with heart failure, mimicking COVID-19. Both cases underline the need for extensive testing.

Vaccine


Excellent review on vaccine development. Outlook on new platforms for RNA and DNA vaccines that can be made quickly because they require no culture or fermentation, instead using synthetic processes. Hope and despair.
April 2020

1 April

Virology


Analysis of 56 genomic sequences from distinct patients, showing high sequence similarity (> 99%). A few variable genomic regions exist, mainly at the ORF8 locus (coding for accessory proteins).


Consensus statement (a little wordy), defining the place of SARS-CoV-2 (provisionally named 2019-nCoV) within the Coronaviridae.


Important work on viral entry, using a rapid and cost-effective platform with allows to functionally test large groups of viruses for zoonotic potential. Host protease processing during viral entry is a significant barrier for several lineage B viruses. However, bypassing this barrier allows several coronaviruses to enter human cells through an unknown receptor.

Clinical


Defining the case fatality rate (CFR) remains challenging and simply dividing the number of deaths by the number of cases can be misleading. Using indi-
individual-case data and after careful modelling, CFR was 1.38% (95% CI, 1.23–1.53) in this analysis. The mean duration from symptom onset to death was 17.8 days (95% 16.9–19.2).

Comorbidities


Don’t forget people with mental health conditions! A few thoughts on these patients who could be more substantially affected, resulting in relapses or worsening of an already existing mental health condition because of high susceptibility to stress compared with the general population.


And don’t forget the staff! Some thoughts on how to maintain staff mental health during such a crisis.


Interesting case report on a patient with CLL. Clinical and biochemical features of COVID-19 might be partly masked by coexisting CLL. Longer incubation period was presumed.

Diagnostics


Among 133 patients, 22 patients who had positive RT-qPCR results for SARS-CoV-2 in the sputum or feces (up to 39 and 13 days, respectively) after pharyngeal swabs became negative. Although uncontrolled, this study raises concern about whether patients with negative pharyngeal swabs are truly virus-free, or sampling of additional body sites is needed.
Therapy and Procedures

Harsh criticism at the Gautret-Study (on a potential benefit of hydroxychloroquine), making clear that essential standards of data generation and interpretation were lacking, leading to undesirable downstream effects.


Extensive comment on someone’s swanky twitter claiming that the combination of HCQ and azithromycin has “a real chance to be one of the biggest game changers in the history of medicine” (March 21). Careful review about the risks of HCQ and how pretentious dissemination of overpromised data may cause severe harm.

2 April

Epidemiology

Review of data and inconsistencies in official guidelines and expert opinions about face masks, confusing both the public and health care professionals. Still wondering, after reading this review.


Morbidity in China exhibited a Gaussian distribution (peak 50-59 years), while morbidity in ROK had a bimodal distribution (peak 20-29 years). Careless youth? Authors speculate that this was possibly due to differences in public
health intervention practices and age-related sociocultural factors (lower rates of compliance among younger people with social distancing and self-quarantine recommendations).


Elegant models illustrating the potential impact of the COVID-19 pandemic globally and highlighting the challenging decisions faced by governments. In the absence of interventions, COVID-19 would have resulted in 7.0 billion infections and 40 million deaths globally this year. Mitigation strategies focusing on shielding the elderly (60% reduction in social contacts) and slowing but not interrupting transmission (40% reduction) could reduce this burden by half, saving 20 million lives.


Complex epidemiological models, showing that border controls, airport screening and travel restrictions likely slowed the rate of exportation from mainland China to other countries, but were insufficient to contain the global spread of COVID-19. Rapid contact tracing remains essential.

Clinical


In a case series from China, 12/38 patients (32%, more common in severe COVID-19 cases) had ocular manifestations consistent with conjunctivitis, including conjunctival hyperemia, chemosis, epiphora, or increased secretions. Two patients had positive PCR results from conjunctival swabs.

Brief review on the potential for direct and indirect adverse effects of SARS-CoV-2 on the heart and especially so in those with already established heart disease.

Comorbidities

Thoughts on diabetes management, glucocorticoid use, pituitary or other neuroendocrine diseases.


No, the situation in the US does not differ from other countries. Among 7,162 patients with underlying health conditions or potential risk factors reported to the CDC, those with these conditions were more likely admitted to the hospital and to an ICU. And yes, “persons with underlying health conditions who have symptoms of COVID-19 should immediately contact their health care provider”.

Diagnostics

Important work, showing active virus replication in upper respiratory tract tissues (in contrast to SARS). In a detailed virological analysis of nine cases, pharyngeal virus shedding was very high during the first week of symptoms (peak at 7.11 × 10⁸ RNA copies per throat swab, day 4), more than 1000 times higher than seen with SARS-CoV. Infectious virus was readily isolated from throat- and lung-derived samples, but not from stool samples, in spite of high
virus RNA concentration. Blood and urine never yielded virus. Shedding of viral RNA from sputum continued after the end of symptoms.

Treatment

Some new ideas on treatment. Using a computer-aided drug discovery protocol, possible covalent drugs targeting 3CLpro protease of SARS-CoV-2 were identified. For drug repurposing, the following ones (indication) might have priority: Telcagepant (migraine), Vidupiprant (asthma), Poziotinib (breast cancer), and Fostamatinib (rheumatoid arthritis).

3 April
Virology

Using cryo–electron microscopy, it is shown how SARS-CoV-2 binds to human cells. The first step in viral entry is the binding of the viral trimeric spike protein to the human receptor angiotensin-converting enzyme 2 (ACE2). Authors present the structure of human ACE2 in complex with a membrane protein that it chaperones, B0AT1. The structures provide a basis for the development of therapeutics targeting this crucial interaction.


To elucidate the SARS-CoV-2 RBD and ACE2 interaction at a higher resolution/atomic level, authors used X-ray crystallography. Binding mode was very similar to SARS-CoV, arguing for convergent evolution of both viruses. The epitopes of two SARS-CoV antibodies targeting the RBD were also analysed with the SARS-CoV-2 RBD, providing insights into the future identification of cross-reactive antibodies.

How well does SARS-CoV-2 recognize hACE2? Better than other coronaviruses. Compared to SARS-CoV and RaTG13 (isolated from bats), ACE2 binding affinity is higher. Functionally important epitopes in SARS-CoV-2 RBM are described that can potentially be targeted by neutralizing antibody drugs.

**Epidemiology**


A cluster-spreading event in Huai’an, China, in which a patient may have transmitted the virus to 8 other individuals via bathing in a public bath center (sauna, bath, 25 to 41°C and humidity of approximately 60%). Transmissibility appears not to be reduced in warm and humid conditions.


Still looking for patient zero in Italy (not found). However, this important study of 6,000 laboratory-confirmed cases tracks how the outbreak unfolded in the region. By the time the first case was detected, the virus had already spread (since January) to most towns and cities in southern Lombardy.

**Comorbidities**


A joint statement of the European Academy of Allergology and Clinical Immunology, following the results of a questionnaire. Bottom line: Stopping intranasal steroids is not advised, until we know better.
Clinical


Thoughts about how to communicate as a clinician in this crisis. Talking maps for communication tasks that none of us have faced before, including facilitating virtual goodbyes between family members and dying patients with restricted access. And explaining decisions on why a particular patient will not receive a scarce resource: “I can see how it feels unfair”. Phew. Could anyone ever have imagined that?

Procedures


Brief workflow to prevent SARS-CoV-2 transmission in the endoscopy center.

Diagnostics


Is the virus everywhere? No. Not in the vaginal fluid (of 10 women with severe COVID-19).


Case report of a patient who did not produce sputum. Gargle lavage testing was sensitive. If confirmed by larger studies, this can be done by patients themselves without putting healthcare professionals at increased risk.
Epidemiology


Using an analytically solvable model, authors show that viral spread is too fast to be contained by manual contact tracing. Spread could be controlled if this process was faster, more efficient and happened at scale. A contact-tracing app that builds a memory of proximity contacts and immediately notifies contacts of positive cases can achieve epidemic control if used by enough people, without need for lockdowns.


Infection-control measures such as national lockdowns in many European countries are reducing the spread of coronavirus. Across 11 countries, between 21,000 and 120,000 deaths were probably avoided by the end of March, according to a model by a group at Imperial College London.


Do face masks work? Yes, but it depends. This important study from Hong Kong (performed 2013-16) quantified virus in respiratory droplets and aerosols in exhaled breath. In total, 111 participants (infected with seasonal coronavirus, influenza or rhinovirus) were randomized to wear (or not) a simple surgical face mask. Results suggested that masks could be used by ill people to reduce onward transmission. But note the small numbers: in respiratory droplets, seasonal coronavirus was found in 0/11 droplets (aerosols: 0/11) from participants wearing face masks, compared to 3/10 (aerosols: 4/10) without masks. Influenza viruses were detected in 1/27 (aerosols: 6/27!) with face masks, compared to 6/23 (8/23) without. For rhinovirus, there were no significant differences at all. Of note, authors also identified virus in some participants who did not cough at all during the 30-min exhaled breath collection, suggesting droplet and aerosol routes of transmission from individuals with no obvious signs or symptoms.

Don’t put your masks in the fridge for recycling! Heating is probably better. This important work shows that the virus was highly stable at 4°C (almost no reduction on day 14) but sensitive to heat (70°C: inactivation 5 min, 56°C: 30 min, 37°C: 2 days). It also depends on the surface: No infectious virus could be recovered from printing and tissue papers after 3 hours, from treated wood and cloth on day 2, from glass and banknotes on day 4, stainless steel and plastic on day 7. Strikingly, a detectable level of infectious virus (~0.1% of the original inoculum) could still be present on the outer layer of a surgical mask on day 7.

Clinical


Case report and series on isolated sudden onset anosmia, urging to consider this presentation.

Comorbidities


First study arguing against any deleterious effect of RAAS inhibitors (ACE inhibitors or sartans) in COVID-19! Among 42 of 417 patients admitted to Shenzhen Hospital while on antihypertensive therapy, those receiving RAAS inhibitors had a lower rate of severe diseases than patients without (5/17 compared to 12/25) and a trend toward a lower level of IL-6 in peripheral blood.


Thoughts on how the pandemic affects treatment of patients with cancer and how it will hit the wider oncology community. Substantial changes for re-
search, education, and collaboration are expected, including reduced international travel and increased remote networking and telemedicine.

**Procedures**


Patients with prolonged ventilation may require tracheostomy to optimize weaning from ventilatory support. Review of the literature and practical issues.

**Diagnostics**


Brief report about current knowledge and development on antibody testing.

**Treatment**


Important open-label, randomized trial conducted in 3 hospitals in China, comparing arbidol and favipiravir in 236 patients with COVID-19 pneumonia. Primary outcome was the 7-day clinical recovery rate (recovery of fever, respiratory rate, oxygen saturation and cough relief). In “ordinary” COVID-19 patients (not critical), the recovery rates were 56% with arbidol (n = 111) and 71% (n = 98) with favipiravir (p = 0.02) that was well tolerated, except for some elevated serum uric acid levels. Striking! But can we trust? In the whole study population, no difference was evident. Many cases were not confirmed by PCR. There were also imbalances between subgroups of “ordinary” patients and even favipiravir was incorrectly spelt 7 times: 3x famiravir, 4x fabiravir (come on guys - did anybody read the manuscript?). This paper needs a careful (and major) review...
5 April

Epidemiology


Is symptom severity a proxy for infectivity? Case report of a patient with mild illness and positive tests for up to 18 days after diagnosis, without evidence of transmission to 16 close contacts, among them 10 high-risk contacts.


Outbreak in a restaurant. The distances between index patient and persons at other tables were all > 1 m, suggesting that droplet transmission was prompted by air-conditioned ventilation.


Korean study of seven asymptomatic blood donors who were later identified as COVID-19 confirmed cases. None out of 9 recipients of platelets or red blood cell transfusions tested positive for SARS-CoV-2 RNA. Transfusion transmission is unlikely.


With screening of 2,430 donations in real-time, including 1,656 platelet and 774 whole blood donations from Wuhan, the authors found plasma samples positive for viral RNA from 4 asymptomatic donors. It remains unclear whether detectable RNA signifies infectivity.
Diagnostics


Experience from Italy with lung ultrasound as a bedside tool to improve evaluation of lung involvement, and also reduce the use of chest x-rays and CT. A point scoring system is employed by region and ultrasound pattern.

Clinical


Outbreak in a long-term care facility: Test them all, immediately! Following identification of a case of SARS-CoV-2 in a health care worker, 13/23 residents who tested positive were asymptomatic or presymptomatic on the day of testing.

Comorbidities


This mini-review outlines the mechanisms by which RAAS inhibitors (ACEIs/ARBs) may be of benefit in COVID-19. Overview of the current recommendations for their use in infected patients. According to the authors, the biological plausibility of the salutary effects of RAAS inhibitors is intriguing and several trials of starting losartan in patients with COVID-19 are currently being planned.

Detailed and important review for oncologists, addressing current challenges associated with managing cancer patients during the COVID-19 pandemic.


Don’t forget or marginalize persons with substance use disorders during this crisis!


Four COVID-19 cases with cardiovascular presentations are described. In patients presenting with what appears to be a typical cardiac syndrome, COVID-19 infection should be in the differential during the current pandemic, even in the absence of fever or cough.

6 April

Epidemiology


Thoughts on universal masking in hospitals. Pros and cons. Bottom line: The main value is probably psychological: giving health care workers the confidence to absorb and implement prevention practices.

“All models are wrong, but some are useful”, statistician George Box supposedly once said. This model shows how non-pharmaceutical measures have worked in China. Without the Wuhan travel ban, there would have been 744,000 cases by February 19, day 50 of the epidemic. With the Wuhan travel ban alone, the number of cases would have decreased to 202,000. Other control measures such as the national emergency response, together with the travel ban, limited the number of cases, 96% fewer than expected in the absence of interventions.


China is now addressing an issue every country and location in the world will eventually (hopefully) face: how to normalize and restore societal activities, while at the same time minimizing disease-related dangers from the outbreak.


Infection of health-care workers (HCWs) is not inevitable! A female in her 60s who travelled to Wuhan on Dec 25, 2019, and returned to Illinois on Jan 13, 2020, transmitted the infection to her husband. Although both were hospitalised in the same facility and shared hundreds (n = 348) of contacts with HCWs, nobody else became infected, supporting recommendations regarding appropriate infection control.
Diagnostics


Don’t put your swabs in the sun! In this small study, all samples were inactivated by incubation in a water bath at 56˚ for 30 minutes. 7/15 specimens with low virus levels converted to false negative. Longer storage could also cause false-negative results.

Virology


Let’s pray that SARS-CoV-2 remembers its origins. And that it behaves like other human coronaviruses (hCoVs). A longitudinal surveillance cohort study of children and their households from Michigan found that hCoV infections were sharply seasonal, showing a peak for different hCoV types (229E, HKU1, NL63, OC43) in February. Over 8 years, almost no hCoV infections occurred after March. Will SARS-CoV-2 remember this? It’s April....

Procedures


Careful and well-balanced review about the pros and cons of this treatment strategy.

Treatment


This mini-review (not open access) focusses on the pharmacokinetics of favipiravir and potential drug-drug interactions (DDIs). As the parent drug un-
dergoes metabolism in the liver mainly by aldehyde oxidase (AO), potent AO inhibitors such as cimetidine, amlodipine, or amitriptyline are expected to cause relevant DDIs.

**Pregnancy**


For those of you who are not gynecologists: No, it’s not Luís Figo. It’s FIGO, the International Federation of Gynaecology and Obstetrics which gives “interim” recommendations about how to deal with pregnant women: 46 pages on ambulatory antenatal care, management in the setting of the obstetrical triage, intra/postpartum management and neonatal care. Among others, IRCCS, PAHO, ECDC, SIN, SEGO, RCOG, SOGC, SOAP, ISUOG and RANZCOG also contributed.

**7 April**

**Diagnostics**


Don’t put your swabs in the sun! In this small study, all samples were inactivated by incubation in a water bath at 56˚ for 30 minutes. Of note, 7/15 specimens with low virus levels converted into false negative. Longer storage also caused false negative results in a few cases.


Insights into antibody recognition and how SARS-CoV-2 can be targeted by the humoral response, revealing a conserved epitope shared between SARS-
CoV and SARS-CoV-2. This epitope could be used for vaccines and the development of cross-protective antibodies.

Clinical


Important work, providing sobering evidence about the burden of critical illness. Over a period of 28 days, 1,591 COVID-19 patients (88% requiring endotracheal intubation and ventilatory support) were admitted to 72 Italian ICUs, an average of 22 patients per ICU (median length of stay was 9 days). Of note, 82% were male and median age was only 63 years (IQR 56-70), suggesting that older age alone is not a risk factor for admission to the ICU. As of March 25, ICU mortality was 26%. However, 58% were still in the ICU. Scary study, telling us a lot about the fragility of health care systems in even the wealthiest countries.


Interesting article on Copenhagen’s polio epidemic in 1952, when over 300 patients (see below) developed respiratory paralysis within a few weeks, completely overwhelming the ventilator facilities. Does this remind you of something?


Yes, it’s old. But, please, read this incredible story on hope and despair, on enormous medical challenges and true heroes, highly topical after almost 60 years. A comprehensive review about a forgotten epidemic occurring 1952 at the Belgdam Hospital in Copenhagen, Denmark: about 3,000 polio patients were admitted between August and December, among them 1,250 with paralysis and 345 with respiratory failure - due to bulbar or bulbspinal polio affecting brainstem or nerves that control breathing. The heroic solution was to recruit 1,500 medical and dental students, providing round-the-clock man-
ual ventilation using rubber bags, with only the patient’s appearance to guide them. For a total of 165,000 hours. Think about it. The students were flying by sight. Sometimes, only the patients' rolling back eyes signalled that more ventilation was needed. Watery eyes while reading this heartbreaking article. A perfect story for anti-vaxxers (if these damned trolls would take notice). And about how fast we forget!

Procedures
Careful and well-balanced review about the pros and cons of this treatment strategy.

8 April
Epidemiology
Very small study, but both surgical and cotton masks appear to be ineffective in preventing the virus dissemination from the coughs of patients with COVID-19 to the environment and external mask surface.

Diagnostics
Nice review on how to use and interpret troponin results in COVID-19 patients. According to the authors, clinicians must recognize that troponin is not a test for myocardial infarction, and it never was. No biomarker has ever had the ability to detect acute atherothrombotic occlusion in a coronary artery. Elevations of cardiac troponin can inform the diagnosis of a number of cardiac conditions related to COVID-19.
Clinical

Short but interesting viewpoint on current clinical insights and key questions. Is PCR always positive? What about reinfection, immunity? What do we know about transmission?

Comorbidities

Is hypertension a true risk factor for severe COVID-19 courses? According to the authors, there is as yet (March 29) “no evidence” that hypertension is related to outcomes of COVID-19, or that ACE inhibitor or ARB use is harmful, or for that matter beneficial.


Some thoughts on how to manage patients suffering from Inflammatory Bowel Diseases, regarding their ongoing immunosuppressive therapies which could render them more susceptible to acquire COVID-19 infection and develop severe courses.

Treatment

A single dose (200 mL) of convalescent plasma was given to 10 patients (9 treated with umifenovir, 6 with methylprednisolone, 1 with remdesivir). In all 7 patients with viremia, serum SARS-CoV-2 RNA decreased to an undetectable level within 2-6 days. Meanwhile, clinical symptoms and paraclinical criteria rapidly improved within three days. Using antibodies from convalescents could be an option in severe cases. It’s now time for larger studies.
Pregnancy, pediatrics


Summarized in this nice review published on April 6, “what is known about COVID-19 in children and adolescents until now”. No, not until now. Until March 12, 2020 (a far-off age). What has happened since then?

9 April

Virology


Ferrets shed the virus in nasal washes, saliva, urine, and feces up to 8 days post-infection. They may represent an infection and transmission animal model of COVID-19 that may facilitate development of SARS-CoV-2 therapeutics and vaccines.

Clinical


The American Association of Medical Colleges (AAMC) recommends that “unless there is a critical health care workforce need locally, we strongly suggest that medical students not be involved in any direct patient care activities”. The authors disagree (for good reasons).


In a meta-analysis of 60 studies comprising 4,243 patients, the pooled prevalence of gastrointestinal symptoms was 17.6% (95% CI, 12.3% - 24.5%). Preva-
llence was lower in studies from China than other countries. Pooled prevalence of stool samples that were positive for virus RNA was 48.1% and could persist for up to ≥ 33 days from onset of illness even after viral RNA negativity in respiratory specimens. Stool viral RNA was detected at higher frequency among those with diarrhea.


This viewpoint summarizes key considerations for supporting the health care workforce.

Comorbidities


Don’t forget the dentists! And test them with the same high priority as that of medical health-care workers in hospitals!


“Since December 2019, patients with unexplained pneumonia have been found in Wuhan, Hubei Province, China, which was caused by a novel coronavirus that had not been previously identified (1). Tentatively defined as 2019 novel coronavirus (2019-nCoV), the pathogen has now been named Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2) (2), while the disease termed Coronavirus Disease 2019 (COVID-19).” This abstract was published on April 6, with references. In all seriousness. Come on guys, we all know that already! Is it to be feared that nobody will read your interesting mini-review on mechanisms and clinical implications of liver injury, unmet clinical needs and main research questions?
Treatment


Several studies have speculated that baricitinib could act on AT2 cells and AAK1 mediated endocytosis. The authors argue that the drug would not be an ideal option, due to the fact that baricitinib causes lymphocytopenia, neutropenia and viral reactivation. Sounds reasonable.


Ongoing clinical trials with HCQ use different dosing regimens. In this PK study on 13 patients critically ill with COVID-19, 200 mg three times daily was inappropriate to reach a supposed target blood level of 1 - 2 mg/L. Authors proposed 800 mg once daily on day 1, followed by 200 mg twice daily for 7 days. Further PK studies needed.


An overview of treatment with convalescent plasma on current evidence of benefit, regulatory considerations, logistical work-flow (recruitment of donors, etc) and proposed clinical trials.

Procedures


According to the authors, the evidence shows a favourable risk/benefit profile for patient decolonization with nasal povidone and oral chlorhexidine rinse to help mitigate the perioperative spread.
10 April

Diagnostics


Among 172 discharged COVID-19 patients, 25 (14.5%) had positive testing again 2 to 13 days after discharge, without aggravation of symptoms. Two negative RT-PCR tests 24 hours apart may not be sufficient for viral clearance evaluation, suggesting the need for additional measures to confirm illness resolution.


Can chest CT be used as a primary tool for detecting COVID-19 in epidemic areas? Some early studies from China said yes. The authors comment that this is a cautionary tale about the consequences of rushing the scientific review process: harsh criticism on faulty design, incomplete methods, biased patient cohorts, confounding and scant discussion, calling into question the broad conclusions that were made in these studies. Bottom line: CT should not be used to screen for or as a first-line test to diagnose COVID-19, all the more considering that performing CT safely is problematic.


Same issue. The British Society of Thoracic Imaging has explored different scenarios integrating CT into a diagnostic algorithm. Of note, the clinical value, even in the absence of PCR availability, remains unclear. Again: CT can help, but probably not as a tool for diagnosing COVID-19.
Clinical

Case series on 3 patients with critical illness, developing antiphospholipid antibodies. These antibodies may rarely lead to thrombotic events that are difficult to differentiate from other causes of multifocal thrombosis in critically patients, such as disseminated intravascular coagulation, heparin-induced thrombocytopenia, and thrombotic microangiopathy.


This important study shows that in Europe, otolaryngologic symptoms are much more common than in Asia (it remains unclear whether this is a true difference). Among 417 mild-to-moderate COVID-19 patients (from 12 European hospitals), 86% and 88% reported olfactory and gustatory dysfunctions, respectively. The vast majority was anosmic (hyposmia, parosmia, phantosmia did also occur), and the early olfactory recovery rate was 44%. Females were more affected than males. Olfactory dysfunction appeared before (12%), at the same time (23%) or after (65%) the appearance of other symptoms. There is no doubt that sudden anosmia or ageusia need to be recognized as important symptoms of COVID-19.


Neuroinvasive propensity has been demonstrated as a common feature of human coronaviruses. These viruses can invade brainstem via a synapse-connected route from the lung and airways. With regard to SARS-CoV-2, early occurrences such as olfactory symptoms (see above) should be further evaluated for CNS involvement. Potential late neurological complications in cured COVID-19 patients are discussed. No data are available yet. However, after reading this, you will ask yourself whether herd immunity (infection of broader populations) is such a good idea.
Epidemiology
Stafford N. Covid-19: Why Germany’s case fatality rate seems so low. BMJ. 2020 Apr 7;369:m1395. PubMed: https://pubmed.gov/32265194. Full-text: https://doi.org/10.1136/bmj.m1395

Guess why? It’s probably testing and nothing else. The more people with no or mild symptoms you test, the lower the fatality rate. Reliable PCR methods are reported through the end of January. In Germany’s public health system, testing is not restricted to a central laboratory as in many other nations but can be conducted at quality-controlled laboratories throughout the country. Within a few weeks, overall capacity reached half a million PCR tests a week. The same low fatality rate is seen in South Korea, another country with high testing rates.


A word from Cochrane. Current evidence for COVID-19 “is limited”. However, findings “consistently indicate that quarantine is important in reducing incidence and mortality”. In order to maintain the best possible balance of measures, “decision makers must constantly monitor the outbreak situation and the impact of the measures implemented”. Well.

Pregnancy

Systematic review among 108 pregnancies published in 18 articles. 91% were delivered by cesarean section. Three maternal intensive care unit admissions were noted but no maternal deaths. One neonatal death and one intrauterine death were also reported.

Statement on how to rationalize ultrasound and to manage early pregnancy complications in this crisis.

**11 April**

**Virology**


SARS-CoV-2 replicates poorly in dogs, pigs, chickens, and ducks. However, ferrets and cats are permissive to infection and cats susceptible to airborne infection. But cat owners can relax. Experiments were done in a small number of cats exposed to high doses of the virus, probably not representing real-life. It remains also unclear if cats secrete enough coronavirus to pass it on to people.


It remains unclear whether SARS-CoV-2 can also infect T cells, resulting in lymphocytopenia. Using a model with pseudoviruses, authors showed that SARS-CoV-2 infects (but does not replicate in) T cells through S protein-mediated membrane fusion. T cell lines were significantly more sensitive to SARS-CoV-2 infection when compared with SARS-CoV. Of note, a very low expression level of hACE2 was found, indicating that a novel receptor might mediate SARS-CoV-2 entry into T cells.
**Vaccine**


Brief data-driven overview by seven experts. The conclusion is that efforts are unprecedented in terms of scale and speed and that there is an indication that a vaccine could be available by early 2021. As of 8 April 2020, the global vaccine landscape includes 115 candidates, of which the 5 most advanced candidates have already moved into clinical development, including mRNA-1273 from Moderna, Ad5-nCoV from CanSino Biologicals, INO-4800 from Inovio, LV-SMENP-DC and pathogen-specific aAPC from Shenzhen Geno-Immune Medical Institute. The race is on!

**Diagnostics**


In a cohort of 113 symptomatic patients from two hospitals outside Wuhan, the median duration of SARS-CoV-2 RNA detection was 17 days (IQR, 13-22 days) as measured from illness onset. Male sex, delayed hospital admission, and invasive mechanical ventilation were independent risk factors for prolonged SARS-CoV-2 RNA shedding.


Small study, demonstrating that most PCR-confirmed SARS-CoV-2-infected persons seroconverted by 2 weeks after disease onset. Sensitivity varied between the assays (IgA ELISA showed higher sensitivity). It remains crucial to calibrate and standardize assays developed by different laboratories by using well-defined standard references as part of diagnostic assay validation.
Clinical


Large single-center case study on 344 severe and critically ill patients admitted to Tongji hospital from January 25 through February 25, 2020. 133 (38.7%) patients died at a median of 15 days. Beside older age, hypertension and COPD were more common in non-survivors but not diabetes. No difference was seen between patients with or without ACE inhibitors.


CURB-65 severity score may not be suitable for COVID-19. In 208 patients, a risk factors scoring system was developed, for prediction of progression, based on patients’ age, comorbidities, lymphocyte count and serum LDH at presentation. Needs to be validated by larger studies.

Treatment


A compassionate use program of remdesivir for patients with severe COVID-19 is described. Clinical improvement was observed in 36/53 (68%) patients. Since published yesterday, data are celebrated in the media. Unjustifiably. Although the authors have made some efforts to discuss their data carefully, even more caution is needed. We believe that with this “study”, any (yes, any!) clinical benefit of remdesivir remains unproven. Moreover, several issues in this data set seem to be very implausible. We have written a correspondence letter to NEJM and will keep you updated.

The ribonucleoside analog beta-D-N(4)-hydroxycytidine (NHC, EIDD-1931) has broad spectrum antiviral activity against all CoVs, as well as increased potency against resistance mutations to the nucleoside analog inhibitor remdesivir. But how long will it take to bring this compound to clinical trials?


Virtual drug screening to identify new drug leads that target the COVID-19 virus main protease M(pro) which plays a pivotal role in mediating viral replication and transcription. Six compounds inhibited M(pro) with IC<sub>50</sub> values ranging from 0.67 to 21.4 muM, among them with disulfiram and carmofur (a pyrimidine analogue used as an antineoplastic agent), two approved drugs.

12 April

Virology


Cell experiments on replication capacity and the immune activation profile of SARS-CoV-2 and SARS-CoV infection in human lung tissues. Both viruses were similar in cell tropism, with both targeting types I and II pneumocytes, and alveolar macrophages. SARS-CoV-2 generated 3.20 x more infectious virus particles than SARS-CoV from the infected lung tissues.


Some thoughts on the immunopathological changes in patients with COVID-19 and how this may provide potential targets for drug discovery and may be important for clinical management.

Atomic details of the crystal structure of the C-terminal domain of SARS-CoV-2 spike protein in complex with human ACE2 are presented. The hACE2 binding mode of SARS-CoV-2 seems to be similar to SARS-CoV, but some key residue substitutions slightly strengthen the interaction and lead to higher affinity for receptor binding. Antibody experiments indicate notable differences in antigenicity between SARS-CoV and SARS-CoV-2.

**Epidemiology**


In hospitals, the virus is everywhere. SARS-CoV-2 was widely distributed in the air and on object surfaces in both the intensive care units and general wards, implying a potentially high infection risk for medical staff. Contamination was greater in ICU. Virus was found on floors, computer mice, trash cans, and sickbed handrails and was detected in air approximately 4 m from patients.


Coronavirus infection spreads in clusters, and early identification of these clusters is critical for slowing down the spread of the virus. Short daily population-wide online surveys that assess the development of symptoms could serve as a strategic and valuable tools for identifying such clusters and informing epidemiologists, public health officials and policymakers.

**Diagnostics**

Throat washing may be used for monitoring due to its non-invasiveness and reliability. Throat washing was harvested by asking patients to oscillate over the posterior pharyngeal wall with 20 ml sterile normal saline. After 5-10 seconds, they spit out normal saline from their throat to a sterile container. In 24 paired throat washings and nasopharyngeal swab specimens, the positive testing rate of throat washing was much higher than that of swabs.


Negative does not mean absolutely negative. Among 70 COVID-19 patients, 15 (21%) experienced a "turn positive" of SARS-CoV-2 PCR after two consecutive negative results (up to 45 days after symptom onset).

Clinical


This retrospective, observational case series found 78/214 patients (36%) with neurologic manifestations, ranging from fairly specific symptoms (loss of sense of smell or taste, myopathy, and stroke) to more non-specific symptoms (headache, low consciousness, dizziness, or seizure). Whether these more non-specific symptoms are manifestations of the disease itself remains to be seen.


Among 81 severe COVID-19 patients, incidence of venous thromboembolism (VTE) was 25%. A significant increase of D-dimer was a good index for identifying high-risk groups of VTE.
Treatment
In the year 1925, the BMJ cautiously endorsed Moellgaard's gold treatment for tuberculosis, although it found his pharmacological reasoning “both interesting and instructive”. In 2020, the BMJ is similarly cautious about (hydroxy)chloroquine treatment for SARS-CoV-2. In cell and animal studies, the effects on avian influenza, Epstein-Barr, chikungunya or Zika have been variable. Wide use of these drugs will expose patients to rare but potentially fatal harms, including serious cutaneous adverse reactions, fulminant hepatic failure, and ventricular arrhythmias (especially when prescribed with azithromycin).

13 April
Virology
Using cryogenic electron microscopy, the authors describe the structure of the RNA-dependent RNA polymerase, another central enzyme of the viral replication machinery. It is also shown how remdesivir and sofosbuvir bind to this polymerase.

Epidemiology
Some clusters are described, including a 9-yr-old child who attended three different schools (why 3 is not described) and one ski class while symptomatic. Coinfected with both picornavirus + influenza A(H1N1), the child transmitted only these viruses to others but not SARS-CoV-2, suggesting that these viruses are more easily transmitted than SARS-CoV-2.

Why is SARS-CoV-2 so highly transmissible? This interesting overview describes current knowledge of airborne transmission. It’s not only the “droplet spray”, typically greater than 5 µm in diameter. Alternatively, a susceptible person can inhale microscopic aerosol particles consisting of the residual solid components of evaporated respiratory droplets, which are tiny enough to remain airborne for hours. The authors conclude that speech plausibly serves as an underrecognized transmission mechanism: “it is up to ‘aerosol scientists’ to provide the technology and hard data to either corroborate or reject that.” So please, get on the scene, aerosol scientists on this planet!

Clinical


Is there a genetic predisposition for severe diseases? This report from Iran describes three brothers aged 54-66 years, all dying from COVID-19 with a relatively similar pattern after less than 2 weeks of illness. All were previously healthy, without histories of underlying diseases.


All in-hospital COVID-19 patients should receive pharmacological thromboprophylaxis according to a risk stratification score, unless contraindicated. In patients with creatinine clearance > 30 ml/min, low molecular weight heparin (LMWH) should be administered according to the prescribing information. These guidelines also suggest regularly monitoring prothrombin time, D-dimers, fibrinogen, platelet count, LDH, creatinine and ALT daily or at least 2-3 times per week.

“Flu plus ‘loss of smell’ means COVID-19”. Among 263 patients presenting in March (in a single center in San Diego) with flu-like symptoms, loss of smell was found in 68% of COVID-19 patients (n=59), compared to only 16% in negative patients (n=203). Smell and taste impairment were independently and strongly associated with positivity (anosmia: adjusted odds ratio 11, 95%CI: 5-24). Conversely, sore throat was independently associated with negativity.

**Comorbidities**


Patients with cutaneous immune-mediated diseases (including psoriasis, atopic dermatitis, and hidradenitis suppurativa) may continue their treatment even during the COVID-19 outbreak, preventing disease flares. However, in patients with active COVID-19 infection, it is generally recommended to withhold immunosuppressive or biologic treatment.


In order to reduce hospital visits to a minimum and to ease pressure on workforce, detailed guidelines on radiation therapy for breast cancer are given, mainly focussing on hypofractionation.

**Treatment, procedures**


In whom to perform bronchoscopy and how to perform it safely? This paper describes different guidelines (based on expert opinions).

Evidence? Well. Serum 25(OH)D concentrations tend to decrease with age, which may be important for COVID-19 because case-fatality rates increase with age. That’s the whole story. After all, the “hypothesis that vitamin D supplementation can reduce the risk of influenza and COVID-19 incidence and death should be investigated in trials”.

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**14 April**

**Virology**


This study shows that human recombinant soluble ACE2 (hrsACE2) blocks SARS-CoV-2 infections of different cells, human blood vessel organoids and human kidney organoids. In ARDS patients, hrsACE2 was ineffective but safe at a broad range of doses. Apeiron Biologics plans a randomized study on 200 COVID-19 patients in April.

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**Epidemiology**


This important work was published a few weeks ago. Today, no less than 6 correspondence letters mainly discuss airborne transmission and viability of SARS-CoV-2 in aerosols. The bottom line: viability was investigated under experimental conditions and should not be used to draw conclusions about airborne transmission. However, according to the authors, aerosol-generating medical procedures should be examined as well as decontamination techniques.
Between March 22 and April 4, 2020, all pregnant women who delivered infants were tested in a hospital located on the northern tip of Manhattan, New York City. Nasopharyngeal swabs obtained from 210 asymptomatic women were positive in 29 (13.7%). All four women with symptoms of COVID-19 on admission were positive. In other words: \textbf{29/33 women were asymptomatic.}

Re-analysing 640 throat swabs collected from patients in Wuhan with influenza-like illness from 6 October 2019 to 21 January 2020, the authors found 9 to be positive for SARS-CoV-2. The onset date of the earliest case was 4 January 2020, one week after the outbreak was reported by hospitals.

Morphologic changes in the peripheral blood over time in a few COVID-19 patients from Italy. In the early phase of symptom aggravation, a pronounced granulocytic reaction with immaturity, dysmorphism and apoptotic-degenerative morphological evidence was seen. Later the hematologic picture tended to shift toward impressive reactive lymphocyte activation, often with numerical increase, and heterogeneous morphological expression.

Some thoughts on dementia care in this crisis.
Treatment

De Meyer S, Bojkova D, Cinati J, et al. **Lack of Antiviral Activity of Darunavir against SARS-CoV-2.** Full-text: [https://doi.org/10.1101/2020.04.03.20052548](https://doi.org/10.1101/2020.04.03.20052548)

Usually we hesitate to refer to www.medrxiv.org. Preprints published at this website are preliminary reports of work that have not been certified by peer review. Well, it’s time to make an exception. Because this is important: **Darunavir, an HIV protease inhibitor, is not active against SARS-CoV-2.** There was no *in vitro* antiviral activity against a clinical isolate at clinically relevant concentrations (EC$_{50}$ > 100 μM). Remdesivir, used as a positive control, showed potent activity (EC$_{50}$ = 0.38 μM). However, the clinical trial on 3,040 participants treated with darunavir in Spain is still ongoing ([www.clinicaltrials.gov](http://www.clinicaltrials.gov) assessment on April 13).


If you give HIV PIs, please be always aware of drug-drug interactions. Ritonavir is a strong pharmaco-enhancer. For example, **tacrolimus** has to be **reduced by 10-100 fold** to maintain concentration within the therapeutical range. In this case report, a woman with kidney transplantation was treated with lopinavir/r (the “r” indicates ritonavir) for COVID-19 while receiving the full dose of tacrolimus. Levels went incredibly high and were still above the therapeutic range 9 days after stopping both lopinavir/r and tacrolimus. Fortunately, everything turned out alright.


Treating the inflammatory excess in patients with COVID-19: why anti-tumour necrosis factor (TNF) antibodies could be a good idea.

The debate about the optimal mode of respiratory support (outside ICU) continues. Advocate high flow nasal cannulae (HFNC) over non-invasive ventilation (NIV) or vice versa? In the absence of randomised control trials in the use of either HFNC or NIV in COVID-19, this commentary discusses current knowledge.

15 April

**Epidemiology**


SARS-CoV-2 in Iceland. As of April 4, a total of 1,221 of 9,199 tested persons (13.3%) were positive. Why is this of interest? Because the country serves as a perfect epidemiological model. Key findings: The percentage of participants who tested positive in population screening remained stable (0.8%) in March, and the infection rates in two screening groups (recruited through open invitation and through random sampling) were not substantially different. Notably, 43% of the participants who tested positive reported having no symptoms.


Bottom line of this editorial (addressed to nurses): surgical facemasks by the general public is not recommended unless you are looking after a sick person in a household setting or are suffering from an illness. Far more effective is handwashing and maintaining a safe distance from other people.


Forecasts obtained with a simple iteration method that only needs the daily values of confirmed cases as input. The method takes into account expected recoveries and deaths, and it determines maximally allowed daily growth rates that lead away from exponential increase toward stable and declining
numbers. Keeping the daily growth rates to below 5% is an important target for a promising outlook.

Diagnostic


Comprehensive review of the current array of tests for SARS-CoV-2, highlighting gaps in current diagnostic capacity, and proposing potential solutions.


Limits of detection of six commercial kits differed substantially (up to 16-fold difference), with the poorest limits likely leading to false-negative results when RT-PCR were used to detect SARS-CoV-2 infection. According to the authors, manufacturers should analyze the existing problems according to the clinical application and further improve their products.


One aftershock of the pandemic will be the huge number of post-intensive care survivors who have been mechanically ventilated and will likely experience short- and medium-term consequences. These patients will require not only adequate screening but early rehabilitation and other interventions.

Comorbidities

In the current crisis with limited resources to protect the work force, fibrinolytic therapy (FT) may be considered for patients with myocardial infarction (STEMI). FT may even be preferred over primary percutaneous coronary intervention. Arguments for this strategy are summarized.


COVID-19 was observed in two transplant recipients (liver and kidney), with different treatments and prognoses. Both patients recovered.

Treatment


Fantastic review on current knowledge on potential therapies (as of April 5).


Thoughts on how clinical trials should be performed during the current pandemic. And how the processes for evaluating and approving drugs can go awry during a public health crisis.

16 April


Today, we will not discuss the Top Ten Papers. Instead, we will talk about remdesivir and give you 10 good reasons to be careful. Last Friday, on April 10, the New England Journal of Medicine published data on patients who were treated with 10 days of remdesivir on a compassionate use basis (Grein 2020). These results gained a lot of media attraction and Daniel O’Day, Gilead’s CEO, wrote the same day that “the majority” of patients “demonstrated clinical
improvement”. There is no doubt that remdesivir is currently the biggest hope for COVID-19. Results of two large Phase III randomized clinical trials are expected by the end of this month. Remdesivir is also among the four drugs tested in WHO’s huge SOLIDARITY trial.

Grein et al. offer an optimistic view on remdesivir. Although viral data were not available, they concluded with a clinical “improvement in 68%” (36/53) and a “noteworthy” low mortality of 13%, seemingly lower than seen in a randomized clinical trial (RCT) of lopinavir/r (Cao 2020). The authors also emphasize repeatedly the severity of disease in their patients, as many required ventilation – more than in the lopinavir/r trial.

Is the author’s optimism justified? We don’t believe so. We think that, given the published data, remdesivir has only low or at best moderate clinical activity. We are concerned that remdesivir which was not effective against Ebola, will fail in COVID-19 as well.

First, 8/61 patients were not included in the analysis, among them 7 with no post-treatment data. Any reader will wonder what happened to these patients – did they die while on treatment? If these patients had been included in the analysis, we would have observed “improvement in 59%” (36/61).

One patient was excluded due to an “erroneous start date”. This is remarkable as at least 13/51 received less than the planned treatment of 10 days but remained in the analysis. The same is true for at least two patients with, let’s say, an “erroneous stop date” (treatment given for 13 days). The author’s statement that treatment duration was not uniform, “largely because clinical improvement enabled discharge”, is misleading. Only 3/13 subjects who were treated for less than 10 days were discharged early.

In the mentioned randomized clinical trial comparing lopinavir/r and standard of care, day 14 clinical improvement rates on a predefined ordinal scale were 46% with lopinavir/r and 30% with standard care (Cao 2020). According to an NEJM editorial commenting on this trial, results were “disappointing” (Baden 2020). Applying the same scale to the “study” presented here, the day 14 rate would have been at best 49% with remdesivir.

The authors emphasize the severity of their patients’ health, indicated by the fact that 34/53 required invasive mechanical ventilation (IMV), more than in the lopinavir/r trial. But IMV is not the only indicator for severity. The patients in the lopinavir/r trial were sick, too. Inclusion criteria were CT-confirmed pneumonia and an oxygen saturation of 94 % or less while breathing ambient air.

Age and comorbidities in the lopinavir/r trial looked much the same as in the remdesivir study.
The median duration from onset of disease until treatment initiation was 12 days (IQR 9-15) with remdesivir and 13 days (IQR 11-16) in the lopinavir/r trial. Thus, considering points 4-6, it remains unclear if the remdesivir patients were more severely ill.

If we focus on the 41 remdesivir patients who required at least high-flow oxygen at baseline, clinical improvement at day 14 was seen in only 39%. Is this more than we would have seen with placebo?

This study provided data on ALT, AST, and creatinine. They were “fluctuating” during follow-up. Inexplicably, other easily performed and more important parameters such as lymphocytes, D-dimer and lactate dehydrogenase were unavailable. Several studies have identified these parameters to be highly predictive for clinical progression (Zhou 2020, Ji 2020).

The data quality is poor. For some subjects (31, 32), duration remained (mistakenly?) unclear and subject 43 was discharged while worsening.

The final argument: patients who were too ill for an antiviral agent (the “point of no return”) doesn’t count. Of 17 patients without IMV at baseline, at least 4 patients worsened during remdesivir treatment.

In conclusion, for a number of reasons, this report published in the New England Journal of Medicine is a cautionary tale for “science in a hurry”. Fragmentary data arouse false expectations. This paper is not helpful. Safety of the drug was shown in the Ebola trial. It might have been preferable to postpone the publication – after all, the eagerly awaited results from the randomized clinical trials on remdesivir are just days to a few weeks away.

Will remdesivir be to COVID-19 what AZT was to AIDS? (AZT, approved in 1987, was the first and only antiretroviral drug to treat HIV/AIDS for years. Unfortunately, dosage was complicated and efficacy was minimal.) We hope this is not the case because we badly need efficient drugs in our fight against the SARS-CoV-2 pandemic.

We sincerely hope that our objections to the study by Grein et al. are wrong.

References


**17 April**

**Epidemiology**


Some critical thoughts on the use of cloth masks. The physical properties of a cloth mask, reuse, the frequency and effectiveness of cleaning, and increased moisture retention, may potentially increase the infection risk.

**Diagnostics**


Important work on viral shedding: this may begin 2 to 3 days before the appearance of the first symptoms and infectiousness profile may more closely resemble that of influenza than that of SARS. Analyzing a total of 414 throat swabs in 94 patients, the highest viral load was found at the time of symptom onset. Infectiousness started from 2.3 days (95% CI, 0.8–3.0 days) before symptom onset and peaked at 0.7 days (95% CI, −0.2–2.0 days) before symptom onset. The authors estimated that 44% (95%CI 25-69%) of secondary cases were infected during the index cases' presymptomatic stage. Infectiousness was estimated to decline quickly within 7 days.

A critical review concluding that current evidence does not substantiate the use of CT as a diagnostic test for COVID-19. At present, CT should be reserved for evaluation of complications of COVID-19 pneumonia or for assessment if alternative diagnoses are suspected.


The virus was not found in the semen of 12 patients recovering from COVID-19 and in a testis sample of one deceased patient.


In six women, SARS-CoV-2 was not detected in amniotic fluid, cord blood, neonatal throat swab, or breastmilk samples.

Clinical


In China, among 3387 healthcare workers infected with SARS-CoV-2, 23 persons died. Median age was 55 years (range, 29 to 72). Eleven of these persons had been rehired after retirement and 8 were surgeons. Only 2 of the 23 health care workers were physicians in respiratory medicine who had been specifically assigned to treat patients with COVID-19.
Hendren NS, Drazner MH, Bozkurt B, Cooper LT Jr. **Description and Proposed Management of the Acute COVID-19 Cardiovascular Syndrome.** Circulation. 2020 Apr 16. PubMed: [https://pubmed.gov/32297796](https://pubmed.gov/32297796). Full-text: [https://doi.org/10.1161/CIRCULATIONAHA.120.047349](https://doi.org/10.1161/CIRCULATIONAHA.120.047349)

SARS-CoV-2 has the potential to infect cardiomyocytes, pericytes and fibroblasts via the ACE2 pathway leading to direct myocardial injury, but that pathophysiological sequence remains unproven. A second hypothesis to explain COVID-19 related myocardial injury centers on cytokine excess and/or antibody mediated mechanisms. Clinically, COVID-19 can manifest with an acute cardiovascular syndrome (termed “ACovCS”). This review shows surveillance, diagnostic and management strategies for ACovCS that balances potential patient risks and healthcare staff exposure.


Review focussing on thrombocytopenia which is commonly seen in COVID-19. Three mechanisms are discussed: direct infection of bone marrow cells by the virus and inhibition of platelet synthesis, platelet destruction by the immune system and platelet aggregation in the lungs, resulting in microthrombi and platelet consumption.

**Treatment**


A brief review on ECMO which remains a therapeutic option in some well selected patients with severe COVID-19.


The humanized anti-IL-6 receptor antibody tocilizumab was given to three patients with severe COVID-19. All showed rapid relief of respiratory symptoms, resolution of fever and reduction in CRP following tocilizumab administration.
18 April

Epidemiology


During February 12-April 9, among 315,531 COVID-19 cases reported to CDC, 49,370 (16%) included data on whether the patient was a health care worker (HCW). Detailed data were available on 8,945 of these HCW. Most HCW (90%) were not hospitalized; however, severe outcomes, including 27 deaths, occurred across all age groups. ICU admission and death were observed in 2.1–4.9% and 0.3-0.6%, respectively. These rates were markedly higher in HCW older than 65 years, with 6.9-16.0 % and 2.0-4.2%.


You remember Depeche Mode’s hit ‘Enjoy the Silence’? Then look at this video, a person saying “stay healthy”, a laser light-scattering experiment in which speech-generated droplets and their trajectories were visualized. The louder the speech, the higher the numbers of flashes. The number of flashes was highest when the “th” sound in the word “healthy” was pronounced. Depeche Mode were right: “Words are very unnecessary/They can only do harm”.


These authors emphasize that breathing and talking produce even smaller and much more numerous particles, known as aerosol particles, than those visualized in the (above mentioned) laser experiment. They recommend wearing a suitable mask whenever it is thought that infected persons may be nearby and of providing adequate ventilation of enclosed spaces where such persons are known to be or may recently have been.
Diagnostics


Brief review on laboratory biosafety practices necessary to safely process clinical specimens.


Small study on 16 critically ill patients, demonstrating higher viral load and prolonged shedding in lower respiratory tract specimens, as compared with upper respiratory tract specimens.


There is a big debate whether chest CT contributes to COVID-19 diagnosis. Chinese researchers say yes, everyone else says no. This meta-analysis found a high sensitivity but low specificity. In areas with low prevalence, chest CT has a low positive predictive value (1.5-30.7%).

Clinical


Clinical characteristics of the first 393 consecutive patients who were admitted to two hospitals in New York City, among them 130 needing invasive mechanical ventilation. The latter were more likely to be male, to be obese, and to have elevated liver-function values and inflammatory markers (ferritin, D-dimer, C-reactive protein, and procalcitonin). Diarrhea (23.7%), and nausea...
and vomiting (19.1%) were more frequent than in the reports from China (it remains unclear whether this difference reflects geographic variation or differential reporting).


In this case series of 18 patients who had ST-segment elevation, there was variability in presentation, a high prevalence of non-obstructive disease, and a poor prognosis. 6/9 patients undergoing coronary angiography had obstructive disease. Of note, all 18 patients had elevated D-dimer levels.


A risk prediction nomogram for severe COVID-19 was evaluated, including older age, and higher serum lactate dehydrogenase, C-reactive protein, the coefficient of variation of red blood cell distribution width, blood urea nitrogen, direct bilirubin and lower albumin. Interesting, but needs to be validated in larger trials.


In this observational series of 58 patients, ARDS due to SARS-CoV-2 infection was associated with encephalopathy, prominent agitation and confusion, and corticospinal tract signs. It remained unclear which of these features were due to critical illness-related encephalopathy, cytokines, or the effect or withdrawal of medication, and which features were specific to SARS-CoV-2 infection.
19 April

Epidemiology


Interesting and incredibly diligent work on seasonal coronaviruses (sCoVs) and other co-circulating viruses over a thirteen years period in Western Scotland, UK. Different sCoVs were detected in 4.0% (2,958/74,519) of tested patients overall, contributing to 10.7% of all respiratory virus detections. All were winter pathogens, on average peaking between January and March, alongside influenza viruses and RSV. However, there were notable variations between sCoV types and between years. A potential for cross-protective immunity was also seen between some subtypes.

Diagnosis


Experimental pools were created, mixing positive and negative nasopharyngeal specimens. Results: if the incidence rate of SARS-CoV-2 infection is 10% or less, group testing will result in the saving of reagents and personnel time with an overall increase in testing capability of at least 69%.


Comprehensive review on recent (last two weeks) developments in antibody testing, a very rapidly evolving field of research. Brief overview on promises and perils of different testing systems, including ELISA and lateral flow assays.

Older age is a risk factor for severe disease. This also applies to HCW. In China 11/23 deceased HCWs had been reactivated from retirement. In Italy, most of the 74 doctors who died were in their 60s, and only four were women. This brief letter to BMJ addresses this issue. Author declared the following competing interests: “I am an older, male GP”.

**Clinical**


Detailed analysis of symptoms of all laboratory-confirmed SARS-CoV-2 infections in HCP residing in King County. Screening only for fever, cough, shortness of breath, or sore throat might have missed 17% of symptomatic HCP at the time of illness onset; expanding criteria for symptoms screening to include myalgias and chills may still have missed 10%.


Examination of the peripheral blood films of 32 patients found reactive lymphocytes in 72%. This seems to be in stark contrast to the SARS outbreak where reactive lymphocytes of this type were only rarely seen.

**Treatment**


Were we wrong with our critical review on remdesivir? Again, we hope so. A case of successful late initiation of remdesivir is presented. Sixty hours after starting the drug, the patient was extubated and was able to transition to room air within 24 hours of extubation.

Retrospective case series, comparing lopinavir/r (34 cases) and arbidol (16 cases). On day 14 after the admission, no viral load was detected in the arbidol group, but the viral load was found in 15 (44.1%) patients treated with lopinavir/ritonavir. Patients in the arbidol group had a shorter duration of positive RNA test compared to those in the lopinavir/ritonavir group (P < 0.01).

Pregnancy

Experience from Wuhan. A total of 109 of 118 women (92%) had mild disease, and 9 (8%) had severe disease (hypoxemia), 1 of whom received non-invasive mechanical ventilation (critical disease). There were 3 spontaneous abortions, 2 ectopic pregnancies, and 4 induced abortions (all owing to patients’ concerns about COVID-19).


Case report from Lima, Peru, describing a severe presentation of COVID-19 in pregnancy requiring invasive ventilatory support, suggesting possible vertical transmission.

20 April

Epidemiology
The bottom line: the tighter you control the infected, the less restriction you have to impose on the uninfected. With this strategy, Hong Kong and Singapore are very successful. But look at the controls: hospitalizing all those who test positive, regardless of whether they have symptoms, two weeks of self-quarantine to all close contacts, electronic wristbands, etc. You want to see where the infected people in Hong Kong are? You’ll find them here: https://chp-dashboard.geodata.gov.hk/covid-19/en.html


The authors review current recommendations and conclude that mass masking for source control is a useful and low-cost adjunct to social distancing and hand hygiene, shifting the focus from self-protection to altruism, actively involving every citizen, and is a symbol of social solidarity in the global response to the pandemic.

Virology/Pathogenesis


This animal study was performed to understand the pathogenesis, showing SARS-CoV-2-infected macaques provide a new model to test therapeutic strategies. Virus was excreted from nose and throat in the absence of clinical signs, and detected in type I and II pneumocytes in foci of diffuse alveolar damage and in ciliated epithelial cells of nasal, bronchial, and bronchiolar mucosae. In SARS-CoV infection, lung lesions were typically more severe, while they were milder in MERS-CoV infection, where virus was detected mainly in type II pneumocytes.
Diagnostics

Brief but important comment on several papers reporting on prolonged viral shedding. PCR does not distinguish between infectious virus and non-infectious nucleic acid. This is well known from many viral infections such as Ebola or measles.

Clinical

Observational cohort from Italy, involving five patients with COVID-19-associated Guillain-Barré syndrome which probably should be distinguished from critical illness neuropathy and myopathy, which tend to appear later in the course of critical COVID-19 illness.


The next paper on neurological complications seen with COVID-19, probably due to an aberrant immune response.


It’s only age. Multivariate analysis of a retrospective cohort of 1590 hospitalized subjects with COVID-19 throughout China revealed the following factors associated with mortality: Age 75 or older (HR: 7.86, 95% CI: 2.44-25.35), Age 65-74 years (HR: 3.43, 95% CI: 1.24-9.5), coronary heart disease (HR: 4.28, 95% CI: 1.14-16.13), cerebrovascular disease(HR: 3.1, 95% CI: 1.07-8.94), dyspnea (HR: 3.96, 95% CI:1.42-11), procalcitonin > 0.5ng/ml (HR: 8.72, 95% CI:3.42-3.21).
22.28), AST > 40 U/L (HR: 2.2, 95% CI: 1.1- 6.73). Not very new, but by now the largest cohort with detailed information.

**Comorbidities**

Don’t stop your sartans or ACE inhibitors! The authors hypothesize that the benefits of treatment with renin-angiotensin system inhibitors in SARS-COV-2 may outweigh the risks and at the very least should not be withheld.


Making recommendations in the absence of data is not that easy. The authors have made heroic attempts to balance the risk of immune modifying drugs with the risk associated with active disease.

**Severe COVID-19**

Brief but fantastic overview about the current knowledge and the pathways leading to cytokine release syndrome.

21 April
Vacation
22 April

Vaccine

Callaway E. **Hundreds of people volunteer to be infected with coronavirus.** Nature 22 April 2020. Full-text: https://www.nature.com/articles/d41586-020-01179-x

What about a ‘human challenge’ vaccine study? Such a trial would be much faster: a much smaller group of young, healthy volunteers would receive a candidate vaccine and then be intentionally infected with the virus, to judge the efficacy of the immunization. No trial is yet planned, but the debate is on. The approach is also gaining some political support.

Epidemiology


Detailed paper from Hong Kong modeling the effects of non-pharmaceutical interventions (NPIs, including border restrictions, quarantine and isolation, distancing, and changes in population behaviour). NPIs were associated with reduced transmission of COVID-19 and were also likely to have substantially reduced influenza transmission. Findings strongly suggest that social distancing and population behavioural changes – that have a social and economic impact that is less disruptive than a total lockdown – can meaningfully control COVID-19.


Forget herd immunity! Overall prevalence is still incredibly low. Even in hotspots like Wuhan! From April 3 to 15, SARS-CoV-2-specific IgG positive rate among 1,021 people applying for a permission to resume travel, only 98 (9.60%) were IgG positive and IgM and NAT (SARS-CoV-2 nucleic acid test) negative.
Diagnostics


Evidence suggestive of airborne spread is growing. Authors discuss several 'aerosol-generating procedures' and current evidence (limited). A precautionary approach should be considered to assure healthcare worker safety.


It's not that trivial to obtain a NP-swab. Watch this video on protection, preparation, equipment, handling, removing personal protective equipment, etc.


More on antibodies, as a complementary approach for PCR. The seroconversion of specific IgM and IgG antibodies were observed as early as the 4th day after symptom onset. In the confirmed patients with COVID-19, sensitivity, specificity, positive predictive value of IgM were 77.3% (51/66), 100% and 100%, and those of IgG were 83.3% (55/66), 95.0% and 94.8%. Both antibodies performed well in serodiagnosis for COVID-19 and rely on great specificity. The antibodies against SARS-CoV-2 can be detected in the middle and later stage of the illness.

Clinical


Fecal calprotectin (FC) has evolved as a reliable fecal biomarker allowing detection of intestinal inflammation in inflammatory bowel diseases and infectious colitis. This report on 40 patients provides some evidence that SARS-
CoV-2 infection instigates an inflammatory response in the gut, as elevated FC (largely expressed by neutrophil granulocytes) and diarrhea.

**Severe COVID-19**


Case report of a patient who succumbed to COVID-19. Hypothesis that a powerful function of neutrophils – the ability to form neutrophil extracellular traps (NETs) – may contribute to organ damage and mortality in COVID-19. Targeting NETs directly and/or indirectly with existing drugs may reduce clinical severity.


Case series of 22 patients with acute respiratory failure present a severe hypercoagulability rather than consumptive coagulopathy. Fibrin formation and polymerization may predispose to thrombosis and correlate with a worse outcome.

**Treatment**


Evidence-based guidelines which are, in the absence of large RCTs, not very helpful. Recommendations for all drugs acknowledge the current “knowledge gap”. HCQ, lopinavir/r, tocilizumab and convalescent plasma should be given "only in the context of a clinical trial". Great.
23 April

Epidemiology


Detailed cluster analysis, confirming that transmission by individuals with asymptomatic or paucisymptomatic infections is possible. An asymptomatic mother transmitted the virus to her son, and a paucisymptomatic father transmitted the virus to his three-month-old daughter. SARS-CoV-2 was detected in the environment of one household.

Diagnostics


Among 96 consecutively admitted patients (22 mild, 74 severe COVID-19), RNA viral load was measured in 3,497 respiratory, stool, serum, and urine samples. Infection was confirmed in all patients by testing sputum and saliva samples, in the stool of 59% and in the serum of 41%. The median duration of virus in stool (22 days) was significantly longer than in respiratory (18 days, severe cases: 21 days) and serum samples (16 days). However, the main limitation is that RNA PCR cannot distinguish between viable and non-viable virus.

Clinical


The numbers are becoming huge now. This case series from New York included 5,700 COVID-19 patients admitted to 12 hospitals between March 1 and April 4, 2020. Median age was 63 years (IQR 52-75), the most common comorbidities were hypertension (57%), obesity (42%), and diabetes (34%). At triage,
31% of patients were febrile, 17% had a respiratory rate greater than 24 breaths/minute, and 28% received supplemental oxygen. Of 2,634 patients with an available outcome, 14% (median age 68 years, IQR 56-78, 33% female) were treated in ICU, 12% received invasive mechanical ventilation and 21% died. Mortality for those requiring mechanical ventilation was 88.1%.


Retrospective analysis of 26 persistently asymptomatic patients. The median period from contact to the last positive nucleic acid test was 21.5 days (10-36 days). At least 10 patients had typical ground-glass or patchy opacities on CT.


Telephone survey, analyzing 202 adult COVID-19 patients with mild symptoms, 5-6 after the positive swab was performed. Any altered sense of smell or taste was reported by 130 patients (64%, 95% CI, 57%-71%, more frequent in women, 73%). This was seen in 12% before, in 23% at the same time and in 27% after other symptoms. An altered sense of smell or taste was reported as the only symptom by 6 patients (3.0%).


Some thoughts on the pathogenesis of hyposmia. According to the authors, the most likely cause for transient hypogeusia and hyposmia in SARS-CoV-2-infected patients is a direct contact and interaction of the virus with gustatory receptors or olfactory receptor cells.
Comorbidities


Brief review on obesity as a unifying risk factor for severe COVID-19 infection, reducing both protective cardiorespiratory reserve as well as potentiating the immune dysregulation. Possible patho-mechanisms are discussed.

Treatment


In this Viewpoint article, the authors present their opinion on the benefits and potential limitations of using IFN-λ to prevent, limit, and treat SARS-CoV-2 infections.

Severe COVID-19


Proning helps, even in awake, non-intubated patients. Among 50 patients, the median SpO2 at triage was 80%. After application of supplemental oxygen was given to patients on room air it was 84%. After 5 minutes of proning was added, SpO2 improved to 94%.

Pediatric


Of 171 children with confirmed SARS-CoV-2 infection in Wuhan, most appeared to have a milder clinical course. Asymptomatic infections were not uncommon (16%). During the course of hospitalization, 3 patients (all with co-
existing conditions) required intensive care support and invasive mechanical ventilation.

24 April

Virology


Elegant paper, confirming the expression of ACE2 in multiple tissues shown in previous studies, with added information on tissues not previously investigated, including nasal epithelium and cornea and its co-expression with TMPRSS2. Potential tropism was analyzed by surveying expression of viral entry-associated genes in single-cell RNA-sequencing data from multiple tissues from healthy human donors. These transcripts were found in specific respiratory, corneal and intestinal epithelial cells, potentially explaining the high efficiency of SARS-CoV-2 transmission.

Epidemiology


Interesting new model that predicts the course of the epidemic, considering eight stages of infection: susceptible (S), infected (I), diagnosed (D), ailing (A), recognized (R), threatened (T), healed (H) and extinct (E), collectively termed SIDARTHE. The model discriminates between infected individuals depending on whether they have been diagnosed and on the severity of their symptoms. Authors demonstrate that restrictive social-distancing measures will need to be combined with widespread testing and contact tracing to end the ongoing pandemic.

They have a dream: These UK researchers recommend the evaluation of weekly antigen testing of the whole population after lockdown. As they say, “a voluntary Dunkirk spirit” would be the only way for 10 million tests to be done daily.

**Transmission**


Epidemiologic characteristics of a COVID-19 outbreak centered in a call center in South Korea, indicating an attack rate of 8.5% within the whole building. If results were restricted to one floor, the attack rate was as high as 43.5%. Among the 97 confirmed case-patients, 92% were symptomatic at the time of investigation and 4% were presymptomatic. Only 4% remained asymptomatic after 14 days of isolation.


Brief review. The authors highly recommend mass masking around the world during the pandemic. Whereas surgical masks are the preferred recommendation for the general public, cloth masks should be considered as a substitute if supplies are limited or surgical masks are not available.

**Clinical**

The ACE2 receptor is widely expressed on endothelial cells. Three cases, indicating direct viral infection of the endothelial cell and diffuse endothelial inflammation, induced by SARS-CoV-2 infection.


In 100 patients with severe COVID-19, a high prevalence (23%, 95%CI 15-33%) of acute pulmonary embolism was found. Pulmonary embolus was diagnosed at mean of 12 days from symptom onset. In multivariable analysis, requirement for mechanical ventilation (OR = 3.8, 95%CI 1.02-15) remained associated with acute pulmonary embolus.

Comorbidities


Nice review. Data from 12 animal studies and from 12 human studies overwhelmingly imply that administration of ACEIs/ARBs does not increase ACE2 expression. Available evidence does not support the hypothesis that ACEI/ARB use increases ACE2 expression and the risk of complications from COVID-19. The authors conclude that patients being treated with ACEIs and ARBs should continue their use for approved indications.


Same idea: in this retrospective, multi-center study of 1128 adult patients with hypertension diagnosed with COVID-19, 188 patients taking ACEI/ARB were compared with 940 patients without using ACEI/ARB. Unadjusted mortality rate was lower in the ACEI/ARB group versus the non-ACEI/ARB group (3.7% vs. 9.8%). In a Cox model, after adjusting for age, gender, comorbidities, and in-hospital medications, the detected risk for all-cause mortality was lower in the ACEI/ARB group (adjusted HR 0.42; 95%CI, 0.19-0.92).
Treatment

Check ECG if you do this! In this important study, authors followed the corrected QT (QTc) interval in a consecutive cohort of 84 patients receiving hydroxychloroquine and azithromycin which were administered orally for 5 days. A prolongation of the QTc from a baseline average of 435 ± 24 ms to a maximal average value of 463 ± 32 ms was found, occurring on day 3.6 ± 1.6 of therapy. In a subset of nine (11%) patients, the QTc was severely prolonged to > 500 ms, a known marker of high risk of malignant arrhythmia and sudden cardiac death. Five of nine patients with severe QTc prolongation had a normal QTc at baseline.

25 April

Epidemiology

Complex models from Italy, quantifying the effect of local containment measures. The bottom line: the sequence of restrictions posed to mobility and human-to-human interactions have reduced transmission by 45% (42 to 49%). Models unquestionably support strong governmental decisions like those made in Italy.

Transmission

The next outbreak in King County, Washington: a skilled nursing facility facing rapid and widespread transmission of the virus, leading to 17 deaths in 57 residents. Of note, 27/48 with positive test results were asymptomatic at the
time of testing and most likely contributed to transmission. Infection-control strategies focussing solely on symptomatic residents are not sufficient! Test them all, immediately!


Measuring temperature’s impact on transmission rates is almost impossible in such a dynamic pandemic. The authors have made a heroic attempt, showing that the number of diagnosed cases may increase below a maximum temperature of 10° C and linearly decreasing afterward. Thus, the arrival of summer could reduce the transmission of the COVID-19. However, this is only a first clue that has to be confirmed.

**Diagnostics**


Brief but excellent review on the pitfalls and problems of antibody tests. At present, a positive antibody result does not guarantee non-infectious status nor immunity. What about asymptomatic or minimally symptomatic persons? The molecular heterogeneity of SARS-CoV-2 subtypes, imperfect performance of available tests and cross-reactivity with seasonal CoVs are discussed.


The dynamics profile of SARS-CoV-2 shedding from 56 recovered patients. The negative results of RT-PCR test for SARS-CoV-2 (throat or deep nasal cavity swab samples) began to be dominant from week 4 after onset of symptoms and by the end of follow-up (6 weeks), all results of RT-PCR test were negative.

Do asymptomatic individuals develop antibodies? Serial investigation on 21 individuals from Jiangsu Province, including 17 COVID-19 patients and 5 asymptomatic carriers, using gold immunochromatography assay supplied by Innovita (China). All of 17 symptomatic patients were seropositive by week 6. Only 1/5 asymptomatic cases generated SARS-CoV-2 specific antibody responses within the first 4 weeks.

Comorbidities


The first large cohort of COVID-19 in transplant recipients. Of 90 patients (median age 57 years), 46 were kidney recipients, 17 lung, 13 liver, 9 heart and 5 dual-organ transplants. Sixteen patients died (18% overall, 24% of hospitalized, 52% of ICU), indicating that transplant recipients appear to have more severe outcomes.


Single center experience with 36 kidney transplant recipients. Patients appear to have less fever as an initial symptom, lower CD3/4/8 cell counts and more rapid clinical progression: after 21 days, 10 died.


Some helpful recommendations on how to modify clinical care for people with epilepsy and what general advice can be given to these patients during this crisis.
Treatment


More on a key enzyme, SARS-CoV-2’s main protease (Mpro). The authors synthesized two lead compounds (11a and 11b) targeting Mpro, exhibiting good inhibitory activity, good PK properties and low toxicity in animal experiments. Pre-clinical.

26 April

Epidemiology


Complex transmission models, using epidemiological data from China. The authors concluded that the travel quarantine introduced in Wuhan on 23 January 2020 only delayed epidemic progression by 3 to 5 days within China, but international travel restrictions did help slow spread elsewhere by nearly 80% in the world until mid-February. The results suggest that even sustained 90% travel restrictions to and from mainland China only modestly affect the epidemic trajectory. Early detection, hand washing, self-isolation, and household quarantine will likely be more effective.

Transmission


Good news. Among 21 healthcare workers who had contact with an initially undiagnosed COVID-19 case, transmission risk was low, especially during short contacts.
Comorbidities


Brand new information: smoking is not the best idea. However, this is particularly true in the current pandemic. Ever having smoked significantly and substantially increased pulmonary ACE2 expression by 25%. The significant smoking effect on ACE2 pulmonary expression may suggest an increased risk for viral binding and entry of SARS-CoV-2 in lungs of smokers.

Severe COVID-19


Is there anybody still twaddling about herd immunity? Let him read this detailed feature, describing the map of the devastation that COVID-19 can inflict not only on the lungs but on other organs as well, including blood vessels, heart, brain, kidneys and other organs. Scientists are just beginning to probe the nature of that harm.

Servick K. **Survivors' burden.** Science 24 Apr 2020: Vol. 368, Issue 6489, pp. 359. [https://science.sciencemag.org/content/368/6489/359](https://science.sciencemag.org/content/368/6489/359)

Discharge from ICU is not the end of it. Clinicians are now turning their attention to potential lingering effects of both the virus and the emergency treatments that allow people to survive. Scarring can cause long-term breathing problems. This article also discusses other topics of concern such as muscle atrophy and weakness, mental problems but also cognitive impairment after leaving long-term intensive care.


Useful review on the unique lung injury induced by SARS-CoV-2 infection. It has become clear that acute respiratory distress syndrome (ARDS) in COVID-19 is different from ARDS. “CARDs” appears to include an important vascular insult that potentially mandates a different treatment approach than cus-
tomarily applied for ARDS. The authors review their experiences and propose to categorize patients. In type L (low lung elastance, high compliance, low response to PEEP), infiltrates are often limited in extent and initially characterized by a ground-glass pattern on CT that signifies interstitial rather than alveolar edema. Many patients do not appear overtly dyspneic and may stabilize at this stage without deterioration. Others may transit to a clinical picture more characteristic of typical ARDS: Type H shows extensive CT consolidations, high elastance (low compliance) and high PEEP response. Clearly, types L and H are the conceptual extremes of a spectrum that includes intermediate stages.


Case series from Lille, France showing a high prevalence of Pulmonary Embolism (PE) in severe COVID-19. Among the first 107 COVID-19 patients admitted to the ICU for pneumonia in March, the authors identified 22 (20.6%) cases. It is of note that at the time of diagnosis of PE, 20/22 were receiving prophylactic antithrombotic treatment (UFH or LWMH) according to the current guidelines in critically ill patients.

**Treatment**


Less is more? This double-masked, randomized, Phase IIb clinical trial in Manaus, Brazil allocated severe COVID-19 patients to receive high-dose CQ (600 mg BID for 10 days) or low-dose CQ (450 mg BID on day 1, QD for 4 days). The data safety monitoring board terminated the trial after 81/440 individuals had been enrolled. By day 13 of enrolment, 6 of 40 patients (15%) in the low-dose group had died, compared with 16 of 41 patients (39%) in the high-dose group. Viral RNA was detected in 78% and 76%, respectively. This trial also shows how dramatically mechanisms to execute research have accelerated: the first patient had been enrolled in this trial on March 26, 2020.

People with lupus (SLE) who take hydroxychloroquine (HCQ) are not protected. This cohort describes 17 SLE patients with COVID-19, among them several severe cases. The duration of HCQ treatment prior to COVID-19 was relatively long, with a median of 7.5 years. Some patients were also treated with steroids and/or with immunosuppressants.


What if remdesivir doesn’t work? The next nucleoside analog is on its way. Beta-D-N(4)-hydroxycytidine (NHC, EIDD-1931) has broad spectrum antiviral activity against all human and bat CoVs, including CoVs resistant to remdesivir. In mice, both prophylactic and therapeutic administrations improved pulmonary function and reduced virus titer.

27 April

Epidemiology


Review of key epidemiological concepts and discussion of some of the preventable methodologic errors.
Outbreaks in homeless shelters. If you test more than one person to be PCR positive, you already have many positive cases. Overall, 1,192 residents and 313 staff members were tested in 19 shelters from 4 US cities. When testing followed identification of a cluster, high proportions of positive tests were found, ranging from 16-66%. Testing in shelters where only one or no previous case had been identified found low prevalence (1-5%).

Interesting idea. Epidemiological data from Tibet, Bolivia and Ecuador suggest that COVID-19 infection is decreased in populations living at an altitude of above 3,000 m. Highland inhabitants may be less susceptible to SARS-CoV-2 virus infection due to physiological acclimatization to hypoxia. High-altitude environmental factors may contribute to reduce the virulence of SARS-CoV-2. But can we be sure? The methods section of this paper contains one sentence. And the fact that the virus was written incorrectly even in the title, does not enhance credibility.

Preliminary results of an old-fashioned vaccine consisting of a chemically inactivated version of the virus (which could be produced easily and in huge quantities). The vaccine worked in 8 rhesus macaques, while no obvious side effects were observed. Sinovac Biotech, an experienced vaccine maker from China, has now started Phase I clinical trials in 144 healthy volunteers to evaluate safety.
Transmission

The next outbreak, occurring in a pediatric dialysis unit in Münster, Germany, comprising a total of 12 cases. After careful investigation, the authors found that none of 32 persons with type II exposure became infected (= shared indoor environment without cumulative 15 minutes face-to-face contact, HCWs exposed during treatment or nursing in a distance of > 2 meters, without appropriate personal protective equipment such as surgical masks, etc.).


Several reports from China have suggested prolonged shedding of the virus by measuring viral RNA in different body fluids. The authors emphasize an important issue in the current discussion. The presence of nucleic acid alone cannot be used to define viral shedding or infection potential. For many viral diseases including SARS-CoV or MERS-CoV, it is well known that viral RNA can be detected long after the disappearance of infectious virus.

Diagnostics
Qu J, Wu C, Li X. Profile of IgG and IgM antibodies against severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). Clinical Infectious Diseases. 2020. Full-text: https://doi.org/10.1093/cid/ciaa489

Seroconversion patterns of IgM and IgG antibodies using 347 serum samples from 41 patients. Using combined N and S proteins as capture antigen to increase sensitivity of their in-house assay, IgG and IgM antibodies were found in the majority of the patients during the first three weeks of the disease. Of note, the seroconversion time of IgG antibody was earlier than IgM. IgG antibody reached the highest concentration on day 30, while IgM antibody peaked on day 18, and then began to decline.
Severe COVID-19
Triage? Nobody is prepared, according to this survey among 67 Bioethics Program Directors from North American hospitals. Over one half of respondents did not have ventilator triage policies. Policies have substantial heterogeneity, and many omit guidance on fair implementation. Of note, among the most frequently cited triage criteria was “lottery” (35%). Great.

Treatment
After hearing politicians touting the potential benefits, many patients are turning away from clinical trials of other therapies that would require them to give up chloroquine treatments. This report reviews these issues which have already led to serious delays in trial enrolment, muddled efforts to interpret data and endangered clinical research on COVID-19.

Famotidine for COVID-19? By reviewing 6212 Chinese patient records, it became obvious that many survivors had been suffering from chronic heartburn and were on famotidine rather than the more expensive omeprazole. On 7 April, the first COVID-19 patients at Northwell Health in the New York City area began receiving famotidine intravenously, at nine times the heartburn dose. Interim results of this clinical trial which has enrolled an incredibly huge number of patients, will be available within a few weeks. Don’t tell your politicians.
28 April

Epidemiology


This brief review outlines the ways in which different types of mobile phone data can help to better target and design measures to contain and slow the spread of the COVID-19 pandemic.


This important analysis of 391 early SARS-CoV-2 cases and their close contacts in Shenzhen, China, provides insight into the natural history and transmission. This work further supports a short incubation period (4–6 days). Notably, 5% took 14 days or more to develop symptoms. In multiple conditional logistic regression analysis of contact types, household contact (OR 6.3; 95% CI 1.5–26.3) and travelling together (OR 7.1; 1.4–34.9) were significantly associated with infection. The secondary attack rate was relatively low with 11.2% (95% CI 9.1–13.8) among household contacts and was similar across all age categories. However, this could be considered an underestimate, since transmission chains were cut short: index cases detected by symptom-based surveillance were rapidly isolated outside of the home.


Huge study from China. Based on 2,907 confirmed cases, the median incubation period was 5 days, and more than 95% of cases had an incubation period of less than 13 days. From January 23, the incubation period among imported confirmed cases outside Hubei Province showed a gradual upward trend, but this trend was not obvious in non-imported cases.
Diagnostics

The bottom line of this comment: we don’t know enough. There is no certainty as to the immunological correlates of antiviral protection or the proportion of the population who must attain them, making it impossible to identify a point when this level of immunity has been reached.


Many groups have initiated trials of prophylactic drugs and have envisioned efficacy trials of vaccine candidates. The authors argue for serological testing of trial participants at the start and end of these trials (and at intermediate points), in order to enhance the value and interpretability of these studies.

Virology

An elegant study explaining distinct clinical features of COVID-19 and SARS. Authors investigated cell susceptibility, species tropism, replication kinetics, and virus-induced cell damage from both SARS-CoVs, using live infectious virus particles. SARS-CoV-2 replicated more efficiently in human pulmonary cells, indicating that SARS-CoV-2 has most likely adapted better to humans. SARS-CoV-2 replicated significantly less in intestinal cells (might explain lower diarrhea frequency compared to SARS) but better in neuronal cells, highlighting the potential for neurological manifestations.

Pseudorabies virus (PRV), an alphaherpesvirus, is sorted and transported in axons in the anterograde direction by the kinesin-3 motor KIF1A. Why is this of interest? Because it’s currently (April 28, 2020, 7:15 a.m. CET) the headline article of the Journal of Virology, the Journal of the American Society of Microbiology (Impact Factor 4.3). No work, no link on COVID-19, nothing on their website. This journal aims for “reporting important new discoveries and pointing to new directions in research”. Just saying.

Clinical

Nice review on clinical manifestations, evaluation and management, but also on infection control and prevention efforts.


Protecting health care workers is an important component of public health measure! This cross-sectional survey of 1257 health care workers in Chinese hospitals found considerable proportions of participants with symptoms of depression (50%), anxiety (47%), insomnia (34%), and distress (72%). Participants reported experiencing psychological burden, especially nurses, women, those in Wuhan, and frontline health care workers directly engaged in the care for patients with COVID-19.

Treatment

The next new idea. Dipeptidyl peptidase 4 (DPP4) is a serine exopeptidase expressed ubiquitously in several tissues, including but not limited to lung, kidney, liver, gut, and immune cells. Some careful thoughts on whether DPP4 modulation or inhibition (by diabetes drugs such as gliptins) may prevent infection and/or progression of the COVID-19.
29 April

Epidemiology


Between March 28, 2020, and April 1, 2020, authorities became aware of a few cases in a single large homeless shelter in Boston, prompting SARS-CoV-2 testing of all remaining shelter residents. In total, 147/408 (36%) were positive. Of note, 88% had no symptoms and no fever at the time of diagnosis.

Transmission


Toilets are the hot spots! Important study, sampling airborne SARS-CoV-2 and its aerosol deposition at 30 sites in two designated hospitals and public areas in Wuhan in February/March. The concentration in isolation wards and ventilated patient rooms was very low, but it was elevated in the patients’ toilet areas. Levels were undetectable in the majority of public areas outside the hospitals and was undetectable except in two areas prone to crowding. Room ventilation, open space, sanitization of protective apparel as well as proper use and disinfection of toilet areas can effectively limit the concentration of SARS-CoV-2 RNA in aerosols.


Vaginal delivery is associated with low risk of intrapartum infection. Of 42 women with COVID-19 (19 with pneumonia), 24 delivered vaginally. Only 1/24 new-born had a positive test. Two women transmitted the virus while breastfeeding without a mask.
Diagnostics

One of the largest studies to date, reporting on acute antibody responses (using magnetic chemiluminescence enzyme immunoassay) in 285 patients (mostly non-severe COVID-19, 39 treated at ICU). Within 19 days after symptom onset, 100% of patients tested positive for antiviral IgG. Seroconversion for IgG and IgM occurred simultaneously or sequentially. Both IgG and IgM titers plateaued within 6 days after seroconversion. The median day of seroconversion for both IgG and IgM was 13 days post-symptom onset. No association between plateau IgG levels and clinical characteristics of the patients was found.

Clinical

Five cases of large-vessel stroke in younger patients (age 33-49, 2 without any risk factors) who presented in New York City. By comparison, every 2 weeks over the previous 12 months, on average 0.73 patients younger than 50 years of age with large-vessel stroke had been treated.


Excellent review of coagulation abnormalities that occur in association with COVID-19, and clinical management questions likely to arise. The initial coagulopathy of COVID-19 presents with prominent elevation of D-dimer and fibrin/fibrinogen degradation products, while abnormalities in prothrombin time, partial thromboplastin time, and platelet counts are relatively uncommon. Coagulation test screening, including the measurement of D-dimer and fibrinogen levels, is suggested. Current data do not suggest the use of full intensity anticoagulation doses unless otherwise clinically indicated.
Comorbidities


The authors report a significant decrease in acute coronary syndrome-related hospitalization rates across several cardiovascular centers in northern Italy during the early days of the outbreak.


Brief review: adjuvant treatment and continuation of pre-existing statin therapy could improve the clinical course of patients with COVID-19, either by their immunomodulatory action or by preventing cardiovascular damage.

Procedures


Interesting simulation experiment. The authors used adult and pediatric mannequins and a fluorescent marker to visualize deposition of simulated exhaled respiratory secretions and material onto HCWs performing or assisting in endotracheal intubation procedures. HCWs wore N95 respirators, eye protection, isolation gowns, and gloves. Fluorescent markers were found on the uncovered facial skin (7/8), hair, and shoes of the HCWs, suggesting that the current recommendations may not fully prevent exposures. Clothing that covers all skin may further diminish exposure risk.


Brief review on current knowledge on the risk during intubation, discussing the study above. Fundamental research is needed to better inform recommendations. A better understanding of the duration of infectivity and level of
risk posed by airborne SARS-CoV-2 would help to guide recommendations for respiratory protection.

30 April

Virology
Fantastic graphical review on current vaccine development. Easy to understand, it explains different approaches such as virus, viral-vector, nucleic-acid and protein-based vaccines.

Clinical
By April 25, the Bronx (which has the highest proportion of racial/ethnic minorities, the most persons living in poverty, and the lowest levels of educational attainment) had higher rates (almost two-fold) of hospitalization and death related to COVID-19 than the other four New York City boroughs Brooklyn, Manhattan, Queens and Staten Island.

Comorbidities
Baseline use of biologics is not associated with worse COVID-19 outcomes. A case series of 86 patients with immune-mediated inflammatory disease (rheumatoid arthritis, psoriatic arthritis, ankylosing spondylitis, psoriasis, inflammatory bowel disease, or related conditions) and symptomatic COVID-19, among them 62 (72%) receiving biologics or Janus kinase (JAK) inhibitors. The percentage of patients who were receiving biologics or JAK inhibitors at baseline was higher among the ambulatory patients than among the hospital-
ized patients. In contrast, hospitalization rates were higher in patients treated with oral glucocorticoids, hydroxychloroquine and methotrexate.


Best paper title of the day. Using a French Registry, the authors found a spectacular drop of 25% for admission due to STEMI between March 2019 and March 2020. The steep decline was found for both acute (< 24hrs) and late presentation (> 24 hrs) STEMI. But where did they go? According to the authors, explanations may be patients’ fear of coming to the hospital or disturbing busy caregivers, especially in the case of mild STEMI clinical presentation. Other hypothetical reasons are reduced air pollution, better adherence to treatment, limited physical activity or absence of occupational stress during lockdown. When will we ever learn?


Avoiding hospitals, staying at home, dying of fear? Using data from the Lombardy Cardiac Arrest Registry for the provinces of Lodi, Cremona, Pavia, and Mantua during the first 40 days of the COVID-19 outbreak (February 21 through March 31, 2020), the authors found a 58% increase of out-of-hospital cardiac arrest compared to the same period in 2019.

**Treatment**


The next example of “Fauci said”. Anthony Fauci, director of the US National Institute of Allergy and Infectious Disease (NIAID) had announced that a clinical trial of “more than a thousand people showed that people taking remdesivir recovered in 11 days on average, compared to 15 days for those on a placebo”. That’s all. We believe that this is not an appropriate way to share data.

And here it is, the first randomized, double-blind, placebo-controlled trial of remdesivir (and not the study Fauci was talking about)! This multicenter trial at ten hospitals in Hubei, China enrolled patients with severe COVID-19 to receive 10 days of single infusions or placebo. Clinical improvement up to day 28 was defined as the time (in days) to the point of a decline of two levels on a six-point ordinal scale of clinical status (from 1 = discharged to 6 = death) or discharged alive from hospital, whichever came first. In the 237 patients enrolled between Feb 6 and March 12, remdesivir use was not associated with a difference in time to clinical improvement (hazard ratio 1.23, 95% CI 0.87–1.75). Remdesivir was stopped early because of adverse events in 18 (12%) patients versus four (5%) patients who stopped placebo early. The trial did not attain the predetermined sample size because the outbreak of COVID-19 was brought under control in China. Disappointing. More data are eagerly awaited.


Bill Gates, talking about billions of dollars. He will donate some. According to this perspective, he has committed “substantial resources”. Well done.

Severe COVID-19


Treat it like ARDS! The authors provide a pathophysiologic justification for the use of established ARDS therapies, including low tidal volume and early prone ventilation. In their retrospective cohort of 66 COVID-19 patients (median age 58 years) with respiratory failure, fatality was only 17%. The authors conclude that their patients exhibit similar gas exchange, respiratory system mechanics, and response to prone ventilation as prior large cohorts of patients with ARDS.
Procedures

The authors present the creation of a novel negative-pressure aerosol cover made out of readily available operating room materials as an additional barrier to limit the spread of aerosols during tracheostomy. This cover was easy to create and deploy using readily available materials found in operating centers.
May 2020

1 May

Epidemiology


When people move, they take contagious diseases with them. Using detailed mobile phone geolocation data to compute aggregate population movements, the authors tracked the transit of people from Wuhan to the rest of China. The geographic flow of people anticipated the subsequent location, intensity, and timing of outbreaks in the rest of China.

Virology, Immunology


Authors from China report on a SARS-CoV-2 subtype which seems to be more aggressive and to spread more quickly. This paper has gained much attraction in the media.


In this paper, Scottish researches now demonstrate very clearly that Tang et al. were wrong and that the major conclusions of that paper cannot be substantiated. Using examples from other viral outbreaks, the authors discuss the difficulty in demonstrating the existence or nature of a functional effect of a viral mutation, and advise against overinterpretation of genomic data during the pandemic. Although rapid publication is critical for unfolding dis-
ease outbreaks, thorough and independent peer review should not be bypassed to get results published quickly.


A brilliant overview of the pathophysiology of SARS-CoV-2 infection. How SARS-CoV-2 interacts with the immune system, how dysfunctional immune responses contribute to disease progression and how they could be treated.

Diagnostics

Yin L, Moi H, Shao J. Correlation between Heart fatty acid binding protein and severe COVID-19: A case-control study. PLOS One, 29 Apr 2020. https://doi.org/10.1371/journal.pone.0231687

Heart fatty acid-binding protein (HFABP), a serum biomarker for myocardial injury, is highly cardiac-specific. Elevated serum HFABP may be used as an indicator of severe COVID-19. This small retrospective analysis included 45 patients, in which HFABP was measured on the day of hospital admission. In the HFABP positive group (n = 15), severe illness was more common during hospitalization (87.5% vs 40%, p = 0.002).

Clinical


The first study providing some evidence for a predisposition for severe disease. The authors analyzed a genetic variant of IFITM3. This gene encodes an immune effector protein critical to viral restriction and homozygosity for the C allele that has been associated with influenza severity. The CC genotype was found in 12/24 (50%) patients with severe COVID-19, compared to 16/56 (29%) with mild disease. After adjusting for age groups, the odds ratio for severe disease in patients with CC genotype was 6.3 (p < 0.001).
Meng Y, Wu P, Lu W, et al. *Sex-specific clinical characteristics and prognosis of coronavirus disease-19 infection in Wuhan, China: A retrospective study of 168 severe patients.* PLOS Pathogens 2020, April 28, 2020. https://doi.org/10.1371/journal.ppat.1008520. This retrospective cohort highlights sex-specific differences in clinical characteristics and prognosis. Older age and the presence of comorbidities were prognostic risk factors in 86 males but not in 82 females. Some laboratory parameters also showed significant differences.

**Comorbidities**

Stefanini GG, Montorfano M, Trabattoni D, et al. *ST-Elevation Myocardial Infarction in Patients with COVID-19: Clinical and Angiographic Outcomes.* Circulation. 2020 Apr 30. PubMed: https://pubmed.gov/32352306. Full-text: https://doi.org/10.1161/CIRCULATIONAHA.120.047525 STEMI may represent the first clinical manifestation of COVID-19. In 11 out of 28 patients (39%) with STEMI, a culprit lesion was not identifiable by coronary angiography. According to the authors, a dedicated diagnostic pathway should be delineated for COVID-19 patients with STEMI, aimed at minimizing patients’ procedural risks and healthcare providers’ risk of infection.

Yang G, Tan Z, Zhou L, et al. *Effects Of ARBs And ACEIs On Virus Infection, Inflammatory Status And Clinical Outcomes In COVID-19 Patients With Hypertension: A Single Center Retrospective Study.* Hypertension. 2020 Apr 29. PubMed: https://pubmed.gov/32348166. Full-text: https://doi.org/10.1161/HYPERTENSIONAHA.120.15143 The next retrospective study analysing COVID-19 patients with hypertension, arguing against deleterious effects of angiotensin II receptor blockers or angiotensin-converting enzyme inhibitors. Patients on these drugs (n=43) had significantly lower concentrations of CRP (p = 0.049) and procalcitonin (p = 0.008) than patients on other antihypertensive drugs (n = 83). Furthermore, trends toward lower proportions of critical diseases (9.3% vs 22.9%; p = 0.061) and death rates (4.7% vs 13.3%; p = 0.216) were observed.
Treatment


Don’t be too late: Of 6 patients with respiratory failure receiving convalescent plasma at a median of 21 days after first detection of viral shedding, all tested RNA negative by 3 days after infusion. However, 5 died eventually.

2 May

Dermatology

This has been the week of the dermatologists: numerous studies reported on cutaneous manifestations seen in the context of COVID-19. The most prominent phenomenon, the so-called “COVID toes”, are chilblain-like lesions which mainly occur at acral areas [chilblain: Frostbeule (de), engelure (fr), sabañón (es), gelone (it), frieira (pt), 冻疮 (cn)]. These lesions can be painful (sometimes itchy, sometimes asymptomatic) and may represent the only symptom or late manifestations of SARS-CoV-2 infection. Of note, in most patients with “COVID toes” the disease is only mild to moderate. It is speculated that the lesions are caused by inflammation in the walls of blood vessels, or by small micro-clots in the blood. However, whether “COVID toes” represent a coagulation disorder or a hypersensitivity reaction is still unknown. In addition, in many patients, SARS-CoV-2 PCR was negative (or not done) and serology tests (to prove the relationship) are still pending.


Authors describe two different patterns of acute acro-ischemic lesions, which can overlap. The chilblain-like pattern was present in 95 patients (72.0%). It is characterized by red to violet macules, plaques and nodules, usually at the distal aspects of toes and fingers. The erythema multiforme-like pattern was present in 37 patients (28.0%).

Hoffmann – Kamps
The authors describe five clinical cutaneous manifestations of lesions: acral areas of erythema with vesicles or pustules (pseudo-chilblain) (19%), other vesicular eruptions (9%), urticarial lesions (19%), maculopapular eruptions (47%) and livedo or necrosis (6%). Vesicular eruptions appear early in the course of the disease (15% before other symptoms). The pseudo-chilblain pattern frequently appears late in the evolution of the COVID-19 disease (59% after other symptoms).

Preliminary results of a survey among Italian dermatologists and pediatrics, reporting on 63 cases (only a few patients with confirmed COVID-19).

A dermatology unit in Italy reports on 14 cases including 11 children. Lesions were localized on the feet in 8 cases, on the hands in 4 cases, on both sites in 2.

In a Whatsapp group of 400 French dermatologists, a total of 295 atypical skin eruptions or lesions of suspected or confirmed COVID-19 patients were posted between March 14 and April 10. Chilblains or chilblain-like lesions represented 146 posts, and 149 posts included other suspected COVID-19-related skin eruption, e.g. urticaria, rash, chickenpox-like or pityriasis rosea.

Case series on 22 adult patients with varicella-like lesions. Typical features were constant trunk involvement, usually scattered distribution and mild/absent pruritus, the latter being in line with most viral exanthems but unlike true varicella. Lesions generally appeared 3 days after systemic symptoms and disappeared by 8 days.


Case report on digitate papulosquamous eruption in a patient with severe COVID-19. This paraviral dermatosis could be a secondary result of the immune response against the virus.


And yes, of course, rash may also occur. A case report with petechial skin rash with striking absence of lesions in the crural folds.


Another patient with impressive rash (a 61-year-old Spanish medical doctor).

A word of caution. Not all rashes or cutaneous manifestations seen in patients with COVID-19 can be attributed to the virus. Coinfections or medical complications have to be considered. Comprehensive mucocutaneous examinations, analysis of other systemic clinical features or host characteristics, and histopathologic correlation, will be vital to understanding the pathophysiologic mechanisms of what we are seeing on the skin.

3 May

Epidemiology


An elegant model demonstrating the impact of lockdown by using contact survey data for Wuhan and Shanghai before and during the outbreak. Daily contacts were reduced 7-8-fold during the social distancing period, with most interactions restricted to the household. Of note, children 0-14 years were less susceptible to infection than adults (however, numbers were low). Social distancing alone, as implemented during the outbreak, was sufficient to control COVID-19. While proactive school closures cannot interrupt transmission on their own, they can reduce peak incidence by 40-60% and delay the epidemic.


A comprehensive study on genomic epidemiology of SARS-CoV-2 in Guangdong province. The authors generated 53 genomes from infected individuals in Guangdong and deduce that following the first COVID-19 case detected in early January, most infections were the result of virus importation from elsewhere, and that chains of local transmission were limited in size and duration.
Virology, Immunology


A blueprint for future therapies. This heroic work, emerging from a worldwide collaboration (> 100 co-authors!), systematically maps the interaction landscape between SARS-CoV-2 proteins and human proteins. The authors cloned, tagged and expressed 26 of the 29 SARS-CoV-2 proteins in human cells and analyzed the human proteins physically associated with each using affinity-purification mass spectrometry (AP-MS), identifying 332 high-confidence SARS-CoV-2-human protein-protein interactions (PPIs). In total 66 human proteins or host factors targeted by 69 compounds (29 FDA approved drugs, 12 drugs in clinical trials, and 28 preclinical compounds) were found. Screening a subset of these in multiple viral assays identified two sets of pharmacological agents that displayed antiviral activity: inhibitors of mRNA translation and predicted regulators of the Sigma1 and Sigma2 receptors.

Yin W, Mao C, Luan X. Structural basis for inhibition of the RNA-dependent RNA polymerase from SARS-CoV-2 by Remdesivir. Science 01 May 2020. Full-text: https://science.sciencemag.org/content/early/2020/04/30/science.abc1560

Convincing data from clinical trials are still lacking (mostly rumours and press releases). However, this work shows how remdesivir inhibits the SARS-CoV-2 RdRp activity in theory. The authors describe the structure of the SARS-CoV-2 RdRp complex in the apo form and in the complex with a template-primer RNA and the active form of remdesivir. The cryo-EM structures reveal how the template-primer RNA is recognized by the enzyme and how chain elongation is inhibited by remdesivir (and why other nucleotides such as EIDD-2801 may be more potent).


SARS-CoV and SARS-CoV-2 infected enterocyte lineage cells in a human intestinal organoid model. Similar infection rates of enterocyte-precursors and
enterocytes were observed and low levels of ACE2 may be sufficient for viral entry. This study explains why gastrointestinal symptoms are observed in a subset of patients and why viral RNA can be found in rectal swabs, even after nasopharyngeal testing has turned negative.

**Diagnostics**


A CT-based artificial intelligence (AI) system was shown to have the potential to assist in the early diagnosis and monitoring of pneumonia. For the classification model, 361,221 CT images from 2,246 patients including 752 NCP, 797 common pneumonia patients and 697 normal control patients were used for training. In brief, the AI system performance was overall superior to that of junior radiologists and comparable to mid-senior radiologists.

**Clinical**


Brief review on the current knowledge on the remarkable heterogeneity of disease patterns from a clinical, radiological, and histopathological point of view. The idiosyncratic responses of individual patients may be in part related to underlying genetic variations.

**Comorbidities**


Check your HbA1c! The hitherto largest retrospective study on the impact of type 2 diabetes (T2D) has carefully analyzed 7,337 cases of COVID-19 in Hubei Province, China, among them 952 with pre-existing T2D. The authors found that subjects with T2D required more medical interventions and had a significantly higher mortality (7.8% versus 2.7%; adjusted hazard ratio, 1.49) and multiple organ injury than the non-diabetic individuals. Well-controlled
blood glucose was associated with markedly lower mortality (in-hospital death rate 1.1% versus 11.0%) compared to individuals with poorly controlled BG.


Collateral damage of the current pandemic: data from Italy providing evidence that the outbreak of COVID-19 was associated with a decline by 32% in the number of percutaneous coronary intervention for acute coronary syndromes.

**Treatment**


Comprehensive review on current immunotherapies which either neutralize cytokines, SARS-CoV-2 or exert immunomodulation. Immunotherapies may not only reduce inflammation, inflammation-associated lung damage, or viral load, but could also prevent intensive care unit hospitalization.

**4 May**

**Top Ten Special on**

ACE inhibitors/ARBs – continue them (or start them up again)!

There has hardly been a topic in the last weeks of this pandemic that has kept doctors (mainly internists) and their patients as busy as the question of whether ACE inhibitors or angiotensin-receptor blockers (ARBs) can cause harm to patients. Early observations of an increased risk for mortality or severe COVID-19 in patients with hypertension, cardiovascular diseases and diabetes (Guan 2020) raised concerns. These diseases share underlying renin-angiotensin-aldosterone system pathophysiology that may be clinically insightful. In particular, activity of the angiotensin-converting enzyme 2 (ACE2) is dysregulated (increased) in cardiovascular disease (Vaduganathan 2020). As
SARS-CoV-2 cell entry depends on ACE2 (Hoffmann 2020), increased ACE2 levels may increase the virulence of the virus within the lung and heart. ACE inhibitors or ARBs which are frequently used to treat cardiovascular diseases may alter ACE2 and variation in ACE2 expression may in part be responsible for disease virulence.

Although a recent review of 12 animal studies and 12 human studies overwhelmingly implies that administration of both drug classes does not increase ACE2 expression (Sriram 2020), some concerns on deleterious effects remain and some media sources and health systems have called for the discontinuation of these drugs.

However, some small retrospective studies from China have shown no negative effect (Meng 2020). In the largest study, 188 patients taking ACEIs/ARBs were compared with 940 patients who did not use them. Of note, unadjusted mortality rate was lower in the ACEI/ARB group (3.7% vs. 9.8%) and a lower risk was also found in a multivariate Cox model (Zhang 2020).

Last week, three studies were published in the NEJM that will hopefully put an end to this discussion. Although all three were observational studies with the possibility of confounding, their message was consistent — none of the three studies showed any evidence of harm (Jarcho 2020).

The first study analyzed a total of 8,910 COVID-19 patients (from 169 hospitals located in 11 countries) for whom discharge status was available by March 29 (Mehra 2020). A total of 515 (5.8%) died in the hospital. Factors independently associated with an increased risk of in-hospital death were an age greater than 65 years (odds ratio, 1.93), coronary artery disease (2.70), heart failure (2.48; 95% CI, 1.62 to 3.79), cardiac arrhythmia (1.95; 95% CI, 1.33 to 2.86), chronic obstructive pulmonary disease (2.96; 95% CI, 2.00 to 4.40), and current smoking (1.79; 95% CI, 1.29 to 2.47). No increased risk was found for the use of ACE inhibitors (0.33; 95% CI, 0.20 to 0.54) or the use of ARBs (1.23; 95% CI, 0.87 to 1.74). Of note, use of either ACE inhibitors or statins was associated with better survival. However, these associations should be considered with extreme caution as the study design cannot exclude the possibility of confounding.

The second study analyzed 2,573 COVID-19 patients with hypertension from New York City (Reynolds 2020). In total, 634 (24.6%) had severe disease, as indicated by ICU admission, mechanical ventilation, or death by April 15, 2020. After looking at different classes of antihypertensive medication — ACE inhibitors, ARBs, beta-blockers, calcium-channel blockers, and thiazide diuretics, the authors ruled out any substantial difference in the likelihood of severe COVID-19, with at least 97.5% certainty for all medication classes.
The third study looked at a possible independent relationship between RAAS blockers and the susceptibility to COVID-19 (Mancia 2020). The authors matched 6,272 Italian cases (positive for SARS-CoV-2) with 30,759 beneficiaries of the Regional Health Service (controls) according to sex, age, and municipality of residence. There was no evidence that ACE inhibitors or ARBs modify susceptibility to COVID-19. The results applied to both sexes as well as to younger and older persons.

We think that’s it. Take your ACE inhibitors or ARBs. We do not agree with the NEJM editorial that “one or more randomized trials will be needed to answer definitively the question of whether ACE inhibitors or ARBs pose a harm to patients with COVID-19” (Jarcho 2020). Let’s not waste time and/or resources. We have bigger fish to fry.

Top 10 references


5 May

Get it done!

On remdesivir, rumors of recovery, rolling reviews, and random noise

“That’s very exciting. Get it done, Daniel.” If you want to get an idea about the incredible pressure on and expectations from researchers, then please read the protocol from the White House (Trump 2020). NIAID’s Anthony Fauci and Gilead’s CEO Daniel O’Day make heroic attempts to explain the situation to decision makers. This pressure has its consequences. What we’ve seen during the last few days has probably never happened during the last 500 years on this planet: a drug the authorities (read: FDA) give “Emergency Use Authorization”, two days after the first randomized trial practically shows ineffectiveness. Crazy times. What is whispered at press conferences counts more than peer-reviewed scientific evidence. Because the window for learning is so short, the need to balance scientific rigor against speed seems inevitable. But should that really be the case? Last Friday, a smart comment in SCIENCE argued “against pandemic research exceptionalism”. Even in such a crisis, the rules of good science should not be thrown overboard. Releasing the full data is essential to allow scientists to understand studies (London 2020).

Let’s take a closer look on the scarce data we have on remdesivir:
1. **Compassionate Use Program**: this was a fragmentary case series (Grein 2020) on some patients (only 53/61 patients were analyzed) with varying disease severity. Some improved, some didn't: random noise. We believe, for a number of reasons, this case series published in the New England Journal of Medicine is a cautionary tale for “science in a hurry”, arousing false expectations. It might have been preferable to postpone the publication. However, Daniel O’Day, Gilead’s CEO, wrote the same day that “the majority” of patients “demonstrated clinical improvement”.

2. **NCT04257656**: This multicentre trial, funded by the Chinese Ministry of Science and Technology, was conducted between Feb 6 and March 12 at ten hospitals in Hubei (Wang 2020). A total of 237 patients with pneumonia confirmed by chest imaging, oxygen saturation of 94% or lower on room air and within 12 days of symptom onset were randomized to receive 10 days of single infusions or placebo. Clinical improvement was defined as the days to the point of a decline of two levels on a six-point clinical scale (from 1=discharged to 6=death) or discharged alive from hospital, whichever came first. Patients were 65 years old (IQR 56–71), 56% male, many were co-treated with lopinavir (28%) and corticosteroids. The trial did not attain the predetermined full sample size because the outbreak was brought under control in China. However, from the analyzable data, remdesivir was not associated with a difference in time to clinical improvement (hazard ratio 1.23, 95% CI 0.87–1.75). Clinical improvement rates were 27% versus 23% at day 14 and 65% versus 58% at day 28. Day 28 mortality was 14% versus 13%. Of note, the viral load decreased similarly in both groups. Some patients with remdesivir had dosing prematurely stopped due to adverse events (12% versus 5%, mainly gastrointestinal symptoms and increases of liver enzymes). But let’s think positive: Time to recovery was “numerically” shorter in the remdesivir group than the control group, particularly in those treated within 10 days of symptom onset.

3. **SIMPLE 1**: This Phase III trial evaluated 5-day and 10-day dosing durations in 397 hospitalized patients with severe COVID-19. On April 29, Gilead announced that no difference was seen in clinical improvement (odds ratio: 0.75, 95% CI 0.51 – 1.12] on day 14. The most common adverse events were nausea (9.5 %) and acute respiratory failure (8.3%). Grade 3 or higher liver enzyme elevations occurred in 7.3%, with 3.0 % discontinuing remdesivir. Gilead plans to submit the full data for publication in a peer-reviewed journal “in the coming weeks”. An expansion phase will enrol an additional 5,600 (!) patients around the world.

4. **ACTT** (Adaptive COVID-19 Treatment Trial): Sponsored by NIH, this was the first phase III study launched in the United States. ACTT began on February 21 (the first participant was repatriated after being quarantined on the
Diamond Princess) and enrolled 1,063 hospitalized patients with advanced COVID-19 and lung involvement. The design was “adaptive” to incorporate additional investigative treatments (and, surprisingly, to adapt new response criteria, see below). A total of 68 sites participated, among them 47 in the US and 21 in Europe and Asia. On April 16, it was decided to modify the primary endpoint (from mortality to time of recovery), facing “evolving clinical data”. Only 11 days later, an independent DSMB noted that remdesivir was better than placebo with regard to the new primary endpoint, time to recovery (defined as being well enough for hospital discharge or returning to normal activity level). With the drug, recovery was 31% faster (11 versus 15 days, p<0.001). For the initial primary endpoint, mortality, results suggested an only marginal benefit (8.0% versus 11.6%, p=0.059). “Whenever you have clear-cut evidence a drug works, you have an ethical obligation to immediately let the people in the placebo group know so they can have access to it”, said Anthony Fauci. Fine. But now we have waited another week. So where is the data? It will be probably not that easy to explain why such a major trial switched the key outcome measure only a few days before the interim analysis was done. At that time, they were still blinded for the results, correct? There is no doubt that this paper will have a complex and interesting discussion.

In the meantime, both the optimists and the pessimists can hold onto their opinions (see table).

What comes next?

Several additional trials are ongoing. Some have been suspended such as NCT04252664, a trial in adults with mild and moderate COVID-19, because during the last few weeks no eligible patients could be recruited. The second SIMPLE trial, NCT04292730 (GS-US-540-5774) is probably the most interesting study, evaluating the efficacy of two remdesivir regimens compared to standard of care in 600 patients with moderate COVID-19, with respect to clinical status assessed by a 7-point ordinal scale on day 11. Estimated study completion date is May 2020. INSERM in France has initiated a study evaluating remdesivir and other potential treatments, using a master protocol (SOLIDARITY) developed by WHO. This study (NCT04315948) is a multi-centre, adaptive, randomized, open clinical trial of the safety and efficacy of treatments of COVID-19 in hospitalized adults. Adults hospitalized for severe COVID-19 will be randomized to one of 4 treatment arms, including standard of care, remdesivir, lopinavir/r plus interferon ß-1a and hydroxychloroquine.
Table 1. Remdesivir, optimistic and pessimistic view

<table>
<thead>
<tr>
<th>Study</th>
<th>Optimistic view</th>
<th>Pessimistic view</th>
</tr>
</thead>
<tbody>
<tr>
<td>Compassionate Use</td>
<td>Encouraging, the majority demonstrated clinical improvement</td>
<td>No control group, fragmentary data without any message</td>
</tr>
<tr>
<td>SIMPLE</td>
<td>Similar efficacy with 5- and 10-day dosing, no new safety signals</td>
<td>No control group. Placebo for 5 vs 10 days would’ve produced the same results</td>
</tr>
<tr>
<td>NCT04257656</td>
<td>Time to recovery numerically shorter</td>
<td>No effect on mortality, no effect on viral load, some side effects</td>
</tr>
<tr>
<td>ACTT</td>
<td>Faster time to recovery, strong trend towards lower mortality (8 versus 12%)</td>
<td>No significant effect on mortality in &gt;1,000 patients, and is 4 days of “faster recovery” relevant?</td>
</tr>
</tbody>
</table>

In the meantime, EMA’s human medicines committee (CHMP) has started a ‘rolling review’ of data. This speeds up the assessment of a promising investigational medicine during a public health emergency but does not imply that its benefits outweigh its risks. We’ll see what happens. By the way, the EUA allows for the distribution and emergency use of remdesivir only for the treatment of COVID-19; remdesivir remains an investigational drug and has not been approved anywhere. The fact sheet for health care providers is found here: FDA 2020.

Yes, very exciting.

References


6 May

**Epidemiology**


This review summarizes the risk factors for coronavirus infections in HCWs. There was evidence that more consistent and full use of recommended PPE measures was associated with decreased risk for infection, suggesting a dose-response relationship. This association was most consistent for masks but was also observed for gloves, gowns, and eye protection, as well as handwashing. Some evidence was found that N95 masks might be associated with decreased risk for infection versus surgical masks. Evidence also indicated an association between certain exposures (such as involvement in intubations, direct contact with infected patients, or contact with bodily secretions).

Another study on the impact of non-pharmaceutical interventions (NPIs) in China. Without NPIs, the COVID-19 cases would likely have shown a 67-fold increase (interquartile range 44-94) by February 29. Early detection and isolation of cases was estimated to have prevented more infections than travel restrictions and contact reductions, but combined NPIs achieved the strongest and most rapid effect. The lifting of travel restrictions does not appear to lead to an increase in cases if social distancing interventions are maintained.

**Virology**


An important technical advance, enabling the rapid generation and functional characterization of evolving RNA virus variants. The authors show the functionality of a yeast-based synthetic genomics platform to genetically reconstruct diverse RNA viruses (which are cumbersome to clone and manipulate due to size and instability). They were able to engineer and resurrect chemically-synthetized clones of SARS-CoV-2 in only a week after receipt of the synthetic DNA fragments.

Cyranoski D. **Profile of a killer: the complex biology powering the coronavirus pandemic.** Nature. 2020, 581, 22-26. Full-text: [https://www.nature.com/articles/d41586-020-01315-7](https://www.nature.com/articles/d41586-020-01315-7)

Fantastic, a thrilling feature on what we know about how the virus operates, where it came from and what it might do next. Leading scientists are asked about their hypotheses and current research projects on the origin and on the heterogeneity of the clinical course of COVID-19.

Viral variants which contain 15-30-bp deletions (Del-mut) or point mutations respectively at the S1/S2 junction are described. Some of them were less pathogenic in a hamster model. It would be interesting to see the prevalence of these variants in asymptomatic infected cases. The potential of the Del-mut variants as an attenuated vaccine or laboratory tool should also be evaluated.

Clinical


In multivariate regression, age > 65 years, smoking, critical disease status, diabetes, high hypersensitive troponin I (>0.04 pg/mL), leukocytosis (>10 x 10⁹/L) and neutrophilia (>75 x 10⁹/L) predicted unfavorable clinical outcomes. Of note, the administration of hypnotics was significantly associated with favorable outcomes (p<0.001). Dextropropoxyphene, a drug for insomnia, was administered at a dose of 1.0 mg per day to 82 patients for the duration of their hospitalization. Overall, favorable outcomes were recorded for these patients, including a better survival rate. Hypnotics may be an effective ancillary treatment for COVID-19.


Among their 179 COVID-19 patients, the authors identified four risk factors, age ≥65 years, pre-existing concurrent cardiovascular or cerebrovascular diseases, CD3+CD8+ T cells ≤75 cell·μL⁻¹, and cardiac troponin I ≥0.05 ng·mL⁻¹. Especially the latter two factors were predictors for mortality. Two predictive models for in-hospital mortality are presented.


Post-mortem examination of 21 COVID-19 cases, indicating a strong virus-induced vascular dysfunction. Interesting co-finding: 65% of the deceased
patients had blood group A. Coincidence? Probably not. Blood group A may be associated with the failure of pulmonary microcirculation and coagulopathies in COVID-1. Another explanation could be the direct interaction between antigen A and the viral S protein, thus facilitating virus entry via ACE2.


Of 216 patients with SARS-CoV-2, 44 (20%) were found to have a prolonged aPTT. After excluding 9 patients, 31/34 (91%) had positive lupus anticoagulant assays. As this is not associated with a bleeding tendency, authors recommend that prolonged aPTT should not be a barrier to the use of anticoagulation therapies in the prevention and treatment of venous thrombosis.

**Pediatrics**


Among a total of 100 children with SARS-CoV-2 from Italy, 21% were asymptomatic, 58% had mild disease, 19% had moderate disease, 1% had severe disease, and 1% were in critical condition.

**7 May**

**Epidemiology**

Persad G, Emanuel EJ. **The Ethics of COVID-19 Immunity-Based Licenses (“Immunity Passports”).** JAMA. Published online May 6, 2020. Full-text: [https://jamanetwork.com/journals/jama/fullarticle/2765836](https://jamanetwork.com/journals/jama/fullarticle/2765836)

Chile, Germany and the UK, among others, have indicated they will implement certifications that a person has contracted and recovered from COVID-19. According to the authors, immunity-based licenses require careful implementation to be ethical in practice. These “licenses” may allow immune people to engage in economic activity and safer care for vulnerable populations. However, major concerns remain as community licensing could stigmatize people, undermining the value of equal treatment. Businesses may use un-
regulated evidence of immunity, such as test results, or use assumptions about immunity or vulnerability that are likely to be arbitrary and biased.

**Virology**


The surface of the envelope spike is dominated by host-derived glycans. These glycans facilitate immune evasion by shielding specific epitopes from antibody neutralization. The SARS-CoV-2 S gene encodes 22 N-linked glycan sequons per protomer. Using a site-specific mass spectrometric approach, authors reveal these glycan structures on a recombinant SARS-CoV-2 S immunogen.

**Transmission**


How can we re-use N95 respirators? Heat is better than sun or vapors. At 85°C, 50 cycles of heat treatment did not significantly change filtration efficiency. At low humidity and temperatures up to 100 degrees, 20 cycles were possible. Ultraviolet irradiation was a secondary choice, which was able to withstand 10 cycles of treatment and showed small degradation by 20 cycles. However, UV can potentially impact the material strength. Treatments involving liquids and vapors require caution, as steam, alcohol, and household bleach all may lead to degradation of the filtration efficiency.

**Diagnostics**


Using available evidence, a clinically useful timeline of diagnostic markers for detection of COVID-19 is devised.
Clinical


The next study reporting on an incredibly high number of venous thromboembolism (VTE). In this single-center study from Amsterdam on 198 hospitalized cases, the cumulative incidence of VTE at 7, 14, and 21 days were 16%, 33% and 42%. In 74 ICU Patients, cumulative incidence was 59% at 21 days, despite thrombosis prophylaxis. The authors have changed their practice during the follow-up period by performing screening compression ultrasound in the ICU every 5 days.


Same idea: In this prospective study from France, 64/150 (43%) patients were diagnosed with clinically relevant thrombotic complications. Authors argue for higher anticoagulation targets in critically ill patients.


Three patients, two of them with hemorrhagic manifestation and severe thrombocytopenia responded to IVIG fairly quickly with a sustained response over weeks.


Three cases of COVID-19-associated ulcers in the oral cavity, with pain, desquamative gingivitis, and blisters.
Treatment

The first report of a human monoclonal antibody that neutralizes SARS-CoV-2. 47D11 binds a conserved epitope on the spike RBD explaining its ability to cross-neutralize SARS-CoV and SARS-CoV-2, using a mechanism that is independent of receptor-binding inhibition. This antibody could be useful for development of antigen detection tests and serological assays targeting SARS-CoV-2.


Interesting discussion about the results of the large open-label randomized trial which was published in March. In this trial, administration of lopinavir/r did not result in a shorter time until clinical improvement compared to placebo. Bottom line of most comments: “absence of evidence is not evidence of absence”. Lopinavir/r may still be a potential therapeutic agent against COVID-19, especially when given earlier.

8 May
Epidemiology

First documentation of the epidemic in correctional and detention facilities. Aggregated data on COVID-19 cases reported to CDC by 37 of 54 state and territorial health department jurisdictions in the US. Prison bars do not work: As of April 21, 2020, 4,893 cases and 88 deaths among incarcerated and detained persons and 2,778 cases and 15 deaths among staff members have been reported.

Brief review. The transmissibility of SARS-CoV-2, combined with the scarcity of crucial health equipment and the challenges of implementing widespread physical distancing and case isolation, poses a grave threat to the African continent.


Authors speculate on the reasons why 95/100 of deceased Italian doctors were men. Could different habits between men and women have played a role too? According to some research, women are supposedly more scrupulous in performing hand hygiene than men.

**Virology**


In transgenic mice bearing human ACE2 and infected with SARS-CoV-2, pathogenicity of the virus was demonstrated. This mouse model will be valuable for evaluating antiviral therapeutics and vaccines as well as understanding the pathogenesis of COVID-19.


In a wildlife rescue center, authors found coronavirus in 25 Malayan pangolins (some of whom were very sick), showing 90-100% amino acid identity with SARS-CoV-2 in different genes. Comparative genomic analysis suggested that SARS-CoV-2 might have originated from the recombination of a Pangolin-CoV-like virus with a Bat-CoV-RaTG13-like virus. As the RBD of Pangolin-CoV is virtually identical to that of SARS-CoV-2, the virus in pangolins presents a potential future threat to public health. Pangolins and bats are both nocturnal animals, eat insects, and share overlapping ecological niches,
which make pangolins the ideal intermediate host. Stop illegal pangolin trade!

Clinical


CD3+, CD4+ and CD8+T cells but also NK cells were significantly decreased in COVID-19 patients and related to the severity of the disease. Thresholds of CD8+T and CD4+T used for distinguishing between COVID-19 patients and healthy controls were 285.5/µl and 386.0/µl. According to the authors, CD8+T and CD4+T cell counts can be used as diagnostic markers of COVID-19 and predictors of disease severity.


Some ideas on how to treat community-acquired pneumonia (CAP) during these days and how to interpret CAP guidelines.


Discharge from ICU is not the end. Challenges remain for appropriate rehabilitation—physical, cognitive, and psychological. And whether this will be available for the huge numbers of people who will need to deal with the enormous impact of a stay in critical care.

Treatment

The end of hydroxychloroquine (HCQ)? Incredible large observational study from New York City. Of 1,376 consecutive hospitalized patients, 811 (59%) received HCQ (600 mg BID day 1, then 400 mg QD, 60% also received azithromycin). The decision to prescribe the drugs was “left to the discretion of the treating team for each individual patient”. HCQ-treated patients were more severely ill at baseline. Authors adjusted for likely confounders, including age, race and ethnic group, body-mass index, diabetes, underlying kidney or lung disease, hypertension, baseline vital signs, Pao2:Fio2, and inflammatory markers of the severity of illness. There was no significant association between HCQ use and intubation or death. However, despite this extensive adjustment, it is still possible that some amount of unmeasured confounding remains. According to the authors, the study should not be taken to rule out either benefit or harm of HCQ but the results do not support the use of HCQ outside randomized clinical trials.


Authors argue that therapeutic off-the-shelf SARS-COV-2-specific HLA-matched cytotoxic T cells prepared from convalescent COVID-19 patients is the most pressing need. It remains unclear why.

9 May

Top 10 Special on

Kawasaki-like syndrome in children (March/April 2020)

A new twist in this new pandemic: at the end of March 2020, Jones et al. described the case of a six-month-old baby girl with fever, rash and swelling characteristic of a rare pediatric inflammatory condition, Kawasaki syndrome (Jones 2020). The child is treated according to treatment guidelines with a single dose of 2g/kg intravenous immunoglobulin and high dose acetylsalicylic 20mg/kg four times daily. The fever breaks within hours.

A month later, on 27 April, the National Health Service (NHS) sends an email alert to members of the British Paediatric Critical Care Society (PICS) highlighting “a small rise in the number of cases of critically ill children presenting with an unusual clinical picture.” Many of these children have tested pos-
Positive for COVID-19, while some had not. The alert indicates that “the cases have in common overlapping features of toxic shock syndrome and atypical Kawasaki disease with blood parameters consistent with severe COVID-19 in children. Abdominal pain and gastrointestinal symptoms have been a common feature as has cardiac inflammation”, (see the PICS statement).

A few days later, Sylvain Renolleau, head of the intensive care unit at Necker hospital, Paris, reports more than 20 children and adolescents 3 to 17 years old hospitalized in intensive care. The first cases were seen around 15 April. Symptoms included abdominal pain, diarrhea and vomiting, sometimes fever, myocarditis, and a strong inflammatory syndrome. Although not all children tested positive for SARS-CoV-2, all seem to have been in contact with the virus. No deaths have been reported so far. At the end of April, nearly 100 cases had been found in children in France, Great Britain, Italy, Spain, Switzerland and the United States.

On 1 May 2020, the Royal College of Paediatrics and Child Health released guidance describing a systemic inflammatory response sharing “common features with other pediatric inflammatory conditions including: Kawasaki disease, staphylococcal and streptococcal toxic shock syndromes, bacterial sepsis, and macrophage activation syndromes (Royal College of Paediatrics and Child Health 2020).” On 4 May, New York City’s Department of Health issued a similar alert (NYC Health 2020). Two days later, 64 cases were reported from New York (New York Department of Health 2020).

Kawasaki Disease

Kawasaki disease (KD) is an acute-onset systemic vasculitis of medium-sized vessels that mostly affects infants and toddlers (Hedrich 2017).

The first English-language report of 50 patients goes back to Tomisaku Kawasaki in 1974 (Kawasaki 1974, Burns 2000). The KD incidence is much higher in Northeast Asian countries including Japan, South Korea, China, and Taiwan, 10–30 times higher than that of KD in North America and Europe (see the world map in Kim GB 2019).

More than 90% of children were less than 5 years old in a study from Inner Mongolia (Zhu 2015). Untreated, KD leads to coronary artery aneurysms in around 25% of cases (don’t miss this paper: McCrindle 2017). The diagnosis of “classic KD” is based on the presence of ≥5 days of fever plus four out of five diagnostic criteria including erythema of the lips or mouth, trunk rash, swelling or erythema of the hands or feet, conjunctivitis, and lymph node swelling (see the detailed discussion in McCrindle 2017).
Prompt diagnosis is essential, immune globulin being the mainstay of initial treatment. Even in these COVID-19 times, physicians should keep an eye out for KD in all children with prolonged fever, especially in those younger than 1 year (Harasheh 2020).

The cause of KD remains unknown. Some lines of evidence point to a post-infectious trigger causing hyperreaction of the immune system (Dietz 2017) and an association between viral respiratory infections and KD (Jordan-Villegas 2010, Kim JH 2012, Turnier 2015). The primarily winter-spring KD seasonality and well-documented Japanese epidemics with wave-like spread also support an infectious trigger (Rowley 2018).

The Future

It is still unknown if there is a correlation between the cases described above and COVID-19. If there is a correlation, it is unclear whether COVID-19-associated inflammatory disorder and Kawasaki disease are identical (COVID-19-associated cases seem to have more severe abdominal pain, nausea and vomiting; those with severe shock are often older than the typical Kawasaki patients; and in Kawasaki cases, heart vessels seem to be more involved).

Summary

- A new Kawasaki-like syndrome may be emerging in children of all ages.
- The syndrome is rare.
- This syndrome may be related to SARS-CoV-2 but could as well be related to a different infectious pathogen with similar characteristics.
- So far, little is known about the new syndrome.
- To be remembered: serious COVID-19 complications are very rare among children. Throughout Europe, SARS-CoV-2 has caused very few victims among children. In Britain, only 9 children aged 0 to 19 have died after testing positive for coronavirus (0.05% of the 21,678 deaths recorded at the end of April).

See also selected press articles from France (Le Monde, Libération), UK (The Guardian), Spain (El País), Italy (Corriere della Sera) and Germany (FAZ).

References


(IMPORTANT) – This is the first report about Kawasaki disease and concurrent SARS-CoV-2 infection. The authors describe the case of a six-month-old baby girl with fever, rash and swelling characteristic of Kawasaki syndrome. The child had minimal respiratory symptoms. She was treated with a single dose of 2g/kg intravenous immunoglobulin (IVIG) and high dose acetylsalicylic acid (ASA 20mg/kg four times daily) according to treatment guidelines.


10 May

Epidemiology


The authors propose an approach to limit transmission, which is both complementary to and intended to lessen the multifaceted costs of mitigation and suppression. The core idea is to leverage a mechanism of ‘interaction substitution’ by identifying recovered individuals who have protective antibodies and deploying them back into the community. The intention is to develop population-level ‘shield immunity’ by amplifying the proportion of interactions with recovered individuals relative to those of individuals of unknown status.

Immunology


Brilliant review on the current knowledge of innate and adaptive immune responses elicited by SARS-CoV-2 infection and the immunological pathways that likely contribute to disease severity and death.

SARS-CoV-2-specific humoral and cellular immunity was characterized in 14 recovered patients. Of these, 13 displayed serum neutralizing activities in a pseudotype entry assay. Notably, there was a strong correlation between neutralization antibody titers and the numbers of virus-specific T cells. These findings suggest that both B and T cells participate in immune-mediated protection.

**Diagnostics**


A new antibody assay, based on a peptide from the S protein, which was screened out from 20 candidate peptides deduced from the genomic sequence. Using a synthetic peptide may enhance the stability and repeatability of the assay, and theoretically would be more specific. A high specificity was shown. Sensitivity was lower: in 276 infection-confirmed patients, IgG was detected in 71.4% and was higher than the detection rate of IgM (57.2%).

**Comorbidities**


Like SARS-CoV-2, influenza A viruses have been shown to use the ACE2 receptor. Using the linked electronic health care records of 5.6 million persons in the United Kingdom, authors have investigated the incidence of influenza among adults who received a prescription for an ACE inhibitor from 1998 through 2016. Main results: the use of ACE inhibitors and ARBs was associated with either no effect on the incidence of influenza or a lower incidence.

**Clinical**

Five patients from Atlanta, USA, with profound hemodynamic instability due to the development of acute cor pulmonale. Although acute pulmonary thromboembolism was the most likely cause of right ventricular failure in these patients (4/5 were younger than 65 years of age), this was not definitively confirmed in all cases.


Autopsy findings from 12 COVID-19 patients who died in Hamburg, Germany. Seven of the twelve had deep vein thrombosis, and pulmonary embolism was the direct cause of death in four cases. Of note, viremia was found in 6 of 10 patients tested and 5/12 patients demonstrated high viral RNA titers in the liver, kidney, or heart.

Ong SW, Young BE, Leo YS. Association of higher body mass index (BMI) with severe coronavirus disease 2019 (COVID-19) in younger patients. Clinical Infectious Diseases 2020, May 8. Full-text: https://doi.org/10.1093/cid/ciaa548

Retrospective analysis of 182 patients from Singapore. Among those aged <60 years, a BMI ≥25 was significantly associated with pneumonia on chest radiograph on admission (p value = 0.017), requiring low-flow supplemental oxygen (OR 6.32, 95% CI 1.23 – 32.34) and mechanical ventilation (OR 1.16, 95% CI 1.00 – 1.34).

Treatment


Great overview about antibodies as a potential treatment. Many researchers are optimistic that these antibodies will, relatively quickly, prove their worth as a preventive or as a remedy that buys the world some time until a vaccine arrives (if it does). The main questions will be the capacity to manufacture at scale, distribute, and the cost.
Here is one. In addition to conventional antibodies, camelids also produce heavy-chain-only antibodies (HCAbs), which contain a single variable domain (VHH) instead of two variable domains (VH and VL) that make up the equivalent antigen-binding fragment (Fab) of conventional immunoglobulin G (IgG) antibodies. These so-called ‘nanobodies’ have several potential therapeutic advantages, including increased stability and ease of production. Using llamas immunized with prefusion-stabilized betacoronavirus spike proteins, the authors identified neutralizing cross-reactive VHH camelid antibodies, which may serve as potential therapeutic candidates. Crystal structures further reveal how these antibodies bind to spike proteins to prevent viral entry into cells.

11 May

Epidemiology


Quantitative analysis of the impact of control measures between 31 December 2019 and 19 February 2020. Travel restrictions in and out of Wuhan were too late to prevent the spread of the virus. However, measures such as closing citywide public transport and entertainment venues and banning public gatherings combined to avert hundreds of thousands of cases of infection.

Virology


Molecular insights into how SARS-CoV-2 can be targeted by the humoral immune response. The authors determined the crystal structure of CR3022, a neutralizing antibody previously isolated from a convalescent SARS patient,
in complex with the receptor binding domain of the SARS-CoV-2 spike protein.


A novel bat-derived coronavirus was identified from a metagenomics analysis of samples from 227 bats collected from Yunnan Province between May and October 2019. Notably, RmYN02 shares 93.3% nucleotide identity with SARS-CoV-2 at the scale of the complete genome and 97.2% identity in the 1ab gene, in which it is the closest relative of SARS-CoV-2 reported to date. However, RmYN02 showed low sequence identity (61.3%) in the receptor binding domain and might not bind to ACE2.


The pandemic has resulted in numerous conspiracy theories and misinformation, mainly spread through social media. WHO has declared an "infodemic" of incorrect information about the virus, which poses risks to global health. In a video that has exploded on social media in the past few days, virologist Judy Mikovits claims the virus is being wrongly blamed for many deaths. Fortunately, there are intelligent science journalists who take the time to refute this crap.

Diagnostics


The first substantial study to examine the association between plasma ACE2 concentrations and the use of RAAS blockers in patients with cardiovascular disease. Authors measured ACE2 concentrations in 1485 men and 537 women with heart failure (index cohort, 11 European countries). Results were validated in 1123 men and 575 women (validation cohort from Scotland). In both cohorts, plasma concentrations of ACE2 were markedly higher in men than in
women, but not the use of either an ACE inhibitor or an ARB. Data might explain the higher fatality rate of COVID-19 in men, but do not support the hypothesis that RAAS blockers increase the vulnerability for COVID-19.

Clinical


Meta-analysis of 20 retrospective studies with 3,428 COVID-19 infected patients (1,455 severe cases and 1,973 mild cases). Higher serum levels of ALT, AST, bilirubin and lower serum levels of albumin were associated with a significant increase in the severity of COVID-19.


Peter Piot, 71, one of the discoverers of the Ebola virus in 1976, former UN-AIDS director and coronavirus adviser to European Commission President Ursula von der Leyen, discusses a severe case of COVID-19 occurring in March: his own. Interesting reflections on the disease and on death.

Comorbidities


The first larger case series in HIV-infected patients. No excess morbidity and mortality was found among symptomatic COVID-19 cases. As the majority (22/33) was treated with tenofovir, including those developing severe or critical disease, data indicate no or only minimal clinical effect of tenofovir against SARS-CoV-2. Four patients also were on darunavir when they developed COVID-19 symptoms.

First large (multicenter retrospective) study about epidemiologic and clinical characteristics of patients undergoing hemodialysis with COVID-19. There were 101 mild/moderate and 30 severe/critical cases. Of note, 28 (21%) were asymptomatic over the whole course of the disease and were diagnosed only by universal screening. Morbidity was around 2% and only 52% of patients experienced fever.

Treatment

Targeting IL-6 and other cytokines with JAK-dependent signaling is one way to restrain the excessive level of cytokine signaling. JAK kinase inhibitors are being investigated as a way of managing the cytokine storm in severe COVID-19 patients. However, this well-balanced review also discusses potential concerns on side effects, such as the reduction of NK cells or thromboembolic risks seen with baricitinib and tofacitinib treatment.


Some helpful (and very practical) clinical management suggestions, derived from the direct experience of Italian physicians.

12 May
Virology
More insights into transmissibility and pathogenesis. Using ex-vivo cultures, authors evaluated tissue and cellular tropism of SARS-CoV-2 in the human respiratory tract and conjunctiva in comparison with other coronaviruses. In the bronchus and in the conjunctiva, SARS-CoV-2 replication competence was higher than SARS-CoV. In the lung, it was similar to SARS-CoV but lower than MERS-CoV.


The full development pathway for an effective vaccine for SARS-CoV-2 will require that industry, government, and academia collaborate in unprecedented ways, each adding their individual strengths. Authors discuss one such collaborative program that has recently emerged: the ACTIV (Accelerating COVID-19 Therapeutic Interventions and Vaccines) public-private partnership.


A computational method is proposed that globally scans unmapped scRNA-seq data for the presence of viral RNA, enabling transcriptional cell sorting of infected versus bystander cells. It is shown how SARS-CoV-2 infects epithelial cells and alters the immune landscape in patients with severe disease.


Brief but nice review and several hypotheses about SARS-CoV-2 pathogenesis. What happens during the second week - when resident macrophages initiating lung inflammatory responses are unable to contain SARS-CoV-2 infection and when both innate and adaptive immune responses are insufficient to curb the viral replication and the patient doesn’t recover quickly.
Clinical


A total of 18,401 participants from US/UK reported potential symptoms on a smartphone app and underwent a SARS-CoV-2 test. The proportion of participants who reported loss of smell and taste was higher in those with a positive test result (65% vs 22%). A combination of symptoms, including anosmia, fatigue, persistent cough and loss of appetite was appropriate to identify individuals with COVID-19.


By no doubt the weirdest paper title of the day. In a large online survey, the authors determined the levels of COVID-19 fear, anxiety and depression in 12,244 respondents during two weeks in March. Concurrent with Angela Merkel’s speech on March 16, a reduction of anxiety and depression was noticeable in the German population.

Diagnostics


A brain MRI was performed in 27/50 patients with neurologic symptoms. The most common imaging finding was cortical signal abnormalities on FLAIR images (10/27, 37%), accompanied by cortical diffusion restriction or leptomeningeal enhancement. However, the complex clinical course including comorbidities, long ICU stay with multidrug regimens, and respiratory distress with hypoxia episodes can all act as confounding factors - a clear cause-effect relationship between COVID-19 infection and MRI findings will be hard to establish.
Treatment


Some evidence that interferon may be helpful, when given during the first week: this Phase II, multicentre, open-label trial from Hong Kong randomized 127 patients with mild-to-moderate COVID-19 (median 5 days from symptom onset) to receive lopinavir/r only or a triple combination. Triple therapy was given only to patients with less than 7 days from symptom onset and consisted of lopinavir/r, ribavirin (400 mg BID), and interferon beta-1b (1-3 doses of 8 Mio IE per week). Combination therapy led to a significantly shorter median time to negative results in nasopharyngeal swab (7 versus 12 days, p=0.001) and other specimens. Clinical improvement was significantly better, with a shorter time to complete alleviation of symptoms and a shorter hospital stay. Of note, all differences were driven by the 76 patients who started treatment less than 7 days after onset of symptoms.


Different dosage regimens of hydroxychloroquine are currently used to manage COVID-19. The concentrations measured in 57 patients showed that hydroxychloroquine exposure was relatively low and in most instances lower than the values reported in systemic lupus erythematosus patients, in particular for the standard regimen of 200 mg TID. A full hydroxychloroquine kinetic exploration is needed.

Pediatrics


Unprecedented cluster of eight children (all previously fit and well) with hyperinflammatory shock, showing features similar to atypical Kawasaki dis-
ease, Kawasaki disease shock syndrome, or toxic shock syndrome. Two children (one died) were positive for SARS-CoV-2 and four children had a known family exposure to COVID-19. This case cluster formed the basis of a national alert.

13 May

Transmission


The next study on a relatively low transmission rate among household contacts. A total of 35 index cases from Zhuhai, China and their 148 household contacts were carefully analyzed, using questionnaires, active symptom monitoring and nasopharyngeal swabs. The second infection rate in the household context was 32% (95% CI 22-44%). Multivariate analysis showed that household contacts with underlying medical conditions, a history of direct exposure to Wuhan, and shared vehicle with an index patient were associated with higher susceptibility.


Wanna make sure that SARS-CoV-2 is transmitted with almost 100% efficacy? Then use advisory boards or comparable settings: Eight dermatologists and 6 scientists from the same company attended a meeting at a hotel in Munich. The meeting was held in a room (~70 m²) with conventional radiators; a U-shaped set-up of tables were separated by a central aisle >1 m wide. Refreshments were served buffet style in the same room 4 times during the day. After the 9.5 hours of discussions, participants had dinner in a nearby restaurant. Additional direct contacts were handshakes during welcome and farewells with a few short hugs without kisses and a 45 min. taxi ride with 3 participants. Results: The asymptomatic (!) index patient managed to infect at least 11/13 (!) participants. Note: The meeting was held on February 20; the country had <20 diagnosed cases at the time.
Comorbidities


Time to quit smoking. Meta-analysis of 15 studies, including a total of 2,473 confirmed cases. COPD patients were at a higher risk of more severe disease (calculated RR 1.88). Current smokers were 1.45 times more likely to have severe complications compared to former and never smokers. Current smokers also had a higher mortality rate of 39%.


This paper offers some recommendations on the optimization of leukemia management during high-risk COVID-19 periods. Instead of reducing patient access to specialized cancer centers and modifying therapies to ones with unproven curative benefit, there is more rationale for less intensive yet effective therapies that may require fewer visits to the clinic or hospitalizations.

Diagnostics


After reading this viewpoint on the knowledge gaps on post-infection immunity, you will realize that any “COVID pass” would be about as accurate as issuing a certificate that she or he is “a kind person”. 😊


However, Chile is poised to become the first country to provide COVID passes to people who have recovered from the infection. We’ll see how this works.
Treatment


Given the lack of effective pharmacological concepts, this review (re)considers historical reports on low-dose radiation therapy for pneumonia. Although these reports are of low-level evidence, they indicate effectiveness in the dose range between 0.3 and 1Gy, similar to more recent dose concepts in the treatment of inflammatory/degenerative benign diseases with, e.g., a single dose per fraction of 0.5Gy. The authors (known experts in the field) critically review the evidence for low-dose radiation treatment of COVID-19 pneumopathy and discuss whether it is worth investigating (answer: yes).


The next large retrospective cohort study of 1,438 patients from a random sample of all admitted patients with COVID-19 in 25 hospitals in the New York metropolitan region between March 15 and 28. In adjusted Cox models, compared with patients receiving neither drug, there were no significant differences in mortality for patients receiving hydroxychloroquine (HCQ) + azithromycin, HCQ alone, or azithromycin alone. In logistic models, cardiac arrest was significantly more likely in patients receiving HCQ + azithromycin (adjusted OR 2.13). The main limitation was the observational design. HCQ patients were more sick and had more comorbidities – the key (and unresolved) question is whether adjustment was sufficient.

Pediatrics


Cross-sectional study including 48 children with COVID-19 (median age 13 years) admitted to 46 North American pediatric ICUs between March 14 and
April 3, 2020. Forty patients (83%) had significant preexisting comorbidities and 18 (38%) required invasive ventilation. Targeted therapies were used in 28 patients (61%, mainly HCQ). Two patients (4%) died and 15 (31%) were still hospitalized, with 3 still requiring ventilatory support and 1 receiving extracorporeal membrane oxygenation.


Retrospective review (from Spain) of 22 children and adolescents with acute chilblain-like lesions [chilblain: Frostbeule (de), engelure (fr), sabañón (es), gelone (it), frieira (pt), 冻疮 (cn)]. All patients had lesions clinically consistent with chilblains of the toes or feet, with 3 also having lesions of the fingers. Pruritus and mild pain were the only skin symptoms elicited. All cases showed spontaneous marked improvement or complete healing.

14 May

Epidemiology


A suite of modeling analyses was used to characterize the dynamics of SARS-CoV-2 transmission in France and the impact of the lockdown on these dynamics. The authors estimated that 3.6% of infected individuals were hospitalized and 0.7% died. The lockdown reduced the reproductive number from 2.90 to 0.67. By 11 May 2020, authors project 2.8 million infections in France (or 4.4% of the population (range: 2.8–7.2)). Population immunity appeared to be insufficient to avoid a second wave.

Transmission


Three domestic cats were inoculated with SARS-CoV-2. One day later, an uninfected cat was co-housed with each of the inoculated cats. All six cats became infected but none showed any symptoms. All cats had developed anti-


Could it be possible that a BCG vaccination is protective? No. In this very large cohort of Israeli adults aged 35 to 41 years, BCG vaccination in childhood was associated with a very similar rate of positive test results for SARS-CoV-2 compared with no vaccination.

Diagnostics


A simple solution is the use of a binding assay, e.g. an enzyme-linked immunosorbent assay (ELISA), with recombinant antigen as substrate, especially if ELISA results correlate with neutralization assay results. The authors report the development of such an assay and provide a protocol for both recombinant antigen production as well as the ELISA methodology. The method is based on reactivity to the immunogenic S protein of the virus, is relatively simple and quick in its execution and can be performed at biosafety level 2 as it does not involve live virus.

Clinical


SARS-CoV-2 viral load was quantified in autopsy tissue samples obtained from 22 deceased patients. The highest levels were detected in the respiratory tract, but lower levels were also detected in the kidneys, liver, heart, brain, and blood, indicating a broad organotropism of SARS-CoV-2.

Authors demonstrate active replication of SARS-CoV-2 in human intestinal organoids and isolation of infectious virus from the stool specimen of a patient with diarrheal COVID-19. They also established the first expandable organoid culture system of bat intestinal epithelium and present evidence that SARS-CoV-2 can infect bat intestinal cells.


Using a development cohort of 1590 patients and a validation cohort of 710 patients, a risk score was developed (COVID-GRAM) to predict development of critical illness. The risk factors used in the score were: chest radiography abnormality, age, hemoptysis, dyspnea, unconsciousness, number of comorbidities, cancer history, neutrophil-to-lymphocyte ratio, lactate dehydrogenase, and direct bilirubin. The score has been translated into an online risk calculator that is freely available to the public (http://118.126.104.170/)

Comorbidities

Is there a higher mortality risk in heart transplanted patients? Probably yes. In this case series of 28 patients who had received a heart transplant in a large academic center (New York), 22 patients (79%) were hospitalized. At the end of the follow-up, 4 remained hospitalized and 7 (25%) had died.

Treatment
Neutralizing antibodies are promising candidates for prophylactic and therapeutic treatment against COVID-19 virus. Four human-origin monoclonal antibodies were isolated from a convalescent patient, all of which displayed neutralization abilities. B38 and H4 block the binding between virus S protein RBD and cellular receptor ACE2. A competition assay indicates their different epitopes on the RBD. In a mouse model, both antibodies reduced virus titers in infected lungs. The RBD-B38 complex structure revealed that most residues on the epitope overlap with the RBD-ACE2 binding interface, explaining the blocking effect and neutralizing capacity.

Pediatrics


According to this review of 24 studies, children appear to be less affected by COVID-19 than adults by observed rate of cases in large epidemiological studies. Limited data on attack rate indicate that children are just as susceptible to infection. Data on clinical outcomes are scarce but include several reports of asymptomatic infection and a milder course of disease in young children, though radiological abnormalities have been noted.

15 May

Immunology


Cellular response is a major knowledge gap. This important study identified circulating SARS-CoV-2-specific CD8 and CD4 T cells in around 70 and 100% of 20 COVID-19 convalescent patients, respectively. CD4 T cell responses to the spike protein were robust and correlated with the magnitude of IgG titers. Of note, the authors detected SARS-CoV-2-reactive CD4 T cells in 40-60% of unexposed individuals, suggesting cross-reactive T cell recognition between circulating seasonal coronaviruses and SARS-CoV-2.

The increase in inflammatory mediators is correlated with a reduction of innate and adaptive cytotoxic antiviral function. Authors found a lower perforin+ NK cell number in 7 intensive care unit (ICU) patients compared to 41 non-ICU patients, suggesting an impairment of the immune cytotoxic arm as a pathogenic mechanism.

**Diagnostics**


The authors estimated the false-negative rate by day since infection, reviewing 7 studies with a total of 1,330 respiratory samples analyzed by RT-PCR. Over the 4 days before symptom onset, the rate decreased from 100% to 67%. On the day of symptom onset (day 5), the rate was 38%, decreased to 20% (day 8) and then began to increase again, from 21% (day 9) to 66% (day 21). If clinical suspicion is high, infection should not be ruled out on the basis of RT-PCR alone. The false-negative rate is lowest 3 days after onset of symptoms, or approximately 8 days after exposure.


Answer is: probably no, because specificity is not 100%. Average sensitivity and specificity of FDA-approved antibody tests is 84.9% and 98.6%, respectively. Given the variable prevalence of COVID-19 (1%-15%) in different places, the positive predictive value can be statistically as low as 30% to 50% in areas with low prevalence.
Clinical

COVID-19 and the eye: Using optical coherence tomography (OCT) as a non-invasive imaging technique that is useful for demonstrating subclinical retinal changes, the authors describe their experience in 12 adult patients (9 were physicians). All patients showed hyper-reflective lesions at the level of the ganglion cell and the inner plexiform layers more prominently at the papillomacular bundle in both eyes.

Treatment

The answer is: no. These “Living Practice Points” From the American College of Physicians (based on an evidence review conducted on 17 April 2020) very clearly say that both drugs should not be used as prophylaxis or treatment of patients with COVID-19. In light of known harms and very uncertain evidence of benefit in patients with COVID-19, however, clinicians may treat hospitalized COVID-19–positive patients in the context of a clinical trial.


Although lopinavir trough levels were approximately 2-fold higher in 8 COVID-19 patients than in HIV infected patients receiving the same dose, levels may be too low for COVID-19. Approximately 60- to 120-fold higher concentrations are required to reach the assumed EC50 at trough levels, making effective treatment of COVID-19 with lopinavir/r at the currently used dose unlikely.

Among six anti-influenza drugs, only arbidol efficiently inhibited SARS-CoV-2 infection in cell experiments. Functionally, arbidol appeared to block virus entry by impeding viral attachment and release from the endolysosomes. However, higher dosages may be required to achieve therapeutic efficacy (800 mg?) than the current dose (200 mg, 3 times/day) as recommended by the Chinese Guidelines.


This study randomized a total of 86 patients with mild to moderate COVID-19 to receive lopinavir/r, arbidol (200 mg TID) or no antiviral medication (control). The primary endpoint, the rate of positive-to-negative conversion of SARS-CoV-2 nucleic acid, was similar between groups. There were no differences between groups in the secondary endpoints, the rates of antipyresis, cough alleviation, or improvement of chest CT at days 7 or 14. Again, dosage of arbidol may have been too low.

Pediatric

From 177 infected pediatric patients, 44 were hospitalized and 9 were critically ill. Of these, 6/9 were adolescents and young adults > 15 years of age. Although asthma was the most prevalent underlying condition overall, it was not more common among patients with severe disease. There were no significant differences in the presence of underlying conditions overall or any specific underlying diagnosis. Asthma exacerbation is not the primary determinant of more severe disease.
16 May

Epidemiology


Focusing on the COVID-19 spread in Germany, these elegant models detected three change points in the effective growth rate that correlated well with interventions. First, the spreading rate decreased from 0.43 to 0.25, the decrease initiating around March 7 (cancellation of large public events, such as trade fairs and soccer matches). Second, the rate decreased further to 0.15 (around March 16, closure of schools, childcare facilities, non-essential stores). Third, the spreading rate decreased further to 0.09 (initiated around March 24, strict contact ban). While the first two change points were not sufficient to trigger a shift from the growth of novel cases to a decline, the third brought this crucial reversal. This model can be used for future scenarios – the code is freely available and can be readily adapted to any country. The paper also highlights the impact of time: delaying restrictions by only 5 days may have an incredible impact on case numbers. Sleep well, Boris, Jair, Mark etc.

Transmission


By now, the most comprehensive data on infections among HCW. Among 2,457 infected HCW in Wuhan, China, 52% were nurses, 34% were doctors and 14% were medical staff. Case infection rate of nurses (2.22%) was higher than that of doctors (1.92%). The majority (89%) came from general hospitals. The case infection rate of HCW (2.10%) was dramatically higher than that of non-HCW (0.43%). The case fatality rate of was significantly lower (0.69% versus 5.30%).
Diagnostics

Point-of-care testing is based on easy-to-use devices to facilitate testing outside laboratory settings. They are eagerly awaited. On May 6, the FDA granted an emergency use authorization for a clustered regularly interspaced short palindromic repeats (CRISPR)-based SARS-CoV-2 fluorescent assay marketed by Sherlock Biosciences. This method gives results in an hour and has successfully diagnosed 12 positive and 5 negative COVID-19 patients, with at least 2 of 3 replicates scoring positive in infected persons. However, use still remains limited to laboratories certified to perform high-complexity tests. On May 6, FDA also authorized Quidel’s Sofia 2 SARS Antigen Fluorescent Immunoassay. The test must be read on a dedicated analyser and detects SARS-CoV-2 nucleocapsid protein from nasopharyngeal swabs in 15 min. According to the manufacturer, the assay demonstrated acceptable clinical sensitivity and detected 47/59 infections (80%). Unfortunately, no peer-reviewed papers have been published to date.

Comorbidities

According to this review (data cut on May 4), evidence is of moderate certainty that ACEI and ARB use is not associated with a higher likelihood of receiving a positive SARS-CoV-2 test result. Evidence is of high certainty (14 observational studies, involving 23,565 adults) that neither medication is associated with more severe COVID-19 illness. Four registered randomized trials plan to evaluate ACEIs and ARBs for treatment of COVID-19. For more information, see our special from May 4: [https://covidreference.com/top-10-may-4](https://covidreference.com/top-10-may-4).

Severe COVID-19

Comprehensive overview about current knowledge (and knowledge gaps) about treatment of patients who develop severe disease. Basics of respiratory
care, ventilation management and supportive care. Areas of uncertainties are also discussed.


The next autopsy study on 11 deceased patients with COVID-19 (10 selected randomly). Death may be caused by the thrombosis observed in segmental and subsegmental pulmonary arterial vessels despite the use of prophylactic anticoagulation.


Well-balanced editorial, condensing current knowledge on the contributions of pulmonary thrombosis, embolism, or their combination to deaths of patients with COVID-19. Some studies have found pulmonary embolism with or without deep venous thrombosis, as well as presence of recent thrombi in prostatic venous plexus, in patients with no history of VTE, suggesting de novo coagulopathy in these patients with COVID-19. Others have highlighted changes consistent with thrombosis occurring within the pulmonary arterial circulation, in the absence of apparent embolism.

**Treatment**


Four letters, making critical comments on the NEJM paper about the remdesivir compassionate use program. We have discussed many of these issues on April 16, see here: [https://covidreference.com/remdesivir](https://covidreference.com/remdesivir)

This retrospective cohort study at the San Raffaele Hospital in Milan, Italy, included patients with moderate-to-severe ARDS and hyperinflammation (serum C-reactive protein, CRP ≥100 mg/L) who were managed with non-invasive ventilation and HCQ and lopinavir/r. At 21 days, treatment with high-dose anakinra was associated with reductions in CRP and progressive improvements in respiratory function in 21/29 (72%) patients.


Another small case series of critically ill patients with secondary hemophagocytic lymphohistiocytosis (sHLH) characterized by pancytopenia, hypercoagulation, acute kidney injury and hepatobiliary dysfunction. At the end of treatment, ICU patients had less need for vasopressors and significantly improved respiratory function. Although 3/8 patients died, the mortality was lower than historical series of patients with sHLH in sepsis.

17 May

Epidemiology


The authors provide a simple model and an online tool for understanding excess mortality over 1 year from the COVID-19 pandemic, based on age, sex, and underlying condition-specific estimates. For the UK, 293,991 deaths would be expected in a “do-nothing scenario”. With mitigation (ie, less rigorous and voluntary measures), authors predict between 18,000 and 37,000 deaths.
Virology

Another study analyzing the RNA synthesizing machine. Using cryoelectron microscopy, the authors determined a 2.9 angstrom resolution structure of the RNA-dependent RNA polymerase (also known as nsp12), which catalyzes the synthesis of viral RNA, in complex with two cofactors, nsp7 and nsp8.

Immunology

Incredible in-depth analysis of host response to SARS-CoV-2 and other human respiratory viruses in cell lines, primary cell cultures, ferrets, and COVID-19 patients. Data consistently revealed a unique and inappropriate inflammatory response to SARS-CoV-2 which is imbalanced with regard to controlling virus replication versus activation of the adaptive immune response. It is defined by low levels of type I and III interferons juxtaposed to elevated chemokines and high expression of IL-6. The authors propose that reduced innate antiviral defenses coupled with exuberant inflammatory cytokine production are the defining and driving features of COVID-19. Given this dynamic, treatments for COVID-19 have less to do with the IFN response and more to do with controlling inflammation.

Transmission

The German patient zero was a Chinese person who visited Germany for professional reasons. Sixteen persons became infected. This thorough description of transmission dynamics revealed that attack rates were 75% among members of a household cluster in common isolation, 10% among household contacts only together until isolation of case, and 5% among non-household high-risk contacts. Although most patients presented with only mild and non-
specific symptoms, infectiousness before or on the day of symptom onset was substantial. Additionally, the incubation period was often very short and false-negative tests occurred.


What a disaster! Among 61 persons who attended a March 10 choir practice, 32 confirmed and 20 probable secondary COVID-19 cases occurred. Three were hospitalized (5.7%), and two died (3.7%). The 2.5 hour singing practice provided several opportunities for droplet and fomite transmission, including members sitting close to one another, sharing snacks, and stacking chairs at the end of the practice. Chairs were arranged in six rows of 20 chairs each, spaced 6–10 inches apart with a center aisle dividing left and right stages. Most choir members sat in their usual rehearsal seats (see full paper for more details). The act of singing itself might have contributed to transmission through emission of aerosols, which is affected by the loudness of vocalization.

**Clinical**

New York City Department of Health and Mental Hygiene (DOHMH) COVID-19 Response Team. **Preliminary Estimate of Excess Mortality During the COVID-19 Outbreak — New York City, March 11–May 2, 2020.** Morb Mortal Wkly Rep 2020; 69:603-605. Full-text: [http://dx.doi.org/10.15585/mmwr.mm6919e5](http://dx.doi.org/10.15585/mmwr.mm6919e5)

Anybody out there still doubting excess mortality? Please show them this paper, including the most impressive figure of the day. It depicts the total excess all-cause deaths in New York, calculated as observed deaths minus expected deaths as determined by a seasonal regression model using mortality data from the period January 1, 2015–May 2, 2020.

Smith JC, Sauswille EL, Girish V, et al. **Cigarette smoke exposure and inflammatory signaling increase the expression of the SARS-CoV-2 receptor ACE2 in the respiratory tract.** Development Cell, May 16, 2020. Full-text: [https://doi.org/10.1016/j.devcel.2020.05.012](https://doi.org/10.1016/j.devcel.2020.05.012)
Quit smoking, immediately! Lung ACE2 levels do not vary by age or sex, but smokers exhibit upregulated ACE2. Cigarette smoke triggers an increase in ACE2+ cells by driving secretory cell expansion. The overabundance of ACE2 in the lungs of smokers may partially explain why smokers are significantly more likely to develop severe COVID-19.


Well, it’s not that easy (quitting smoking and finding clinical correlations to cell experiments). Within a surveillance centre primary care sentinel network, multivariable logistic regression models were used to identify risk factors for positive SARS-CoV-2 tests. Of note, active smoking was associated with decreased odds (yes, decreased: adjusted OR 0.49, 95% CI 0.34–0.71). According to the authors, their findings should not be used to conclude that smoking prevents SARS-CoV-2 infection, or to encourage ongoing smoking. Several explanations are given, such as selection bias (smokers are more likely to have a cough, more frequent testing could increase the proportion of smokers with negative results). Active smoking might also affect RT-PCR test sensitivity.

Severe COVID-19


This prospective, before-after study was conducted in Aix-en-Provence (France) among 24 awake, non-intubated, spontaneously breathing patients with COVID-19 and hypoxemic acute respiratory failure requiring oxygen supplementation. Efficacy of prone positioning was only moderate. Only 63% were able to tolerate PP for more than 3 hours. Oxygenation increased in only 25% and was not sustained in half of those after resupination. However, prone sessions were short, partly because of limited patient tolerance.

This editorial summarizes current knowledge on prone position. PP during spontaneous and assisted breathing may become a therapeutic intervention. Tolerance may be a limitation of the technique and the benefits of short sessions remain to be seen. Several larger trials are ongoing, addressing the question whether PP prevents intubation.

**18 May**

**Virology**


SARS-CoV-2 caused respiratory disease in 8 infected rhesus macaques, lasting 8-16 days. Pulmonary infiltrates were visible in lung radiographs. High viral loads were detected in swabs as well as in bronchoalveolar lavages. Taken together, this rhesus macaque “model” recapitulates COVID-19, with regard to virus replication and shedding, the presence of pulmonary infiltrates, histological lesions and seroconversion.

Sia SF, Yan L, Chin AWH. et al. **Pathogenesis and transmission of SARS-CoV-2 in golden hamsters.** Nature 2020. [https://doi.org/10.1038/s41586-020-2342-5](https://doi.org/10.1038/s41586-020-2342-5)

In most cases, you don’t need monkeys. Golden Syrian hamsters may also work as an animal model. SARS-CoV-2 transmitted efficiently from inoculated hamsters to naïve hamsters by direct contact and via aerosols. Transmission via fomites in soiled cages was less efficient. Inoculated and naturally-infected hamsters showed apparent weight loss, and all animals recovered with the detection of neutralizing antibodies.
**Immunology**


The authors describe a SARS-CoV-2 cell infection system to determine changes in host-cell pathways upon infection, resulting from host-cell (antiviral) responses or viral effector proteins, and assess some potential inhibitors.

**Transmission**


Two out of fifteen dogs (one Pomeranian and one German Shepherd) from households with confirmed human cases of COVID-19 in Hong Kong were found to be infected. Both dogs remained asymptomatic but later developed antibody responses detected using plaque reduction neutralization assays. Genetic analysis suggested that the dogs caught the virus from their owners. It still remains unclear whether infected dogs can transmit the virus to other animals or back to humans.


Sunlight reaching the ground lacks germicidal ultraviolet C radiation. According to the authors, scientists should avoid voicing assumptions on the effect of sunlight on viral transmission.

**Clinical**


Nice overview on a symptom which is frequently overlooked in clinical practice. Headache was observed in 11-34% of hospitalized patients (in 6-10% as presenting symptom). Significant features are moderate to severe, bilateral headache with pulsating or pressing quality in the temporo-parietal, forehead or periorbital region. The most striking features are sudden to gradual onset and poor response to common analgesics. Possible pathophysiological mech-
anisms include activation of peripheral trigeminal nerve endings by SARS-CoV2 directly or through vasculopathy and/or increased circulating pro-inflammatory cytokines and hypoxia.

Comorbidities


Data from Switzerland. Overall, 21 patients were included with a median age of 56 years (10 kidney, 5 liver, 1 pancreas, 1 lung, 1 heart and 3 combined transplantations). Ninety-five percent and 24% of patients required hospitalization and ICU admission, respectively. After a median of 33 days of follow-up, 16 patients were discharged, 3 were still hospitalized and 2 patients died.

Treatment


Fantastic work, identifying 14 potent neutralizing antibodies by high-throughput single B-cell RNA-sequencing from 60 convalescent patients. The most potent one, BD-368-2, exhibited an IC50 of 15 ng/mL against SARS-CoV-2. This antibody displayed strong therapeutic and prophylactic efficacy in mice, the epitope overlaps with the ACE2 binding site. Time to go into the clinic!


Some arguments supporting the use of alisporivir, a non-immunosuppressive analogue of cyclosporine A developed by Novartis. Arguments include the cyclophilin-dependency of the lifecycle of many coronaviruses and preclinical data on antiviral and cytoprotective properties.
Pediatrics


The largest cohort of European children and adolescents, comprising 168 patients with laboratory-confirmed COVID-19. Nearly 40% were under 1 year of age and the majority of them were hospitalized. However, all patients, including those with comorbidities, recovered fully, and no sequelae were reported at the last follow-up.

19 May

Diagnostics


Nice overview on different platforms, including binding assays such as enzyme-linked immunosorbent assays (ELISAs), lateral flow assays, or Western blot-based assays. In addition, functional assays that test for virus neutralization, enzyme inhibition, or bactericidal assays can also inform on antibody-mediated immune responses. Many caveats and open questions with regard to antibody testing are also discussed.


No cross-reactivity between autoantibodies and SARS-CoV-2 antibodies: in 290 older serum samples from patients with rheumatoid arthritis, systemic lupus erythematosus, and Sjogren's syndrome, no IgG and IgM antibodies against SARS-CoV-2 were detected.

While cross-reactivity in antibody binding to the spike protein is common, cross-neutralization of the two live SARS viruses may be rare, indicating the presence of a non-neutralizing antibody response to conserved epitopes in the spike.


Combining study results of 26 studies, 54% of those patients tested for fecal RNA were positive. Duration of fecal viral shedding ranged from 1 to 33 days after a negative nasopharyngeal swab. Evidence is still insufficient to suggest that COVID-19 is transmitted via fecally shed virus.

Clinical

Analysis of 340 hospitalized patients in Lyon with information on BMI. In multivariable analyses, odds of critical COVID-19 versus non-critical COVID-19 were higher in patients with obesity than in patients without obesity when adjusted for age and sex. The association remained significant after adjustment for the other potential specific risk factors, with age-sex-adjusted ORs ranging between 1:80 and 2:03.


It’s time to talk about possible psychiatric and neuropsychiatric implications of the current pandemic. According to this systematic review, preliminary data suggest that patients with COVID-19 might experience delirium, confusion, agitation, and altered consciousness, as well as symptoms of depression, anxiety, and insomnia. High-quality peer-reviewed research into psychiatric
symptoms as well as into potential mitigating factors and interventions is needed.


One common argument in the current discussion is that some of the people who died “with” COVID-19 did not actually die “from” it. This would overestimate the “real” mortality. This is probably true. However, the opposite is also true – that many who died from the infection without testing positive never contribute to the official death toll. In the small town of Nembro (around 11,500 residents) that was among the first Italian cities hit by COVID-19, monthly all-cause mortality between 2012 and February 2020 fluctuated around 10 per 1000 person years, with a maximum of 21.5. In March 2020, mortality reached a peak of 154.4 (driven by older men) and decreased to 23.0 in early April. From the outbreak onset until 11 April 2020, only half (85/166) of deaths had a confirmed COVID-19 diagnosis. The full implications of this crisis can only be completely understood if all-cause mortality in a given region and time frame is considered.

Severe COVID-19

Two patients required ECMO for refractory hypoxia secondary to COVID-19 and developed neurologically devastating intraparenchymal hemorrhage despite lacking the classical risk factors. Authors recommend CT screening to identify brain injury that would otherwise go undetected due to the poor reliability of classic coagulation markers as accurate clinical predictors of hemorrhage in this cohort, as well as the inability to perform neurological assessments in the setting of paralysis, sedation, and proning.
Comorbidities
Review of the literature on thromboembolic events (TE) associated with COVID-19. The causation between the effects of ibuprofen and TE remains speculative. The role of ibuprofen on a vascular level remains unclear as well as whether ibuprofen is able to interact with SARS-CoV-2 through some mechanism. However, the authors recommend careful consideration to avoiding a high dosage of ibuprofen in subjects at particular risk of thromboembolic events.

Treatment
Why not favipiravir for COVID-19? This purine nucleoside analogue acts as a competitive inhibitor of RNA-dependent RNA polymerase and can be given orally (in contrast to remdesivir, another RdRp inhibitor). Authors give a brief overview on clinical studies. The results of several ongoing randomized controlled trials are eagerly awaited. 20 May

20 May
Transmission
Prevention works only through training and demonstrated competency in putting on and removing personal protective equipment (PPE). This video demonstrates a procedure for “donning and doffing” PPE.

High transmission rates of SARS-CoV-2 have been reported from hospitals, long-term care facilities, family gatherings, choir practice. This report de-
scribes church events. In total, 35 confirmed COVID-19 cases occurred among 92 attendees at church events during March 6–11; estimated attack rates ranged from 38% to 78%. Of note, a higher proportion of adults aged 19–64 years and ≥65 years received positive test results than did younger persons.


No link between vitamin D and infection risk. Of 348,598 UK biobank participants, 449 had confirmed COVID-19 infection. Ethnicity was associated with COVID-19 infection (blacks versus whites OR = 5.32, South Asians versus whites OR = 2.65). Vitamin D was not associated with COVID-19 infection, after adjustment for confounders. Vitamin D did not explain ethnic differences.

Diagnostics

Testing coagulation profile for ten consecutive days since admission in 279 COVID-19 patients, this study gives some insights into the dynamic changes of D-dimer level that are of prognostic value.

Clinical

Old white men. From the start of the epidemic until 18 April, an overall 4,805 (+45%) excess deaths were observed in Italian cities, with a significantly higher excess in the north (+76%, +4,295 deaths) compared with the center and the south (+10%, +510 deaths). Overall, the excess in mortality was higher among men than among women in cities in the north vs the center and the south (men: +87% and +70% and women: +17% and +9%, respectively), with an increase in the trend by age. The greatest excess in the north was among elderly men (+76% in 65–74 year-olds, +89% in 75–84 year-olds and +102% in those 85 years and older). In central and southern Italy, the excess in mortality
among men was lower, with a statistically significant excess only among elderly men: +13% and +28%, respectively, in the 75–84 years and ≥85 years age group.


The next study emphasizes the high thrombosis risk. Of 143 patients hospitalized with COVID-19 (aged 63 ± 14 years; 52% men), 66 patients developed lower extremity Deep Vein Thrombosis (DVT) (46.1%), among them 23 with proximal DVT. Compared with patients without DVT, patients were older and had a lower oxygenation index, a higher rate of cardiac injury, and worse prognosis. Multivariate analysis found CURB-65 score 3-5 (OR = 6.122), Padua prediction score ≥4 (OR = 4.016), and D-dimer >1.0 μg/ml (OR = 5.818) to be associated with DVT.

Comorbidities

Brenner Ej, Ungaro RC, Gearry RB, et al. Corticosteroids, but Not TNF Antagonists, Are Associated With Adverse COVID-19 Outcomes in Patients With Inflammatory Bowel Diseases: Results From an International Registry. Gastroenterology 2020 May 18. Full-text: https://doi.org/10.1053/j.gastro.2020.05.032

An important and large study, analysing 525 patients with IBD from 33 countries. Thirty-seven patients (7%) had severe COVID-19, and 16 patients died (3% case fatality rate). Risk factors for severe COVID-19 among IBD patients included increasing age, ≥2 comorbidities, systemic corticosteroids (aOR 6.9, 95% CI 2.3-20.5), and sulfasalazine or 5-aminosalicylate use (aOR 3.1, 95% CI 1.3-7.7). Maintaining remission with steroid-sparing treatments will be important in managing patients with IBD through this pandemic. However, a causal relationship cannot be definitively established. Notably, TNF antagonist treatment was not associated with severe COVID-19.


In a large diverse community setting in California, the incidence of hospitalization for acute myocardial infarction declined after March 4 by up to 48%
more than would be expected on the basis of typical seasonal variation alone. Similar findings have been noted in northern Italy.

Severe COVID-19


This brilliant article gives an overview on the (potentially high) burden of fibrotic lung disease following SARS-CoV-2 infection. Post-viral fibrosis may lead to severe physiological impairment. Available antifibrotic therapies such as pirfenidone (a pyridone with a poorly understood mechanism of action) and the thyrosine kinase inhibitor nintedanib have broad antifibrotic activity regardless of etiology, and these drugs might have a role in attenuating profibrotic pathways in SARS-CoV-2 infection. Current knowledge and future strategies are discussed.

Treatment


The next interesting antibody study. The authors describe multiple monoclonal antibodies targeting SARS-CoV-2 spike identified from memory B cells of an individual who was infected with SARS-CoV in 2003. One antibody, named S309, potently neutralizes SARS-CoV-2 by engaging the S receptor-binding domain. Using cryo-electron microscopy and binding assays, authors show that S309 recognizes a glycan-containing epitope that is conserved within the sarbecovirus subgenus, without competing with receptor attachment.

Procedures


This article provide detailed consensus guidelines and recommendations on the conduct and management of tracheostomy during the pandemic. All important issues such as timing of tracheostomy (delayed until at least day 10 of
COVID Reference Top 10

mechanical ventilation and considered only when patients are showing signs of clinical improvement), optimal setting (hierarchic approach to operative location, enhanced PPE), optimal procedure as well as management after tracheostomy are discussed.

21 May

A Top 10 Speciel

An update on HIV infection in the current crisis

HIV infection is of particular interest in the current crisis. First, many patients take antiretroviral therapies that are thought to have some effects against SARS-CoV-2. Second, HIV serves as a model of cellular immune deficiency. Third and by the far most important point, the collateral damage caused by COVID-19 in the HIV population may be much higher than that of COVID-19 itself.

Inexplicably, information on the HIV population is still scarce. However, preliminary data suggest no elevated incidence of COVID-19. In 5,700 patients from New York, only 43 (0.8%) were found to be HIV-positive (Richardson 2020). Similar findings were reported from Chicago (Ridgeway 2020). In Barcelona where a local protocol included HIV serology for all hospitalized COVID-19 patients, 32/2102 (1.5%) were HIV-infected, among them only one single new HIV diagnosis (Miro 2020). Given the fact that HIV+ patients may be at higher risk for other infectious diseases such as STDs, these percentages were so low that some experts have already speculated on potential “protective” factors (i.e., antiviral therapies or immune activation). Moreover, a defective cellular immunity could paradoxically be protective for severe cytokine dysregulation, preventing the cytokine storm seen in severe COVID-19 cases.

Appropriately powered and designed studies that are needed to draw conclusions on the effect of COVID-19 are still lacking. However, our own retrospective analysis of 33 confirmed SARS-CoV-2 infections between March 11 and April 17 in 12 participating German HIV centers revealed no excess morbidity or mortality (Haerter 2020). The clinical case definition was mild in 25/33 cases (76%), severe in 2/33 cases (6%), and critical in 6/33 cases (18%). At the last follow up, 29/32 of patients with documented outcome (90%) had recovered. Three out of 32 patients had died. One patient was 82 years old, one had a CD4 T-cell count of 69/µl and one suffered from several comorbidities. A similar observation was made in Milan, Italy, where 45/47 patients with HIV and COVID-19 (only 28 with confirmed SARS-CoV-2 infection) recovered
In this study, as in our cohort, severe immune deficiency was rare. The last median CD4 count was 670/µl (range, 69 to 1715) and in 30/32 cases in our cohort, the latest HIV RNA was below 50 copies/mL (Härter 2020). It remains to be seen whether HIV patients with uncontrolled viremia and/or low CD4 cells are at higher risk for severe disease. It is also unclear whether immunity after infection remains impaired. However, there are case reports on delayed antibody response in HIV patients (Zhao 2020).

Another issue making HIV patients an interesting population is a potential effect of antiretroviral therapies against SARS-CoV-2. For lopinavir/r, some reports on beneficial effects in patients with SARS, MERS and COVID-19 exist, but the evidence remains poor. Several studies on lopinavir are still underway (see Treatment chapter). According to both the US DHHS and EACS statement, an ART regimen should not be changed to include a PI to prevent or treat COVID-19 (EACS 2020, US 2020). In our cohort, 4/33 (12%) patients were on darunavir when they developed COVID-19 symptoms. In the Milan Cohort, the rate of patients on a PI was 11% (Gervasoni 2020). Both studies indicate that PIs do not protect from SARS-CoV-2 infection. Beside the PI, we did not find any clear evidence for a protective effect of tenofovir. Tenofovir alafenamide has some chemical similarities to remdesivir and has been shown to bind to SARS-CoV-2 RNA polymerase (RdRp) with binding energies comparable to those of native nucleotides and to a similar extent as remdesivir. Consequently, tenofovir has recently been suggested as a potential treatment for COVID-19 (Elfiky 2020). In Spain, a large randomized Phase III placebo-controlled study (EPICOS, NCT04334928) compares the use of tenofovir disoproxil fumarate/emtricitabine, hydroxychloroquine or the combination of both versus placebo as prophylaxis for COVID-19 in healthcare workers. Our observation that the majority (22/33) of HIV+ patients with COVID-19 were treated with tenofovir, including those developing severe or critical disease, indicate no or only minimal clinical effect against SARS-CoV-2 (Härter 2020). In Milan, 42% were receiving a tenofovir-based regimen (Gervasoni 2020).

The most serious concern regarding HIV, however, is the collateral damage induced by COVID-19. In Western countries, only few HIV+ patients had problems in gaining access to their HIV medications or had trouble taking them due to COVID-19 or the plans to manage it (Sanchez 2020). In contrast, disruption to delivery of health care in sub-Saharan African settings could well lead to adverse consequences beyond those from COVID-19 itself. Lockdown, transport restrictions and fear of coronavirus infection have already led to a dramatic drop in HIV and TB patients collecting medication in several African countries (Adepoju 2020). Using five different existing mathematical models...
of HIV epidemiology and intervention programmes in sub-Saharan Africa, investigations have already estimated the impact of different disruptions to HIV prevention and treatment services. Predicted average relative excess in HIV-related deaths and new HIV infections (caused by unsuppressed HIV RNA during treatment interruptions) per year over 2020-2024 in countries in sub-Saharan Africa that would result from 3 months of disruption of specific HIV services, were 1.20-1.27 for death and 1.02-1.33 for new infections, respectively. A 6-month interruption of ART would result in over 500,000 excess HIV deaths in sub-Saharan Africa (range of estimates 471,000 - 673,000). Disrupted services could also reverse gains made in preventing mother-to-child transmission. According to WHO, there is a clear need for urgent efforts to ensure HIV service continuity and preventing treatment interruptions due to COVID-19 restrictions in sub-Saharan Africa.

References


Sanchez TH, Zlotorzynska M, Rai M, Baral SD. Characterizing the Impact of COVID-19 on Men Who Have Sex with Men Across the United States in April, 2020. AIDS Behav. 2020 Apr

COVID Reference Top 10
22 May

Epidemiology


Is it necessary to stay home during the epidemic’s peak? Probably, yes. This well-conducted study focused on the effects of a general stay-at-home-order. On March 21, Illinois did so while Iowa didn’t. Authors compared daily incidence in 8 Iowa counties bordering Illinois with those in the 7 Illinois counties bordering Iowa. Within a month after the stay-at-home order, the curves started to diverge considerably. Cases increased more quickly in Iowa and more slowly in Illinois, leading to an excess of about 30% in Iowa counties. Sensitivity analyses addressing differences in timing of closing schools and nonessential businesses and differences in population density and poverty rates between the two states supported these findings.


No herd immunity in LA. Participants were offered testing at 6 study sites or at home in mid-April. Among 865 cases, the prevalence of antibodies was 4.65%. However, even this low number may be biased due to nonresponse or due to the fact that symptomatic persons may have been more likely to participate.
Virology

No re-infection in macaques. Following initial viral clearance and on day 35 following initial viral infection, 9 rhesus macaques were re-challenged with the same doses of virus that were utilized for the primary infection. Very limited viral RNA was observed in bronchoalveolar lavage on day 1, with no viral RNA detected at subsequent timepoints. These data show that SARS-CoV-2 infection induced protective immunity against re-exposure in non-human primates.

Transmission

Increasing sunlight exposure in the upcoming weeks may help flatten the curve! UVB radiation from sunlight (the primary source of UV radiation) is the principal environmentally effective virucide, probably much more relevant than temperature and humidity. Authors studied the relationship between the incidence of COVID-19, demographic, and climatologic measurements in different regions across the world. They show a significant association of the incidence of COVID-19 and both reduced solar irradiance and increased population density, highlighting the sterilizing properties of UV radiation.


This lab data supports the above observation of inactivation. Store your masks in the sun! Simulated sunlight rapidly inactivated SARS-CoV-2 suspended in either simulated saliva or culture media and dried on stainless steel plates. Ninety percent of infectious virus was inactivated every 6.8 minutes in simulated saliva and every 14.3 minutes in culture media when exposed to simulated sunlight representative of the sun on a clear summer day. No significant decay was observed in darkness over 60 minutes.

Is this the reason for lower infection rates in children? As the nasal epithelium is one of the first sites of infection, investigators evaluated the expression of ACE in nasal epithelial samples collected 2015-2018 as part of an asthma study. Among a cohort of 305 patients, all age groups had higher expression of ACE2 in the nasal epithelium compared with younger children (4-9 years old). ACE2 expression was age-dependent and higher with each subsequent age group after adjusting for sex and asthma. A good argument for opening a day care center for children.

**Diagnostics**


A positive RT-qPCR result may not necessarily mean the person is still infectious or that they still have any meaningful disease. The RNA could be from nonviable virus and/or the amount of live virus may be too low for transmission. RT-qPCR provides quantification by first reverse transcribing RNA into DNA, and then performing qPCR where a fluorescence signal increases proportionally to the amount of amplified nucleic acid. The test is positive if the fluorescence reaches a specified threshold within a certain number of PCR cycles (Ct value, inversely related to the viral load). Many qPCR assays use a Ct cut-off of 40, allowing detection of very few starting RNA molecules. The authors suggest to use this Ct value or to calculate viral load which can help to refine decision-making (re: shorter isolation etc.).

**Severe COVID-19**


It’s not influenza. The authors carefully examined lungs from 7 deceased COVID-19 patients with lungs from 7 patients who died from ARDS secondary
to influenza A and 10 age-matched, uninfected control lungs. In COVID-19 or influenza, the histologic pattern was diffuse alveolar damage with perivascular T-cell infiltration. However, the COVID-19 lungs showed distinctive vascular features, consisting of severe endothelial injury associated with the presence of intracellular virus and disrupted cell membranes. Histologic analysis of pulmonary vessels showed widespread thrombosis with microangiopathy. Alveolar capillary microthrombi and the amount of vessel growth were 9 and almost 3 times as prevalent as in influenza, respectively.

Treatment

The price for the most cryptic abstract of the day goes to this FDA group. “Translation of in vitro antiviral activity to the in vivo setting is crucial to identify potentially effective dosing regimens of hydroxychloroquine. In vitro EC50/EC90 values for hydroxychloroquine should be compared to the in vivo free extracellular tissue concentration, which is similar to the free plasma hydroxychloroquine concentration.” Did they not dare to tell the truth? Their (important, yet cryptic) message was: HCQ doses tolerable for humans are too low to have any antiviral effect.


Most almost-misleading title of the day: Comparative, not comparable. A series of anti-HIV nucleosides were compared with remdesivir for antiviral activity against seasonal HCoV-229E in MRC-5 cells. Remdesivir was found to be potent, with an EC50 value of 0.07 μM. Only emtricitabine (FTC) showed modest activity, with an EC50 value of 82 μM. Other NRTIs did not show comparable activity. But it was comparative, yes.
23 May

Epidemiology

Kofler N, Baylis F. Ten reasons why immunity passports are a bad idea. Nature 2020, 581, 379-381. Full-text: https://doi.org/10.1038/d41586-020-01451-0

Forget the COVID pass! During the past weeks, we have shared several reasons why immunity passports are a bad idea. This commentary provides 10 more reasons. Restricting liberty on the basis of biology threatens freedom, fairness and public health.


Randomized controlled trials can be used for non-pharmaceutical interventions. Surprisingly they have received little attention in the current pandemic, despite a long history in epidemiology and social science. In this interesting commentary, authors describe how RCTs can be practically and ethically implemented in a pandemic, how compartmental models from infectious disease epidemiology can be used to minimize measurement requirements, and how to control for spillover effects and harness their benefits.

Virology


The cryo-electron microscopic structure of the SARS-CoV-2 RdRp in its active form, mimicking the replicating enzyme. Long helical extensions in nsp8 protrude along exiting RNA, forming positively charged ‘sliding poles’. These sliding poles can account for the known processivity of the RdRp that is required for replicating the long coronavirus genome. A nice video provides an animation of the replication machine.

Viral variants do not affect outcome. This important study on 326 cases found at least two major lineages with differential exposure history during the early phase of the outbreak in Wuhan. Patients infected with these different clades did not exhibit significant difference in clinical features, mutation rate or transmissibility. Lymphocytopenia, especially a reduced CD4+ and CD8+ T cell counts upon admission, was predictive of disease progression. High levels of IL-6 and IL-8 during treatment were observed in patients with severe or critical disease and correlated with decreased lymphocyte count. The determinants of disease severity seemed to stem mostly from host factors such as age, lymphocytopenia, and its associated cytokine storm.


A series of different DNA vaccine candidates expressing different forms of the spike protein were evaluated in 35 rhesus macaques. Vaccinated animals (especially those receiving a vaccine encoding the full-length spike protein) developed humoral and cellular immune responses, including neutralizing antibody titers comparable to those found in convalescent humans. Protection was likely not sterilizing but instead appeared to be mediated by rapid immunologic control following challenge.

Transmission


Using ACE2 mice, authors simulated different transmission modes. Close contact and droplets worked better than aerosol exposition. Animals could not be experimentally infected via aerosol inoculation until continuous exposition for up to 25 min even with high virus concentrations.

Clinical

Clinical data from 20,133 patients, admitted to (or diagnosed in) 208 acute care hospitals in the UK until April 19. Median age was 73 years (interquartile range 58-82) and 60% were men. Comorbidities were common, namely chronic cardiac disease (31%), diabetes (21%), non-asthmatic chronic pulmonary disease (18%). Overall, 41% of patients were discharged alive, 26% died, and 34% continued to receive care. 17% required admission to high dependency or intensive care units; of these, 28% were discharged alive, 32% died, and 41% continued to receive care. Of those receiving mechanical ventilation, 17% were discharged alive, 37% died, and 46% remained in hospital. Increasing age, male sex, and comorbidities including chronic cardiac disease, non-asthmatic chronic pulmonary disease, chronic kidney disease, liver disease and obesity were associated with higher mortality in hospital.

Severe COVID-19


This report describes clinical characteristics, imaging findings, and outcomes among 24 critically ill COVID-19 patients who presented with acute hypoxic respiratory failure in the Seattle metropolitan area. Mortality was high (at least 50%, three patients still intubated at last follow-up).

Treatment


It took almost a month to publish this eagerly awaited paper: does remdesivir work? Yes, in some patients. The conclusion of this double-blinded study that randomized 1,063 COVID-19 patients throughout the world to the drug or to placebo, was remarkably short: “Remdesivir was superior to placebo in shortening the time to recovery in adults hospitalized with COVID-19 and evidence of lower respiratory tract infection”. Median recovery time was 11 versus 15 days. The benefit was most apparent in patients with a baseline ordinal score of 5 (requiring oxygen but no high-flow oxygen). In patients requiring mechanical ventilation or ECMO, there was no effect at all (although the numbers were low). Gender, ethnicity, age or symptom duration had no impact. The Kaplan-Meier estimates of mortality at 14 days were 7.1% and somewhat (not significantly) lower with remdesivir compared to 11.9% with placebo.
(hazard ratio for death, 0.70; 95% CI, 0.47 to 1.04). This is, however, preliminary. The full analysis of the entire trial population will occur soon, although more comparative data may be hard to find as all patients were rolled over to the active agent at this point in the study.”


In this study of 76 patients with severe COVID-19, Tα1 supplement (subcutaneous injections of 10 mg) appeared to reduce mortality, especially in those with low CD4 and CD8 cell counts. This immunomodulating thymic peptide reversed T cell exhaustion and recovered immune reconstitution through promoting thymus output during SARS-CoV-2 infection. However, this is uncontrolled retrospective data and results should be interpreted with caution.

**24 May**

**Epidemiology**

Le Quéré C, Jackson RB, Jones MW et al. **Temporary reduction in daily global CO2 emissions during the COVID-19 forced confinement.** Nat Clim Chang 2020. Full-text: https://doi.org/10.1038/s41558-020-0797-x

The global CO2 emissions have decreased by 17% by early April 2020 compared with the mean 2019 levels, just under half from changes in surface transport (cars, truck, buses). More than one billion tons of carbon emissions less. At their peak, emissions in individual countries decreased by an average of 26%, admittedly extreme and probably unseen before, but just to the level of emissions in 2006. The impact on 2020 annual emissions will depend on the duration of the confinement, with a low estimate of −4% if pre-pandemic conditions return by mid-June, and a high estimate of −7% if some restrictions remain worldwide until the end of 2020. These figures are comparable to the rates of decrease needed year-on-year over the next decades to limit climate change to a 1.5 °C warming.


COVID Reference Top 10
With regard to case numbers, Saudi Arabia already ranks #15 in the world. Beside routine travel, authors describe two factors driving the epidemic. First, each month about 1 million incoming pilgrims from 180 countries merge with about 1 million Saudi national Sunni pilgrims at Saudi Arabia’s two holy sites. Second is the returning Shiite Saudi national pilgrims (4·9 million Shiite population in Saudi Arabia) who travel to Iran for pilgrimage. Of note, men and woman older than 60 years are overrepresented among pilgrims. Bad prospects.

Vaccine


Open-label Phase I trial of an Ad5 vectored COVID-19 vaccine, using the full-length spike glycoprotein. A total of 108 healthy adults aged between 18 and 60 years from Wuhan, China, were given three different doses. ELISA antibodies and neutralising antibodies increased significantly and peaked 28 days post-vaccination. Specific T cell response peaked at day 14 post-vaccination. Follow-up is still short and the authors are going to follow up the vaccine recipients for at least 6 months, so more data will be obtained. Of note, adverse events were relatively frequent, encompassing pain at injection sites (54%), fever (46%), fatigue (44%) and headache (39%). Phase II studies are underway.

Transmission


Of 9,705 HCWs from the Netherlands, 1353 (14%) reported fever or respiratory symptoms and were tested. Of those, 86 HCWs (6%) were infected. Hospital acquisition was unlikely to explain the vast majority of cases. Of note, 54 HCWs (63%) mentioned having worked while being symptomatic.

Overall, 110 of 9,684 HCWs in Tongji Hospital tested positive, with an infection rate of 1.1%. Most infections occurred at the early stage of the epidemic (before January 25), before protective measures were taken. Of those who worked in fever clinics or wards, 17/3110 were infected, indicating an infection rate of 0.5% among first-line HCWs. Of note, a higher rate of infection was found in non-first-line HCW (93/6,574, 1.4%). Authors speculate that this was due to insufficient protective measures available in clinical departments other than fever clinics and wards.


According to the authors, there is high-quality, consistent evidence that many (but not all) cloth masks reduce droplet and aerosol transmission and may be effective in reducing contamination of the environment. No direct evidence indicates that public mask wearing protects either the wearer or others. However, the possible benefit of a modest reduction in transmission likely outweighs the possibility of harm.

Severe COVID-19


More on critically ill patients. Among 1,150 adults who were admitted to two NYC hospitals with COVID-19 in March, 257 (22%) were critically ill. The median age of patients was 62 years (IQR 51-72), 67% were men and 82% patients had at least one chronic illness. As of the end of April, 101 (39%) patients had died and 94 (37%) remained hospitalised. 203 (79%) patients received invasive mechanical ventilation for a median of 18 days, 66% received vasopressors and 31% received renal replacement therapy. In the multivariable Cox model, older age, chronic cardiac disease (adjusted HR 1.76), chronic pulmonary dis-
ease (2.94) were independently associated with in-hospital mortality. This was also seen for higher concentrations of interleukin-6 and D-dimer, highlighting the role of systemic inflammation and endothelial-vascular damage in the development of organ dysfunction. Studies on immunomodulating and anticoagulant drugs are urgently needed.


Endothelial cell dysfunction may explain the vascular microcirculatory complications seen in different organs in patients with COVID-19. The authors discuss the framework of endotheliitis, providing explanation for the unique predilection of SARS-CoV-2 in those individuals with hypertension, diabetes, or established cardiovascular disease, groups known to have pre-existing endothelial dysfunction.


The authors reviewed evidence regarding the benefits and harms of ventilation techniques. Indirect and low-certainty evidence suggests that use of non-invasive ventilation, similar to invasive mechanical ventilation, probably reduces mortality but may increase the risk for transmission of COVID-19 to health care workers.

Treatment


Probably the end of chloroquine. And the end of hydroxychloroquine. And the end of chloroquine plus azithromycin or clarithromycin. And, yes, the end of hydroxychloroquine plus azithromycin or clarithromycin. We should no longer use these four drug regimens as COVID-19 treatments! In this incredible large multinational registry, analysis from 671 hospitals in six con-
tinents, 14,888 patients treated with these regimens were compared with 81,444 control patients. Each drug regimen was associated with decreased in-hospital survival and an increased frequency of ventricular arrhythmias. However, the study (including a 20-page supplement) is too complex to be discussed here in a few words. We will come back to this soon.

25 May

A brief (and probably the last) review on hydroxychloroquine and chloroquine

A few months ago, lab experiments suggested that hydroxychloroquine (HCQ) and chloroquine (CQ) might have some antiviral effects against SARS-CoV-2 due to an increase in the endosomal pH value which disrupts the virus-cell fusion and some post-entry steps (Wang 2020, Yao 2020). An early enthusiastic mini-review stated “results from more than 100 patients” showed that chloroquine phosphate would be able to alleviate the course of the disease (Gao 2020). Other experts, however, dampened the enthusiasm, pointing out that a benefit of chloroquine would be the first positive signal, after decades of unsuccessful studies conducted in a huge number of acute viral diseases (Touret 2020). On March 17, a preliminary report from Marseille/France appeared to show some benefit in a small non-randomized study on 36 patients (Gautret 2020). Although this work lacked essential standards of data generation and interpretation (Kim 2020), someone’s swanky tweet claiming on March 21 that the combination of HCQ and azithromycin has “a real chance to be one of the biggest game changers in the history of medicine”, attracted world-wide attention and led to tens of thousands of uncontrolled treatments. Moreover, many patients decided against clinical trials of other therapies that would require them to give up chloroquine treatments. This has already prompted serious delays in trial enrolment, muddled efforts to interpret data and endangered clinical research (Ledford 2020). Some countries have stockpiled CQ and HCQ, resulting in a shortage of these medications for those that need them for approved clinical indications.

Only a few weeks later, we are now facing an overwhelming amount of data strongly arguing against any use of both HCQ and CQ.

• The by-far most convincing data were published last Friday, May 22 (Mehra 2020). In this extraordinary multinational registry analysis from 671 hospitals on six continents, 14,888 patients (1,868 received CQ; 3,783 received CQ with azithromycin or clarithromycin; 3,016 received HCQ; and 6,221 received HCQ with a macrolide) were compared to 81,144 control pa-
Patients who did not receive these drugs. Mortality was higher in all treatment groups than in the controls (18.0-23.8% versus 9.3%) and each treatment regimen was independently associated with an increased risk of in-hospital mortality and with de novo ventricular arrhythmia, especially in the combination groups (4.3-8.1 versus 0.3%). Adjustment for multiple confounding factors, a propensity score matching analysis and a tipping-point analysis (an analysis that shows the effect size and prevalence of an unmeasured confounder that could shift the upper boundary of the CI towards null) did not affect the results. Although the authors concluded that a cause-and-effect relationship between drug therapy and survival should not be inferred and that their data do not apply to the use of any treatment regimen used in the ambulatory, out-of-hospital setting, it is hard to find any argument for any of these strategies. Data do not support the use of these regimens outside randomized clinical trials (RCTs). Researchers who conduct and supervise RCTs should consider whether ongoing recruitment is necessary.

Other key studies arguing against HCQ in recent weeks

1. In an observational study from New York City of 1,376 consecutive hospitalized patients, 811 received HCQ (60% received also azithromycin) (Geleris 2020). After adjusting for several confounders (HCQ patients were more severely ill at baseline), hydroxychloroquine administration was not associated with either a greatly lowered or an increased risk of the composite end point of intubation or death.

2. Another retrospective cohort of 1,438 patients from 25 hospitals in the New York metropolitan region looked at 1,438 patients (Rosenberg 2020). In adjusted Cox models, compared with patients receiving neither drug, there were no significant differences in mortality for patients receiving HCQ + azithromycin, HCQ alone, or azithromycin alone. Cardiac arrest was significantly more likely with HCQ + azithromycin (adjusted OR 2.13).

3. A randomized, Phase IIb clinical trial in Brazil allocated severe COVID-19 patients to receive high-dose CQ (600 mg BID for 10 days) or low-dose CQ (450 mg BID on day 1, QD for 4 days). The DSMB terminated the trial after 81/440 individuals were enrolled (Borba 2020). By day 13 of enrollment, 6/40 patients (15%) in the low-dose group had died, compared with 16/41 (39%) in the high-dose group. Viral RNA was detected in 78% and 76%, respectively.
4. In a retrospective study of 251 patients receiving HCQ plus azithromycin, extreme new QTc prolongation to >500 ms, a known marker of high risk for torsade de pointes, had developed in 23% (Chorin 2020).
5. HCQ does not work as prophylaxis. A case series described 17 lupus patients with COVID-19, among them several severe cases (Mathian 2020).
6. Free plasma HCQ concentration achieved with HCQ doses tolerable for humans are probably too low to have any antiviral effects (Fan 2020).

References


26 May

Epidemiology


Complex models, comparing individual quarantine (separation from others of an individual who is believed to be exposed to the disease but not currently showing symptoms) with active monitoring targeted by contact tracing (assessing for symptoms at regular intervals such as twice-daily visits by HCW or phone-based self-monitoring, and if symptoms are detected, the individual is promptly isolated). Bottom line: It depends. It depends on the assumptions regarding the serial interval, the amount of transmission that occurs before symptom onset, and the feasibility setting. With a short mean serial interval of 4.8 days and hence substantial pre-symptomatic infectiousness, individual quarantine was considerably more effective than active monitoring at reducing onward transmission. With longer serial intervals both active monitoring and individual quarantine effectively reduce transmission.


One hypothesis about the fatal spread of SARS-CoV-2 in Italy is that the supposed closeness between younger and older generations in Italian families may have played a major role. In this study, this was not confirmed. Paradoxically, it seemed that the variables associated with social isolation were risk factors for higher rates among the elderly. Social relationships may be protective against increased mortality rates during a crisis impacting the frailest populations. Instead, availability of beds in nursing homes were one of the determinants of infection rate among individuals aged >80.
Transmission

Screen the staff! Incredible story about a man who sought help for coronavirus symptoms on March 9, spending only a few hours at the emergency department of a hospital in Durban, South Africa. He was kept separate in a triage area, but that room was reached through the main resuscitation bay, where a stroke patient occupied a bed. Both patients were seen by the same doctor. After likely transmitting the virus to the stroke patient, the results, eight weeks later were: 39 patients and 80 staff linked to the hospital had been infected, and 15/39 patients had died. Lesson learnt: Nosocomial outbreaks may be a major amplifier of COVID-19 transmission.


SARSCoV2 RNA in milk samples from an infected mother (two mothers were examined) was found on 4 consecutive days. Detection of viral RNA in milk coincided with mild COVID19 symptoms and a SARS CoV2 positive diagnostic test of the newborn.

Diagnostics

Should we measure the “viral load”? Unfortunately, there is wide heterogeneity and inconsistency of the standard curves calculated from studies that provided Ct values from serial dilution samples and the estimated viral loads. According to the authors, precautions are needed when interpreting the Ct values of SARS-CoV-2 RT-PCR results shown in COVID-19 publications to avoid misunderstanding of viral load kinetics for comparison across different studies.

In 359 patients, CRP performed better than other parameters (age, neutrophil count, platelet count) in predicting adverse outcome. Besides, admission serum CRP level was identified as a moderate discriminator of disease severity.

Clinical


Of 5,279 cases confirmed in a large medical center in New York, 52% were admitted to hospital, of whom 1,904 (69.5%) were discharged alive without hospice care and 665 (24.3%) were discharged to hospice care or died. Of 647 (23.6%) patients requiring mechanical ventilation, 391 (60.4%) died and 170 (26.2%) were extubated or discharged. The strongest risk for hospital admission was associated with age with an odds ratio of 37.9 for ages 75 years and older. Other risks were heart failure (OR 4.4), male sex (2.8), chronic kidney disease (2.6), and BMI >40 (2.5). Admission oxygen saturation of <88% (3.7), troponin level >1 (4.8), CRP >200 (5.1), and D dimer level >2500 (3.9) were more strongly associated with critical illness than age or comorbidities. Risk of critical illness decreased significantly over the study period. Similar associations were found for mortality alone.

Cormorbidities


Brief guide for clinicians for managing different cases of STEMI/NSTEMI ACS with potential or known COVID-19 infection, based on recent worldwide evidence and standardization protocols.
Treatment


The hypothesis that quelling the cytokine storm with anti-inflammatory therapies directed at reducing interleukin-6 (IL-6), IL-1, or even tumour necrosis factor α (TNFα) might be beneficial has led to several ongoing trials. The authors are less enthusiastic and urge caution. Past attempts to block the cytokine storm associated with other microbial infections and with sepsis have not been successful and, in some cases, have worsened outcomes. Moreover, there is concern that suppressing the innate and adaptive immune system to address increased cytokine concentrations, could enable unfettered viral replication, suppress adaptive immunity, and delay recovery processes. There is growing recognition that potent immunosuppressive mechanisms are also prevalent in such patients. Giving immunosuppressive agents seems not to be a good idea.


Lopinavir concentrations in 12 COVID-19 patients at the Nantes University Hospital, France, were extremely high compared with those usually observed in HIV-infected patients (trough: 18,000 ng/mL versus 5365 ng/mL with 400/100 mg q12h).

27 May

Epidemiology


Overview on the basic concepts of herd immunity and its implications. There is no straightforward, ethical path to reach herd immunity, as the societal consequences of achieving it are devastating. Instead, an emphasis should be placed on policies that protect the most vulnerable groups in the hopes that
herd immunity will eventually be achieved as a “byproduct” of such measures, although not the primary objective itself.


Were people really more stoic in 1918, 1957, and 1968? Or were there other factors that might account for the dampened social and emotional responses to these pandemics? And what should historians make of functionalist and, arguably, selective readings of history that seek to draw moral lessons from the past? This intelligent article has some interesting thoughts on these issues.

Transmission


This study quantitated differences in ACE2 receptor expression and SARS-CoV-2 infectivity in the nose (high) vs the peripheral lung (low). If the nasal cavity is the initial site mediating seeding of the lung via aspiration, these studies argue for the widespread use of masks to prevent aerosol, large droplet, and/or mechanical exposure to the nasal passages.

Diagnostics


In this cross-sectional study, 10 of 60 patients previously diagnosed with and treated for COVID-19 had RT-PCR test results positive for SARS-CoV-2 from 4 to 24 days after index hospital discharge. In total, 6/10 patients had positive anal swab results. However, the infectivity remains unclear, as infectious viruses have not been isolated from stool samples. Positive results were presumed to be persistent viral shedding rather than reinfection.
Clinical


The largest study to date, analysing these important symptoms. Of 2,013 patients, 1,754 patients (87%) reported loss of smell, whereas 1,136 (56%) reported taste dysfunction. Most patients had loss of smell after other general and otolaryngologic symptoms. Mean duration of olfactory dysfunction was 8.4 days. The prevalence of self-reported smell and taste dysfunction was higher than previously reported and may be characterized by different clinical forms. Anosmia may not be related to nasal obstruction or inflammation. Of note, only two thirds of patients reporting olfactory symptoms and who had objective olfactory testing had abnormal results.


The authors investigated the association between different ApoEe4 alleles and COVID-19 severity, using the UK Biobank data. ApoEe4e4 homozygotes were more likely to be COVID-19 test positives (OR = 2.31, 95% CI: 1.65 to 3.24) compared to e3e3 homozygotes. The ApoEe4e4 allele increased risks of severe COVID-19 infection, independent of pre-existing dementia, cardiovascular disease, and type 2 diabetes. This interesting observation needs to be confirmed (and explained).

Comorbidities


The authors describe their way of taking care of the most vulnerable patient groups using telemedicine. They contacted 236/465 adult patients who received an allogeneic transplantation. Physicians felt confident about the management of patients using teleconsultations, and patients—reassured that they were not left alone while in quarantine—provided positive feedback on this approach.

Of 18 SLE patients with COVID-19, most recovered. Previous intake of immunosuppressants before admission to hospital did not seem to influence the severity of infection.


Weekly prescriptions of PEP at a large center in London dropped from a peak of 54 (from Feb 17–23, 2020) to four (from March 30–April 5, 2020) during lockdown. The most obvious explanation for this decline is that individuals are engaging in less condomless sex during lockdown. However, this might also reflect people's reluctance to travel during this period, which would mean that individuals are not accessing the PEP they require.

Comment of the copy-editor: “And might also mean, that if they have less desire to travel, are hooking up less, and perhaps less sex is happening.”

**Treatment**


As long as all other therapies fail or have only modest effects, antibodies are the hope for the near future. Isolation and characterization of 206 RBD-specific monoclonal antibodies were derived from single B cells of eight SARS-CoV-2 infected individuals. Some antibodies showed potent anti-SARS-CoV-2 neutralization activity that correlates with their competitive capacity with ACE2 for RBD binding. Surprisingly, neither the anti-SARS-CoV-2 antibodies nor the infected plasma cross-reacted with SARS-CoV or MERS-CoV RBDs, although substantial plasma cross-reactivity to their trimeric Spike proteins was found.
28 May

Epidemiology


A simple framework to help clinicians counsel patients about continuing to work in the midst of the pandemic based on their occupational risk of contracting SARS-CoV-2 and their risk of death if they are infected.


From April 2, 2020, to April 29, 2020, screening and testing of patients admitted for childbirth was initiated at 3 Yale New Haven Health hospitals in southern Connecticut. Of 770 patients, 30 (3.9%) tested positive for SARS-CoV-2, of whom 22 (73%) were asymptomatic.

Transmission


This perspective clearly shows that masks and testing are necessary and essential to combat asymptomatic spread in aerosols and droplets. It cannot be repeated often enough: infectious aerosol particles can be released during breathing and speaking by asymptomatic infected individuals. No masking maximizes exposure, whereas universal masking results in the least exposure.

Over the last few weeks, it has become very clear that some individuals spread to a disproportionate number of individuals, compared to most individuals who infect a few or no-one. This important paper looked at transmission heterogeneity and the emergence of these super-spreading events (SSEs). In total, 135 cases from official public sources in Tianjin, China were grouped into 43 transmission chains. The reproductive number $R$ and the dispersion parameter $k$ (lower value indicating higher heterogeneity) were estimated to be $0.67$ (95% CI: 0.54-0.84) and $0.25$ (95% CI: 0.13-0.88), respectively. Transmission was very heterogeneous and one SSE was identified. Transmission characteristics of COVID-19 need more exploration and investigation on a large scale.


Contact-tracing surveillance data collected in Guangzhou, China during January 28 – March 15, 2020, to explore the secondary attack rate from different types of contact with 38 pre-symptomatic patients. The secondary attack rates (SAR) among household contacts was 16.1% and was 1.1% for social contacts, and 0 for workplace contacts. Older close contacts had the highest SAR compared to other age groups.

Comorbidities


Realizing the need to reduce the exposure of patients and staff to potential infection with COVID-19, a task force makes recommendations for alternative radiation treatment schemes. The emphasis is on maintaining clinical efficacy and safety by increasing the dose per fraction while reducing the number of daily treatments.

Treatment

In this randomized, open-label, Phase III trial in 397 hospitalized patients with severe COVID-19 and not requiring IMV, clinical improvement at day 14 was 64% with 5 days remdesivir and 54% with 10 days. After adjustment for (significant) baseline imbalances in disease severity, outcomes were similar. The most common adverse events were nausea (9%), worsening respiratory failure (8%), elevated ALT level (7%), and constipation (7%). Because the trial lacked a placebo control, it was not a test of efficacy for remdesivir.


Another interesting specific human monoclonal antibody (MAb) from a convalescent patient, CB6 demonstrated potent neutralization activity in vitro against SARS-CoV-2 and worked in 6 rhesus monkeys at both prophylactic and treatment settings. This MAb recognizes an epitope that overlaps with ACE2 binding sites in SARS-CoV-2 receptor binding domain (RBD), thereby interfering with the virus/receptor interactions by both steric hindrance and direct interface-residue competition.


Five Waldenstrom macroglobulinemia patients on Bruton tyrosine kinase (BTK) inhibitor ibrutinib, 420 mg/d, did not require hospitalization. Their course was marked by steady improvement, and resolution or near resolution of COVID-19 symptoms during the follow-up period. Clinical trials examining the benefit of BTK inhibitors to abrogate lung injury are being initiated.

29 May

Epidemiology


This article shows how analysts and researchers have been scrambling to track and analyse the disparate falsehoods floating around — both ‘misinformation’, which is wrong but not deliberately misleading, and ‘disinformation’,
which refers to organized falsehoods that are intended to deceive. Inaccurate information doesn't only mislead, but could be a matter of life and death if people start taking unproven drugs, ignoring public-health advice, or refusing a coronavirus vaccine if one becomes available.

Lam TT. Tracking the genomic footprints of SARS-CoV-2 transmission. Trends in Genetics 2020. Full-text: https://doi.org/10.1016/j.tig.2020.05.009

Analysis of SARS-CoV-2 genomes provides insights into the origin, transmission, spread and evolution. Brief review on current knowledge and research.

**Virology, Immunology**


Molecular insights into the pathogenesis of SARS-CoV-2 infection. Authors applied proteomic and metabolomic technologies to analyze the proteome and metabolome of sera from COVID-19 patients and several control groups. Pathway analyses and network enrichment analyses of the 93 differentially expressed proteins showed that 50 of these proteins belong to three major pathways, namely activation of the complement system, macrophage function and platelet degranulation. It was found that 80 significantly changed metabolites were also involved in the three biological processes revealed in the proteomic analysis.


The interferon (IFN) response constitutes the major first line of defense against viruses. This complex host defense strategy can, with accurate understanding of its biology, be translated into safe and effective antiviral therapies. In their comprehensive review, authors describe the recent progress in our understanding of both type I and type III IFN-mediated innate antiviral responses against human coronaviruses and discuss the potential use of IFNs as a treatment strategy.
Transmission


Super-spreading events in an outbreak can change the nature of an epidemic. Therefore, it is useful for public health teams to determine if an ongoing outbreak has any contribution from such events, which may be amenable to interventions. The dispersion factor (k) from empirical data on clusters of epidemiologically-linked COVID-19 cases in Hong Kong, Japan and Singapore was relatively high, indicating that large cluster sizes, compatible with super-spreading, were unlikely.

Comorbidities


Cohort study from the USA, Canada, and Spain, analysing 928 cancer patients with COVID-19. Median age was 66 years (IQR 57–76) and the most prevalent malignancies were breast (21%) and prostate (16%). In total 121 (13%) patients had died. Beside general risk factors (age, male sex etc), independent factors associated with increased mortality were an ECOG status of 2 or higher and “active” cancer.


Single center study from Madrid, comparing 51 HIV+ patients with COVID-19 (35 confirmed cases) with 1,288 HIV patients without COVID-19. Six patients were critically ill and two died. There was no evidence that any specific antiretroviral drug (such as tenofovir or PIs) affected COVID-19 susceptibility or severity.

COVID-19 has halted many ongoing CNS clinical trials, especially in Alzheimer’s disease. While some of these trials will need to restart, others can re-start at different points with substantial protocol amendments. Authors propose the concept of mechanistic model-based virtual twin patients as a possible solution to harmonize the readouts from these complex and fragmented clinical datasets in a biologically relevant way.

**Severe COVID-19**


240 consecutive patients with confirmed SARS-CoV-2 were admitted to one of three US hospitals and 109 were critically ill. Venous thromboembolism was diagnosed in 31 patients (28%) 8 ± 7 days after hospital admission. Authors conclude that routine chemical venous thromboembolism prophylaxis may be inadequate in preventing venous thromboembolism in severe COVID-19.

**Treatment**


The main conclusion of this review is that there is insufficient and often conflicting evidence on the benefits and harms of using hydroxychloroquine or chloroquine to treat COVID-19. As such, it is impossible to determine the balance of benefits to harms. There are no assessments of hydroxychloroquine or chloroquine for prophylaxis against COVID-19.
30 May

Epidemiology


A first analysis of the SARS-CoV-2 viral genotypes collected from patients seeking medical care in the New York City metropolitan area. Main message: The NYC epidemic has been mainly sourced from untracked transmission between the US and Europe, with limited evidence of direct introductions from China where the virus originated. Isolates were distributed throughout the phylogenetic tree; consistent with multiple independent introductions.


Staying at home works. In 4 US states (Colorado, Minnesota, Ohio, and Virginia) with stay-at-home orders, cumulative hospitalizations for COVID-19 deviated from projected best-fit exponential growth rates after these orders became effective. The deviation started 2 to 4 days sooner than the median effective date of each state’s order and may reflect the use of a median incubation period for symptom onset and time to hospitalization to establish this date.

Virology


The replication of coronavirus is operated by a set of non-structural proteins (nsp5) encoded by the open-reading frame 1a (ORF1a) and ORF1ab in its genome, which are initially translated as polyproteins followed by proteolysis cleavage for maturation. These proteins assemble into a multi-subunit polymerase complex to mediate the transcription and replication of viral genome. Among them, nsp12 is the catalytic subunit with RNA-dependent RNA polymerase (RdRp) activity. The nsp12 itself is capable of conducting polymerase reaction with extremely low efficiency, whereas the presence of nsp7 and nsp8 cofactors remarkably stimulates its polymerase activity. Using cryo-EM,
near-atomic resolution structure of SARS-CoV-2 nsp12-nsp7-nsp8 core polymerase complex is described.

Clinical


It’s poverty and obesity, but not race. In a large cohort of 3,481 patients in Louisiana, 76.9% of the patients who were hospitalized with COVID-19 and 70.6% of those who died were black, whereas blacks comprise only 31% of the population. Of note, black race was not associated with higher in-hospital mortality than white race, after adjustment for differences in sociodemographic and clinical characteristics on admission.


Viral neuro-invasion may be achieved by several routes, including transsynaptic transfer across infected neurons, entry via the olfactory nerve, infection of vascular endothelium, or leukocyte migration across the blood-brain barrier. This review summarizes available information regarding coronaviruses in the nervous system, identify the potential tissue targets and routes of entry of SARS-CoV-2 into the central nervous system.


Interesting case report, describing in vivo brain alteration during COVID-19. A patient with COVID-19 showed a signal alteration compatible with viral brain invasion in a cortical region (ie, posterior gyrus rectus). Slight and reversible olfactory bulb changes were also seen.

Case series, including carefully selected data for 78 patients (33 asymptomatic) from 26 cluster cases of exposure to the Hunan seafood market or close contact with other patients with COVID. Asymptomatic patients were younger and had a median shorter duration of viral shedding from nasopharynx swabs (median duration, 8 days vs 19 days)

Comorbidities


232 COVID-19 patients with cancer and were compared with 519 matched patients without cancer. Patients with cancer were more likely to have severe COVID-19 (64% versus 32%). Risk factors (of those well-known) for severe disease were advanced tumour stage (OR 2.60), elevated tumour necrosis factor α (1.22), elevated N-terminal pro-B-type natriuretic peptide (1.65).


This large cohort includes 1128 patients who had surgery between Jan 1 and March 31, 2020, among them 835 (74%) emergency surgery and 280 (25%) elective surgery. SARS-CoV-2 infection was confirmed preoperatively in 294 (26%) patients. 30-day mortality was 24% and pulmonary complications occurred in 577 (51%). In adjusted analyses, 30-day mortality was associated with male sex (Odds Ratio 1.75), age 70 years or older (2.30), ASA grades 3–5 versus grades 1–2 (2.35), malignant versus benign (1.55), emergency versus elective surgery (1.67), and major versus minor surgery (1.52).
Treatment


This study from Paris compared 52 consecutive patients treated with anakinra with 44 historical patients. Admission to the ICU for invasive mechanical ventilation or death occurred in 25% patients in the anakinra group and 73% patients in the historical group. Treatment effect of anakinra remained significant in the multivariate analysis. Controlled trials are needed.

Epidemiology


Information from diverse data sources suggests that limited community transmission of SARS-CoV-2 in the United States occurred between the latter half of January and the beginning of February, following an importation from China. This importation initiated a lineage, the Washington State clade, which subsequently spread throughout the Seattle metropolitan area and possibly elsewhere. Several importations of SARS-CoV-2 from Europe followed in February and March. Of note, overall disease incidence before February 28 was too low to be detected through emergency department syndromic surveillance data.


Transmission is likely to remain high at warmer temperatures. Using negative binomial regression modelling, authors investigated whether daily maximum temperature, precipitation and UV index were related to COVID-19 incidence. Incidence declined with increasing temperature up to 52°F and was somewhat lower at warmer versus cooler temperatures. However, the association between temperature and transmission was small.
Transmission
They work! Even in a hamster model. Surgical mask partition for challenged index or naïve hamsters significantly reduced transmission.

Diagnostics
Four commercial ELISAs and two rapid tests performed well in 77 patients with PCR-confirmed SARS-CoV-2 infection, grouped by intervals from symptom onset. While test sensitivities were low (<40%) within the first 5 days post disease onset, IgM-, IgA- and total antibody-ELISAs increased in sensitivity to >80% between the 6th and 10th day post-symptom onset. The evaluated tests (including IgG and rapid tests) provided positive results in all patients at or after the 11th day post-onset of disease.

Clinical
One of the largest studies evaluating liver injury. Among 2,273 patients who tested positive, 45% had mild, 21% moderate, and 6.4% severe liver injury. In multivariate analysis, severe acute liver injury was significantly associated with elevated inflammatory markers including ferritin and IL-6. Peak ALT was significantly associated with death or discharge to hospice (OR 1.14, p = 0.044), controlling for age, body mass index, diabetes, hypertension, intubation, and renal replacement therapy.

Staying at home is not always the best decision. During the COVID-19 pandemic in the Paris area, authors observed a significant (two-fold) and transient increase in the incidence of out-of-hospital cardiac arrest (OHCA), coupled with a major reduction in survival at hospital admission. Although this finding might be partly related to direct COVID-19 deaths, indirect effects related to lockdown and reorganisation of healthcare systems may account for a substantial part.


According to this review, low proportions of COVID-19 patients have a bacterial co-infection, less than in previous influenza pandemics. These findings do not support the routine use of antibiotics in the management of confirmed COVID-19 infection.

Treatment


Nice article describing convalescent plasma as a promising new strategy. However, controlled clinical data are still lacking. Other issues such as supply (may become a challenge), consistency (concentration differs) and risks (transfusion-related acute lung injury, in which transferred antibodies damage pulmonary blood vessels, or transfusion-associated circulatory overload) are also discussed.

Some more clinical data on this strategy. In 25 patients with severe and/or life-threatening COVID-19 disease enrolled at a Houston hospital, convalescent plasma was safe. By day 14 post-transfusion, 19 (76%) patients had at least a 1-point improvement in clinical status and 11 were discharged.
June 2020

1 June

Epidemiology


Again and again: Test them all, immediately. On March 28, 2020, two residents of a long-term care skilled nursing facility in Los Angeles had positive test results. From March 29-April 23, all residents, regardless of symptoms, underwent serial (approximately weekly) nasopharyngeal PCR testing. 8/99 (19%) residents and 8/136 (6%) staff members had positive test results. 14/19 residents were asymptomatic at the time of testing. Among these, eight developed symptoms 1-5 days after specimen collection and were later classified as presymptomatic.


Japan has done a good job. This article explains why. Public adherence to the rules, along with cluster tracing and a ban on mass gatherings, seems to have achieved success in bringing the outbreak under control, alongside widespread mask use and hygiene being a normal part of Japanese etiquette. Japan has ended its state of emergency a week after its new infections fell below 50 a day.

Transmission


Doors and windows open! Important study, analyzing droplet production due to coughs and speech by measuring the droplet size distribution, travel dis-
tance and velocity, and the airborne time in relation to the level of air ventilation (no ventilation, mechanical ventilation only, and mechanical ventilation supported by the opening of an entrance door and a small window). In the best ventilated room, after 30 s the number of droplets had halved, whereas with no ventilation this took about 5 min!


A second case of detectable SARS-CoV-2 RNA from human milk in a patient with COVID-19. Despite mild clinical symptoms, the patient had detectable virus in human milk in two separate samples taken ten days apart but interspersed with a number of negative results.

Clinical


Characterization of the first 1000 consecutive patients with COVID-19 who received care at the emergency department in NYC hospital. Rates of renal complications were high: 33.9% of all patients and 78% of patients in intensive care units developed acute kidney injury. Concomitantly, 13.8% of all patients and 35.2% of patients in intensive care units required in-patient dialysis, leading to a shortage of equipment for dialysis and continuous renal replacement therapy.


100 consecutive patients diagnosed with COVID-19 infection underwent complete echocardiographic evaluation within 24 hours of admission and were compared to reference values. Thirty two patients (32%) had a normal echocardiogram at baseline. The most common cardiac pathology was RV right ventricular (RV) dilatation and dysfunction (observed in 39% of patients),
followed by LV diastolic dysfunction (16%) and LV systolic dysfunction (10%). The authors concluded that LV systolic function is preserved in the majority of patients, but LV diastolic and RV function are impaired.

Severe COVID-19

Empiric therapeutic anti-coagulation (AC) is now being employed in clinical practice in many centers, and will be evaluated in randomized clinical trials. To adjust for bias due to non-random allocation of potential covariates among COVID-19 patients, the authors applied propensity score matching methods. Among > 3000 patients, propensity matching yielded 139 patients who received AC and 417 patients who did not receive treatment with balanced variables between the groups. Results suggest that AC alone is unlikely to be protective for COVID-19-related morbidity and mortality.

Comorbidities

31 people living with HIV (PLWH) were hospitalized for COVID-19. All patients were on antiretroviral therapy and virologically suppressed at the time of admission. One was mild (3%), 2 moderate (6.5%), 21 severe (60%) and 7 were critical (23%). At the time of analysis, 8 (25.8%) patients had died, 21 (67.7%) were alive and discharged and 2 (6.5%) were alive and hospitalized. Four deaths occurred in subjects over 65 years of age and 4 in patients between 50 and 65 years of age.

Treatment

The World Health Organization has halted the hydroxychloroquine arm of the SOLIDARITY trial after a large registry study found that the drug was linked
with an increased risk of mortality and heart arrhythmias. The registry data are discussed.


Whether or not to adopt HCQ to treat COVID-19 has turned into a political dispute that seems to benefit no one. This article describes how unfavorable outcomes have provoked animosity. Brazilian authors of the important JAMA study showing that higher doses are associated with higher mortality (the trial was discontinued) received death threats through social media and had to request police protection, which was kept for more than 2 weeks. The Brazilian president’s son Eduardo Bolsonaro (who has 2 million Twitter followers) had called it “a fake study aimed at demonizing the drug”.

2 June

Epidemiology


Efforts to activate high level national response not only led to a decrease in COVID-19, but also a substantial decrease in seasonal influenza activity. During the period of enforced social distancing from week 9 to 17 of 2020 in Korea, influenza hospitalization cases were 11.9-26.9-fold lower compared with previous seasons. This is good news, because nobody needs influenza.

Transmission


Plasma and whole blood units infected with SARS-CoV-2 underwent treatment with riboflavin and UV light. Riboflavin and UV light effectively reduced the titer of SARS-CoV-2 to the limit of detection in human plasma and by 3.30 ± 0.26 on average in whole blood. This is good news, because these
treatments may reduce blood-borne pathogens in high-risk settings while maintaining blood product quality.


Of 509 medical staff members working to treat COVID-19 patients at the Hyogo Prefectural Kakogawa Medical Center, a large medical institution for infectious diseases in Japan (mean number of hospitalized COVID-19 patients was 20), none had IgG antibodies for SARS-CoV-2 on May 1-8. This is good news, because results show that standard preventive measures against infectious diseases can prevent SARS-CoV-2 exposure in medical staff.

**Diagnostics**


This retrospective cross-sectional study determined PCR positive samples for their ability to infect cell lines. Of 90 samples, only 29% demonstrated viral growth. There was no growth in samples with a Ct > 24 (the lower the cycle threshold, the higher the viral load) or duration of symptoms > 8 days. This is very good news, because positive PCR does not mean infectivity. And infectivity duration is short.


In 104 patients, a decrease in B cells was independently associated with prolonged viral RNA shedding. The viral RNA shedding from respiratory tract in patients with normal B cell count was significantly shorter than patients with decreased B cell on admission (median 11 vs 16 days). This is good news, because these observations may help to individualize monitoring of COVID-19 patients.

A total of 45 studies comprising 4,410 (!) patients were included in this review. Ground glass opacities (GGOs), whether isolated (50%) or coexisting with consolidations (44%) in bilateral and subpleural distribution, were the most prevalent chest CT findings in adult COVID-19 patients. Follow-up CT shows a progression of GGOs into a mixed pattern, reaching a peak at 10-11 days, before gradually resolving or persisting as patchy fibrosis. Younger people tend to have more GGOs. Older or sicker people tend to have more extensive involvement with consolidations. This is good news, because it's good to see that there are nerds out there (like us) who have nothing better to do than look through 4,410 CT scans.


The authors evaluated the recently released Abbott ID NOW COVID-19 assay (uses isothermal nucleic acid amplification of the RdRp viral target) which is capable of producing positive results in as little as 5 minutes. Results were compared with RT-PCR Cepheid Xpert Xpress SARS-CoV-2 using nasopharyngeal swabs. Regardless of method of collection and sample type, the rapid test had negative results in a third of the samples that tested positive by PCR when using nasopharyngeal swabs in viral transport media and 45% when using dry nasal swabs. This is good news, well, because this is the-good-news-day. However, these rapid tests (if further improved) may find their role in clinical settings such as emergency departments where rapid diagnosis is crucial.

**Comorbidities**

Case series of 600 COVID-19 patients with rheumatic diseases from 40 countries. Nearly half of the cases were hospitalized (277 or 46%) and 55 (9%) died. In multivariable-adjusted models, prednisone dose ≥10 mg/day was associated with higher odds of hospitalization but not the use of conventional disease-modifying anti-rheumatic drug (DMARD) alone or in combination with biologics, the Janus Kinase inhibitors. This is good news because only high glucocorticoid exposure (which has well-known side effects anyway) is associated with a higher odds of hospitalization but not either DMARDs or NSAIDs.


Famotidine is a histamine-2 receptor antagonist that suppresses gastric acid production. It is thought to inhibit the 3-chymotrypsin-like protease (3CLpro) and/or to act via its antagonism or inverse-agonism of histamine signalling. This retrospective study looked at 1,620 patients, including 84 patients (5.1%) who received different doses of famotidine within 24 hours of hospital admission. After adjusting for baseline patient characteristics, use of famotidine remained independently associated with a reduced risk for death or intubation (adjusted hazard ratio 0.42, 95% CI 0.21-0.85) and this remained unchanged after careful propensity score matching to further balance the co-variables. Of note, there was no protective effect associated with use of PPIs. The maximum plasma ferritin value during hospitalization was lower with
famotidine, indicating that the drug blocks viral replication and reduces the cytokine storm. RCTs are underway, keep an eye on this! This is damned good news!

3 June

Epidemiology


Herd immunity? Forget it. Using a stochastic age-structured transmission model to explore a range of intervention scenarios, tracking 66 million people in England, Wales, Scotland, and Northern Ireland, the authors projected a median unmitigated burden of 23 million (95% prediction interval 13–30) clinical cases and 350,000 deaths (170,000–480,000) due to COVID-19 in the UK by December, 2021. Bad news because extreme measures are probably required to bring the epidemic under control.

Virology


Human challenge studies could accelerate vaccine development, helping to test multiple candidate vaccines. This personal view on ethical issues explains why this will be difficult. This is bad news. However, this is also somewhat good news (exception today!), as the authors argue that human challenge studies can “reasonably be considered ethically acceptable insofar as such studies are accepted internationally and by the communities in which they are done, can realistically be expected to accelerate or improve vaccine development, have considerable potential to directly benefit participants, are designed to limit and minimise risks to participants, and are done with strict infection control measures to limit and reduce third-party risks.”
Transmission

Eskew EA, Carlson CJ. **Overselling wildlife trade bans will not bolster conservation or pandemic preparedness.** Lancet Planetary Health, June 01, 2020. Full-text: [https://doi.org/10.1016/S2542-5196(20)30123-6](https://doi.org/10.1016/S2542-5196(20)30123-6)

Nice comment about a wildlife trade ban. Many (including us) have been quick to advocate for complete restriction of commercial trade, particularly in wet markets (like Wuhan) given their potential role as hotspots of cross-species viral transmission. This collective rhetoric suggests that eliminating wildlife trade is a simple, effective defense against zoonotic pandemics. According to the authors, stopping pandemics is not as simple as stopping wildlife trade. The bad news is that even with extensive wildlife trade bans, crippling zoonotic disease burden remains a near certainty.

Baer S, Kim MC, Kim JY. **Notice of Retraction: Effectiveness of Surgical and Cotton Masks in Blocking SARS-CoV-2.** Annals Int Med 2020, June 2. [https://doi.org/10.7326/L20-0745](https://doi.org/10.7326/L20-0745)

Come on, guys. “We are retracting our article....we had not fully recognized the concept of limit of detection (LOD) of the in-house RT-PCR used in the study (2.63 log copies/mL), and we regret our failure to express the values below LOD as “<LOD (value).” The LOD is a statistical measure of the lowest quantity of the analyte that can be distinguished from the absence of that analyte. Therefore, values below the LOD are unreliable and our findings are uninterpretable.“ We regret, too.


This was our comment on this study in April: “Very small study, but both surgical and cotton masks appeared to be ineffective in preventing the virus dissemination from the coughs of patients with COVID-19 to the environment and external mask surface.”

We will have to deal with upper-room germicidal UV filters (GUV). According to the authors, preparation for future respiratory viral pathogens should include consideration of the use of upper-room GUV to help mitigate airborne transmission. Sounds complicated, expensive. Bad news.

**Diagnostics**


The authors compared the clinical performance of several serologic assays (Abbott, EUROIMMUN and the Roche Elecsys assay). The Abbott assay demonstrated the fewest false negative results > 14d post-symptom onset and the fewest false positive results. While the Roche assay detected more positive results earlier after onset of symptoms, none of the assays demonstrated high enough clinical sensitivity before day 14 from symptom onset to diagnose acute infection. This is bad news because we still have to rely on PCR during the first two weeks.

**Clinical**


Intelligent comment. The psychosocial burden of COVID-19 will become increasingly evident in the coming months as the effects of social measures such as physical distancing, loneliness, death of friends and family members, and job losses manifest. Bad news, no good prospects (but the best author name of the month!).

**Comorbidities**


Ooops. They don’t trust their own authors (Mehra 2020). “Recently, substantive concerns have been raised about the quality of the information in that database”, editor Eric Rubin writes, washing NEJM’s hands in innocence. “We have asked the authors to provide evidence that the data are reliable. In the interim and for the benefit of our readers, we are publishing this Expression of Concern about the reliability of their conclusions.” Ok. Let’s wait and see.
what happens. But bad news because even in a journal like NEJM, bad data quality is possible.


This was the original work of concern. Bad news that we cannot trust it. This was our comment: “The first study analyzed a total of 8,910 COVID-19 patients (from 169 hospitals located in 11 countries) for whom discharge status was available by March 29 (Mehra 2020). A total of 515 (5.8%) died in the hospital. Factors independently associated with an increased risk of in-hospital death were an age greater than 65 years (odds ratio, 1.93), coronary artery disease (2.70), heart failure (2.48; 95% CI, 1.62 to 3.79), cardiac arrhythmia (1.95; 95% CI, 1.33 to 2.86), chronic obstructive pulmonary disease (2.96; 95% CI, 2.00 to 4.40), and current smoking (1.79; 95% CI, 1.29 to 2.47). No increased risk was found for the use of ACE inhibitors (0.33; 95% CI, 0.20 to 0.54) or the use of ARBs (1.23; 95% CI, 0.87 to 1.74). Of note, use of either ACE inhibitors or statins was associated with better survival. However, these associations should be considered with extreme caution as the study design cannot exclude the possibility of confounding.”

4 June

Epidemiology


Herd immunity? Forget it. Using a stochastic age-structured transmission model to explore a range of intervention scenarios, tracking 66 million people in England, Wales, Scotland, and Northern Ireland, the authors projected a median unmitigated burden of 23 million (95% prediction interval 13–30) clinical cases and 350,000 deaths (170,000–480,000) due to COVID-19 in the UK by December, 2021. Bad news because extreme measures are probably required to bring the epidemic under control.
Virology

Human challenge studies could accelerate vaccine development, helping to test multiple candidate vaccines. This personal view on ethical issues explains why this will be difficult. This is bad news. However, this is also somewhat good news (exception today!), as the authors argue that human challenge studies can “reasonably be considered ethically acceptable insofar as such studies are accepted internationally and by the communities in which they are done, can realistically be expected to accelerate or improve vaccine development, have considerable potential to directly benefit participants, are designed to limit and minimise risks to participants, and are done with strict infection control measures to limit and reduce third-party risks.”

Transmission
Eskew EA, Carlson CJ. **Overselling wildlife trade bans will not bolster conservation or pandemic preparedness.** Lancet Planetary Health, June 01, 2020. Full-text: [https://doi.org/10.1016/S2542-5196(20)30123-6](https://doi.org/10.1016/S2542-5196(20)30123-6)

Nice comment about a wildlife trade ban. Many (including us) have been quick to advocate for complete restriction of commercial trade, particularly in wet markets (like Wuhan) given their potential role as hotspots of cross-species viral transmission. This collective rhetoric suggests that eliminating wildlife trade is a simple, effective defense against zoonotic pandemics. According to the authors, stopping pandemics is not as simple as stopping wildlife trade. The bad news is that even with extensive wildlife trade bans, crippling zoonotic disease burden remains a near certainty.

Baer S, Kim MC, Kim JY. **Notice of Retraction: Effectiveness of Surgical and Cotton Masks in Blocking SARS-CoV-2.** Annals Int Med 2020, June 2. [https://doi.org/10.7326/L20-0745](https://doi.org/10.7326/L20-0745)

Come on, guys. “We are retracting our article….we had not fully recognized the concept of limit of detection (LOD) of the in-house RT-PCR used in the study (2.63 log copies/mL), and we regret our failure to express the values below LOD as “<LOD (value).” The LOD is a statistical measure of the lowest quantity of the analyte that can be distinguished from the absence of that
analyte. Therefore, values below the LOD are unreliable and our findings are uninterpretable. “We regret, too.


This was our comment on this study in April: “Very small study, but both surgical and cotton masks appeared to be ineffective in preventing the virus dissemination from the coughs of patients with COVID-19 to the environment and external mask surface.”


We will have to deal with upper-room germicidal UV filters (GUV). According to the authors, preparation for future respiratory viral pathogens should include consideration of the use of upper-room GUV to help mitigate airborne transmission. Sounds complicated, expensive. Bad news.

Diagnostics


The authors compared the clinical performance of several serologic assays (Abbott, EUROIMMUN and the Roche Elecsys assay). The Abbott assay demonstrated the fewest false negative results > 14d post-symptom onset and the fewest false positive results. While the Roche assay detected more positive results earlier after onset of symptoms, none of the assays demonstrated high enough clinical sensitivity before day 14 from symptom onset to diagnose acute infection. This is bad news because we still have to rely on PCR during the first two weeks.
Clinical


Intelligent comment. The psychosocial burden of COVID-19 will become increasingly evident in the coming months as the effects of social measures such as physical distancing, loneliness, death of friends and family members, and job losses manifest. Bad news, no good prospects (but the best author name of the month!).

Comorbidities


Ooops. They don’t trust their own authors (Mehra 2020). “Recently, substantive concerns have been raised about the quality of the information in that database”, editor Eric Rubin writes, washing NEJM’s hands in innocence. “We have asked the authors to provide evidence that the data are reliable. In the interim and for the benefit of our readers, we are publishing this Expression of Concern about the reliability of their conclusions.” Ok. Let’s wait and see what happens. But bad news because even in a journal like NEJM, bad data quality is possible.


This was the original work of concern. Bad news that we cannot trust it. This was our comment: “The first study analyzed a total of 8,910 COVID-19 patients (from 169 hospitals located in 11 countries) for whom discharge status was availably by March 29 (Mehra 2020). A total of 515 (5.8%) died in the hospital. Factors independently associated with an increased risk of in-hospital death were an age greater than 65 years (odds ratio, 1.93), coronary artery disease (2.70), heart failure (2.48; 95% CI, 1.62 to 3.79), cardiac arrhythmia (1.95; 95% CI, 1.33 to 2.86), chronic obstructive pulmonary disease (2.96; 95% CI, 2.00 to 4.40), and current smoking (1.79; 95% CI, 1.29 to 2.47). No increased risk was found for the use of ACE inhibitors (0.33; 95% CI, 0.20 to 0.54) or the use of ARBs (1.23; 95% CI, 0.87 to 1.74). Of note, use of either ACE inhibitors or statins was associated with better survival. However, these associations should be considered with extreme caution as the study design cannot exclude the possibility of confounding.”
In total, 821 asymptomatic participants were randomized to receive hydroxychloroquine or placebo within 4 days after exposure (88% with a high-risk exposure). Incidence of confirmed SARS-CoV-2 was 11.8% with CQ and 14.3% with placebo. Side effects were more common with hydroxychloroquine than with placebo (40.1% vs. 16.8%), but no serious adverse reactions were reported.

This is bad news because after high-risk or moderate-risk exposure to Covid-19, HCQ did not prevent infection when used as postexposure prophylaxis within 4 days after exposure.

5 June

The Lancet and the NEJM: Retractions

We suspected it. Yesterday, two papers that were considered milestones in COVID-19 research (and were well-reviewed in our Top Ten section) were retracted by the authors.

Which papers are we talking about?

1. The first is a NEJM paper reporting that ACE inhibitors had proven to be harmless.


   “Because all the authors were not granted access to the raw data and the raw data could not be made available to a third-party auditor, we are unable to validate the primary data sources underlying our article, “Cardiovascular Disease, Drug Therapy, and Mortality in Covid-19.” We therefore request that the article be retracted. We apologize to the editors and to readers of the Journal for the difficulties that this has caused.”
2. The second is a Lancet paper of the same group in which chloroquine-based therapies were more dangerous than effective.


“After publication of our Lancet Article, several concerns were raised with respect to the veracity of the data and analyses conducted by Surgisphere Corporation and its founder and our co-author, Sapan Desai, in our publication. We launched an independent third-party peer review of Surgisphere...(they) informed us that Surgisphere would not transfer the full dataset.” “We deeply apologize”, and so on.

Apologize? This is inexcusable. Both papers are probably based on fake data. Gathered together and fantasized by a mailbox company. It is of concern to see how in the current situation the pressure on science is exploited by unscrupulous authors. And how such crooks will play into the hands of conspiracy theorists. But let’s also hope that it be an incentive for these high-ranked medical journals to take a closer scrutiny of the submitted data in the future.

Scientific publishing is a fantastic business model and you're always surprised that everyone participates. Scientific authors write the manuscripts for free (they have to publish), according to rigorous instructions for authors, thick as a book. Reviewers read the submitted manuscripts within a few days, again, for free (they want to get their own papers peer-reviewed). There are many journals where authors are required to pay charges “to share in the high costs of production”. Or supplemental data fees. Or reprints. They are all extra. On the other hand: readers pay. Subscribers pay, institutional subscribers pay (a lot). Pharmaceutical companies pay (a lot) for supported supplements. Conference organisations pay to get their abstract supplements published. In addition there is advertising revenue.

But where is the substantial contribution of the journals, apart from editing and layout? One has to take these cases as an opportunity to reflect on the practice of scientific publishers. It can't go on like this. Scientific journals must provide the resources for reviewing the data sets and basic information.
of their origin. They have enough money to do that. Simply publishing “Ex-
pressions of Concern” and then a “Retraction” without further comment of
the editors is not enough. It’s like playing Pontius Pilate, washing their hands
of responsibility. We want to know how this could happen.

We have to postpone the fourth edition of COVID Reference another few days.
Some parts need to be revised.

Fortunately, nothing has changed in the essential messages regarding the two
topics of these fake papers. ACE inhibitors are probably not harmful in the
current pandemic, and hydroxychloroquine and chloroquine are probably
useless (Boulware 2020, Horby and Landray 2020).

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6 June

Virology

Sun SH, Chen Q, Gu HJ, et al. A Mouse Model of SARS-CoV-2 Infection and
Pathogenesis. Cell Host Microbe. 2020 May 27;S1931-3128(20)30302-4. Pub-

Human ACE2 knockin mice were generated by using CRISPR-Cas9 technology.
Bottom line: SARS-CoV-2 led to robust replication in the lung, trachea, and
brain. SARS-CoV-2 caused interstitial pneumonia and elevated cytokines. A
high dose of virus could establish infection via an intragastric route.
Transmission

Nothing really new, but this incredible work had to be done. This systematic review identified 172 observational studies across 16 countries and six continents and 44 relevant comparative studies in health-care and non-health-care settings. Transmission of viruses was lower with physical distancing of 1 m or more, compared with a distance of less than 1 m (n=10,736, pooled adjusted odds ratio 0.18), protection was increased as distance was lengthened. Face mask use could result in a large reduction in risk of infection (n=2,647; AOR 0.15), stronger associations with N95 or similar respirators compared with disposable surgical masks or similar. Eye protection also was helpful (n=3,713; AOR 0.22). The findings support face masks, eye protection and physical distancing of 1 m or more.


Another review of N95 masks. Four RCTs involving 8,736 HCWs were included. There was no direct high quality evidence on whether N95 respirators are better than surgical masks for HCWs protection from SARS-CoV-2. However, wearing N95 respirators could prevent 73 more clinical respiratory infections per 1000 HCWs compared to surgical masks (low quality evidence).


Recycle your masks 2-3 times but not more! Authors have analyzed 4 different decontamination methods – UV light (260–285 nm), 70°C dry heat, 70% ethanol, and vaporized hydrogen peroxide (VHP), for their ability to reduce contamination with infectious SARS-CoV-2 and their effect on N95 respirator
function. UV light inactivated virus rapidly from steel but more slowly on N95 fabric, probably because of its porous nature. Heat caused more rapid inactivation on N95 than on steel; inactivation rates on N95 were comparable to UV. In conclusion, N95 respirators can be decontaminated and reused up to 3 times by using UV light and VHP and 1–2 times by using dry heat. Subsequent rounds of decontamination caused sharp drops in filtration performance.

**Diagnostics**


Let the patients do their own swabs! A total of 530 patients with upper respiratory infection were provided with instructions and asked to collect tongue, nasal, and mid-turbinate samples. A nasopharyngeal (NP) sample was then collected from the patient by a HCW. When this NP sample was used as the comparator, the estimated sensitivities of the tongue, nasal, and mid-turbinate samples collected by the patients were 89.8%, 94.0% and 96.2%, respectively. This study shows the clinical usefulness of these samples. This may reduce PPE use and provide a more comfortable patient experience.


Important article on false negative tests (which are frequent), with several conclusions. According to the authors, FDA should ensure that manufacturers provide details of tests’ clinical sensitivity and specificity at the time of market authorization. It will also be important to develop prediction rules for estimating the pre-test probability of infection (for asymptomatic and symptomatic people) to allow calculation of post-test probabilities after positive or negative results.

**Clinical**

Review of the available evidence on asymptomatic SARS-CoV-2 infection. Asymptomatic persons seem to account for approximately 40-45% of infections, and they can transmit the virus to others for an extended period, perhaps longer than 14 days. The absence of COVID-19 symptoms might not necessarily imply an absence of harm as subclinical lung abnormalities are frequent.

Severe COVID-19

Retrospective study, describing the rate and severity of hemostatic and thrombotic complications of 400 hospital-admitted COVID-19 patients (144 critically ill), receiving standard-dose prophylactic anticoagulation. The overall and major bleeding rates were 4.8% and 2.3%. RCTs are needed to determine any potential benefit of intensified anticoagulant prophylaxis in COVID-19 patients.

Treatment

The first randomized trial of well-characterized plasma units with a high titer of antibody to SARS-CoV-2. Unfortunately, the study was terminated before it reached its targeted original sample size of 200 patients; only 103 were enrolled (when the epidemic was under control in China, no more patients could be recruited). Consequently, the study was underpowered. Of 103 patients who were randomized, clinical improvement (discharged alive or reduction of 2 points on a 6-point disease severity scale) occurred within 28 days in 52% vs 43%. There was no significant difference in 28-day mortality (16% vs 24%) or time from randomization to discharge. Of note, convalescent plasma treatment was associated with a negative conversion rate of viral PCR at 72 hours in 87% of the convalescent plasma group versus 38% (OR, 11.39). Main take-homes: convalescent plasma is not a silver bullet and antiviral efficacy does not necessarily lead to better survival.

Careful discussion of the previous study. According to the authors, the study provides an important signal of possible benefit in the subgroup of severely ill patients and suggests that high titer antibody against SARS-CoV-2 may have antiviral efficacy. These results suggest that future studies should focus on determining efficacy in less severely ill patients.

7 June

Epidemiology


Learning from China. Case finding and management, with identification and quarantine of close contacts: the authors describe the next steps planned in China following the containment effort.

Virology

Cyranoski D. The biggest mystery: what it will take to trace the coronavirus source. Nature 2020, June 05. Full-text: https://www.nature.com/articles/d41586-020-01541-z

Elegant article summarizing the current (and limited) knowledge of the origin of SARS-CoV-2. Most researchers say the more likely explanation is that bats passed it to an intermediate animal, which then spread it to people. However, this finding will be tricky, as will calming speculations of a “lab escape”. This would require a forensic investigation, looking for viruses that matched the genetic sequence of SARS-CoV-2 and. Authorities would need to take samples from the lab, interview staff, review lab books and records of safety incidents, and see what types of experiment researchers had done.
Transmission

This study raises doubts on the hypothesis that children are less infectious. Of 12 children (median 6.5 years), 9 were mildly symptomatic and 3 were asymptomatic. Viral RNA load in the nasopharyngeal swabs (and saliva) peaked early at high levels, achieving a median of 7.56 (range 6.19–10.56) log_{10} copies/mL. Along with positive SARS-CoV-2 RNA in nasopharyngeal swabs, viral RNA was detectable at high concentration for >3 weeks in fecal samples.

Diagnostics

The cycle threshold (Ct) PCR values (low = more virus) were compared in posterior oropharyngeal saliva, collected at five different time points within the same day from 18 COVID-19 patients. There was an overall trend of lower Ct values from specimens collected in the early morning, with a gradual decrease of viral load towards night time. Eight out of 13 subjects had highest viral load in the early morning than the rest of the four time points. The results suggest a diurnal variation of viral shedding from the upper respiratory tract.

Comorbidities

First large analysis on liver transplant recipients. At a median follow-up of 18 days, 16/100 died from COVID-19. Of note, mortality was observed only in patients aged 60 years or older (16/73) and was more common in male recipients than in female recipients. Although not statistically significant, more patients who were transplanted at least 2 years earlier died than did those
who received their transplant within the past 2 years (15/82, 18% vs 1/21, 5%).

Severe COVID

For this network meta-analysis of trials of adult patients with acute hypoxemic respiratory failure, the authors included 25 studies with 3,804 patients. Compared with standard oxygen therapy, helmet NIV (3 trials with 330 patients), face mask NIV (14 trials with 1725 patients) and HFNC (5 trials with 1479 patients) were associated with a lower risk of endotracheal intubation. Both forms of NIV, helmet and face mask, were also associated with a lower risk of death.


This article reviews the meta-analysis and describes how COVID-19 has accelerated the need to add clarity to the ongoing debate of whether to intubate early and, if not, which type of non-invasive support (NIV, HFNC, or standard oxygen therapy) is the most efficacious. Future clinical trials comparing these strategies should not focus on declaring a “winner” per se but rather on identifying the patient phenotypes that stand to benefit from each non-invasive oxygenation support method. According to the authors, a heterogeneous syndrome like AHRF requires multiple options.


Autopsy findings of six patients (four men and two women, aged 58–82 years) who died from COVID-19 in April 2020. A pronounced CNS involvement with pan-encephalitis, meningitis, and brainstem neuronal cell damage were key events in all cases. In patients younger than 65 years, CNS hemorrhage was a fatal complication of COVID-19.
Treatment


Canakinumab is a human monoclonal antibody against IL-1β, approved for treatment of juvenile rheumatoid arthritis and other chronic autoinflammatory syndromes. In a pilot trial, 10 patients with hyperinflammation (defined as CRP ≥ 50 mg/L) and respiratory failure showed a rapid improvement in serum inflammatory biomarkers and an improvement in oxygenation.

Pediatrics


Of 21 children and adolescents (3.7-16.6 years, 19 with recent SARS-CoV-2 infection) with features of Kawasaki disease who were admitted between 27 April and 11 May 2020, 12 (57%) presented with Kawasaki disease shock syndrome and 16 (76%) with myocarditis. 17 (81%) required intensive care support. All 21 patients had noticeable gastrointestinal symptoms and high levels of inflammatory markers. All 21 patients received intravenous immunoglobulin and 10 (48%) also received corticosteroids. The clinical outcome was favourable in all patients.

8 June

Epidemiology


To estimate the cumulative prevalence, authors evaluated IgM and IgG antibodies in 17,368 individuals from Wuhan, China. The seropositivity in Wuhan was low, varying between 3.2% and 3.8% in different sub-cohorts. As seen in other studies, an early and a higher level of IgG response was observed, compared to IgM.

Hoffmann – Kamps

Outbreak investigation involving 394 residents and 70 staff in 4 nursing homes in central London. Overall, 26% of residents died over a two-month period. Systematic testing identified 40% of residents as positive for SARS-CoV-2 and of these, 43% were asymptomatic and 18% had only atypical symptoms during the two weeks prior to testing. Of note, this was also true of many residents in the days leading up to death indicating that even in severe COVID-19, fever and cough were commonly absent. 4% of asymptomatic staff also tested positive.

Immunology


Nice review about the immune response to respiratory viruses. What happens when the virus reaches the respiratory mucosa? What are the consequences of infection in the host?

Virology, Vaccine


Will this be the first vaccine? Compared with the adenovirus-vector and the DNA vaccine, inactivated vaccine development and production is a conventional and mature technology (main pro: large amounts of vaccine doses can be easily manufactured, main con: safety issues, including an antibody-dependent worsening of the infection). BBIBP-CorV, an inactivated SARS-CoV-2 vaccine, induced high levels of neutralizing antibody in several animal models, including 8 rhesus macaques, protecting them against SARS-CoV-2 infection. There was no observable antibody-dependent infection enhancement or immunopathological exacerbation. A Phase I clinical trial of BBIBP-
CorV is currently in progress and a Phase II clinical trial has recently been initiated.

Transmission

American cats are not protected: Two domestic cats with respiratory illnesses lasting 8 and 10 days were the first reported companion animals with SARS-CoV-2 infection in the United States. Both cats were owned by persons with suspected or confirmed COVID-19. According to the authors, persons with COVID-19 should avoid contact with animals. Companion animals that test positive for SARS-CoV-2 should be monitored and separated from persons and other animals until they recover. Good news: both cats fully recovered.

Diagnostics

For SARS-CoV-2, the accuracy of antibody test results and the appropriate test interpretation both depend on clinical context. This article discusses key use cases for SARS-CoV-2 antibody detection tests and their application to serologic studies, reviews currently available assays, highlights key areas of ongoing research, and proposes potential strategies for test implementation. This review also includes a decision tree for interpreting antibody test results.


If the first PCR is negative, a second PCR only yields a small number of positive results. Using data for 20,912 patients, authors analyzed the frequency of SARS-CoV-2 RT-PCR test discordance among individuals initially testing negative by nasopharyngeal swab who were retested on clinical grounds within 7
days. The frequency of subsequent positivity within this window was only 3.5% and similar across institutions.

Treatment

Ex vivo analysis revealed significantly elevated bruton tyrosine kinase (BTK, regulates macrophage signalling and activation) activity, as evidenced by autophosphorylation, and increased IL-6 production in blood monocytes from patients with severe COVID-19 compared with blood monocytes from healthy volunteers. In a pilot study, 19 patients with severe COVID-19 received the BTK inhibitor acalabrutinib. Within 10-14 days, oxygenation improved “in a majority of patients”, often within 1-3 days, and inflammation markers and lymphopenia normalized quickly in most patients. At the end of acalabrutinib treatment, 8/11 (72.7%) patients in the supplemental oxygen cohort had been discharged on room air. These results suggest that targeting excessive host inflammation with a BTK inhibitor is a therapeutic strategy. A confirmatory RCT is underway.

Pediatrics

This case series included 58 hospitalized children, meeting definitional criteria for (attention, a novel term/syndrome) “PIMS-TS”, including fever, inflammation, and organ dysfunction. Of these children, all had fever and non-specific symptoms, such as abdominal pain (53%), rash (52%), and conjunctival injection (45%); 50% developed shock and required inotropic support or fluid resuscitation; 22% met diagnostic criteria for Kawasaki disease; and 14% had coronary artery dilatation or aneurysms. Some clinical and laboratory characteristics had important differences compared with Kawasaki disease, Kawasaki disease shock syndrome, and toxic shock syndrome.
Hoffmann – Kamps


Nice editorial on current knowledge (and knowledge gaps) on PIMS-TS and Kawasaki Disease (KD), noting that the differences between PIMS-TS and Kawasaki Disease (KD) are just as interesting as the similarities. For PIMS-TS, SARS-CoV-2 may be acting either as the trigger or an immune-modulating factor. 9 June

9 June

Epidemiology


This world-leading group of epidemiologists and statisticians estimated the total infection rates across 11 European countries. Main results: between 12 and 15 million individuals have been infected with SARS-CoV-2 up to May 4th, representing between 3.2% and 4.0% of the population. Percentages of total population infected were for Austria 0.76% (0.59% - 0.98%), Belgium 8.0% (6.1% - 11%), Denmark 1.0% (0.81% - 1.4%), France 3.4% (2.7% - 4.3%), Germany 0.85% (0.66% - 1.1%), Italy 4.6% (3.6% - 5.8%), Norway 0.46% (0.34% - 0.61%), Spain 5.5% (4.4% - 7.0%), Sweden 3.7% (2.8% - 5.1%), Switzerland 1.9% (1.5% - 2.4%) and United Kingdom 5.1% (4.0% - 6.5%). Results also showed that major non-pharmaceutical interventions and lockdown in particular have had a large effect on reducing transmission.


Detective work, analysing the genomic epidemiology of SARS-CoV-2 in Northern California from late January to mid-March 2020, using samples from 36 patients spanning 9 counties and the Grand Princess cruise ship. Phylogenetic analyses revealed the cryptic introduction of at least 7 different SARS-CoV-2 lineages into California, including epidemic WA1 strains associated with
Washington State, with a lack of predominant lineage, and limited transmission between communities.

**Immunology**


A robust humoral immune response occurs early during severe or moderate COVID-19 infections: in this cross-sectional study of 44 hospitalized COVID-19 patients, receptor-binding domain (RBD)-specific IgG responses became detectable in all patients 6 days after PCR confirmation. Neutralizing antibody titers were detectable in 40/44 cases, mostly by 20 days of symptom onset. Of note, RBD-specific IgG titers seemed to correlate with the neutralizing potency, indicating that RBD-specific IgG titers could be used as a surrogate of neutralization activity against SARS-CoV-2 infection.


The authors isolated B cells specific for the SARS-CoV-2 envelope glycoprotein spike (S) from a COVID-19-infected subject. Main findings: The 45 S-specific monoclonal antibodies generated had undergone minimal somatic mutation, with limited clonal expansion. Most anti-S antibodies that were generated in this patient during the first weeks of COVID-19 infection were non-neutralizing and targeted epitopes outside the RBD. Neutralizing antibodies targeting the interaction of the S protein with ACE2 were minimally mutatated.


Outstanding article on unresolved questions. Why do some patients develop severe disease, while others do not; and what roles do genetic variabilities play in the individual immune response to this viral infection? The authors discuss the critical role T cells play in the orchestration of the antiviral response underlying the pathogenesis of COVID-19.
Transmission

Environmental conditions affect the stability of the virus in nasal mucus and sputum. The virus is more stable at low temperature and low humidity conditions, whereas warmer temperatures and higher humidity shortened half-life. Although infectious virus was undetectable after 48 hours, viral RNA remained detectable for 7 days.

Diagnostics

Head-to-head comparison of four high-throughput, commercially available anti-SARS-CoV-2 IgG serologic tests from Abbott Laboratories, Epitope Diagnostics Inc, Euroimmun, and Ortho-Clinical Diagnostics, using serially collected acute and convalescent sera from both hospitalized patients and outpatients with RT-PCR confirmed COVID-19. All four immunoassays performed similarly with respect to sensitivity in COVID-19 hospitalized patients, and except for the Epitope assay, also in individuals with milder forms of the infection. The Abbott and Ortho-Clinical immunoassays provided the highest overall specificity, of over 99%.

Severe COVID-19

Lung tissue samples from 38 patients who died from COVID-19 in two hospitals in northern Italy were analyzed. The predominant pattern was diffuse alveolar damage, as described in patients infected with SARS and MERS. Hyaline membrane formation and pneumocyte atypical hyperplasia were frequent. However, the presence of platelet-fibrin thrombi in small arterial ves-
sels was consistent with coagulopathy, which appears to be common in patients with COVID-19.

**Treatment**


How stable are antibodies that are found in convalescent plasma? Very stable. Pathogen inactivation (using psoralen and UV light) did not impair the stability and neutralising capacity of SARS-CoV-2-specific antibodies that was also preserved at 100% when the plasma was shock frozen at -30°C after pathogen-inactivation or stored as liquid plasma for up to 9 days.


A total of 807 COVID-19 patients hospitalized in US Veterans Administration medical centers in March and April were classified based on their exposure to HCQ or with azithromycin (HCQ+AZ) or no HCQ as treatments. Compared to the no-HCQ group, after propensity score adjustment for clinical characteristics, the risk of death from any cause was higher in the HCQ group (adjusted hazard ratio (1.83; 95% CI, 1.16 to 2.89) but not in the HCQ+AZ group (1.31, 95% CI, 0.80 to 2.15). Both the propensity score-adjusted risks of mechanical ventilation and death after mechanical ventilation were not significantly different in the two HCQ groups, compared to the no HCQ group.

**Epidemiology**


In late March 2020, a large outbreak on the aircraft carrier USS Theodore Roosevelt was characterized by widespread transmission with relatively mild symptoms and asymptomatic infection among mostly young, healthy adults.
with close, congregate exposures. One fifth of infected participants reported no symptoms. Preventive measures, such as using face-coverings and observing social distancing, reduced risk for infection: among 382 service members, those who reported taking preventive measures had a lower infection rate than did those who did not report taking these measures (e.g., wearing a face-covering, 56% versus 81%; avoiding common areas, 54% versus 68%; and observing social distancing, 55% versus 70%, respectively).

**Immunology**


Using single-cell RNA sequencing, the authors profiled peripheral blood mononuclear cells from seven patients hospitalized for COVID-19 and six healthy controls. The cell atlas of the peripheral immune response to severe COVID-19 included a heterogeneous interferon-stimulated gene signature, HLA class II down-regulation and a developing neutrophil population that appeared closely related to plasmablasts appearing in patients with acute respiratory failure requiring mechanical ventilation. Of note, peripheral monocytes and lymphocytes did not express substantial amounts of pro-inflammatory cytokines.

**Transmission**


Around 1 in 10 HCW becomes infected: This prospective international multicentre cohort study recruited 1,718 healthcare workers participating in 5,148 tracheal intubation episodes of patients with suspected or confirmed COVID-19 from 503 hospitals in 17 countries. The overall incidence of the primary endpoint (lab-confirmed COVID-19 diagnosis or new symptoms requiring self-isolation or hospitalisation) was 10.7% over a median follow-up of 32 days. The cumulative incidence within 7, 14 and 21 days of the first tracheal intubation episode was 3.6%, 6.1%, and 8.5%, respectively. The risk varied by country and was higher in females, but was not associated with other factors.
Diagnostics

According to this study analysing 77 patients, IL-6 levels at hospital admission seem to be a good "prognosticator" for the combined endpoint progression to severe disease and/or in-hospital mortality, and it seems to be the best prognosticator for negative outcome.

Clinical

Acute pulmonary embolism (APE) is not limited to severe or critical COVID-19. Five of 13 (38%) patients with APE in this small study had a moderate clinical COVID-19 type.


Myocardial injury is prevalent. Among 2,736 COVID-19 patients admitted to one of five Mount Sinai Health System hospitals in New York City who had troponin-I measured within 24 hours of admission, 985 (36%) patients had elevated troponin concentrations. After adjusting for disease severity and relevant clinical factors, even small amounts of myocardial injury (0.03-0.09 ng/mL) were significantly associated with death (adjusted HR: 1.75, 95% CI 1.37-2.24) while greater amounts (>0.09 ng/dL) were significantly associated with higher risk (adjusted HR 3.03, 95% CI 2.42-3.80).

Treatment
In macaques, remdesivir works, if given early. Twelve rhesus macaques were inoculated with SARS-CoV-2. Twelve hours later, six animals received 10mg/kg intravenous remdesivir and the other six an equal volume of vehicle solution (2ml/kg). In contrast to vehicle-treated animals, animals treated with remdesivir did not show signs of respiratory disease and had reduced pulmonary infiltrates and reduced virus titers in bronchoalveolar lavages. Virus shedding from the upper respiratory tract was not reduced. At necropsy, lung viral loads of remdesivir-treated animals were lower and there was a reduction in damage to the lungs. According to the authors, treatment should be initiated as early as possible to achieve the maximum treatment effect. But is this realistic in clinical practice? We would need a new way of application, instead of the current infusions (i.e., tablets, inhalators).


In this retrospective study, 12/14 patients treated with the JAK inhibitor ruxolitinib achieved significant reduction of the newly developed “COVID-19 Inflammation Score” by ≥ 25% on day 7 with sustained clinical improvement in 11/14 patients without short-term red-flag warnings of Rux-induced toxicity. Rux treatment for COVID-19 in patients with hyperinflammation was safe with some signals of efficacy to prevent or overcome multi-organ failure. A multi-center Phase II clinical trial has been initiated (NCT04338958).

Pregnancy


Outcome of 427 pregnant women admitted to hospital with confirmed SARS-CoV-2 infection between 1 March 2020 and 14 April 2020: Most (but not all) outcomes were good, and transmission of SARS-CoV-2 to infants was uncommon. Of note, there were 233 (56%) women from black or other ethnic minority groups, 281 (69%) were overweight or obese, 175 (41%) were aged 35 or over, and 145 (34%) had pre-existing comorbidities. 266 (62%) women gave birth or had a pregnancy loss; 196 (73%) gave birth at term. Forty one (10%) women admitted to hospital needed respiratory support, and five (1%) wom
en died. Twelve (5%) of 265 infants tested positive for SARS-CoV-2 RNA, six of them within the first 12 hours after birth.


Of 82 pregnant patients, 4 presented with severe COVID-19 symptoms, including 1 with concomitant preeclampsia; all 4 underwent cesarean delivery and required ICU admission. Among patients with mild symptoms at presentation, all patients with a vaginal birth had excellent outcomes. In contrast, 13.5% of women undergoing cesarean delivery had severe maternal outcomes and 21.6% had clinical deterioration. Women undergoing cesarean delivery may have been at higher risk of adverse outcomes, but after adjusting for confounding factors, cesarean birth remained independently associated with an increased risk of clinical deterioration. The physiological stress induced by surgery is known to increase postpartum maternal complications.

11 June

Epidemiology


Residents in long-term care facilities contribute 30–60% of all COVID-19 deaths in many European countries. This article provides an overview of the importance of surveillance and infection prevention and control measures, in order to identify clusters early, decrease the spread within and between facilities and reduce the size and severity of outbreaks.

Sad story on several outbreaks at Dutch mink farms. That mink are susceptible wasn’t a surprise, because they are closely related to ferrets. Once COVID-19 reaches a farm, the virus appears to spread like wildfire, even though the animals are housed in separate cages. The government decided to cull thousands of animals because the problem could become bigger in the months ahead.

Transmission

The gap between perceived risk and evidence: Upon enrollment, HCW in Hannover, Germany, were asked to estimate their personal likelihood of having had a SARS-CoV-2 infection (How high do you rate the probability of having been infected so far? 0–100%). Of 201 study participants, 19% rated their probability greater than 50%. In contrast to the high percentage of self-perceived positive SARS-CoV-2 infection status, only two tested frontline HCPs showed a clearly positive reaction to the ELISA.

Diagnostics

This study analysed antibody response in 192 RT-PCR confirmed COVID-19 patients, using two commercial microparticle chemiluminescence immunoassays (Wantai). Patients were stratified by disease severity. Severe cases had significantly higher IgM titers than mild cases after day 6 post-onset. Strikingly, 34% and 14% of mild patients were consistently serologically negative for IgM and total antibody, respectively.


Residual sera from 177 symptomatic COVID-19 patients, and 163 non-COVID-19 patients were tested for antibody with the Abbott SARS-CoV-2 IgG assay. Specificity of the assay was 100%. The clinical sensitivity varied depending on
time from onset of symptoms, increasing with longer periods since onset of clinical illness. The clinical sensitivity at ≤ 6 days was 8.6%, 7-13 days: 43.6%, 14-20 days: 84.0%, and ≥ 21 days: 84.4%.


In this meta-analysis of 17 studies, the pooled detection rate of fecal SARS-CoV-2 RNA was 43.7% and 33.7% by patient and number of specimens, respectively. Female individuals (59.6% vs. 53.5%), those who presented with gastrointestinal symptoms (77.1% vs. 57.7%), and patients with more severe disease (68.3% vs. 34.6%) tended to have a higher detection rate.

Clinical

Of 69 patients aged 80-98 years who presented at a large center in Rome, Italy, 36% had a critical COVID-19 disease. Multivariate Cox regression analysis showed that, among other factors, severe dementia was an independent risk factor for death (Hazard Ratio 3.9, 95% CI 1.2-12.2).

Treatment

More insights into the research scandal about two fake COVID-19 treatment papers (published in The Lancet and the NEJM) that were retracted last week. There were several red flags that the studies warranted intensive scrutiny – scrutiny that the two journals unforgivably failed to provide. This scandal tells us a lot about scientific publishing. Answers, comments, explanations by the two journals are still pending.

Galidesivir is a nucleoside RNA polymerase inhibitor with a broad-spectrum activity in vitro against more than 20 RNA viruses in nine different families, including coronaviruses and viral disease families that include filoviruses, togaviruses, bunyaviruses, arenaviruses, paramyxoviruses, and flaviviruses. A NIAID-funded, randomized, double-blind, placebo-controlled clinical trial to assess the safety, clinical impact and antiviral effects of galidesivir in patients with COVID-19 is underway. Of note, the drug also works against Zika: In the study presented here, galidesivir dosing in rhesus macaques was safe and offered postexposure protection against Zika virus infection.


Some thoughts about the possibility of using sofosbuvir against SARS-CoV-2, a nucleoside analog antiviral approved for hepatitis C virus infections. The structural superposition of the hepatitis C virus polymerase bound to sofosbuvir with the SARS-CoV polymerase shows that the residues that bind to the drug are present in the latter.

12 June

Epidemiology


Bye, bye, karaoke. The Japanese authors defined a cluster as > 5 cases with primary exposure reported at a common event or venue, excluding within-household transmissions. In total, 61 COVID-19 clusters were found in various communities in the country: 18 (30%) in healthcare facilities; 10 (16%) in care facilities of other types, such as nursing homes and day care centers; 10 (16%) in restaurants or bars; 8 (13%) in workplaces; 7 (11%) in music-related events, such as live music concerts, chorus group rehearsals, and karaoke parties; 5
(8%) in gymnasiums; 2 (3%) in ceremonial functions; and 1 (2%) in transportation-related incident in an airplane. Of note, 41% of probable primary case-patients were pre-symptomatic or asymptomatic at the time of transmission. 45% had cough. Many clusters were associated with heavy breathing in close proximity.


Geneva was a COVID-19 hot spot in Switzerland (5000 cases over < 2.5 months in half a million people). Authors performed 5 consecutive weekly sero-surveys among 2,766 randomly selected participants from a previous population-representative survey, and 1,339 household members aged 5 years and older. Each participant was tested for anti-SARS-CoV-2-IgG antibodies. Seroprevalence increased from about 5% to about 11%. Of note, young children (5–9 years) and older people (≥ 65 years) had significantly lower seroprevalence than the other age groups. Authors estimated that there were 11 infections for every COVID-19 confirmed case.

**Virology**


Outstanding essay about what little is currently known about the evolution of SARS-CoV-2. At present, there is a lack of compelling evidence that any existing variants impact the progression, severity, or transmission of COVID-19 in an adaptive manner. The authors discuss the potential evolutionary routes that SARS-CoV-2 might take and dispel some of the current misinformation that is circulating in the media.

This in-depth molecular analysis reconstructs key genomic features that differentiate SARS-CoV-2, SARS-CoV and MERS-CoV from less pathogenic coronaviruses. Exploring the regions identified within the nucleocapsid that predict the high case fatality rate of coronaviruses, the authors found that these deletions and insertions result in substantial enhancement of motifs that determine nuclear localization. The deletions, insertions, and substitutions in the N proteins of the high-CFR coronaviruses map to two monopartite nuclear localization signals. These findings imply an important role of the subcellular localization of the nucleocapsid protein in coronavirus pathogenicity.

**Immunology**


Most mice are not readily infected by SARS-CoV-2 because of species-specific differences in their ACE2 receptors. US researchers transduced replication-defective adenoviruses encoding human ACE2 via intranasal administration into BALB/c mice and established receptor expression in lung tissues. hACE2-transduced mice were productively infected with SARS-CoV-2, and this resulted in high viral titers in the lung and lung pathology. Neutralizing mAbs protect from SARS-CoV-2 induced lung infection, and inflammation. This accessible mouse model will expedite the testing and deployment of therapeutics and vaccines.


Another murine model, but from China. After exogenous delivery of human ACE2 with a replication-deficient adenovirus, Ad5-hACE2-sensitized mice developed pneumonia and high-titer virus replication in lungs. Type I interferon, T cells and, most importantly, signal transducer and activator of transcription 1 (STAT1) were critical for virus clearance and disease resolution. This murine model of broad and immediate utility will help to investigate COVID-19 pathogenesis, and to evaluate new therapies and vaccines.
Transmission

PPE works well: This study analyzed 420 healthcare professionals (116 doctors and 304 nurses) who were deployed to Wuhan by two affiliated hospitals of Sun Yatsen University and Nanfang Hospital of Southern Medical University for 6-8 weeks from 24 January to 7 April 2020. All were provided with appropriate personal protective equipment to deliver healthcare to patients admitted to hospital with COVID-19. Although all were involved in aerosol generating procedures (high risk of exposure), no-one contracted infection.


Again, it’s sunlight! This study examined the effect of simulated sunlight and relative humidity on the stability of SARS-CoV-2 in aerosols. A 90% loss of virus in simulated saliva was 19 minutes under simulated sunlight levels representative of late winter/early fall, 6 minutes of summer levels and 125 minutes without simulated sunlight across all relative humidity levels. Aerosol transmission of SARS-CoV-2 may be dependent on environmental conditions, particularly sunlight.

Clinical

Among 578 CSF samples analyzed at the virology laboratory of Lyon University Hospital during the COVID-19 epidemic (Feb 1 to May 11, 2020), all were negative, except for two samples that were slightly positive for SARS-CoV-2 corresponding to post-mortem samples from two adults with confirmed COVID-19. Importantly, the other 21 CSF samples from patients with confirmed COVID-19 were negative. These data suggest that, although SARS-CoV-2 is able to replicate in neuronal cells in vitro, SARS-CoV-2 testing in CSF is not relevant in the general population.
Comorbidities


The authors analyzed over 700 lung transcriptome samples of patients with comorbidities associated with severe COVID-19 and found that ACE2 was highly expressed in these patients, compared to control individuals. Findings suggest that the higher expression of ACE2 in the lungs is associated with higher chances of developing a severe form of COVID-19, by facilitating SARS-CoV-2 entry into lung cells during the infection.

13 June

Epidemiology


An in-depth analysis of the potential impact of the pandemic in low- and middle-income countries (LMIC). The analysis gives insight into how differences in demography, social structure and health care availability and quality combine and potentially influence the impact of measures that can help reduce the spread of the virus. However, the bottom line is: We don’t know yet. On one hand, we have an overall younger population and a shorter time for lockdown measures to be in place in LMIC. On the other hand, there is a higher burden of infectious diseases such as AIDS and TB already, and of poverty-related determinants of poorer health outcomes such as malnutrition. There is also a more persistent spread to older age categories (higher levels of household-based transmissions) and poorer quality health care and lack of health care capacity.

Despite a law approved by the Dutch parliament in 2012 that will ban mink farming as of 2024 for ethical reasons, there are still around 125 mink farms in the Netherlands, with an average of 5,000 female breeding animals. In 2019, 4 million minks were “produced”. This article describes several outbreaks on these farms. Detection of viral RNA in the airborne inhalable dust clearly suggests dust and/or droplets as means of transmission between the minks and occupational risk of exposure for the workers on the farms. On 3 June, the Dutch Ministry of Agriculture decided to cull all minks of SARS-CoV-2-infected farms, starting on 5 June. This may be the right time to speed up the final ban.

**Immunology**


Key message: Interferon may be helpful during early infection and harmful at later stages. IFN-λ mainly signals in epithelia, inducing localized antiviral immunity, and has a key role in the reduction of epithelial proliferation and differentiation during lung repair. In animal and cell experiments, the authors show that IFN-induced p53 directly reduces epithelial proliferation and differentiation, increasing disease severity and susceptibility to bacterial superinfections. Excessive or prolonged IFN production may aggravate viral infection by impairing lung epithelial regeneration.


Same direction as above: Detrimental activities of IFN-λ only occur upon chronic exposure and in the presence of tissue damage. In mice, IFN-λ produced by lung dendritic cells in response to a synthetic viral RNA-induced barrier damage, causing susceptibility to lethal bacterial superinfections.
Diagnostics

This review of the diagnostic accuracy of SARS-CoV-2 serological tests includes 9 studies, using different test kits. Random-effects models yielded a summary sensitivity of 82% for IgM, and 85% for IgG and total antibodies. For specificity, the pooled estimates were 98% for IgM and 99% for IgG and total antibodies. In populations with ≤ 5% of seroconverted individuals, the positive predictive value would be ≤ 88%. According to the authors, serological tests should be used for prevalence surveys only in hard-hit areas.


Among 215 adult (≥ 18 years) passengers from Hong Kong who had been on board the Diamond Princess cruise ship and who had been found to be PCR-negative before disembarking, 9 became positive during quarantine. Those with evidence of pneumonia on imaging tended to have an increased antibody response. However, positive IgG or IgM confirmed infection of COVID-19 in both symptomatic and asymptomatic patients.

Clinical

More on asymptomatic infection: The authors followed 90 persons from the cruise ship Diamond Princess who were asymptomatic at the time of the positive PCR test and remained so until the resolution of infection (as determined by two consecutive negative PCR tests). 27% had coexisting medical conditions. The median time between the first positive PCR test result (either on the ship or at the hospital) and the first of the two serial negative PCR results was 9 days (range, 3 to 21), and the cumulative percentages of persons with resolution of infection 8 and 15 days after the first positive PCR were 48% and 90%, respectively.

Among 104 people from the Diamond Princess cruise ship who were admitted to a Tokyo hospital, 33 (32%) participants were confirmed as being asymptomatic, 43 (41%) as having mild COVID-19, and 28 (27%) as having severe COVID-19. Serum lactate hydrogenase concentrations were significantly higher in the ten participants who were asymptomatic on admission but developed symptomatic COVID-19 compared with the 33 participants who remained asymptomatic throughout the observation period.


Histopathological examination of brain specimens obtained from 18 patients who died 0 to 32 days after the onset of symptoms showed only hypoxic changes and did not show encephalitis or other specific brain changes referable to the virus. The virus was detected at low levels in 6 brain sections obtained from 5 patients; it remains to be seen whether this was due to in situ virions or viral RNA from blood.

Wright Hr KP, Linton SK, Withrow D. Sleep in University Students Prior to and During COVID-19 Stay-at-Home Orders. Current Biology, June 10, 2020 Full-text: https://doi.org/10.1016/j.cub.2020.06.022

Good to know: during lockdown, they sleep better. This ground-breaking study investigated sleep behaviors prior to and during Stay-at-Home orders in 139 university students. During Stay-at-Home, nightly time in bed devoted to sleep increased by 30 min during weekdays and by 24 mins on weekends and regularity of sleep timing improved by 12 min. Sleep timing became later by 50 min during weekdays and 25 min on weekends, and thus the difference between weekend and weekday sleep timing decreased—hence reducing the amount of social jetlag. A subsequent study on changes in breakfast behaviors is eagerly awaited (proposed hypothesis: less coffee, more jam).
14 June

Health Care Workers


This article summarises the available management strategies to increase resilience in healthcare workers during the COVID-19 pandemic and beyond. According to the authors, some of the strategies require substantial lead time and will potentially challenge negotiations with organisational stakeholders. This might require increasing the number of or reallocation of support staff; reallocating how revenue is distributed throughout the organisation; ensuring physicians feel valued and heard; and changing reimbursement and compensation models. However, in the current crisis, some strategies can be implemented quickly and easily such as: mindfulness interventions; Battle Buddies (a rapidly-deployable psychological resilience intervention based on the “Battle Buddy” system of the US army); and staff feedback sessions.


Touching article about an emergency room physician who took her own life, after spending weeks caring for COVID-19 patients in New York City. Considering the profound effects of the crisis on clinicians' mental health, leaders must protect their clinicians by carefully considering appropriate time off in scheduling and ensuring that colleagues, superiors, and trainees use this time.

Behaviour


20% - young male trolls. This cross-sectional study investigated how and from when Japanese citizens changed their precautionary behavior under circumstances in which the government simply requested their cooperation. For the 11,332 participants, the most important event influencing precautionary ac-
tions (frequent hand washing, social distancing etc) was the infection aboard the Diamond Princess. However, about 20% of the participants were reluctant to implement proper prevention measures. Typical characteristics were male, younger (under 30 years old), unmarried, from lower-income households, a drinking or smoking habit, and a higher extraversion score.


Probably the most burning issue in the current health crisis: Who hoards toilet paper? This article wins our new award for the best introduction (“empirical studies on the psychological underpinnings of toilet paper stockpiling are still scarce”). In an online survey across 22 countries among the 996 (!) respondents, those who felt more threatened and who had a predisposition towards emotionality and high conscientiousness, stockpiled more toilet paper. But of course, many open questions remain, and according to the authors, “experimental studies would be required in order to explicitly test the directionality implied in (their) investigation of indirect effects”.

Psychological impact


Apart from its physical burden on patients and health-care services, COVID-19 has enormous psychosocial impact. This comprehensive article reviews “coronaphobia”, a plethora of psychiatric manifestations across the different strata of society. But why is this in a diabetes journal?

Lockdown effects


This work used Google mobility data to map spatial and temporal changes in mobility across the UK in six areas during lockdown: residential areas; supermarkets, grocery shops, and pharmacies; workplaces; retail and recreational areas; transit stations (subway, bus, and train stations); and parks. The authors saw a 63% overall reduction in movement, with retail and recreation-
al areas (decreased by 85%; not surprising given restrictions imposed on this sector) and transit stations (decreased by 75%) showing the largest reductions. Good news: “park use initially decreased but has now increased to levels seen before the lockdown restrictions, perhaps because of good weather or people adapting their exercise requirements”.


Harsh criticism on a previous article, summarizing that, during the COVID-19 pandemic, domestic abuse experienced by men is of ‘lower severity’. The authors want to steer the domestic abuse conversation away from a gender divide and open up the discussion to promote zero tolerance of domestic abuse towards both men and women. They propose that “domestic abuse towards men, although less frequent, is of equal severity to the domestic abuse suffered by women”. Best conclusion of the day: “Abuse is abuse.”


Yesterday we learned that US students slept better during lockdown. In Europe, however, things went differently. According to this study on 435 (!) people in 3 countries, the lockdown led to an improved individual sleep-wake timing and overall, yes, more sleep. At the same time, however, many people suffered a decrease in sleep quality in this exceptional situation. Well. Data from other continents pending.

Other issues


Prize for the most megalomaniac paper title of the day. According to the authors of this Lancet letter, the origins and solutions of all three threats “are remarkably similar”: “First, each threat must be recognised. Second, political leaders must respect truth and defer to expertise. Third, the threats are global and require global cooperation. Fourth, we all have to focus on our collective survival, and that includes care for the least privileged”. Well then, if that’s the case, let’s get to work!
McManus S, D’Ardenne J, Wessely S. *Covid Conspiracies: Misleading Evidence Can Be More Damaging Than No Evidence at All*. Psychol Med, June 2020. Full-text: [https://doi.org/10.1017/S0033291720002184](https://doi.org/10.1017/S0033291720002184)

Well-written commentary on the myriad of articles publishing on the incredible number of people believing in conspiracy theories. Many of these studies suffer from serious methodological problems and severely overestimate the prevalence of conspiracy thinking, trying to attract media attention. Headlines like “One fifth of English people blamed Jews or Muslims for COVID-19” are nonsense and dangerous. See paper title, maybe “can be” should be “are”.

15 June

Epidemiology


Important comment on mass religious gatherings. The authors recommend restrictions on the entry of Hajj pilgrims who are from epicentres and hotspots, from countries with suboptimal disease surveillance systems or with inadequate quarantine and diagnostic infrastructure for returning pilgrims who are over 50 years old or suffer from chronic disease, ie patients with diabetes and cardiovascular complications. Saudi Arabia needs to deploy a pre-emptive approach. We’ll see whether this is feasible.

Habib H. *Has Sweden’s controversial covid-19 strategy been successful?* BMJ 2020; 369. Full-text: [https://doi.org/10.1136/bmj.m2376](https://doi.org/10.1136/bmj.m2376)

Probably not. Some thoughts on Sweden’s controversial decision not to lock down the country. They are still far away from herd immunity (an ongoing nationwide study on 20 May found that just 7.3% of Stockholm residents had developed antibodies) and the death toll is immense.

No. Epidemiological data suggest that no country has yet seen infection rates sufficient to prevent a second wave of transmission, should controls or behavioural precautions be relaxed without compensatory measures in place.

Transmission


This commentary describes the spontaneous formation of an international team of 115 researchers who summarized the literature on safe methods for decontaminating N95 filtering facepiece respirators in response to the supply crisis. The summary reports and fact sheets on the www.n95decon.org website are frequently being updated with new research findings and have had more than 200,000 visits.

Diagnostics


Best conclusion of the day: “Buccal swabs are not good” as COVID-19 screening specimens in children. In 11 children positive via nasopharyngeal swabs, 2 remained negative using buccal swabs. There was a general trend for buccal specimens to contain lower SARS-CoV-2 viral loads (higher Ct values) compared with nasopharyngeal specimens. The sensitivity of buccal swabs compared with nasopharyngeal swabs ranged from 25% to 71.4% on different days of collection during the first week of illness/diagnosis. Buccal SARS-CoV-2 was undetectable by day 8 of admission/diagnosis, although the nasopharyngeal SARS-CoV-2 was still detectable.

The authors describe a “fast and robust assay for detection of SARS-CoV-2 in 30–45 minutes”. This simple assay (Reverse Transcription Loop-Mediated Isothermal Amplification, RT-LAMP) could be used outside of a central laboratory on various types of biological samples. This assay can be completed by individuals without specialty training or equipment and may provide a new diagnostic strategy for combatting the spread of SARS-CoV-2 at the point-of-risk. However, numbers of tested samples were low. Sensitivity and specificity have to be tested in larger populations.


The authors examined the performance of N, S1 and RBD proteins from SARS-CoV-2 and SARS-CoV in four different test platforms. Results show that the RBD protein provides the best specificity, whereas the N protein of either virus is not suitable to detect virus-specific antibodies due to a very high level of cross-reactivity.

Severe COVID-19


Of 90 patients with severe COVID-19, 17 deteriorated within 2 weeks and no longer responded to prone positioning. All (!) of these patients had major pulmonary embolism established by lung CT or cardiac ultrasound. A plasma D-dimer concentration greater than 4 μg/mL, combined with increasing inflammatory markers such as interleukin-6 (the authors recommend to measure it regularly), and loss of response to prone positioning might be useful parameters to identify patients at risk of pulmonary embolism.

One of the best reviews on this topic to date. AKI is prevalent in critically ill COVID-19 patients. Several mechanisms are possibly involved, including direct invasion of SARS-CoV-2 into the renal parenchyma, an imbalanced RAAS and microthrombosis, but also kidney injury secondary to hemodynamic instability, inflammatory cytokines and the consequences of therapeutics that are used in ICU (nephrotoxic drugs, mechanical ventilation).

**Comorbidities**


There is no good time for surgery: In this cohort study of 41 surgical patients with COVID-19 and 82 tightly matched control patients, significant differences were documented regarding rates of early mortality and complications (odds ratios 9.5 and 5.0, respectively), mainly pneumonia and thrombotic complications, were significantly associated with COVID-19, and different models identified COVID-19 as the first variable associated with surgical complications. These data suggest that, whenever possible, surgery should be postponed in patients with COVID-19.

**16 June**

**Epidemiology**

Stoke EK, Zambrano LD, Anderson KN. **Coronavirus Disease 2019 Case Surveillance — United States, January 22–May 30, 2020.** MMWR June 15, 2020. Full-text: [https://www.cdc.gov/mmwr/volumes/69/wr/mm6924e2.htm](https://www.cdc.gov/mmwr/volumes/69/wr/mm6924e2.htm)

A detailed picture of the epidemic in the US. This report describes demographic characteristics, underlying health conditions, symptoms, and outcomes among 1,320,488 laboratory-confirmed COVID-19 cases individually
reported to CDC during January 22–May 30, 2020. Some key messages: Overall, 14% of patients were hospitalized, 2% were admitted to an intensive care unit (ICU), and 5% died. Among cases with known race and ethnicity, 33% of persons were Hispanic, 22% were black, and 1.3% were non-Hispanic American Indian or Alaska Native. These findings suggest that persons in these groups, who account for 18%, 13%, and 0.7% of the U.S. population, respectively, are disproportionately affected by the COVID-19 pandemic.

Thornton J. Covid-19: Africa’s case numbers are rising rapidly, WHO warns. BMJ 2020; 369. Full-text: https://doi.org/10.1136/bmj.m2394
A brief but concerning review on the situation in Africa. Since the virus was first detected in Egypt on 14 February, it took 98 days to reach 100,000 cases and only 18 days to move to 200,000 cases on the continent. More than 5,600 people have died from the illness, 70% of whom were in just five countries: Algeria, Egypt, Nigeria, South Africa, and Sudan.

Transmission
This study from Norway shows that detection of seroconversion might provide a more accurate picture of attack rates in households than intermittent RT-PCR testing. Of 158 cases, 125 (79%) tested positive for antibodies and 12 (8%) were defined as borderline. In 77 household members, 24 (31%) tested positive and two (3%) were borderline.

Comorbidities
This perspective aims to provide a guide based on the Italian and French experience to better face the difficulties encountered by endoscopists during this pandemic. Some helpful recommendations regarding the use of personal protective equipment (both for patients and HCW) are proposed and different
scenarios in endoscopic IBD management are evaluated to suggest when endoscopy could be rescheduled and replaced by alternative biomarkers.

Treatment


Neutralizing monoclonal antibodies to SARS-CoV-2 have the potential for both therapeutic and prophylactic applications (probably more than all antiviral drugs that are currently being tested). This viewpoint summarizes current knowledge. Several mAbs are poised to enter clinical trials during the summer of 2020. Trials will include treatment of patients with SARS-CoV-2 infection, with varying degrees of illness, to block disease progression. Given the long half-life of most mABs (approximately 3 weeks for IgG1), a single infusion should be sufficient.


Elegant cell experiments, showing that a combination of antibodies may provide a powerful way to minimize mutational escape by SARS-CoV-2; in particular, two antibodies were chosen so as to bind to distinct and non-overlapping regions of the viral target (in this case, the RBD of the spike protein), in order to thus require the unlikely occurrence of simultaneous mutations at two distinct genetic sites for viral escape.


Using a high-throughput rapid system for antibody discovery, the authors isolated more than 1000 mAbs from 3 convalescent donors by memory B cell selection using SARS-CoV-2 S or RBD (receptor-binding domain) recombinant proteins. Of note, only a small fraction of these Abs was neutralizing, highlighting the value of deep mining of responses to access the most potent Abs. RBD-nAbs that directly compete with ACE2 are clearly the most preferred for prophylactic and therapeutic applications, and as reagents to define nAb
epitopes for vaccine. With these nABs, Syrian hamsters were protected from weight loss. However, animals that received higher doses also showed body weight loss, possibly indicating antibody-mediated enhanced disease.


Antibodies from convalescent COVID-19 patients had low levels of somatic hypermutation and showed a strong enrichment in VH1-69, VH3-30-3 and VH1-24 gene usage. A subset of the antibodies were able to potently inhibit authentic SARS-CoV-2 infection as low as 0.007 μg/mL. Competition and electron microscopy studies illustrate that the SARS-CoV-2 spike protein contains multiple distinct antigenic sites. The authors isolated 19 neutralizing antibodies that target a diverse range of antigenic sites on the S protein, of which two showed picomolar (very strong!) neutralizing activities.


The authors report on unpublished data (their own), indicating that quantification of specific antibody to the receptor-binding domain (RBD) will indicate levels of neutralising antibodies. This may help to find the best plasma donors. So why don’t they publish their data?

Pediatrics


Of 52 hospitalized children, 24 (46%) had elevated serum creatinine, and 15 (29%) met the diagnostic criteria for acute kidney injury (AKI). Most AKI cases occurred in those admitted to the pediatric ICU (93%), and in those with pediatric inflammatory multisystem syndrome temporarily associated with SARS-CoV-2 (PIMS-TS; 73%). This underlines the importance of renal function surveillance in all hospitalised pediatric cases of COVID-19, while simultaneously avoiding factors that exacerbate kidney injury, such as hypovolemia and the use of nephrotoxic drugs. According to the authors, standard care should in-
volve screening for nephritis and follow-up for long-term sequelae of acute kidney injury, such as hypertension and proteinuria.

17 June

Epidemiology


Do children have a lower susceptibility to infection? Probably yes. The authors used epidemic data from Canada, China, Italy, Japan, Singapore, and South Korea to determine the level of susceptibility and clinical symptoms in various age groups. Susceptibility to infection in individuals under 20 years of age was approximately half that of adults aged over 20 years, and clinical symptoms manifest in 21% (95% confidence interval: 12–31%) of infections in 10- to-19-year-olds, rising to 69% (57–82%) of infections in people aged over 70 years. These estimates have implications for the expected global burden of COVID-19, as a result of demographic differences across settings.


Another mathematical modelling study, using pandemic data from 40,162 UK participants and simulating the effect of a range of different testing, isolation, tracing, and physical distancing scenarios. If combined with moderate physical distancing measures, self-isolation and contact tracing would be more likely to achieve control of SARS-CoV-2 transmission.

Prevention

Cai C, Floyd EL. Effects of Sterilization With Hydrogen Peroxide and Chlorine Dioxide on the Filtration Efficiency of N95, KN95, and Surgical Face Masks. JAMA Netw Open. 2020 Jun 1;3(6):e2012099. [IMPORTANT]
This quality improvement study found that the sterilization process had different effects on the filtration efficiencies of different masks. Sterilization with H$_2$O$_2$ had fewer negative effects than ClO$_2$.

**Diagnostics**


Among persons with specimens collected early in the course of illness, SARS-CoV-2 RNA diagnostic results were highly concordant between OP and NP swabs (95.2%). However, NP swab Ct values were lower (indicating more virus) in 66.7% of concordant-positive pairs, suggesting NP swabs may more accurately detect SARS-CoV-2.

**Transmission**


In this large, hospital-wide screening study for SARS-CoV-2 antibodies among hospital staff in a Belgian tertiary care center, neither direct involvement in clinical care nor working in a COVID-19 unit increased the odds of being sero-positive, while having a suspected COVID-19 household contact did. Overall, 197 staff (6.4%, 95% CI, 5.5%-7.3%) had IgG antibodies for SARS-CoV-2.

**Clinical**


Case series of 463 consecutive patients with COVID-19 (72.1% African American), evaluated at Henry Ford Health System in metropolitan Detroit, Michigan. Most patients (94%) had at least 1 comorbidity, including hypertension (64%), chronic kidney disease (39.3%), and diabetes (38%). 355 patients (77%)
were hospitalized; 141 (40%) required intensive care unit management and 114 (81%) of those patients required invasive mechanical ventilation. Male sex (OR, 1.8) and age older than 60 years (OR 5.3) were significantly associated with mortality, whereas African American race was not.


Of 126 residents tested at a skilled nursing facility in Illinois, 33 had confirmed SARS-CoV-2. Nineteen (58%) had symptoms at the time of testing, 1 (3%) developed symptoms over follow-up, and 13 (39%) remained asymptomatic. Thirty-five residents who tested negative on March 15 developed symptoms over follow-up; of these, 3 were re-tested and 2 were positive. The 30-day probability of death among cases was 29%.

Comorbidities


This study investigated the association between the outbreak of COVID-19 and PCI rates for ACS (Acute Coronary Syndromes) in the Campania region, which, with 5.8 million residents, represents ≈10% of the Italian population. The outbreak was associated with a decline in the number of PCIs for ACS by 32%. In the last 2 weeks of the observational period, PCIs for ACS were reduced by 50%. In comparison with PCI volumes for the same time in 2019, the decline in PCI rates was of a similar magnitude (between 36% and 38%).


Of 200 patients with COVID-19 and thoracic cancers (76% NSCLC) from eight countries were identified and included in the TERAVolt registry, 152 (76%) were hospitalised and 66 (33%) died. Of note, in a multivariable analysis, only
smoking history (OR 3.18, 95% CI 1.11-9.06) was associated with increased risk of death.

Treatment

Several inflammatory cytokines that correlate with adverse clinical outcomes in COVID-19 employ a distinct intracellular signalling pathway mediated by Janus kinases (JAKs). JAK-STAT signalling may be an excellent therapeutic target. This article reviews the possibilities and challenges of targeting this pathway in COVID-19.

18 June

Epidemiology

Madrid has been the most deeply hit region by COVID-19 in Spain, with 65,000 confirmed cases and 9,000 deaths up to May 10th, eight weeks after the country’s lockdown had been implemented on March 14th. The authors found that roughly 10.9% of adults in Madrid (excluding those living in communities of 10 to 25 persons) had SARS-CoV-2 antibodies at the time of lockdown release on May 10th.

Transmission
Jing JQ, Liu MJ, Yuan J. **Household secondary attack rate of COVID-19 and associated determinants in Guangzhou, China: a retrospective cohort study**. Lancet Infect Dis. 2020; (published online June 17.) [https://doi.org/10.1016/S1473-3099(20)30471-0](https://doi.org/10.1016/S1473-3099(20)30471-0)

Are children less susceptible? Using a comprehensive contact tracing dataset, the authors estimated secondary attack rate among household contacts to be 12.4% (95% CI 9.8–15.4) when household contacts were defined on the basis of close relatives, and 17.1% (13.3–21.8) when household contacts were defined on the basis of residential address. Compared with the oldest age group (≥ 60
years), the risk of household infection was lower in the youngest age group (<
20 years; odds ratio 0.23) and among adults aged 20–59 years (OR 0.64).

Med: https://pubmed.gov/32546439. Full-text: https://doi.org/10.1016/j.jiph.2020.05.025
During follow-up examination after discharge, seven out of ten children con-
tained SARS-CoV-2 virus RNA in their fecal specimens, despite all patients
showing negative results in respiratory tract specimens. One out of those sev-
en patients relapsed. The median time from onset to being negative in respira-
trary tract and fecal specimens was 9 days and 34.43 days, respectively.

Dhand R, Li J. Coughs and Sneezes: Their Role in Transmission of Respira-
Everything you always wanted to know about... coughs and sneezes. A total of
79 references are used to explain how larger droplets produced by coughing
and sneezing settle quickly, and the force with which they are expelled de-
termines how far they are dispersed. Nice visuals in the supplement at the end
of the paper.

Prevention

Lyu W, Wehby GL. Community Use Of Face Masks And COVID-19: Evidence
From A Natural Experiment Of State Mandates In The US. Health Aff
https://doi.org/10.1377/hlthaff.2020.00818
Masks, masks, masks. This study provides evidence from a natural experi-
ment on the effects of state government mandates in the US for face mask use
in public issued by 15 states plus DC between April 8 and May 15. Mandating
face mask use in public was associated with a decline in the daily COVID-19
growth rate by 0.9, 1.1, 1.4, 1.7, and 2.0 percentage-points in 1–5, 6–10, 11–15,
16–20, and 21+ days after implementation, respectively. Estimates suggest as
many as 230,000–450,000 COVID-19 cases possibly averted by May 22, 2020
due to these mandates.
Clinical


The authors identified a 3p21.31 gene cluster as a genetic susceptibility locus in patients with COVID-19 with respiratory failure and confirmed a potential involvement of the ABO blood-group system. A blood-group-specific analysis showed a higher risk in blood group A than in other blood groups (odds ratio, 1.45; 95% CI, 1.20 to 1.75) and a protective effect in blood group O as compared with other blood groups (odds ratio, 0.65; 95% CI, 0.53 to 0.79). However, please don’t measure the blood groups of your patients now. The risk elevations are low (male gender possibly, see below). These results are much more relevant with regard to the underlying pathophysiology (the locus also contains genes encoding chemokine receptors).


No good prospects. Analyzing data from 188 nations, the team estimates that 1.7 billion people worldwide have an elevated risk of ‘severe’ illness. The researchers also estimate that 349 million (186–787) people (4% of the global population) are at high risk of severe COVID-19 and would require hospital admission if infected (ranging from < 1% of those younger than 20 years to approximately 20% of those aged 70 years or older). In total, 6% of males were found to be at high risk compared with 3% of females.

Severe COVID-19


The next study on proning. In this small single-center cohort study, use of the prone position for 25 awake, spontaneously breathing patients with COVID-19 was associated with improved oxygenation. In addition, patients with an Spo2 of 95% or greater after 1 hour of the prone position was associated with a lower rate of intubation. Unfortunately, there was no control group and the
sample size was very small. Ongoing clinical trials of prone positioning in non-mechanically ventilated patients (NCT04383613, NCT04359797) will hopefully help clarify the role of this simple, low-cost approach for patients with acute hypoxemic respiratory failure.

**Treatment**


Mavrilimumab, an anti-granulocyte macrophage colony stimulating factor receptor-α monoclonal antibody, was added as a single intravenous dose to standard management in 13 patients with severe COVID-19 pneumonia, hypoxia, and systemic hyperinflammation (26 patients with “contemporaneous patients with similar baseline characteristics“ were used a control group. During the 28-day follow-up, no patients in the mavrilimumab group died, and seven (27%) patients in the control group died (p=0.086). At day 28, all patients in the mavrilimumab group and 17 (65%) patients in the control group showed clinical improvement (p=0.030), with earlier improvement in the mavrilimumab than in the control group. Comment: Interesting, but larger trials are needed. Small sample size, an absence of randomisation, and a short follow-up period may reduce the full generalisability.


Granulocyte macrophage colony-stimulating factor (GM-CSF) is an immunoregulatory cytokine with a pivotal role in initiation and perpetuation of inflammatory diseases. In this nice review, the authors consider the scientific rationale and potential risks for therapeutic targeting of GM-CSF in COVID-19-associated hyperinflammation.
19 June

Epidemiology

This cross-sectional study of 396 pregnant New York City residents delivering at New York hospitals showed that the likelihood of SARS-CoV-2 varied substantially across measures of built environment and neighborhood socioeconomic status. Large household membership, household crowding, and low socioeconomic status were associated with a 2-3 fold higher risk of infection.


Brief overview. Iran was one of the first countries to experience a COVID-19 epidemic, and began relaxing restrictions in April. Cases dropped, with fewer than 1000 new cases per day by the start of May, but daily cases have since increased, with the Iranian Health Ministry reporting 2,410 new cases on June 13.


Numerous challenges exist in terms of sample collection, what the presence of antibodies actually means, and appropriate analysis and interpretation to account for test accuracy and sampling biases. The authors review strengths and limitations of different assay types and study designs, and discuss methods for rapid sharing and analysis of serologic data.

Transmission

The virus is so fast: This database with detailed demographic characteristics, travel history, social relationships, and epidemiological timelines for 1,407
transmission pairs that formed 643 transmission clusters in mainland China used statistical model fittings to identify the super-spreaders and estimate serial interval distributions. There were 34 primary cases identified as super-spreaders, with 5 super-spreading events occurring within households. Serial intervals were short and were estimated as 5.0 (95% CI: 4.4-5.5) and 5.2 (95% CI: 4.9-5.7) days for household transmissions and 5.2 (95% CI: 4.6-5.8) and 5.3 (95% CrI: 4.9-5.7) days for non-household transmissions, respectively.


The authors have established two high-throughput employee testing centers in Seattle, Washington with drive-through and walk-through options for symptomatic employees at the University of Washington Medicine system and its affiliated organizations. Between March 12 and April 23, a total of 3,477 symptomatic employees were tested; 185 (5.3%) employees tested positive for COVID-19. The prevalence of SARS-CoV-2 was similar when comparing frontline HCWs (5.2%) to non-frontline staff (5.5%).

Diagnostics


“COVID-19 passes” will last a few weeks, at least in patients with mild symptoms: Compared to symptomatic patients, 37 asymptomatic patients had a significantly longer duration of viral shedding. The virus-specific IgG levels were significantly lower in the acute phase. IgG levels and neutralizing antibodies started to decrease within 2–3 months after infection. Of note, 40% became seronegative (13% of the symptomatic group) for IgG in the early convalescent phase.

Clinical

In 535 patients, multivariable analysis showed that a doubling of cortisol concentration was associated with a significant 42% increase in the hazard of mortality, after adjustment for age, the presence of comorbidities, and laboratory tests. Cortisol seemed to be a better independent predictor than other laboratory markers associated with COVID-19, such as CRP, D-dimer, and neutrophil to leukocyte ratio.


Among 40 young patients with chilblain lesions and with suspected SARS-CoV-2 infection, COVID-19 serology was positive in 12 (30%) patients. All had negative PCR results at the time of presentation, suggesting that in young patients SARS-CoV-2 is completely suppressed before a humoral immune response is induced.

Comorbidities


Results of this French cohort of 83 patients suggest that COVID-19, even if potentially severe, does not seem to carry an increased risk of morbidity or mortality in patients with sickle cell disease, as most patients worldwide have the SS/Sβ0 genotype and are younger than 45 years.


This article summarise key changes related to service allocation, clinical and supportive care, clinical trial participation, and ethical considerations regarding the use of lifesaving measures for these patients. It also offers a consensus on clinical practice guidance for optimal care in both the university and community health-care settings.
Treatment

HIV protease inhibitors (PIs) such as darunavir or lopinavir probably don’t work. These authors have developed better ones, based on analyzing the structure of the Mpro active site. Both PIs strongly inhibited the activity of Mpro and showed good antiviral activity in cell culture. Compound 11a had good pharmacokinetic properties and low toxicity when tested in mice and beagle dogs, suggesting that it is a promising drug candidate.

20 June
Epidemiology

Bangladesh hosts almost 1 million Rohingya refugees from Myanmar, with 600,000 concentrated in the Kutupalong-Balukhali Expansion Site. Using different transmission models and considering the age distribution in the camp, the authors expect 2,040-2,880 deaths (assuming that age was the primary determinant of infection severity and hospitalization). They also expect that comorbidities, limited hospitalization, and intensive care capacity may increase this risk.

Vaccine

Recent interest in messenger RNA (mRNA) vaccines has been fueled by methods that increase mRNA stability and protein production and improve delivery. The mRNA vaccines do not need to enter the nucleus to express the antigen. Avoidance of the risk of integration into the host genome is thus considered a comparative advantage. The authors describe new techniques in this field. The most promising seems to be a strategy that is based on two RNA
vectors — one retaining the replicase-encoding gene and the other encoding the antigen.


The monoclonal antibody CR3022 tightly binds the receptor binding domain (RBD) and neutralizes SARS-CoV-2. The highly conserved, structure-stabilising, CR3022 epitope is inaccessible in the prefusion Spike, suggesting that CR3022 binding facilitates conversion to the fusion-incompetent post-fusion state. The mechanism of neutralisation is new and was not seen before for coronaviruses, suggesting that the CR3022 epitope should be a major target for therapeutic antibodies.

**Clinical**


Among 410 patients with COVID-19 who underwent CT at emergency department admission in three hospitals in Lombardy, Italy, 76 (19%) patients had mediastinal lymphadenopathies (ie, lymph nodes with a short-axis diameter > 1 cm). Data suggest that lymphadenopathy may be considered a predictor of a worse outcome. The pathophysiological meaning of this finding remains to be investigated.

**Comorbidities**


ACE inhibitors are not harmful, even in Denmark (one of the countries with the best epidemiological data). In a retrospective cohort study of 4,480 (!) patients diagnosed as having COVID-19, prior ACEI/ARB use, compared with no use, was not significantly associated with mortality (adjusted hazard ratio, 0.83). In a nested case-control study of a cohort of 494,170 patients with hypertension, use of ACEI/ARB, compared with use of other antihypertensive medications, was not significantly associated with COVID-19 diagnosis (adjusted hazard ratio, 1.05).

In this population-based cross-sectional study of 5,325 patients with out-of-hospital cardiac arrests in New York City, the number undergoing resuscitation was 3-fold higher during the COVID-19 period compared with the similar period in 2019. The authors report 2,653 excess out-of-hospital cardiac arrests (90% of these excess cases resulted in out-of-hospital deaths).


Question of the day. Answer: Some did so, yes. Out of the 2,102 participants of this survey, 34.7% reported drinking “more or much more” alcohol since the beginning of the lockdown. Binary logistic regression analyses showed that especially low educated subjects and subjects with higher levels of perceived stress due to the lockdown were at risk of consuming more alcohol during the lockdown.


This prospective cohort study enrolled 56 patients with COVID-19-related pneumonia receiving supplemental oxygen or non-invasive continuous positive airway pressure. Prone positioning was feasible in most patients and effective in rapidly ameliorating blood oxygenation. The effect was maintained after resupination in half of the patients.
Treatment


This may help to explain why convalescent plasma does not work in all patients. In plasma from 149 patients collected an average of 39 days after the onset of symptoms, neutralizing titres were extremely variable. Most plasmas did not contain high levels of neutralizing activity. Nevertheless, rare but recurring RBD-specific antibodies with potent antiviral activity were found in all individuals tested, suggesting that a vaccine designed to elicit such antibodies could be broadly effective.


IFN may work, when given early. Several clinical trials into the administration of IFN to COVID-19 patients are currently ongoing. These in vitro observations shed light for the first time on antiviral activity of IFN-β1a against SARS-CoV-2 when administered after the infection of cells, highlighting its possible efficacy in an early therapeutic setting.

21 June

Epidemiology


Brief overview on the burden and outcomes associated with COVID-19 in Africa, showing substantial variations across countries. Some explanations why many multiple mathematical models have failed to project the epidemic on the continent.

It’s not completely gone. After the outbreak in Wuhan, China, the authors assessed 29,299 workers screened with PCR during March 13–April 25, 2020. They noted 18 (0.06%) cases of asymptomatic infection; 13 turned negative within 8.0 days, and 41 close contacts tested negative. Of 22,633 persons tested for SARS-CoV-2 antibodies, 617 (2.7%) cases had positive IgG but negative IgM; 196 (0.87%) cases had positive IgG and IgM; and 40 (0.18%) cases had negative IgG but positive IgM.


Most people agree: during the week of May 5–12, 2020, a survey among 2,402 adults in New York City and Los Angeles and broadly across the United States found widespread support of stay-at-home orders and nonessential business closures and high degree of adherence to COVID-19 mitigation guidelines. 74-82% reported they would not feel safe if these restrictions were lifted nationwide at the time the survey was conducted. In addition, among those who reported that they would not feel safe, some indicated that they would nonetheless want community mitigation strategies lifted and would accept associated risks (13-17%, respectively).

**Virology**


SARS-CoV-2 genomic and subgenomic RNA (sgRNA) transcripts hijack the host cell’s machinery. But where is the viral RNA localized in the cell? Computational modeling of SARS-CoV-2 viral RNA subcellular residency across eight subcellular neighborhoods, predicted the SARS-CoV-2 RNA genome and sgRNAs to be enriched towards the host mitochondrial matrix and nucleolus.
The authors interpret the mitochondrial residency signal as an indicator of intracellular RNA trafficking with respect to double-membrane vesicles, a critical stage in the coronavirus life cycle.

Clinical


The direct antiglobulin test (DAT) detects immunoglobulin or complement bound in vivo to red blood cells (RBC), and is widely used to diagnose immune mediated hemolytic anemias. A positive DAT was found in 52 of 113 COVID-19 patients (46%) using the microcolumn screening assay. Thus, anti-RBC antibodies were detectable in almost half of the patients. Although the serologic features of DAT reactivity in COVID-19 patients were somewhat different from those generally observed in autoimmune hemolytic anemia, DAT positivity was associated with increasing frequency of anemia and greater transfusion requirements.

Severe COVID


Nice review of the laboratory and clinical findings of patients with COVID-19-associated coagulopathy. The authors hypothesize that an imbalance between coagulation and inflammation may result in a hypercoagulable state. Although thrombosis initiated by the innate immune system is hypothesized to limit SARS-CoV-2 dissemination, aberrant activation of this system can cause endothelial injury resulting in loss of thromboprotective mechanisms, excess thrombin generation, and dysregulation of fibrinolysis and thrombosis.

Treatment

The duration of cytochrome P-450 (CYP) 3A inhibition after stopping lopinavir/r treatment is not well understood, leading to some uncertainty as to how long to maintain adjusted doses of co-medications or when to restart drug therapies against comorbidities. The authors investigated the duration of hepatic and intestinal CYP3A inhibition after stopping lopinavir/r treatment by a verified modelling approach. In all age groups, there was more than 80% disappearance of CYP3A inhibition 5 days after stopping lopinavir/r under the consideration of population variability. Complete disappearance of CYP3A inhibition, however, took 21 days in all simulated age groups.


The next case series on early clinical experience of 20 hospitalized patients treated with CP. Compared to 20 matched controls with severe or life-threatening COVID-19 infection, laboratory and respiratory parameters were improved in patients following CP infusion. The 7- and 14-day case fatality rate in CP patients compared favorably to that in controls. However, sample size was small and the study was not randomized. Larger trials are eagerly awaited.

Pediatrics


Huge numbers, giving a clearer picture of what happens in children: Of 7,256 children tested for SARS-CoV-2, 424 (6%) tested positive. By race, 10% of black children tested positive vs. 3% of white children. Of the 424 patients who tested positive for SARS-CoV-2, 77 (18%) were hospitalized, of which 24 required respiratory support. Twelve (2.8%) SARS-CoV-2 positive patients developed critical illness requiring mechanical ventilation and 2 patients required ECMO. Two patients died.
22 June

Epidemiology


This study evaluated SARS-CoV-2 RNA and neutralizing antibodies in blood donors (BD) residing in the highly affected “Lodi Red Zone”, Italy (an area of 169 km², including 10 municipalities and 51,500 inhabitants, which went into lockdown in February 2020). Of 390 BDs recruited after 20 February – when the first COVID-19 case in Lombardy was identified, 91 (23%) aged 19–70 years were antibody positive.


Some intelligent thoughts on a “partial” lockdown for the elderly. The authors think that ethically, selective isolation is permissible. It is not unjust discrimination. It is analogous to only screening women for breast cancer: selecting those at a higher probability of suffering from a disease. Even if it were unjust discrimination, it would be proportionate because it brings benefits to the elderly and is necessary given the grave risks to the economy and subsequent well-being of the larger population of an indiscriminate lockdown. To oppose selective isolation of the elderly is to engage in a levelling down of equality which is itself morally questionable. There is no Hollywood happy ending here where everyone is a winner. Everything has its upsides and its downsides.

Transmission


A good example for working up a catastrophe, learning from mistakes. Of 435 cases of PCR-positive inpatients in a London hospital, 47 (11%) met the definition for definite hospital acquisition, with a further 19 (4%) probable hospital-
acquired. Symptom onset for these 66 hospital acquired cases was a median of 26 days (IQR 13-55) from admission. 24 (36%) patients died. Evidence of patient-to-patient transmission through contact in the same hospital bay was found in 55%.

Diagnostics

The authors compared 11 different RT-PCR test systems used in seven diagnostic laboratories in Germany in March 2020. The majority of RT-PCR assays detected ca 5 RNA copies per reaction, reflecting a high sensitivity and their suitability for screening purposes worldwide. A reduced sensitivity was noted for the original Charité RdRp gene confirmatory protocol, which may have impacted the confirmation of some cases in the early weeks of the pandemic. The CDC N1 primer/probe set was sensitive and robust for detection of SARS-CoV-2 in nucleic acid extracts from respiratory material, stool and serum from COVID-19 patients.


In this study, the authors detected the serum levels of 48 cytokines and chemokines (!) in a cohort of 74 patients including asymptomatic, mild, moderate and severe cases with laboratory confirmed COVID-19 in Jiangsu, China. IL-6, IL-7, IL-10, IL-18, G-CSF, M-CSF, MCP-1, MCP-3, IP-10, MIG, and MIP-1α were found to be associated with the severity of COVID-19. Some cytokines were significantly higher in men and many were elevated in asymptomatic patients.

Clinical
Among 18 patients with COVID-19 who had ST-segment elevation indicating potential acute myocardial infarction 6/9 patients who underwent coronary angiography had obstructive disease. However, prognosis was dismal: A total of 13 patients (72%) died in the hospital (4 with myocardial infarction and 9 with noncoronary myocardial injury).


In a systematic review of the literature, 82 cases of COVID-19 with neurological complications were identified. Conclusion: Neurological manifestations of COVID-19 are not rare, especially large vessel stroke, Guillain–Barré syndrome, and meningoencephalitis.


In 5/5 patients with acute phase DAD (≤ 7 days from onset of respiratory failure), SARS-CoV-2 was detected in pulmonary pneumocytes and ciliated airway cells, and in 2/5 in upper airway epithelium. In two patients with organizing DAD (> 14 days from onset of respiratory failure), no virus was detected in the lungs or airways. No endothelial cell infection was observed. The findings suggest that the virus is absent in the organizing phase.

Comorbidities


The authors review the evidence to date to see whether a history of haematological malignancy is associated with increased risk of COVID-19. Results: Multivariable analysis does indicate that patients with haematological malignancy, especially those diagnosed recently, are at increased risk of death with COVID-19 compared to the general population. The evidence that this risk is higher than for those with solid malignancies is conflicting. There is suggestive evidence from smaller cohort studies that those with myeloid malignan-
cy may be at increased risk within the blood cancer population, but this needs to be confirmed through larger studies.


In middle-aged patients with COVID-19, the FIB-4 index may have a relevant prognostic role. In a multivariate analysis, among other risk factors, a FIB-4 > 2.67 increased the risk of ICU admission significantly (OR 3.41; 95% CI 1.30-8.92).

23 June

Immunology


Some novel insights into pathogenesis: Dendritic cells (DCs) and macrophages are sentinel cells for innate and adaptive immunity. The authors demonstrate that these cells were permissive to SARS-CoV-2 infection but did not support productive virus replication. SARS-CoV-2 launched an attenuated interferon response in both cell types and an attenuated immune response in DCs. The latter was associated with viral antagonism of STAT1 phosphorylation (STAT1 plays a critical role in the innate immune response in the clearance of SARS-CoV).

Diagnostics


“Variable” performance means that some performed badly: Among 62 COVID-19 patients with neutralising antibodies, the specificity and sensitivity values
of the commercial antibody tests were as follows: 95%/81% (Abbott Architect), 95%/44% (Diasorin Liaison), 68%/88% (Euroimmun IgA), 87%/71% (Euroimmun IgG), 74%/56% (Acro IgG), 70%/46% (Acro 2019 IgM), 98%/72% (Xiamen IgG), and 89%/81% (Xiamen IgM). The variable performance highlights the need for laboratories to carefully consider their testing process in order to optimize the overall performance of SARS-CoV-2 serodiagnostics.


Don’t use conjunctival swabs, even in patients with conjunctivitis. Among 40 patients (10 with conjunctivitis) who tested positive by RT-PCR of nasopharyngeal and oropharyngeal swabs, conjunctival swab rRT-PCR was positive for 3 patients (one with conjunctivitis).

Clinical


In total, 506 patients from 34 studies (68 single cases and 438 from case series) with an asymptomatic course were identified. Main findings: Asymptomatic patients tend to be younger and may be more socially active. Laboratory findings in most asymptomatic cases were unremarkable. However, 62% had lung opacities, most frequently ground glass opacities.


Of 632 asymptomatic and mildly symptomatic patients admitted to community treatment centers for isolation in South Korea, 75 (12%) had symptoms at admission, 186 (29%) were asymptomatic at admission but developed symptoms during their stay, and 371 (59%) remained asymptomatic during their entire clinical course. The mean virologic remission period was 20.1 days (SD
+ 7.7 days). The virologic remission period was longer in symptomatic patients than in asymptomatic patients. In mildly symptomatic patients, the mean duration from symptom onset to virologic remission was 11.7 days (SD + 8.2 days).

**Comorbidities**


National syndromic surveillance data has found that emergency department (ED) visits declined 42% during the early months of the pandemic. This report describes trends in ED visits for three acute life-threatening health conditions, immediately before and after declaration of the COVID-19 pandemic as a national emergency: in the 10 weeks following the declaration, ED visits declined 23% for heart attack, 20% for stroke, and 10% for hyperglycemic crisis. The substantial reduction might be explained by many pandemic-related factors including fear of exposure to COVID-19, unintended consequences of public health recommendations to minimize non-urgent health care, stay-at-home orders, or other reasons.

**Severe COVID-19**


Important statements including observations about the pathophysiology of acute respiratory failure (ARF). Pulmonary damage in advanced COVID-19 often differs from acute respiratory distress syndrome (ARDS). Two types (type L and type H) are differentiated, corresponding to early- and late-stage lung damage. This differentiation should be taken into consideration in respiratory support. Based on current knowledge, inhalation therapy, nasal high-flow therapy (NHF), continuous positive airway pressure (CPAP), or non-invasive ventilation (NIV) can be performed without an increased risk of infection to staff if PPE is provided. In ARF, NIV should be carried out in an intensive care unit or a comparable setting by experienced staff. If the ARF pro-
gresses under CPAP/NIV, intubation should be implemented without delay in patients who do not have a “do not intubate”.

Treatment


The authors isolated and characterized monoclonal antibodies (mAbs) from ten convalescent COVID-19 patients, among them the most interesting mAb, named 4A8. Of note, 4A8 exhibited high neutralization potency but did not bind the RBD (like most other mAbs). Cryo-EM revealed that the epitope of 4A8 seems to be the N terminal domain (NTD) of the S protein.


Some ideas on remdesivir as an inhalation therapy. Local instillation or aerosol in the first phase of infection, both in asymptomatic but nasopharyngeal swab positive patients, together with antiseptic-antiviral oral gargles and povidone-iodine eye drops for conjunctiva would attack the virus directly through the receptors to which it binds, significantly decreasing viral replication and risk of severe COVID-19. Gilead is working on this (knowing that “early intravenous infusions” are not feasible).


Large retrospective, case-control, single-center study in patients with severe to critical COVID-19 disease. In total, 96 patients received tocilizumab, while 97 served as control group. There was a non-statistically significant lower mortality in the treatment group (52% versus 62%). When excluding intubated patients, there was statistically significant lower mortality in patients treated with tocilizumab (6% vs. 27%, p = 0.024). Bacteremia was more common in the control group, while fungemia was similar.
24 June

**Epidemiology**

Britton T, Ball F, Trapman P. *A mathematical model reveals the influence of population heterogeneity on herd immunity to SARS-CoV-2*. Science 23 Jun 2020. Full-text: [https://doi.org/10.1126/science.abc6810](https://doi.org/10.1126/science.abc6810)

43%, not 60%: Disease-induced herd immunity may be achieved at a substantially lower percentage than the classical herd immunity level derived from mathematical models assuming homogeneous immunization. The model indicates a reduction of herd immunity from 60% under homogeneous immunization down to 43% (assuming R0 = 2.5) in a structured population, but this should be interpreted as an illustration, rather than an exact value or even a best estimate.

**Immunology**


Incredible work, providing a glimpse (67 pages!) into diverse antibody responses in neutralizing plasmas from donors who recovered from COVID-19. Polyclonal plasma IgGs exhibited different degrees of cross-reactive binding between S proteins from SARS-CoV-2, SARS-CoV, and MERS-CoV and showed that the plasma IgGs also included non-cross-reactive antibodies against common cold virus RBDs. By mapping SARS-CoV-2 S epitopes targeted by convalescent plasma IgGs, the authors not only observed the expected targeting of the S protein RBD, but also discovered an S1A epitope outside of the RBD, which may represent an alternative binding site for neutralizing antibodies.

**Transmission**


This review paper “intends to outline the literature” (no doubt they've done it, 139 references!) concerning the transmission of virus-laden droplets and
aerosols in different environmental settings. Nice pictures, demonstrating the behavior of droplets and aerosols resulting from a cough-jet of an infected person in various confined spaces.


The average customer has no reliable way of knowing whether those in a restaurant kitchen or in employee-only areas are following good hygiene, wearing facial coverings, and observing social distancing. Many jurisdictions are relying on public health recommendations for businesses, which depend on cooperation and are legally unenforceable. The authors propose a tactic that could provide some of the requisite knowledge individuals need to make more informed decisions.


Reviewing the current literature, these authors come to the conclusion that COVID-19 airborne spread via particulates is not a major transmission route. Virus persistence in water, wastewater, and sludge is very low at more than 20 °C.


Don’t touch your nose: This cross-sectional study was conducted among 92 frontline members of medical staff. The main factor that contributed to COVID-19 infections was touching the cheek, nose and mouth while working, emphasizing the need to strengthen hand, oral and nasal hygiene practices. Wearing the right type or size of PPE every time as required and following the operation specifications and operation instructions improved self-protection.
Diagnostics
Summary of a virtual workshop convened on May 7, 2020 by leading US experts (from NIAID and CDC) in the field. Recommendations for advancing serology assays and conducting crucial serology field studies to advance our understanding of immunity to SARS-CoV-2 will lead to protection and duration of protection, including the correlation between serological test results and risk of reinfection.

Sera inactivated by heating may minimize the risk of virus contamination of laboratory staff. In this study in 62 patients, heat-activation at 56°C for 30 minutes did not impair the diagnostic efficacy of SARS-CoV-2 IgM or IgG antibodies (ELISA-immunoassay).

Clinical
What hard work. Of 851 unique citations, 148 articles were included which comprised 24,410 adults with confirmed COVID-19 from 9 countries. The most prevalent symptoms were fever (78%), cough (57%) and fatigue (31%). Overall, 19% of hospitalized patients required non-invasive ventilation (44 studies, 6,513 patients), 17% required intensive care (33 studies, 7504 patients), 9% required invasive ventilation (45 studies, 6933 patients) and 2% required ECMO (12 studies, 1,486 patients).
Comorbidities

The survey was conducted from 6 to 15 April, 2020 and filled out by 762 researchers from 52 countries. It captured opinions from across all career stages on how COVID-19 has severely impacted laboratory research (i.e., 65% of laboratories were mostly or completely shut). From the crippling of ongoing and planned clinical trials across the full breadth of stem cell research to the devastating loss of productivity for those researchers near career transitions, the survey revealed some of the bleak truths on the impact of COVID-19 in the stem cell community.

25 June

Epidemiology

A college spring break trip mid-March led to 64 cases (14 asymptomatic and 50 symptomatic at the time of testing), including 60 among 183 vacation travelers, one among 13 household contacts, and three among 35 community contacts. Asymptomatic persons or those with mild symptoms likely played an important role in sustaining transmission. Prompt epidemiologic investigation contributed to outbreak control.

Immunology/Pathogenesis

To date, the largest quantitative repository on the plasma lipidome and metabolome distinctly associated with COVID-19. Evaluation of metabolic pathway alterations based on differential correlation network analyses, highlighting two lipid modules possibly implicated in COVID-19 pathogenesis.

A small but important retrospective study of 39 COVID-19 patients and 32 control participants, examining the expression of endothelial cell adhesion molecules by enzyme-linked immunosorbent assays (ELISA). Serum levels of fractalkine, vascular cell adhesion molecule-1, intercellular adhesion molecule-1, and vascular adhesion protein-1 were elevated in mild patients, elevated dramatically in severe cases, while decreased in the convalescence phase. The increased expression may contribute to coagulation dysfunction.

Transmission


According to this “living rapid” review of 39 studies (18 randomized controlled trials and 21 observational studies; 33,867 participants), evidence on mask effectiveness for respiratory infection prevention is stronger in health care than community settings. N95 respirators might reduce SARS-CoV-1 risk versus surgical masks in health care settings, but applicability to SARS-CoV-2 is uncertain.

Clinical


High number of asymptomatic patients: the authors obtained a total of 5,869 samples, 3,214 from residents and 2,655 from facility staff in 69 nursing homes. Overall, 768 (23.9%) residents and 403 (15.2%) staff members tested positive for SARS-CoV-2. The presence of fever or respiratory symptoms during the preceding 14 days was recorded in 2,624 residents (81.6%) and 1,772 staff members (66.7%). Among those testing positive with information about symptoms, 69.7% of the residents and 55.8% of staff were asymptomatic. However, the ascertainment process could lead to misclassification due to atypical symptoms in the elderly. Moreover, cross-sectional symptom as-
assessment did not allow the authors to differentiate between presymptomatic and asymptomatic cases.

Comorbidities

Zhang XJ, Quin JJ, Cheng X, et al. **In-hospital Use of Statins is Associated with a Reduced Risk of Mortality among Individuals with COVID-19**. Cell Metabolism June 24, 2020. Full-text: [https://doi.org/10.1016/j.cmet.2020.06.015](https://doi.org/10.1016/j.cmet.2020.06.015)

Retrospective study on 13,981 patients in Hubei Province, China, among which 1,219 received statins. Based on a Cox model with time-varying exposure and after propensity score-matching, 28-day all-cause mortality was 5.2% and 9.4% in the matched statin and non-statin groups, respectively. Randomized controlled trials involving statin treatment for COVID-19 are needed.

Robilotti EV, Babady NE, Mead PA, et al. **Determinants of COVID-19 disease severity in patients with cancer**. Nat Med June 24, 2020. Full-text: [https://doi.org/10.1038/s41591-020-0979-0](https://doi.org/10.1038/s41591-020-0979-0)

Among 423 cases of symptomatic COVID-19 who were diagnosed at Memorial Sloan Kettering Cancer Center, 40% were hospitalized for COVID-19 and 12% died within 30 days. Age older than 65 years and treatment with immune checkpoint inhibitors (ICIs) were predictors for hospitalization and severe disease, whereas receipt of chemotherapy and major surgery were not.

Treatment


The largest retrospective, observational cohort study (from Italy) to date, reporting on IL-6 receptor blocker tocilizumab which was given either intravenously or subcutaneously. 57 (16%) of 365 patients in the standard of care (SOC) group needed mechanical ventilation, compared with 33 (18%) of 179 patients treated with tocilizumab (88 patients treated intravenously). 73 (20%) patients in the SOC group died, compared with 13 (7%; p<0.0001) patients treated with tocilizumab. After adjustment for sex, age, duration of symptoms, and SOFA (Sequential Organ Failure Assessment) score, tocilizumab treatment was associated with a reduced risk of invasive mechanical
ventilation or death (adjusted hazard ratio 0.61, 95% CI 0.40–0.92). However, the precise group of patients who might benefit from tocilizumab and the optimal biomarkers for identifying the cytokine storm in the setting of COVID-19 remain unknown.


In this prospective, open-label, randomized clinical trial, 105 patients hospitalized with COVID-19 in Greece were randomized to either standard medical treatment or colchicine plus standard medical treatment. Participants who received colchicine had statistically “significantly improved time to clinical deterioration”. However, there were no significant differences in biomarkers and the observed difference was based on a narrow margin of clinical significance; according to the authors their observations “should be considered hypothesis generating” and “be interpreted with caution”.


Important viewpoint on monitoring remdesivir use, pricing, and drug supply. Gilead has yet to comment what the bounds of a reasonable price could be. According to the authors, the FDA should revise its current EUA for remdesivir to require the creation of a patient registry that includes information on patient demographics, treatment dose and duration, and safety outcomes.

26 June

Virology

This study showed that even if a clinical sample, containing both human influenza and SARS-CoV-2, was inoculated into substrates used to prepare seeds for influenza vaccine production (embryonated chicken eggs or MDCK-based cell lines), SARS-CoV-2 would be unlikely to be propagated and would be undetectable after a small number of passages. This finding reassures influenza vaccine production staff and laboratory scientists who might be concerned about potential exposure to SARS-CoV-2 and also suggests that loss of potentially important influenza candidate vaccine viruses or final vaccine lots due to SARS-CoV-2 contamination is unlikely.

Immunology

Experts in basic and clinical immunology have joined forces to provide a consensus report on the basic molecular and immune mechanisms associated with susceptibility, clinical presentations and severity of COVID-19. This report summarizes current immunological data, including the differences between adequate innate and adaptive immune response in mild disease and the deep immune dysfunction in the more severe multi-organ disease.

Clinical

In this case series from Valencia following 20 patients aged 1 to 18 years with new-onset acral inflammatory lesions, all lacked systemic manifestations of COVID-19. Surprisingly, both PCR and serologic test results were negative for SARS-CoV-2, questioning an association between acral skin disease and COVID-19.

Same in Belgium. Of 31 patients (mostly teenagers) who had recently developed chilblains, histopathologic analysis of skin biopsy specimens (22 patients) confirmed the diagnosis of chilblains and showed occasional lymphocytic or microthrombotic phenomena. In all patients, PCR and serology remained negative. Chilblains appeared not to be directly associated with COVID-19 in this case series. According to the authors, lifestyle changes associated with community containment and lockdown measures are a possible explanation for these lesions.


Online network study from the UK, including 125 patients with data and with neurologic/neuropsychiatric complications. Of these, 77 (62%) presented with a cerebrovascular event, of whom 57 (74%) had an ischemic stroke, nine (12%) an intracerebral hemorrhage, and one (1%) CNS vasculitis. Altered mental status was the second most common presentation (31%), comprising encephalopathy or encephalitis and primary psychiatric diagnoses, often occurring in younger patients.


Maintain your exercise routine! Among 2524 subjects completing an online survey, total physical activity significantly decreased between before and during the COVID-19 pandemic. A significant positive correlation was found between the variation of physical activity and mental well-being, suggesting that the reduction of total physical activity had a profoundly negative impact on psychological health and well-being of population.

Mallapaty S. **Mounting clues suggest the coronavirus might trigger diabetes.** Nature 2020, June 24. Full-text: [https://www.nature.com/articles/d41586-020-01891-8](https://www.nature.com/articles/d41586-020-01891-8)
Does COVID-19 lead to diabetes? Some comments on preprint papers indicating growing evidence from tissue studies and some clinical cases that the virus damages insulin-producing cells. It remains to be seen how relevant this problem is.

Comorbidities


A small case series on patients with MS and COVID-19, treated with the anti-CD20 monoclonal antibodies (mAbs) ocrelizumab and rituximab. Although the severity of the clinical picture varied, patients' development was good, indicating that B cells and immunoglobulin may not be absolutely necessary for viral elimination. Not all patients developed antibodies against SARS-CoV-2.


Anticoagulants, or other antithrombotic agents such as antiplatelet drugs, might counteract the coagulopathic effects of COVID-19 resulting in improved outcomes. This small, matched-control study shows that this is probably not the case. Patients on aspirin (n=18), on clopidogrel (n=8), apixaban (n=12), warfarin (n=7) and some other drugs did not have a significantly different mortality risk to patients not taking these drugs. According to the authors, this could suggest these agents negate any potential increased mortality risk attributable to whichever disease the drugs had been prescribed, but further data on comorbidities is required to confirm this assertion.

Treatment


Comprehensive review on ruxolitinib. As many of the elevated cytokines signal through Janus kinase (JAK)1/JAK2, inhibition of these pathways with rux-
olitinib has the potential to mitigate the COVID-19-associated cytokine storm and reduce mortality. This is supported by preclinical and clinical data from other diseases with hyperinflammatory states, where ruxolitinib has been shown to reduce cytokine levels and improve outcomes. However, it is important to consider that this work was supported by Incyte, a manufacturer of the drug.

**Pediatrics**


One of the largest registries to date, confirming that COVID-19 is generally a mild disease in children. Of 582 children and adolescents (median age 5.0 years, 25% with pre-existing conditions) with PCR-confirmed SARS-CoV-2 infection, 363 (62%) were admitted to hospital and 48 (8%) individuals required ICU admission. Significant risk factors for requiring ICU admission in multivariate analyses were being younger than 1 month (odds ratio 5.1), male sex (2.1) and pre-existing medical conditions (3.3). Four children died.

**27 June**

**Epidemiology**


Not in a good mood today? Then don’t read this important comment on what will likely happen during the next months. The first wave of the 1918 influenza pandemic took place between March and July. It proved relatively mild. The second wave arrived in August. It was much worse. Most of the 50–100 million deaths caused by influenza took place during 13 weeks between September and December, 1918. In many countries, the test, trace, and isolate system is still not fully functional and we have angry debates about whether physical distancing should be 1 m or 2 m. Scientists predict that a second wave will arrive in September, peaking by the end of 2020. Just sayin’.
Transmission

Helpful video, demonstrating the complex procedure for putting on and removing PPE that has been recommended by the CDC to minimize the risk of exposure to infectious material during the care of patients with COVID-19.


Aerosol transmission of viruses must be acknowledged as a key factor leading to the spread of infectious respiratory diseases. This viewpoint summarizes current research that is already leading to a better understanding of the importance of airborne transmission.

Diagnostics

Bad performance of the commercially available rapid BIOCREDIT COVID-19 antigen test. This test was 10,000 fold less sensitive than RT-PCR and detected between 11.1 % and 45.7 % of RT-PCR-positive samples from COVID-19 patients. It serves only as adjunct to RT-PCR test because of the potential for false-negative results.


Due to the overwhelming use of SARS-CoV-2 RT-PCR tests worldwide, availability of test kits has become a major bottleneck. The authors show how to overcome these challenges by pooling samples, performing RNA extraction and RT-PCR in pools. A comparison of 184 samples tested individually and in pools of 8 samples, showed that test results were not significantly affected.
A new microneutralization assay is described in detail. This assay can be used to assess in a quantitative manner if antibodies or drugs can block entry and/or replication of SARS-CoV-2 in vitro. Compared to the most common neutralization assay, the plaque reduction neutralization test (PRNT), more samples can be analyzed. Compared to RBD-ACE2 inhibition assays, the test will also detect neutralizing antibodies binding to epitopes outside of the RBD. Different virus isolates can be used, and the assay can likely be adapted for staining antibodies other than mAbs (e.g., polyclonal sera, antibodies targeting S or M, etc.).


This Cochrane analysis on 57 publications with 15,976 samples says that the sensitivity of antibody tests is too low in the first week from symptom onset to have a primary role in the diagnosis of COVID-19. However, these tests may still have a role complementing other testing in individuals presenting later, when RT-PCR tests are negative, or are not done. Antibody tests are likely to have a useful role for detecting previous SARS-CoV-2 infection if used 15 or more days after the onset of symptoms. Data beyond 35 days post-symptom onset is scarce. According to the authors, studies of the accuracy of COVID-19 tests require considerable improvement. Studies must report data on sensitivity disaggregated by time from onset of symptoms. Updates of this living systematic review are planned.

Clinical


What a nice understatement. The authors describe “some hypotheses regarding the deleterious impact of obesity on the course of COVID-19”. This brilliant overview summarizes current knowledge on the underlying mecha-
nisms. These are: 1. Increased inflammatory cytokines (potentiate the inflammatory response), 2. reduction in adiponectin secretion (abundant in the pulmonary endothelium), 3. increases in circulating complement components, 4. systemic insulin resistance (associated with endothelial dysfunction and with increased plasminogen activator inhibitor-1), and 5. ectopic lipid deposited in type 2 pneumocytes (pre-disposing to lung injury).

Comorbidities

This registry-based cohort study from France has included 347 patients with MS with a confirmed or highly suspected diagnosis of COVID-19. In total, 73 patients (21.0%) had a COVID-19 severity score of 3 or more, and 12 patients (3.5%) died. Age, Expanded Disability Severity Scale score (EDSS; ranging from 0 to 10, with cutoffs at 3 and 6), and obesity were independent risk factors for severe COVID-19; there was no association found between exposure to disease-modifying therapies and severity.

Treatment

This study with 206 patients suggests that the effect of corticosteroids on viral shedding may be in a dose-response manner. High-dose (80 mg/d) but not low-dose corticosteroids (40 mg/d) delayed viral shedding of patients with COVID-19.

28 June
Anything goes
Here we present the best or weirdest (depending on your point of view) case reports on COVID-19 published in the first 6 months. Focus of this first issue will be gastrointestinal manifestations...

Believe it or not: COVID-19 may atypically present as persistent hiccups for four days (62 year old man, Chicago).


And yes, of course, as appendicitis, the abdominal chameleon (40 year old woman, Quatar).


In the case of epigastric tenderness in the abdominal examination and if melena is present at the rectal examination, consider also COVID-19-associated gastrointestinal bleeding (53-year-old male from Adana, Turkey).


Or an obstructive suppurative cholangitis (71-year-old woman with a one-week history of yellow skin, Wuhan, China).


But, attention! If amylase and lipase levels increase to 6-700 U/l, it may be also be acalculous pancreatitis (36-year-old woman, Lisbon, Portugal).

A pancreatic pseudocyst in which the virus can be detected and which can be successfully treated with endoscopic ultrasound-guided transgastric drainage using AXIOS™ Stent and Electrocautery Enhanced Delivery System (67-year-old woman, Rome, Italy).


Or, of course, in the case of a female patient of child-bearing age, an abdominal pregnancy has to be considered (33-year-old primigravida from Bari, Italy, presenting at 14 weeks of pregnancy with persistent abdominal pain lasting 15 days). But, please, be prepared when reading this report: worrying photos of the fetus located behind the posterior wall of the uterus, close to the rectosigmoid junction.


Or consider both. Pregnancy AND pancreatitis (36-year-old woman, G4P2, at 33 weeks of gestation, from Denver, CO).


But be careful: in male patients, it may be wiser to consider the testicles (42-year-old male with 8 days of abdominal, testicular, and back pain who had been, it’s worth mentioning, seated in the ED waiting room for 2 h prior to being roomed).

And please, finally, be also very careful these days while beekeeping, especially if you fall down on the ground near your beehives (65-year-old male from Niigata, Japan). A garden pole may poke directly into your right nostril, leading to serous rhinorrhea. Not in all cases your CSF leakage will be caulked by endonasal endoscopic using an FFG plug which, according to the authors, is useful, “in particular for the post-COVID-19 era, because it is simple, low-cost, and timesaving: requiring no special skills or no sophisticated instruments, thus reducing infection risks during the surgery”. 😊

**29 June**

**Epidemiology**

Nagler AR, Goldberg ER, Aguero-Rosenfeld ME, et al. **Early Results from SARS-CoV-2 PCR testing of Healthcare Workers at an Academic Medical Center in New York City.** Clin Inf Dis, June 28, 2020. Full-text: [https://doi.org/10.1093/cid/ciaa867](https://doi.org/10.1093/cid/ciaa867)

Widespread testing of HCW offers valuable information for hospital workflow and workforce amid an epidemic that threatened to overwhelm the healthcare system. Over eight weeks, 14,764 employees were tested: 33% of employees were symptomatic, 8% of asymptomatic employees reported COVID-19 exposure, 3% of employees returning to work were antibody-positive. Positivity rates declined over time.


The incidence of COVID-19 doubled (19.0% vs. 8.1%) for local residents who had close contact with people returning from Wuhan, who did not wear masks and turned out to be pre-symptomatic COVID-19 patients. In this

Hoffmann – Kamps
study, a cluster of 21 local COVID-19 patients originated from a couple returning from Wuhan who played cards sequentially in a space-limited Chess and Card Room or who were living together over a longer-term with pre-symptomatic or asymptomatic relatives. No bridge for grandma during these days.

Transmission

In this study, 3,398 occupationally-exposed HCW were followed prospectively, among them 1,599 (47.1%) with low-risk, 765 (22.5%) with moderate-risk, and 1,031 (30.4%) with high-risk exposures. Of the 66 HCW with COVID-19, 46, 7, and 13 had a history of high-, moderate- or low-risk exposure. Male gender, administrative personnel, underlying disease and high-risk exposure were significantly associated with an increased risk for the onset of COVID-19. HCW with high-risk occupational exposure to COVID-19 had increased probability of serious morbidity, healthcare seeking, hospitalization and absenteeism.


Infectivity lasts ten days. In 230 HCW with non-severe COVID-19, viral loads declined by orders of magnitude within a few days of symptom onset. Of the area under the curve (the distribution of transmission potential over time during the course of illness) spanning symptom onset to 30 days, 86.3% lay within the first 5 days, 96.9% within the first 7 days, and 99.7% within the first 10 days. The only variable significantly associated with viral load was time from onset of symptoms.


Clean surfaces! The authors observed a steady infectivity (< 1 log\textsubscript{10} drop) on plastic, a 3.5 log\textsubscript{10} decrease on glass, and a 6 log\textsubscript{10} drop on aluminum within 96 hours. Data showed that SARS-CoV-2 infectivity was remarkably preserved in
the presence of proteins (bovine serum albumin), regardless of the type of surface.

Diagnostics


Mid-turbinate nasal swab is not sufficient. Testing of paired MT nasal and nasopharyngeal (NP) swabs, collected by trained personnel from 40 patients with COVID-19 showed more NP (76/95, 80%) than MT swabs tested positive (61/95, 64%; p=0.02). Among samples collected a week after study enrollment, fewer MT than NP samples were positive (45% vs 76%; p=0.001). Patients whose NP swabs are PCR-positive but have a lower viral load as suggested by high CT values (> 30), may often test negative by MT swab.


Lateral flow immunoassay (LFIA) can be used easily as point of care tests or in the laboratory, with a result in less than 15 min. In this study, a LFIA (NG-Test®) was reliable and accurate. The authors compared LFIA and two immunoassays (Abbott CLIA and Euroimmun ELISA) in 293 specimens. Overall sensitivity for IgG was equivalent (around 80%) among all tests and reached 100% > 14 days after onset of symptoms. Overall specificity for IgG was greater for CLIA and LFIA (more than 98%) compared to ELISA (95.8%). Specificity was significantly different between IgA ELISA (78.9%) and IgM LFIA (95.8%) (p < 0.05).

Clinical

It’s not ethnicity. Of a total of 3,481 COVID-19 patients, seen within an integrated-delivery health system in Louisiana, 70.4% were black non-Hispanic. Although black patients represent 31% of the patients routinely cared for in the system, they made up 76.9% of hospitalized COVID-19 patients. Black patients had higher prevalences of obesity, diabetes, hypertension, and chronic kidney disease than white patients. However, black race was NOT associated with higher in-hospital mortality than white race, after adjustment for sociodemographic and clinical differences on admission. Of note, there were racial differences in several laboratory results, indicating a longer wait to access care among black patients, resulting in more severe illness on presentation to health care facilities.


Important finding that was long suspected: viral inoculum during infection or mode of transmission may be key factors determining the clinical course of COVID-19. The authors prospectively studied an outbreak in Switzerland among a population of 508 predominantly male soldiers with a median age of 21 years. Infections were followed in two spatially separated cohorts with almost identical baseline characteristics - before and after implementation of stringent social distancing. Results: of 354 soldiers infected prior to the implementation of social distancing, 30% fell ill. In contrast, none out of 154 soldiers in which infections (confirmed by NP swabs or serology) appeared after implementation of social distancing developed COVID-19.

Treatment

Acute hepatotoxicity related to remdesivir (now sold under the brand name Veklury®), with probable interaction of P-glycoprotein (P-gp) inhibitors. Five days after start of remdesivir, a patient developed an acute increase in ALT (1305 IU/L) and AST (1461 U/L). Total bilirubin was 8 μmol/L. The patient was treated with the P-gp inhibitors chloroquine (last administration nine days before remdesivir, with a half-life of two weeks) and amiodarone (concomitantly with remdesivir). Authors recommend physicians to be cautious with the prescription of P-gp inhibitors in patients receiving remdesivir therapy.
30 June

Epidemiology


High COVID-19 attack rates can occur in correctional and detention facilities. During May 7–21, among 98 incarcerated and detained persons in Louisiana who were quarantined because of virus exposure, 71 (72%) had lab-confirmed SARS-CoV-2 infection identified through serial testing, among them 45% without any symptoms at the time of testing. These findings suggest ongoing transmission among quarantined persons living in close settings; therefore, serial testing of contacts of persons with COVID-19 in correctional and detention facilities can identify asymptomatic and presymptomatic persons who would be missed through symptom screening alone.


No big surprise: classroom interaction between an infected teacher and students might result in virus transmission. After returning from Europe to the United States on March 1, 2020, a symptomatic teacher received positive test results. In total 2/21 students exposed to the teacher in the classroom had positive serologic results.


Interview with Jayaprakash Muliyil, an epidemiologist and advisor of the Indian government, providing insight into the epidemic in India where the virus seems to spread much faster and the infection rates are higher. A discussion on why officials in some badly affected cities seem reluctant to say that outbreaks are being driven by community transmission — where cases cannot be linked to known sources.
Immunology, Vaccine


Even if the optimists are right and a COVID-19 vaccine is approved for widespread use as early as this fall, it is likely to be in short supply at first. This article summarizes WHO’s and CDC’s plans to deal with this problem. For the US, a top tier includes 12 million people referred to as “critical health care and other workers,” with the first doses going to a subset of these people who are the “highest risk medical, national security, and other essential workers”. Tiers two and three would include 110 million people who also work in health care and other essential jobs, or are in these groups: 65 and older, living in long-term care facilities, or those with medical conditions known to increase the risk of developing severe COVID-19. And then everyone else.

Transmission


Important viewpoint emphasizing that N95 respirators achieve better filtration of airborne particles than medical masks if used properly and continuously. According to the authors, guideline recommendations that do not support N95 use for all inpatient COVID-19 management should consider reevaluating existing data or at least acknowledging the issues raised.


Interesting survey on 770 adolescents’ beliefs about COVID-19 and community attachment as well as attitudes and psychological factors that inform their response to the pandemic. Many teens reported not engaging in pure social distancing (69%), but they were monitoring the news (89%) and disinfecting daily (88%). Some teens reported hoarding (20%). Greater social responsibility was associated with more disinfecting and news monitoring and less hoard-
ing. Greater self-interest values were associated with less social distancing and more hoarding.

Diagnostics


The authors compared levels of SARS-CoV-2 neutralizing antibodies in recovery plasma from 7 completely asymptomatic patients with those in symptomatic patients in South Korea. Serologic diagnostic testing was positive for 71% (5/7) of completely asymptomatic patients, but neutralizing antibody response occurred in all 7 patients.

Comorbidities


Big data: Using data from a popular health and wellness smartphone app (Argus), a rapid worldwide step count decrease was seen during the COVID-19 pandemic, with regional variability. Samples from different countries varied widely in the number of days after pandemic declaration that a 15% step count decrease was seen: Italy (5 days), Spain (9 days), France (12 days), India (14 days), the United States (15 days), the United Kingdom (17 days), Australia (19 days), and Japan (24 days).

Severe COVID-19


Interesting discussion about the diffuse, alveolar-centred inflammation that triggers immunothrombosis in the lung microvasculature of patients with COVID-19 pneumonia. It seems highly probable that multiple mechanisms contribute to the pulmonary intravascular coagulopathy.
Facing the storm: In their nice overview, the authors explain the protective function of cytokines in “ideal” responses; the multi-factorial origins that can drive these responses to become pathological; and how this ultimately leads to vascular damage, immunopathology, and worsening clinical outcomes. Of note, not all cytokine storms are the same, and there are many variables—the nature of the insult, host immune status, tissue affected, crosstalk with immune thrombosis, and complement activation—that influence the magnitude and kinetics of these responses and thus the clinical manifestations.

Pediatrics


The largest study on multisystem inflammatory syndrome in children (MIS-C) to date. The authors report on 186 patients with MIS-C in 26 states. The median age was 8.3 years, 115 patients (62%) were male, 135 (73%) had previously been healthy, 131 (70%) were positive for SARS-CoV-2 by RT-PCR or antibody testing. Detailed analysis of clinical manifestation revealed the gastrointestinal system (92%), cardiovascular (80%), hematologic (76%), mucocutaneous (74%), and respiratory involvement (70%). In total 148 patients (80%) received intensive care, 37 (20%) received mechanical ventilation, and 4 (2%) died. Coronary-artery aneurysms were documented in 15 patients (8%), and Kawasaki’s disease–like features were documented in 74 (40%).
July 2020

1 July

Epidemiology


Telephone interviews in a random sample of 350 adults aged ≥ 18 years who had positive RT-PCR in outpatient and inpatient settings at 11 U.S. academic medical centers in nine states revealed that only 46% were aware of recent close contact with someone with COVID-19, highlighting a need for increased screening, case investigation, contact tracing, and isolation of infected persons during periods of community transmission. Of note, approximately one third of symptomatic outpatients reported that they had not returned to baseline health by the interview date 14–21 days after testing positive.

Vaccine


The CoV spike receptor-binding domain (RBD) is an attractive vaccine target but is undermined by limited immunogenicity. The authors identified a dimeric form of MERS-CoV RBD that overcomes this limitation and significantly increased the immunogenicity. The RBD-dimer significantly increased neutralizing antibody (NAb) titers compared to conventional monomeric form and protected mice against MERS-CoV infection. This can be a generalizable strategy for beta-CoV vaccine design.

Pathogenesis


Nothing to do next weekend? Then read this incredible work of 66 pages (>400 references!). In brief: proteomics approaches that globally quantify
changes in protein abundance and phosphorylation represent a powerful tool to elucidate mechanisms of viral pathogenesis by providing a snapshot of how cellular pathways and processes are rewired upon infection. Using a quantitative mass spectrometry-based phosphoproteomics survey of SARS-CoV-2 infection in Vero E6 cells, the 78 (!) authors present the global phosphorylation and protein abundance landscape of SARS-CoV-2 infection, map phosphorylation changes to disrupted kinases and pathways, and use these profiles to find drugs with the potential to treat SARS-CoV-2 infection. In total, 87 compounds (10 FDA-approved drugs) were identified.

Transmission

Harsh, relentless (maybe justified?) critical letter on the methodological flaws of the experiment of visualizing speech-generated oral fluid droplets (see below). The authors are “surprised that experiments in one person were published in a leading scientific journal” and state that the experiment had “more to do with sialoquence (spraying saliva when speaking) than with SARS-CoV-2”.


Clinical
Lavezzo E, Franchin E, Ciavarella C et al. *Suppression of a SARS-CoV-2 outbreak in the Italian municipality of Vo’*. Nature 2020, June 30. Full-text: https://doi.org/10.1038/s41586-020-2488-1

On the 21st of February 2020 a resident of the municipality of Vo’, a small town near Padua, Italy, died of pneumonia due to SARS-CoV-2 infection. At the start and the end of the lockdown, NP swabs were performed for 85.9% and 71.5% of the population (n=2,812), yielding to a prevalence of infection of 2.6% (95% CI 2.1-3.3%) and 1.2% (95% CI 0.8-1.8%), respectively. Of note, 42.5% of the confirmed SARS-CoV-2 infections detected across the two surveys were asymptomatic. Viral load of symptomatic versus asymptomatic infections did not differ.

Using the clinical frailty scale (CFS), 1,564 patients from the UK and Italy were grouped according to their score (1–2=fit; 3–4=vulnerable, but not frail; 5–6=initial signs of frailty but with some degree of independence; and 7–9=severe or very severe frailty). Not very surprising: Compared with CFS 1–2, the adjusted hazard ratios for time from hospital admission to death were 1.55 for CFS 3–4, 1.83 for CFS 5–6, and 2.39 for CFS 7–9. Of note, disease outcomes were better predicted by frailty than either age or comorbidity.

Severe COVID-19


In 68 COVID-19 patients, the authors assessed several markers of endothelial cell and platelet activation, including von Willebrand Factor (VWF) antigen, soluble thrombomodulin, soluble P-selectin, and soluble CD40 ligand, as well as coagulation factors, endogenous anticoagulants, and fibrinolytic enzymes. Markers of endothelial cell and platelet activation were significantly elevated in ICU patients compared with non-ICU patients, including VWF antigen and soluble P-selectin. Some were of prognostic value, indicating that endotheliopathy is present in COVID-19 and is likely to be associated with critical illness and death.

Comorbidities


Is there an effect of TDF? Of 77,590 HIV-positive persons receiving ART, 236 were diagnosed with COVID-19, 151 were hospitalized, 15 were admitted to the ICU, and 20 died. The risk for COVID-19 hospitalization was 20.3 (95% CI, 15.2 to 26.7) among patients receiving TAF/FTC, 10.5 (CI, 5.6 to 17.9) among those receiving TDF/FTC, 23.4 (CI, 17.2 to 31.1) among those receiving ABC/3TC, and 20.0 (CI, 14.2 to 27.3) for those receiving other regimens. How-
ever, residual confounding by comorbid conditions cannot be completely excluded.

Treatment

Small PK pilot study on remdesivir (Veklury®) and the nucleoside analog GS-441524 (of which remdesivir is a prodrug). After intravenous administration, in both patients remdesivir showed a peak at the end of infusion and a half-life of 1 h, while GS-441524 reached a peak 1 h after infusion and then remained detectable until the next remdesivir administration. GS-441524 plasma concentrations were higher in the patient with renal impairment, indicating that renal excretion was a major route of elimination.

Pediatrics

No differences between adults and children. The authors isolated culture-competent virus in vitro from 12 (52%) of 23 SARS-CoV-2–infected children; the youngest was 7 days old. SARS-CoV-2 viral load and shedding patterns of culture-competent virus in the 12 symptomatic children resembled those in adults. Therefore, transmission of SARS-CoV-2 from children is plausible.

2 July
Immunity

Insights on adaptive immunity. The authors analyzed COVID-19 patients with active, severe infection (n=20) or after recovery of mild disease (n=19) and created a repository of currently > 14 million B and T cell receptor (BCR, TCR)
sequences from the blood of these patients. The B cell response showed converging IGHV3-driven BCR clusters closely associated with SARS-CoV-2 antibodies. The T cell pools of patients with active disease were considerably diminished and showed shifts towards CD4+ and expanded T_{reg} cells. Clonality and skewing of TCR repertoires was associated with interferon type I and III responses and early CD4+ and CD8+ T cell activation.

Vaccine

The authors review practical considerations relevant to the development of a SARS-CoV-2 controlled human infection models (CHIMs) and the prerequisites for using such a model. Large, randomized, controlled trials of SARS-CoV-2 vaccines are still the most efficient, generalizable, and scientifically robust path to establishing vaccine efficacy. However, SARS-CoV-2 CHIM development might be able to accelerate the development of later rounds of vaccine candidates.

Diagnostics

Validated protocols are described for generating high-quality, full-length genomes from primary samples. One protocol uses multiplex reverse transcription PCR, followed by MinION or MiSeq sequencing; the other uses singleplex, nested reverse transcription PCR and Sanger sequencing. These protocols enable sensitive virus sequencing in different laboratory environments.

Clinical

Relative bradycardia is a characteristic physical finding in some intracellular bacterial infections, viral infections, and non-infectious diseases. In this case
series of 54 patients with mild-to-moderate COVID-19 in Japan, it was also a common finding. This clinical sign could help clinicians to diagnose this disease. Only body temperature was independently associated with pulse rate by multivariate analysis. The predicted change in pulse rate was 7.37 beats/min for each 1°C increase in body temperature.


There were approximately 781,000 deaths in the US from March 1 to May 30, 2020, representing 122,300 (95% prediction interval, 116,800 - 127,000) more deaths than would typically be expected. The number of excess all-cause deaths was 28% higher than the official tally of COVID-19-reported deaths during that period. There was substantial variability between states in the difference between official COVID-19 deaths and the estimated burden of excess deaths.


Same idea: the weekly death data for the 50 US states and the District of Columbia were obtained from the National Center for Health Statistics for January through April 2020 and the preceding 6 years. The authors provide state-by-state estimates of excess deaths and a more detailed account of the 5 states most affected by COVID-19. It was estimated that the number of COVID-19 deaths reported in the first weeks of the pandemic captured only two-thirds of excess deaths in the US.

Severe COVID-19


“Cytokine storm” has no definition. Broadly speaking, it denotes a hyperactive immune response characterized by the release of interferons, interleukins, tumor necrosis factors, chemokines, and several other mediators. In this
editorial, a critical evaluation of the term cytokine storm and its relevance is given. The authors point out that although the term “cytokine storm” conjures up dramatic imagery and has captured the attention of the mainstream and scientific media, the current data do not support its use. Until new data establish otherwise, the linkage of cytokine storm to COVID-19 may be nothing more than a tempest in a teapot.

Comorbidities

COVID-19 is associated with hyperglycemic emergencies in COVID-19. In this case series of 35 patients from three hospitals in north London, UK, March 1–30, 2020, an over-representation of type 2 diabetes in patients presenting with diabetic ketoacidosis and long-lasting ketosis was observed. Findings suggest acute insulinopenia in patients with COVID-19 and with type 2 diabetes, which persisted up until the time of discharge in 30% of patients previously not insulin-treated. Moreover, the study sample, with almost half of patients of African background, had protracted ketonemia and ketoacidosis.

Pediatrics

Another large cohort of 95 patients with a multi-system inflammatory syndrome in children (MIS-C), reported to the New York State Department of Health. Detailed analysis of the characteristics: Elevated levels of C-reactive protein, d-dimer, and troponin were found in 100%, 91%, and 71% of the patients, respectively; 53% had evidence of myocarditis, 80% were admitted to an intensive care unit, and 2 died.


A case series of 4 children with COVID-19 and neurological symptoms is described. Symptoms included encephalopathy, headaches, brainstem and cere-
bellar signs, muscle weakness, and reduced reflexes. All 4 patients had signal changes in the splenium of the corpus callosum on neuroimaging and required intensive care admission for the treatment of COVID-19 pediatric multisystem inflammatory syndrome.

3 July

Epidemiology


Reopening colleges and universities poses a special challenge worldwide. Taiwan is one of the few countries where schools are functioning normally. To secure the safety of students and staff, the Ministry of Education in Taiwan established general guidelines, including a combination of strategies such as – our future? - active campus-based screening and access control; school-based screening and quarantine protocols; student and faculty quarantine when warranted; mobilization of administrative and health center staff; regulation of dormitories and cafeterias; and reinforcement of personal hygiene, environmental sanitation, and indoor air ventilation practices. Somewhat depressing, but necessary?


Following admission of two patients with SARS-CoV-2 infection on April 13, 2020, in the absence of specific guidance on prevention and management of COVID-19 in psychiatric facilities, the state hospital implemented expanded admission screening and infection prevention and control procedures. The results of the point prevalence survey, indicating no further transmission among patients and HCW almost 3 weeks after admission of the two SARS-CoV-2-positive patients, suggested that the expanded procedures might have been effective.
**Virology**


(IMPORTANT)

Based on 28,576 sequences until May 29, 2020, the authors show that a SARS-CoV-2 variant carrying the Spike protein amino acid change D614G (caused by an A-to-G nucleotide mutation at position 23,403 in the Wuhan reference strain) has become the most prevalent form in the global pandemic within a month. G614 has replaced D614 as the dominant pandemic form and the consistent increase of G614 at regional levels may indicate a fitness advantage. Moreover, G614 is associated with lower RT-PCR CT in the upper respiratory tract, suggestive of higher viral loads in patients. The G614 variant also grows to higher titers as pseudotyped virions. However, there was no association between G614 and disease severity.


Comment on the above work. Main message = title. While clinical and in vitro data suggest that D614G changes the virus phenotype, the impact of the mutation on transmission, disease, vaccine and therapeutic development are largely unknown. As these forces can work in tandem, it’s often hard to differentiate when a virus mutation becomes common through fitness or by chance. It is even harder to determine if a single mutation will change the outcome of an infection, or a pandemic.

**Transmission**


No virus in the semen: all of 23 brave patients with SARS-CoV-2 infections (12 of them still positive in sputum and fecal specimens) tested negative for SARS-CoV-2 RNA in semen specimens.

Another case report of a pregnant woman with subclinical COVID-19 whose breast milk sample obtained after delivery tested positive for SARS-CoV-2 by RT-PCR. In addition, although an initial nasopharyngeal swab (NPS) sample from the neonate resulted negative, neonatal NPS, stool, and blood samples obtained after breastfeeding were all positive in real-time RT-PCR assay.

Diagnostics


Viral load matters: admission SARS-CoV-2 viral load among hospitalized patients with COVID-19 independently correlated with the risk of intubation and in-hospital mortality. In 678 patients with COVID-19, higher viral load was associated with increased age, comorbidities, smoking status, and recent chemotherapy. In-hospital mortality was 35.0% with a high viral load (Ct < 25; n = 220), 17.6% with a medium viral load (Ct 25-30; n=216), and 6.2% with a low viral load (Ct > 30; n = 242; P < 0.001). The risk of intubation was also higher in patients with a high viral load (29.1%), compared to those with a medium (20.8%) or low viral load (14.9%; P < 0.001). High viral load was independently associated with mortality (adjusted odds ratio 6.05; 95% CI: 2.92-12.52) and intubation (aOR 2.73; 95% CI: 1.68-4.44) in multivariate models.

Clinical


The most extensive study (cross-sectional observational) of COVID-19 hospital survival in Brazil ranks second worldwide in total number of COVID-19 cases and deaths. Survivors were more likely to be younger, be women, and have fewer comorbidities, keeping with worldwide findings. In addition, Pardo ethnicity (mixed race) was the second most important risk factor (after age)
for death. The ethnicity effect might be related to differences in susceptibility to COVID-19 and access to health care (including intensive care) across ethnicities.

Feaster M, Goh Y-Y. **High proportion of asymptomatic SARS-CoV-2 infections in 9 long-term care facilities, Pasadena, California, USA, April 2020.** Emerg Infect Dis 2020, Jul 2. Full-text: https://doi.org/10.3201/eid2610.202694

SARS-CoV-2 prevalence in 9 long-term care facilities demonstrated a high proportion (40.7%, 257/631) of asymptomatic infections among residents and staff members. The prevalence of asymptomatic infection differed markedly between facilities: among staff members from 17.4% to 30.6%, among residents from 19.0% to 85.7%.

**Treatment**


Where are the results of the hundreds of clinical trials conducted during the last months? This article describes the challenges that clinical trials are facing world-wide. Some details on WHO’s SOLIDARITY are given. With recruitment running at about 500 patients per week now, SOLIDARITY’s three remaining treatment arms are likely to yield answers “soon” (whatever that means), raising the question of what drugs to test afterward. Some repurposed drugs such as camostat mesylate or favipiravir are still being discussed, but increasingly the attention is turning to monoclonal antibodies, designed to target the virus.

**Epidemiology**


No cryptic transmission before early officially confirmed cases. In this retrospective screening for SARS-CoV-2 RNA in 1,271 nasopharyngeal swab samples, as well as the prevalence of IgM, IgG, and total antibodies against SARS-CoV-2 in 357 matched serum samples collected from hospitalized patients with influenza-like illness between December 1, 2018 and March 31, 2020 in
Shanghai Ruijin Hospital, the onset date of the earliest COVID-19 case was January 25.

**Immunology, vaccine**


Four rhesus macaques were re-challenged intratracheally with the same dose of the SARS-CoV-2 strain at 28 days post-initial challenge with the identical SARS-CoV-2 strain. Animals did not show detectable viral dissemination, clinical manifestations of viral disease, or histopathological changes. Comparing the humoral and cellular immunity between primary infection and rechallenge revealed notably enhanced neutralizing antibody and immune responses.

**Transmission**


A comprehensive review of the available data (by May 21, 2020) on the stability of coronaviruses, including SARS-CoV-2, from previous reports, to help understand its environmental survival.

Edwards SJL, Santini JM. *Anthroponotic risk of SARS-CoV-2, precautionary mitigation, and outbreak management*. Lancet Microbe, July 02, 2020. Full-text: [https://doi.org/10.1016/S2666-5247(20)30086-0](https://doi.org/10.1016/S2666-5247(20)30086-0)

Important comment on the evidence of infection of animals with SARS-CoV-2 that has been shown experimentally both *in vivo* and *in vitro* for mammals including monkeys, cats, ferrets, rabbits, foxes, and hamsters, while bioinformatic studies also predict infectivity of pigs and wild boar among other mammals. According to the authors, we should also consider the potential for transmissibility, not just infection.

Social events outside the hospital. In this cross-sectional study at three hospitals located in the south of the Netherlands, from 50 HCWs (and ten patients), complete and near-complete genome sequences were analyzed. Most sequences were grouped into three clusters, with two clusters showing local circulation within the region. The genomic diversity recorded was consistent with multiple introductions through community-acquired infections, and some local amplification related to specific social events in the community, rather than widespread within-hospital transmission. Thus, data do not support widespread nosocomial transmission as the source of infection in patients or health-care workers.

Diagnostics

Sensitivity of rapid tests is at best moderate: the authors evaluated diagnostic performance of eleven rapid tests for detection of antibodies to SARS-CoV-2 in 20 hospitalized patients with PCR-confirmed COVID-19, 23 recovered outpatients with former PCR-confirmed COVID-19, and 49 participants with suspected COVID-19 presenting at a primary care emergency room. All eleven tests detected antibodies in hospitalized COVID-19 patients, though with varying sensitivities. In former outpatients recovered from COVID-19, there were differences between tests in the immunoglobulin type G (IgG) sensitivity, with five tests having a sensitivity below 65%. In participants with suspected COVID-19 infection, the rapid tests had very low sensitivities.

Clinical

The authors present preliminary pooled estimates of all-cause mortality for 24 European countries/federal states participating in the European monitor-
ing of excess mortality for public health action (EuroMOMO) network, for the period March–April 2020. Excess mortality particularly affected ≥65-year-olds (91% of all excess deaths), to a lesser extent those 45–64 (8%) and 15–44-year-olds (1%). The cumulative excess mortality from week 1 to week 18, 2020 reached a total of 185,287 deaths, including 24,438 (13%) in persons aged 65–74 years, 55,226 (30%) in persons aged 75–84 years, and 88,598 (48%) in persons aged ≥85 years.


SARS-CoV-2 RNA clearance time was associated with sex, disease severity and lymphocyte function. Among 99 patients, 61 patients had SARS-CoV-2 clearance (virus-negative group), but 38 patients had sustained positive results (virus-positive group). Male sex (HR, 0.58), immunoglobulin use (0.42), APACHE II score (0.89), and lymphocyte count (1.81) were independent factors associated with a prolonged duration of SARS-CoV-2 shedding. Antiviral therapy and corticosteroid treatment were not independent factors.


At 4 weeks from onset, most patients experience complete resolution or even improvement of altered sense of smell or taste. Of 202 patients completing the survey at baseline, 187 (92.6%) also completed the follow-up survey. The evaluation of 113 patients reporting sudden onset of these symptoms at baseline showed that 55 patients (49%) reported complete resolution of smell or taste impairment, 46 (41%) reported an improvement in the severity, and only 12 (11%) reported the symptom was unchanged or worse. Persistent loss of smell or taste was not associated with persistent SARS-CoV-2 infection.

**Treatment**

Gendelman O, Amital H, Bragazzi NL, Watad A, Chodick G. Continuous hydroxychloroquine or colchicine therapy does not prevent infection with SARS-CoV-2: Insights from a large healthcare database analysis. Auto-
No protection with HCQ and colchicine. An overall sample of 14,520 subjects from Israel were screened for SARS-CoV-2 infection and 1317 resulted positive. No significant difference was found in terms of rates of usage of hydroxychloroquine or colchicine between those who were found positive for SARS-CoV-2 and those who were found negative (0.23% versus 0.25% for hydroxychloroquine, and 0.53% versus 0.48% for colchicine, respectively).

**Epidemiology**


The basic reproductive rate (R0) for SARS-CoV-2 is estimated to be 2·5 (range 1·8–3·6) compared with 2·0–3·0 for SARS-CoV and the 1918 influenza pandemic, 0·9 for MERS-CoV, and 1·5 for the 2009 influenza pandemic. In their viewpoint, the authors postulate that historical evidence from prior influenza pandemics indicates that pandemics tend to come in waves over the first 2–5 years as population immunity builds-up (naturally or through vaccination) and that this is the most likely trajectory for SARS-CoV-2. A combination of physical distancing, enhanced testing, quarantine, and contact tracing will be needed for a long time.

**Transmission**


A note of caution, to curb excesses that become counterproductive. According to the author, the chance of transmission through inanimate surfaces is very small, and only in instances where an infected person coughs or sneezes on the surface, and someone else touches that surface soon after the cough or sneeze (within 1–2 h). Although periodically disinfecting surfaces and use of gloves are reasonable precautions especially in hospitals, he believes that fomites that have not been in contact with an infected carrier for many hours do not pose a measurable risk of transmission.
Prevention

The amount of waste generated due to COVID-19 indeed threatens the existing waste management streams, meaning that plastic leakage/pollution may impose severe risks to both environmental and human health. Thus, it is imperative to increase monitoring (aquatic, terrestrial and aerial surveys) of plastic waste under post-COVID-19, around the world. This paper provides an overview of plastic policies and discusses the readjustments of these policies during the COVID-19 pandemic along with their potential environmental implications. Policy recommendations and future research directions are also discussed.

Diagnostics

Systematic review of 40 studies on sensitivity and specificity, stratified by method of serological testing (enzyme linked immunosorbent assays, ELISAs), lateral flow immunoassays (LFIAs), or chemiluminescent immunoassays, CLIAs). The pooled sensitivity of ELISAs measuring IgG or IgM was 84.3% (95% confidence interval 75.6% to 90.9%), of LFIAs was 66.0% (49.3% to 79.3%), and of CLIAs was 97.8% (46.2% to 100%). According to the authors, higher quality clinical studies assessing the diagnostic accuracy of serological tests for COVID-19 are urgently needed. Currently, available evidence does not support the continued use of existing point-of-care serological tests.


This comprehensive review summarizes the principles and related details of PCR and serological assays for SARS-CoV-2 as well as the quality assurance measures for these assays.

The next study reporting that initial viral load is positive correlated to illness severity. Among 195 patients, the two conversely correlated indexes for initial viral load, log_{10} (copies/mL) and Ct value, were found to be respective significantly positive and negative correlated to severity.


Case report of an infected mother, in which IgG and IgA antibodies were detected in breast milk, indicating the potential immune protection for the neonates. The infant negative for SARS-CoV-2 at birth had elevated IgG in serum but it quickly decayed.

Clinical


Following a mass testing campaign in long-term care facilities in Belgium, no symptoms were reported for 2,185 (74.0%) staff and 4,059 (75.3%) residents. Given the cross-sectional nature of this analysis, however, it was not possible to determine whether any of the asymptomatic individuals went on to develop symptoms. If pre-symptomatic or asymptomatic: risk of under-ascertainment of symptoms, although mitigated by medical assessment, persists.

Comorbidities


The pandemic has major implications for blood transfusion. There are uncertain patterns of demand, and transfusion institutions need to plan for reduc-
tions in donations and loss of crucial staff because of sickness and public health restrictions. This article provides a synthesis of the published literature and guidance during times of potential or actual shortage. However, a reduction in donor numbers has largely been matched by reductions in demand for transfusion.


Patients with autoimmune rheumatic disease might be more susceptible. Within 42 families with at least one member suffering from a rheumatic disease, COVID-19 was diagnosed in 27 (63%) of 43 patients with a rheumatic disease and in 28 (34%) of 83 of their family members with no rheumatic disease (adjusted odds ratio 2.68, 95% CI 1.14–6.27). Patients with rheumatic disease who were taking hydroxychloroquine had a lower risk of COVID-19 infection than patients taking other disease-modifying anti-rheumatic drugs (OR 0.09, 0.01–0.94).

6 July

Epidemiology


Nice article about what R, the reproduction number, can and can’t tell us about managing COVID-19. Politicians seem to have embraced R with enthusiasm but it’s far more important to watch for clusters of cases and to set up comprehensive systems to test people, trace their contacts and isolate those infected, than to look at R.


The vast majority (95%) of the Spanish population is seronegative, even in hotspot areas. In this nationwide, representative study, 61,075 participants were tested. Seroprevalence was 5.0% (95% CI 4.7–5.4) by the point-of-care
test and 4.6% (4.3–5.0) by immunoassay, with a lower seroprevalence in children younger than 10 years (< 3.1% by the point-of-care test). There was high geographical variability, with higher prevalence around Madrid (> 10%) and lower in coastal areas (< 3%).


Comment on these findings. Most of the population appears to have remained unexposed to SARS-CoV-2, even in areas with widespread virus circulation. Any proposed approach to achieve herd immunity through natural infection is not only highly unethical, but also unachievable. With a large majority of the population being infection-naïve, virus circulation can quickly return to early pandemic dimensions in a second wave once measures are lifted.

Diagnostics


The authors present a novel alternate multiple swab protocol that is based on incubation of a respiratory swab first in a single-sample tube, and then again in a multiple-sample tube. No significant difference in the amount of virus was detected by NAT in the single-sample or multiple-swab tube. The novel protocol was able to reduce the total number of required NAT tests by up to 80%, without loss of diagnostic sensitivity.

Comorbidities


Hypertension has been proven to be more prevalent in patients with an adverse outcome. So far, there is no study that demonstrates the independent predictive value of hypertension on mortality in COVID-19 patients. This review summarizes the current knowledge about the relationship between hypertension and COVID-19 patients.
Severe COVID-19


Some thoughts about the heterogeneity in the reported VTE risk as well as in the thromboembolic phenotypes of COVID-19 patients (isolated DVT, isolated pulmonary embolism/thrombosis, concurrent DVT and pulmonary embolism/thrombosis). It might be suggested that variation in VTE accounts for this heterogeneity: characteristics of the patients include well-established risk factors for VTE, hospitalization conditions and interventions as well as SARS-CoV-2 specific factors.


Small retrospective study of 24 patients. According to the authors, with careful patient selection and close monitoring, CPAP can be a successful treatment strategy in critically ill patients with type 1 respiratory failure in COVID-19, and that it can be safely deployed outside the critical care environment.

Treatment


When is the best time to donate plasma? In 49 donors, S-RBD-specific and N-specific IgG antibodies increased after 4 weeks from the onset of symptoms, with no significant correlation to age, sex, or ABO blood type. Donors with disease presentation of fever exceeding 38.5°C or lasting longer than 3 days exhibited higher levels of S-RBD-specific IgG antibodies at the time of donation. The authors recommend the following selection criteria for optimal donation of COVID-19 convalescent plasma: 28 days after the onset of symptoms.
and with a disease presentation of fever lasting longer than 3 days or a body temperature exceeding 38.5°C. Selection based on these criteria can ensure a high likelihood of achieving sufficiently high S-RBD-specific IgG titers.


Open-label study of sarilumab (a recombinant human IL-6Rα antagonist) in severe COVID-19 pneumonia with hyperinflammation. Sarilumab 400 mg was administered intravenously in addition to standard of care to 28 patients and results were compared with 28 contemporary matched patients treated with standard of care alone. At day 28, 61% of patients treated with sarilumab experienced clinical improvement and 7% died. These findings were not significantly different from the comparison group. However, sarilumab was associated with faster recovery in a subset of patients showing minor lung consolidation at baseline.

Pediatrics


First study on detection and decline over time of antibodies in infants born to women with COVID-19. Among the 24 infants born to women with COVID-19, 15 (62.5%) had detectable IgG and 6 (25.0%) had detectable IgM; nucleic acid test results were all negative. Among 11 infants tested at birth, all had detectable IgG and 5 had detectable IgM. IgG titers with positive IgM declined more slowly than those without.

7 July

Immunology

In this Viewpoint, the authors describe the five currently leading vaccine candidates, all of which are aimed at inducing antibodies directed against the receptor-binding domain of the surface spike S protein of SARS-CoV-2. These vaccine candidates are messenger RNA-based (Moderna, Pfizer), recombinant vesicular stomatitis virus vectored (MSD) and adenovirus replication-defective vectored (Johnson & Johnson, AstraZeneca). All 5 candidates are undergoing rigorous investigation of their safety profile, including unintended adverse events.


Using an infectious molecular clone of vesicular stomatitis virus (VSV), researchers replaced the glycoprotein gene (G) with the spike protein of SARS-CoV-2 (VSV-eGFP-SARS-CoV-2) and developed a high-throughput imaging-based neutralization assay at biosafety level 2. This provides a tool for testing inhibitors of SARS-CoV-2 mediated entry under reduced biosafety containment.


Same direction. This group from the Albert Einstein College in New York have also generated a highly infectious recombinant VSV bearing the SARS-CoV-2 spike glycoprotein S as its sole entry glycoprotein and show that this recombinant virus, rVSV-SARS-CoV-2 S, closely resembles SARS-CoV-2 in its entry-related properties. Another step towards robust, scalable, and readily deployable surrogate viral assays to screen antiviral humoral responses, define correlates of immune protection, and down-select candidate antivirals.

**Transmission**

Morawska L, Milton DK. **It is Time to Address Airborne Transmission of COVID-19.** Clinical Infectious Diseases, July 6, 2020. Full-text: https://doi.org/10.1093/cid/ciaa939 (IMPORTANT)

In their comment, the authors appeal to the medical community and to all relevant national and international bodies to recognize the potential for air-
borne spread of COVID-19. Given the significant potential for inhalation exposure to viruses in microscopic respiratory droplets (microdroplets) at short to medium distances (up to several meters, or room scale), the authors are advocating for the use of preventive measures. This includes sufficient and effective ventilation (supply clean outdoor air, minimize recirculating air) particularly in public buildings, workplace environments, schools, hospitals, and aged care homes, but also supplement general ventilation with airborne infection control (such as local exhaust, high efficiency air filtration, and germicidal ultraviolet lights). Third, overcrowding has to be avoided, particularly in public transport and public buildings.


Among 249 HCW who worked in hospital units with COVID-19 patients for one month, 19 (7.6%) tested positive for SARS-CoV-2 antibodies. Only 11/19 (57.9%) reported symptoms of a prior illness, suggesting asymptomatic HCW could be an important source of SARS-CoV-2 transmission.

**Diagnostics**


In this study, 23 (3%) of 651 patients tested positive on a retest for SARS-CoV-2 by RT-qPCR assay in a routine health check. Of note, 52% had IgG anti-viral antibodies and 30% had IgM antibodies, indicating partial immune system recognition of SARS-CoV-2. Of note, 35% of patients had one or more COVID-19-related symptoms, questioning the usefulness of viral antibodies in COVID-19 clearance.

**Clinical**

Again, it’s NOT a flu. In this retrospective cohort study, 1,916 COVID-19 patients and 1,486 influenza patients (with emergency department visits or hospitalizations) were compared. There were 31 (1.6%; 95% CI, 1.1% - 2.3%) acute ischemic strokes with COVID-19, compared to 3 with influenza (0.2%; 95% CI, 0.0% - 0.6%). After adjustment for age, sex, and race, the likelihood of stroke was almost 8-fold higher with COVID-19 (odds ratio, 7.6; 95% CI, 2.3 - 25.2).


More on obesity. In this study of 1,687 adults hospitalized with COVID-19 in New York City, obesity was an independent risk factor for respiratory failure but not for in-hospital mortality. These findings explain the extensive use of invasive mechanical ventilation reported in the US, where the prevalence of obesity exceeds 40%. The risk conferred by obesity was similar across age, sex, and race.

Severe COVID-19


In their Viewpoint, the authors address ventilation strategies in the context of recent discussions on phenotypic heterogeneity in patients with COVID-19-associated ARDS. Although early reports suggested distinctive features that set it apart from historical ARDS, emerging evidence indicates that the respiratory system mechanics are broadly similar. In the absence of evidence to support a shift away from the current paradigm of ventilatory management, we strongly recommend adherence to evidence-based management, informed by bedside physiology, as resources permit.

Treatment


Forget HCQ, lopinavir, etc. Over the last months, it has become increasingly clear that monoclonal antibodies will be the most promising therapeutic can-
didates for COVID-19. The authors identified 178 S1 and RBD binding human monoclonal antibodies from the memory B cells of 11 recently recovered patients. Of 8 antibodies showing robust authentic viral neutralizing activities, the best one, 414-1, showed neutralizing IC50 at 1.75 nM. Epitope mapping revealed that the antibodies bound to 3 different RBD epitopes, and epitope B antibody 553-15 could substantially enhance neutralizing abilities of most other neutralizing antibodies.

8 July

Epidemiology


Despite low incidence, superspreading related to visiting nightclubs has the potential to spark a resurgence of cases. This article describes large-scale testing for active case-finding among persons who visited 5 Itaewon nightclubs in downtown Seoul, South Korea. Nightclubs had reopened ahead of the April 30–May 5 Golden Week holiday. Among the 41,612 total tests (!) conducted by May 25, positive results were found in 0.19% (67/35,827) of nightclub visitors, 0.88% (51/5,785) of their contacts, and 0.06% (1/1,627) of anonymously tested persons. 246 COVID-19 cases were associated with the reopening of nightclubs in Seoul. Hooray for the Asian thoroughness and some strong arguments against reopening nightclubs...


Every day counts. In this large, nationwide study, later statewide emergency declarations and school closures were associated with higher COVID-19 mortality. Each day of delay increased mortality risk by 5 to 6%.


COVID Reference Top 10
One more reason to go veg. Overall, 239 facilities reported 16,233 COVID-19 cases and 86 COVID-19–related deaths among workers. The percentage of workers with COVID-19 ranged from 3.1% to 24.5% per facility. Among seven facilities that implemented facility-wide testing, the crude prevalence of asymptomatic or presymptomatic infections among 5,572 workers who had positive SARS-CoV-2 test results was 14.4%.

**Virology**


In this study, human induced pluripotent stem cell-derived cardiomyocytes (hiPSC-CMs) were used as a model to examine the mechanisms of cardiomyocyte-specific infection by SARS-CoV-2. Microscopy and RNA-sequencing demonstrated that SARS-CoV-2 can enter hiPSC-CMs via ACE2. Viral replication and cytopathic effect induce hiPSC-CM apoptosis and cessation of beating after 72 hours of infection.


The virus is not only in the heart but also in the rectum. In this case report, quantitative RT-PCR was performed on rectal tissue specimens obtained from surgical resection in a COVID-19 patient with rectal adenocarcinoma. RNA of SARS-CoV-2 was detected in surgically resected rectal specimens, but not in samples collected 37 days after discharge. Notably, coinciding with rectal tissues of surgical specimens nucleic acid positive for SARS-CoV-2, typical coronavirus virions in rectal tissue were observed under electron microscopy. Moreover, abundant lymphocytes and macrophages (some are SARS-CoV-2 positive) infiltrating the lamina propria were found with no significant mucosal damage.

**Transmission**

Cross-sectional observational study in a multi-site London hospital. Air and surface samples were collected from several areas. Viral RNA was detected on 114/218 (52.3%) of surfaces and 14/31 (38.7%) air samples but no virus was cultured. Viral RNA was more likely to be found in areas immediately occupied by COVID-19 patients than in other areas. The high PCR Ct value for all samples (>30) indicated that the virus would not be culturable.


Lucky pigs. The authors intranasally inoculated twelve fruit bats (Rousettus aegyptiacus), 12 ferrets (Mustela putorius), pigs (Sus scrofa domesticus), and 20 chickens (Gallus gallus domesticus) with TCID50 of a SARS-CoV-2 isolate per animal. Pigs and chickens could not be infected intranasally or oculo-oronasally by SARS-CoV-2, whereas fruit bats showed characteristics of a reservoir host. Virus replication in ferrets resembled a subclinical human infection with efficient spread.

Diagnostics


The authors present a rapid, easy-to-implement real-time PCR based assay with automated analysis using a novel COVID qPCR Analyzer tool with graphical user interface to analyze the raw qRT-PCR data in an unbiased manner at a cost of less than $3 per reaction and turn-around time of less than 2h, to enable in-house SARS-CoV-2 testing across laboratories.


In 8/12 patients with severe COVID-19, viral shedding was shown in a variety of tissues for 20-40 days post-onset of disease; in contrast 9/11 patients with mild disease had viral shedding restricted to the respiratory tract and had no detectable virus RNA after 10 days post-onset.
Treatment


Regulatory T cells (also known as T_{reg}) migrate into inflamed tissues, dampening inflammatory responses and hastening tissue repair. Two patients who became critically ill despite receiving tocilizumab were treated with T_{reg} and recovered. Infusions were rapidly followed by decreases in interleukin-6, tumor necrosis factor-α, and interferon-γ.

9 July

Epidemiology


By June 6, 2020, there had been 42,107 cases of COVID-19 and 510 deaths among 1.3 million prisoners in the US. The case rate was initially lower in prisons but surpassed the US population on April 14, 2020. The mean daily case growth rate was 8.3% per day in prisons and 3.4% per day in the US population.

Maxmen A. California’s San Quentin prison declined free coronavirus tests and urgent advice — now it has a massive outbreak. Nature NEWS 07 July 2020. Full-text: https://doi.org/10.1038/d41586-020-02042-9

And this is a story behind the numbers. San Quentin Prison, which got through most of May without a single reported case among inmates, is now dealing with the third-largest coronavirus outbreak in the US. More than one-third of the inmates and staff (1,600 people) have tested positive. Six have died. Researchers fear that other institutions are at risk.

Transmission

Among 335 passengers on a flight from Singapore to Hangzhou in China (a Boeing 787, 5-hour flight, seat occupancy 89%), a total of 16 COVID-19 patients were diagnosed among all passengers, yielding an attack rate of 4.8%. However, after careful investigation, only one case was identified who appears to have become infected during the flight. He was seated near four infected passengers from Wuhan for approximately an hour (he had moved a seat) and did not wear his facemask correctly during the flight. The sources of infection in the other 15 passengers were complex and the passengers could have acquired their infections in Wuhan before the tour, or during the group tour before boarding.

Clinical


Using a secure health analytics platform covering 40% of all patients in England, primary care records of 17,278,392 adults were pseudonymously linked to 10,926 COVID-19-related deaths. COVID-19-related death was associated with being male (hazard ratio 1.59, 95% CI 1.53–1.65); older age and deprivation, ie marginalized, (both with a strong gradient); diabetes; severe asthma; and various other medical conditions. Compared with people with white ethnicity, Black and South Asian people were at higher risk even after adjustment for other factors (HR 1.48 and 1.44, respectively).


A broad spectrum of neurological complications: among 43 patients (29 with confirmed diagnosis) admitted to a London hospital, five major categories emerged: 1. Encephalopathies (n = 10) with delirium/psychosis and no distinct MRI or CSF abnormalities 2. Inflammatory CNS syndromes (n = 12) including encephalitis 3. Ischemic strokes (n = 8) 4. Peripheral neurological disorders (n = 8), seven with Guillain-Barré syndrome. 5. Miscellaneous central disorders (n = 5) who did not fit these categories.

Is the conjunctival epithelium a potential portal of infection? These authors doubt it. A brief review on current knowledge is given.

Severe COVID-19
This study examined the morphologic and molecular features of seven lungs obtained during autopsy from COVID-19 patients and found three distinctive angiocentric features: 1. Severe endothelial injury associated with intracellular virus and disrupted endothelial cell membranes. 2. Widespread vascular thrombosis with microangiopathy and occlusion of alveolar capillaries (9 times as prevalent as in patients with influenza). 3. significant new vessel growth through a mechanism of intussusceptive angiogenesis (2.7 x higher).

Comorbidities
Sickle cell disease (SCD) disproportionately affects Black or African-American persons in the United States and can cause multisystem organ damage and reduced lifespan. Among 178 persons with SCD in the US who were reported to an SCD–coronavirus disease case registry, 122 (69%) were hospitalized and 13 (7%) died. According to the authors, this is alarming, given that the mean patient age was < 40 years. However, there may be bias toward more severe cases in this registry.

Treatment
Brief overview on current trials evaluating synthetic interferons given before or soon after infection, in order to tame the virus before it causes serious disease. Controlled clinical trials are eagerly awaited.
Pediatrics


Of 100 children (median age 3 years), 21% were asymptomatic, 58% had mild disease, 19% had moderate disease, 1% had severe disease, and 1% were in critical condition. The incidence of transmission through apparent exposure to a family cluster was lower than that in other cohorts, possibly because of the late lockdown in Italy.

10 July

Epidemiology


A total of 200 high-risk frontline HCWs were enrolled between March 26 and April 8 in a prospective cohort study in an acute National Health Service hospital trust in London. 25% of HCWs were already seropositive at enrolment and a further 20% became seropositive within the first month of follow-up. Most infections occurred between March 30 and April 5, the week with the highest number of new cases in London.


What a depressing editorial. Don’t read this if you’re in a bad mood. Five months after WHO declared the SARS-CoV-2 outbreak a global health emergency, the virus continues to beat a concerning and complex path. For much of the globe, the worst may be yet to come.


There are no international or national conventions on pathogen screening associated with animals, animal products or their movements. Capacity for emerging infectious disease (EID) diagnostics is limited along much of the human-wildlife interface. EID risks associated with the wildlife trade remain the largest unmet challenge of current disease surveillance efforts. According
to this comment, an internationally recognized standard for managing wildlife trade on the basis of known disease risks should be established.

**Immunology**


Using a rapid antibody discovery platform, the authors isolated hundreds of human monoclonal antibodies (mAbs) against the SARS-CoV-2 spike protein. Antibodies could be grouped into five binding patterns on the basis of domain recognition and cross-reactivity. There were 178 mAbs that recognized the RBD domain and 43 that recognized the NTD domain. Most of the neutralizing antibodies (67/70) mapped to the RBD, revealing the RBD to be the principal site of vulnerability for SARS-CoV-2 neutralization.

**Transmission**


These researchers examined the added value of near real-time genome sequencing of SARS-CoV-2 in a subpopulation of infected patients during the first 10 weeks of COVID-19 containment in Australia. Genomic evidence was used to cluster 38.7% (81 out of 209) of cases for which the available epidemiological data could not identify direct links. This included clustering 12.4% (26 out of 209) of cases with a history of recent arrival from overseas with other cases without a travel history and 5.3% (11/209) of locally acquired cases with unknown epidemiological links. Twenty-two (10.5%) of the 209 cases were epidemiologically classified as ‘locally acquired—contact not identified’.


The effectiveness of masks to protect wearers from airborne particles is known to be a function of both materials and fit. The authors present a rapid testing protocol for evaluation of loose-fitting type masks to provide quanti-
tative, intercomparable data for particle removal efficacy of masks made with different types of fabrics and with different designs/fits, independently providing an assessment of the quality of the mask fit and the material used. Commercial surgical masks marketed for medical use had mean particle removal efficiencies from 50-75% when worn as designed but up to 90% when close fitting to the face under a nylon layer. Cloth masks tested had widely varying mean particle removal efficiencies (< 30% to near 90%), with some cloth masks achieving similar particle removal efficiencies as commercial surgical masks.

Diagnostics

Review of several hurdles and nuances which need to be addressed to deploy Ct value as a meaningful clinical metric. Facing the variability of specimen collection and different diagnostic platforms with varying sensitivity, laboratory professionals will need to develop a standard equivalency across their own diagnostic platforms and specimen types.

Clinical

This article reviews the extrapulmonary organ-specific pathophysiology, presentations and management considerations for patients with COVID-19 (248 references!). These conditions include thrombotic complications, myocardial dysfunction and arrhythmia, acute coronary syndromes, acute kidney injury, gastrointestinal symptoms, hepatocellular injury, hyperglycemia and ketosis, neurologic illnesses, ocular symptoms, and dermatologic complications.


The long-term effects on recovering patients remains unknown. According to this commentary, we must marshal our resources and develop strong collaborative approaches that combine clinical and sports medicine disciplines.
**Pediatrics**


In 78 cases of PIMS-TS reported by 21 of 23 centres in the UK, male patients (67%) and those from ethnic minority backgrounds (78%) were over-represented. In total, 36 (46%) were invasively ventilated and 28 (36%) had evidence of coronary artery abnormalities (18 aneurysms and ten echogenicity). Three children needed ECMO and two children died.

**11 July**

**Epidemiology**


In this school-based outbreak in Santiago, Chile identified on March 12, affecting nearly 50 people among school and household members, antibody positivity rates based on a self-administered test were 9.9% for 1,009 students and 16.6% for 235 staff. Among students, positivity was associated with younger age (p = 0.01), lower grade level (p = 0.05), prior RT-PCR positivity (p = 0.03), and history of contact with a confirmed case (p < 0.001). Among staff, positivity was higher in teachers (p = 0.01) and in those previously RT-PCR positive (p < 0.001). Teachers were more affected during the outbreak and younger children were at higher infection risk, likely because index case(s) were teachers and/or parents from preschool. Reopening schools should focus on avoiding new cases among teachers.

**Virology**

SARS-CoV-2 contains the furin cleavage PRRA motif in the S1/S2 region, which enhances viral pathogenicity but is absent in closely related bat and pangolin coronaviruses. It remains unknown if bat-like coronaviral variants without PRRA (ΔPRRA) can establish natural infection in humans. In this study, these variants were readily detected among acute patients, including a family cluster showing that these variants exist naturally and are currently transmitting in COVID-19 patients. Although these variants only consisted of a very small fraction in the wild type viral challenge stock, they were also consistently detected in intranasally inoculated hamsters.

Immunology


Delayed IFN-I response contributes to pathological inflammation whereas early IFN-I response controls viral replication. The authors performed single-cell RNA-seq using tens of thousands of peripheral blood mononuclear cells (PBMCs) obtained from 4 healthy donors, 8 patients with mild or severe COVID-19, and 5 patients with severe influenza. Patients with COVID-19 exhibited hyper-inflammatory signatures across all types of cells among PBMCs, particularly up-regulation of the TNF/IL-1β-driven inflammatory response as compared to severe influenza. The IFN-I response might contribute to the hyper-inflammatory response by potentiating TNF/IL-1β-driven inflammation in severe progression of COVID-19.

Transmission


While masking remains contentious, there is bipartisan agreement among policy makers that medical exemptions for masking are necessary and appropriate. Yet there is a dearth of guidance for clinicians on how to approach a request for an exemption. The authors analyze the medical and legal standards to guide this debate. In this evidence-free zone, clinicians must make individual determinations as to whether a patient should be exempt from mask wearing. There is no obligation to provide a mask exemption to patients if it is not medically warranted.
Clinical


Long time to recover: 143 patients discharged from the hospital after recovery from COVID-19 were assessed for follow-up post-acute care after a mean of 60 days after onset of the first COVID-19 symptom. Only 18 (12.6%) were completely free of any COVID-19 related symptom, while 32% had 1 or 2 symptoms and 55% had 3 or more. None of the patients had fever or any signs or symptoms of acute illness. Worsened quality of life was observed among 44.1% of patients. Many patients still reported fatigue (53%), dyspnea (43%), joint pain (27%) and chest pain (28%).

Severe COVID


This retrospective cohort study focussed on hematological and coagulation parameters in patients with moderate, severe, and critical COVID-19, along with specific analyses of coagulopathy in non-survivors. Among 380 patients, thrombocytopenia was more frequent in patients with critical disease (49%) than in those with severe (14%) or moderate (6%). In multivariate analyses, death was associated with increased neutrophil to lymphocyte ratio (odds ratio 5.39), thrombocytopenia (OR 8.33), prolonged prothrombin time (OR 4.94), and increased D-dimer (OR 4.41). The onset of sepsis-induced coagulopathy was typically before overt disseminated intravascular coagulation.


Careful comment on these findings. According to the author, the study is a valuable contribution to the knowledge of the coagulation profile of patients with COVID-19 and highlights the established role of routine coagulation tests as predictive variables for mortality and morbidity. However, the question of whether the observed changes in routine coagulation tests are just markers of the severity of illness or whether they show a significant and specific pathophysiology that drives morbidity and mortality in itself is still unanswered.

Interesting new finding: iloprost as a therapy to mitigate the pathological effects of COVID-19. Iloprost is a prostacyclin receptor agonist that promotes vasodilation of circulatory beds with minimal impact on hemodynamic parameters. It is licensed for the treatment of pulmonary arterial hypertension and is widely used for the management of peripheral vascular disease and digital vasculopathy, including digital ulcers and critical digital ischemia in systemic sclerosis. The authors describe three morbidly obese patients with severe COVID-19 and systemic microvasculopathy who obviously benefitted from its use. Its potential ability to reduce endothelial dysfunction and systemic inflammation could make iloprost a key player in management of COVID-19 vasculopathy.

Comorbidities


How will we deal with influenza next winter? Baloxavir marboxil (baloxavir) is a prodrug of the cap-dependent endonuclease inhibitor baloxavir acid and was approved as a single-dose treatment for uncomplicated influenza A and B in Japan and in the US in 2018. Among 752 household contacts of 545 index patients (96% influenza A) virus infection, the percentage in whom clinical influenza developed was significantly lower in the baloxavir group than in the placebo group (1.9% vs. 13.6%).

Uyeki TM. Baloxavir for Postexposure Prophylaxis against Influenza in Households. NEJM July 8, 2020. Full-text: https://doi.org/10.1056/NEJMe2022702

This editorial discusses some caveats of the above trial, including resistance issues. Moreover, 73% of the household contacts received baloxavir or placebo rapidly - within 24 hours after the onset of illness. Last but not least, clinicians are reminded that the primary prevention of influenza is through annual influenza vaccination. We have to be prepared next winter.
12 July

Epidemiology


Multiply deaths by nine. These authors created a “bereavement multiplier", an indicator that clarifies the downstream impact of COVID-19 mortality and can be applied to different epidemiological projections of death counts: how many people are at risk for losing a grandparent, parent, sibling, spouse, or child for each COVID-19 death. In the US, every death from COVID-19 will leave approximately nine bereaved.


Interested in bats these days? They are smart. And they know where they are. This article summarizes current research on the path-finding strategies of fruit bats. Bats do not systematically follow known routes, nor do they directly sense cues such as landmarks or beacons: they rely on a cognitive map frame of reference for their current positions in relation to a goal that they had not yet detected.

Clinical


Using national case-based surveillance and supplementary data reported from 16 jurisdictions, detailed characteristics of 10,647 COVID-19 deaths that occurred during February 12–April 24, 2020 are described. More than one third of Hispanic decedents (34.9%) and nearly one third (29.5%) of non-white decedents were aged < 65 years, but only 13.2% of white decedents were aged < 65 years. Most decedents had one or more underlying medical conditions reported (76.4%) or were aged ≥ 65 years (74.8%). Among reported underlying medical conditions, cardiovascular disease and diabetes were the most common.

Post-mortem histological analysis of the olfactory epithelium in two COVID-19 patients showed prominent leukocytic infiltrates in the lamina propria and focal atrophy of the mucosa. However, it is unclear whether the observed inflammatory neuropathy is a result of direct viral damage or is mediated by damage to supporting non-neural cells.


Based on ICU admission or death during hospital admission, 197 COVID-19 patients were compared with 354 patients in whom COVID-19 was ruled out (controls). At admission, anemia, leukocytosis and neutrophilia were more prevalent in controls than in COVID-19 patients. In agreement with recent reports, thrombocyte counts were lower in COVID-19 patients, and thrombocytopenia was associated with an increased risk of in-hospital mortality.

**Diagnostics**


The authors have determined analytical limits of detection for seven SARS-CoV-2 assays using serial dilutions of pooled patient material quantified with droplet digital PCR. Limits of detection ranged from ≤ 10-74 copies/mL for commercial high-throughput laboratory analyzers (Roche Cobas, Abbott m2000, Hologic Panther Fusion) and 167-511 copies/mL for sample to answer (Diasorin Simplexa, Genmark ePlex) and point-of-care instruments (Abbott ID NOW). The CDC assay yielded limits of detection ranging from 85-499 copies/mL, depending on the extraction method and thermocycler used.
Treatment


Discussion about the preliminary report on the large Phase III US trial of remdesivir (remember the Fauci press conference). Several letters elucidate the challenges arising from the dissemination of early results. The authors promise solemnly that they have begun to analyze the final data and will revise the report after that analysis is complete, including a more detailed analyses of the duration of illness and its relationship to baseline disease severity and outcomes, as well as concomitant medications during the trial. Why this seemingly takes months (perceived years), remains unclear. We are very curious.


Comparison of 78 patients who received tocilizumab (TCZ) and 76 who did not. TCZ-treated patients were younger, less likely to have chronic pulmonary disease, and had lower D-dimer values at time of intubation. In IPTW-adjusted models, tocilizumab was associated with a 45% reduction in hazard of death and improved status on the ordinal outcome scale. Though tocilizumab was associated with an increased proportion of patients with superinfections (54% vs. 26%, mainly S. aureus), there was no difference in 28-day case fatality rate among TCZ-treated patients with versus without superinfection. We urgently need adequately powered RCT.


The UK’s flagship COVID-19 clinical trial may help in this regard. Patients enrolled in the open label RECOVERY trial are randomised to standard care or to one of six treatment arms: hydroxychloroquine (now closed), dexamethasone (also closed, press release June 16), lopinavir/ritonavir, azithromycin, convalescent plasma, and, in a second randomisation for patients who deteriorate, the anti-inflammatory drug tocilizumab. The authors unpack the criticisms that still surround this mammoth task, of mounting a large scale trial amid the first major pandemic in 100 years in record time.
**Pregnancy**

Pregnancy outcomes at St George’s University Hospital, London, were evaluated in two periods: from October 2019 to January 2020 and from February to June 2020. The incidence of stillbirth was significantly higher during the pandemic period (9.31 per 1000) than during the pre-pandemic period (2.38 per 1000). Of note, the increase in stillbirths may have also resulted from indirect effects such as reluctance to attend hospital when needed, fear of contracting infection, or not wanting to add to the National Health Service burden. Changes in obstetric services may have played a role secondary to staff shortages or reduced antenatal visits, ultrasound scans, and/or screening.

**13 July**

**Virology**

Dry heat is bad, damp cold is good (for the virus). Dried SARS-CoV-2 virus on glass retained viability for over 3-4 days at room temperature and for 14 days at 4°C, but lost viability rapidly (within one day) at 37°C. SARS-CoV-2 in solution remained viable for much longer under the same different temperature conditions. Commonly used fixatives, nucleic acid extraction methods and heat inactivation were found to significantly reduce viral infectivity.


The authors have retracted this article (which has been discussed in the Virology chapter of the 4th issue of covidreference.com) after it came to the authors’ attention that in order to support the conclusions of the study, the authors should have used primary T cells instead of T cell lines. In addition, there were concerns that the flow cytometry methodology applied here was
flawed. These points resulted in the conclusions being considered invalid. The question remains why the reviewers (a highly ranked Cell journal would have at least 2-4 for each paper) did not see this. But again, good news: bad science will not stand the test of time.


While we're at it: See the title. The authors say no. It should also be noted that COVID-19 papers are being subjected to a high rate of scrutiny, which means that flaws are being detected more frequently than they might otherwise.

Transmission

Among 850 US residents participating in a survey, the authors found that social distancing compliance could be predicted by individual differences in working memory (WM) capacity. WM retains a limited amount of information over a short period of time at the service of other ongoing mental activities. Its limited capacity constrains our mental functions, such that higher WM capacity is often associated with better cognitive and affective outcomes. Of note, the unique contribution of WM capacity to the individual differences in social distancing compliance could not be explained by other psychological and socioeconomic factors (e.g., moods, personality, education, and income levels). The message that the authors hide using scientific language can be said more clearly: if you see a guy sitting in the bus not wearing a mask: poor idiot, don't get closer. His WM capacity is poor.

Clinical
Comprehensive review of multiple novel assays for SARS-CoV-2 diagnosis, including molecular and serologic-based tests, some with point-of-care testing capabilities.

**Prevention**


Again, put your masks in the sun. But not too often as at higher UV dosages and cycles, strengths of the material can be reduced. The maximum number of cycles under different conditions is still unclear. However, among 14 studies reporting on the different decontamination methods that might allow disposable N95 FFRs to be reused, ultraviolet germicidal irradiation (UVGI) and vaporized hydrogen peroxide (VHP) seem to be the most promising decontamination methods for N95 FFRs. This is based on their biocidal efficacy, filtration performance, fitting characteristics, and residual chemical toxicity, as well as other practical aspects such as the equipment required for their implementation and the maximum number of decontamination cycles.

**Clinical**


This literature review includes 61 articles on a wide array of cardiovascular manifestations (including heart failure, cardiogenic shock, arrhythmia, and myocarditis among others) and cardiac-specific biomarkers (including CK-MB, CK, myoglobin, troponin, and NT-proBNP) as prognostic tools. But who did review this review? In the methods, there is no date re: when this analysis was performed.

Interesting finding: among 49 confirmed COVID-19 patients with anosmia, there were no significant pathological changes in the paranasal sinuses on CT scans. Olfactory cleft and ethmoid sinuses appeared normal while in other sinuses, partial opacification was detected only in some cases. Conductive causes of anosmia (i.e., mucosal disease) do not seem play a significant role.


How many patients stay how long in which hospital unit? This work introduces statistical models and machine learning (ML)-based approaches that can be directly applied to real-world COVID-19 data to predict the patient discharge time from hospital and evaluate how the patient clinical information could have an impact on the length of stay in hospital. These estimations are important for decision-makers for efficient allocation of equipment and managing hospital overload.

**Treatment**


After reviewing all remdesivir studies until May 31, the authors make some recommendations on use. Remdesivir (5 days) should be prioritized for hospitalized patients requiring low-flow supplemental oxygen as it appears these patients derive the most benefit. The data also support some benefit in hospitalized patients breathing ambient air (if there is adequate drug supply). Current data do NOT suggest benefit for those requiring high-flow oxygen or either non-invasive or invasive mechanical ventilation. While it appears that progression of disease plays an important role in the efficacy of remdesivir, the amount of time from onset of symptoms does not.
14 July

**Epidemiology**


Outbreak in an hemodialysis unit in Barcelona, involving 18% of patients receiving treatment in this facility. In total, 22 symptomatic and 14 of the 170 asymptomatic patients became infected. The main risk factors for SARS-CoV-2 infection were sharing health-care transportation, living in a nursing home and having been admitted to the reference hospital within the previous 2 weeks.

**Virology**


No, dogs are not intermediate hosts. The authors clearly refute the conclusions of another group that dogs are a likely intermediate host of a SARS-CoV-2 ancestor, highlighting major flaws in the inference process and analysis.

**Immunology**


Not the first, but the largest study to date, analyzing the integrated immune analysis on a cohort of 50 COVID-19 patients with various disease severity. The picture is clearer now: SARS-CoV-2 infection is characterized by an absence of circulating IFN-β with all disease-severity grades. In addition, most severe COVID-19 patients display impaired IFN-α production that is associated with lower viral clearance and an exacerbated inflammatory response. Inflammation is partially driven by the transcriptional factor NF-κB and characterized by increased tumor necrosis factor (TNF)-α and interleukin (IL)-6 production and signaling.

Individuals in the population harbor single nucleotide polymorphisms (SNPs) across a variety of genes (eg, ACE2, TMPRSS2, HLA, CD147, MIF, IFNG, IL6) that have been implicated in the pathology and immunology of SARS-CoV-2 and other pathogenic coronaviruses. This well-written review gives an overview on current knowledge on host factors involved in coronavirus infections and proposes a large research agenda.


Among 294 anti-SARS-CoV-2 antibodies, IGHV3-53 was the most frequently used IGHV gene for targeting the receptor-binding domain (RBD) of the spike protein. Co-crystal structures of two IGHV3-53 neutralizing antibodies with RBD revealed that the germline-encoded residues dominate recognition of the ACE2 binding site. These IGHV3-53 antibodies show minimal affinity for maturation and high potency, which is promising for vaccine design.

Diagnostics
Mallapaty S. The mathematical strategy that could transform coronavirus testing. Nature 10 July 2020. Full-text: https://www.nature.com/articles/d41586-020-02053-6

If you are interested in math, then this article is for you (everyone else should avoid it). Beautiful mental exercise about how to best pool samples from as many people as possible, in order to save time and/or resources. It’s not that trivial. Some sophisticated strategies are discussed.

Clinical

In this retrospective multicentre study, 103/1,240 (8.3%) consecutive patients hospitalized for COVID-19 (patients who were directly admitted to an ICU were excluded) had evidence for PE. In a multivariable analysis, male gender,
anticoagulation with a prophylactic or therapeutic dose, elevated C-reactive protein, and time from symptom onset to hospitalization were associated with PE risk. PE risk factors in the COVID-19 context do not include traditional thromboembolic risk factors but rather independent clinical and biological findings at admission, including a major contribution of inflammation.


The more you know, the more afraid you’ll be of COVID-19. In this cross-sectional study on 15,704 German residents, trust in governmental actions to face COVID-19 and the subjective level of information regarding COVID-19 were negatively associated with mental health burden. However, the subjective level of information regarding COVID-19 was positively associated with increased COVID-19-related fear.

**Comorbidities**


The collateral damage is just as great. Using established transmission models, data indicate that in countries with a high burden of malaria, HIV and tuberculosis, COVID-19 related disruptions in care could lead to a loss of life-years of over 5 years, that is of the same order of magnitude as the direct impact from COVID-19. The authors estimate that deaths due to HIV, tuberculosis, and malaria over 5 years could increase by up to 10% due to HIV (mainly due to treatment interruptions), 20% to TB (less timely diagnosis and treatment of new cases), and 36% to malaria (interruption of planned net campaigns), respectively.

**Treatment**


COVID-19 patients have an altered gut microbiome. Well, okay, but who doesn’t? Several letters discuss whether probiotics represent a complemen-
tary approach for the prevention and restoration of SARS-CoV-2-induced mucosal damage or inflammation through the modulation of gut microbiota. Some groups are optimistic, others aren’t.
Notes
Notes
Here we publish in a single PDF the daily Top 10 scientific papers we have presented ever since COVID Reference’s first edition on 29 March 2020. There is no secret to our procedure: the daily scanning of the literature helps us to stay afloat in the never-ending waves of new publications about SARS-CoV-2 and COVID-19. Most papers discussed in the Top 10 will eventually make it into subsequent editions of COVID Reference.

We dedicate this book to our students. May this selection of approx. 1,000 fine articles and full-text links deepen their understanding of the new coronavirus and prepare them for the challenges ahead.