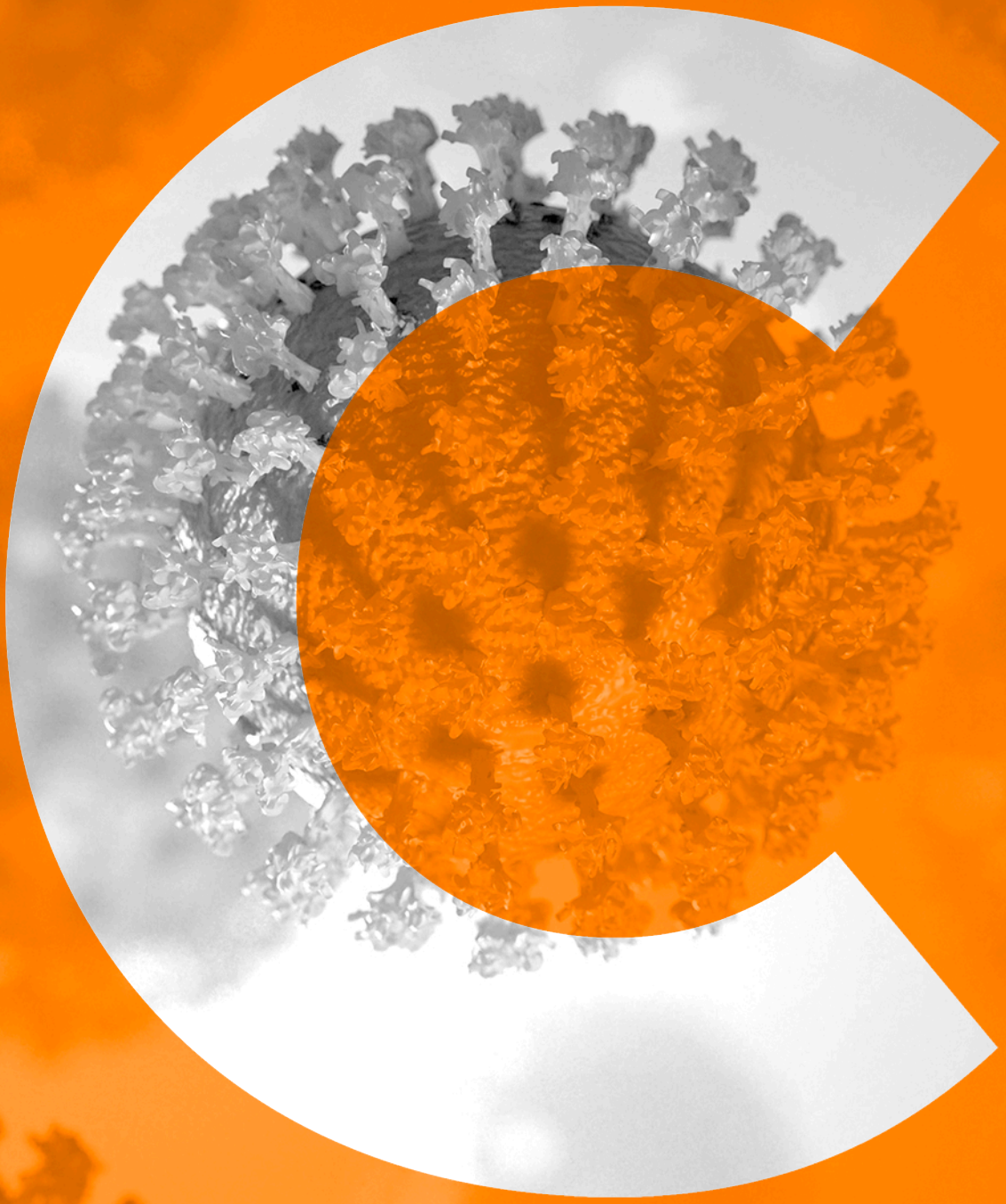

COVID-19 Epidemic Scientific Updates

2020
FEB - DEC

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COVID-19 EPIDEMIC

Epidemiological situation (13/02/2020):

-Globally:
46,997 confirmed cases* and 1,369 deaths
-Outside China (China includes Hong Kong):
447 cases, and 1 death
-25 affected countries

- Sustained virus transmission is suspected to be occurring in Singapore, where 50 cases have been reported.
- The number of passengers quarantined in the cruise ship off the coast of Yokohama has risen to 175 people. Japan is planning to test all passengers abroad.
- There are fears about virus circulating under the radar in African countries. The 13 countries most at risk based on volume of travel with China are: Algeria, Angola, Cote d'Ivoire, DRC, Ethiopia, Ghana, Kenya, Mauritius, Nigeria, South Africa, Tanzania, Uganda and Zambia.

*apparently, China has decided to change confirmation criteria (from 30 Jan onwards) so as to exclude asymptomatic individuals who test positive. They will be confirmed only if they develop symptoms.
https://www.nytimes.com/2020/02/12/world/asia/china-coronavirus-cases.html

Future scenarios:
WHO epidemiologist Mike Ryan discusses three possible scenarios:
- The outbreak will be halted and the virus eradicated, as with SARS (unlikely)
- The virus joins the other circulating coronaviruses, causing asymptomatic, mild and a few serious infections
- The virus returns in a seasonal manner, like influenza (most likely)

https://www.statnews.com/2020/02/04/two-scenarios-if-new-coronavirus-isnt-contained/
He also raises the question of how long immunity to SARS-CoV2 will last (it is not long-lasting for the other coronaviruses infecting humans), and how fast it mutates (doesn't seem to be mutating quickly in this outbreak. Maybe, like SARS, it has a proof-reading system that reduces its mutation rate).

Virus nomenclature
The WHO announced this week that it was naming the disease as COVID19. At the same time, the International Committee on Virus Taxonomy announced it was naming the virus SARS-CoV2.
Both names are currently being used, which causes some confusion.

Response
This week, the WHO held a 2-day global research and innovation forum in collaboration with GloPID-R to accelerate and fund priority research to stop this outbreak. Key gaps:

- Reservoirs
- Transmission dynamics
- Period of infectiousness
- Samples to use for diagnosis and monitoring

https://www.who.int/news-room/detail/12-02-2020-world-experts-and-funders-set-priorities-for-covid-19-research

Diagnosis
A paper in *Clin Infect Dis* suggests saliva as a promising non-invasive specimen for diagnosis and monitoring of SARS-CoV2 infection.
https://www.ncbi.nlm.nih.gov/pubmed/32047895

Incubation period
An analysis of infections among travellers from Wuhan estimates a mean incubation period of 6.4 days (95% credible interval: 5.6-7.7), ranging from 2.1 to 11.1 days (2.5th to 97.5th percentile). https://www.ncbi.nlm.nih.gov/pubmed/32046819

Symptoms
A study published last Friday in JAMA, with the first 138 patients diagnosed at one hospital in Wuhan found that:

- 41% of patients were presumed to be infected in that hospital
- About 10% of patients did not have the usual symptoms, but instead had diarrhea and nausea.
- Some patients who at first appeared mildly ill worsened after several days or a week

http://dx.doi.org/10.1101/2020.02.06.20020974

Case fatality rate:
WHO reported on Feb 7 that detailed data on 17,000 cases show that 82 percent are mild, 15 percent are severe and 3 percent are critical.
Less than 2% of patients who have fallen ill with 2019-nCoV have died, most often from multi-organ failure in older people and those with underlying health conditions.

Transmission
The question whether asymptomatic patients can transmit and how much this contributes to viral spread remains open. The NEJM report of an asymptomatic woman transmitting the virus to her colleagues in Germany before flying back to China was apparently flawed, but experts in China think that people with no or mild symptoms may be transmitting the disease. https://www.sciencemag.org/news/2020/02/paper-non-symptomatic-patient-transmitting-coronavirus-wrong

Reservoir

A study led by South China Agricultural University identified pangolins as probable intermediate hosts for SARS-CoV2. They found that the sequence of the coronavirus strain assembled from metagenomes was 99 percent identical to that of infected people in the recent coronavirus outbreak. http://www.xinhuanet.com/english/2020-02/07/c_138764153.htm

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COVID-19 EPIDEMIC

Epidemiological situation (21/02/2020):

-Globally:
75,748 confirmed cases and 2,129 deaths
-Outside China (China includes Hong Kong):
1,073 cases, and 8 deaths
26 affected countries

- Egypt reported its 1st confirmed case of COVID-19. This is the 2nd country in the WHO EMRO region to confirm a case, and the 1st reported case from the African continent. Case was asymptomatic but tested.
- Authorities in Iran have confirmed 3 new cases of the coronavirus a day after 2 people died from the infection in the city of Qom. Not clear if imported cases.
- The number of countries reporting local transmission (outside China) remains at 14 (Japan, Singapore, South Korea, Viet Nam, Malaysia, Australia, Thailand, USA, France,
Germany, Spain, UK, UAE, and Egypt).

Transmission, Incubation period, Symptoms

According to a comment in *Lancet*, COVID-19 seems to have different epidemiological characteristics from SARS-CoV:

- COVID-19 replicates efficiently in in the upper respiratory tract and appears to cause less abrupt onset of symptoms, similar to conventional human coronaviruses.
- In contrast with SARS, Infected individuals produce a large quantity of virus in the upper respiratory tract during onset, are mobile, and carry on usual activities, contributing to the spread of infection.

There seem to be 3 major patterns of the clinical course of infection: mild illness with upper respiratory tract presenting symptoms; non-life-threatening pneumonia; and severe pneumonia with acute respiratory distress syndrome (ARDS) that begins with mild symptoms for 7-8 days and then progresses to rapid deterioration.
https://www.thelancet.com/journals/lancet/article/PIIS0140-6736(20)30374-3/fulltext

Case fatality rate:

According to an analysis of all 72,342 cases diagnosed as of 11/02, the disease is mild for 81% of patients with a low overall CFR of 2.3% .
http://weekly.chinacdc.cn/en/article/id/e53946e2-c6c4-41e9-9a9b-fea8db1a8f51

Scenarios

A plausible scenario is that COVID-19 causes, like seasonal influenza, mild and self-limiting disease in most people who are infected, with severe disease more likely among older people or those with comorbidities. https://www.thelancet.com/journals/lancet/article/PIIS0140-6736(20)30374-3/fulltext

An analysis of cases in China indicates that COVID-19 spread quickly, taking only 30 days to expand from Hubei to the rest of Mainland China. While authorities note a levelling off of transmission, they caution there may be another increase in transmission as people return to work and school as the isolation measures are lifted. http://weekly.chinacdc.cn/en/article/id/e53946e2-c6c4-41e9-9a9b-fea8db1a8f51

Treatment

China has more than 80 running or pending clinical trials on potential treatments for COVID-19. New pharmaceutical drugs are listed beside thousand-year-old traditional therapies in a public registry of China's clinical trials. https://www.nature.com/articles/d41586-020-00444-3

Drugs being tested include: HIV-drug combination (lopinavir and ritonavir) and an experimental antiviral called remdesivir, which was shown to prevent MERS in monkeys. https://www.nih.gov/news-events/news-releases/remdesivir-prevents-mers-coronavirus-disease-monkeys

Convalescent plasma -- taken from the blood of recovered COVID-19 patients -- on 11 people with the virus has so far yielded positive results. A 300-person controlled trial — will test serum from COVID-19 survivors.

Chloroquine, an antimalarial agent, had responded well and was being tested on about 100 patients in Beijing and the southern province of Guangdong.

A computer model has been built to screen more than 70 000 drugs, eventually shortlisting about 100 existing medications for further experiment. https://www.nature.com/articles/d41586-020-00444-3

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COVID-19 EPIDEMIC

Epidemiological situation (27/02/2020):

-Globally:
82,132 confirmed cases and 2,801 deaths
-Outside China (China includes Hong Kong):
3,503 cases, and 54 deaths
46 affected countries

- For the first time, more new cases were reported outside China than in China.
- For China, the epidemic seems to have peaked between Jan. 23 and Feb. 2
- The WHO has not yet called it a pandemic but it urged countries to prepare for its arrival on the assumption that a declaration may come.
- The epidemic has picked up pace outside China and has entered a 'next-level phase', with a fast increase in cases over the last 6 days, mainly in Iran and Italy.
- 4 "new" countries reported confirmed cases in the Eastern Mediterranean region (Bahrain, Oman, Iraq and Afghanistan), with a history of travel from Iran.
- 3 "new" countries in Europe and 1 in North Africa reported cases with a link to travel from Italy (Croatia, Switzerland, Austria and Algeria) and Romania that hosted one of the infected cases (Croatia) from Italy and a first case was confirmed in South America (Brazil).
- The number of cases on the Diamond Princess continues to increase (705)

Case fatality rate:
The WHO Commission in China led by Bruce Aylward concluded that there is no data to support a huge amount of undetected cases, which means that the case fatality rate may not decrease significantly.

Diagnosis
ECDC-EU has updated its testing recommendation to test people with symptoms who have been a close contact of a case or have been in a place with presumed community spread of COVID-19.
https://www.ecdc.europa.eu/en/case-definition-and-european-surveillance-human-infection-novel-coronavirus-2019-ncov

An MRC analysis suggests that 2/3 of all COVID-19 cases exported from China have been missed
https://www.imperial.ac.uk/mrc-global-infectious-disease-analysis/news--wuhan-coronavirus/

A faulty diagnostic test issued by the CDC has limited the capacity to test for the virus in the US. Currently, only a dozen of laboratories are performing the test and less than 500 people have been tested.
https://www.washingtonpost.com/health/2020/02/25/cdc-coronavirus-test/
The recent case in California (with no travel history) indicates there is ongoing community transmission of the virus in the US.

China and Singapour both announced new serological diagnosis tests for COVID-19
https://www.scmp.com/week-asia/health-environment/article/3052311/coronavirus-singapore-bans-visitors-south-korean
https://www.prnewswire.com/news-releases/wuxi-diagnostics-integrated-testing-solution-for-covid-19-epidemiological-investigation-and-diagnosis-301012326.html

Transmission
An article in STAT highlights the importance of understanding the role of children in COVID-19 transmission, to guide public health decision such as closing down schools. Out of more than 44,000 confirmed cases in China, only 416 or about 1% of the total cases were >9 years old. None of them died. However, they could be playing a role in spreading the disease, as seen with flu.
https://www.statnews.com/2020/02/27/coronavirus-kids-what-role-transmission/

Virus
An article in Nat Microbiol confirms that human ACE2 is the receptor for SARS-CoV2, and that bypassing host protease processing during viral entry allows several beta lineage coronaviruses (including SARS-CoV2) to enter human cells.
https://www.ncbi.nlm.nih.gov/pubmed/32094589

Scientific community response
A group of scientists called the Wu-han Clan on the Slack platform is one example of how the COVID-19 outbreak is transforming the way scientists communicate during the crisis and are making ample use of preprint servers and social media.
https://www.sciencemag.org/news/2020/02/completely-new-culture-doing-research-coronavirus-outbreak-changes-how-scientists

Public health response
A comment in *Science* says what countries can do to prepare: hospitals can stockpile respiratory equipment and add beds. More intensive use of the vaccines against influenza and pneumococcal infections could help reduce the burden of those respiratory diseases on the health care system and make it easier to identify COVID-19 cases, which produce similar symptoms. Governments can issue messages about the importance of handwashing and staying home if you're ill.
https://www.sciencemag.org/news/2020/02/coronavirus-seems-unstoppable-what-should-world-do-now

Japan will close down schools starting next Monday
https://www.nytimes.com/2020/02/27/world/asia/japan-schools-coronavirus.html

The EC announced a financial contribution of 232M USD to fight the outbreak
https://ec.europa.eu/commission/presscorner/detail/en/IP_20_316
Germany announced an additional 3M contribution.

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03/03/2020

COVID-19 EPIDEMIC

Epidemiological situation (02/03/2020):

-Globally:
89,068 confirmed cases and 3,046 deaths
-Outside China (China includes Hong Kong):
9,037 cases, and 134 deaths
65 affected countries

- On Feb 29, the WHO raised the risk assessment to very high globally, due to the difficulty in identifying cases with non-specific symptoms and the potential for major impact on healthcare systems in some countries
- The WHO Commission in China concluded in its report that China's aggressive measures considerably slowed viral spread but measures may not work in other countries https://www.sciencemag.org/news/2020/03/china-s-aggressive-measures-have-slowed-coronavirus-they-may-not-work-other-countries
- Sub-Saharan Africa reported its first case, in Nigeria
- A case in Ecuador suggests that the virus was circulating in Spain since February
- Washington State, USA, issued a state of emergency after 6 deaths have occurred (3 of them in a nursing home). The US has been extremely slow in screening for COVID-19, partly due to the rollout of a faulty test kit.
- The WHO updated its guidance on global surveillance for infection with COVID
- As of Feb 27, 36,117 cases have recovered from COVID19 in China

The *NEJM* publishes a perspective by Bill Gates, discussing what countries can do over the next few weeks to slow the virus's spread and better prepare for the next crisis (strong healthcare systems, trained healthcare workers, better disease surveillance, safe vaccine platforms, international collaboration and data sharing)
https://www.nejm.org/doi/full/10.1056/NEJMp2003762

Diagnosis
A study with 82 infected individuals shows that viral loads in throat swab and sputum samples peaked at around 5–6 days after symptom onset, ranging from around 10^4 to 10^7 copies per ml. Sputum samples generally showed higher viral loads than throat swab samples. Around half of stool samples analysed were positive for RT-PCR although viral loads were around 10x lower.
https://www.thelancet.com/journals/laninf/article/PIIS1473-3099(20)30113-4/fulltext
Another study from Wuhan evaluating the fluorescence-based RT-PCR (Chinese CDC) suggests that nasopharyngeal swabs offer greater consistency than sputum samples.
https://www.medrxiv.org/content/10.1101/2020.02.12.20022327v2

Symptoms and Transmission (Children)

An article in *Clin Infect Dis* describes SARS-CoV2 infection in 10 children outside Wuhan. Disease is mild and epidemiological exposure is a key clue to recognising pediatric cases. Prolonged virus shedding is observed in respiratory tract and feces. https://www.ncbi.nlm.nih.gov/pubmed/32112072

Another article describes a 6 month old infant with high viral load in nasopharyngeal swabs but no symptoms. https://www.ncbi.nlm.nih.gov/pubmed/32112082

Treatment

The table below shows a summary of ongoing and planned clinical trials with repurposed drugs for COVID19 treatments. Remdesivir has showed encouraging results in vitro and in vivo.

Vaccine

Moderna therapeutics has shipped the first batches of its experimental COVID19 mRNA-based vaccine to the NIAID, which will start human tests in April (see Table) https://time.com/5790545/first-covid-19-vaccine/

Animal reservoir

A dog belonging to a patient in Hong Kong has tested positive for SARS-CoV2 (nasal and oral samples). The dog has not exhibited any clinical sings. Mammalian pets from households with confirmed human cases of COVID-19 will be placed under quarantine for 14 days as preventive measure https://promedmail.org/

New genetic analyses indicate that, although pangolins are still considered possible intermediate hosts, the mystery is “far from solved”. The genetic match between pangolin coronaviruses and SARS-CoV2 is not 99% as originally described, but 90%. https://www.nature.com/articles/d41586-020-00548-w

See Table below on Clinical Trials

I. Ongoing / planned clinical trials with repurposed drugs

(adapted from https://www.nature.com/articles/d41587-020-00003-1. Last search: 01/03/2020). Excludes stem cells, convalescent plasma and traditional Chinese medicines. All trials are being performed in China)

Drug or cocktail	Company or Sponsor	Mechanism and status	Clinical trials (date posted)
ASC09/ritonavir, lopinavir/ritonavir + or - umifenovir	Ascletis, AbbVie, Pharmstandard	ASC09: experimental HIV1 protease inhibitor. Ritonavir, lopinavir/ritonavir: approved HIV protease inhibitors. Umifenovir: approved entry inhibitor for influenza	At least three trials (e.g. ChiCTR2000029603, Feb 6, 2020)
ASC09/oseltamivir, ritonavir/oseltamivir, oseltamivir	Ascletis, Gilead, AbbVie	Oseltamivir: approved sialidase inhibitor for influenza	One trial (NCT04261270, Feb 7, 2020)
Azvudine	Zenghzhou Granlen PharmaTech	Experimental HIV1 reverse transcriptase inhibitor	One trial (ChiCTR2000029853, Feb 15, 2020)
Combinations of baloxavir marboxil/favipiravir and lopinavir/ritonavir	Shionogi, Toyama Chemical	Baloxavir marboxil: approved endonuclease inhibitor for influenza. Favipiravir: approved RNA polymerase inhibitor for influenza.	Two trials (ChiCTR2000029544, 3 Feb 2020, ChiCTR2000029554, 4 feb 2020)
Combinations of darunavir/cobicistat + or – lopinavir/ritonavir and thymosin α1		Darunavir: approved HIV1 protease inhibitor. Cobicistat: approved HIV1 Cytochrome P450 inhibitor. Thymosin a1: immune response boosting agent	Two trials (NCT04252274, Feb 5, 2020; ChiCTR2000029541, Feb 3, 2020)
Remdesivir*	Gilead	Adenine analog used for Ebola and Marburg.	Two trials (NCT04252664, 5 Feb 2020; NCT04257656, 6 Feb 2020)
Chloroquine or hydroxychloroquine	Shanghai Zhongxi Pharmaceutical, Shanghai Ziyuan Pharmaceutical, Wuhan Wuyao Pharmaceutical	Approved endosomal acidification fusion inhibitor, for malaria	At least ten trials (ChiCTR2000029826, Feb 2, 2020; NCT04261517, 14 Feb 2020)
Methylprednisolone	Generic	Anti-inflammatory corticosteroid	One trial (NCT04263402, Feb

			10, 2020)
Interferon α-2b + or – lopinavir/ritonavir and ribavirin **	Biogen, Merck	IFNα2b: cytokine with antiviral properties; ribavirin – guanine derivative	Two trials (NCT04254874, 5 Feb 2020, ChiCTR2000029308, 23 Jan, 2020)
Camrelizumab and thymosin	Incyte, Shanghai Hengrui Pharmaceutical	Camrelizumab: PD-1 monoclonal antibody	Two trials (ChiCTR2000029806, 14 Feb 2020, NCT04268537, 14 Feb 2020)
Tocilizumab	Chugai Pharmaceutical, Zhejiang Hisun Pharmaceutical, Jiangsu Qyun Bio-Pharmaceutical	Humanized mAb targeting interleukin 6	One trial (ChiCTR2000029765, 13 Feb 2020
Eculizumab	Hudson Medical	Distal complement modulator	One trial (NCT04288713, Feb 28, 20020)
Thalidomide + or – low-dose hormones	First Affiliated Hospital of Wenzhou	Immunomodulator	Two trials (NCT04273529, Feb 21, 2020; NCT04273581, Feb 21, 2020)

Most of the drugs in the above table inhibit key components of the coronavirus infection lifecycle. These include viral entry into the host cell (blocked by umifenovir, chloroquine or interferon), viral replication (blocked by lopinavir/ritonavir, ASC09 or darunavir/cobicistat, which inhibit the 3C-like protease (3CLpro)) and viral RNA synthesis (inhibited by remdesivir, favipiravir, emtricitabine/tenofovir alafenamide or ribavirin).

According to the WHO R&D Blueprint report released at the end of January:

- Remdesivir is considered the most promising candidate based on the broad antiviral spectrum and available in vitro and in vivo data (including studies in mice).
- Lopinavir/ritonavir alone or in combination with IFNbeta is considered a suitable second option for rapid implementation; ribavirin does not appear as worth further investigation.
- Other agents in Phase I clinical development such as a TMPRSS-2 inhibitor might merit further investigation, since SARS-CoV-2 uses angiotensin-converting enzyme 2 (ACE2) and the transmembrane protease serine 2 (TMPRSS2) to enter target cells
- Immunosuppressants and immunostimulators to be deprioritised due to potential harmful effects in mild illness.

II. Ongoing / planned clinical trials for vaccines

Vaccine	Company / Sponsor	Platform	Clinical trials (date posted)
mRNA-1273	National Insitute of Allergy & Infectious Diseases (NIAID) / US biotech Moderna	Lipid nanoparticle encapsulated mRNA coding for S protein of SARS-CoV2	Phase I trial (NCT04283461, Feb 25, 2020)
LV-DC/SMENP	Shenzhen Geno-Immune Medicla Institute	Lentiviral vector to modify dendritic cells for S and M viral protein expression	Phase I, II (NCT04276896, Feb 19, 2020)

Other vaccine initiatives announced (not yet registered as clinical trials): The Coalition for Epidemic Preparedness Innovation (CEPI) is funding:

- The Wistar Institute and Inovio, for DNA-based vaccine encoding SARS-CoV2 proteins
- NIAID / Moderna collaboration for mRNA vaccine (see Table above)
- University of Queensland for a vaccine composed of synthetic viral proteins stabilised with a molecular clamp
- CureVac for developing an mRNA printer to produce thousands of doses of mRNA vaccine encapsulated in lipid nanoparticles

GSK is offering its adjuvant platform to others, in collaboration with CEPI. BARDA and SANOFI Pasteur are developing their recombinant protein-based vaccine

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06/03/2020

COVID-19 EPIDEMIC

Epidemiological situation (06/03/2020; ECDC situation report):

-Globally:
98,171 confirmed cases and 3,385 deaths
-Outside China (China includes Hong Kong):
17,504 cases, and 341 deaths
82 affected countries

- The EU reports 5,544 confirmed cases (3,853 of them in Italy), in 27 countries and the ECDC classifies the risk of widespread and sustained transmission in the EU/EEA in the coming weeks as moderate to high.
- China reported 139 new cases on Thursday- all but 5 are in Hubei, suggesting the outbreak outside Hubei may be under control (https://twitter.com/HelenBranswell/status/1235404612779245570?s=20)
- To manage infodemics, WHO has developed an innovative communication strategy that leverages all communications platforms and utilizes trusted channels to amplify evidence-based accurate information. https://www.epi-win.com/advice-and-information/myth-busters

Virus

Science publishes the cryo-EM structure of full length ACE2 with or without the receptor binding domain (RBD) of the S protein of SARS CoV2. This will provide insights for coronavirus recognition and infection.
https://science.sciencemag.org/content/early/2020/03/03/science.abb2762

Chinese scientists published in *National Science Review* an article claiming there are two strains currently affecting humans, based on mutations at two sites. They suggest that SARS-CoV2 first crossed into humans and the ancestral strain (S) subsequently evolved into another lineage (L). Both are now apparently circulating. They also suggest that the L form may be more virulent, but this remains to be confirmed.
https://academic.oup.com/nsr/advance-article/doi/10.1093/nsr/nwaa036/5775463

Metatranscriptome sequencing for bronchoalveolar lavage fluid of 8 COVID19 patients found a median of 1-4 intra-host variants but no evidence for transmission of these variants to other persons. Authors recommend strengthened surveillance of viral evolution in the population https://www.ncbi.nlm.nih.gov/pubmed/32129843

Transmission

A paper in JAMA shows extensive environmental contamination by a SARS-CoV-2 patient with mild upper respiratory tract involvement, including toilet bowl and sink. Also shows that current measures to decontaminate surfaces are effective.
https://jamanetwork.com/journals/jama/fullarticle/2762692

A baby born by C-section to a woman infected with SARS-CoV2 was negative for the virus, suggesting that mother-to-child transmission is unlikely for this virus.
https://wwwnc.cdc.gov/eid/article/26/6/20-0287_article?deliveryName=USCDC_333-DM21761

Diagnosis
A NEJM report on 4 patients findings suggest that at least a proportion of 'recovered' patients still may be virus carriers.
https://jamanetwork.com/journals/jama/fullarticle/2762452

Symptoms
Data on the first 38 cases in the EU (all of them with history of travel to China) has been published
https://www.eurosurveillance.org/content/10.2807/1560-7917.ES.2020.25.9.2000178#html_fulltext

Treatment
WHO posts a flexible clinical trial protocol for hospitals around the world to test remdesivir vs placebo to facilitate pooling of data from many places. Other therapeutics (HIV drugs, etc) can be added. https://www.who.int/blueprint/priority-diseases/key-action/multicenter-adaptive-RCT-of-investigational-therapeutics-for-COVID-19.pdf?ua=1

A comment in *Nature Reviews Drug Discovery* discusses potential drug targets for beta-coronaviruses and the potential for repurposing existing antiviral agents to treat 2019-nCoV infection https://www.nature.com/articles/d41573-020-00016-0

Stat news reviews coronavirus drugs and vaccines in development
https://www.statnews.com/2020/03/02/coronavirus-drugs-and-vaccines-in-development/
(see also Table sent in the previous update)

ISGlobal

10/03/2020

COVID-19 EPIDEMIC

Epidemiological situation (09/03/2020; ECDC situation report):

-Globally:
114.243 confirmed cases and 4.023 deaths
-Outside China (China includes Hong Kong):
33.364 cases, and 884 deaths
115 affected countries

- The WHO has said the threat of a pandemic is real and encouraged aggressive action, as early as possible. For the moment, only a handful of countries have signs of sustained community transmission.
- A comment in *The Lancet* analyses how country-based mitigation measures will influence the course of the epidemic https://www.thelancet.com/journals/lancet/article/PIIS0140-6736(20)30567-5/fulltext
- Italian authorities have put the whole country in lockdown, while the situation in Spain (particularly Madrid) has considerably worsened. Schools, institutions and universities in Madrid have closed down. People have been recommended to stay at home when possible.
- Israel imposed quarantine for everyone entering the country

Transmission

A detailed analysis of nine mild COVID-19 cases (Germany) provides important information on viral shedding and infectiousness. Results indicate:

- Early and active virus replication in upper respiratory tract tissues (in contrast with SARS) despite low expression of ACE-2 receptor, followed by replication in lower tract (as in SARS)
- High pharyngeal virus shedding during the first week of symptoms (peak at 7.11 X 108 RNA copies per throat swab, day 4), indicating efficient transmission of SARS-CoV2 at a time when symptoms are appearing or mild (unlike SARS)
- Infectious virus readily isolated from throat and lung samples, but not from blood, urine or stool samples in spite of high virus RNA concentration in the latter.
- Decrease of infectiousness after day 10 of symptoms, despite high RNA levels in sputum
- Seroconversion around days 6-10, coinciding with slow but steady decline in sputum viral load

Preprint: https://www.medrxiv.org/content/10.1101/2020.03.05.20030502v1.full.pdf

A China study that followed 391 people who were diagnosed based on symptoms and their 1,286 contacts, suggests children are as likely to be infected as adults. Children under 10 who were potentially exposed to the virus were just as likely to become infected. It is still not clear whether children are important in transmitting.
https://www.medrxiv.org/content/10.1101/2020.03.03.20028423v1

Incubation period

A new study (Annals of Internal Medicine) estimates that the median time from exposure to onset of symptoms is 5.1 days. 97.5% of people who develop symptoms do so within 11.5 days. This supports the suggested quarantine period of 14 days. https://www.jhsph.edu/news/news-releases/2020/new-study-on-COVID-19-estimates-5-days-for-incubation-period.html

ISGlobal

13/03/2020

COVID-19 EPIDEMIC

Epidemiological situation (09/03/2020; ECDC situation report):

-Globally:
133,860 confirmed cases and 4.967 deaths
-Outside China (China includes Hong Kong):
52,906 cases, and 1,778 deaths
117 affected countries

- The WHO has declared a pandemic, arguing two main reasons: the speed and scale of transmission, and the lack of political commitment in some countries to control it.
- Italian authorities have closed all shops in the country (except supermarkets and pharmacies)
- The situation in Spain has considerably worsened. Schools, institutions and universities have closed down in several communities (Madrid, Catalonia…) and people have been recommended to stay at home when possible to help slow transmission and "flatten the curve" to avoid overwhelming health systems.
- The infectious disease modelling unit at LSTHM has calculated the R0 in countries with most COVID-19 cases currently, and shows that Spain and USA are the countries with the highest R0 (around 3 for Spain) https://cmmid.github.io/topics/covid19/current-patterns-transmission/global-time-varying-transmission.html

WHO has defined four transmission scenarios for COVID-19:
1. Countries with no cases (No cases);
2. Countries with 1 or more cases, imported or locally detected (Sporadic cases);
3. Countries experiencing cases clusters in time, geographic location and/or common exposure (Clusters of cases);
4. Countries experiencing larger outbreaks of local transmission (Community transmission).

This document describes the preparedness, readiness and response actions for COVID-19 for each transmission scenario. https://www.who.int/publications-detail/critical-preparedness-readiness-and-response-actions-for-covid-19

Another document provides technical guidance for government authorities, health workers, and other key stakeholders to guide response to community spread. https://www.who.int/publications-detail/responding-to-community-spread-of-covid-19

Transmission

Work shows that SARS-CoV-2 may live in the air for several hours and on some surfaces for as long as two days. This alone does not explain its higher transmissibility since similar data were observed with SARS.
https://www.medrxiv.org/content/10.1101/2020.03.09.20033217v1.full.pdf

To a certain extent, temperature could decrease COVID-19 transmission – in China, every 1°C increase in the minimum temperature led to a decrease of the cumulative number of cases by 0.86, according to an analysis.
https://www.medrxiv.org/content/10.1101/2020.02.22.20025791v1

The blood test result of a pet dog which had repeatedly tested weakly positive for COVID-19 virus is negative, indicating there was no infection (ProMed mail).

Case Fatality Rate: Risk factors

A study with 1079 patients of which 173 had severe disease, shows 23.7% had hypertension 23.7% and 16.2% diabetes mellitus.
https://www.nejm.org/doi/full/10.1056/NEJMoa2002032
Another study of 82 death cases also confirms that 78% of them had comorbidities, more than half had hypertension
https://www.medrxiv.org/content/10.1101/2020.02.26.20028

A Letter in *Lancet* provides an interesting explanation on why patients with hypertension and diabetes mellitus could have an increased risk of death upon COVID-19 infection. It postulates that ACE inhibitors and angiotensin receptor blockers (ARB) lead to overexpression of ACE2 overexpression, thereby facilitating infection by SARS-CoV2 https://www.thelancet.com/pdfs/journals/lanres/PIIS2213-2600(20)30116-8.pdf

In an interview with Bloomberg, one of the co-authors of the NEJM paper cited above also mentioned:

- of those who require invasive mechanical ventilation, most of those who recover are those who were put on invasive ventilation early.
- most patients can be cured without a specific anti-viral drug, but
- teamwork among specialists and nurses in intensive care units is fundamental
- pregnant women and children do not seem to be affected by the coronavirus in a serious manner

https://www.bloomberg.com/news/articles/2020-03-09/top-virus-doctor-says-high-blood-pressure-is-major-death-risk

ISGlobal

17/03/2020

COVID-19 EPIDEMIC

Epidemiological situation (09/03/2020; ECDC situation report):

-Globally:
180,159 confirmed cases and 7,103 deaths
-Outside China (China includes Hong Kong):
99,029 cases, and 3,877 deaths
Over 120 affected countries

- The WHO renews its call to all countries to 'test, test, test' all cases of suspected infection
- A comment in Science talks about the potential consequences of Covid-19 spread in Africa https://www.sciencemag.org/news/2020/03/ticking-time-bomb-scientists-worry-about-coronavirus-spread-africa
- Along the same line, Lancet publishes some reflections on COVID.19 preparedness in malaria endemic countries https://www.thelancet.com/journals/lancet/article/PIIS0140-6736(20)30561-4/fulltext

Approaches by Different Countries
Following the Italian example, Spain declared a national state of emergency on March 14, and closed all bars / restaurants and shops with the exception of supermarkets and pharmacies.

France followed on Monday 17, declaring a nation-wide lockdown for at least 15 days.

The UK on the other hand announced a response based on implementing restrictions for the most vulnerable people while betting on herd immunity among the "healthy population" in order to avoid a second peak at ends of this year. After some confusion, it seems they may be backtracking following a report issued by the Imperial College that concludes that the strategy would likely 'lead to hundreds of thousands of deaths'. https://www.imperial.ac.uk/media/imperial-college/medicine/sph/ide/gida-fellowships/Imperial-College-COVID19-NPI-modelling-16-03-2020.pdf

A mathematical modelling exercise estimates that 779 cases would have been exported by February 15, 2020 without any border or travel restrictions and that the travel lockdowns enforced by the Chinese government averted 70.5% of these cases. https://www.ncbi.nlm.nih.gov/research/coronavirus/publication/32170017

Another paper describes the combination of measures taken by Singapore to contain COVID19 and shares some early lessons learnt from the experience. https://academic.oup.com/jtm/advance-article/doi/10.1093/jtm/taaa039/5804843

Outbreak origin
According to Chinese government data, a 55 year-old from Hubei province could have been the first person to have contracted Covid-19 on November 17. From that date onwards, one to five new cases were reported each day and by December 20, the total number of confirmed cases had reached 60. So far at least 266 people who were

infected last year have been identified.
https://www.scmp.com/news/china/society/article/3074991/coronavirus-chinas-first-confirmed-covid-19-case-traced-back

Genomic epidemiology
Nextstrain.org/ncov provides updated information of genome samples of SARS-Cov-2 (currently showing 566 samples between Dec 2019 and March 2020).
Thanks Pau for the tip!

Transmission
A study in Science estimated SARS-CoV2 transmission dynamics during the early stage of the outbreak (10–23 January 2020). Analyses indicate that for every confirmed case of coronavirus, another 5 to 10 are were undetected. These cases are often milder and, on average, about half as infectious as confirmed ones -- but are responsible for nearly 80 percent of new cases. They conclude that a radical increase in the identification and isolation of currently undocumented infections would be needed to fully control SARS-CoV2 https://science.sciencemag.org/content/early/2020/03/13/science.abb

A study with SARS-CoV2 infected rhesus macaques found that the monkeys could not be re-infected, indicating that primary SARS-CoV-2 infection protects from subsequent exposures https://www.biorxiv.org/content/10.1101/2020.03.13.990226v1

Diagnosis
A comment in Lancet a series of acovid19 triage strategies for low income countries
https://www.thelancet.com/journals/lanres/article/PIIS2213-2600(20)30114-4/fulltext

Case Fatality Rate
A study estimated the case-fatality risk for Covid19 cases in China (3.5%); China, excluding Hubei Province (0.8%); 82 countries, territories, and areas (4.2%); and on a cruise ship (0.6%). Lower estimates might be closest to the true value, but a broad range of 0.25%-3.0% probably should be considered
https://www.ncbi.nlm.nih.gov/research/coronavirus/publication/32168463

Treatment
A viewpoint in JCI argues that human convalescent serum is an option for prevention and treatment of COVID-19 disease that could be rapidly available when there are sufficient numbers of people who have recovered and can donate immunoglobulin-containing serum. https://www.jci.org/articles/view/138003

A letter in Clinical Science provides rationale for soluble ACE2 as a potential therapy.https://www.ncbi.nlm.nih.gov/research/coronavirus/publication/32167153

Children
describe the clinical and epidemiological characteristics of 34 paediatric patients https://www.medrxiv.org/content/10.1101/2020.03.12.20034686v1

Health/well-being during Quarantine
A study assessed the health and wellbeing of 369 normal adults living and working after one month of public health emergencies into the COVID-19 outbreak in China. Those who suspended working reported worse health conditions as well as distress.
https://www.medrxiv.org/content/10.1101/2020.03.13.20034496v1

ISGlobal

20/03/2020

COVID-19 EPIDEMIC

Epidemiological situation (20/03/2020; ECDC situation report):

-Globally:
242,488 confirmed cases and 9,885 deaths
-Outside China (China includes Hong Kong):
161,151 cases, and 6,631 deaths
Over 120 affected countries

- Mainland China has gone 2 days without any locally transmitted cases
- The total number of confirmed cases reported from outside of China now represents 66.9% of the total number of reported cases. The epicenter has shifted to Western Europe.
- An editorial in *Nature* gives advice on what all governments must do now: follow World Health Organization advice, end secrecy in decision-making, and cooperate globally. https://www.nature.com/articles/d41586-020-00772-4

Virus

A study in Nature addresses the origin of SARS-CoV-2 and proposes two plausible scenarios: (i) natural selection in an animal host before zoonotic transfer; and (ii) natural selection in humans following zoonotic transfer.
https://www.nature.com/articles/s41591-020-0820-9

Transmission

The proportion of pre-symptomatic transmission was estimated at 48% (95%CI 32-67%) for Singapore and 62% (95%CI 50-76%) for Tianjin, China.
https://www.medrxiv.org/content/10.1101/2020.03.05.20031815v1

A study estimated that the proportion of asymptomatic cases on the Diamond Princess cruise ship was 17.9% (95% credible interval (CrI): 15.5-20.2%). Most infections may have occurred before the quarantine start.
https://www.ncbi.nlm.nih.gov/research/coronavirus/publication/32183930

Treatment

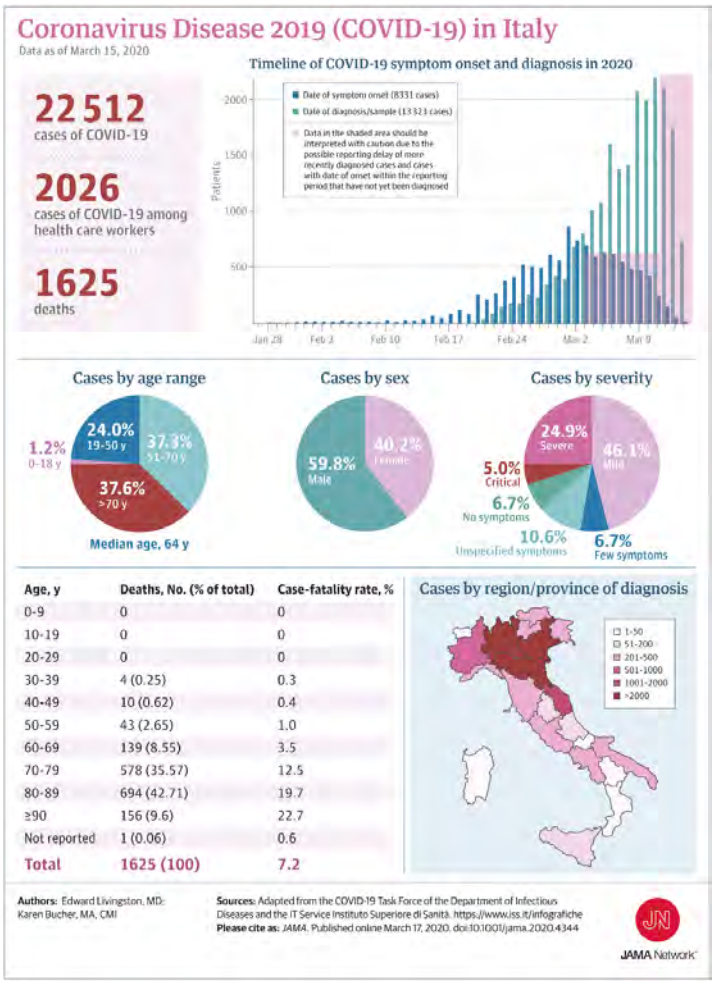
An initial trial with lopinavir/ritonavir in China with 199 patients showed no benefit as compared to standard care. https://www.nejm.org/doi/full/10.1056/NEJMoa2001282

A trial with anti-IL6-Receptor (Tocilizumab) on 20 severe COVID-19 patients reports that 19 patients were discharged an average of 13.5 days later, and that patients showed reduced lung lesions, fever, CRP and lymphopenia.
http://chinaxiv.org/abs/202003.00026

BMJ publishes a news story on using – or not- ibuprofen to manage COVID19. The conclusion is that further studies are needed but it may be "sensible to stick to paracetamol as first choice". https://www.bmj.com/content/368/bmj.m1086

Children
The NEJM describes a spectrum of illness from SARS-CoV-2 infection in children. In contrast with infected adults, most infected children appear to have a milder clinical course. https://www.nejm.org/doi/full/10.1056/NEJMc2005073

Case Fatality Rate
A study published in JAMA shows the most recent statistics emerging from Italy regarding the country's experience with #COVID-19.



Age, y	Deaths, No. (% of total)	Case-fatality rate, %
0-9	0	0
10-19	0	0
20-29	0	0
30-39	4 (0.25)	0.3
40-49	10 (0.62)	0.4
50-59	43 (2.65)	1.0
60-69	139 (8.55)	3.5
70-79	578 (35.57)	12.5
80-89	694 (42.71)	19.7
≥90	156 (9.6)	22.7
Not reported	1 (0.06)	0.6
Total	1625 (100)	7.2

The first preliminary description of outcomes among patients with COVID-19 in the United States indicates that fatality was highest in persons aged 85 years or older, ranging from 10% to 27%, followed by 3% to 11% among persons aged 65-84 years, 1% to 3% among persons aged 55-64 years, less than 1% among persons aged 20-54 years, and no fatalities among persons aged 19 years or younger.
http://dx.doi.org/10.15585/mmwr.mm6912e2

ISGlobal

27/03/2020

COVID-19 EPIDEMIC

Epidemiological situation (27/03/2020; ECDC situation report):

Globally:
378,041 confirmed cases and 16,365 deaths

- Globally, there has been an increase of 30,457 cases when compared with the data on 21 Mar 2020, with the USA accounting for 7434 cases of the newly confirmed cases, Italy accounting for 5560 cases, and Spain for 3272 of newly reported cases. The total number of confirmed cases reported from outside of China now represents 75.7% of the total number of reported cases.

- In Europe, Italy accounts for 28.8% of newly confirmed cases, Spain for 21.7%, and Germany for 13.8% (the total of these 3 countries accounting for 64.4% of newly confirmed cases in Europe).

- A letter in *Lancet* urges all countries to acknowledge the Italian lesson and to immediately adopt very restrictive measures to limit viral diffusion, ensure appropriate health-system response, and reduce mortality. https://www.thelancet.com/journals/lancet/article/PIIS0140-6736(20)30690-5/fulltext

- An estimation of the outbreak size in Italy on Feb 29 suggests the non-identification of 72% (61–79%) of cases. https://www.thelancet.com/journals/laninf/article/PIIS1473-3099(20)30227-9/fulltext

- Mozambique confirmed its first case of COVID19 http://opais.sapo.mz/mocambique-com-um-caso-confirmado-do-covid19

Virus

A unique furin cleavage site located between the residues 682 and 685 of the Spike protein, distinct from SARS-CoV and all other SARS-like coronaviruses, may be related to its high transmissibility. https://link.springer.com/article/10.1007%2Fs12250-020-00212-7

Diagnosis

The FDA approved the 1st coronavirus test that can be conducted entirely at the point of care for a patient - and deliver results in 45 minutes. The FDA granted "emergency use authorization" to Cepheid, a California company that makes a rapid molecular test for the coronavirus. The specimen can be collected either by a nasal swab or by a saline wash using a small catheter. The test is designed to operate on the company's automated GeneXpert Systems. The sensitivity and specificity of this test is not known. https://www.fiercebiotech.com/medtech/fda-greenlights-first-45-min-point-care-coronavirus-diagnostic

A report describes a potential RNA-based POC diagnostic device for detecting COVID-19 that combines both a paper-based POC diagnostic device and LAMP assay technology. It can be integrated with a smartphone application to provide a rapid, sensitive, and highly accessible COVID-19 diagnostic tool.
https://www.mdpi.com/2075-4418/10/3/165/htm

Drive through (DT) screening centers were designed and implemented in South Korea for safe and efficient COVID-19 screening The overall concept, advantages, and limitations of the COVID-19 DT screening centers are described
https://www.ncbi.nlm.nih.gov/research/coronavirus/publication/32193904

A study with 30 Chinese patients shows that posterior oropharyngeal saliva samples for diagnosis are a non-invasive specimen more acceptable to patients and health-care workers. Unlike severe acute respiratory syndrome, patients with COVID-19 had the highest viral load near presentation. Older age was correlated with higher viral load. It also shows that serological assays can complement RT-qPCR for diagnosis.
https://www.thelancet.com/journals/laninf/article/PIIS1473-3099(20)30196-1/fulltext

Along this line, a study with 208 plasma samples collected from 82 confirmed and 58 probable cases shows that the median duration of IgM and IgA antibody detection was 5 days (IQR 3-6), while IgG was detected on 14 days (IQR 10-18) after symptom onset. It concludes that the humoral response to SARS-CoV-2 can aid to the diagnosis of COVID-19, including subclinical cases.
https://www.ncbi.nlm.nih.gov/research/coronavirus/publication/32198501

A research team at Mount Sinai describes a serological enzyme-linked immunosorbent assays (ELISA) they developed using recombinant antigens derived from the spike protein of SARS-CoV-2, and how to replicate it.
https://www.medrxiv.org/content/10.1101/2020.03.17.20037713v1
A story in Science describes the above report and underlines the importance of widespread antibody testing https://www.sciencemag.org/news/2020/03/new-blood-tests-antibodies-could-show-true-scale-coronavirus-pandemic

Clinical Course

A study of viral RNA shedding patterns in 76 patients in China with mild and severe COVID-19 indicates that, similar to SARS, patients with severe COVID-19 tend to have a high viral load and a long virus-shedding period.
https://www.thelancet.com/journals/laninf/article/PIIS1473-3099(20)30232-2/fulltext
A study shows that the chest CT of COVID-19 patients is characterised by the onset of bilateral ground-glass lesions located in the subpleural area of the lung, and progressive lesions that result in consolidation with no migratory lesions.
https://www.ncbi.nlm.nih.gov/research/coronavirus/publication/32199619

Treatment

Clinical Trials

The WHO announced a large global trial, called SOLIDARITY to test what it considers to be the most promising therapies: remdesivir; chloroquine and hydroxychloroquine; lopinavir and ritonavir; and that same combination plus interferon beta. The trial will include many thousands of patients in dozens of countries, and has been designed to be

as simple as possible so that even hospitals overwhelmed by COVID-19 patients can participate. The design is not double-blind.
INSERM (France) announced it will coordinate an add-on trial in Europe, named Discovery, that will follow WHO's example and will include 3200 patients from at least 7 countries, including 800 from France. That trial will test the same drugs, with the exception of chloroquine.
https://www.sciencemag.org/news/2020/03/who-launches-global-megatrial-four-most-promising-coronavirus-treatments

A letter signed by Mitjà et al in *Lancet Global Health* describes a multicentre randomised controlled trial (NCT04304053) to evaluate the efficacy of antiviral treatment in anyone found to be infected, and the efficacy of prophylactic hydroxychloroquine in preventing secondary SARS-CoV-2 infections and symptoms among contacts (following the ring principle as was done for Ebola vaccination).
https://www.thelancet.com/journals/langlo/article/PIIS2214-109X(20)30114-5/fulltext

A comment in *Science* states that scientific evidence does not indicate that consumption of nonsteroidal anti-inflammatory drugs (i.e. ibuprofen) puts patients at risk of more severe disease.
https://science.sciencemag.org/content/early/2020/03/20/science.abb8034

A letter in *Lancet* examines the pros and cons of pharmacological immunosuppression in a critically unwell patient with COVID-19
https://www.thelancet.com/journals/lancet/article/PIIS0140-6736(20)30691-7/fulltext

Vaccine
Researchers in four countries (including the NL, Greece, Australia) will soon start a clinical trial to test whether the century-old TB vaccine can boost the immune response towards SARS-CoV-2 https://www.sciencemag.org/news/2020/03/can-century-old-tb-vaccine-steel-immune-system-against-new-coronavirus

Ethics
The *NEJM* publishes 6 recommendations on how to handle life or death decisions in the absence of sufficient equipment and supplies.
https://www.nejm.org/doi/full/10.1056/NEJMsb2005114

ISGlobal

27/03/2020

COVID-19 EPIDEMIC

Epidemiological situation (27/03/2020; ECDC situation report):

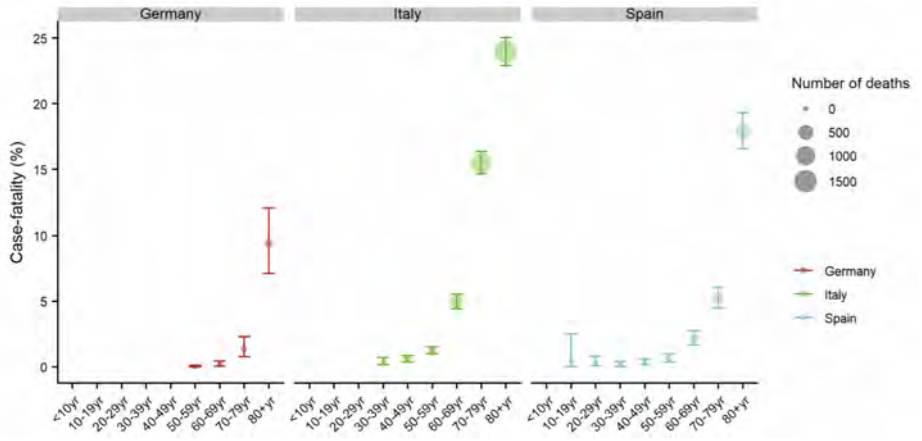
Globally:
467,710 confirmed cases and 20,947 deaths

- The USA has become number one for numbers of confirmed cases of COVID-19 (exceeding those in China)
- The WHO WhatsApp Health Alert has now attracted 10 million users since launching on March 20.
- The COVID-19 Solidarity Response Fund has raised more than USD 70 million, in just 10 days.
- The risk of healthcare system capacity being exceeded in the EU/EEA/UK in the coming weeks is considered high, according to ECDC's latest risk assessment
- A group of experts signs a request to the Spanish government for complete lockdown https://www.thelancet.com/lancet/article/s0140-6736(20)30753-4

Transmission
A study estimates the mean serial interval of COVID-19 (i.e. the time duration between a primary case-patient (infector) having symptom onset and a secondary case-patient (infectee) having symptom onset) at 3.96 days. 12.6% of case reports indicated presymptomatic transmission
https://wwwnc.cdc.gov/eid/article/26/6/20-0357_article?deliveryName=USCDC_333-DM23277 (paper posted one week ago)

Diagnosis
Nature biotechnology sums up the commercial rapid tests (molecular and serological) for SARS-CoV-2 that are being currently developed and could reach the market soon
https://www.nature.com/articles/d41587-020-00010-2

Symptoms, Clinical Course
ECDC's latest update includes 43,488 cases reported from 17 European countries:
-Hospitalisation occurred in 30% of cases reported and severe illness (requiring ICU and/or respiratory support) accounted for 4% of cases.
-Among hospitalised cases: Severe illness was reported in 15% (1 894 of 12 961 cases from 15 countries) and death occurred in 1 457 of 12 551 (12%) of hospitalised cases.
https://www.ecdc.europa.eu/sites/default/files/documents/RRA-seventh-update-Outbreak-of-coronavirus-disease-COVID-19.pdf



A paper in *The Lancet Resp Med* provides recommendations for the use of extracorporeal membrane oxygenation (ECMO) for patients with respiratory failure from acute respiratory distress syndrome (ARDS). It also gives recommendations for training health-care personnel, resolving equipment and facilities issues, implementing systems for infection control and personal protection, providing overall support for health-care staff, and mitigating ethical issues.
https://www.thelancet.com/journals/lanres/article/PIIS2213-2600(20)30127-2/fulltext

A Rockefeller University project seeks to identify gene mutations / polymorphisms that make some younger patients especially vulnerable to COVID-19 -kids and young adults hit hard by the illness who didn't have any of the usual risk factors, such as age or underlying illness. https://www.hhmi.org/news/patients-with-severe-forms-of-coronavirus-disease-could-offer-clues-to-treatment
Thanks Anna Massaneda for the tip!

Treatment
Hospitals in New York City are gearing up to use convalescent plasma to help keep people out of ICU. The FDA has classified convalescent plasma as an 'investigational new drug' against coronavirus, allowing scientists to test it in clinical trials, and use it compassionately to treat patients with serious or life-threatening COVID-19 infections. Johns Hopkins, the Mayo Clinic and Washington University in St. Louis, are planning to infuse patients at an early stage of the disease and see how often they advance to critical care. Another trial would enrol severe cases. The third would explore its use as preventive measure for people in close contact with confirmed cases.
https://www.nature.com/articles/d41586-020-00895-8

Vir Biotechnology, a San Francisco-based biotechnology firm, announced that two of its antibody drugs appeared to neutralize SARS-CoV-2 and that it would pursue testing them in people in three to five months https://www.statnews.com/2020/03/25/vir-biotechnology-reports-early-progress-in-antibody-treatment-for-covid-19/

The rheumatoid arthritis drug Sarilumab is set to enter a multicenter, double-blind, phase 2/3 trial program for patients hospitalized with severe COVID-19 infection. Sarilumab (Kevzara) – developed by Regeneron and Sanofi -- is a fully human, mAb that inhibits the interleukin-6 (IL-6) pathway by binding and blocking the IL-6 receptor. According to the researchers, advanced disease with hypoxemic pneumonia is associated with a marked pro-inflammatory state or 'cytokine storm' phenotype. https://bit.ly/2Uxd8Pn.

Along this line, tocilizumab, another IL-6 inhibitor, was used to treat 21 COVID-19 positive patients with severe illness patients with severe COVID-19 infection. Nineteen patients were discharged on average 13.5 days after the treatment with tocilizumab and the rest are recovering well https://www.ser.es/wp-content/uploads/2020/03/TCZ-and-COVID-19.pdf

Another group reviewed TH17 responses in patients with SARS-CoV-2 and proposed an FDA-approved JAK2 inhibitor (Fedratinib) for reducing mortality of patients with a TH17-type pro-inflammatory profile.
https://www.ncbi.nlm.nih.gov/research/coronavirus/publication/32205092

One Health

A US-based commercial company informed recently about the screening of "more than 4000 canine, feline, and equine specimens" from the US and South Korea with their new SARS-CoV-2 RealPCR Test. No positives were detected. They are expanding to canine and feline specimens in US, Canada and some European countries.
https://www.idexx.com/en/veterinary/reference-laboratories/idexx-sars-cov-2-covid-19-realpcr-test/

Cities for Health

Citiesforglobalhealth.org is sharing more than 80 initiatives designed to respond to the COVID19 outbreak and other global health challenges.
https://www.citiesforglobalhealth.org/
Thanks for the tip/tweet Raul!

Modeling

An interactive and instructive tool to play with, allows to see the impact of social distancing and its duration, as well as other factors, published in the NYT
https://www.nytimes.com/interactive/2020/03/25/opinion/coronavirus-trump-reopen-america.html

ISGlobal

31/03/2020

COVID-19 EPIDEMIC

Epidemiological situation (31/03/2020; ECDC situation report):

Globally:
777,798 confirmed cases and 37,272 deaths

- The World Health Organization launches an official app on iOS and Android to provide information on covid-19 *https://www.dailymail.co.uk/sciencetech/article-8159571/World-Health-Organization-launch-official-app-iOS-Android.html*
- Two roadmaps to end coronavirus confinement in the US have been proposed *The first,* by Ezekiel Emanuel, a health policy expert, suggests that a national shelter-in-place order over the next eight to 10 weeks, excluding essential services workers, should bring down transmission of the virus. Lockdowns could ease up in June, when case identification and contact tracing capacity should be deployed at large scale. https://www.nytimes.com/2020/03/28/opinion/coronavirus-economy.html *The second*, by Scott Gottlieb, former FDA chief and colleagues, envisions four phases. Phase 1 represents the current situation, in which the outbreak is growing. Only once certain thresholds are met — hospitals are able to cope with the flow of incoming patients and new cases have dropped in a particular area for at least 14 days — could Phase 2 begin, where schools and some other types of societal functions can resume, though people 70 and older and others at highest risk from the virus would still need to restrict their movements. Phase 3, the lifting of all restrictions, would only occur when a vaccine to prevent infection and therapeutics to save people who become infected are available. Phase 4 would entail planning to build the country's capacity to respond to the next biological threat. https://www.aei.org/research-products/report/national-coronavirus-response-a-road-map-to-reopening/ See also: https://www.statnews.com/2020/03/29/two-new-road-maps-lay-out-possible-paths-to-end-coronavirus-lockdowns/

- A Harvard Business Review article draws lessons from Italy. It says that what truly characterizes the effective responses of some Asian countries is the multitude of actions that were taken at once. Testing is effective when it's combined with rigorous contact tracing, and tracing is effective if combined with an effective communication system that collects and disseminates information on the movements of potentially infected people. It concludes that if policymakers want to win the war against COVID-19, it is essential to adopt an approach that is systemic, prioritizes learning, and is able to quickly scale successful experiments. https://hbr.org/2020/03/lessons-from-italys-response-to-coronavirus

- More than a dozen cruise ships remain stranded at sea right now, with covid19 cases and deaths (eg: 4 passengers have died and dozens have fallen ill on the Zaandam, which was stranded off the coast of Panama, and the Artania in Fremantle has 46 confirmed cases of COVID-19 on board).

Virus

Nature reports the identification of SARS-CoV-2-related coronaviruses in Malayan pangolins (*Manis javanica*) seized in anti-smuggling operations in southern China. They identify two sublineages of SARS-CoV-2-related coronaviruses, one that exhibits strong similarity to SARS-CoV-2 in the receptor-binding domain. The authors suggest that pangolins should be considered as possible hosts of novel coronaviruses and should be removed from wet markets. https://www.nature.com/articles/s41586-020-2169-0_reference.pdf

Transmission

A study analysing temperature and humidity conditions of over 100 countries with sustained SARS-CoV-2 transmission suggests that seasonality cannot be considered a key modulating factor of SARS-CoV-2 transmissibility.
https://cmmid.github.io/topics/covid19/current-patterns-transmission/role-of-climate.html

The Imperial College publishes a report where they used a model to infer the impact of ongoing interventions across 11 European countries. They estimate that, across all 11 countries, 7 to 43 million individuals have been infected with SARS-CoV-2 (up to 28th March), representing between 1.88% and 11.43% of the population. With current interventions remaining in place to at least ends of March, these interventions may have averted 59,000 deaths. In Italy, the effective reproduction number dropped to close to 1 around the time of lockdown. For most of the countries it remains too early to be certain that recent interventions have been effective.
https://www.imperial.ac.uk/media/imperial-college/medicine/sph/ide/gida-fellowships/Imperial-College-COVID19-Europe-estimates-and-NPI-impact-30-03-2020.pdf *Thanks for the tip/tweet Alberto García-Basteiro!*

A study reviews the role of super-spreaders in the ongoing pandemic. They argue that the slow transmission continuing in many countries and exponential propagation in others could be partly explained by cascading superspreading events. F.ex. in South Korea, during the 1st month of viral propagation there were only 2 to 3 reports of new infections per day. However, the rapid spread began after one case was linked to 3900 secondary cases in Daegu. They suggest that superspreaders generate new superspreaders by exposing susceptible people to large viral loads
https://www.researchgate.net/publication/340227854

Diagnosis

A new COVID-19 test from Abbott can return positive results in five minutes — and it can be run in a doctor's office. The test has been approved by the FDA (*molecular amplification, not by PCR, assume it is LAMP*)
https://www.theverge.com/2020/3/28/21197944/coronavirus-test-fast-doctors-office-abbott-fda

Symptoms, Clinical Course, CFR

A paper in *The Lancet Inf Dis* estimated the mean duration from onset of symptoms to death to be 17.8 days and to hospital discharge to be 24.7 days. The best adjusted estimate of the case fatality ratio in China is of 1.38% (1.23–1.53), with substantially higher ratios in older age groups (6.4% in those aged ≥60 years), up to 13.4% in those aged >80). The estimated overall infection fatality ratio for China was 0.66% (0.39–1.33), with an increasing profile with age.
https://www.thelancet.com/journals/laninf/article/PIIS1473-3099(20)30243-7/fulltext

A study has estimated infection and case fatality ratio for covid-19 based on data from the Princess Diamond cruise ship. Overall 3,063 PCR tests were performed among passengers and crew members. The all-age estimated cIFR on the Diamond Princess was 1.3% and the cCFR was 2.6%. For individuals 70 years and older, the cIFR was 6.4% and the cCFR was 13%
https://www.eurosurveillance.org/content/10.2807/15607917.ES.2020.25.12.2000256

The Host genetics initiative is bringing together the human genetics community to generate, share and analyze data to learn the genetic determinants of COVID-19 susceptibility, severity and outcomes. https://www.covid19hg.com/

Treatment

JAMA publishes a report of 5 critically ill patients (China) treated with convalescent plasma- 3 were discharged and 2 were stable.
https://jamanetwork.com/journals/jama/fullarticle/2763983

A study by Raoult et al. tested hidroxycholorquine and azithromycin in 80 patients with mild to severe symptoms. Authors claim clinical improvement and drop in viral load (83% of them negative at d7)
https://drive.google.com/file/d/1M_sj43FkGfiKE-7eaqIu0VsPHDWekC-i/view
However, the study (and a previous one by the same group) has received strong criticism on methodology and data reporting.

Another Chinese pilot study with 30 Covid-19 does not report benefit of the hydroxychloroquine treated group as compared to the control group.
http://subject.med.wanfangdata.com.cn/UpLoad/Files/202003/43f8625d4dc74e42bbcf24795de1c77c.pdf

Meanwhile, the FDA has approved the widespread use of hydroxychloroquine and chloroquine to treat COVID-19 in seriously ill patients.
https://www.washingtonpost.com/business/2020/03/30/coronavirus-drugs-hydroxychloroquin-chloroquine/

A letter in BMJ reviews candidate treatments for COVID-19
https://www.bmj.com/content/368/bmj.m1252

Vaccine

Peter Hotez and colleagues review the SARS-CoV2 vaccine pipeline. They conclude that a pan-coronavirus vaccine is urgently needed and appears to be scientifically feasible if sufficient resources are made available in due time
https://www.ncbi.nlm.nih.gov/research/coronavirus/publication/32219057

The Jenner Institute and Oxford Vaccine has started recruiting volunteers for their COVID-19 vaccine trial. The vaccine is based on the modified chimpanzee adenovirus vector expressing the spike proteins
https://twitter.com/jenneratingVacc/status/1243515685701144577?s=20

A study published one year ago, with SARS-CoV and macaques, suggests that anti-Spike antibodies may make disease worse by switching macrophages from a wound-healing to proinflammatory phenotype. May be relevant – or not- for SARS-CoV-2 vaccines expressing spike proteins https://insight.jci.org/articles/view/123158

Modeling

A team of mathematicians from the UB, UPC and Humboldt University in Berlin are developing a model to estimate the real number of infected people by COVID-19 https://underreported.cs.upc.edu/
Thanks Raul Toran for the tip

One Health
The medicine faculty in Liege reported that a coronavirus infection has been determined in a cat, which developed symptoms. They stress that this means human to animal transmission and not the other way round.
https://www.rtl.be/info/belgique/societe/un-premier-cas-de-transmission-du-covid-19-de-l-homme-vers-un-chat-confirme-a-liege-ce-n-est-pas-la-regle--1207988.aspx?dt=13:32

Others
The Portuguese government is granting citizenship rights to all migrants and asylum seekers to ensure they have access to social security and health care while the country battles the coronavirus. https://www.euronews.com/2020/03/29/coronavirus-portugal-grants-temporary-citizenship-rights-to-migrants

Planeloads of medical supplies from China are being flown to the US as part of a public-private partnership "Project Airbridge" designed to expedite delivery of badly needed equipment. Meanwhile, several countries have returned medical supplies imported from China; The Netherlands has recalled tens of thousands of "defective" face masks; Spain is returning 600,000+ rapid testing kits after one imported batch had just a 30% detection rate.

ISGlobal

COVID-19 EPIDEMIC

Epidemiological situation (03/04/2020):

-Globally:
46,997 confirmed cases* and 1,369 deaths
-Outside China (China includes Hong Kong):
447 cases, and 1 death
-25 affected countries

- Sustained virus transmission is suspected to be occurring in Singapore, where 50 cases have been reported.
- The number of passengers quarantined in the cruise ship off the coast of Yokohama has risen to 175 people. Japan is planning to test all passengers abroad.
- There are fears about virus circulating under the radar in African countries. The 13 countries most at risk based on volume of travel with China are: Algeria, Angola, Cote d'Ivoire, DRC, Ethiopia, Ghana, Kenya, Mauritius, Nigeria, South Africa, Tanzania, Uganda and Zambia.

*apparently, China has decided to change confirmation criteria (from 30 Jan onwards) so as to exclude asymptomatic individuals who test positive. They will be confirmed only if they develop symptoms.
https://www.nytimes.com/2020/02/12/world/asia/china-coronavirus-cases.html

Future scenarios:
WHO epidemiologist Mike Ryan discusses three possible scenarios:
- The outbreak will be halted and the virus eradicated, as with SARS (unlikely)
- The virus joins the other circulating coronaviruses, causing asymptomatic, mild and a few serious infections
- The virus returns in a seasonal manner, like influenza (most likely)

https://www.statnews.com/2020/02/04/two-scenarios-if-new-coronavirus-isnt-contained/
He also raises the question of how long immunity to SARS-CoV2 will last (it is not long-lasting for the other coronaviruses infecting humans), and how fast it mutates (doesn't seem to be mutating quickly in this outbreak. Maybe, like SARS, it has a proof-reading system that reduces its mutation rate).

Virus nomenclature
The WHO announced this week that it was naming the disease as COVID19. At the same time, the International Committee on Virus Taxonomy announced it was naming the virus SARS-CoV2.
Both names are currently being used, which causes some confusion.

Response
This week, the WHO held a 2-day global research and innovation forum in collaboration with GloPID-R to accelerate and fund priority research to stop this outbreak. Key gaps:

- Reservoirs
- Transmission dynamics
- Period of infectiousness
- Samples to use for diagnosis and monitoring

https://www.who.int/news-room/detail/12-02-2020-world-experts-and-funders-set-priorities-for-covid-19-research

Diagnosis
A paper in *Clin Infect Dis* suggests saliva as a promising non-invasive specimen for diagnosis and monitoring of SARS-CoV2 infection.
https://www.ncbi.nlm.nih.gov/pubmed/32047895

Incubation period
An analysis of infections among travellers from Wuhan estimates a mean incubation period of 6.4 days (95% credible interval: 5.6-7.7), ranging from 2.1 to 11.1 days (2.5th to 97.5th percentile). https://www.ncbi.nlm.nih.gov/pubmed/32046819

Symptoms
A study published last Friday in JAMA, with the first 138 patients diagnosed at one hospital in Wuhan found that:

- 41% of patients were presumed to be infected in that hospital
- About 10% of patients did not have the usual symptoms, but instead had diarrhea and nausea.
- Some patients who at first appeared mildly ill worsened after several days or a week

http://dx.doi.org/10.1101/2020.02.06.20020974

Case fatality rate:
WHO reported on Feb 7 that detailed data on 17,000 cases show that 82 percent are mild, 15 percent are severe and 3 percent are critical.
Less than 2% of patients who have fallen ill with 2019-nCoV have died, most often from multi-organ failure in older people and those with underlying health conditions.

Transmission
The question whether asymptomatic patients can transmit and how much this contributes to viral spread remains open. The NEJM report of an asymptomatic woman transmitting the virus to her colleagues in Germany before flying back to China was apparently flawed, but experts in China think that people with no or mild symptoms may be transmitting the disease. https://www.sciencemag.org/news/2020/02/paper-non-symptomatic-patient-transmitting-coronavirus-wrong

Reservoir

A study led by South China Agricultural University identified pangolins as probable intermediate hosts for SARS-CoV2. They found that the sequence of the coronavirus strain assembled from metagenomes was 99 percent identical to that of infected people in the recent coronavirus outbreak. http://www.xinhuanet.com/english/2020-02/07/c_138764153.htm

ISGlobal

COVID-19 EPIDEMIC

Epidemiological situation (03/04/2020, ECDC data):

Globally:
1,000,249 confirmed cases and 51,515 deaths

- New York state, with 75,983 cumulative case reports and 8658 newly confirmed cases over the past 24 hours, is clearly the epicentre of the outbreak in the USA.
- China announced it will include data about asymptomatic infections in its daily epidemic reports. 1541 asymptomatic cases are currently under medical observation on the Chinese mainland. The size of the asymptomatic carrier population has become one of the biggest risks to China's battle against the pandemic.
- As seen in China, South Korea is identifying increasing numbers of imported cases returning to the country. They have now identified 560 imported cases, with 60% confirmed in the community and not through airport screening.
- In Spain, of the 102,136 cases, 51,418 (50.3%) were hospitalized and 5,872 (5.7%) were admitted to the ICU. The crude reported case fatality rate was 8.9% with more deaths occurring than reported ICU admissions.

Stat has launched its covid-19 tracker
https://www.statnews.com/2020/03/26/covid-19-tracker/

ECDC published its update on COVID-19 infection prevention and control in healthcare settings https://www.ecdc.europa.eu/en/publications-data/infection-prevention-and-control-and-preparedness-covid-19-healthcare-settings

Taiwan's 'rapid and proactive response' is described in detail
https://www.sciencedirect.com/science/article/pii/S0929664620300814?via%3Dihub

The LSHTM conducted a survey among 1,356 UK adults and compared to data from a study conducted in 2006. They found a 73% reduction in the average daily number of contacts observed per participant which should lead to a substantial impact and decline in cases in the coming weeks https://cmmid.github.io/topics/covid19/current-patterns-transmission/comix-impact-of-physical-distance-measures-on-transmission-in-the-UK.html

Virus
A genomic survey of SARS-CoV-2 reveals multiple introductions into Northern California without a predominant lineage
https://www.medrxiv.org/content/10.1101/2020.03.27.20044925v1

NextSpain.uv.es. is a tool created by FISABIO and the Universidad de Valencia that allows to share and visualise viral genome data collected in Spain. The first 40 samples from Spanish patients are already uploaded. Data suggest multiple introductions of the virus into the country. https://www.vozpopuli.com/altavoz/next/Nace-herramienta-rastrear-coronavirus-Espana_0_1341767345.html

Testing
Scotland set up a community testing team to carry out sampling in the community. This enabled individuals to remain in self-isolation in their own homes and to prevent healthcare settings and services from being overwhelmed.
https://www.eurosurveillance.org/docserver/fulltext/eurosurveillance/25/12/eurosurv-25-12-4.pdf

An article in *Science* argues that a contact-tracing app which builds a memory of proximity contacts and immediately notifies contacts of positive cases can achieve epidemic control if used by enough people. By targeting recommendations to only those at risk, the epidemic could be contained without need for mass quarantines that are harmful to society. They also consider related ethical issues.
https://science.sciencemag.org/content/early/2020/03/30/science.abb6936.full
Thanks for the tip, Kate Whitfield!

According to Michael Ryan, executive director of the WHO Health Emergencies Program, a good benchmark of adequate number of tests performed is a ratio of 10 negative tests to 1. https://www.npr.org/sections/coronavirus-live-updates/2020/03/30/824127807/if-most-of-your-coronavirus-tests-come-back-positive-youre-not-testing-enough

Germany has its sights set on testing people who have recovered for antibodies to the virus, and issuing certificates that allow them to return to work
https://www.telegraph.co.uk/news/2020/03/29/germany-will-issue-coronavirus-antibody-certificates-allow-quarantined/

Symptoms
Almost 60% of patients who were subsequently confirmed as positive for COVID-19 reported losing their sense of smell and taste, compared with 18% of those who tested negative, according to data collected via a symptom tracker app developed by British scientists. They estimate some 50,000 people in Britain may have as yet unconfirmed COVID-19 infections https://www.reuters.com/article/us-health-coronavirus-taste/loss-oftaste-smell-key-covid-19-symptoms-british-scientists-study-idUSKBN21I3KE

An Italian survey also shows that loss of smell and taste are fairly frequent in patients with SARS-Cov2 infection and may precede the onset of full-blown clinical disease.
https://www.ncbi.nlm.nih.gov/research/coronavirus/publication/32215618

Clinical course, Case fatality rate
A paper raises the possibility that SARS CoV2 may be neurotropic and neuroinfection may contribute to pathophysiology of COVID19
https://onlinelibrary.wiley.com/doi/epdf/10.1111/apha.13473

A review article concludes that an inflammatory primary cytokine storm (i.e. mainly produced by alveolar macrophages, epithelial cells and endothelial cells) is common in patients with severe COVID-19 and that the immune systems was impaired in critical patients. The authors argue for the importance of a timely anti-inflammation treatment, at the right window time.
https://www.sciencedirect.com/science/article/pii/S1521661620301984?via%3Dihub

A review article discusses gastrointestinal features in covid19 and the possibility of faecal transmission.
https://www.ncbi.nlm.nih.gov/research/coronavirus/publication/32222988
However, no data on infectiousness of virus recovered from stool are provided, in contrast with a study (mentioned in a previous update) with a group of German patients, that found viral shedding but no evidence of infectious virus in stool and that has been published in Nature. https://www.nature.com/articles/s41586-020-2196-x

Out of 16 patients with COVID-19 who were treated and released from the Treatment Center of PLA General Hospital in Beijing, half kept shedding the virus even after resolution of their symptoms. The authors propose that more severe infections may have even longer shedding times. However, they did not test infectiousness https://www.atsjournals.org/doi/pdf/10.1164/rccm.202003-0524LE

CDC numbers show that 78% of US cases requiring ICU admission had at least 1 underlying condition.

Treatment
Hydroxychloroquine Trial: 62 patients suffering from mild to moderated COVID-19 were diagnosed and admitted to Renmin Hospital of Wuhan University. All participants were randomized in a parallel-group trial, 31 patients were assigned to receive an additional 5-day HCQ (400 mg/d) treatment. The HCQ group had a shorter time to clinical recovery and a larger proportion of patients with improved pneumonia (80.6%, 25 of 32) as compared with the control group (54.8%, 17 of 32).
https://www.medrxiv.org/content/10.1101/2020.03.22.20040758v2
Thanks Pau for the tip!

Soluble decoy receptors: A preprint in Cell (signed by a team at IBEC, Barcelona) suggests that human recombinant soluble ACE2 could inhibit SARS-CoV-2 infection. In vitro experiments with cell lines and organoids show that hrsACE2 can block early stages of viral infection.
https://www.cell.com/pb-assets/products/coronavirus/CELL_CELL-D-20-00739.pdf

Antibodies: A team of Chinese scientists has isolated several antibodies that it says are "extremely effective" at blocking the ability of the new coronavirus to enter cells. Team isolated 206 monoclonal antibodies from 19 patients. Two were extremely effective in blocking viral entry to the cell. hopes the antibodies can be tested on humans in six months. https://www.reuters.com/article/us-health-coronavirus-china-scientists/chinese-scientists-seeking-potential-covid-19-treatment-find-effective-antibodies-idUSKBN21J4QW

Vaccine
Johnson & Johnson (J&J) announced on 30 March that it and the U.S. government, through a military research agency, would together devote up to 1 billion USD to move a candidate product made by its Janssen division. Vaccine based on an engineered version of adenovirus 26 (Ad26) platform. J&J's chief scientific officer says the effort will be nonprofit and the vaccine will be accessible to all through some global mechanism still to be determined. https://www.sciencemag.org/news/2020/03/1-billion-bet-pharma-giant-and-us-government-team-all-out-coronavirus-vaccine-push

In a large-scale study, several clinics in Germany are to test whether the VPM1002 tuberculosis vaccine protects against Covid-19. The vaccine contains weakened tuberculosis-like bacteria and is based on the BCG vaccine, developed in the early 20th century. A phase III study in Germany will evaluate its effectiveness in older people and

healthcare workers https://www.berliner-zeitung.de/gesundheit-oekologie/tuberkulose-impfstoff-soll-Gegen-corona-einsesetzt-werden-li.79094

One Health

A study found that SARS-CoV-2 replicates poorly in dogs, pigs, chickens, and ducks, but efficiently in ferrets and cats.
https://www.biorxiv.org/content/10.1101/2020.03.30.015347v1

ISGlobal

COVID-19 EPIDEMIC

Epidemiological situation (07/04/2020, ECDC data):

Globally:
1,316,988 confirmed cases and 74,066 deaths

- Italy today had the lowest number of deaths reported since 19 March, together with a sustained decrease in patients admitted to intensive care.
- Transmission of SARS-CoV-2 in Spain appears to be levelling off and beginning a decrease
- Turkey is recording one of the steepest trajectories of new cases in the world, amid worries it might end up being a pandemic epicentre.
- Japan has declared a state of emergency in Tokyo, Osaka and 5 other COVID-19 hotspots; Prime Minister Shinzo Abe had come under fire for weeks of hesitating to take decisive action to stem the outbreak.
- The WHO director-general has endorsed the idea of creating a voluntary pool to collect patent rights, regulatory test data, and other information that could be shared for developing drugs, vaccines, and diagnostics. The concept was proposed two weeks ago by Costa Rican government officials https://www.statnews.com/pharmalot/2020/04/06/covid19-coronavirus-patents-voluntary-pool-world-health/
- A letter signed by Ilona Kickbusch and colleagues (Global Health Programme, Geneva) stresses that Covid-19 has taught us that 'health is the basis of wealth, that global health is no longer defined by Western nations and must also be guided by Africa and Asia, and that international solidarity is an essential response and a superior approach to isolationism'. https://www.bmj.com/content/369/bmj.m1336

Roadmaps to deconfinement

An article in the *Financial Times* describes how countries including France and Spain plan their exit strategies while seeking to avoid a second wave of infections.
https://www.ft.com/content/1fa5ae87-b3b6-4708-b9c5-58d2077b8d95

Virus

An analysis of the RNA of 68 coronaviruses, including SARS-CoV-2 and SARS, estimates that the ancestor of SARS-CoV-2 split 40 to 70 years ago from the closely related bat virus RaTG13 (which does not infect humans).
https://doi.org/10.1101/2020.03.30.015008

Testing

Our ISGlobal colleagues Garcia Basteiro et al. sign a comment in *Lancet Resp Med* on monitoring the COVID-19 epidemic in the context of widespread local transmission. Despite some limitations, the incidence of people admitted to hospital for COVID-19 seems a pragmatic indicator of transmission (and the time lag is shorter than for deaths). https://www.thelancet.com/pdfs/journals/lanres/PIIS2213-2600(20)30162-4.pdf

The UK government has pledged to carry out 100,000 tests for covid-19 per day in England by the end of April, ramping up its current capacity. Based on a five-pillar plan:

- Scale up swab testing in Public Health England laboratories and NHS hospitals for those with a medical need and key workers to 25,000 a day by mid to late April
- Deliver increased commercial swab testing for critical key workers in the NHS, later expanding to key workers in other sectors
- Develop antibody blood tests, currently being tested for validation, but not yet launched
- Conduct surveillance testing to learn more about the virus's spread and help develop new tests and treatments
- Build mass testing capacity at "a completely new scale" by working with industry, academia, and the NHS

https://www.bmj.com/content/369/bmj.m1392

The FDA approves a serological test, made by Cellex, to measure SARS-CoV-2-specific IgM and IgG antibodies. The test delivers results in about 15 minutes.
https://www.fda.gov/media/136622/download

The CDC announced three serosurvey studies: The first, which has already begun, will be looking at blood samples from people never diagnosed as a case in some of the nation's Covid-19 hot spots. Second, a national survey, using samples from different parts of the country, will be conducted. A third will look at special populations — health care workers are a top priority — to see how widely the virus has spread within them. https://www.statnews.com/2020/04/04/cdc-launches-studies-to-get-more-precise-count-of-undetected-covid-19-cases/comment-page-1/

A team of researchers will start analysing wastewater for the new coronavirus as a way to estimate the total number of infections in a community, Wastewater testing could also be used as an early-warning sign if the virus returns.
https://www.nature.com/articles/d41586-020-00973-x

Researchers from the University of Goettingen used estimates of COVID-19 mortality and time until death from a recent study in *Lancet Infectious Diseases*. Their data suggests that countries have only discovered on average about 6% of coronavirus infections, and the true number of infected people worldwide may already have reached several tens of millions. Germany, which has detected an estimated 15.6% of infections compared to only 3.5% in Italy or 1.7% in Spain. South Korea appears to have discovered almost half of all its SARS-CoV-2 infections. http://www.uni-goettingen.de/de/document/download/ff656163edb6e674fdbf1642416a3fa1.pdf/Bommer%20&%20Vollmer%20(2020)%20COVID-19%20detection%20April%202nd.pdf

Asymptomatic infections

China is rigorously testing arrivals from overseas for fear of importing a fresh outbreak of covid-19. A total of 130 of 166 new infections (78%) identified in the 24 hours to the afternoon of April 1 were asymptomatic, said China's National Health Commission. The *South China Morning Post* said that China had already found more than 43,000 cases of asymptomatic infection through contact tracing. These data seem to contradict a WHO report in February that suggested that the proportion of truly asymptomatic infections appears to be relatively rare https://www.bmj.com/content/369/bmj.m1375

From a total of 328 adults that were diagnosed with COVID-19 in Shanghai, 13 patients were asymptomatic at the diagnosis although they revealed slight laboratory abnormalities. Three patients developed symptoms later. Nine continued asymptomatic

even with pulmonary involvement. Only one had subclinical infection. Positive swab RT-PCR in asymptomatic patients suggests that they may have the potential to infect others, but viral load tests were not performed. No chronic asymptomatic carriers were found in the cohort. https://www.clinicalmicrobiologyandinfection.com/article/S1198-743X(20)30169-5/fulltext

In Northern Italy, 60 volunteers who thought they'd never suffered COVID-19 gave blood. 40 of them tested positive for antibodies to the virus.
https://www.lastampa.it/topnews/primo-piano/2020/04/02/news/coronavirus-castiglione-d-adda-e-un-caso-di-studio-il-70-dei-donatori-di-sangue-e-positivo-1.38666481

Transmission
A review of 31 studies concludes that masks had a consistent but small protective effect—particularly in shared public spaces. Evidence is too uncertain to support the widespread use of face masks but enough to support their use by vulnerable people for short periods when in temporary higher risk situations (shared public spaces transport or shops) https://medicalxpress.com/news/2020-04-mask-spaces-vulnerable-people-coronavirus.html

On the other hand, scientists detected coronavirus RNA in both coarse droplets and finer 'aerosol' droplets emitted by volunteers who were not wearing masks, whereas masks reduced detection of viral RNA in both types of droplet.
https://www.nature.com/articles/d41586-020-00502-w

Findings from 10 cases suggest that no SARS-CoV-2 virus existing in the vaginal fluids of severe COVID-19 patients.
https://www.ncbi.nlm.nih.gov/research/coronavirus/publication/32241022

Mechanisms
A paper in EMBO J shows that ACE2 and TMPRSS2 are predominantly expressed in a transient secretory cell type. These cells show an enrichment for pathways related to RHO GTPase function and viral processes, suggesting increased vulnerability for SARS-CoV-2 infection.
https://www.ncbi.nlm.nih.gov/research/coronavirus/publication/32246845

Clinical course, Case fatality rate
Italian researchers mined around 7000 exomes from the Network of Italian Genomes (NIG) looking for ACE2 variants. A number of variants with a potential impact on protein stability were identified including three missense changes which have never been reported in the Eastern Asia population. The findings suggest that a predisposing genetic background may contribute to the observed inter-individual clinical variability associated with COVID-19.
https://www.medrxiv.org/content/10.1101/2020.04.03.20047977v1

A meta-analysis concludes that Neutrophil-to-Lymphocyte ratio (NLR) and Lymphocyte-to-C-reactive protein ratio (LCR) are established inflammation markers that help predict clinical severity in patients with COVID-19.
https://www.ncbi.nlm.nih.gov/research/coronavirus/publication/32242950

Treatment
A French team posts a case report on successful treatment of a patient with respiratory failure related to Covid-19 and treated with tocilizumab.
https://www.annalsofoncology.org/article/S0923-7534(20)36387-0/pdf

In vitro experiments show that ivermectin is an inhibitor of SARS-CoV-2: a single treatment of Vero cells led to a 5000-fold reduction in virus after 48h of culture.
https://www.sciencedirect.com/science/article/pii/S0166354220302011
As Carlos Chaccour points out, the concentration needed to cut viral replication in half is 50-fold more than the concentration normally used in humans, but ivermectin is worth investigating in controlled clinical trials.

A mini review summarizes the pharmacokinetic characteristics of favipiravir and possible drug-drug interactions from the view of drug metabolism.
https://www.ncbi.nlm.nih.gov/research/coronavirus/publication/32246834

A research team from VIB in Ghent identified two llama antibodies that bind the SARS-CoV-2 spike proteins and could be further explored as treatment
https://doi.org/10.1101/2020.03.26.010165

Sera of mice treated with pseudotyped SARS exhibited low titer of SARS-CoV2 neutralization activity, implying that it may not be practical to treat covid-19 with anti-SARS antibodies and that people with history of SARS infection many years ago may not be resistant to 2019-nCoV infection.
https://link.springer.com/article/10.1007/s12250-020-00214-5

Vaccine
The Norway-based Coalition for Epidemic Preparedness Innovations (CEPI) calls for investing in manufacturing capacity for candidate vaccines, and even beginning full-scale manufacturing before we know if the vaccine even works. This could cost tens of billions of dollars. CEPI is supporting eight vaccines at this point (including the mRNA vaccine from Moderna-NIAID that has started clinical trials) and will announce a couple more soon. https://www.statnews.com/2020/04/07/pandemic-expert-calls-for-making-coronavirus-vaccines-before-we-know-they-work/

One Health
In the Bronx Zoo, NY, 2 Malayan tigers, 2 Amur tigers, and 3 African lions developed respiratory signs over the course of a week**.** Swabs yielded presumptive positive results for SARS-CoV-2, presumably transmitted from a zoo keeper. (ProMed mail)

Others
A letter in *Lancet Public Health* calls for adoption of modern strategies to increase communication between patients and family. F.ex. volunteers can help patients use devices and record and share messages to their family, thereby improving their quality of life. Enhancing communication during this outbreak might also help the emotional burden on affected families and health-care workers
https://www.thelancet.com/pdfs/journals/lanpub/PIIS2468-2667(20)30079-7.pdf

The UCL, LSHTM, University of York and EPPI Centre have developed a "living map" of scientific evidence on COVID-19:
http://eppi.ioe.ac.uk/COVID19_MAP/covid_map_v5.html
Thanks for the tip, Nuria Balanza!

ISGlobal

COVID-19 EPIDEMIC

Epidemiological situation (10/04/2020, ECDC data):

Globally:
1,563,857 confirmed cases and 95,044 deaths

- Almost 90 per cent of the world's students are now affected by nationwide school closures -- that's more than 1.5 billion children and young people. Together with UNICEF and the International Publishers Association, the World Health Organization has launched the 'Read the World' children's reading initiative. https://www.who.int/news-room/detail/02-04-2020-ipa-who-and-unicef-launch-read-the-world-on-international-children-s-book-day-to-support-children-and-young-people-in-isolation
- New research indicates that the coronavirus began to circulate in the New York area by mid-February, weeks before the first confirmed case, and that travelers brought in the virus mainly from Europe, not Asia. https://www.nytimes.com/2020/04/08/science/new-york-coronavirus-cases-europe-genomes.html
- Mario Ferrari, president of the European Union's ERC scientific research council, has resigned claiming he "lost faith in the system after he failed to set up a special programme for the coronavirus" https://www.bbc.com/news/world-europe-52212390
- A list of ERC-funded research projects related to coronavirus (3 from Spain) can be found here https://erc.europa.eu/list-erc-funded-research-projects-related-coronavirus (*Thanks Raul Toran for the tip!*)

Roadmaps to deconfinement
The German Society for Hospital Hygiene has issued a document detailing the most important next steps for the transition from Phase 1 to Phase 2:
1. Extension of testing and strategic use of testing with priority for members of the critical infrastructure
2. Maximum ensuring adequate protection for staff in hospitals, nursing homes, home care services as well as for the employees inside the critical care areas
3. Maximum protection of the residents of nursing homes as well as persons with an increased risk of infection in the family or other private environment
4. Strict separation of infected and non-infected individuals, creation of alternative accommodation for Infected to relieve the private milieu of persons at risk.
5. focus of crisis management at reducing the number of cases of severe infections in intensive care, as opposed to a reduction in the overall infection numbers regardless of the risk profile of those infected
6. Extension of the emergency task forces and expert groups by specialists in hygiene, occupational safety and clinical disciplines, for diagnostic and therapeutic quality of medical care and protection of staff and with patients from infection
https://www.krankenhaushygiene.de/ (and attached doc)

The German National Academy of Sciences Leopoldina has issued a series of recommendations – in addition to the existing recommendations for physical distancing and hygiene- that include the use of masks in public, the short-term use of

mobile phone data, and increase in testing capacities.
https://www.leopoldina.org/en/press-1/news/ad-hoc-statement-coronavirus-pandemic/
Thanks Kurt Straif for the info!

Testing
An analysis by the Centre for Mathematical Modelling of Infectious Diseases uses a delay-adjusted case fatality ratio to estimate under-reporting of COVID-19 cases in different countries. The analysis uses a CFR baseline of 1.4%. It estimates that the proportion of symptomatic cases reported for Spain is 5.4%. For South Korea, Israel, South Africa and Australia it would be above 50%.
https://cmmid.github.io/topics/covid19/severity/global_cfr_estimates.html

A study describes the validation and test of various antigens in different in-house and commercial ELISAs for detection of SARS-CoV-2 antibodies in sera of patients.
https://www.ncbi.nlm.nih.gov/research/coronavirus/publication/32267220

Risk Factors
An analysis performed by a Harvard University team suggests that people living in areas with higher air pollution levels are more likely to die from COVID-19 than those living in cleaner areas. The research indicates that even a small increase in fine particle levels is associated with a 15% increase in the death rate.
https://projects.iq.harvard.edu/covid-pm
Another Italian study also notes that the high fatality rates observed in the north of the country correlate with the highest levels of air pollution.
https://www.sciencedirect.com/science/article/pii/S0269749120320601
In this sense, data from China already suggested that smokers seemed to be more susceptible to severe forms of disease
https://www.preprints.org/manuscript/202002.0408/v1

Black American men in the US are dying in much higher numbers. Reasons likely include higher exposure (less prone to telework), risk factors (obesity, diabetes), health care access. https://www.theguardian.com/world/2020/apr/08/its-a-racial-justice-issue-black-americans-are-dying-in-greater-numbers-from-covid-19

A comment in *Nature* discusses COVID-19 in humanitarian settings and lessons learned from past epidemics. Refugees and migrants are among the most vulnerable people during a pandemic—to both the virus itself and the measures enacted to control it. https://www.nature.com/articles/s41591-020-0851-2

Symptoms
A survey study with 417 mild-to-moderate COVID-19 patients from 12 European hospitals indicates that the most prevalent general symptoms consisted of cough, myalgia, and loss of appetite. 85.6% and 88.0% of patients reported olfactory and gustatory dysfunctions, respectively. Females were significantly more affected by olfactory and gustatory dysfunctions than males.
https://www.ncbi.nlm.nih.gov/research/coronavirus/publication/32253535

Treatment
A literature review summarises the state of clinical research for COVID-19, highlights the research gaps, and provides recommendations for the implementation of standardised protocols. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7125419/

Science Translational Med describes an orally bioavailable broad-spectrum antiviral (the ribonucleoside analog NHC/EIDD2801) with broad spectrum antiviral activity against SARS-CoV-2, SARS, MERS and related Bat-CoVs. Prophylactic and therapeutic administration of EIDD2801 was effective in mice infected with SARS and MERS. https://stm.sciencemag.org/content/early/2020/04/03/scitranslmed.abb5883

Immune modulation: A meta-analysis of papers reporting IL6 levels in COVID patients finds evidence that circulating IL6 levels are closely related with severity of disease https://www.sciencedirect.com/science/article/pii/S0399077X20300883
A report of 15 patients with COVID-19 treated with Tocilimuzab (a mAb against IL6) indicates that it appears to be an effective treatment option in COVID-19 patients with a risk of cytokine storm. For critically ill patients with elevated IL-6, repeated doses of the TCZ is recommended.
https://www.ncbi.nlm.nih.gov/research/coronavirus/publication/32253759

Using single-cell RNA sequencing of bronchoalveolar lavage fluid, a preprint in *Nat Rev Immunol* describes a dysregulation of lung myeloid cells in COVID-19depletion of tissue-resident alveolar macrophages and the accumulation of monocyte-derived inflammatory macrophages associate with disease severity
https://www.nature.com/articles/s41577-020-0303-8

Chloroquine**:**
A brief report in JCI discusses the optimization of hydroxychloroquine dosing in intensive care unit COVID19 patients https://academic.oup.com/cid/advance-article/doi/10.1093/cid/ciaa394/5816960
The *Science Translational Medicine* blog publishes a post exploring evidence from small trials and preprints that hydroxychloroquine is not effective against COVID-19
https://blogs.sciencemag.org/pipeline/archives/2020/04/06/hydroxychloroquine-update-for-april-6

Convalescent Plasma
According to the Globe and Mail, Canada is beginning the world's largest clinical trial for treating COVID-19 with convalescent plasma against COVID-19. The study will involve 1,000 patients in at least 40 hospitals
https://www.theglobeandmail.com/canada/article-canada-begins-clinical-trial-of-experimental-covid-19-treatment-using/
The FDA approved a clinical trial specifically for Johns Hopkins that will allow its researchers to test convalescent plasma as a means of preventing healthy people, notably front-line medical staff, from getting sick.https://hub.jhu.edu/2020/04/08/arturo-casadevall-blood-sera-profile
A Review in JCI provides an overview of convalescent plasma, from evidence of benefit, regulatory considerations, logistical work flow and proposed clinical trials
https://www.jci.org/articles/view/138745

According to the South China Morning Post, some patients discharged from a Shanghai hospital show very low levels of antibodies, casting doubt on their level of protection.
https://www.scmp.com/news/china/science/article/3078840/coronavirus-low-antibody-levels-raise-questions-about *These early findings are to be taken with caution.*

A case report describes 3 patients with severe COVID-19 who received high-dose intravenous immunoglobulin (IVIg- polyclonal IgGs recovered from health patients) with satisfactory recovery.
https://academic.oup.com/ofid/article/7/3/ofaa102/5810740

A literature review summarises the state of clinical research for COVID-19, highlights the research gaps, and provides recommendations for the implementation of standardised protocols. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7125419/

Children

JAMA publishes a report of severity of COVID19 in children, during the first 2 weeks of the epidemic in Madrid. 41 of 365 children screened were positive (0.8% of total confirmed cases). The median age of positive children was 1 year. 25% was hospitalised and 9% were in intensive care. None died.
https://jamanetwork.com/journals/jamapediatrics/fullarticle/2764394

A review summarises what we know of COVID19 in children
https://www.sciencedirect.com/science/article/pii/S0929693X20300713

Vaccine

BCG vaccination has been reported to offer broad protection to respiratory infections. A study compared large number of countries BCG vaccination policies with the morbidity and mortality for COVID-19. It found that countries without universal policies of BCG vaccination (Italy, Nederland, USA) have been more severely affected compared to countries with universal and long-standing BCG policies.
https://www.medrxiv.org/content/10.1101/2020.03.24.20042937v1
These results however are to be interpreted with caution

A review in *Immunity* discusses therapeutic and prophylactic interventions for SARS-CoV-2 with a focus on vaccine development and its challenges. It argues the vaccine will likely come too late to affect the first wave of a potential pandemic but will be essential to reducing morbidity and mortality if the virus establishes itself in the population.
https://www.ncbi.nlm.nih.gov/research/coronavirus/publication/32259480

One Health and Animal Model of COVID-19

A German team reports in ProMed that pigs and chickens were not susceptible to intranasal infection by SARS-CoV-2. Intranasal inoculation of _Rousettus aegyptiacus_ fruit bats resulted in a transient infection in the respiratory tract. Most efficient virus replication was observed in ferrets, with high yields of viral RNA in nasal washing fluids from 8 of 9 animals, 2-8 days post-infection.

A study in *Cell Host Microbe* reports a ferret model of SARS-CoV-2 infection and transmission that recapitulates aspects of human disease. Infected ferrets exhibit elevated body temperatures and virus replication, although fatalities were not observed.
https://www.ncbi.nlm.nih.gov/research/coronavirus/publication/32259477

ISGlobal

COVID-19 EPIDEMIC

Epidemiological situation (14/04/2020, ECDC data):

Globally:

1,873,265 cases confirmed cases and 118,854 deaths

- The IHME has published a website with its projections for different countries in Europe and the US covid19.healthdata.org/projections**.** The projections find that most regions of Italy and Spain have passed their peaks in the number of deaths, while other nations are approaching their peaks and still others face peak mortality later in April. IHME's projections for all locations assume social distancing measures throughout May. *Thanks Kurt Straif for the info!*
- The WHO lists two covid-19 tests (PCR) for emergency use https://www.who.int/news-room/detail/07-04-2020-who-lists-two-covid-19-tests-for-emergency-use
- A comment in Lancet discusses how to maintain the HIV care continuum during the COVID-19 pandemic, https://doi.org/10.1016/S2352-3018(20)30105-3
- The pandemic may push 500 million people into poverty, according to a UN University Working paper and could double the number of people with chronic hunger https://www.wider.unu.edu/publication/estimates-impact-covid-19-global-poverty; https://www.theguardian.com/world/2020/apr/09/coronavirus-could-double-number-of-people-going-hungry

Roadmaps to deconfinement

The Leopoldina has published its 3rd ad-hoc statement, again focused on the exit strategy (in German for the moment)
https://www.leopoldina.org/publikationen/detailansicht/publication/coronavirus-pandemie-die-krise-nachhaltig-ueberwinden-13-april-2020/
Thanks Kurt Straif for the info!

A new modelling study in *Lancet* concludes that close monitoring of Rt and cCFR is needed to inform strategies against a potential second wave to achieve an optimal balance between health and economic protection.
https://www.thelancet.com/pdfs/journals/lancet/PIIS0140-6736(20)30746-7.pdf

Testing

A new app from Stanford Medicine with help from Apple will help connect first responders to drive-through COVID-19 testing if they are showing symptoms of the coronavirus. https://www.cnbc.com/2020/04/09/stanford-apple-app-connects-first-responders-to-covid-19-tests.html

Transmission

A study collected swab samples from potentially contaminated objects in the ICU (severe patients) and General Ward (mild patients) of a hospital. Results led to 3 conclusions. First, SARS-CoV-2 was widely distributed in the air and on object surfaces in both the ICU and GW, implying a potentially high infection risk for medical staff and

other close contacts. Second, the environmental contamination was greater in the ICU than in the GW. Third, the SARS-CoV-2 aerosol distribution characteristics in the GW indicate that the transmission distance of SARS-CoV-2 might be 4 m.
https://wwwnc.cdc.gov/eid/article/26/7/20-0885_article

Risk Factors
A retrospective analysis of of BMI [body mass index] stratified by age in COVID-19-positive symptomatic patients in a Hospital in NYC suggests that obesity may be a risk factor for hospital admission and need for critical care. This has important and practical implications, where nearly 40% of adults in the US are obese with a BMI equal to or greater than 30.
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https://www.cdc.gov/mmwr/volumes/69/wr/mm6915e3.htm

Treatment

Antiviral drugs: The *NEJM* publishes results for compassionate use of remdesivir in 53 patients (22 from US, 22 in Europe or Canada, 7 in Japan). clinical improvement was observed in 36 of 53 patients (68%)
https://www.nejm.org/doi/full/10.1056/NEJMoa2007016

A study in vitro with remdesivir provides a unifying, refined mechanism of drug-mediated RNA synthesis inhibition in coronaviruses
https://www.jbc.org/content/early/2020/04/13/jbc.RA120.013679

Chloroquine**:** The highly politicized debate about the use of chloroquine and hydroxychloroquine, two antimalarial drugs, to treat COVID-19 has reached an extreme in France, after Macron visited Didier Raoult, who conducted two trials for the drugs. survey released by IFOP Confidence in the drugs is higher on the far right and far left, and reached 80% among sympathizers of the "yellow vest" movement. His advocacy has made him a kind of medical prophet. France is witnessing a form of "medical populism" that is "slowing the emergence of the truth."
https://www.sciencemag.org/news/2020/04/france-s-president-fueling-hype-over-unproven-coronavirus-treatment
In this sense, a trial in Manaus testing choloroquine in patients with severe COVID-19 had to be ended prematurely due to heart complications in the high-dose arm. The study is co-authored by our colleague Quique Bassat.
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Sweden has also recommended to stop using the drug outside clinical trials due to "a serious effect on the heart" linked to using the medication.
See also https://edition.cnn.com/2020/04/13/health/chloroquine-risks-coronavirus-treatment-trials-study/index.html

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Antibodies / Immunity

Plasma collected from 175 COVID-19 recovered patients with mild symptoms were screened using a pseudotyped-lentiviral-vector-based neutralization assay. SARS-CoV-2-specific NAbs were detected in patients from day 10-15 after the onset of the disease and remained thereafter. Elderly and middle-age patients had significantly higher plasma NAb titers and spike-binding antibodies than young patients. Ten patients had NAb titers were below the detectable level of the assay.
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Relying on the deCODE study in Iceland, which offers large scale testing among the general population, a research team estimated the magnitude and uncertainty of the number of undetected cases of the COVID-19 disease in Austria. It found that the estimated number of infections could be on average 9 times higher than the recorded number of infection, although the range of estimates depends on the statistical method employed. https://www.csh.ac.at/covid-19-prevalence-in-austria/

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https://www.sciencemag.org/news/2020/04/these-are-answers-we-need-who-plans-global-study-discover-true-extent-coronavirus

Solidarity III trial is also in the works, the WHO announced. It will test possible drugs that health care workers and others at high risk for contracting the virus could take to protect them from getting sick

An article in Stat news reviews the ethical and practical implications of immunity certificates for covid-19 https://www.statnews.com/2020/04/10/immunity-certificates-covid-19-practical-ethical-conundrums

Others

Latin American countries are struggling to help women at risk of domestic violence during lockdowns by keeping shelters open, expanding hotlines, and adding messaging services. Thomson Reuters Foundation

ISGlobal

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- President Trump halted US funding to the WHO Tuesday pending a review of its "role in severely mismanaging and covering up the spread of coronavirus." Trump faulted the WHO for failing to call out China's lack of transparency and for intervening in Wuhan too late—though Trump himself praised China's efforts and transparency early on in the outbreak (CNN reports)
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- Richard Horton, editor in chief of Lancet, writes a comment on the bewilderment caused by this outbreak, the danger of using war metaphors, and the need to hear different voices https://www.thelancet.com/pdfs/journals/lancet/PIIS0140-6736(20)30850-3.pdf
- A letter in *Lancet* urges all involved in collecting COVID-19 data to follow guidelines (eg, CONSORT, STROBE) and include age and sex in demographic data. Addressing the health needs of men and women equally will "help societies recover and resist future human tragedies". https://www.thelancet.com/pdfs/journals/lancet/PIIS0140-6736(20)30823-0.pdf

Tools:

- The Agencia de Salut Publica de Barcelona has a website with data on daily COVID-19 cases in Barcelona #COVID19aldiaBCN https://aspb.shinyapps.io/COVID19_BCN/ *Thanks Toni Plasencia for the tip!*
- The NIH has a website to search for all COVID-19 related literature https://icite.od.nih.gov/covid19/search/
- The Norwegian Institute of Public Health has developed a Live Map of COVID-19 evidence https://www.fhi.no/en/qk/systematic-reviews-hta/map/ *Thanks Payam Dadvand for the tip!*

Roadmaps to deconfinement

Spain: The Sociedad Española de Medicina Preventiva, Salud Pública e Higiene (SEMPSPH) posts a document recommending over 140 measures for the descalating the confinement phase https://www.sempsph.com/es/noticias/118490-la-sempsph-recomienda-mas-de-140-medidas-para-la-fase-de-desescalamiento.html
Meanwhile, some non-essential businesses (like manufacturing and construction) have been allowed to resume. Shope, restaurants, bars and public spaces remain closed.

Other European countries:
Denmark lets young children (up to 11) go back to school after having closed schools on 12 March. Austria reopened thousands of smaller shops on Tuesday. The Czech government has set out a five-stage timetable. Spain has allowed the reopening of non-essential businesses. Italian bookshops and clothing stores for youngsters have

reopened their doors in some regions. In Germany, the Leopoldina academy proposes that schools would have to observe hygiene rules as they opened, then shops and restaurants could follow as long as social distancing was observed. Everyone would have to wear masks in public, with the strategy based on reducing the rate of infection. In France, lockdown measures were extended until 11 May.
https://www.bbc.com/news/world-europe-52291326

A news story in *Science* discusses the uncertainty related to exit strategies and says that ending the lockdowns will be a process of trial and error. "We've managed to get to the life raft," says epidemiologist Marc Lipsitch of the Harvard T.H. Chan School of Public Health. "But I'm really unclear how we will get to the shore."
https://www.sciencemag.org/news/2020/04/ending-coronavirus-lockdowns-will-be-dangerous-process-trial-and-error

The 'suppress and lift' strategies in Hong Kong and Singapour seem to be working despite recent rise in cases. Both cities have the highest testing rates in the world and both hospitalize those who test positive, regardless of whether they have symptoms, to prevent them from infecting others. Close contacts of cases and all recent returnees must self-quarantine at home for 2 weeks.
https://www.sciencemag.org/news/2020/04/suppress-and-lift-hong-kong-and-singapore-say-they-have-coronavirus-strategy-works

A 36-page CDC/FEMA plan guides state and local governments through phases. It gradually reopens schools, child-care facilities, restaurants, etc. The 3-phase plan moves from preparing the public before May1 and accelerating test kit and PPE production through May 15, followed by staged reopenings.
https://www.washingtonpost.com/health/2020/04/14/cdc-fema-have-created-plan-reopen-america-heres-what-it-says/

A modelling study in *Science* has suggested that prolonged or intermittent social distancing may have to extend into 2022 to prevent hospitals from being overwhelmed. The analysis considers yet poorly known variables such as seasonality, duration of immunity and possible cross-reactivity with other betacoronaviruses. It projects that recurrent wintertime outbreaks of SARS-CoV-2 will probably occur after the initial, most severe pandemic wave. If SARS-CoV-2 immunity lasts for two years, mild (30%) cross-immunity from HCoV-OC43 and HCoV-HKU1 could effectively eliminate the transmission of SARS-CoV-2 for up to three years before a resurgence
https://science.sciencemag.org/content/early/2020/04/14/science.abb5793

Virus
Science publishes the structure of the RNA-dependent RNA polymerase from COVID-19 virus, providing a basis for the design of new therapeutics targeting viral RdRp
https://science.sciencemag.org/content/early/2020/04/09/science.abb7498

A Canadian team is creating organs-on-a-chip (i.e. miniscule models of the nose, mouth, eyes and lungs) to study the early innate immune response to the virus.
https://healthcare-in-europe.com/en/news/organ-on-a-chip-model-to-find-out-how-covid-19-invades-our-bodies.html

Testing
The two-step ELISA developed by Florian Krammer's lab (Mount Sinai) has received emergency use authorization by the FDA.
https://twitter.com/florian_krammer/status/1250798201923305473?s=20

Apparently, antibody levels detected by the ELISA would correlate with neutralizing antibodies https://twitter.com/florian_krammer/status/1250798201923305473?s=20
Thanks for the tip, Carlota Dobaño!

A report describes patients that resulted positive again after hospital discharge, in Guangzhou, China. Discharged patients followed the criteria of: (a) normal temperature for more than 3 days (b) disappearance of respiratory symptoms, (c) substantially improved acute exudative lesions on chest CT images, and (d) two consecutive negative nucleic acid tests separated by at least 1 day. Out of 161 discharged patients, 22 (13.6%) retested positive on subsequent tests. The authors suggest nasal swab sampling to reduce false negative rate.
https://www.sciencedirect.com/science/article/pii/S1477893920301368?via%3Dihub

Transmission
The *NEJM* publishes results of the population-wide screening exercise (deCODE) in Iceland. The study performed targeted screening in persons at high risk for infection (with compatible symptoms, travellers returning from high-risk countries, or case contacts) as well as population screening by invitation. In total, 6% of the population was screened. 1221 of 9199 persons (13.3%) who were recruited for targeted testing were positive for infection with SARS-CoV-2. In the general population, 0.6-0.8% tested positive. Symptoms were reported by 93% of those in the targeted-testing group and by 57% of those in the overall population-screening group. Children under 10 years of age and females had a lower incidence of SARS-CoV-2 infection than adolescents or adults and males. https://www.nejm.org/doi/full/10.1056/NEJMoa2006100

Another study in *NEJM* implemented universal testing with nasopharyngeal swabs and a quantitative PCR to detect SARS-CoV-2 infection in 210 women who were admitted for delivery at a hospital in NYC. 29 of the 33 patients who were positive for SARS-CoV-2 at admission (87.9%) had no symptoms at presentation. This universal testing approach can help determine hospital isolation practices and bed assignments, inform neonatal care, and guide the use of personal protective equipment.
https://www.nejm.org/doi/10.1056/NEJMc2009316

A study in *Nature Medicine* analysed viral shedding in 94 patients and modelled infectiousness in 74 infector-infectee pairs. They observed the highest viral load in throat swabs at the time of symptom onset, which suggests that infectiousness peaks on or before symptom onset. The authors estimated that 44% of secondary cases were infected during the index cases' presymptomatic stage.
https://www.nature.com/articles/s41591-020-0869-5

A letter in *NEJM* shows that speaking generates small droplets, raising the possibility of SARS-CoV-2 transmission by normal speech.
https://www.nejm.org/doi/full/10.1056/NEJMc2007800

A study published in *Nature Microbiology* reports that a re-analysis of throat swabs from patients in Wuhan with influenza-like-illness (ILI) found that some of the patients were positive for SARS-CoV-2, suggesting community transmission of the virus in Wuhan in early January 2020. https://www.nature.com/articles/s41564-020-0713-1

Another study applied retrospective sample pooling to evaluate nasopharyngeal and bronchoalveolar lavage samples collected between 1 Jan and 26 Feb in the San Francisco Bay Area. A total of 292 pools were screened (2740 nasopharyngeal and 148 bronchoalveolar lavage samples). Positivity rate for SARS-CoV-2 was 0.07% (2/2888), indicating that transmission in the San Francisco Bay Area early in the pandemic was

low. Strategies such as pooled screening may facilitate detection of early community transmission. https://jamanetwork.com/journals/jama/fullarticle/2764364

Clinical symptoms
A NY-based team describes a case of COVID-19 pneumonia requiring hospitalization that presented with fever and extensive rash as the primary presenting symptoms. Rash has only been rarely reported in COVID-19 patients.
https://escholarship.org/uc/item/29j8q4pm
Other reports of rash as a clinical manifestation of covid-19 include:
https://www.jaad.org/article/S0190-9622(20)30556-9/pdf,
https://www.ncbi.nlm.nih.gov/research/coronavirus/publication/32282312

A case report in *NEJM* describes a patient with COVID-19 and clinically significant coagulopathy, antiphospholipid antibodies, and multiple infarcts.
https://www.nejm.org/doi/full/10.1056/NEJMc2007575

Treatment
Antiviral drugs: Late initiation of remdesivir may be effective in treating SARS-CoV-2. 40 yo male that quickly progressed to intubation and ventilator support was given remedesivir 9d after hospitalization (13d after symptom onset). Sixty hours after initiating remdesivir, the patient was successfully extubated
https://www.ncbi.nlm.nih.gov/research/coronavirus/publication/32281114

Preliminary results presented by the University of Chicago on a clinical trial with remedeisivir on 125 Covid-19 patients (113 of them with severe disease) indicate rapid recoveries and most patients discharged in less than a week.
https://www.statnews.com/2020/04/16/early-peek-at-data-on-gilead-coronavirus-drug-suggests-patients-are-responding-to-treatment/

Ivermectin:
A letter in JAAD hypothesizes that hydroxychloroquine and ivermectin could act in a consequential and synergistic manner. Indeed, HCQ would behave as a first level barrier by inhibiting the entry of the virus into the host cell, while ivermectin could reduce viral replication if the virus could get in, strengthening HCQ antiviral effects
https:/ /www.jaad.org/article/S0190-9622(20)30557-0/pdf

An editorial in the ASTMH Journal signed by our colleagues Chaccour and Rabinovich reviews the potential use of ivermectin as COVID-19 treatment and underlines the need for rigorous, well-conducted clinical trials to test it.
http://www.ajtmh.org/docserver/fulltext/10.4269/ajtmh.20-0271/tpmd200271.pdf

Immune modulation: A French team describes a 45 yo patient with sickle cell disease and severe covid.19 symptoms that was successfully treated with tocizilumab (he was also treated with hydroxychloroquine).
https://onlinelibrary.wiley.com/doi/epdf/10.1002/ajh.25833

Antibodies / Immunity
A South Korean team describes two cases of COVID-19 treated with convalescent plasma infusion. Both patients presented severe pneumonia with acute respiratory distress syndrome and showed a favorable outcome after the use of convalescent plasma in addition to systemic corticosteroid.
https://www.ncbi.nlm.nih.gov/research/coronavirus/publication/32281317

Vaccine
The vaccine candidate Coravax, developed by the Jefferson Vaccine center, is made from the coronavirus spike protein combined with the rabies vaccine. The benefit of using rabies as a carrier vaccine is that there are already at least 20 manufacturing facilities around the world producing some 100 million doses a year of the rabies vaccine. Plus, it can be produced in a shelf-stable, dehydrated form that is easy to reconstitute anywhere. https://healthcare-in-europe.com/en/news/COVID-19-vaccine-candidate-could-cover-global-demand.html

Others
A perspective in *NEJM* discusses mental health and the covid19 pandemic
https://www.nejm.org/doi/10.1056/NEJMp2008017

ISGlobal

COVID-19 EPIDEMIC

Epidemiological situation (21/04/2020, ECDC data):

Globally:
2,431,890 confirmed cases and 169,859 deaths

- The USA is number 1 for numbers of confirmed cases of COVID-19; Spain is number 2 and Italy is number 3 followed by France, Germany, UK, Turkey, Iran, China, and Russia as number 10.
- At least 28,000 more people have died during the coronavirus pandemic over the last month than the official Covid-19 death counts report, a review of mortality data in 11 countries shows — providing a clearer, if still incomplete, picture of the toll of the crisis. https://www.nytimes.com/interactive/2020/04/21/world/coronavirus-missing-deaths.html
- The "One World: Together at Home" musical event organized on April 18 by Global Citizen and the World Health Organization, raised $127.9 million for health care workers and coronavirus relief, according to Global Citizen. Over $55 million of the money raised will be donated to the COVID-19 Solidarity Response Fund, while nearly $73 million will go toward local and regional responders. https://www.globalcitizen.org/es/connect/togetherathome/
- UN member states signed a resolution yesterday calling for equitable access to future coronavirus vaccines. https://www.france24.com/en/20200421-un-member-states-call-for-equitable-access-to-future-covid-19-vaccines
- A letter in Science urges Brazil's government to take action in the Amazon to protect the indigenous people. Instead of allowing evangelical missionaries to enter into contact with isolated Indigenous groups, all means of transport to these areas should be restricted. https://science.sciencemag.org/content/368/6488/251.1

Roadmaps to deconfinement
The BMJ editorial on the European roadmap out of the COVID19 pandemic underlines the three key elements. First, no country should consider lifting restrictions until it is certain that the disease is under control (i.e Ro beyond 1). Second, countries should ensure that they have sufficient health system capacity, especially to provide intensive care, given the probability of a second wave. Third, there must be sufficient capacity for large scale testing and monitoring, linked to the ability to track and trace contacts
https://www.bmj.com/content/369/bmj.m1556
The EU Commission has published a toolbox for the use of mobile applications for contact tracing and warning in response to COVID.19
https://ec.europa.eu/health/sites/health/files/ehealth/docs/covid-19_apps_en.pdf

A modelling study posted by a team from the Pasteur Institute team estimates that by 11 May, when interventions are scheduled to be eased, 3.7 million people (5.7% of the population), will have been infected. Population immunity appears insufficient to avoid

a second wave if all control measures are released at the end of the lockdown. https://hal-pasteur.archives-ouvertes.fr/pasteur-02548181/document

A letter in Lancet argues that workers aged 60-69 should also be protected and moved to jobs with minimal person contact, whether it is in the health service, schools, government, or the private sector https://www.thelancet.com/pdfs/journals/laninf/PIIS1473-3099(20)30311-X.pdf

A review discusses how the different models for the covid19 pandemic differ in their approaches, data needs, reproducibility, methodological complexity, and transparency. https://annals.org/aim/fullarticle/2764846/pandemic-surge-models-time-severe-acute-respiratory-syndrome-coronavirus-2

In the US, many conservative states have protested against social distancing measures, with Trump's apparent support and despite his own government's recommendations https://www.bbc.com/news/world-us-canada-52359100

Virus

A review in *Cell* describes what genomic data reveal about the emergence SARS-CoV-2 and discusses the gaps in our understanding of its origins. https://www.sciencedirect.com/science/article/pii/S0092867420303287

Nature reports the crystal structure of the SARS-CoV-2 main protease (Mpro) and identifies several drugs that could specifically target it, including the organoselenium compound ebselen, which has been shown to have a good safety profile in humans. https://www.nature.com/articles/s41586-020-2223-y

A study cloned, tagged and expressed 26 of the 29 viral proteins in human cells and identified the human proteins physically associated with each using affinity-purification mass spectrometry (AP-MS). identify 67 druggable human proteins or host factors targeted by 69 existing FDA-approved drugs, drugs in clinical trials and/or preclinical compounds https://www.biorxiv.org/content/10.1101/2020.03.22.002386v3 comment in https://www.nature.com/articles/s41577-020-0318-1

Testing

A study supports continued sampling in highly suspicious cases, as initial results can be PCR negative. Two patients had persistently negative tests from upper respiratory samples till days 8 and 7 of symptom onset respectively. Another patient's nasopharyngeal specimen remained negative despite positive stool and sputum simples. They propose a decision-making matrix or adjunctive CT scans of the thorax could be implemented to guide decisions on repeat testing and de-isolation in such patients. https://www.ncbi.nlm.nih.gov/research/coronavirus/publication/32306042

JAMA publishes an in-depth overview of the promise and peril of antibody testing for covid19. https://jamanetwork.com/journals/jama/fullarticle/2764954

A diagnostic test based on CRISPR-Cas12 was developed and shown to be as sensitive and specific as the gold standard RT-PCR. It performs simultaneous reverse transcription and isothermal amplification using loop-mediated amplification (RT–LAMP) for RNA extracted from nasopharyngeal or oropharyngeal swabs in universal transport medium (UTM), followed by Cas12 detection of predefined coronavirus sequences, after which cleavage of a reporter molecule. The DETECTR assay can be run in approximately 30–40 min and visualized on a lateral flow strip. It provides a visual and faster alternative to the real-time RT–PCR assay, with 95% positive predictive

agreement and 100% negative predictive agreement.
https://www.nature.com/articles/s41587-020-0513-4

Transmission

"Floating incubators":

Testing of the entire crew of the US carrier Theodore Roosevelt reveals interesting clues: out of almost 4800-members tested, 600 tested positive so far, of which roughly 60 % have not -yet-shown symptoms of COVID-19
https://www.reuters.com/article/us-health-coronavirus-usa-military-sympt/coronavirus-clue-most-cases-aboard-us-aircraft-carrier-are-symptom-free-idUSKCN21Y2GB
In another naval vessel, 1081 of the 2300 people aboard the Charles de Gaulle and its escort vessels have tested positive so far – nearly half the overall personnel. The % of asymptomatic individuals is not mentioned (ProMed mail)

Vertical transmission

A case report of an infant born to a mother with confirmed COVID19 suggests that vertical transmission of COVID is unlikely, but still, more evidence is needed.
https://www.ncbi.nlm.nih.gov/research/coronavirus/publication/32305459
A similar study from Australia reported an uncomplicated vaginal birth in a mother with COVID-19
https://obgyn.onlinelibrary.wiley.com/doi/abs/10.1111/ajo.13173
as did another study of 19 neonates in China
https://link.springer.com/article/10.1007/s11684-020-0772-y
However, another case report of a pregnant woman with severe COVID19 indicates positive RT-PCR in first day of life of the neonate, suggesting possible vertical transmission
https://www.ncbi.nlm.nih.gov/research/coronavirus/publication/32305046

Asymptomatic infections

COVID-19 testing at a homeless shelter in Boston reveals that, of the 397 people tested, 146 people tested positive. Not a single one had symptoms. Not clear though what proportion of these individuals will go on to develop symptoms. (ProMed mail)

A study performed in the Italian town of Vo with 85.9% and 71.5% of the population at two consecutive time points reveals: The first survey, conducted when the lockdown started, found a prevalence of infection of 2.6%. The second survey, at the end of the lockdown, found a prevalence of 1.2%. Notably, 43.2% of the confirmed SARS-CoV-2 infections detected across the two surveys were asymptomatic. New infections in the second survey were infected in the community before the lockdown or from asymptomatic infections living in the same household.
https://www.medrxiv.org/content/10.1101/2020.04.17.20053157v1

Serological studies

Nearly one third of 200 Chelsea (Mass, USA) residents tested positive for antibodies linked to COVID-19. Most appeared healthy, but about half told the doctors they had had at least one symptom of COVID-19 in the past four weeks.
https://www.bostonglobe.com/2020/04/17/business/nearly-third-200-blood-samples-taken-chelsea-show-exposure-coronavirus/

A seroprevalence study of some 3,300 people in Santa Clara County (USA) in early April estimates 2-4% of the population was infected (50 to 85 times more than the official count of cases at the time), implying an infection fatality rate of 0.1 – 0.2%.

However, the study (posted as preprint) has raised many criticisms concerning test specificity and sensitivity, sampling method, etc.
https://www.medrxiv.org/content/10.1101/2020.04.14.20062463v1
See also https://www.nature.com/articles/d41586-020-01095-0

Antibodies / Immunity
A systematic review of antibody mediated immunity to coronaviruses addresses antibody kinetics, correlates of protection, and association of antibody responses with severity of disease. Median time to detection was similar across different antibodies for SARS-CoV-1 (12 days) and SARS-CoV-2 (11 days). Antibody kinetics varied across the severity gradient with longer durations of detectable antibody associated with more severe symptoms. There is cross-reactivity within but minimal reactivity between Alpha- and Beta-CoVs. Authors stress the need for development of serological assays with high sensitivity for screening and sufficient specificity (particularly in context of serological passports)
https://www.medrxiv.org/content/10.1101/2020.04.14.20065771v1.full.pdf

A perspective in *NEJM* on covid19 and immunity in ageing populations calls for a new research agenda and for a shift from investing in disease-specific research to targeting sufficient resources toward decoding the human immune system, particularly for the world's most vulnerable populations.
https://www.nejm.org/doi/10.1056/NEJMp2006761

Clinical symptoms / pathology
COVID-19 co-infections with other respiratory pathogens are 21% higher than once thought according to a paper in JAMA
https://jamanetwork.com/journals/jama/fullarticle/2764787

A study in *Lancet* shows that SARS-CoV-2 directly infects the endothelium and induces endothelial cell apoptosis. This could help understand why the virus disproportionately affects patients with cardiovascular comorbidities
https://www.thelancet.com/coronavirus?dgcid=kr_pop-up_tlcoronavirus20

A letter in *Thrombosis Research* underlines the importance of coagulopathy in severe COVID19 patients and suggest administering higher, possibly therapeutic doses of anticoagulation to these patients.
https://www.thrombosisresearch.com/article/S0049-3848(20)30130-4/pdf

D-dimer levels greater than 2.0microg/mL (fourfold increase) on admission could effectively predict in-hospital mortality in patients with Covid-19, according to a brief report https://www.ncbi.nlm.nih.gov/research/coronavirus/publication/32306492

An editorial in *BMJ* reviews the clinical features of covid19, including non-respiratory symptoms. https://www.bmj.com/content/369/bmj.m1470

A *Science* story reviews how the coronavirus infects and damages lungs and other tissues, particularly the heart. https://www.sciencemag.org/news/2020/04/how-does-coronavirus-kill-clinicians-trace-ferocious-rampage-through-body-brain-toes#

A study performed immunohistochemistry and immunofluorescence on lymph nodes and spleen post-mortem of 6 patients that died from covid19. ACE2-expressing CD68+CD169+ macrophages were detected in the splenic marginal zone and in marginal sinuses of lymph nodes, and these macrophages contained SARS-CoV-2 nucleoprotein antigen and showed upregulation of IL-6. Virally infected tissues also

showed higher expression of FAS. This suggests that CD169+ macrophages could contribute to viral spread, excessive inflammation and activation-induced lymphocytic cell death during SARS-CoV-2 infection.
https://www.medrxiv.org/content/10.1101/2020.03.27.20045427v1
See also: "Macrophages: a Trojan horse in COVID-19?"
https://www.ncbi.nlm.nih.gov/research/coronavirus/publication/32303696

Peter Hotez and colleagues examine the role of IL17 in COVID19 immunopathology and vaccine-induced immune enhancement. They suggest there may be partial overlap between the underlying immunopathologic processes linked to both coronavirus infection and vaccination (particularly for virus-vectored vaccines), and a role for Th17 in immune enhancement and eosinophilic pulmonary immunopathology.
https://www.sciencedirect.com/science/article/pii/S1286457920300721

Children: An editorial summarizes what is known of COVID19 in children
https://www.sciencedirect.com/science/article/pii/S0021755720301418?via%3Dihub

Treatment
A letter in *Lancet* argues that chloroquine or hydroxychloroquine could be used as prophylaxis for COVID-19, at least in countries non-endemic for malaria
https://www.thelancet.com/journals/laninf/article/PIIS1473-3099(20)30296-6/fulltext

Vaccine
The US company Inovio Pharmaceuticals launched a phase I clinical trial of INO-4800, its DNA vaccine for COVID-19.
China's Shenzhen Geno-Immune Medical Institute (SGIMI) has begun phase I trials of LV-SMENP-DC, a cellular vaccine made up of dendritic cells (DCs) transduced with SARS-CoV-2 spike, membrane, nucleocapsid, envelope and protease (SMENP) minigenes.
Pfizer announced a joint effort with Germany's BioNTechSE to bring its COVID-19 mRNA vaccine into phase I trials by the end of April.

Animal models
A study in Science shows that SARS-CoV-2 causes COVID19-like disease in macaques, providing a new model to test preventive and therapeutic strategies.
https://science.sciencemag.org/content/early/2020/04/16/science.abb7314

Others
An analysis of the association of public interest in coronavirus infections (google trends) with the actual number of infected cases for selected countries across the globe shows that public interest is on average highest 11.5 days before the peak of newly infected cases.
https://www.ncbi.nlm.nih.gov/research/coronavirus/publication/32305520

ISGlobal

COVID-19 EPIDEMIC

Epidemiological situation (24/04/2020, ECDC data):

Globally:
2,668,135 confirmed cases and 190,236 deaths

- The World Food Programme (WFP) warned that 265 million people could be pushed into acute food insecurity by Covid-19, almost doubling last year's total https://insight.wfp.org/covid-19-will-almost-double-people-in-acute-hunger-by-end-of-2020-59df0c4a8072
- WHO is advising a virtual version of Ramadan gatherings. https://apps.who.int/iris/handle/10665/331767

Roadmaps to deconfinement

Nature publishes an interview with Anders Tegnell, the epidemiologist that is counselling Sweden on its different approach to controlling the virus (i.e. no lockdowns, no school closures, no closing borders, and mostly based on voluntary measures and individual responsibility). https://www.nature.com/articles/d41586-020-01098-x

A modelling study proposes the strategic reduction of contacts, allowing some social contact while keeping risks low. Limiting interaction to a few repeated contacts emerges as the most effective strategy https://arxiv.org/abs/2004.07052

Virus

An analysis of SARS-CoV-2 concludes that its genome is closest to that of SARS-related coronaviruses from horseshoe bats, and its receptor binding domain is closest to that of pangolin viruses. They conclude that SARS-CoV2 is most likely a recombinant virus originated from bats, although its origin and direct ancestral viruses have not been identified. https://wwwnc.cdc.gov/eid/article/26/7/20-0092_article

Testing

A study compared performance of oropharyngeal and nasopharyngeal swabs in 353 patients who received both tests simultaneously, and concludes that nasopharyngeal swabs may be more suitable than oropharyngeal swab
https://www.ncbi.nlm.nih.gov/research/coronavirus/publication/32315809
However, saliva tests could be a first-line screening tests particularly in low resource settings, with NPS reserved for patients with a high clinical index of suspicion, concludes a study https://jcm.asm.org/content/early/2020/04/17/JCM.00776-20

Environmental sampling: By sampling raw wastewater samples across greater Paris for more than 1 month, researchers detected a rise and fall in coronavirus concentrations that correspond to the shape of the COVID-19 outbreak in the region. This shows that the technique can pick up a sharp rise in viral concentrations in sewage before cases explode in the clinic.
https://www.medrxiv.org/content/10.1101/2020.04.12.20062679v1

A first study of SARS-CoV-2 RNA in wastewater treatment plants in Brisbane suggests that 0.1% of population in catchment was infected during the sampling period. This would equal 450 cases (potentially up to 764, which would mean 7 undetected cases for every 10 detected).
https://www.sciencedirect.com/science/article/pii/S0048969720322816

The U of Zurich is developing a biosensor to detect SARS-CoV-2 in the environment https://www.uvek.admin.ch/uvek/en/home/detec/media/press-releases.msg-id-78848.html Thanks Sarah Koch for the tip!

Transmission
Analysis of a cluster of Covid-19 in the French Alps reveals that one child, infected with SARS-CoV2 and co-infected with other respiratory viruses, attended three schools while symptomatic, but did not transmit the virus despite coming into contact with 172 people. Raising questions on role of children in transmitting the disease (the boy had low levels of virus when tested).
https://academic.oup.com/cid/article/doi/10.1093/cid/ciaa424/5819060

A retrospective analysis of 26 persistently asymptomatic SARS-CoV-2 carriers reveals small changes in biochemical and inflammatory variables and changes in chest CT in some cases. Authors note the long existence of SARS-CoV-2 in some asymptomatic patients. https://www.ncbi.nlm.nih.gov/research/coronavirus/publication/32318703

Antibodies / Immunity
A comment in *Nature Rev Immunol* reviews the potential danger of suboptimal antibody responses in covid19 The authors argue that ADE should be given full consideration in the safety evaluation of emerging candidate vaccines for SARS-CoV-2. https://www.nature.com/articles/s41577-020-0321-6

Seroprevalence studies**:**
New York: a total of 3,000 customers at supermarkets across the state of New York were randomly tested for coronavirus antibodies this week. Almost 14% tested positive (21% in New York city). This means roughly 2.6 million people statewide and 1.7 million in the city were infected, way above the 263,460 declared cases across the state. If the data are correct, it would mean that the death rate for COVID-19 was 0.5%.
https://medicalxpress.com/news/2020-04-yorkers-infected-coronavirus-antibody.html

In the Netherlands, the national blood bank released an average seroprevalence figure of 3% (although it varied widely between regions, from 1% to 8%), which is lower than hoped for. The study coordinator noted false positives are an issue with the test they used. (ProMed Mail).
https://twitter.com/martinenserink/status/1253443464668340228?s=20

Clinical symptoms / pathology
Analysis of multiple Human Cell Atlas (HCA) consortium datasets of single cell RNA sequencing, from more than 20 different tissues of non-infected people, reveals that mucus-producing goblet cells and ciliated cells in the nose had the highest levels of the ACE2 receptor and the TMPRSS2 protease. These findings highlight the nose cells' potential role in initial viral infection, spread and clearance.
https://www.nature.com/articles/s41591-020-0868-6

COVID-19 co-infections with other respiratory pathogens are 21% higher than once thought https://jamanetwork.com/journals/jama/fullarticle/2764787

Ventilation: An article in statnews says that many doctors are starting to question the widespread use of ventilators for Covid-19 patients, saying that large numbers of patients could instead be treated with less intensive respiratory support. https://www.statnews.com/2020/04/08/doctors-say-ventilators-overused-for-covid-19/ It cites two papers, one stating that covid-19 does not lead to a typical ARDS and that patients need "the lowest possible air pressure and gentle ventilation https://www.atsjournals.org/doi/pdf/10.1164/rccm.202003-0817LE
And another one by physicians who treated Covid-19 patients at two hospitals in China and found that the majority of patients needed no more than a nasal cannula. https://annalsofintensivecare.springeropen.com/articles/10.1186/s13613-020-00653-z

COVID19 and Inflammation
(a series of preprints had escaped my attention. Thanks Mariona Bustamante!)
Single-cell transcriptomes of 13,289 peripheral blood mononuclear cells isolated at three longitudinal stages from 2 severe COVID-19 patients identified a severe stage-specific monocyte subpopulation linked to inflammatory cytokines and receptors. This was attenuated after Tocilizumab treatment, yet immune cells including plasma B cells and CD8+ T cells retained anti-virus immune response
https://www.biorxiv.org/content/10.1101/2020.04.08.029769v1
Patients with COVID-19 have larger than normal monocytes, easily identified on forward scatter, side scatter analysis by flow cytometry. These FSC-high monocytes are CD11b+, CD14+, CD16+, CD68+, CD80+, CD163+, CD206+ and secrete IL-6, IL-10 and TNF-alpha, consistent with an inflammatory phenotype.
https://www.medrxiv.org/content/10.1101/2020.03.24.20042655v1
A cross-sectional analysis of all patients with laboratory-confirmed Covid-19 treated at a single academic health system in New York City revealed that age and comorbidities are powerful predictors of hospitalization; however, oxygen impairment and markers of inflammation at admission are most strongly associated with critical illness.
https://www.medrxiv.org/content/10.1101/2020.04.08.20057794v1

A *Cell Host Microbe* paper studied immune responses of 54 COVID-19 patients, 28 of whom had severe respiratory failure. Findings reveal a unique pattern of immune dysregulation characterized by IL-6-mediated low HLA-DR expression and lymphopenia, and associated with sustained cytokine production and hyper-inflammation. https://www.ncbi.nlm.nih.gov/pubmed/32320677

Risk Factors
A spatial analysis conducted on a regional scale in Italy, Spain, France and Germany shows that 80% of mortality was concentrated in five regions, which also have the highest NO2 levels.
https://www.sciencedirect.com/science/article/pii/S0048969720321215

Treatment
Chloroquine: A retrospective analysis with 368 male veterans in Virginia's Veteran Hospital found no evidence that use of hydroxychloroquine, with or without azithromycin, reduced the risk of mechanical ventilation in patients hospitalized with Covid-19. Furthermore, an association of increased overall mortality was identified in patients treated with hydroxychloroquine alone.
https://www.medrxiv.org/content/10.1101/2020.04.16.20065920v1.full.pdf

Science covers the risk of cardiac arrest when treating covid19 with antimalarials and how to minimize it https://www.sciencemag.org/news/2020/04/antimalarials-widely-used-against-covid-19-heighten-risk-cardiac-arrest-how-can-doctors

Vaccine

A Chinese team has developed a pilot-scale production of a purified inactivated SARS-CoV-2 virus vaccine candidate (PiCoVacc), which induced SARS-CoV-2-specific neutralizing antibodies in mice, rats and non-human primates and without evidence of antibody-dependent enhancement of infection. Importantly, it is the first vaccine reported to protect non-human primates.
https://www.biorxiv.org/content/10.1101/2020.04.17.046375v1
See also https://www.sciencemag.org/news/2020/04/covid-19-vaccine-protects-monkeys-new-coronavirus-chinese-biotech-reports

Rhesus macaques seroconverted rapidly after a single intramuscular vaccination with ChAdOx1 MERS and were protected against respiratory injury and pneumonia. Antibodies elicited by the vaccine were able to neutralize all MERS-CoV strains. Data support further clinical development of ChAdOx1 MERS supported by CEPI and give hope for ChAd-vectored vaccines against SARS-CoV-2
https://www.biorxiv.org/content/10.1101/2020.04.13.036293v1

A research team identified sequence homology between the fusion proteins of SARS-CoV-2 and measles and mumps viruses and a 29% amino acid sequence homology between the Macro (ADP-ribose-1-phosphatase) domains of SARS-CoV-2 and rubella virus. They hypothesize that MMR could protect against poor outcome in COVID-19 infection and propose that vaccination of at-risk age groups with MMR merits further consideration https://www.medrxiv.org/content/10.1101/2020.04.10.20053207v1

Tools:

Researchers at the Precision Immunology Institute at the Icahn School of Medicine (PrIISM), New York, describe their contribution to the global research effort against COVID-19 by 'trying to separate signal from noise in the preprint arena'.
https://www.nature.com/articles/s41577-020-0319-0
See https://observablehq.com/@ismms-himc/covid-19-sars-cov-2-preprints-from-medrxiv-and-biorxiv

ISGlobal

COVID-19 EPIDEMIC

Epidemiological situation (28/04/2020, ECDC data):

Globally:
2 982 688 cases confirmed cases and 210 193 deaths

- The total number of confirmed cases and deaths reported from outside China now represents 97.2% and 97.8% of the total reported, respectively.
- The USA now represents 33.0% of the global cases of COVID-19
- A preprint in *Lancet* estimates that reductions in health coverage of around 45% would cause a 44.7% increase in under-five child deaths and 38.6% increase in maternal deaths per month, across 118 countries. https://papers.ssrn.com/sol3/papers.cfm?abstract_id=3576549
- An analysis by the UNFPA estimates that the COVID-19 crisis could potentially lead to 7 million additional unintended pregnancies and 31 million cases of gender-based violence https://www.unfpa.org/resources/impact-covid-19-pandemic-family-planning-and-ending-gender-based-violence-female-genital

Roadmaps to deconfinement
The WHO Office for Europe has published key considerations for the gradual easing of the lockdown restrictions http://www.euro.who.int/en/health-topics/health-emergencies/coronavirus-covid-19/news/news/2020/4/whoeurope-publishes-considerations-for-gradual-easing-of-covid-19-measures.

In an effort to restart the economy, the Australian government launched a controversial coronavirus tracing app on Sunday and promised to legislate privacy issues. The app is based on Singapore's TraceTogether software and uses Bluetooth signals to log when people have been close to one another. https://www.reuters.com/article/health-coronavirus-australia/australia-launches-controversial-covid-19-tracking-app-as-some-states-start-easing-rules-idUSL5N2CE022

Transmission
A study investigated the aerodynamic nature of SARS-CoV-2 by measuring viral RNA in aerosols in different areas of two Wuhan hospitals. The concentration of SARS-CoV-2 RNA in aerosols detected in isolation wards and ventilated patient rooms was very low, but it was elevated in the patients' toilet areas. The results indicate that room ventilation, open space, sanitization of protective apparel, and proper disinfection of toilet areas can effectively limit the concentration of SARS-CoV-2 RNA in aerosols. https://www.nature.com/articles/s41586-020-2271-3

A model developed by researchers at Northeastern University suggests that by early February the virus was already spreading in several US cities. By March 1, there could have been 28,000 infections in those cities. This agrees with the first coronavirus death traced to Feb 6 in California. https://www.nytimes.com/2020/04/23/us/coronavirus-early-outbreaks-cities.html

An article in *The Conversation* argues it is safe for children to go back to school, citing several studies that suggest that children get less infected, less sick, and are not the

main spreaders of the virus https://theconversation.com/5-reasons-its-safe-for-kids-to-go-back-to-school-137064

A *Lancet* letter reports no virus in amniotic fluid of two pregnant women with COVID-19 https://www.thelancet.com/pdfs/journals/laninf/PIIS1473-3099(20)30320-0.pdf

A retrospective analysis of clinical records of 116 pregnant women with COVID19 pneumonia in China reveals that SARS-CoV-2 infection during pregnancy is not associated with an increased risk of spontaneous abortion or preterm birth. There was no evidence of vertical transmission when the infection manifests during the third-trimester of pregnancy.
https://www.ncbi.nlm.nih.gov/research/coronavirus/publication/32335053

A letter in *Lancet* describes the first screening of health workers in England, between March 10 and 31, 2020, with 1666 SARS-CoV-2 tests in 1654 staff. Overall, SARS-CoV-2 was detected in 240 (14%) tests. Nonclinical staff had similar positivity, suggesting appropriate protection of frontline workers.
https://www.thelancet.com/pdfs/journals/lancet/PIIS0140-6736(20)30970-3.pdf

Antibodies / Immunity
Spain's MoH launched yesterday its first national seroprevalence study(ENE-COVID) in collaboration with ISCIII. The study will consist of two serological tests (an RDT and a lab test when pertinent) plus a survey in 36,000 randomly selected households (roughly 90,000 people) covering all age and geographical ranges.
https://www.isciii.es/Noticias/Noticias/Paginas/Noticias/ComienzoENECOVIDEstudioSeroprevalencia.aspx

Antibody dynamics was studied in 14 COVID-19 patients in Taiwan (6 symptomatic and 8 asymptomatic/mild) using a test with overall sensitivity and specificity of 78.6% and 100%, respectively. In the symptomatic group, all had positive anti-SARS-CoV-2 IgG and 4 had positive anti-SARS-CoV-2 IgM responses, while in the asymptomatic/ mild group none had positive IgM and 3 had negative IgG results. Patients with prominent symptoms and anti-SARS-CoV 2 IgMs tended to have short viral shedding by rRT-PCR.
https://www.journalofinfection.com/article/S0163-4453(20)30230-9/pdf

Clinical symptoms / pathology
A case series of 5,700 COVID-19 patients in New York City hospitals revealed a 9.7% death rate overall—21% when excluding those still hospitalized—and an 88.1% death rate among those requiring mechanical ventilation. The most common underlying conditions were high blood pressure (56.6%), obesity (41.7%), and diabetes (33.8%).
https://jamanetwork.com/journals/jama/fullarticle/2765184

The characterization of over 1,100 hospitalized adults with COVID-19 in an integrated health care system in California indicates that 29% required inpatient care and 8.7% critical care. Adults across age groups, not just elderly individuals, required inpatient care, with persons aged 60 to 69 years most commonly hospitalized.
https://jamanetwork.com/journals/jama/fullarticle/2765303

COVID19 and GBS
A French team reports the case of a 64 year old man that developed GBS after COVID-19 infection. https://www.sciencedirect.com/science/article/pii/S0035378720305221

An Italian team also reports the case of a 70 year old woman who developed GBS
https://link.springer.com/article/10.1007/s00415-020-09849-6

Children
The paediatric intensive care society in UK has warned of an apparent rise in paediatric cases with multi system hyperinflammatory state with overlapping features of toxic shock syndrome and atypical Kawasaki disease, seen in patients that are both positive and negative for SARS CoV2 PCR.
https://twitter.com/PICSociety/status/1254508725227982848?s=20

Risk Factors
Two retrospective studies suggest that drugs for hypertension do not seem to make disease worse, as previously suggested
https://www.sciencenews.org/article/coronavirus-drugs-high-blood-pressure-covid-19-cases-worse

A study performed with the UK-developed covid19 symptom Tracker app, reveals that genetic factors may explain up to 50% of differences between covid19 symptoms.
https://www.medrxiv.org/content/10.1101/2020.04.22.20072124v1

Mortality
The global coronavirus death toll could be 60% higher than reported, according to the Financial Times, which analysed mortality statistics in 14 hard-hit countries. They show there have been 122,000 excess deaths as compared to the same period last year. Overall deaths rose 60%in Belgium, 51%in Spain, 42% in the Netherlands and 34% in France during the pandemic compared with the same period in previous years.
https://www.ft.com/content/6bd88b7d-3386-4543-b2e9-0d5c6fac846c

In a similar exercise, scientists from Berkeley performed a comparison of daily deaths in Italy since January 2020 with those over the previous five years and conclude that the true number of COVID-19 deaths in Italy is around 50,000, more than twice the official figure, as of April 18. They estimate that the fatality rate in that country for those infected with the SARS-CoV-2 is at least 0.8%. The team also estimated, based on the predicted infection fatality rate and confirmed cases for COVID-19 in New York City, that about one-quarter of that city's population has been infected (coinciding with recent seroprevalence data).
https://www.medrxiv.org/content/10.1101/2020.04.15.20067074v2

Treatment
Two clinical trials will be launched in New York and Los Angeles to test whether estrogens cana reduce inflammation and severe disease in men, according to the NYT.
https://www.nytimes.com/2020/04/27/health/coronavirus-estrogen-men.html
Thanks Gemma Castaño for the tip!

A New York hospital has launched a clinical trial with famotidine, the active compound in the over-the-counter heartburn drug Pepcid. Reports from China and molecular modelling results suggest the drug could be effective in blocking the viral protease.
https://www.sciencemag.org/news/2020/04/new-york-clinical-trial-quietly-tests-heartburn-remedy-against-coronavirus

Nature communications reports a recombinant protein made of the extracellular domain of human ACE2 and the Fc region of the human immunoglobulin IgG1 capable

of neutralizing virus pseudotyped with SARS-CoV or SARS-CoV-2 spike proteins *in vitro*. The fusion protein has potential applications in the diagnosis, prophylaxis, and treatment of SARS-CoV-2
https://www.ncbi.nlm.nih.gov/research/coronavirus/publication/32332765

A comment in *Nature* highlights the window of opportunity for obtaining blood from COVID19 trial participants and banking it in anticipation of having accurate serological tests developed in the future.
https://www.nature.com/articles/s41591-020-0887-3

Vaccine
The UK's Health Secretary announced that Phase I/II trials of Oxford University's COVID-19 vaccine would begin this week. The efficacy, safety and immunogenicity trials for ChAdOx1, an attenuated adenoviral construct expressing SARS-CoV-2 spike protein (see previous update), aim to recruit over 500 participants.
https://www.theguardian.com/world/video/2020/apr/21/hancock-uk-human-trials-for-coronavirus-vaccine-to-begin-on-thursday-video
The Oxford vaccine will be the third CEPI-funded vaccine to enter phase 1 trials, along with Inovio's INO-4800 DNA candidate and Moderna's mRNA-1273 candidate.

One Health:
The Netherlands reported SARS-CoV-2 infection among mink being raised on 2 fur farms. The infection is believed to have spread from humans.
https://nltimes.nl/2020/04/26/mink-found-infected-covid-19-two-dutch-fur-farms-areas-now-closed-public

Four more tigers and 3 lions at the Bronx Zoo in New York City have tested positive for the virus https://www.nationalgeographic.com/animals/2020/04/tiger-coronavirus-covid19-positive-test-bronx-zoo/

ISGlobal

COVID-19 EPIDEMIC

Epidemiological situation (01/05/2020, Worldometer data):

Globally:
3,252,587 confirmed cases and 229,832 deaths

Roadmaps to deconfinement

The Spanish government announced a 4-phase strategy based on indicators to gradually exit from the lockdown. Each phase should last at least two weeks. The indicators are based on four criteria: health system capacity, epidemiological situation in the region, protective measures in public spaces, and mobility and socioeconomic criteria. Some provinces or islands are ready to pass from Phase 0 to phase 1. If all goes well, most provinces should reach phase 3 by beginnings of July.
https://elpais.com/sociedad/2020-04-28/el-gobierno-evita-marcar-fechas-para-la-desescalada-y-se-concentra-en-fases-y-marcadores.html

France also announced the gradual easing of lockdown measures, starting on May 11, after a 6-week lockdown they estimate helped save around 60,000 lives.
https://www.theguardian.com/world/2020/apr/28/france-and-spain-announcement-lockdowns-ease

The presidents of Germany's main science institutions (Max Planck, Fraunhofer, Helmholtz and Leibniz) have issued a joint statement on covid19 strategies based on a mathematical analysis of the current situation. The R0 is slightly below 1 as a result of all the measures taken, but even a small increase would lead to renewed exponential growth. Thus, stringent contact restrictions need to remain in place. They argue a two-phase strategy seems reasonable: reduce number of infections until effective contact tracing is possible. Followed by an adaptive strategy (less restrictions) based on a low number of new infections
https://twitter.com/kakape/status/1255482619032109060?s=12

Transmission

The *Lancet Inf Dis* reports epidemiology and transmission for 391 COVID-19 cases and 1286 close contacts in Shenzen China (Jan 14 to Feb 12).

- Among the 391 confirmed cases, men (187 cases) and women (204 cases) were about equally represented, though men were about 2.5 times more likely to show severe symptoms. Children also were about as likely as adults to be infected, though they were less likely to have severe symptoms.
- Among the secondary cases discovered by contact tracing, 20 percent reported no symptoms at the time they were first evaluated—suggesting that a significant proportion of coronavirus carriers are "silent carriers," at least during the early stage of infection.
- Average time from exposure to symptom onset was 4.8 days. The median recovery time (from symptom onset to having no symptoms and testing negative for viral RNA) was 23 days for 60¬–69 year olds, 22 days for 50–59 year olds, and 19 days for 20–29 year olds. The average attack rate was 6.6 percent for close contacts and 11.2 for household contacts (assuming all contacts were tested and all positive

results were recorded).
https://www.thelancet.com/journals/laninf/article/PIIS1473-3099(20)30287-5/fulltext

A German group analysed viral loads in patients of different age categories and found no significant difference between any pair of age categories, including children. This suggests children may be as infectious as adults.
https://zoonosen.charite.de/fileadmin/user_upload/microsites/m_cc05/virologie-ccm/dateien_upload/Weitere_Dateien/analysis-of-SARS-CoV-2-viral-load-by-patient-age.pdf

Antibodies / Immunity
A study using a magnetic chemiluminescence assay reports acute antibody responses to SARS-CoV-2 in 63 patients followed until discharge. Overall seroconversion rate was 96.8%. Median time for seroconversion for both IgG and IgM was 13 days post-symptom onset. Three types of seroconversion were observed: synchronous seroconversion of IgG and IgM (9 patients), IgM seroconversion earlier than IgG (7 patients) and IgM seroconversion later than IgG (10 patients). IgG and IgM titers in the severe group were higher than those in the non-severe group. Additional serological testing of a cluster of 164 close contacts of patients with known COVID-19 shows that all contacts that were PCR positive had IgG and/or IgM antibodies, and that 4.3% (7/164) of the close contacts were missed by the nucleic acid test. Ten of the 164 close contacts who had IgG and/or IgM antibodies had not developed symptoms. The neutralizing activities of the detected IgG antibodies were not analysed.
https://www.nature.com/articles/s41591-020-0897-1

Nature Rev Immunol publishes an overview of the pathophysiology of SARS-CoV-2 infection, its interaction with the immune system and the subsequent contribution of dysfunctional immune responses to disease progression.
https://www.nature.com/articles/s41577-020-0311-8

Clinical symptoms / pathology
“Happy hypoxics”: Doctors are describing patients that, despite extraordinarily low blood-oxygen levels, are feeling quite comfortable. Clinicians call them happy hypoxics. They think subtle clotting might begin early in the lungs, perhaps as a result of inflammation in blood vessels, which could lead to blood clots and prevent proper blood oxygenation.
https://www.sciencemag.org/news/2020/04/why-dont-some-coronavirus-patients-sense-their-alarmingly-low-oxygen-levels

Risk Factors
Gender differences: A paper written by our colleagues A Caceres and JR González argues that the age-related mosaic loss of chromosome Y leads to the downregulation of several immune-response genes (mainly interferon induced genes) and could partly explain increased risk of COVID-19 mortality in men.
https://www.medrxiv.org/content/10.1101/2020.04.19.20071357v1
Another interesting (and not mutually exclusive explanation) could be the fact that females are known to express higher levels of TLR7, a receptor that recognizes viral RNA and whose gene escapes X chromosome inactivation in immune cells.
https://immunology.sciencemag.org/content/3/19/eaap8855?rss=1,
https://www.ncbi.nlm.nih.gov/pubmed/32253888

Treatment

Remdesivir buzz: A clinical trial in China with 237 severe COVID-19 patients (158 treated with remdesivir and 79 with placebo) indicates that remdesivir was not associated with statistically significant clinical benefits. However, they did observe a numerical reduction in time to clinical improvement in those treated earlier, something which requires confirmation in larger studies.
https://www.thelancet.com/journals/lancet/article/PIIS0140-6736(20)31022-9/fulltext

On the other hand, Anthony Fauci announced at the White House the first results of an international NIH-led clinical trial with 1063 patients with advanced COVID-19 disease and lung involvement. Remdesivir shortened by 31% the time for recovery in patients treated with remdesivir as compared to placebo (11 days versus 15 days, respectively). Some survival benefit was also observed (8% vs 11%). The Hospital Clinic is participating in the trial, under Jose Muñoz's coordination.
https://www.niaid.nih.gov/news-events/nih-clinical-trial-shows-remdesivir-accelerates-recovery-advanced-covid-19

An article in *Science* reports the development of multidrug nanoparticles made by conjugating squalene (an endogenous lipid) to adenosine (an endogenous immunomodulator) and then encapsulating α-tocopherol (a natural antioxidant) for the mitigation of uncontrolled inflammation. Selective delivery of adenosine and antioxidants could serve as a novel approach for the treatment of hyperinflammation including that observed in advanced COVID-19 disease.
https://advances.sciencemag.org/content/early/2020/04/27/sciadv.aaz5466cine

Tools:

COVideo19, an initiative led by Bloomberg School Students, is aimed at disseminating science-based information about COVID19. Videos have been translated into 19 languages https://www.globalhealthnow.org/covideo-19-bloomberg-school-students-translate-science

ISGlobal

COVID-19 EPIDEMIC

Epidemiological situation (05/05/2020, ECDC data):

Globally:
3 544 222 confirmed cases and 250 977 deaths

- The Americas region reported 53.2% of the global newly reported cases and 71.8% of the global newly reported deaths.
- The 4 major "trouble" countries now are Brazil, Russia, India, and United States (BRIUS)
- In Brazil (92,200 cases and 6,412 deaths reported), the coronavirus is ravaging poor, tightly packed neighbourhoods, where the disease is harder to control.
- Viet Nam, in contrast, reported its 1st new coronavirus infection in 9 days, a British traveler quarantined on arrival. The Southeast Asian country has managed a very effective response - a total of 271 cases and no deaths reported. More than 30 500 people have been quarantined and 261 000 tests have been carried out.
- China is facing growing pressure from national governments and international organizations to open its doors to an independent, international investigation into the origins of the novel coronavirus and the country's early response to the outbreak. The Chinese government claims it has launched its own investigation into the origins and early response to the pandemic, but has provided few details. https://www.sciencemag.org/news/2020/05/pressure-grows-china-independent-investigation-pandemic-s-origins
- World leaders raised almost €7.4bn to research Covid-19 vaccines and therapies at a virtual summit convened by EU commission president von der Leyen. The leaders (with the exception of Trump) undertook a two-hour pledging session promising to distribute any vaccine to poorer countries. Along with the US president, the event was not addressed by India and Russia. China was represented by its ambassador to the EU. https://www.theguardian.com/world/video/2020/may/04/world-leaders-pledge-74bn-euros-to-covid-19-research-video

Roadmaps to deconfinement
A modelling study with data from China indicates that without non-pharmaceutical interventions, the COVID-19 cases would have shown a 67-fold increase by February 29, 2020, and that combined NPIs achieved the strongest and most rapid effect. The lifting of travel restrictions since Feb 17 does not appear to lead to an increase in cases across China if the social distancing interventions (even at a 25% reduction) can be maintained. https://www.nature.com/articles/s41586-020-2293-x

The Vienna Airport will on-site coronavirus testing in a move aimed at enabling inbound passengers to avoid quarantine. The test at the airport would cost 190 euros and results would be ready in 2 to 3 hours. (ProMed mail).

In the US, states such as Texas, Indiana, and Florida are easing social distancing restrictions although they haven't met reopening criteria set by the White House (such as a decline in cases over 2 weeks). https://www.washingtonpost.com/

The Institute for Health Metrics and Evaluation at the University of Washington has more than doubled its projections of US COVID-19 deaths to 134,000 by early August. https://covid19.healthdata.org/united-states-of-america

Virus

A report in *Nature* shows the full functionality of a yeast-based synthetic genomics platform to genetically reconstruct diverse RNA viruses, including SARS-CoV-2 https://www.nature.com/articles/s41586-020-2294-9

Using a site-specific mass spectrometric approach, a study in *Science* reveals the glycan structures on a recombinant SARS-CoV-2 S immunogen. Findings show that SARS-CoV-2 S glycans differ from typical host glycan processing, which may have implications in viral pathobiology and vaccine design. https://science.sciencemag.org/content/early/2020/05/01/science.abb9983

Testing

Roche gets US FDA approval for its Elecsys anti-SARS-CoV-2 antibody test which it claims has a specificity greater than 99.8% and a sensitivity of 100% https://www.roche.com/media/releases/med-cor-2020-05-03.htm

A group from Yale compared RT-PCR detection in saliva versus nasopharyngeal swabs. They found that saliva yielded greater detection sensitivity and consistency throughout the course of infection. https://www.medrxiv.org/content/10.1101/2020.04.16.20067835v1

Transmission

Through a retrospective analysis of samples, a French group identified an individual hospitalized on Dec 27, 2019 and positive for SARS-CoV-2. He had not traveled outside of France recently or to China. These results suggest that the COVID-19 epidemic started much earlier. https://www.sciencedirect.com/science/article/pii/S0924857920301643

Testing of staff at a pork plant in Missouri revealed that 17% of the staff (373 employees) were positive by PCR. All of them were asymptomatic at the time of diagnosis. https://edition.cnn.com/2020/05/04/us/triumph-foods-outbreak-missouri/index.html

Antibodies / Immunity

Antibodies: A seroprevalence study performed by our colleagues at Hospital Clinic / ISGlobal reveals that the prevalence of antibodies against the RBD of the SARS-CoV-2 S protein among the hospital's healthcare workers was lower than expected (9.3%) and that the cumulative prevalence of infection (antibodies and/or PCR) was of 11.2%. https://www.medrxiv.org/content/10.1101/2020.04.27.20082289v1

Analysis of antibody responses to 15 SARSCoV2 antigens using Luciferase Immunoprecipitation System (LIPS) shows that antibodies against N, ORF3b, and ORF8 come up at early time points of illness and that N is the immunodominant antigen. The findings highlight the importance of investigating new immunogens that may mediate immune functions other than neutralization and that may be beneficial or harmful to the patient. https://www.medrxiv.org/content/10.1101/2020.04.30.20085670v1

A retrospective study with 112 COVID-19 patients admitted to Renmin Hospital of Wuhan University in February analysed antibodies to envelope protein E and nucleocapsid protein N antigen. 6.25% were negative for both antibodies. The rest were positive for IgG and/or IgM. IgGs were produced 10 days after infection, and lasted for a longer time than IgMs.
https://www.ncbi.nlm.nih.gov/research/coronavirus/publication/32358956

Cellular immunity: A study in *Immunity* assessed both SARSCoV2 antibody responses and cellular immunity in 14 patients recovered from COVID19. Results indicate that most patients developed neutralizing Abs and that their titers correlated with the number of virus-specific T cells.
https://www.cell.com/action/showPdf?pii=S1074-7613%2820%2930181-3

Another study shows the presence of S-reactive CD4+ T cells in 83% of COVID-19 patients, as well as in 34% of SARS-CoV-2 seronegative healthy donors, albeit at lower frequencies. Epitope recognition and activation status of the S-specific T cells differed between infected and healthy donors.
https://www.medrxiv.org/content/10.1101/2020.04.17.20061440v1

Interferon / other cytokine responses
A *Cell* paper identifies ACE2 and TMPRSS2 co-expressing cells within lung type II pneumocytes, ileal absorptive enterocytes, and nasal goblet secretory cells. It finds that ACE2 is a human interferon-stimulated gene (ISG) using airway epithelial cells in vitro, and these findings extend to *in vivo* viral infections. These data suggest that SARS-CoV-2 could exploit species-specific interferon-driven upregulation of ACE2 to enhance infection. https://www.cell.com/cell/pdf/S0092-8674(20)30500-6.pdf

Another *Cell* paper provides an in-depth analysis of the transcriptional response to SARS-CoV-2. It used cell and animal models of SARS-CoV-2 infections, in addition to transcriptional and serum profiling of COVID-19 patients. Findings revealed a unique and inappropriate inflammatory response defined by low levels of type I and III interferons (innate antiviral response) coupled with elevated chemokines and high expression of IL6.
https://www.cell.com/pb-assets/products/coronavirus/CELL_CELL-D-20-00985.pdf
Thanks David Payam for the tip!

Researchers from the Yale School of Public Health used metatranscriptomic sequencing to profile immune signatures in the bronchoalveolar lavage fluid of eight COVID-19 cases. The expression of proinflammatory genes, especially chemokines, was markedly elevated in COVID-19 cases. SARS-CoV-2 robustly triggered expression of numerous IFN-inducible genes (ISGs), with overrepresentation of genes involved in inflammation. Data also revealed increases in activated dendritic cells and neutrophils.
https://www.medrxiv.org/content/10.1101/2020.04.16.20067835v1

In contrast, an analysis of the transcriptome in blood samples from covid-19 patients in France found an impaired type I interferon activity and an exacerbated inflammatory response (partially driven by NFκB) in severe patients.
https://www.medrxiv.org/content/10.1101/2020.04.19.20068015v1

Forty-eight cytokines in the plasma samples from 50 COVID-19 cases including 11 critically ill, 25 severe and 14 moderate patients were measured and analyzed in combination with clinical data. Results show that IP-10 and MCP-3 were excellent predictors for the progression of COVID-19,
https://www.ncbi.nlm.nih.gov/research/coronavirus/publication/32360286

A comment in *Nat Rev Immunol* argues that targeting IL-17 is immunologically plausible as a strategy to prevent acute respiratory distress syndrome (ARDS) in COVID-19. https://www.nature.com/articles/s41577-020-0328-z

Clinical symptoms / pathology

Gut infection: A study in *Science* using human small intestinal organoids (hSIOs) shows that enterocytes were readily infected by SARS-CoV and SARS-CoV-2, as demonstrated by confocal- and electron-microscopy.
https://science.sciencemag.org/content/early/2020/04/30/science.abc1669
Another team in Heidelberg shows that human colon-derived cell lines and non-transformed colon organoids efficiently support SARS-CoV-2 infection and replication. They show a key role for type III interferon in controlling viral replication and spread in colonic epithelial cells https://www.biorxiv.org/content/10.1101/2020.04.24.059667v1

A case report in *NEJM* describes five cases of large-vessel stroke in patients younger than 50 years of age who presented to a hospital in New York City. SARS-CoV-2 infection was diagnosed in all five patients.
https://www.nejm.org/doi/10.1056/NEJMc2009787

The Canadian Medical Association Journal issues five recommendations on covid-19 related coagulopathy https://www.cmaj.ca/content/early/2020/05/01/cmaj.200685

Risk Factors

A third of patients admitted to hospital with covid-19 in the UK died, according to a study which tracked the outcomes of 16 749 patients. The study—the largest detailed description of covid-19 in Europe—found that being obese, male, or elderly reduces the chance of survival.
https://www.medrxiv.org/content/10.1101/2020.04.23.20076042v1

Immunosuppression in children does not seem to increase the risk of severe covid-19, according to UK National Institute for Health and Care Excellence guideline
https://www.bmj.com/content/369/bmj.m1802

Treatment

A single-arm multicentre study with tocilizumab (TCZ) involving 63 hospitalised adults with severe COVID-19 reveals an improvement in respiratory and laboratory parameters (the overall mortality was 11%)
https://www.ncbi.nlm.nih.gov/research/coronavirus/publication/32359035

Sanofi and Regeneron have modified the phase 2/3 trial of sarilumab, their monoclonal antibody against the interleukin-6 receptor. Patients described as critical will only receive the highest dose (400 mg) or placebo.
https://www.sanofi.com/en/media-room/press-releases/2020/2020-04-27-12-58-00

Antibodies from blood donated by people who recovered from the illness and hyper-immunoglobulins are becoming treatments of choice for COVID-19, with recombinant polyclonal antibody approaches to follow. The first results are encouraging but clinical trials are needed (ongoing trials are detailed in a table).
https://www.nature.com/articles/d41587-020-00011-1

The US FDA announced Friday that it would permit emergency use of remdesivir, from Gilead Sciences, to treat patients with Covid-19.

https://www.statnews.com/2020/05/01/fda-to-allow-emergency-use-of-gileads-covid-19-drug/

General reading:
This is a good overview on why the covid-19 situation is so complex
https://www.theatlantic.com/health/archive/2020/04/pandemic-confusing-uncertainty/610819/

Tools:
A team of over 50 faculty and trainees at Johns Hopkins are summarizing the most relevant COVID-19 literature and classifying it into 8 different areas – epi, clinical outcomes, treatment, modeling, vaccines, non-pharmaceutical interventions, diagnostics, and ecology and spillover. https://ncrc.jhsph.edu/
Thanks Quique Bassat for the tip!

Diana Salud (Divulgación de Iniciativas para Analizar la Adecuación en Salud) has added a resource on COVID-19 evidence developed by CiberESP and the Centro Cochrane Iberoamericano. https://es.cochrane.org/es/recursos/evidencias-covid-19
Thanks Aina Casellas for the tip!

ISGlobal

COVID-19 EPIDEMIC

Epidemiological situation (08/05/2020, ECDC data):

Globally:
3 807 852 confirmed cases and 269 068 deaths

- "No oxygen in the lungs of the world": Hospitals in Iquitos, Peru's largest city in the Amazon region, have run out of oxygen. The region, already affected by a large dengue outbreak, has been very hard-hit by covid-19.
- The Stop TB partnership published "The potential impact of the covid-19 response on tuberculosis in high-burden countries: a modelling analysis http://www.stoptb.org/assets/documents/news/Modeling%20Report_1%20May%202020_FINAL.pdf (*Thanks Elisa Lopez Varela for the tip*)

Roadmaps to deconfinement

In a letter to *Lancet*, Johan Giesecke, Karolinska Institute, explains Sweden's approach and says "very little we can do to prevent this spread: a lockdown might delay severe cases for a while, but once restrictions are eased, cases will reappear. I expect that when we count the number of deaths from COVID-19 in each country in 1 year from now, the figures will be similar, regardless of measures taken".
https://www.thelancet.com/action/showPdf?pii=S0140-6736%2820%2931035-7

UK researchers propose a "segment and shield" way to exit lockdown, whereby those most susceptible to the disease would still need to be shielded from anyone potentially infected. To achieve this, people sharing a house with a susceptible person, as well as care workers and health professionals, would need to protect themselves from infection and have frequent tests. All people outside of these groups would be able to come out of full lockdown, as long as they continued to follow some social-distancing measures, and quarantined their whole household if they developed coronavirus symptoms. It would still be vital to keep transmission rates as low as possible through testing and contact tracing. https://www.bbc.com/news/health-52542108

Virus

Los Alamos National Laboratory researchers reported in BioRxiv—not yet peer-reviewed—that 1 strain, named Spike D614G, became dominant quickly in Europe. The team hypothesized that the mutation allows the virus to more easily infect cells.
https://www.biorxiv.org/content/10.1101/2020.04.29.069054v1
However, experts warn this must be interpreted with caution, saying there's no sign that this or any SARS-CoV-2 mutation so far has changed general contagiousness or lethality. The paper's claims are plausible but not justified by the evidence it presents. More important, they're not convinced different strains of the coronavirus exist at all.
https://www.theatlantic.com/health/archive/2020/05/coronavirus-strains-transmissible/611239/

Mouse models

A study in *Nature* used transgenic mice bearing human ACE2 and infected with SARS-CoV-2 to study the pathogenicity of the virus. Intranasal inoculation of the virus resulted in weight loss and viral replication in the lung, together with infiltration of macrophages and lymphocytes in the alveolar interstitium. This model will be valuable for evaluating antiviral therapeutics and vaccines.
https://www.nature.com/articles/s41586-020-2312-y_reference.pdf
Another team used reverse genetics to remodel the S and mACE2 binding interface resulting in a recombinant virus (SARS-CoV-2 MA) that could utilize mACE2 for entry. The disease was more severe in aged mice, and showed more clinically relevant phenotypes than those seen in hACE2 transgenic mice. They show that therapeutic administration of IFN lambda-1a diminished viral replication in mice.
https://www.biorxiv.org/content/10.1101/2020.05.06.081497v1

Testing
Validation of the commercially available Euroimmun assay concludes it displays a nearly optimal diagnostic accuracy using IgG against SARS-CoV-2
https://www.medrxiv.org/content/10.1101/2020.05.02.20080879v1

Very useful *JAMA* viewpoint (and figure) on interpreting diagnostic tests for sars-cov-2
https://jamanetwork.com/journals/jama/fullarticle/2765837

Science describes the first results of the COVID-19 Symptom Tracker mobile app in terms of symptom tracking and spread prediction. Developed by the COronavirus Pandemic Epidemiology (COPE) consortium, it was launched in the UK on March 24, and the US on March 29, 2020, and has more than 2.8 million users as of May 2, 2020.
https://science.sciencemag.org/content/sci/early/2020/05/04/science.abc0473.full.pdf

Transmission
A new study by the LSHTM estimates that up to 75% on board the Diamond Princess may have been asymptomatic, suggesting that extensive testing of asymptomatic people will likely be part of an effective exit strategy.
https://cmmid.github.io/topics/covid19/asymp-transmission.html

A study in JAMA performed semen tests on 38 male patients with laboratory-confirmed COVID-19 aged 15 years and older between January 26 and February 16, 2020, in Shangqiu Municipal Hospital. Six patients had positive SARS-CoV-2 PCR, including 4 of 15 patients who were at the acute stage of infection and 2 of 23 patients who were recovering.
https://jamanetwork.com/journals/jamanetworkopen/fullarticle/2765654
These findings are not unexpected since ACE2 is expressed on testis, and do not prove the virus is viable or can be sexually transmitted

Clinical symptoms / pathology
Children:
Doctors in Europe and the US have been reporting an increase in cases of children (mostly under 4 years of age) who have developed an inflammatory syndrome similar to Kawasaki disease, with concerns over a possible link to the new coronavirus.
The scientific community is unsure as to whether these rare cases are triggered by COVID-19, and will remain vigilant in monitoring it.
https://www.statnews.com/2020/05/05/kids-inflammatory-kawasaki-disease-coronavirus-covid-19/

Eurosurveillance publishes the preliminary results of a national multicentre study, by the Italian Society of Paediatric Infectious Diseases with data from 168 children aged 1 day to 17 years. Hospital admission was inversely related to age. 67.3% of children had at least one parent who tested positive for SARS-CoV-2 infection. Symptom onset in relatives frequently preceded symptoms in the infected child. All children, including those with comorbidities, recovered fully, and no sequelae were reported at the time of submission. https://www.eurosurveillance.org/content/10.2807/1560-7917.ES.2020.25.18.2000600

Nature publishes a News piece on children and covid-19 infection, susceptibility and transmission. https://www.nature.com/articles/d41586-020-01354-0

Blood clotting:
Strong evidence for blood clotting problems in COVID-19 patients is accumulating. A Mount Sinai study analyzed data from more than 2,700 patients hospitalized for Covid-19. For critical patients who were on ventilators, they found mortality difference: 63% of those given anticoagulants survived versus 29% who did not get anticoagulants. The patients however were not randomly assigned to the groups and the authors call for Prospective randomized trials to determine whether systemic anticoagulants confer a survival benefit in hospitalized patients with COVID-19.
http://www.onlinejacc.org/content/early/2020/05/05/j.jacc.2020.05.001

Fatality rate:
A systematic review and meta-analysis of published evidence on COVID-19 until the end of April, 2020, concludes that the IFR of the disease across populations is 0.75% (0.49-1.01%) but with significant heterogeneity.
https://www.medrxiv.org/content/10.1101/2020.05.03.20089854v1

An analysis of 95,467 COVID.19 cases in Catalonia reveals that infection is seen in all age-sex strata, but severe forms of disease cluster in older men and nursing home residents. Although initially managed in primary care, 15% of cases require hospitalization within a month, with overall fatality of 4%.
https://www.medrxiv.org/content/10.1101/2020.05.04.20090050v1

Risk factors
The UK Office of National Statistics shows that black men are 4.2 times more likely to die from coronavirus than their white counterparts. Bangladeshi and Pakistani males were 3,6 times more likely to die from Covid-19 than white males. Differences were also observed with other ethnic groups. The difference in the virus's impact was caused not only by pre-existing differences in communities' wealth, health, education and living arrangements. https://www.theguardian.com/world/2020/may/07/black-people-four-times-more-likely-to-die-from-covid-19-ons-finds

Another study examines the race-ethnic disparities in Orange County, CA, and highlights a disproportionate rise in COVID-19 cases among Hispanic/Latinx communities https://www.medrxiv.org/content/10.1101/2020.05.04.20090878v1

Antibodies / Immunity
Seroprevalence studies:
New seroprevalence data from Geneva, estimates about 10 infections for every COVID-19 confirmed case. The study enrolled 1335 participants coming from 633 households.

The seroprevalence was of 3.1% the first week, 6.1% for the second week and 9.7% for the third week. https://www.medrxiv.org/content/10.1101/2020.05.02.20088898v1

A team in Japan conducted a cross-sectional serologic testing for SARS-CoV-2 antibodies using 1000 samples from outpatients attending a Kobe clinic from 31 Mar to 7 Apr 2020. 33 / 1000 serum samples (3.3%) were positive for IgG. If extrapolated to the Kobe population, this would mean an estimated 50,123 seropositive people, around 500-fold that of cases confirmed with PCR testing.
https://www.medrxiv.org/content/10.1101/2020.04.26.20079822v2

Combined virus RT-PCR testing and assessment for SARS-CoV2 antibodies was performed to determine the total number of individuals with SARS-CoV-2 infections in a small German town exposed to a super-spreading event (carnival festivities). Of the 919 individuals with evaluable infection status (405 households) 15.5% were infected. This is 5-fold higher than the number of officially reported cases for this community (3.1%). The estimated IFR was 0.36%.
https://www.medrxiv.org/content/10.1101/2020.05.04.20090076v1

Antibodies: A study led by Mt Sinai Hospital investigated both seroconversion and PCR-positivity in a cohort of 1343 convalescent serum donors in New York City. There were two groups of donors: those with PCR-confirmed and those with suspected (but not PCR confirmed) disease. The majority were mild cases. 99.5% of confirmed cases had antibodies either at the first or the second screen. The ELISA (developed by Krammer and co.) correlates with neutralizing assay, suggesting these individuals are protected. Many continued to be PCR positive even 28 days after recovery, likely because the PCR is detecting RNA fragments and not infectious virus. Only 38% of suspected cases had antibodies, suggesting many people who think had COVID-19 did not have it. https://www.medrxiv.org/content/10.1101/2020.04.30.20085613v1

A study with 44 COVID-19 patients shows that RBD-specific IgG responses were detectable in all patients 6 days after PCR confirmation. Using a clinical isolate of SARS-CoV-2, neutralizing antibody titers were also detectable in all patients 6 days after PCR confirmation. This dynamics was corroborated in a larger cohort of PCR-confirmed patients (n=231).
https://www.medrxiv.org/content/10.1101/2020.05.03.20084442v1

A study with 15 milk samples obtained from donors previously-infected with SARS-CoV-2 shows indicate that there is strong sIgA-dominant SARS-CoV-2 immune response in human milk after infection
https://www.medrxiv.org/content/10.1101/2020.05.04.20089995v1

T cells:
Circulating innate T cells (MAIT, γδT and iNKT cells) of critically ill Covid-19 patients presented a profound and persistent phenotypic and functional alteration. the expression of the CD69 activation marker on blood iNKT and MAIT cells at inclusion was predictive of disease severity.
https://www.medrxiv.org/content/10.1101/2020.05.03.20089300v1

The Sinai Immunology Review Project has published a very complete review of the current-state-of-knowledge on covid-19 immunology
https://www.cell.com/action/showPdf?pii=S1074-7613%2820%2930183-7

Treatment

Japan has authorised the use of anti-viral drug Remdesivir to treat coronavirus patients. https://www.bbc.com/news/live/world-52568948

A "simulated two-arm controlled study" shows that a remdesivir treatment group had a statistically significantly 29% reduction of deaths as compared to the control group. https://www.medrxiv.org/content/10.1101/2020.05.02.20088559v1

A study describes 21 patients (17 severe and 4 critical) treated with tocilizumab (anti-IL6R mAb). Most clinical and laboratory indicators returned to normal within five days and patients were discharged on average 15d after treatment. *The study did not include a control group* https://www.pnas.org/content/early/2020/04/27/2005615117 the

The antiparasitic drug suramin inhibits SARS-CoV-2 replication in vitro, protecting Vero E6 cells with an EC50 of ~20 μM, which is well below the maximum attainable level in human serum. The authors propose testing it in COVID-19 patients with properly randomized control trials.
https://www.biorxiv.org/content/10.1101/2020.05.06.081968v1

Antibody-mediated treatment:
A team in The Netherlands reports a human monoclonal antibody that neutralizes SARS-CoV-2 (and SARS-CoV) in cell culture. This cross-neutralizing antibody targets a shared epitope on these viruses and may offer potential for prevention and treatment of COVID-19. https://www.nature.com/articles/s41467-020-16256-y

The state-run Israel Institute for Biological Research (IIBR) also claims to have created antibodies that can "defeat the coronavirus inside humans"
https://www.theguardian.com/world/2020/may/05/israel-netherlands-studies-claim-progress-in-covid-19-antibody-trials

A preprint reports the isolation of four human-origin monoclonal antibodies from a convalescent patient in China. All isolated antibodies display neutralization abilities in vitro. Two of them block the binding between RBD and ACE2 in a non-competitive manner. The results highlight the promise of antibody-based therapeutics
https://www.medrxiv.org/content/10.1101/2020.05.01.20077743v1

A team from Belgium describes the isolation of single-domain antibodies (VHHs) from a llama immunized with prefusion-stabilized coronavirus spikes. These VHHs neutralize MERS-CoV or SARSCoV-1 S pseudotyped viruses, respectively. They also demonstrated that the SARS-CoV-1 S-directed VHH cross-reacts with SARS-CoV-2 S and neutralizes SARS-CoV-2 pseudotyped virus when fused with human IgG.
https://www.cell.com/cell/pdf/S0092-8674(20)30494-3.pdf

Climate change
COVID-19 and climate change in five charts: The BBC posts a special report on how the global pandemic is limiting carbon emissions and what this means for climate change
https://www.bbc.com/news/science-environment-52485712

ISGlobal

COVID-19 EPIDEMIC

Epidemiological situation (12/05/2020, ECDC data):

Globally:
4 137 193 confirmed cases and 285 760 deaths

- The 5 major countries with ascent, or no descent, in their log- death curves are: BRIMUS (Brazil, Russia, India, Mexico and US)
- Suspicions are growing that Russia (current mortality rate of 0.9%) is undercounting its coronavirus death toll. An emerging explanation is that it does not automatically list COVID-19 as the cause of death if the deceased tested positive for the coronavirus. This highlights the problem that countries are using varying methods/criteria for counting coronavirus deaths. (ProMed Mail)
- In sub-Saharan Africa, more than 500,000 additional AIDS-related deaths could be caused by 6 months of COVID-19-related disruptions to ARV therapy. https://www.who.int/news-room/detail/11-05-2020-the-cost-of-inaction-covid-19-related-service-disruptions-could-cause-hundreds-of-thousands-of-extra-deaths-from-hiv
- The WHO warns about the situation in Yemen, one of the most difficult globally due to the disruption of the entire health infrastructure.
- A comment in *Cell* points to the dangers of biomedical research becoming COVID-19 centered. It concludes that instead, based on what we have learned during the current crisis, smart, lasting, balanced and joint investments in improving our health as one global society are warranted. https://www.cell.com/action/showPdf?pii=S0092-8674%2820%2930576-6

Roadmaps to deconfinement

Post-deconfinement rebounds

South Korea: A new cluster of COVID-19 cases emerged in the country's capital Seoul, sparking fear of a 2nd wave of infections in the country.

China: is introducing renewed restrictions after 2 cities reported new cases of the virus. A new cluster of 5 cases also detected in Wuhan, none of them travel-related. Wuhan is planning to conduct full-scale nucleic acid testing of its 11 million residents over the next 10 days. https://www.bbc.com/news/world-asia-china-52629213

Virus

Nature has published the isolation of a SARS-CoV-2 related coronavirus from Malayan pangolins. The Pangolin-CoV was detected in 17 of 25 Malayan pangolins analyzed. Circulating antibodies against Pangolin-CoV in infected pangolins reacted with the S protein of SARS-CoV-2. The results suggest SARS-CoV-2 might have originated from the recombination of a Pangolin-CoV-like virus with a Bat-CoV-RaTG13-like virus. https://www.nature.com/articles/s41586-020-2313-x#disqus_thread

Pangolins may be able to tolerate the virus because they lack 2 genes (IFIH1 and ZBP1) that sense viral RNA.
https://www.frontiersin.org/articles/10.3389/fimmu.2020.00939/full

Meanwhile, a paper in *Cell* reports a novel bat-derived coronavirus, RmYN02, identified from a metagenomics analysis of samples from 227 bats collected from Yunnan Province in China in 2019. It shares 93.3% nucleotide identity with SARS-CoV-2 at the complete genome level and 97.2% identity in the 1ab gene, making it the closest relative of SARS-CoV-2 reported to date. However, it shares only 61.3% with SARS-CoV-2 in the receptor binding domain (RBD) and might not bind to ACE2.
https://www.cell.com/current-biology/fulltext/S0960-9822(20)30662-X

One of the features distinguishing SARS-CoV-2 from its more pathogenic counterpart SARS-CoV is the presence of premature stop codons in its ORF3b gene. A study shows that SARS-CoV-2 ORF3b is a potent interferon antagonist. Authors also identify a natural variant (isolated from a severe patient) with an extended ORF3b that may exacerbate COVID-19 symptoms.
https://www.biorxiv.org/content/10.1101/2020.05.11.088179v1

Testing/ Tracing
A policy forum in *Science* points out that the question is not whether to use new data sources for COVID-19 surveillance, but how.
https://science.sciencemag.org/content/early/2020/05/11/science.abb9045

Transmission
An analysis of published data from Hong Kong and China indicates a transmission window between 2.95 days before symptom onset and 1.72 days after symptom onset, and a proportion of pre-symptomatic transmission ranging from 33.7% to 79.9%.
https://www.medrxiv.org/content/10.1101/2020.05.08.20094870v1

Hospital settings: PCR testing of 1574 healthcare workers in Milano revealed positive tests for 138 among 1,573 HCWs (8.8%), with a marked difference between symptomatic (20.2%) and asymptomatic (3.7%) subjects.
https://www.medrxiv.org/content/10.1101/2020.05.07.20094276v1

An antibody seroprevalence study in Bergamo (3,320 tests) reveals rather unexpected results: 61% positivity in the general population by the end of April, versus only 23% among healthcare workers (!) *PPE effect?*
http://www.ats-bg.it/upload/asl_bergamo/gestionedocumentale/CSATSBG2020-04-30CSATSBG2020-04-30coronavirusesitisierologici_784_31010.pdf

Risk factors
A study of 48 children in ICU with COVID19 confirms that severe illness in children is significant but far less frequent than in adults. Six of the children were healthy, with no pre-existing conditions.
https://jamanetwork.com/journals/jamapediatrics/fullarticle/2766037

Antibodies / Immunity
Herd immunity: A UK team argues that a lower fraction of SARS-CoV-2 infected people is required for herd immunity to appear. The underlying reason is that when immunity is induced by disease spreading, the proportion infected in groups with high contact rates is greater than that in groups with low contact rates. They estimate that the

disease-induced herd immunity level is 43% rather than 60%.
https://www.medrxiv.org/content/10.1101/2020.05.06.20093336v1

Post-infection immunity: A viewpoint in JAMA concludes that to date there is no evidence of reinfection (which does occur with the 4 other coronaviruses) and no evidence for spread from a clinically recovered patient, while the duration of neutralizing antibodies is uncertain.
https://jamanetwork.com/journals/jama/fullarticle/2766097

Treatment
Encouraging results for a multicentre, prospective, open-label, randomised phase 2 trial with combined interferon beta-1b, lopinavir–ritonavir, and ribavirin treatment in adults with mild/moderate COVID-19 who were admitted to six hospitals in Hong Kong. The combination group had a significantly shorter median time from start of study treatment to negative nasopharyngeal swab (7 days) than the control group (12 days). No patients died during the study.
https://www.thelancet.com/journals/lancet/article/PIIS0140-6736(20)31042-4/fulltext

In an observational study involving patients with Covid-19 who had been admitted to the hospital, hydroxychloroquine administration was not associated with either a greatly lowered or an increased risk of intubation or death.
https://www.nejm.org/doi/full/10.1056/NEJMoa2012410?query=main_nav_lg

A comment in *Lancet* provides recommendations for the management of coagulopathy in covid-19 patients https://www.thelancet.com/action/showPdf?pii=S2352-3026%2820%2930145-9

STAT news writes on the NIH's controversial decision to stop its big remdesivir study
https://www.statnews.com/2020/05/11/inside-the-nihs-controversial-decision-to-stop-its-big-remdesivir-study/

ACE inhibitors:
- A study with two independent cohorts of patients with heart failure, plasma concentrations of ACE2 were higher in men than in women, but use of neither an ACE inhibitor nor an ARB was associated with higher plasma ACE2 concentrations.
https://academic.oup.com/eurheartj/advance article/doi/10.1093/eurheartj/ehaa373/5834647
- Similarly, a systematic review suggests that prior use of ACEIs /ARBs is even associated with a decreased risk of death or critical outcome among SASR-CoV-2 infected patients. https://www.medrxiv.org/content/10.1101/2020.05.06.20093260v1
- A newly-released WHO scientific brief summarizes the current evidence on the impact of angiotensin-converting enzyme (ACE) inhibitors and receptor blockers on severe acute respiratory illness due to COVID-19. There is low-certainty evidence that patients on long-term therapy with ACE inhibitors or ARBs are not at higher risk of poor outcomes from COVID-19. https://www.who.int/news-room/commentaries/detail/covid-19-and-the-use-of-angiotensin-converting-enzyme-inhibitors-and-receptor-blockers

A comment in *Lancet* provides recommendations for the management of coagulopathy in covid-19 patients https://www.thelancet.com/action/showPdf?pii=S2352-3026%2820%2930145-9

Vaccines
Whether BCG-induced trained immunity can offer protection against COVID-19 is worth investigating, according to a comment in Nat Rev Immunol
https://www.nature.com/articles/s41577-020-0337-y

Tools:
The COVID-19 Disease Map is an effort to build a comprehensive, standardized knowledge repository of SARS-CoV-2 virus-host interaction mechanisms, guided by input from domain experts and based on published work.
https://doi.org/10.17881/covid19-disease-map

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COVID-19 EPIDEMIC

Epidemiological situation (15/05/2020, ECDC data):

Globally:
4 405 680 confirmed cases and 302 115 deaths

- The global daily covid-19 death toll is easing, with the US accounting for 30% of deaths. Brazil has the highest number of daily deaths outside the US.
- In Africa, the five countries reporting most cases are South Africa (12 739), Egypt (10 829), Morocco (6 607), Algeria (6 442) and Ghana (5 530).
- The International Council of Nurses (ICN) warns that at least 90 000 healthcare workers have been infected, and more than 260 nurses have died and that this is surely an underestimation. Only in Iran, a total of 126 medical staffers have died since the virus was first reported. ICN is calling for data on healthcare worker infections and deaths to be systematically collected by national governments and held centrally at the WHO. https://www.icn.ch/news/icn-calls-data-healthcare-worker-infection-rates-and-deaths

Roadmaps to deconfinement

Post-deconfinement rebounds
Up to 11 million people in Wuhan will be tested over a period of 10 days for SARS-CoV-2 within the coming days, after a new cluster of 6 cases (none of them imported) emerged. https://www.bbc.com/news/world-asia-china-52629213

Seroprevalence studies
Only around 5% of the Spanish population has antibodies against the virus, according to the first results of the seroprevalence study with almost 70,000 participants. Big differences between geographical areas were observed: from Soria with 14.3% or Madrid with 11.3% to Murcia or Asturias with 2%. This also indicates that around 2M people were infected (almost 10 times the number of confirmed cases) and that the average infection fatality rate lethality rate would be around 1.1%. According to the study, 33% of seropositive individuals do not recall having symptoms.

A modelling study in *Science* estimates that 2.8 million people in France have been infected with COVID-19 - only 4.4% of the population. Seroprevalence studies in the highly-touched Oise region indicate a seroprevalence of 3%
https://science.sciencemag.org/content/early/2020/05/12/science.abc3517

Antibodies / Immunity

Subclinical infections: A study with 38 participants (patients, staff, nurses, physicians) shows a high prevalence of subclinical seroconversion in individuals interacting in a pediatric dialysis unit. https://jamanetwork.com/journals/jama/fullarticle/2766215

Antibody dynamics: A study that isolated B cells from a COVID19 patient indicates that the majority of antibodies against the viral envelope spike that were generated during the first weeks of COVID-19 infection are non-neutralizing and target epitopes outside the RBD. https://www.biorxiv.org/content/10.1101/2020.05.12.091298v1

T cells and cross-protection by other coronaviruses?: Using HLA class I and II predicted peptide 'megapools', a team from La Jolla Institute of Immunology identified

circulating SARS-CoV-2–specific CD8+ and CD4+ T cells in ~70% and 100% of COVID-19 convalescent patients, respectively. CD4+ T cell responses to spike were robust and correlated with the magnitude of anti-SARS-CoV-2 IgG and IgA titers. Importantly, SARS-CoV-2–reactive CD4+ T cells were detected in ~40-60% of unexposed individuals, suggesting cross-reactive T cell recognition between circulating 'common cold' coronaviruses and SARS-CoV-2. This could help explain why some people develop no or mild symptoms.
https://www.cell.com/action/showPdf?pii=S0092-8674%2820%2930610-3

Transmission
Gut infection: Productive infection of SARS-CoV-2 in ACE2+ mature enterocytes in human small intestinal enteroids is reported. Expression of two mucosa-specific serine proteases, TMPRSS2 and TMPRSS4, facilitated SARS-CoV-2 spike fusogenic activity and promoted virus entry into host cells. Importantly, viruses released into the intestinal lumen were inactivated by simulated human colonic fluid, and infectious virus was not recovered from stool specimens of COVID-19 patients, suggesting that SARS-CoV-2 does not spread via fecal-oral transmission.
https://immunology.sciencemag.org/content/5/47/eabc3582

Another study also shows that SARS-CoV-2 can infect human intestinal organoids as well as bat intestinal cells. Expandable intestinal organoids derived from horseshoe bats (*Rhinolophus sinicus*) can recapitulate bat intestinal epithelium. These bat enteroids are fully susceptible to SARS-CoV-2 infection and sustain robust viral replication. https://www.nature.com/articles/s41591-020-0912-6

A study on 86 convalescent plasma donors shows prolonged viral RNA shedding after COVID-19 symptom resolution in older convalescent donors. No evidence this was viable virus. https://www.medrxiv.org/content/10.1101/2020.05.07.20090621v1

Testing/ Tracing
PCR: Over the 4 days of infection before the typical time of symptom onset (day 5), the probability of a false-negative result in an infected person decreases from 100% on day 1 to 67% on day 4. On the day of symptom onset, the median false-negative rate was 38%. https://www.acpjournals.org/doi/10.7326/M20-1495

Serology: A report by the Doherty Institute Australia presents the results of post-market validation of serological assays for the detection of SARS-CoV-2 antibodies.
https://www.health.gov.au/resources/publications/post-market-validation-of-three-serological-assays-for-covid-19-final-report

Risk factors
Immunodeficiency:
A small study comparing 21 HIV-positive and 40 HIV-negative COVID-19 patients shows a trend toward increased rates of ICU admission, mechanical ventilation, and mortality in HIV-positive patients, but these differences were not statistically significant https://www.medrxiv.org/content/10.1101/2020.05.07.20094797v1

A case report was posted a couple of weeks ago, on two patients with X-linked agammaglobulinemia (XLA) of 34 and 26 years of age with complete absence of B cells from peripheral blood who developed COVID-19 pneumonia but recovered.
https://onlinelibrary.wiley.com/doi/10.1111/pai.13263d

Overwhelmed hospitals: A retrospective analysis of 72 adult patients hospitalized with COVID-19 in 2 hospitals in the San Francisco Bay area (both performing clinical trials with remdesivir) shows that of the 21 (29% of total) intensive care unit patients, 3 (14.3% died). These death rates were lower than those reported from regions of the US experiencing a high volume of COVID-19 patients (40-50%).
https://wwwnc.cdc.gov/eid/article/26/8/20-1776_article

Children: An Italian study found a 30-fold increased incidence of Kawasaki-like disease in children since the start of the epidemic.
https://www.thelancet.com/journals/lancet/article/PIIS0140-6736(20)31103-X/fulltext

Inequality and COVID-19:
UK has published a document analysing covid-19 deaths by occupation. One of the main findings is that men working in the lowest skilled occupations had the highest rate of death involving COVID-19, with 21.4 deaths per 100,000 males; men working as security guards had one of the highest rates, with 45.7 deaths per 100,000.
Thanks for the tip, Kurt Straif!
You can also see this related feature in BBC: https://www.bbc.com/news/uk-52637008

Along this line, an editorial in *Science* explores inequality and pandemics, since the Black Death to COVID-19. Today in Washington DC, 45% of COVID-19 cases but 79% of deaths are of black people. As of late April, black people made up more than 80% of hospitalized COVID-19 patients in Georgia, and almost all COVID-19 deaths in St. Louis. Similar trends have been seen for black and South Asian patients in the UK. And in Iowa, Latinos comprise more than 20% of patients, despite being only 6% of the population. https://www.sciencemag.org/news/2020/05/black-death-fatal-flu-past-pandemics-show-why-people-margins-suffer-most#

Treatment
Convalescent plasma:
Patients (n=25) with severe and/or life-threatening COVID-19 disease enrolled at the Houston Methodist hospitals, were transfused with convalescent plasma obtained from donors with confirmed SARS-CoV-2 infection. By day 14 post-transfusion, 19 (76%) patients had at least a 1-point improvement in clinical status and 11 were discharged.
https://www.medrxiv.org/content/10.1101/2020.05.08.20095471v1

A study analysed key safety metrics after transfusion of ABO-compatible human COVID-19 convalescent plasma in 5,000 hospitalized adults with severe or life threatening COVID-19, with 66% in the intensive care unit. Early indicators suggest that transfusion of convalescent plasma is safe.
https://www.medrxiv.org/content/10.1101/2020.05.12.20099879v1

Tocilizumab: Vall d'Hebron Hospital reports 82 patients with COVID19 who received at least one dose of tocilizumab. Mortality at 7 days was 26.8%. They conclude that time from lung injury onset to tocilizumab administration may be critical to patient recovery. https://www.medrxiv.org/content/10.1101/2020.05.07.20094599v1

Hydroxychloroquine: a no go?
BMJ publishes results from two hydroxychloroquine trials, both negative.
A multicentre, open label, randomised controlled trial in China with 150 patients with mild to moderate covid-19 showed no benefit of hydroxychloroquine in terms of negative conversion. https://www.bmj.com/content/369/bmj.m1849

A comparative observational study using data collected from 181 patients with covid-19 that required oxygen but not intensive care, in four French hospitals. No benefit in survival was observed and adverse cardiac effects were observed in the treated group. https://www.bmj.com/content/369/bmj.m1844

In addition, among 1438 patients hospitalized in metropolitan New York with COVID-19, treatment with hydroxychloroquine, azithromycin, or both, compared with neither treatment, was not significantly associated with differences in in-hospital mortality. https://jamanetwork.com/journals/jama/fullarticle/2766117

Repurposed drugs: 24 FDA-approved drugs which exhibited substantial antiviral effect against SARS-CoV-2 in Vero cells were screened using human lung cells. Nafamostat is the most potent drug in human lung cells (IC50 = 0.0022μM). https://www.biorxiv.org/content/10.1101/2020.05.12.090035v1

Vaccines

The Oxford/Jenner group that recently published results for a chimpanzee adenoviral vectored vaccine for MERS, describes results for its ChAdOx1 nCOV-19 vaccine in mice and non-human primates. A single vaccination with ChAdOx1 nCoV-19 induced a humoral and cellular immune response in rhesus macaques**.** Vaccinated animals had significantly reduced viral load in bronchoalveolar lavage fluid and respiratory tract tissue upon challenge with SARS-CoV-2, as compared with control animals, and no pneumonia was observed in vaccinated animals. Importantly, no evidence of immune-enhanced disease following viral challenge in vaccinated animals was observed. The phase I clinical trial with ChAdOx1 nCoV-19 started on April 23, 2020. As of May 13, more than 1000 volunteers have participated in the trials. https://www.biorxiv.org/content/10.1101/2020.05.13.093195v1.full.pdf

A cohort study compares covid-19 positivity rate among Israelis who received or not the BCG vaccine in childhood. No significant difference was observed. https://jamanetwork.com/journals/jama/fullarticle/2766182

Pets

Experimental infection of cats with SARS-CoV-2 shows there can be cat to cat transmission of the virus. The infected cats showed no disease symptoms and shed virus during 5 days approx. https://www.nejm.org/doi/full/10.1056/NEJMc2013400?query=TOC

Dogs can be infected with SARS-CoV-2 (according to RT-PCR, serology, genome sequencing and virus isolation assays) https://www.nature.com/articles/s41586-020-2334-5

ISGlobal

COVID-19 EPIDEMIC

Epidemiological situation (18/05/2020, ECDC data):

Globally:
4 766 468 confirmed cases and 318 201 deaths

- During the 73rd World Health Assembly yesterday, tensions rose between US and China amid calls for investigations into source of the virus in China and the WHO's COVID-19 pandemic response.
- Brazil is on its way to becoming the next epicenter of the COVID-19 pandemic. Brazil now has 241,000 confirmed cases, topping Spain and Italy—but testing remains far behind other countries and estimates show the actual number could be 15X higher.
- Japan has agreed to contribute over USD 2.7 million to help 9 countries in the Americas strengthen their capacities to detect cases, monitor, and control outbreaks of COVID-19, as well as ensure that reliable public health information on the COVID-19 pandemic is available to people involved in the response and the general public
- A community of youth influencers named the Global Shapers Community is working with WHO Europe to flag rumours, report on the tone of discussions on their channels, and ask questions, as well as share information and project ideas http://www.euro.who.int/en/health-topics/health-emergencies/coronavirus-covid-19/news/news/2020/5/covid-19-who-joins-forces-with-young-global-shapers-to-disseminate-health-advice
- A preprint describes how Vietnam has controlled SARS-CoV-2 spread through the early introduction of communication, contact-tracing, quarantine, and international travel restrictions. One hundred days after SARS-CoV-2 was first reported in Vietnam on January 23rd, 270 cases have been confirmed, with no deaths. https://www.medrxiv.org/content/10.1101/2020.05.12.20099242v1

Roadmaps to deconfinement
Schools: A modelling study suggests that stepping out of lockdown should start with school re-openings while maintaining distancing measures. It estimates that adults aged 30-50 are responsible for the majority of transmission and that micro-distancing is critically important to maintain Reff <1.
https://www.medrxiv.org/content/10.1101/2020.05.12.20099036v1

No asymptomatic carriage of SARS-CoV-2 was detected among a random sample of children (n=84) aged between 6 and 30 months attending daycare in Belgium shortly after the start of the epidemic (February 29th) and before the lockdown (March 18th).
https://www.medrxiv.org/content/10.1101/2020.05.13.20095190v1
Along these lines, UK epidemiologists say there is some evidence children may not spread the virus as much as adults *(Thanks Matiana González for the tip!)*
https://www.nytimes.com/reuters/2020/05/19/world/europe/19reuters-health-coronavirus-britain-epidemiologist.html

Wuhan screening: Preliminary data from the screening effort by Wuhan from May 12 to May 15, May shows that around 350,000 people have been screened and only 36 asymptomatic infections were identified. None of these asymptomatic infections have converted to symptomatic (ProMed-mail).

Testing and contact tracing: A model using data mobility in Boston indicates that, following the strict social distancing measures, a policy based on a robust level of testing, contact-tracing and household quarantine could keep the disease at bay. Assuming the identification of 50% of the symptomatic infections, and the tracing of 40% of their contacts and households, the ensuing reduction in transmission allows the reopening of economic activities while attaining a manageable impact on the health care system. https://www.medrxiv.org/content/10.1101/2020.05.06.20092841v1

Seroprevalence studies
A serology study in Milan on blood from healthy donors indicates that by the end of April, 4.4-10.8% of healthy adults had evidence of seroconversion
https://www.medrxiv.org/content/10.1101/2020.05.11.20098442v1

A perspective in *Science* by Krammer et al reviews the pros and caveats of serological assays in managing covid-19. To reduce false positives, they propose a combined sequential approach whereby a positive lateral flow test result is confirmed with a second test that produces a titer—which also indicates the robustness of the response and could be linked to the presence and duration of protection**.**
https://science.sciencemag.org/content/early/2020/05/14/science.abc1227

Transmission

A meta-analysis provides an estimate of asymptomatic COVID19 rate of 16%, lower than that estimated by other studies, and a lower transmission rate as compared to symptomatic individuals.
https://www.medrxiv.org/content/10.1101/2020.05.10.20097543v1

A climate-dependent epidemic model shows that, while variations in weather may be important for endemic infections, during the pandemic stage of an emerging pathogen the main driver is lack of population immunity and climate has only a modest impact. Authors conclude that strong outbreaks are likely in more humid climates and summer weather will not substantially limit pandemic growth.
https://science.sciencemag.org/content/sci/early/2020/05/15/science.abc2535.full.pdf

In contrast to a study in the previous update, a Chinese team reports the isolation of infectious SARS-CoV-2 from stool samples of COVID-19 patients.
https://wwwnc.cdc.gov/eid/article/26/8/20-0681_article *However, this was observed in 2 out of 28 patients feces specimens analysed.*

Testing/ Tracing

Rapid antigen test: The FDA has issued an Emergency Use Authorization (EUA) for Quidel's Sofia2 SARS Antigen Fluorescent Immunoassay. The test, read on a dedicated analyser, detects SARS-CoV-2 nucleocapsid protein from nasal swabs in 15 min
https://www.quidel.com/immunoassays/rapid-sars-tests/sofia-2-sars-antigen-fia

RNA: The agency also granted an EUA for a CRISPR-based SARS-CoV-2 fluorescent assay marketed by Sherlock Biosciences. The test should give results in an hour.
https://www.fda.gov/media/137747/download

Serology tests: F. Krammer and his team publish in *Nature* their ELISA assay for the screening and identification of human SARS-CoV-2 seroconverters. They show that there is no or only negligible cross-reactivity from human coronaviruses to SARS-CoV-2 and found excellent correlation between ELISA titers against the spike protein and virus neutralization. This assay does not require the handling of infectious virus, can be

adjusted to detect different antibody types in serum and plasma and is amenable to scaling. https://www.nature.com/articles/s41591-020-0913-5

Symptoms / Risk factors
Among individuals with COVID-19 enrolled in a household study, loss of taste and/or smell was the fourth most commonly reported symptom (26/42; 62%), and among household contacts, it had the highest positive predictive value (83%; 95% CI: 55-95%) for COVID-19. https://www.medrxiv.org/content/10.1101/2020.05.13.20101006v1

Children:
Pediatric inflammatory multisystem syndrome associated with SARS-CoV-2 might represent a post-infectious inflammatory syndrome, which might be antibody or immune-complex mediated, according to a comment in Lancet. It refers to an Italian cohort where there was little evidence of viral replication.
https://www.thelancet.com/journals/lancet/article/PIIS0140-6736(20)31129-6/fulltext
In total, about 230 suspected cases of this new paediatric inflammatory multisystem syndrome temporally associated with SARS-CoV-2 infection (PIMS-TS) have been reported in EU/EEA countries and the UK in 2020, including 2 fatalities, one in the UK and one in France. The ECDC classifies the overall risk as low and underlines that this is a rare condition and its potential link with COVID-19 is neither established nor well understood. https://www.ecdc.europa.eu/sites/default/files/documents/covid-19-risk-assessment-paediatric-inflammatory-multisystem-syndrome-15-May-2020.pdf

Inflammatory markers: A multicenter retrospective study of demographic, clinical, laboratory and immunological features of 574 Spanish COVID-19 inpatients showed that 27.7% cases were mild, 42% moderate and 30.3%, severe. Interleukin 6 levels increased with severity.
https://www.medrxiv.org/content/10.1101/2020.05.13.20101345v1

A study with 42 patients identified broad changes in neutrophils, NK cells, and monocytes during severe COVID-19, suggesting excessive mobilization of innate lineages. https://www.biorxiv.org/content/10.1101/2020.05.18.101717v1

Antibodies / Immunity
A Swiss team describes multiple monoclonal antibodies targeting SARS-CoV-2 S identified from memory B cells of an individual infected with SARS-CoV in 2003. One antibody, named S309, potently neutralizes SARS-CoV-2 and SARS-CoV by engaging the S receptor-binding domain. Antibody cocktails including S309 further enhanced SARS-CoV-2 neutralization and may limit the emergence of neutralization-escape mutants. This may be uses as prophylaxis in high-exposure individuals or as a post-exposure therapy to limit or treat severe disease.
https://www.nature.com/articles/s41586-020-2349-y
In contrast, two other studies suggest limited cross-reactivity between SARS and SARS-CoV-2. The first study suggests that while cross-reactivity in antibody binding to the spike protein is common, cross-neutralization of the live viruses may be rare
https://www.cell.com/cell-reports/fulltext/S2211-1247(20)30702-6
The second study provides some good news: they found that there are significant levels of neutralizing antibodies in recovered SARS patients 9–17 years after initial infection. https://www.tandfonline.com/doi/full/10.1080/22221751.2020.1761267

Several studies have now established that the hyperinflammatory response induced by SARS-CoV-2 is a major cause of disease severity and death in infected patients. A *Nat Immunol* review describes the potentially pathological roles of macrophages during SARS-CoV-2 infection and discuss ongoing and prospective therapeutic strategies to

modulate macrophage activation in COVID-19 patients.
https://www.nature.com/articles/s41577-020-0331-4

Treatment
Lopinavir/ritonavir alone: A randomized, controlled, open-label trial of lopinavir–ritonavir failed to detect any reduction in SARS-CoV-2 viral load or significant clinical benefit in 199 severe COVID-19 patients in Jin Yin-Tan Hospital, Wuhan.
https://www.nejm.org/doi/full/10.1056/NEJMoa2001282
Tocilizumab: A preprint describes 11 patients that received tocilizumab in the US and concludes it should be used with caution in severe and critically ill patients and that randomized clinical trials are necessary.
https://www.medrxiv.org/content/10.1101/2020.05.13.20100404v1
A retrospective case-control study in confirmed COVID 19 positive patients with ARDS requiring mechanical ventilation and compared outcome in terms of mortality and length of stay amongst those who received tocilizumab (n=114) opposed to those that did not (n=92). Survival rate was significantly lower in the control group (48%) compared to patients who received tocilizumab (61.36 %).
https://www.medrxiv.org/content/10.1101/2020.05.13.20100081v1

Drug candidates: *Nature medicine* overviews the 15 leading drugs repurposed for covid-19: chloroquine-hydroxychloroquine (antimalarials), liponavir/ritonavir (HIV protease inhibitors), nafamostat and camostat (serine protease inhibitors), famotidine (heart burn medication), umifenovir (prophylaxis for influenza virus), nitazoxanide and ivermectin (antiparasitic drugs), corticosteroids (anti-inflammatory), tocilizumab and sarilumab (IL6 blocking antibodies), bevacizumab (anti-VEGF), fluvoxamine (immunomodulator) https://www.nature.com/articles/d41591-020-00019-9

Vaccines
Moderna announced encouraging early data on its mRNA-1273 vaccine: 8 patients who received two doses of the vaccine at the lowest and middle doses tested (25 and 100 micrograms) developed neutralizing antibodies to the virus at levels similar to people who had recovered from infection. Three volunteers in the highest dose arm (250 ug) developed Grade 3 systemic reactions after receiving the second dose. There were no life-threatening adverse events. A new arm of the trial will test a 50-microgram dose, which may suggest concern that the 25-microgram dose may be too low.
https://www.statnews.com/2020/05/18/early-data-show-moderna-covid-19-vaccine-generates-immune-response/

Impact of Quarantine on Air Pollution
A comment in *Lancet Planetary Health* examines the change in air pollution and the potentially avoided cause-specific mortality during the large-scale quarantine in China. They estimate that improved air quality during the quarantine period avoided a total of 8911 NO2-related deaths and 3214 PM2·5-related deaths
https://www.thelancet.com/journals/lanplh/article/PIIS2542-5196(20)30107-8/fulltext

ISGlobal

COVID-19 EPIDEMIC

Epidemiological situation (22/05/2020, ECDC data):

Globally:
5 067 579 confirmed cases and 332 711 deaths

- World leaders rejected US efforts to punish WHO and China over the pandemic, rallying instead for global solidarity at the World Health Assembly. The EU, China, and even Russia agreed to an "impartial, independent" examination of the pandemic response https://www.nytimes.com/2020/05/19/us/politics/trump-who-coronavirus.html
- The COVID-19 crisis has again exposed the fragilities of social and economic systems, according to a viewpoint in Nature. It calls for a multidisciplinary effort to build better tools to weigh trade-offs between health and wealth. https://www.nature.com/articles/d41586-020-01504-4

Confinement and deconfinement strategies
Late confinement: A Columbia University preprint study estimates that if the U.S. had begun imposing social distancing measures one week earlier, about 36,000 fewer people would have died from covid-19.
https://www.medrxiv.org/content/10.1101/2020.05.15.20103655v1.full.pdf
See also: https://www.nytimes.com/2020/05/20/us/coronavirus-distancing-deaths.html

No confinement: Sweden has the highest per capita death rate in Europe, and only 7.3% of the population in Stockholm had SARS-CoV-2 antibodies by end of April. This raises questions and concerns about the Swedish strategy.
https://www.theguardian.com/world/2020/may/21/just-7-per-cent-of-stockholm-had-covid-19-antibodies-by-end-of-april-study-sweden-coronavirus

Targeted testing: To contain SARS-CoV-2, we need a concerted national testing effort focused on nursing homes, says a statnews article.
https://www.statnews.com/2020/05/22/focus-covid-19-testing-nursing-home-patients-workers/

Seroprevalence studies:
The U.S. CDC plans to launch a nationwide seroprevalence study of up to 325,000 blood donors in 25 metropolitan areas. It will take samples over 18 months to evaluate how the antibodies evolve over time. https://in.reuters.com/article/health-coronavirus-testing-cdc-exclusive/exclusive-u-s-cdc-plans-sweeping-covid-19-antibody-study-in-25-metropolitan-areas-idINKBN22V04T

Nature publishes a comment with "Ten reasons why immunity passports are a bad idea" https://www.nature.com/articles/d41586-020-01451-0

Transmission
England's government surveillance programme shows that the number of active cases in the community remains relatively stable. 0.25% of participants tested positive for the virus, similar to the 0.27% figure provided by the programme last week.
https://www.bbc.com/news/health-52664297

Spain would currently have 124,300 active covid-19 cases, according to modelling by UPC and IGTP, with most of them concentrated in Madrid and Catalonia. *(Thanks for the tip, Raul Toran!)* https://www.upc.edu/ca/sala-de-premsa/noticies/espanya-tindria-actualment-124300-casos-actius-de-covid-19-segons-el-model-matematic-desenvolupat-per-la-upc-i-igtp

A news story in *Science* analyses super-spreading events in Covid-19, and the possibility of transmission clusters. According to A. Kucharski of LSHTM "Probably about 10% of cases lead to 80% of the spread." Most transmission seems to occur indoors. https://www.sciencemag.org/news/2020/05/why-do-some-covid-19-patients-infect-many-others-whereas-most-don-t-spread-virus-all

Testing/ Tracing
Saliva might be an alternative specimen for the diagnosis of #COVID19. The sensitivity and specificity of the saliva sample RT-PCR were 84.2% and 98.9%, respectively.
https://www.clinicalmicrobiologyandinfection.com/article/S1198-743X(20)30278-0/fulltext

Symptoms / Risk factors
A prospective observational study reports the clinical course of 1150 critically-ill adults with COVID-19 in New York City. Older age, chronic cardiac disease, chronic pulmonary disease, higher concentrations of interleukin-6, and higher concentrations of D-dimer were independently associated with in-hospital mortality.
https://www.thelancet.com/journals/lancet/article/PIIS0140-6736(20)31189-2/fulltext

A study with data from 326 covid-19 patients in Shanghai indicates that disease severity depends mostly on host factors such as age, lymphocytopenia, and its associated cytokine storm, whereas viral genetic variation did not significantly affect the outcome. Findings revealed two major virus lineages during the early phase of the outbreak in Wuhan. Nevertheless, both lineages exhibited similar virulence and clinical outcomes. Low T cell counts upon admission together with high levels of IL6 and IL8 during treatment were determinants of disease severity.
https://www.nature.com/articles/s41586-020-2355-0

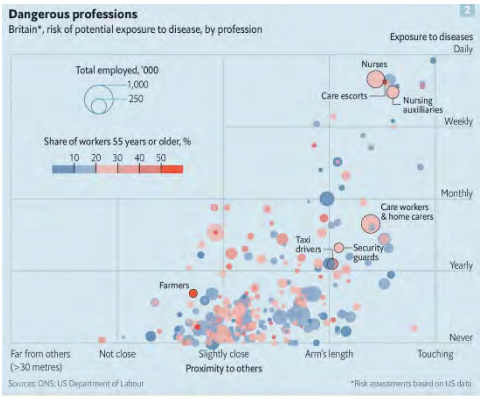
A letter in *NEJM* presents autopsy data from 27 patients showing that SARS-CoV-2 can be detected in multiple organs, including the lungs, pharynx, heart, liver, brain, and kidneys. These findings indicate a broad organotropism of SARS-CoV-2 and would explain clinical signs of kidney injury in patients with Covid-19.
https://www.nejm.org/doi/10.1056/NEJMc2011400

A study with human brain organoids reveals that SARS-CoV-2 may target cortical neurons and lead to neurodegeneration-like effects.
https://www.biorxiv.org/content/10.1101/2020.05.20.106575v1

Children: Nasal epithelium is the first point of contact for SARS-CoV-2 and the human body. A study shows that compared with younger children, ACE2 gene expression in

nasal epithelium was significantly higher in older children, young adults, and adults. This may help explain why COVID-19 is less prevalent in children. (*Thanks for the tip, Elisa Lopez Varela!*) https://jamanetwork.com/journals/jama/fullarticle/2766524

Occupational risk:
The *Lancet* publishes an editorial on the plight of essential workers during the covid-19 pandemic https://www.thelancet.com/action/showPdf?pii=S0140-6736%2820%2931200-9
The economist publishes a graph of risk of covid-19 according to profession. Unsurprisingly, nurses and carers (close contact) are among those at highest risk. https://www.economist.com/science-and-technology/2020/05/21/the-risk-of-severe-covid-19-is-not-uniform



Antibodies / Immunity
Science published the study with macaques showing that SARS-CoV-2 infection induced protective immunity against re-exposure.
https://science.sciencemag.org/content/early/2020/05/19/science.abc4776

A UK study performed deep sequencing of B cell receptor (BCR) heavy chains from a cohort of 19 COVID-19 patients. Findings reveal a stereotypical naive immune response to SARS-CoV-2 which is consistent across patients and may be a positive indicator of disease outcome. https://www.biorxiv.org/content/10.1101/2020.05.20.106294v1

Excessive inflammation: A review in *Immunity* proposes the mechanism underlying the proinflammatory cytokine release observed in covid-19: SARS-CoV-2 is engulfed into the cell along with the ACE2 receptor. This surface reduction of ACE2 receptors leads to an increase of angiotensin II in the blood, which in turn triggers an inflammatory pathway involving NF-κB and IL-6-STAT3, particularly in endothelial cells and epithelial cells. This pathway involving IL-6-STAT3 is enhanced with age, which could be why older people are more at-risk of death, according to the authors. https://www.cell.com/immunity/pdf/S1074-7613(20)30161-8.pdf

A comment in *Nature* postulates that endothelial cells are essential contributors to the initiation and amplification of severe covid-19 inflammation and that the vasculature could be a therapeutic target. https://www.nature.com/articles/s41577-020-0343-0

Treatment
An *in vitro* study with human airway epithelial cultures shows that pre-treatment or post-treatment with type I and III IFNs dramatically reduced SARS-CoV-2 replication

and this corresponded with an upregulation of antiviral effector genes.
https://www.biorxiv.org/content/10.1101/2020.05.19.105437v1

Nature reports the cryo-electron structure of replicating SARS-CoV-2 polymerase. The results enable a detailed analysis of the inhibitory mechanisms that underlie the antiviral activity of substances such as remdesivir.
https://www.nature.com/articles/s41586-020-2368-8

Vaccines
A series of DNA vaccine candidates expressing different forms of the SARS-CoV-2 Spike (S) protein were evaluated in 35 rhesus macaques. Vaccinated animals developed humoral and cellular immune responses, including neutralizing antibody titers comparable to those found in convalescent humans. The vaccine encoding the full-length S protein conferred (non-sterilizing) protection against SARS-CoV-2 in the macaques. Vaccine-elicited serum NAb titers may be immune correlates of protection against SARS-CoV-2 challenge, conclude the authors.
https://science.sciencemag.org/content/early/2020/05/19/science.abc6284

Moderna's announcement that its mRNA vaccine candidate seemed to trigger an immune response to COVID-19 sent stocks soaring, but scientists say the company didn't reveal enough data to ascertain how effective the vaccine really is.
https://www.statnews.com/2020/05/19/vaccine-experts-say-moderna-didnt-produce-data-critical-to-assessing-covid-19-vaccine/

Last month, the Oxford vaccine group started testing the safety of its ChAdOx2 2019nCov vaccine on 1,000 volunteers. The group has announced it plans to vaccinate over 10,000 people in Britain, including older people and children. Earlier this week, AstraZeneca said it had secured its first agreements for 400 million doses of the Oxford vaccine, bolstered by a $1 billion investment from a U.S. government agency, for the development, production and delivery of the vaccine, starting in the fall.
https://medicalxpress.com/news/2020-05-uk-covid-aims-vaccinate.html

Impact of Quarantine on CO2 emissions
Daily global CO2 emissions decreased by −17% (−11 to −25% for ±10) by early April 2020 compared with the mean 2019 levels, just under half from changes in surface transport. The impact on 2020 annual emissions could be between 4% and 7% depending on the duration of restrictions https://www.nature.com/articles/s41558-020-0797-x (*Thanks Kurt Straif for the tip!)*
See also the comment in Nature: https://www.nature.com/articles/d41586-020-01497-0

ISGlobal

COVID-19 EPIDEMIC

Epidemiological situation (26/05/2020, ECDC data):

Globally:
5 459 528 confirmed cases and 345 994 deaths

- The Americas region reported 55 646 new cases (54.8% of the global newly reported cases), and 2932 deaths (68.4%) for the last 24-hour period.
- On Friday, WHO published new guidance on implementing mass vaccine campaigns during the pandemic. At least 80 million children under one are at risk of diseases such as diphtheria, measles, and polio as COVID-19 disrupts routine vaccination efforts, warn GAVI, WHO and UNICEF. https://www.who.int/news-room/detail/22-05-2020-at-least-80-million-children-under-one-at-risk-of-diseases-such-as-diphtheria-measles-and-polio-as-covid-19-disrupts-routine-vaccination-efforts-warn-gavi-who-and-unicef
- The COVID-19 Solidarity Response Fund, launched with the UN Foundation and the Swiss Philanthropy Foundation, has so far raised more than 214 million USD from more than 375 000 individuals, corporations and foundations.
- The United Kingdom will contribute 3.8 million USD for the COVID-19 response in the Caribbean. https://www.paho.org/en/news/22-5-2020-united-kingdom-contributes-38m-covid-19-response-caribbean

Confinement and deconfinement strategies

Japan has lifted its state of emergency after seven weeks of restrictions.
https://www.reuters.com/article/us-health-coronavirus-japan/japanese-face-new-normal-after-coronavirus-emergency-lifted-idUSKBN2320R7

Wuhan has performed 9 million COVID19 tests in 10 days (1.4 M/day, using pooled samples) and found and isolated 180 asymptomatic cases.
https://www.wsj.com/articles/wuhan-tests-nine-million-people-for-coronavirus-in-10-days-11590408910

Seroprevalence studies:
Very low SARS-CoV-2 seroprevalence is reported for two San Francisco Bay Area populations. Seropositivity was 0.26% in 387 hospitalized patients admitted for non-respiratory indications and 0.1% in 1,000 blood donors.
https://www.medrxiv.org/content/10.1101/2020.05.19.20107482v1

Virus

In an open letter to the Trump Administration, 77 Nobel prize-winning American scientists say they are "gravely concerned" about the recent abrupt cancellation of a federal grant to a U.S. non-profit that was researching coronaviruses in China.
https://www.npr.org/sections/goatsandsoda/2020/05/22/861299458/77-nobel-laureates-denounce-trump-officials-for-pulling-coronavirus-research-gra

Transmission

Super-spreading events:

A church service in Frankfurt held on May 10 led to more than 107 people infected by coronavirus. https://www.vox.com/2020/5/24/21268602/germany-church-coronavirus-lockdown

Another COVID19 super-spreading event occurred at a wedding in Jordan. Of 350 identified people attending, 76 (22%) later tested positive. Seventeen cases (22%) were children. 47% were asymptomatic. The index case is believed to be bride's father, who had developed symptoms 2 days before. https://wwwnc.cdc.gov/eid/article/26/9/20-1469_article

Children: *Science* writes on how Sweden wasted a rare opportunity to study SARS-CoV-2 transmission in schools. Swedish officials have not tracked infections among school children—even when large outbreaks led to the closure of individual schools or staff members died of the disease. https://www.sciencemag.org/news/2020/05/how-sweden-wasted-rare-opportunity-study-coronavirus-schools

Breastfeeding? Viral RNA was detected in milk from 1 out of 2 infected breastfeeding mothers, which coincided with mild COVID-19 symptoms and a SARS-CoV-2 positive diagnostic test of the newborn. It is not clear how the newborn was infected https://www.thelancet.com/journals/lancet/article/PIIS0140-6736(20)31181-8/fulltext

Mink to human? The first plausible animal-human infection of SARS-CoV-2 has been documented in a Dutch mink farm https://promedmail.org/promed-post/?id=20200525.7375359

Testing/ Tracing

An MIT team developed a simple point of care test called STOP (SHERLOCK Testing in One Pot) for detecting SARS-CoV-2 in one hour. The sensitivity, based on CRISPR-Cas detection, is comparable to RT-qPCR tests and has a limit of detection of 100 copies of viral genome input in saliva or nasopharyngeal swabs. The test returns results in 70 minutes (with lateral flow readout) or 40 minutes (with fluorescence readout). https://www.medrxiv.org/content/10.1101/2020.05.04.20091231v1

A time course of SARS-CoV-2 RNA concentrations in sewage sludge during the Spring COVID-19 outbreak in New Haven, USA shows that RNA concentrations were a seven-day leading indicator ahead of compiled COVID-19 testing data and led local hospital admissions data by three days.
https://www.medrxiv.org/content/10.1101/2020.05.19.20105999v1.full.pdf

Symptoms / Risk factors

Post-mortem lung examination shows that vascular angiogenesis distinguished the pulmonary pathobiology of Covid-19 from that of equally severe influenza virus infection. https://www.nejm.org/doi/full/10.1056/NEJMoa2015432

Caution for next year's influenza season: an expert in Hubei Province verified that there exists a certain ratio of novel coronavirus patients in critical condition in Wuhan complicated by infection with influenza- 18 out of 50 severe cases (36%), had a co-infection with influenza virus and the SARS-CoV-2.
https://journals.lww.com/pidj/FullText/2020/06000/Coinfection_of_Influenza_Virus_and_Severe_Acute.27.aspx

A study using serum from children with Kawasaki Disease prior to 2020 suggests that paediatric COVID-19 related inflammatory disorder is not due to a non-specific global

cross-reactivity from previous coronaviruses.
https://www.medrxiv.org/content/10.1101/2020.05.24.20111732v1.full.pdf

Antibodies / Immunity
A study with 240 covid-19 patients in an urgent care facility in Brooklyn, New York, indicates that SARSCoV-2 IgG antibody levels are positively correlated with symptom severity, regardless of whether the patient was male or female. SARS-CoV-2 IgG positivity rates in the overall patient population at the Brooklyn facility was near 50%.
https://www.medrxiv.org/content/10.1101/2020.05.23.20111427v1.full.pdf

Treatment
Chloroquine: *The Lancet* published the largest analysis to date on hydroxychloroquine or chloroquine for treatment of COVID-19. The multinational registry analysis with 96,000 patients did not confirm a benefit of hydroxychloroquine or chloroquine, when used alone or with a macrolide, on in-hospital outcomes for COVID-19. Each of these drug regimens was associated with decreased in-hospital survival and an increased frequency of ventricular arrhythmias when used for treatment of COVID-19. *However, the data sources used for the study has raised some concerns*.
https://www.thelancet.com/journals/lancet/article/PIIS0140-6736(20)31180-6/fulltext
As a result, the WHO has decided to suspend temporarily its trials of hydroxychloroquine as COVID-19 treatment
https://www.politico.com/news/2020/05/25/world-health-organization-pauses-study-of-hydroxychloroquine-in-global-trial-280264

Remdesivir: NEJM publishes the results of the multicentre clinical trial on remdesivir with a total of 1063 patients. Results confirm that those who received remdesivir had a median recovery time of 11 days, as compared with 15 days
https://www.nejm.org/doi/full/10.1056/NEJMoa2007764

Vaccines
The world's 1st phase 1 trial findings for a COVID-19 vaccine were published in *Lancet*. Made by China's CanSino Biologics, the adenovirus type-5 vectored vaccine expressing the S glycoprotein was tested in 108 healthy adults ages 18 to 60 in Wuhan. Humoral responses against SARS-CoV-2 peaked at day 28 post-vaccination in healthy adults, and rapid specific T-cell responses were noted from day 14 post-vaccination. Some adverse effects were observed for the high dose, but overall it was well tolerated. *However, the rise in antibodies was less robust in people with pre-existing immunity to adenovirus, confirming pre-existing concerns about this type of vaccine. A phase 2 study, with 508 people enrolled, including people aged over 60, is already underway*.
https://www.thelancet.com/journals/lancet/article/PIIS0140-6736(20)31208-3/fulltext

Operation Warp Speed, the Trump administration's bid to deliver a COVID-19 vaccine faster than any previous vaccine, announced an investment of $1.2 billion USD in the Oxford's Jenner Institute vaccine being developed by AstraZeneca, noting that the delivery of the first of at least 300 million doses should arrive in October. The money comes from the Biomedical Advanced Research and Development Authority (BARDA). This "aggressive" timeline has raised many feasibility doubts and safety concerns.
https://www.sciencemag.org/news/2020/05/doubts-greet-12-billion-bet-united-states-coronavirus-vaccine-october

Animal models
SARS-CoV-2 infection in golden Syrian hamsters resembles features found in humans with mild infections. Inoculated and naturally-infected hamsters showed apparent weight loss, and all animals recovered with the detection of neutralizing antibodies. https://www.nature.com/articles/s41586-020-2342-5

Heat and Covid-19
The Global Heat Health Information Network has published a technical brief on how to reduce heat-related health risks during the covid-19 pandemic. *Thanks for the tip, Joan Ballester!* http://www.ghhin.org/heat-and-covid-19

ISGlobal

COVID-19 EPIDEMIC

Epidemiological situation (29/05/2020, ECDC data):

Globally:
5 776 934 confirmed cases and 360 089 deaths

- The European Commission proposed a 750 billion euro recovery fund to reboot the European economy that has been hit hard by the coronavirus outbreak https://ec.europa.eu/commission/presscorner/detail/en/ip_20_940
- World health leaders urge green recovery from coronavirus crisis Open letter to G20 leaders says addressing climate breakdown key to global revival https://www.theguardian.com/environment/2020/may/26/world-health-leaders-urge-green-recovery-from-coronavirus-crisis
- The COVID-19 Multi-model Comparison Collaboration (CMCC) has been launched by a large number of partners with the purpose of enhancing the use of mathematical models during the COVID-19 outbreak and help policymakers interpret models, foster collaboration between modelers, and assess their fitness in terms of questions related to disease control policies. https://www.cgdev.org/blog/introducing-covid-19-multi-model-comparison-collaboration#disqus_thread

Confinement and deconfinement strategies
Seoul will close public facilities (parks, museums, etc) beginning on Friday after a cluster of >80 COVID-19 cases broke out at a logistics center near the capital.
http://www.koreaherald.com/view.php?ud=20200528000203

Transmission
Masks: *Science* publishes a perspective on the importance of using masks (in addition to testing) to reduce transmission of SARS-Cov-2.
https://science.sciencemag.org/content/early/2020/05/27/science.abc6197
A study with 124 families in Beijing shows reduction of secondary transmission of SARS-CoV-2 in households by face mask use, disinfection and social distancing
https://gh.bmj.com/content/bmjgh/5/5/e002794.full.pdf

A study in a nursing facility in Washington shows rapid and widespread transmission of the virus, with more than half of PCR-positive residents asymptomatic at the time of testing https://www.nejm.org/doi/full/10.1056/NEJMoa2008457

Ships: On a cruise ship to Antarctica, 128 of the 217 passengers and crew tested positive for COVID-19 on reverse transcription–PCR (59%). The majority of positive patients were asymptomatic (81%); 19% were symptomatic; 6.2% required medical evacuation; 3.1% were intubated and ventilated; and the mortality was 0.8% (1).
https://thorax.bmj.com/content/early/2020/05/27/thoraxjnl-2020-215091.full

Schools: Irish investigators report no cases of transmission in a small number of schools that remained open during the lockdown. They examined 6 paediatric cases of Covid-19 attending school during the pre-symptomatic and symptomatic periods of

infection and identified no cases of transmission to other children or adults within the school and other settings (music lessons, etc.) (total of 1025 contacts). https://www.eurosurveillance.org/content/10.2807/1560-7917.ES.2020.25.21.2000903

Testing/ Tracing

A study reports a SARS-CoV-2 surrogate virus neutralization test (sVNT) that is designed to detect total neutralizing antibodies without the need of live virus and BSL3 facilities. The test achieves 100% specificity and 95-100% sensitivity and is capable of differentiating antibody responses from other known human coronaviruses. https://www.researchsquare.com/article/rs-24574/v1

Symptoms / Risk factors

An autopsy study in ten Afro American patients who died from Covid-19 confirms thrombotic and microangiopathic pathology in the lungs, that contributed to death in these patients. https://www.thelancet.com/journals/lanres/article/PIIS2213-2600(20)30243-5/fulltext

Proteomic and metabolomic profiling of sera from 46 COVID-19 and 53 control individuals reveals dysregulation of macrophage, platelet degranulation and complement system pathways, and massive metabolic suppression. https://www.cell.com/cell/fulltext/S0092-8674(20)30627-9

Children: Screening of samples collected from 1,076 children seeking medical care at Seattle's Children Hospital during March and April of 2020 revealed that only one child was seropositive in March, but nine were seropositive in April (period seroprevalence of >1%). Most seropositive children (8/10) were not suspected of having had COVID-19. The sera of most seropositive children had neutralizing activity. https://www.medrxiv.org/content/10.1101/2020.05.26.20114124v1

Antibodies / Immunity

A French study shows that even mild forms of the disease may confer immunity. The study was performed with 160 hospital staff in Strasbourg who developed mild symptoms of the disease. Neutralizing antibodies were detected in 79%, 92% and 98% of samples collected 13-20, 21-27 and 28-41 days after symptom onset, https://www.medrxiv.org/content/10.1101/2020.05.19.20101832v2

Nature publishes two papers on SARSCoV2 human neutralizing antibodies (both from China). The first has a small macaque study showing preclinical data in both prophylactic & therapeutic settings. https://nature.com/articles/s41586-020-2381-y The second reports no cross-reactivity with the MERS-CoV receptor binding domain (RBD) https://nature.com/articles/s41586-020-2380-z

Treatment

Remdesivir: An open-label, randomized, multicenter, phase 3 trial among patients with severe Covid-19 pneumonia shows there is no difference in efficacy between a 5-day and 10-day course of remdesivir. The trial (in which Hospital Clinic participated) lacked a placebo control, and was not a test of the drug's efficacy. https://www.nejm.org/doi/full/10.1056/NEJMoa2015301

Chloroquine: A systematic review for hydroxychloroquine or chloroquine and Covid-19 found 4 randomized controlled trials, 10 cohort studies, and 9 case series that assessed treatment effects of the medications, but no studies evaluated prophylaxis. The authors conclude that evidence on the benefits and harms of using hydroxychloroquine or chloroquine to treat COVID-19 is very weak and conflicting.
https://www.acpjournals.org/doi/10.7326/M20-2496

The French government banned treatment of Covid-19 patients with hydroxychloroquine, after 2 French advisory bodies and the WHO warned that the drug had been shown to be potentially dangerous in several studies. Under the new French rules, the drug can be used only in clinical trials to test its efficacy against the virus**.**

Clinical trials in Spain: The Agencia de Medicamentos y Productos Sanitarios (AEMPS) has a tool for visualizing ongoing clinical trials in Spain:
Visualización de datos sobre ensayos clínicos para evaluar medicamentos sobre COVID
As well as a list of observational studies:
Lista completa de estudios observacionales con medicamentos sobre COVID
(Thanks for the info, Maria José Cavallin!)

Vaccines

Innovio's synthetic DNA-based vaccine candidate targeting SARS-CoV-2 S protein (INO-4800) induces T cell responses and neutralizing antibodies in mice and guinea pigs. https://www.nature.com/articles/s41467-020-16505-0

Merck aims to begin testing two different Covid-19 vaccine candidates. Vienna-based Themis, which is developing an experimental Covid-19 vaccine based on a measles vaccine and the other based on VSV, as Merck's Ebola vaccine.
https://www.statnews.com/2020/05/26/merck-aims-to-begin-human-tests-of-two-different-covid-19-vaccines-this-year/

Indirect impacts

Gender equity: *Nature* publishes two reports on the impact of the crisis on worsening equity gaps in science. The first is an analysis showing that female university staff in Australia have lost more jobs, paid hours and career opportunities than their male colleagues since the pandemic hit. Women are 50% more likely to hold casual and short-term contract positions — which are often the first to go.
https://www.natureindex.com/news-blog/coronavirus-pandemic-job-cutbacks-reverse-equity-gains-women-in-stem-science-research-workforce
The other indicates that women are publishing less during the pandemic:
https://www.nature.com/articles/d41586-020-01294-9
(Thanks Payam Dadvand for the tip!)

ISGlobal

COVID-19 EPIDEMIC

Epidemiological situation (02/06/2020, ECDC data):

Globally:
6 245 352 confirmed cases and 376 427 deaths

- Brazil now tops the cases (>20,000) and deaths (>1,000) per day worldwide; even rising past 25% US cumulative numbers.
- The US long plateau in cases is likely to go into an ascending phase soon due to reopening and mass protests.
- Russia, Mexico, India are still on the rise.
- World health leaders urge green recovery from coronavirus crisis. An open letter to G20 leaders says addressing climate breakdown is key to global revival https://www.theguardian.com/environment/2020/may/26/world-health-leaders-urge-green-recovery-from-coronavirus-crisis

Confinement and deconfinement strategies

Science reports on the success of Japan with a 'unique strategy', emphasizing attention to super-spreader venues and the 3 C's (closed spaces, crowds, and close-contact settings); despite little testing and no lockdown.
https://www.sciencemag.org/news/2020/05/japan-ends-its-covid-19-state-emergency

An article in *The Economist* describes manual contact tracing in Germany as the pillar to block a second Covid-19 wave. The contact tracers' work has three pillars: i) obtain from people who have tested positive for Covid-19 a list of their recent contacts, and to categorise them (spending 15 minutes face-to-face with an infected person, for example, places you in a high-risk bracket); ii) to alert those people and instruct them, if needed, to self-isolate for 14 days; and iii) to check in with them periodically and get them tested, if deemed necessary.
https://www.economist.com/europe/2020/05/28/germanys-contact-tracers-try-to-block-a-second-covid-19-wave

Schools: still controversial
Israel detected a cluster of 160 COVID-19 cases in the Gymnasium High School in Jerusalem, started by a "super spreader" faculty member who was reportedly asymptomatic. The school however was not following recommended preventive measures. https://www.jpost.com/israel-news/anger-frustration-as-coronavirus-rules-neglected-at-jerusalem-school-629792
On the other hand, Denmark, Austria, Norway, Finland, Singapore, Australia, New Zealand and most other countries that have reopened classrooms haven't had outbreaks in schools or day-care centers. https://www.wsj.com/articles/is-it-safe-to-reopen-schools-these-countries-say-yes-11590928949
A modelling study concludes that if UK schools reopen in phases from June 2020, prevention of a second wave would require testing 51% of symptomatic infections, tracing of 40% of their contacts, and isolation of symptomatic and diagnosed cases.
https://www.medrxiv.org/content/10.1101/2020.06.01.20100461v1

Virus
An international team of scientists whose funding for research on bat coronaviruses was recently halted by the U.S. government has posted a preprint with what it calls the most comprehensive analysis ever done of such viruses. They examine partial genetic sequences of 781 coronaviruses found in bats in China, more than one-third of which have never been published. They did not pinpoint a precise origin for SARS-CoV-2 but do confirm that horseshoe bats are a major reservoir of SARS-related coronaviruses. https://www.biorxiv.org/content/10.1101/2020.05.31.116061v1

Transmission
Genetic analyses suggest that the coronavirus arrived more than once in the US or Europe, without starting runaway outbreaks. For example, in Seattle, the first case detected did not ignite the epidemic. The researchers argue that the time before the pandemic took off in the USA was a lost opportunity, when testing and contact tracing could have made a big difference. https://nyti.ms/3chqUN1

A systematic review and meta-analysis supports physical distancing of 1 m or more, face masks and eye protection for preventing SARS-CoV-2 transmission in public and health-care settings https://www.thelancet.com/journals/lancet/article/PIIS0140-6736(20)31142-9/fulltext

A viewpoint in JAMA on airborne spread of SARS-CoV-2 proposes 2 methods for air disinfection besides mechanical ventilation: room air cleaners and germicidal UV fixtures on the wall. https://jamanetwork.com/journals/jama/fullarticle/2766821

HCW: A study in Wuhan shows that seroprevalence of SARS-CoV-2 was 4.39% in asymptomatic healthcare workers using PPE
https://www.medrxiv.org/content/10.1101/2020.05.28.20110767v1

Testing/ Tracing
Neutralizing Abs: Enable Biosciences describes the development and validation of a cell-free neutralization PCR assay using SARS-CoV-2 spike protein S1 and human ACE2 receptor-DNA conjugates. The assay is readily deployable in standard laboratories with biosafety level 2 capability, and can yield results within 2-3 hr.
https://www.medrxiv.org/content/10.1101/2020.05.28.20105692v1

Abs: A Swiss-led team shows that Ternary Automated Blood Immunoassay (TRABI) to assess the IgG response against SARS2 identifies seropositive individuals in large unselected cohorts, discriminates between SARS2 immunity and low-affinity cross-reactivity, and is therefore suitable for large-scale nationwide screening campaigns.
https://www.medrxiv.org/content/10.1101/2020.05.31.20118554v1

Symptoms / Risk factors
In vitro infection of primary human respiratory tract cells with GFP-expressing SARS-CoV-2 found a correlation between viral infection and a cell's ACE2 expression levels. Highest ACE2 expression was seen in the nose with decreasing expression throughout the lower respiratory tract, paralleled by a striking gradient of SARS-CoV-2 infection in proximal (high) vs distal (low) pulmonary epithelial cultures. The authors propose that lower airway infection occurs mainly through oral–lung aspiration.
https://www.cell.com/cell/fulltext/S0092-8674(20)30675-9

A prospective observational study was not able to identify evidence that cancer patients on cytotoxic chemotherapy or other anticancer treatment are at an increased risk of mortality from COVID-19 disease compared with those not on active treatment.

https://www.thelancet.com/journals/lancet/article/PIIS0140-6736(20)31173-9/fulltext

An analysis with UK biobank data from over 1,000 covid-19 patients suggests that the greater risk of severe disease in non-white ethnicities is not explained by cardiometabolic, socioeconomic, or behavioural factors, or by 25(OH)-vitamin D status. https://www.medrxiv.org/content/10.1101/2020.06.01.20118943v1

Children: A report describes 5 children with heart damage from COVID19 who did not have Kawasaki's disease or fulfil criteria for multi-system inflammatory syndrome https://www.thelancet.com/action/showPdf?pii=S2352-4642%2820%2930168-1

Treatment

Choloroquine, Spain: The Agencia Reguladora del Ministerio de Salud (AEMPS) has announced that cholorquine / HCQ for Covid-19 will continue to be tested in the framework of clinical trials. https://www.aemps.gob.es/la-aemps/ultima-informacion-de-la-aemps-acerca-del-covid%e2%80%9119/tratamientos-disponibles-para-el-manejo-de-la-infeccion-respiratoria-por-sars-cov-2/ (*Thanks for the info, Clara Menéndez!*)

Meanwhile, the validity of the data used in the chloroquine study published in *The Lancet* continues to be widely questioned by the scientific community https://www.nytimes.com/2020/05/29/health/coronavirus-hydroxychloroquine.html

ISGlobal

COVID-19 EPIDEMIC

Epidemiological situation (05/06/2020, ECDC data):

Globally:
6 603 329 confirmed cases and 391 732 deaths

- GAVI's Global Vaccine Summit in London successfully mobilized US$8.8 billion plus funding for COVID vaccines. Together with CEPI and WHO, it has launched an initiative to ensure the vaccine reaches the most vulnerable https://twitter.com/GaviSeth/status/1268656450500509697?s=20
- Together with CEPI and WHO, GAVI has launched an initiative to ensure the vaccine reaches the most vulnerable https://www.gavi.org/news/media-room/gavi-launches-innovative-financing-mechanism-access-covid-19-vaccines
- AstraZeneca announced it will double the manufacturing capacity for its potential Covid-19 vaccine to 2bn doses after a deal with CEPI and GAVI aimed at guaranteeing early supply to lower income countries. Last month the company said it could manufacture 1bn doses of the vaccine developed in partnership with Jenner/Oxford University. On Thursday, it announced an agreement with the Serum Institute of India to produce 1bn additional doses for LMIC. It plans to provide 400m doses before the end of 2020 (it has promised 300m doses for US and 100m for UK). *There is still no guarantee that the vaccine will work.* https://www.theguardian.com/business/2020/jun/04/astrazeneca-doubles-capacity-for-potential-covid-19-vaccine-to-2bn-doses

Confinement and deconfinement strategies
A modelling study assesses the potential impact of different control measures for mitigating the burden of COVID-19 in the UK and concludes that only lockdown periods were sufficient to bring R0 near or below 1. https://www.thelancet.com/journals/lanpub/article/PIIS2468-2667(20)30133-X/fulltext

Sweden's chief epidemiologist Anders Tegnell has acknowledged that the country has had too many deaths from Covid-19 and should have done more to curb the spread of the virus. Sweden's death rate per capita was the highest in the world over the seven days to 2 June. https://www.theguardian.com/world/2020/jun/03/architect-of-sweden-coronavirus-strategy-admits-too-many-died-anders-tegnell#maincontent

Seroprevalence studies
Some 5.5% of blood donors in the Netherlands have antibodies against coronavirus in their systems, according to research by blood bank organisation Sanquin. The blood of some 7,000 people who donated between May 10 and May 20 was tested for antibodies. Earlier testing, carried out at the beginning of April, found just 3% of donors had coronavirus antibodies in their blood. https://www.dutchnews.nl/news/2020/06/just-5-5-of-dutch-blood-donors-have-coronavirus-antibodies/

Spain announced the results from the second round of testing in its national seroprevalence study. The average percentage of people with antibodies has risen only

slightly since mid-May – from 5 to 5.2%.
https://www.lavanguardia.com/vida/20200604/481599194789/espanoles-estudio-seroprevalencia-coronavirus-segunda-oleada.html

Virus
A phylogenetic analysis provides evidence of strong purifying selection around the receptor binding motif (RBM) in the spike and other genes among bat, pangolin, and human coronaviruses, suggesting similar evolutionary constraints in different host species. The findings demonstrate that SARS-CoV-2's entire RBM was introduced through recombination with coronaviruses from pangolins
https://advances.sciencemag.org/content/early/2020/05/28/sciadv.abb9153

Transmission
The SARS-CoV-2 outbreak in New York City arose mostly through untracked transmission between the United States and Europe, with limited evidence of direct introductions from China, according to a study in *Science*. Phylogenetic analysis of 84 distinct SARS-CoV2 genomes indicated multiple, independent introductions mainly from Europe and other parts of the United States. Clusters of related viruses found in patients living in different neighbourhoods suggested that community spread was already underway by March 18.
https://science.sciencemag.org/content/early/2020/05/28/science.abc1917

Asymptomatic infections:
A review signed by Eric Topol estimates that asymptomatic persons account for approximately 40% to 45% of SARS-CoV-2 infections, and they can transmit the virus to others for an extended period, perhaps longer than 14 days. Asymptomatic infection may be associated with subclinical lung abnormalities, as detected by computed tomography https://www.acpjournals.org/doi/10.7326/M20-3012

Crowded conditions: 400 of 600 refugees of one reception center in the state of Baden-Wuerttenberg tested positive for the novel coronavirus. And many refugees have a deteriorated physical and mental health, including undiagnosed underlying health conditions that make them particularly vulnerable.
https://www.globalhealthnow.org/2020-06/germany-and-covid-19-what-about-refugees

Testing/ Tracing
Antibodies**:** A review provides an overview of the validity and interpretability of all available SARS-CoV-2 antibody tests, based on real, published data.
https://www.acpjournals.org/doi/10.7326/M20-2854

Symptoms / Risk factors
A genome wide association analysis by European researchers shows that the ABO blood group locus and a cluster of six genes on chromosome 3 associate with SARS-CoV-2 respiratory failure. Type A blood was linked to a 50% increase likelihood of respiratory failure, while O blood group was protective. Variants in ACE2 receptor did not appear to make a difference in the risk of severe Covid-19.
https://www.medrxiv.org/content/10.1101/2020.05.31.20114991v1

Children: A retrospective single-center case series of 50 hospitalized pediatric COVID-19 patients in New York City found that respiratory symptoms were common but not

ubiquitous, that most children had underlying illnesses, and that obese patients were likely to require mechanical ventilation. https://www.cidrap.umn.edu/news-perspective/2020/06/obesity-atypical-immune-response-some-kids-covid-19
Another retrospective study with 157 paediatric patients in China showed that systemic inflammation rarely occurred in paediatric patients with COVID-19, in contrast with the lymphopenia and aggravated inflammatory responses frequently observed in adults with COVID-19. IL-10 levels were increased in moderate cases, as compared to mild cases. https://jamanetwork.com/journals/jamanetworkopen/fullarticle/2766670

Males: A news story in *Science* points to androgens as a possible explanation to why males are hit harder by COVID-19. In the prostate, TMPRSS2 is produced when male hormones bind to the androgen receptor. It is still not known if androgens control TMPRSS2 in the lung, but data on more than 42,000 men with prostate cancer in Italy showed that patients on androgen-deprivation therapy (ADT) were only one-quarter as likely to contract COVID-19 as men not on ADT and were also less likely to be hospitalized and to die. A study in Mount Sinai confirms this trend. Furthermore, two small Spanish studies associate baldness with severe disease in males. Finally, a correlation was observed between active androgens in the blood and the severity of COVID-19 disease in data from several hundred male patients in the UK Biobank. A double-blind, randomized, placebo-controlled trial of the androgen-suppressing drug degarelix in 200 veterans hospitalized with COVID-19 is currently underway in Los Angeles, Seattle, and New York City.
https://www.sciencemag.org/news/2020/06/why-coronavirus-hits-men-harder-sex-hormones-offer-clues

Science journalist Ed Yong writes about the "long-haulers" of the disease: people who have "recovered" from COVID-19 but struggle with debilitating symptoms during months. Many were not hospitalised or even tested. For Akiko Iwasaki, an immunologist at Yale, there are three possible explanations: people might still harbor infectious virus in some reservoir organ, which is missed by nasal swabs. Or persistent fragments of viral genes, though not infectious, may still be triggering an immune overreaction. More likely, the virus is gone but the immune system remains in an overactive state. https://www.theatlantic.com/health/archive/2020/06/covid-19-coronavirus-longterm-symptoms-months/612679/

Treatment
Chloroquine: the show goes on after study retracted
The WHO announced it will continue with all arms of the Solidarity trial, including the use of hydroxychloroquine, after having temporarily paused it last week due to a study published in *The Lancet* and that has just been retracted.
https://www.thelancet.com/journals/lancet/article/PIIS0140-6736(20)31180-6/fulltext#articleInformation
Another study published in the *NEJM* that also used data from Surgisphere (on blood pressure drugs and COVID-19 mortality) was also retracted
https://www.nejm.org/doi/full/10.1056/NEJMoa2007621
A third COVID-19 study also using Surgisphere data and posted in early April as a preprint has been removed. It concluded that ivermectin dramatically reduced mortality in COVID-19 patients, leading governments in Latin America to recommend its use.
See: https://www.sciencemag.org/news/2020/06/two-elite-medical-journals-retract-coronavirus-papers-over-data-integrity-questions

Several of our ISGlobal colleagues have voiced their concerns in open letters (see attached docs- *Thanks Clara Menendez!*), posts, or mass media

Postexposure prophylaxis: A randomized, double-blind, placebo-controlled trial across the United States and parts of Canada testing hydroxychloroquine as postexposure prophylaxis shows that it did not prevent disease or confirmed infection when used as prophylaxis within 4 days after exposure. The study enrolled adults who had household or occupational exposure to someone with confirmed Covid-19 hydroxychloroquine. https://www.nejm.org/doi/full/10.1056/NEJMoa2016638

Convalescent plasma: JAMA publishes a multicenter randomized control trial of convalescent plasma therapy for COVID-19 including 103 patients in Wuhan with severe or life-threatening, confirmed COVID-19, 52 of whom received convalescent plasma. The authors did not find any significant clinical benefits of convalescent plasma treatment, though the study was terminated early and the sample size was small. https://jamanetwork.com/journals/jama/article-abstract/2766943

Animals

The US National Veterinary Services Laboratories announced the 1st confirmed case of SARS-CoV-2 infection in a German shepherd dog in New York state. This is the 1st dog in the United States to test positive for SARS-CoV-2. One of the dog's owners tested positive for COVID-19, and another showed symptoms consistent with the virus prior to the dog showing signs. A 2nd dog in the household has shown no signs of illness; however, antibodies were also identified in the 2nd dog, suggesting exposure. https://www.aphis.usda.gov/aphis/newsroom/stakeholder-info/SA_By_Date/SA-2020/SA-06

Dutch authorities have decided to cull all infected mink farms (7 companies at nine locations) in the country. https://limburg24.nl/nertsenbedrijf-in-venray-wordt-geruimd-na-uitbraak-coronavirus/

ISGlobal

COVID-19 EPIDEMIC

Epidemiological situation (10/06/2020, ECDC data):

Globally:
7 210 462 confirmed cases and 411 195 deaths

- The WHO warns that the number of new cases is growing faster than ever worldwide, with more than 100 000 reported each day. The increase has been driven by emerging hot spots in Latin America, Africa, Asia, and the Middle East.
- The death toll in Brazil, Latin America's largest country, passed 30000 on June 2, with 1262 deaths in one single day. Despite this, businesses have started reopening in major cities, including Rio de Janeiro, Manaus, and Vitoria.
- In Egypt, the number of cases there has been rising significantly, reaching 27 536 on June 2
- South Africa still has a growing number of new cases, despite enacting a strict lockdown in March
- The Democratic Republic of the Congo has reported a new Ebola outbreak as the country continues to respond to the complex Ebola outbreak in the eastern part of the country, the COVID-19 pandemic, the world's largest measles outbreak, and a long-standing humanitarian crisis.
- New Zealand, on the other hand, is set to lift almost all restrictions after reporting it is virus free https://www.bbc.com/news/world-asia-52961539
- Cuba sets example with its successful programme to contain coronavirus https://www.theguardian.com/world/2020/jun/07/cuba-coronavirus-success-contact-tracing-isolation

Confinement and deconfinement strategies

Restrictions including stay-at-home orders and business closures prevented ~285 million cases in China and ~60 million in the US, according to researchers at the University of California, Berkeley. https://www.nature.com/articles/s41586-020-2404-8_reference.pdf
Another study from Imperial College London had already estimated that strict shutdowns may have saved ~3.1 million lives across 11 countries in Europe. https://www.nature.com/articles/s41586-020-2405-7.epdf

WHO now advises the general public to wear nonmedical face masks with at least 3 layers of material in public areas where social distancing is not possible—a shift from previous guidance. https://www.who.int/emergencies/diseases/novel-coronavirus-2019/advice-for-public/when-and-how-to-use-masks

Virus

A PNAS paper provides a molecular explanation of why SARSCoV2 binds its receptor domain (RBD) with 10-15 X higher affinity, which is tied to its higher infectiousness. https://www.pnas.org/content/pnas/early/2020/06/04/2008209117.full.pdf

Testing/ Tracing
A research team of the University of Barcelona (led by Albert Bosch) and Aigües de Barcelona retrospectively analysed SARS-CoV-2 presence in the city's residual water samples and show that by January 15 there were detectable levels of the virus in the samples (40 days before the first case was reported).
https://www.lavanguardia.com/local/barcelona/20200607/481654145204/detectados-restos-coronavirus-covid19-aguas-residuales-barcelona-enero.html

A preprint shows sweat odour of COVID-19+ persons is different, and that dogs can detect a person infected by the SARS-CoV-2 virus.
https://www.biorxiv.org/content/10.1101/2020.06.03.132134v1

Transmission
A study estimates the survival of SARS-CoV-2 suspended in respiratory droplets originated from a COVID-19 infected subject. The likelihood of the survival of the virus (droplet drying time) increases roughly by five times under a humid condition as compared to a dry condition. But it decreases with higher temperatures. Cities with more spread were associated with longer drying times.
https://aip.scitation.org/doi/10.1063/5.0012009

A rapid systematic review indicates that there is preliminary evidence that children and young people have lower susceptibility to SARS-CoV-2, with 56% lower odds of being an infected contact. There is weak evidence that children and young people play a lesser role in transmission of SARS-CoV-2 at a population level. *(Thanks for the tip, Matiana Gonzalez!)* https://www.medrxiv.org/content/10.1101/2020.05.20.20108126v1

An analysis of viral loads by patient age (3,300 patients) concludes that a considerable percentage of infected people in all age groups, including those who are pre- or mild-symptomatic, carry viral loads likely to represent infectivity. One fifth of infected participants reported no symptoms
https://www.medrxiv.org/content/10.1101/2020.06.08.20125484v1

The analysis of 382 young adult U.S. service members aboard the USS Theodore Roosevelt carrier experiencing a COVID-19 outbreak, revealed that 60% had reactive antibodies, and 59% of those also had neutralizing antibodies at the time of specimen collection. One fifth of infected participants reported no symptoms *(Thanks for the tip, Payam Dadvand!)* https://www.cdc.gov/mmwr/volumes/69/wr/mm6923e4.htm

Symptoms / Risk factors
An analysis on patients with mild to moderate disease who had not received immunomodulatory medications revealed that male patients had higher plasma levels of innate cytokines and chemokines including IL-8, IL-18, and CCL5, along with more robust induction of non-classical monocytes. In contrast, female patients mounted significantly more robust T cell activation than male patients.
https://www.medrxiv.org/content/10.1101/2020.06.06.20123414v1

A commentary on racial disparities in the 1918 flu and COVID-19 pandemics reveals that critical structural inequities and health care gaps have historically contributed to and continue to compound disparate health outcomes among communities of colour. It offers a blueprint for approaching this and future crisis through the lens of health equity. https://www.acpjournals.org/doi/10.7326/M20-2223

An analysis on social distancing behaviours in the US reveals variation in behavioural drivers including vulnerability, race, political affiliation, and employment industry,

demonstrating the need for targeted policy messaging and interventions tailored to address specific barriers for improved social distancing and mitigation.
https://www.medrxiv.org/content/10.1101/2020.06.04.20119131v1

Children: Two new studies involving a total of 75 children published in JAMA showed that the pediatric multisystem inflammatory syndrome linked to COVID-19 is novel and different from Kawasaki disease (KD) and toxic shock syndrome (TSS).
https://jamanetwork.com/journals/jama/fullarticle/2767209
https://jamanetwork.com/journals/jama/fullarticle/2767207

Antibodies / Immunity
CD4 and CD8 T cell responses to different SARS-CoV-2 proteins were analysed in UK COVID-19 patients. In mild cases, higher frequencies of multi-cytokine producing M- and NP-specific CD8+ T cells than spike-specific CD8+ T cells were observed, suggesting these antigens should be included in vaccines.
https://www.biorxiv.org/content/10.1101/2020.06.05.134551v1

Treatment
Remdesivir: A study with macaques supports early initiation of remdesivir treatment in COVID-19 patients to prevent progression to pneumonia.
https://www.nature.com/articles/s41586-020-2423-5

Ivermectin: A retrospective cohort study shows that ivermectin treatment was associated with lower COVID-19 mortality. The study includes 280 consecutive COVID-19 patients hospitalized at four hospitals in South Florida. Lower mortality was observed in the ivermectin group (n=173). Mortality was also lower among 75 patients with severe pulmonary disease treated with ivermectin.
https://www.medrxiv.org/content/10.1101/2020.06.06.20124461v1

Hydroxychloroquine: three big trials dim hopes for its use in treating or preventing COVID-19.
Recovery: the largest trial yet, funded by the U.K. government, showed hydroxychloroquine had no benefit for patients hospitalized with Covid-19. A total of 1,542 patients received hydroxychloroquine, and 3,132 received usual care. After 28 days of treatment, 25.7% of those on hydroxychloroquine and 23.5% of those received usual care had died. https://www.recoverytrial.net/news/statement-from-the-chief-investigators-of-the-randomised-evaluation-of-covid-19-therapy-recovery-trial-on-hydroxychloroquine-5-june-2020-no-clinical-benefit-from-use-of-hydroxychloroquine-in-hospitalised-patients-with-covid-19

Post exposure prohylaxis: In a randomized study performed in Barcelona's Germans Trias i Pujol University Hospital with more than 2300 people exposed to the virus, there was no significant difference between the number of people in each group who developed COVID-19, according to trial leader Oriol Mitjà (results have been submitted for publication). https://www.sciencemag.org/news/2020/06/three-big-studies-dim-hopes-hydroxychloroquine-can-treat-or-prevent-covid-19
A randomized trial performed in US and Canada and described in the previous update, sent either hydroxychloroquine or a placebo by mail to 821 people who had been in close contact with a COVID-19 patient for more than 10 minutes without proper protection. 12% of the people who took the drug developed COVID-19 symptoms, versus 14% in a placebo group.
https://www.nejm.org/doi/full/10.1056/NEJMoa2016638

Tocilizumab: In a multi-centre observational study (Madrid), tocilizumab was associated with a lower risk of death or ICU or death in patients with higher CRP levels. https://www.medrxiv.org/content/10.1101/2020.06.08.20125245v1
Another retrospective study in France shows that a single dose of tocilizumab was associated with improved survival without mechanical ventilation in patients with severe COVID-19. https://www.medrxiv.org/content/10.1101/2020.06.06.20122341v1

An in vitro study shows that cholesterol 25-hydroxylase (CH25H), an interferon-stimulated gene (ISG), restricts SARS-CoV-2 spike protein catalyzed membrane fusion. https://www.biorxiv.org/content/10.1101/2020.06.08.141077v1

The US poison centres report a clear rise in exposures to cleaners and disinfectants during the first quarter of 2020.
https://jamanetwork.com/journals/jama/fullarticle/2766883

Vaccines
The WHO published a draft landscape of COVID-19 vaccines. 133 vaccines are in development, 10 already in human trials.
https://www.who.int/publications/m/item/draft-landscape-of-covid-19-candidate-vaccines
The Lancet summarises the 10 leading vaccines that are already in clinical trials
https://www.thelancet.com/action/showPdf?pii=S0140-6736%2820%2931252-6

The Imperial College is starting clinical trials for its "self-amplifying mRNA" vaccine in June, with 300 volunteers. If safe, it will conduct a 6,000-participant phase in October to test the vaccine's effectiveness. This vaccine would require smaller doses than Moderna's mRNA vaccine and less costly manufacturing facilities. In partnership with Morningship Ventures (family Chan, Hong Kong), it is creating an enterprise called VacEquity Global Health to make its vaccine available at the lowest possible cost in Britain, as well as in low- and middle-income countries.
https://www.imperial.ac.uk/news/198053/imperial-social-enterprise-accelerate-lowcost-covid19/

The Oxford adenoviral vectored vaccine will start to be tested in Brazil among 1000 highly exposed volunteers, in collaboration with Sao Paulo's University (Centro de Referencia para Inmunobiológicos Especiales (CRIE) de la Universidad Federal de Sao Paulo (Unifesp).
https://www.lavanguardia.com/internacional/20200607/481656097519/vacuna-oxford-contra-covid-brasil.html

The U.S. government's Operation Warp Speed has selected five vaccine projects to receive billions of dollars in federal funding and support before there's proof that the vaccines work. Scientific experts were not consulted for the final selection process.
https://www.nytimes.com/2020/06/03/us/politics/coronavirus-vaccine-trump-moderna.html

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COVID-19 EPIDEMIC

Epidemiological situation (17/06/2020, ECDC data):

Globally:
8 142 129 confirmed cases and 443 488 deaths

- Brazil and Mexico, along with the rest of Latin America now accounting for ~50% of deaths (and likely more than that). Brazil's total death toll now stands at 41 828, and it has surpassed Britain to become the 2nd worst-affected country by COVID-19 in the world after the USA.
- The LSHTM performed a modelling study to predict the impact of COVID-19 and mitigation strategies in LMIC. Younger populations may reduce overall risk but limited health system capacity coupled with closer inter-generational contact largely negates this benefit. Mitigation strategies that slow but do not interrupt transmission will still lead to the overwhelming of health systems and substantial excess deaths. Many lower income countries have acted while transmission remains at low levels which is likely to have slowed the spread of the virus.
  https://science.sciencemag.org/content/sci/early/2020/06/11/science.abc0035.full.pdf
- A *Nature Sustainability* editorial warns that a narrow focus on fighting the post-pandemic recession could have adverse effects on the environment and health. It suggests that health and sustainability should be at the heart of the economic response. https://www.nature.com/articles/s41893-020-0563-0

Confinement and deconfinement strategies

Beijing's airports cancelled more than 1200 flights and schools were closed again on Wednesday after a fresh cluster of SARS-CoV-2 cases (79 to date) emerged from the city's largest wholesale food market. Inspectors found 40 samples of the virus in the closed market, including on a chopping board for imported salmon. Experts were doubtful the virus was being spread through salmon or other food products. More than 76 000 people were tested on Sunday. (ProMed mail)

A modelling study from over 40,000 participants in UK shows that moderate physical distancing can reduce the proportion of cases that would need to self-isolate and of contacts that would need to be traced, in order to control SARS-CoV-2 transmission.
https://www.thelancet.com/action/showPdf?pii=S1473-3099%2820%2930457-6

Virus

A PNAS study identifies key genomic features that differentiate SARS-CoV-2, SARS-CoV and MERS-CoV from less pathogenic coronaviruses. These features include enhancement of the nuclear localization signals in the nucleocapsid protein and distinct inserts in the spike glycoprotein
https://www.pnas.org/content/pnas/early/2020/06/09/2008176117.full.pdf

A *Nature communications* commentary highlights some of the latest studies that provide structural information details on the virus, imperative for the development of vaccines and antiviral therapeutics. https://www.nature.com/articles/s41467-020-16779-4

Two studies suggest that neuropilin-1 (NRP1) facilitates SARS-CoV-2 infection of host cells, suggesting it can be a therapeutic target. Autopsies revealed SARS-CoV-2 infected NRP1-positive cells in the olfactory epithelium and bulb.
https://www.biorxiv.org/content/10.1101/2020.06.07.137802v2
https://www.biorxiv.org/content/10.1101/2020.06.05.134114v1

Transmission

Clusters: An analysis of over 3,000 cases in Japan identified 61 case-clusters in healthcare and other care facilities, restaurants and bars, workplaces, and music events. It also identified 22 probable primary case-patients for the clusters; most were 20–39 years of age and presymptomatic or asymptomatic at virus transmission.
https://wwwnc.cdc.gov/eid/article/26/9/20-2272_article

An analysis of disease trends and mitigation measures in Wuhan, China, Italy, and New York City reveals that airborne transmission is highly virulent and represents the dominant route to spread the disease, and that the difference with and without mandated face covering represents the determinant in shaping the pandemic trends in the three epicentres. https://www.thelancet.com/journals/lancet/article/PIIS0140-6736(20)31028-X/fulltext

Airborne SARS-CoV-2 is rapidly inactivated by simulated sunlight, according to a study that measured the effect of sunlight, relative humidity, and suspension matrix on the stability of SARS-CoV-2 in aerosols. *(Thanks for the tip, Carlos Chaccour!)*
https://academic.oup.com/jid/advance-article/doi/10.1093/infdis/jiaa334/5856149

By children: Experts from LSHTM developed age-based COVID-19 transmission models based on data from six countries—China, Italy, Japan, Singapore, Canada and South Korea. The team estimated that under-20s are at half the risk of COVID-19 infection than over-20s and only 21% of those aged 10 to 19 were likely to show symptoms compared with 69% of over-70s. The author's modelling also found that school closures had little effect on stopping viral spread.
https://www.nature.com/articles/s41591-020-0962-9

Symptoms / Risk factors

Asymptomatic infections: The outbreak of coronavirus disease 2019 (Covid-19) on the cruise ship Diamond Princess led to 712 persons being infected with SARS-CoV-2 among the 3711 passengers and crew members, and 410 (58%) of these infected persons were asymptomatic at the time of testing. The majority of asymptomatically infected persons remained asymptomatic throughout the course of the infection and the time to the resolution of infection increased with age.
https://www.nejm.org/doi/full/10.1056/NEJMc2013020
The Lancet publishes two other studies on passengers of the Diamond Princess cruise ship. The first study, with 104 passengers that were disembarked in Japan, shows that 32% were asymptomatic, 41% developed mild COVID-19, and 27% had severe COVID-19. Around 50% of asymptomatics showed radiographic abnormalities, including glass opacities on chest CT scans. https://www.thelancet.com/action/showPdf?pii=S1473-3099%2820%2930482-5

Of the 215 adults disembarked in Hong Kong, 9 were infected (8 were positive for RT-PCR). Six remained asymptomatic. Increased levels of serum lactate dehydrogenase was seen in presymptomatic vs asymptomatic patients.
https://www.thelancet.com/journals/laninf/article/PIIS1473-3099(20)30364-9/fulltext

About one in five individuals worldwide could be at increased risk of severe COVID-19, should they become infected, due to underlying health conditions, but this risk varies considerably by age. These estimates do not include socioeconomic factors but provide a starting point for considering the number of individuals that might need to be shielded or vaccinated as the global pandemic unfolds.
https://www.thelancet.com/journals/langlo/article/PIIS2214-109X(20)30264-3/fulltext

Race: An MIT study looks at COVID-19 mortality by county and finds that for every 10% increase in a county's Black population, its Covid-19 death rate roughly doubles. Authors adjusted for age, sex, comorbidities, and income but none of these seemed to explain the higher death rate. Other factors, such as systemic racism that affects the quality of insurance and health care African Americans receive, seem to be in cause.
https://www.statnews.com/2020/06/15/whos-dying-of-covid19-look-to-social-factors-like-race/
See these two comments on COVID-19 and the other pandemic: systemic inequity
https://www.nature.com/articles/s41575-020-0330-8.pdf
https://www.thelancet.com/action/showPdf?pii=S2214-109X%2820%2930276-X

Children:
A seroprevalence study in Geneva concludes that for every for every reported confirmed case, there were 11.6 infections in the community. Overall seroprevalence in the fifth week was 10%, but it was significantly lower in children under 10 years of age or adults over 64 years of age. https://www.thelancet.com/journals/lancet/article/PIIS0140-6736(20)31304-0/fulltext
On the other hand, the Kids Corona study by Hospital Sant Joan de Déu reveals that children have a prevalence of SARS-CoV-2 antibodies similar to that in adults, but most develop very mild symptoms. The study followed 724 children with a COVID-19 positive parent. 17,5% of children and 18.9% of adults living in the same household were infected. (*Thanks for the info, Jordi Sunyer!*)
https://www.sjdhospitalbarcelona.org/es/ninos-tienen-prevalencia-anticuerpos-covid-19-similar-adultos-pero-mayoria-con-sintomas-leves

There is mounting evidence that healthy blood vessels protect children from serious effects of COVID-19, such as stroke, according to a news story in *Nature*.
https://www.nature.com/articles/d41586-020-01692-z

Pregnant women: Hospital Sant Joan de Deu also announced results from the BCNatal study, which analysed 874 pregnant women: 14% had SARS-CoV-2 antibodies, and most were asymptomatic or had mild symptoms. Those infected in the last trimester developed more severe disease.
Transmission of COVID-19 from mother to baby during pregnancy is uncommon, and the rate of infection is no greater when the baby is born vaginally, breastfed or allowed contact with the mother, according to a systematic review by the University of Nottingham that included 655 pregnant women and their babies.
https://obgyn.onlinelibrary.wiley.com/doi/abs/10.1111/1471-0528.16362

Infection Fatality Rate: A preprint based on seroprevalence data from Geneva, Switzerland, estimates an IFR of 0.6% for the total population, and an IFR of 5.6% for people aged 65 and older. https://osf.io/wdbpe/

An analysis of 26 autopsies of deceased people with severe COVID-19 found that septic shock and multi organ failure was the most common immediate cause of death, often due to suppurative pulmonary infection.
https://www.medrxiv.org/content/10.1101/2020.06.15.20131540v1

Antibodies / Immunity
A longitudinal study in a London Hospital shows that 45% of the 181 HCWs enrolled were seropositive at the end of the study period. Many were asymptomatic or pauci-symptomatic. All but one developed antibodies.
https://www.medrxiv.org/content/10.1101/2020.06.08.20120584v1

A seroprevalence study in Barcelona tested 311 asymptomatic individuals from a randomly selected sample (overall mean age 43.7 years, 55% women). Seventeen individuals were seropositive for IgM and/or IgG (overall prevalence of 5.47%). Of 634 symptomatic individuals, almost 40% were seropositive. Fever (>38°C), anosmia, ageusia and contact with a patient diagnosed with COVID-19 were associated with a positive test result. https://www.medrxiv.org/content/10.1101/2020.06.13.20130575v1

A comment in *Nature* dissects what is known of antibody-mediated protection against COVID-19. They argue that neutralizing antibodies may be more critical for protection against infection than for resolving disease. Non-neutralising antibodies may help recruit antibody-dependent cellular phagocytosis (ADCP), complement-dependent cytotoxicity (CDC) and antibody-dependent cellular cytotoxicity (ADCC).
https://www.nature.com/articles/s41577-020-0359-5

Treatment
Anti-inflammatory drugs:
Dexamethasone, a cheap steroid, seems to reduce COVID-19 mortality in critically ill patients, according to an announcement by the UK Recovery trial. For patients on ventilators, it cut the risk of death from 40% to 28%. For patients needing oxygen, it cut the risk of death from 25% to 20%. Researchers estimate that if the drug had been available in the UK from the start of the pandemic, up to 5,000 lives could have been saved. *However, the data have not been published.*
https://www.recoverytrial.net/files/recovery_dexamethasone_statement_160620_v2final.pdf

Bruton tyrosine kinase (BTK) regulates macrophage signaling and activation. Acalabrutinib, a selective BTK inhibitor, was administered off-label to 19 patients hospitalized with severe COVID-19 Over a 10-14 day treatment course, 8/11 patients in the supplemental oxygen cohort had been discharged on room air, and 4/8 patients in the mechanical ventilation cohort had been successfully extubated
https://immunology.sciencemag.org/content/5/48/eabd0110

Nature publishes a comment on off-label therapy targeting pathogenic inflammation in COVID-19 https://www.nature.com/articles/s41420-020-0283-2.pdf

Antibodies: Researchers at Scripps Institute used plasma from recovered COVID-19 patients to isolate potent neutralizing antibodies (nAbs) to two epitopes on the receptor binding domain (RBD) and to distinct non-RBD epitopes on the spike (S) protein. Passive transfer of these nAb provided protection against disease in high-dose SARS-

CoV-2 challenge in Syrian hamsters
https://science.sciencemag.org/content/early/2020/06/15/science.abc7520

Regeneron has launched clinical trials of its dual antibody cocktail REGN-COV2, for treating COVID-19. The two monoclonal antibodies non-competitively target the SARS-CoV-2 spike protein's receptor binding domain. It will be tested as a therapeutic agent for COVID-19 patients and as a preventive therapy in high-exposure-risk groups.
https://newsroom.regeneron.com/news-releases/news-release-details/regeneron-begins-first-clinical-trials-anti-viral-antibody

Hydroxychloroquine: The Food and Drug Administration has withdrawn an emergency approval for use of hydroxychloroquine as Covid-19 treatment.
https://www.statnews.com/2020/06/15/fda-revokes-hydroxychloroquine/

Vaccines
Oral polio vaccine: Robert Gallo and colleagues proposed using the oral polio vaccine to prevent or ameliorate COVID-19 symptoms. They base their proposal on i) evidence that live attenuated vaccines can also induce broader protection against unrelated pathogens, by inducing interferon and other innate immunity mechanisms that are yet to be identified; ii) OPV and Coronaviruses are positive strand RNA viruses which may be affected by common innate immune mechanisms; iii) there are millions of doses of OPV available; iv) it is safer than BCG (which is currently being tested in trials); and v) it will protect even if SARS-CoV-2 mutates.
https://science.sciencemag.org/content/368/6496/1187.full

An inactivated SARS-CoV-2 vaccine candidate, BBIBP-CorV, developed by the Beijing Institute of Biological Products Company, protected macaques against SARS-CoV-2 infection in the lung and showed no evidence of antibody dependent enhancement
https://www.cell.com/cell/fulltext/S0092-8674(20)30695-4

Italy, Germany, France and the Netherlands have signed a contract with Astrazeneca to supply European citizens with the vaccine developed by the University of Oxford, according to the Italian prime minister

Animal models
Exogenous delivery of human ACE2 with a replication-deficient adenovirus (Ad5-hACE2) in mice provides a model to evaluate therapies and vaccines. Ad5-hACE2-sensitized mice developed pneumonia characterized by weight loss, severe pulmonary pathology, and high-titer virus replication in lungs.
https://www.cell.com/action/showPdf?pii=S0092-8674%2820%2930741-8

Indirect lockdown effects
Sleep: A one-time online survey addressing people in Switzerland, Germany, and Austria, studied the effects of the 'lockdown' on social jetlag, social sleep restriction and sleep between March and April 2020. The lockdown led to an improved individual sleep-wake timing and overall, more sleep, although the quality was less. Exposure to daylight and exercising may help increase sleep quality in these situations.
https://www.cell.com/action/showPdf?pii=S0960-9822%2820%2930837-X
Similar results were observed with University students in the US
https://www.cell.com/action/showPdf?pii=S0960-9822%2820%2930838-1

ISGlobal

COVID-19 EPIDEMIC

Epidemiological situation (24/06/2020, ECDC data):

Globally:
9 229 049 confirmed cases and 477 269 deaths

- Brazil, Chile, Peru, Mexico, India, Saudi Arabia, South Africa, and Pakistan are reporting increased numbers of new and cumulative cases.
- An op-ed by Scott Gottlieb on COVID19 argues that the dissociation between the increasing number of cases and decreasing number of deaths in the US is primarily due to more young people getting infected and better protection of the old. He also discusses how the UK is showing the right way to do clinical trials by keeping them simple and randomizing. https://www.wsj.com/articles/rules-for-clinical-trials-in-a-pandemic-11592770800
- *PNAS* and *Science* write on COVID-19 and gender inequity in academics https://www.pnas.org/content/pnas/early/2020/06/16/2010636117.full.pdf https://science.sciencemag.org/content/368/6497/1317/tab-pdf
- A comment (signed by our colleague JV Lazarus) points out that, in average, 367 COVID-19 journal articles were published per week and the median time from submission to acceptance was 6 days.This raises concerns about the quality of the evidence base and the risk of misinformation. https://www.nature.com/articles/s41562-020-0911-0
- *Nature* publishes a manifesto for best practices for responsible mathematical modelling. https://www.nature.com/articles/d41586-020-01812-9

Confinement and deconfinement strategies

Confinement:
An analysis by statnews concludes that if the U.S. had acted as effectively as Germany, 70% of U.S. coronavirus deaths in the country might have been prevented. To compare each country's responses to the pandemic, they used a stringency index developed by an Oxford University team, based on 13 policy responses (lockdowns, border closings, tests), to measure how strongly each country responded over time. Fourteen days from the 15th confirmed case, the U.S. stringency score of 5.7 was 25% of Australia's (23), 23% of Germany's (25), 18% of Singapore's (32), and only 15% of South Korea's (38). https://www.statnews.com/2020/06/19/faster-response-prevented-most-us-covid-19-deaths/

Deconfinement
A policy forum in *Science* stresses the need to know which non-pharmaceutical interventions (NPIs) work best in a pandemic and describes how randomized clinical trials for NPIs can be practically and ethically implemented.
https://science.sciencemag.org/content/368/6495/1063

In this sense, a model developed by our colleague Xavier Rodó allows to quantitatively evaluate the relevance of NPIs as containment strategies. The model shows that deconfinement must be gradual and that individual behaviour (social distancing, use of

face masks, hand hygiene) is key to avoiding future waves.
https://www.nature.com/articles/s41562-020-0908-8

ECDC publishes its 10th update on rapid risk assessment of covid-19. It stresses that the pandemic is not over and that a rise in cases is likely in the coming weeks due to 'isolation fatigue'. Four key risk communication messages are proposed: i) This is a marathon, not a sprint. ii) We must not drop our guard. Iii) We all need to adjust to a 'new normal'. iv) Together, our actions give us the power to control the spread of the virus. https://www.ecdc.europa.eu/en/publications-data/rapid-risk-assessment-coronavirus-disease-2019-covid-19-pandemic-tenth-update

Re-emerging outbreaks:
Germany has reported its highest daily increase in coronavirus cases in a month. The Robert Koch Institute listed 770 new confirmed cases related to an outbreak at a slaughterhouse in the western region of Guetersloh. All 6400 employees of the plant and their close contacts are now in quarantine after the plant was closed on June 17. Since the country relaxed its restrictions in late April, it has largely kept infection rates low, except for local outbreaks linked to slaughterhouses, church services and a restaurant. https://www.dailymail.co.uk/news/article-8439939/Germany-reports-highest-daily-rise-coronavirus-cases-month.html
The UK also reported the emergence of 3 separate COVID-19 clusters at meat-processing factories in England and Wales. https://www.telegraph.co.uk/global-health/science-and-disease/revealed-meat-processing-plants-ideal-incubator-coronavirus/
Various factors may make meat-processing plants ideal breeding grounds for the virus: difficulty in maintaining physical distance, particularly in production lines and in break rooms; pace and physical demands of the work incompatible with use of face masks; housing in crowded conditions; precarious working conditions and no paid sick leave.

Spain: Huesca goes back to phase 2 after an outbreak in a fruit producing plant in Zaidin was detected, with 14 mild and asymptomatic cases. In Lleida, an outbreak was detected in an elderly care residence (13 residents and 5 staff).

Iran has seen an upsurge of cases since it relaxed restrictions in April
https://www.thelancet.com/journals/lancet/article/PIIS0140-6736(20)31407-0/fulltext

In India, authorities have re-imposed a 12 day strict lockdown in the southern city of Chennai (Madras). It is one of India's largest hotspots of transmission. After a strict lockdown imposed in March, the country started easing restrictions earlier this month. (ProMed Mail)

Virus
A study with human pluripotent stem cell-derived cells and organoids shows that human pancreatic beta cells and liver organoids are highly permissive to SARS-CoV-2 infection. This results in robust chemokine induction, similar to what is observed in autopsy samples from COVID-19 patients. Interestingly, several cell types expressing ACE2, such as endothelium, macrophages, and cortical neurons show low or no permissiveness to infection, suggesting other factors involved in viral entry (e.g. the TMPRSS2 effector protein). https://www.cell.com/cell-stem-cell/fulltext/S1934-5909(20)30282-4
Diabetes link? The above results with beta-islet cells add to evidence suggesting coronavirus may trigger diabetes, although further studies are needed.
https://www.nature.com/articles/d41586-020-01891-8

Researchers used CRISPR-Cas9 to alter genes in cultured monkey cells and evaluate viral infection and host-cell death. They found genes that code for several proteins not reported previously to assist coronavirus infection, including proteins in the TGF-β signalling pathway https://www.biorxiv.org/content/10.1101/2020.06.16.155101v1

Transmission

A study investigating a spike in Influenza like illness (ILI) in the US suggests that there were over 8.7 million new undiagnosed SARS-CoV-2 infections between March 8 - 28, 2020. https://stm.sciencemag.org/content/early/2020/06/22/scitranslmed.abc1126

Scientists in Italy have found traces of SARS-CoV2 in wastewater collected from Milan and Turin in December 2019, suggesting COVID-19 was already circulating in northern Italy before China reported the first cases. However, it does not automatically imply this was the source of the large epidemic in Italy, or there were later introductions into the country. https://www.reuters.com/article/us-health-coronavirus-italy-sewage/italy-sewage-study-suggests-covid-19-was-there-in-december-2019-idUSKBN23Q1J9

Asymptomatic transmission:

A study at a quarantine center in Vietnam (30 participants) indicates that asymptomatic SARS-CoV-2 infection is common (47%) and can be detected by analysis of saliva or nasopharyngeal swabs (NTS). NTS viral loads fall faster in asymptomatic individuals, but they appear able to transmit the virus to others.
https://academic.oup.com/cid/advance-article/doi/10.1093/cid/ciaa711/5851471
A longitudinal surveillance for SARS-CoV-2 RNA among asymptomatic staff in five Colorado skilled nursing facilities reveals a high degree of asymptomatic infection (up to 22%), a strong correlation between RNA detection and the presence of infectious virus in NP swabs (although the detection window for infectious virus is shorter than that for RNA), and persistent RNA (2 to 4 weeks) in some individuals.
https://www.medrxiv.org/content/10.1101/2020.06.08.20125989v1

Triplets born prematurely Mexico tested positive for coronavirus on the day of their birth. Investigations are going on to determine if the mother was asymptomatic.
https://www.bbc.com/news/world-latin-america-53147483

A study reveals an unexpected increase in particulate matter during China's COVID19 lockdown, and discusses implications for potential aerosol transmission.
https://science.sciencemag.org/content/early/2020/06/16/science.abb7431

Testing

Seroprevalence studies:

A study performed in Lodi (a highly affected region in northern Italy) with 390 blood donors recruited between 18 March and 6 April shows some interesting results: 20 (5%) tested positive by RTPCR and 91 (23%) were positive for SARS-CoV-2 specific neutralizing Abs (total infection prevalence of 28%). Most had no or mild symptoms. Compared to convalescent patients, the majority of nAb-positive blood donors had lower nAb titres: 57 (63%) had low nAb titres (between 1:10 and 1:40), 29 (32%) had medium titers (1:40 - 1:160) and five (5%) had high titers (> 1:160). Interestingly 5 stored blood samples from Feb. 12-17 tested positive for nAbs, suggesting that the virus was circulating a few weeks before the first patient was identified.
https://www.eurosurveillance.org/content/10.2807/1560-7917.ES.2020.25.24.2001031

Active infections:

A “no-swab” saliva test (based on RT-LAMP) is being trialled in southern England and could result in a simpler and quicker way to detect outbreaks of the virus, the British government said on Monday. It will be validated against PCR nasal swabs. The pilot will run for four weeks, testing people on a weekly basis, resulting in a total of 33,000 – 40,000 tests. https://www.reuters.com/article/us-health-coronavirus-britain-tests/no-swab-saliva-test-for-coronavirus-piloted-in-britain-idUSKBN23T0Y7

In Johannesburg, South Africa, researchers will start a trial to assess a rapid breath test for COVID-19, developed by US-based Canary Health Technologies. If successful, the test, which detects metabolic footprints in breath and can deliver results in less than 5 minutes, would offer the advantages of being non-invasive, easy to use, and appropriate in settings other than hospitals. https://www.the-scientist.com/news-opinion/in-south-africa-covid-19-breath-test-trial-set-for-june-67631

Contact tracing: Based on a survey of >5800 people, a UK team addresses the proportion and impact of missed COVID19 infections. They conclude that tracing using a contact definition requiring more than 4 hours of contact is unlikely to control spread. https://jech.bmj.com/content/early/2020/06/16/jech-2020-214051

Antibody tests: The European Network for Health Technology Assessment has published a review on the current role of antibody tests for SARS-CoV-2 in the management of the pandemic (*Thanks Kurt Straif for the info!*) see attached pdf.

Symptoms / Risk factors

An analysis of 5,484 contacts of SARS-CoV-2 index cases in Lombardy, Italy reveals that roughly half of the contacts became infected but 73.9% of all infected individuals aged less than 60 years did not develop symptoms. The risk of symptoms increased with age. 6.6% of infected subjects older than 60 years had critical disease, with males at significantly higher risk. https://arxiv.org/abs/2006.08471

A comment in *The Lancet* points to the potential association between encephalitis lethargica and the 1918 flu and that we should not underestimate the potential long-term neurological sequelae of this novel coronavirus.
https://www.thelancet.com/pdfs/journals/laneur/PIIS1474-4422(20)30189-7.pdf

Ethnicity:
The seroprevalence study performed in NY state has been published. Cumulative incidence was highest in New York City (NYC) with 22.7%, and higher among Hispanic/Latino (29.2%), non-Hispanic black/African American (20.2%), and non-Hispanic Asian (12.4%) than non-Hispanic white adults (8.1%, p<.0001). An estimated 8.9% of infections in NY State were diagnosed
https://www.sciencedirect.com/science/article/pii/S1047279720302015
In Baltimore, PCR testing of samples collected between March 11, 2020, and May 25, 2020, from 5 hospitals and 30 outpatient clinics, reveals that more than 40% of Latinos in the Baltimore-Washington, DC metropolitan region who were tested for SARS-CoV-2 were positive, a much higher proportion than for any other racial/ethnic group.
https://jamanetwork.com/journals/jama/fullarticle/2767632

Antibodies / Immunity

Short-lived/low-level antibodies?
A Chinese team studied 37 asymptomatic individuals (Wanzhou District) who were diagnosed by RT–PCR for SARS-CoV-2 infection but without any relevant clinical symptoms. Compared to age and sex-matched patients with mild symptoms, the asymptomatic group had a longer duration of viral shedding (median 19 days) and

lower IgG and neutralising Ab levels in the acute phase. Eight weeks after hospital discharge, IgG and nAb levels decreased in both groups. 40% of asymptomatic individuals became seronegative for IgG. In addition, asymptomatic individuals exhibited lower levels of 18 pro and anti-inflammatory cytokines, suggesting a weaker immune response in asymptomatic individuals. These results might have implications for immunity strategy and serological surveys.
https://www.nature.com/articles/s41591-020-0965-6

A study with 149 convalescent PCR-confirmed patients (most with mild symptoms) shows that most do not have high levels of neutralizing activity (80% were below 1:1000). 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. https://www.nature.com/articles/s41586-020-2456-9

T cell responses: T cell responses may be more sensitive indicators of SARS-Co-V-2 exposure than antibodies, according to a study that investigated the humoral and cellular immune responses against SARS-CoV-2 in seven households with at least 1 known positive Covid-19 case. Six of 8 household contacts had blood samples with measurable T-cell responses, but no measurable antibodies.
https://www.medrxiv.org/content/10.1101/2020.06.21.20132449v1

A preprint suggests a role of eosinophils in lung hyperinflammation and a potential role of basophils in enhancing the humoral response to COVID-19. The authors used mass cytometry and Olink to longitudinally profile immune cells and protein biomarkers in the blood of 39 patients with severe COVID-19 from acute infection to recovery. They describe activation of a IFNg-CD62L+ eosinophil axis prior to lung hyperinflammation.
https://www.medrxiv.org/content/10.1101/2020.06.03.20121582v2

Monogenic disorders?: A comment in Nature suggests that young patients may become critically ill because of monogenic inborn errors that disrupt protective immunity to SARS-CoV-2 (they may be autosomal and X-linked disorders; recessive, dominant or co-dominant traits; resulting in loss of function or gain of function…).
https://www.nature.com/articles/s41577-020-0373-7

Treatment

Dexamethasone: The preprint with the results from the RECOVERY trial has been posted. Dexamethasone reduced deaths by one-third in patients receiving invasive mechanical ventilation (29.0% vs. 40.7%, RR 0.65; p<0.001), by one-fifth in patients receiving oxygen without invasive mechanical ventilation (21.5% vs. 25.0%, RR 0.80; p=0.002), but did not reduce mortality in patients not receiving respiratory support (17.0% vs. 13.2%, RR 1.22; p=0.14).
https://www.medrxiv.org/content/10.1101/2020.06.22.20137273v1

Rendesivir: The American biopharmaceutical company Gilead Sciences will soon start trials of an inhalable version of remdesivir, which is currently given intravenously.
https://www.nytimes.com/2020/06/22/health/gilead-remdesivir-coronavirus-nebulizer.html

Hydroxychloroquine: another nail to the coffin. NIH halts its blinded, placebo-controlled, randomized trial of hydroxychloroquine for treating COVID-19. The ORCHID study shows treatment does no harm, but provides no benefit.
https://www.nih.gov/news-events/news-releases/nih-halts-clinical-trial-hydroxychloroquine

Antibodies:
A study with 20,000 hospitalized patients that received COVID-19 convalescent plasma provides evidence that it is safe, and shows some effectiveness in reducing mortality, although it was not a clinical trial.
https://mayoclinicproceedings.org/pb/assets/raw/Health%20Advance/journals/jmcp/jmcp_ft95_6_8.pdf

A Chinese team isolated and characterised mAbs from ten convalescent COVID-19 patients. One mAb with potent neutralising activity binds to the N terminal domain of the spike protein (outside the RBD), indicating this site may be a promising target for therapeutic antibodies.
https://science.sciencemag.org/content/sci/early/2020/06/19/science.abc6952.full.pdf

Vaccines
Preclinical data on the mRNA vaccine candidate by Moderna show that immunization of mice with mRNA encoding stabilized prefusion SARS-CoV-2 spike trimers elicited dose-dependent neutralizing antibody and CD8+ T cell responses. Two doses given in prime–boost combination (2 x 1 μg/mouse) protected mice against infection of the nasal mucosa and lungs after challenge with mouse-adapted SARS-CoV-2. Importantly, there was no indication of enhanced immunopathology in animals that received sub-protective doses. A phase III efficacy trial in humans (using a single 100 μg dose) is set to start in July. https://www.biorxiv.org/content/10.1101/2020.06.11.145920v1

Data on the Oxford-Astrazeneca Covid19 vaccine have been finally posted as a preprint: results in pigs suggest a 2-dose regimen may be necessary.
https://www.biorxiv.org/content/10.1101/2020.06.20.159715v1

Sanofi Pasteur has announced the start of a Phase 1/2 clinical trial for a recombinant vaccine it is developing with GSK's adjuvants. It is also partnering with Translate Bio to develop and test an mRNA vaccine candidate.
https://www.statnews.com/2020/06/23/sanofi-a-straggler-in-the-covid-19-vaccine-race-accelerates-its-plans/

Indirect effects
Cancer mortality: The COVID-19 crisis could cause 10,000 excess deaths from colorectal and breast cancer in the USA due to interruptions in diagnosis and treatment. https://science.sciencemag.org/content/368/6497/1290.full

ISGlobal

COVID-19 EPIDEMIC

Epidemiological situation (01/07/2020, ECDC data):

Globally:
10,610,065 confirmed cases and 514,468 deaths

- Today marks six months since WHO received the first reports of a cluster of cases of pneumonia of unknown cause in China. The WHO has published a covid timeline of its response https://www.who.int/news-room/detail/29-06-2020-covidtimeline
- These days have also been marked by record numbers of new cases globally, with several countries reporting their highest number of new cases in 24h.
- The Americas region reported 60.9% of the global newly reported cases and 68.9% of newly reported deaths for this 24-hour period.
- *Nature* writes its last research brief on COVID-19 by summarising the most relevant findings of these six months https://www.nature.com/articles/d41591-020-00026-w
- Rapid Reviews for COVID-19 preprints: The MIT Press is launching an open access journal that will publish reviews of preprints related to Covid-19, in an effort to "quickly and authoritatively call out misinformation as well as highlight important, credible research". The project will use an artificial intelligence system developed at Lawrence Berkeley National Laboratory to categorize new preprints by discipline and degree of novelty. Rapid reviews will be done (by a pool of 1600 potential reviewers) on studies flagged as interesting. https://www.statnews.com/2020/06/29/new-journal-vet-covid-19-preprints/

Keeping an eye on another virus with pandemic potential:
Chinese pigs are more and more frequently becoming infected with a strain of influenza that has the potential to jump to humans, according to a study that analyzed nearly 30,000 nasal swabs taken from pigs at slaughterhouses in 10 Chinese provinces, between 2011 and 2018. They identified a G4 variant whose core is an avian influenza virus with bits of mammalian strains and the potential to jump to humans. https://www.sciencemag.org/news/2020/06/swine-flu-strain-human-pandemic-potential-increasingly-found-chinese-pigs

Confinement and deconfinement strategies

The UK's first full local lockdown has been announced in Leicester, with stricter measures imposed in the city. Non-essential shops have shut, and schools will close for most pupils on Thursday because of a rise in coronavirus cases. https://www.bbc.com/news/uk-england-leicestershire-53229371

The American Academy of Pediatrics calls for bringing students back to school next fall, where and when it can be safely done. The academy cites "mounting evidence" that transmission of the coronavirus by young children is uncommon, partly because they are less likely to contract it in the first place. https://services.aap.org/en/pages/2019-novel-coronavirus-covid-19-infections/clinical-guidance/covid-19-planning-considerations-return-to-in-person-education-in-schools/

Virus
A quantitative mass spectrometry-based phosphoproteomics survey of SARS-CoV-2 infection in Vero E6 cells, reveals "dramatic rewiring of phosphorylation" on host and viral proteins. SARS-CoV-2 infection promoted casein kinase II (CK2) and p38 MAP kinase activation, production of diverse cytokines, and shutdown of mitotic kinases resulting in cell cycle arrest. Pharmacologic inhibition of p38, CK2, CDKs, AXL and PIKFYVE kinases show antiviral efficacy, representing potential COVID-19 therapies. https://www.cell.com/cell/fulltext/S0092-8674(20)30811-4

Transmission
Nature publishes the study performed in the Italian municipality of Vo at two different timepoints of the epidemic. Notably, 42.5% of the confirmed SARS-CoV-2 infections detected across the two surveys were asymptomatic (i.e. did not have symptoms at the time of swab testing and did not develop symptoms afterwards). The authors found no statistically significant difference in the viral load of symptomatic versus asymptomatic infections https://www.nature.com/articles/s41586-020-2488-1

The CDC reports data collected through a multistate telephone survey of 350 adult inpatients and outpatients who tested positive for SARS-CoV-2 infection. Only 46% reported recent contact with a COVID-19 patient. Most participants' contacts were a family member (45%) or a work colleague (34%). Only 17% were able to telework. Approximately one third reported that they had not returned to baseline health by the interview date 14–21 days after testing positive.
https://www.cdc.gov/mmwr/volumes/69/wr/pdfs/mm6926e3-H.pdf

The number of coronavirus infections in many parts of the US is more than 10 times higher than the reported rate, according to data from antibody surveys released by the CDC. The survey includes people who had blood specimens taken (March-April) for reasons unrelated to COVID-19, across 10 sites/states. Results ranged between 7% for NYC and 1.85% for Utah. The CDC plans to repeat the surveys in all of the regions to see how the prevalence changes over time. https://www.cdc.gov/coronavirus/2019-ncov/cases-updates/commercial-lab-surveys.html

Testing / Tracing
A Cochrane Systematic Review covers antibody tests for identification of current and past infection with SARS-CoV-2 (*Thanks for the tip, Kurt Straif!)*
https://www.cochranelibrary.com/cdsr/doi/10.1002/14651858.CD013652/full

A statement by Dr Hans Henri Kluge, WHO Regional Director for Europe, talks about the resurgence threat and actions taken in Europe, the need to find, isolate, test, and care for every case, and the role of digital technology in tracing contacts. Regarding the former, he underlines 3 messages:
1. Go digital, but go wisely
2. Build trust by respecting privacy
3. Address the digital gap

Along this line, a paper in *Lancet Digital Health* proposes a navigation aid for policy makers and other decision makers for the ethical development and use of digital public health tools. https://www.thelancet.com/journals/landig/article/PIIS2589-7500(20)30137-0/fulltext

Symptoms / Risk factors

Endothelial attack*: Science* covers how the attack on blood vessels could trigger coronavirus' fatal 'second phase'. By attacking endothelial cells, COVID-19 infection causes vessels to leak and blood to clot. Those changes in turn spark inflammation throughout the body and fuel the acute respiratory distress syndrome (ARDS) responsible for most patient deaths.
https://www.sciencemag.org/news/2020/06/blood-vessel-attack-could-trigger-coronavirus-fatal-second-phase
A single-centre, cross-sectional study with 68 patients and 13 controls shows that endotheliopathy is present in COVID-19 and is likely to be associated with critical illness and death. Markers of endothelial cell and platelet activation were significantly elevated in ICU patients compared with non-ICU patients, including VWF antigen (565% vs 278%) and soluble P-selectin (15·9 ng/mL vs 11·2 ng/mL).
https://www.thelancet.com/journals/lanhae/article/PIIS2352-3026(20)30216-7/fulltext

Neurological effects: A UK study reports 125 COVID-19 cases with some kind of neurological or neuropsychiatric complication. The most common brain complication observed was stroke, which was reported in 77 patients (57 of which were due to a blood clot). 39 patients showed signs of confusion or changes in behaviour, seven of which had encephalitis. https://www.thelancet.com/journals/lanpsy/article/PIIS2215-0366(20)30287-X/fulltext

Obesity: A perspective in *Med* (Cell Press) presents some hypotheses regarding the deleterious impact of obesity on the course of COVID-19.
https://www.cell.com/med/fulltext/S2666-6340(20)30010-6

HIV: A study from New York finds people with HIV who contract Covid19 do not have worse outcomes than people without HIV.
https://academic.oup.com/cid/article/doi/10.1093/cid/ciaa880/5864410

A comment in *The Lancet* reviews how to identify/triage patients that need respiratory support in COVID-19. The clinical course of the disease follows three main patterns which may require different respiratory support.
https://www.thelancet.com/action/showPdf?pii=S2213-2600%2820%2930279-4

Children:
Researchers looked at 582 children that tested positive for COVID-19, aged from three days to 18 years and across 25 European countries. A quarter had underlying health conditions. More than half of the children studied were admitted to hospital, and 8% needed treatment in intensive care. Children co-infected with other respiratory viruses were more likely to be admitted to intensive care. Of the four deaths during the study (0.69%), none were in children under 10, and two of those who died had pre-existing health conditions. https://www.thelancet.com/journals/lanchi/article/PIIS2352-4642(20)30177-2/fulltext

NEJM reports 186 paediatric patients with multisystem inflammatory syndrome (MIS) in 26 states across the US, 70% were positive for SARS-CoV2 RT-PCR. The median age was 8.3 years, 73% had previously been healthy. Immunomodulatory therapies were used in most cases. Four patients died.
https://www.nejm.org/doi/full/10.1056/NEJMoa2021680
A comment in *The Lancet* reviews what is known on COVID-19 and young patients and possible immunological mechanisms
https://www.thelancet.com/action/showPdf?pii=S2665-9913%2820%2930212-5

Antibodies / Immunity
Asymptomatics: South Korean scientists report finding neutralizing antibodies in 7/7 completely asymptomatic patients 8 weeks after lab diagnosis, while serologic diagnostic testing was positive for 71% (5/7). They conclude that seroconversion in asymptomatic patients might take longer.
https://wwwnc.cdc.gov/eid/article/26/10/20-2211_article

T cells: A study with 10 COVID-19 patients who required admission to an intensive care unit detected SARS-CoV-2-specific CD4+ and CD8+ T cells in 10 out of 10 and 8 out of 10 patients, respectively. The strongest T-cell responses were directed to the spike surface glycoprotein, and SARS-CoV-2-specific T cells predominantly produced effector and Th1 cytokines https://immunology.sciencemag.org/content/5/48/eabd2071/tab-pdf

Researchers from the Karolinska Institute in Sweden systematically mapped the functional and phenotypic landscape of SARS-CoV-2-specific T cell responses in a large cohort of unexposed individuals as well as exposed family members and individuals with acute or convalescent COVID-19. SARS-CoV-2-specific T cells were detectable in antibody-seronegative family members and individuals with a history of asymptomatic or mild COVID-19. These results suggest that immunity to COVID-19 is probably higher than antibody tests have shown.
https://www.biorxiv.org/content/10.1101/2020.06.29.174888v1

Treatment
Lopinavir-ritonavir: another one bites the dust? The HIV drug does not provide clinical benefit in hospitalised COVID-19 patients, according to a statement from the UK-led RECOVERY trial. A total of 1596 patients were randomised to lopinavir-ritonavir and compared with 3376 patients randomised to usual care alone. There was no significant difference in the primary endpoint of 28-day mortality (22.1% lopinavir-ritonavir vs. 21.3% usual care; p=0.58) and no evidence of beneficial effects on the risk of progression to mechanical ventilation or length of hospital stay.
https://www.recoverytrial.net/news/no-clinical-benefit-from-use-of-lopinavir-ritonavir-in-hospitalised-covid-19-patients-studied-in-recovery
The RECOVERY trial consists of 11,800 patients randomised to the following treatment arms, or no additional treatment:
• Lopinavir-Ritonavir (an HIV treatment, no clinical benefit)
• Low-dose Dexamethasone (now stopped due to clear benefit among patients requiring ventilation or oxygen)
• Hydroxychloroquine (which has now been stopped due to lack of efficacy)
• Azithromycin (a commonly used antibiotic)
• Tocilizumab (an anti-inflammatory treatment given by injection)
• Convalescent plasma (collected from COVID-19 recovered donors)

Tocilizumab: A retrospective, observational cohort study included 544 adults (≥18 years) with severe COVID-19 pneumonia who were admitted to tertiary care centres in Italy. After adjustment for sex, age, recruiting centre, duration of symptoms, and SOFA score, tocilizumab treatment (in 179 patients) was associated with a reduced risk of invasive mechanical ventilation or death
https://www.thelancet.com/journals/lanrhe/article/PIIS2665-9913(20)30173-9/fulltext

Remdesivir price tag: Gilead has set the price of remdesivir at 347 euros per dose (meaning 2,076 euros or 2,340 USD per patient) in developed countries.
https://elpais.com/sociedad/2020-06-29/la-farmaceutica-gilead-fija-en-unos-2000-euros-la-primera-terapia-aprobada-para-la-covid-19.html

Vaccines
Disulfide-linked dimers of the spike receptor binding domain induced high titers of neutralising antibodies in mice and could potentially represent a universal vaccine against betacoronaviruses. https://www.cell.com/action/showPdf?pii=S0092-8674%2820%2930812-6

China has approved CanSino's adenovirus vaccine for military use for the next year, according to the NYT coronavirus vaccine tracker, while the Sinopharm (inactivated virus) vaccine is starting phase III trials.
https://www.nytimes.com/interactive/2020/science/coronavirus-vaccine-tracker.html

Indirect effects
Women and people aged under 35 are suffering disproportionately from the consequences of the economic crisis generated by the pandemic, warns the Bank of Spain in its annual report
https://www.lavanguardia.com/economia/20200630/482032889762/crisis-coronavirus-mujeres-jovenes-impuestos-iva-banco-de-espana.html

Phsysical activity: A study used individual-level data from 19 January to 1 June 2020 collected from a convenience sample of users of the free, popular health and wellness smartphone app Argus. Worldwide, within 10 days of the pandemic declaration, there was a 5.5% decrease in mean steps (287 steps), and within 30 days, there was a 27.3% decrease in mean steps (1432 steps), with wide regional variation: a 48.7% maximal decrease in Italy versus 6.9% in Sweden.
https://www.acpjournals.org/doi/10.7326/M20-2665

ISGlobal

COVID-19 EPIDEMIC

Epidemiological situation (08/07/2020, ECDC data):

Globally:
11 801 805 confirmed cases and 543 902 deaths

- Yesterday, the Trump administration formally withdrew the US from the WHO http://hill.cm/zsenggq
- The WHO held a two half-day virtual summit on 1 and 2 July with over 1000 researchers to take stock of the evolving science on COVID-19 and examine progress made so far in developing effective health tools to improve the global response to the pandemic. They noted that most internationally funded research projects have so far favoured high-income countries, with very few funded in low- and middle-income countries, highlighting the importance of the ACT-Accelerator Initiative. More evidence is emerging that transmission from humans to animals is occurring, namely to felines (including tigers), dogs and minks. https://www.who.int/news-room/feature-stories/detail/global-scientific-community-unites-to-track-progress-on-covid-19-r-d-identifies-new-research-priorities-and-critical-gaps
- A comment in *Nature* calls for resetting the Sustainable Development Goals for a pandemic world. They argue that COVID-19 is exposing the fragility of the goals adopted by the United Nations two-thirds of which are now unlikely to be met. https://www.nature.com/articles/d41586-020-01999-x

Confinement and deconfinement strategies
USA: 57 former science and public health administration officials signed a statement expressing concern over the Trump administrations response, and calling for data-informed production and allocation decisions for PPE and ventilators and the sharing of data on new cases, deaths and hospitalizations.
https://medium.com/@FmrGovScientistsnOfficials/statement-from-former-gov-bcf9dc631f7d
According to the CDC data, the percentages of laboratory specimens testing positive forSARS-CoV-2 with a molecular assay is 9% positive tests out of 35 542 936 tests performed, consistent with the ongoing, yet not under control pandemic in the country
https://www.cdc.gov/coronavirus/2019-ncov/cases-updates/testing-in-us.html

Australia: Melbourne has entered a 6-week strict lockdown to contain the virus amid a surge of cases https://www.aljazeera.com/news/2020/07/australia-melbourne-heads-coronavirus-lockdown-200707081202649.html

Israel re-imposed on Monday a series of restrictions to fight a spike in coronavirus infections, including the immediate closure of bars, gyms and event halls, while also redeploying a contentious phone surveillance programme used to order people into quarantine. https://en.qantara.de/content/israel-re-imposes-restrictions-amid-new-surge-in-coronavirus-cases

Madagascar has placed its capital Antananarivo under a fresh lockdown following a new surge in coronavirus infections, 2 months after the restrictions were eased, the presidency announced.

Spain: Lleida and El Segria have been confined for at least 2 weeks due to an upsurge in cases: more than 500 COVID-19 cases and over 14 clusters. Since 11 May, 118 local outbreaks have been identified in Spain, and 67 remain active.
https://www.lavanguardia.com/vida/20200708/482188648628/sanidad-preocupacion-rebrotes-lleida-lugo.html

The European Union has reopened its borders to visitors from 15 countries but excluded the United States, where deaths are spiking once again.
https://www.consilium.europa.eu/en/press/press-releases/2020/06/30/council-agrees-to-start-lifting-travel-restrictions-for-residents-of-some-third-countries/

Virus
Nature has published the study on the evolution of two major lineages of SARS-CoV-2, distinguished by two distinctive nucleotide differences, together with information regarding human-host determinants of disease severity of 326 people in Shanghai who were infected with SARS-CoV-2. The data suggest that the market might not have been the origin of the epidemic and that clades I and II originated from a common viral ancestor and spread independently at the same time (clade I through the market and clade II outside it). No difference in disease severity between the two clades was observed. https://www.nature.com/articles/d41586-020-01915-3

On the other hand, a paper in *Cell* reports a SARS-CoV-2 variant (with spike G614 instead of D614) as the dominant pandemic form. The consistent increase of G614 at regional levels may indicate a fitness advantage. G614 is associated with lower RT PCR Ct's, suggestive of higher viral loads in patients. In vitro results also indicate better replication, but whether this makes it more transmissible still needs confirmation.
https://www.cell.com/cell/pdf/S0092-8674(20)30820-5.pdf

Transmission
An analysis of data received from Belgian long-term care facilities reveals that no symptoms were reported for 6244 (74·8%) of 8343 people who tested positive, including 2185 (74·0%) staff and 4059 (75·3%) residents. However, this percentage may include pre-symptomatic individuals.
https://www.thelancet.com/journals/laninf/article/PIIS1473-3099(20)30560-0/fulltext

Researchers report on a cluster of 21 infections in Heilongjiang Province, China, that likely resulted from one asymptomatic case that returned from the US.
https://wwwnc.cdc.gov/eid/article/26/9/20-1798

Over 200 scientists sign an open letter addressed to the WHO on SARS-CoV-2 and aerosol transmission. They argue that aerosol transmission appears to be the only way to explain several "super-spreading" events, including the infection of diners at a restaurant in China who sat at separate tables and of choir members in the US state of Washington who took precautions during a rehearsal. However, a group of more than 30 international experts advising the WHO “has not judged the existing evidence sufficiently convincing to consider airborne transmission as having an important role in COVID-19 spread".
See also (*Thanks for sharing the link, Kurt Straif!*):
https://academic.oup.com/cid/article/doi/10.1093/cid/ciaa939/5867798

Science publishes a special story on evidence to date on COVID-19 transmission by children and the impact of school closures

https://www.sciencemag.org/news/2020/07/school-openings-across-globe-suggest-ways-keep-coronavirus-bay-despite-outbreaks

Testing / Tracing
Seroprevalence studies:
ENE-COVID study in Spain: The results of the first round have been published in The Lancet, confirming a 5% overall prevalence of SARS-CoV-2 IgG antibodies (measured by POC test and immunoassay). Overall seroprevalence was 5% with substantial geographical variability: highest prevalence around Madrid (>10%) and lowest in coastal areas (<3%). Lower seroprevalence was observed in children younger than 10 years. Around a third of seropositive participants were asymptomatic.
https://www.thelancet.com/journals/lancet/article/PIIS0140-6736(20)31483-5/fulltext
Spanish authorities presented the results for the second round of ENE-COVID (IgG by rapid test). The overall estimated prevalence of IgG antibodies against SARS-Cov2 in Spain is 5.2%, slightly lower for men (5%) than women (5.4%) and marked geographical variability (10% for Madrid). In relation to age, the prevalence is lower in babies, children and young people. 80.5% of the participants who reported having had a PCR + more than 2 weeks ago presented IgG antibodies. In relation to participants from round 1, 0.8% have seroconverted.
https://www.lamoncloa.gob.es/serviciosdeprensa/notasprensa/sanidad14/Documents/2020/040620-ENE-COVID_Informe2.pdf

The seroprevalence study performed in Geneva, which found 10·8% seroprevalence in early May, has also been published in The Lancet (described in a previous update).
https://www.thelancet.com/pdfs/journals/lancet/PIIS0140-6736(20)31304-0.pdf

Frequent group testing, aided by machine learning, is a promising and inexpensive surveillance strategy according to a paper by the US National Bureau of Economic Research http://ziadobermeyer.com/wp-content/uploads/2020/07/GroupTesting-NBER-WP-Jul-2020.pdf

Symptoms / Risk factors
A preprint claims that the major genetic risk factor for severe COVID-19 (a segment of 50 kb within a gene cluster on chromosome 3) is inherited from Neandertals and occurs at a frequency of ~30% in south Asia and ~8% in Europe.
https://www.biorxiv.org/content/10.1101/2020.07.03.186296v1 See also
https://www.nytimes.com/2020/07/04/health/coronavirus-neanderthals.html

Science has published the study (described in a previous update) with human intestinal organoids that demonstrates that SARS-CoV-2 readily replicates in enterocytes, resulting in the production of large amounts of infective virus particles in the intestine.
https://science.sciencemag.org/content/369/6499/50

Antibodies / Immunity
A paper in Cell analysed the antibody response of 12 COVID-19 patients from 8 to 69 days post diagnosis. By screening 4,313 SARS-CoV-2-reactive B cells, they isolated 255 antibodies from different time points as early as 8 days post diagnosis. Of these, 28 potently neutralized authentic SARS-CoV-2 (IC100 as low as 0.04 μg/ml), showing a broad spectrum of V genes and low levels of somatic mutations.
https://www.cell.com/cell/fulltext/S0092-8674(20)30821-7

A comment in Lancet reviews cases of patients who tested positive for COVID-19 after recovery. The positive retest in symptomatic patients suggests the potential for

recurrence of active disease https://www.thelancet.com/action/showPdf?pii=S1473-3099%2820%2930433-3

A single cell RNA sequencing analysis shows that, compared to moderate cases, critical COVID-19 cases exhibited stronger interactions between epithelial and immune cells, as indicated by ligand–receptor expression profiles, and activated immune cells, including inflammatory macrophages expressing CCL2, CCL3, CCL20, CXCL1, CXCL3, CXCL10, IL8, IL1B and TNF. The data suggest that pharmacologic inhibition of the CCR1 and/or CCR5 pathways might suppress immune hyperactivation in critical COVID-19. https://www.nature.com/articles/s41587-020-0602-4

An autopsy-based study of 11 people who died from COVID-19 shows a mismatch between viral hotspots in the body and sites of inflammation and organ damage. Findings support virus-independent immunopathology being one of the primary mechanisms underlying fatal Covid-19 and prioritising pathogen tolerance as a therapeutic strategy in Covid-19
https://www.medrxiv.org/content/10.1101/2020.07.02.20145003v1

Treatment
WHO announced that it was discontinuing its trials of hydroxychloroquine and combination HIV drug lopinavir/ritonavir in hospitalised patients with COVID-19 after the medications failed to reduce mortality.

A brief review of over 1000 COVID-19 clinical trials launched to date examined 309 unique interventions, with the 10 most prevalent interventions being tested in 65% of studies. The analysis shows that most are small, lack emphasis on prevention and lack placebo control (76%) https://www.cell.com/action/showPdf?pii=S2666-6340%2820%2930012-X

Remdesivir: The United States has bought nearly all the available global supplies for the next 3 months of anti-viral drug remdesivir, one of 2 drugs proven to be effective against COVID-19.

Regulatory T cells: Johns Hopkins researchers report the use of allogeneic "off-the-shelf" cord-blood derived regulatory T cells (Treg) to treat two critically COVID-19 cases that became critically ill despite having received tocilizumab. Both recovered and neither patient had an infusion reaction, inflammatory rebound, or other adverse reaction. https://www.acpjournals.org/doi/10.7326/L20-0681

Vaccines
Pfizer posted its phase 1 results with the mRNA candidate vaccine it is developing with BioNTech. The vaccine spurred immune responses in healthy patients, but also caused fever and other moderate side effects, especially at higher doses. Healthy adults, 18-55 years of age, were randomized to receive 2 doses, separated by 21 days, of 10 µg, 30 µg, or 100 µg of BNT162b1, a lipid nanoparticle-formulated, nucleoside-modified, mRNA vaccine that encodes trimerized SARS-CoV-2 spike glycoprotein RBD. Neutralizing titers reached 1.8- to 2.8-fold that of a panel of COVID-19 convalescent human sera.
https://www.medrxiv.org/content/10.1101/2020.06.30.20142570v1.full.pdf

Almost 1 in 6 Britons say they would refuse a COVID-19 vaccine, a YouGov poll found; people who rely on traditional media rather than social media for information were more likely to say they'd get a vaccine
https://www.theguardian.com/media/2020/jul/07/almost-one-in-six-britons-say-would-refuse-covid-19-vaccine

Other hosts
Pigs and chickens could not be infected intranasally by SARS-CoV-2, whereas fruit bats showed characteristics of a reservoir host, according to an experimental study. Virus replication in ferrets resembled a subclinical human infection with efficient spread.
https://www.thelancet.com/journals/lanmic/article/PIIS2666-5247(20)30089-6/fulltext

Indirect effects
Deaths from overdoses appear to be rising during the pandemic, likely as a result of social distancing and isolation, according to an article in the Washington Post
https://www.washingtonpost.com

A new piece in *Nature* focuses on the socioeconomic impact of pandemics on women - lessons from past outbreaks and actions to minimize the gendered impact of COVID-19
https://www.nature.com/articles/d41586-020-02006-z

ISGlobal

COVID-19 EPIDEMIC

Epidemiological situation (15/07/2020, ECDC data):

Globally:
13 299 163 confirmed cases and 578 319 deaths

- WHO launches an independent review of the international response to the Covid-19 pandemic, led by former Liberian President Ellen Johnson Sirleaf (Nobel Peace Prize winner) and Helen Clark, former prime minister of New Zealand. https://www.statnews.com/2020/07/09/who-review-covid19-pandemic-response/
- GloPID-R is putting together a series of 3-hour virtual COVID-19 Research Synergy Meetings (July 16 to 21) to bring together funded researchers and other key stakeholders on four themes: Vaccines, Therapeutics, Stopping Transmission, Social Sciences. Registration for each session is open online until July 15 in the corresponding links. (*Thanks Payam Dadvand for the info!*)
https://www.glopid-r.org/covid-19-research-synergies-meetings/
- ECDC has published a report on protecting the medically and socially vulnerable populations during the COVID-19 pandemic
https://www.ecdc.europa.eu/en/publications-data/guidance-medically-and-socially-vulnerable-populations-covid-19
- Governments must be held accountable for the deaths and health of essential workers who they have failed to protect from COVID-19, said Amnesty International in a new report documenting the experiences of health workers around the world.
https://www.amnesty.org/en/documents/pol40/2572/2020/en/

A review in *JAMA* summarises current evidence regarding the pathophysiology, transmission, diagnosis ant treatment of COVID-19
https://jamanetwork.com/journals/jama/fullarticle/2768391

Confinement and Deconfinement Strategies

An IMF article describes how Vietnam's success in containing COVID-19 can offer lessons for other developing countries. Their strategy was based on the rapid introduction of strict containment measures together with extensive contact tracing, isolation and quarantine.
https://www.imf.org/en/News/Articles/2020/06/29/na062920-vietnams-success-in-containing-covid19-offers-roadmap-for-other-developing-countries

Virus

Origin: A WHO-led mission arrives in China to set the bases for an investigation on the pandemic's origin. A comment in *Science* pinpoints the main questions to ask, including more detail on samples collected at Wuhan market, data on earliest cases identified, possibility of testing sewage samples from 2019, etc.

https://www.sciencemag.org/news/2020/07/who-led-mission-may-investigate-pandemic-s-origin-here-are-key-questions-ask

A UK team investigates the relationship of spike (S) glycoprotein from SARS-CoV-2 with the S protein of a closely related bat virus, RaTG13. They detect key differences, including a more stable precleavage form of SARS-CoV-2 S and about 1,000-fold tighter binding to the ACE2 human receptor.
https://www.nature.com/articles/s41594-020-0468-7.pdf

Transmission
The WHO has updated its guidelines on SARS-CoV-2 transmission. It states that most transmission occurs via droplets, from symptomatic people or right before they develop symptoms. The contribution of truly asymptomatic people is not known but is thought to be low. It acknowledges that short-range aerosol transmission, particularly in specific indoor locations, such as crowded and inadequately ventilated spaces over a prolonged period of time with infected persons cannot be ruled out.
https://www.who.int/news-room/commentaries/detail/transmission-of-sars-cov-2-implications-for-infection-prevention-precautions

Several studies indicate that SARS-CoV-2 transmission by aerosols is possible. What is less clear is the extent to which this type of transmission actually leads to infections. A viewpoint in JAMA concludes that currently available evidence suggests that long-range aerosol-based transmission is not the dominant mode of SARS-CoV-2 transmission. (*Thanks Kurt Straif for the tip!*)
https://jamanetwork.com/journals/jama/article-abstract/2768396

In a JAMA editorial, the CDC says the science shows masks reduce the spread of COVID-19 and calls on Americans to wear them.
https://www.cdc.gov/media/releases/2020/p0714-americans-to-wear-masks.html

A modelling exercise based on individual-level data indicates that the majority of infections may be attributable to silent transmission from a combination of the presymptomatic stage and asymptomatic infections. The model also indicates that over 1/3 of silent infections must be isolated to suppress a future outbreak below 1% of the population https://www.pnas.org/content/early/2020/07/02/2008373117

A case report describes transplacental transmission of SARS-CoV-2 in a neonate born to a mother infected in the last trimester and presenting with neurological compromise. Placental infection was demonstrated by immunohistochemistry and high viral load
https://www.nature.com/articles/s41467-020-17436-6

Testing / Tracing
The first SARSCoV2 seroprevalence study from Brazil, from over 4,000 individuals, indicates a very low rate (<1%) early in their epidemic (April/May)
https://www.nature.com/articles/s41591-020-0992-3

Genome Canada is leading a project that intends to create genetic maps from SARS-CoV-2 isolated from 150 000 patients, in order to get a better picture of how the virus spread. The results will be loaded into a global site comparing all known infections of COVID-19, but also be analyzed for national and regional reports.
https://www.cbc.ca/news/canada/hamilton/genetic-detectives-covid19-1.5647391

Symptoms / Risk factors

Ethnicity and death:
The OpenSAFELY study has analysed factors associated with COVID-19 death in 17 million patients in UK. COVID-19-related death was associated with: being male (hazard ratio (HR) 1.59); older age and deprivation (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 https://www.nature.com/articles/s41586-020-2521-4

Along the same lines, the CDC published the analysis of supplementary data for 10,647 COVID-19 deaths. They found that a majority were aged ≥65 years and most had underlying medical conditions. In those that were aged under 65, 34.9% were Hispanic and 29.5% nonwhite, compared with only 13.2% of white, non-Hispanic decedents.
http://dx.doi.org/10.15585/mmwr.mm6928e1

Neurological symptoms:
A case report in *the Lancet* describes inflammation of the brain's smell center in 2 patients with #COVID19 at autopsy.
https://thelancet.com/action/showPdf?pii=S0140-6736%2820%2931525-7

The emerging spectrum of COVID-19 neurology SARS-CoV-2 infection is associated with a wide spectrum of neurological syndromes affecting the whole neuraxis, including the cerebral vasculature and, in some cases, responding to immunotherapies. high incidence of acute disseminated encephalomyelitis, not related to the severity of the respiratory COVID-19 disease
https://academic.oup.com/brain/article/doi/10.1093/brain/awaa240/5868408

Persistent symptoms: An Italian team assessed persistent symptoms in a cohort o f143 patients recovered from COVID-19, during a 2 month follow-up. 87% of discharged patients had persistence of one or more symptoms, including fatigue, breathing difficulty, joint and chest pain.
https://jamanetwork.com/journals/jama/fullarticle/2768351

Antibodies / Immunity
Using sequential serum samples collected up to 94 days post-onset of symptoms from 65 RT-qPCR confirmed SARS-CoV-2-infected individuals, a UK team shows seroconversion in >95% of cases and neutralizing antibody (nAb) responses when sampled beyond 8 days after symptom onset. The magnitude of the nAb response (but not the kinetics) is dependent on disease severity. Declining nAb titres were observed during the follow-up period, particularly in individuals with lower levels. These findings suggest that this transient nAb response is a feature shared by both low severity SARS-CoV-2 infection and common cold seasonal coronaviruses. *However, they did not measure cellular immunity (virus-specific T cells, memory B cells) which could still confer immunity even if antibodies have waned.*
https://www.medrxiv.org/content/10.1101/2020.07.09.20148429v1

Another group characterized humoral and circulating follicular helper T cell (cTFH) immunity against *spike* in recovered patients with COVID-19. S-specific antibodies, memory B cells and cTFH are consistently elicited after SARS-CoV-2 infection. Neutralizing activity was variable and inversely correlated with the proportion of CCR6+CXCR3- spike-specific circulating T follicular helper cells, providing a biomarker for measuring efficacy of S-based vaccines.
https://www.nature.com/articles/s41591-020-0995-0

Five independent studies have observed T cell reactivity against SARS-CoV-2 (against non-spike but also spike antigens) in unexposed people. However, the source and

clinical relevance of this reactivity remains unknown. It is hypothesized, but not yet proven, that it might be due to immunity to common cold coronaviruses. A *Nature Rev Immunol* Comment discusses the potential implications of these findings for disease severity, herd immunity and vaccine development.
https://www.nature.com/articles/s41577-020-0389-z

A unique immune phenotype was observed in 50 severe and critical COVID-19 patients, consisting of a highly impaired IFN type I response, persistent blood viral load, and an exacerbated inflammatory response (partly driven by NFkb and elevated TNFa, IL6).
https://science.sciencemag.org/content/sci/early/2020/07/10/science.abc6027.full.pdf

A series of autopsies found that inflammation and organ dysfunction in fatal Covid-19 did not map to the widespread tissue and cellular distribution of SARS-CoV-2 RNA. The authors conclude that death in Covid-19 is primarily a consequence of immune-mediated, rather than pathogen- mediated, organ inflammation and injury. The findings support prioritising pathogen tolerance as a therapeutic strategy.
https://medrxiv.org/content/10.1101/2020.07.02.20145003v1

The enhancement of disease by antibody-dependent mechanisms (ADE) is a major concern for SARSCoV2 vaccines and neutralizing antibodies. A *Nature* perspective gives details of what needs to be done to address this issue
https://www.nature.com/articles/s41586-020-2538-8

Treatment

Tocilizumab: A retrospective, single-center analysis with 74 severe or critical COVID-19 patients who started tocilizumab (TCZ) treatment versus 148 matched controls in a Milan hospital shows that TCZ was associated with a better overall survival (HR 0.499, p=0.035) compared to controls but with a longer hospital stay due to adverse effects.
https://www.journalofinfection.com/article/S0163-4453(20)30467-9/fulltext#%20

In another single-center cohort of mechanically ventilated COVID-19 patients, tocilizumab was associated with lower mortality (HR 0.55) despite higher superinfection occurrence.
https://academic.oup.com/cid/article/doi/10.1093/cid/ciaa954/5870306

Antibodies*: Cell* covers how new technologies have allowed to develop potent SARSCoV2 neutralizing antibodies and get them ready for the clinic for Phase 1 testing in a matter of weeks. https://www.cell.com/action/showPdf?pii=S0092-8674%2820%2930748-0

A Dutch pre-print study suggests that anti-Spike IgG from serum of severely ill COVID-19 patients may induce a hyper-inflammatory response by human macrophages, at least *in vitro*. https://www.biorxiv.org/content/10.1101/2020.07.13.190140v1

Remdesivir: Gilead Sciences announced new findings that its antiviral drug remdesivir reduced the risk of death for severely sick COVID-19 patients by 62% compared with standard care alone, saying more research is needed. The company compared patients in its late-stage trial with patients receiving care in a real-world context.
https://www.gilead.com/news-and-press/press-room/press-releases/2020/7/gilead-presents-additional-data-on-investigational-antiviral-remdesivir-for-the-treatment-of-covid-19

Vaccines
The Phase 1 results of the Moderna SARS-CoV-2 vaccine have been published in *NEJM*. 45 healthy participants received two vaccinations, 28 days apart, with escalating doses of the mRNA-1273 vaccine. Anti–SARS-CoV-2 immune responses (nAbs) were observed in all participants. No trial-limiting safety concerns were identified although systemic adverse effects were common, particularly in the high dose group. https://www.nejm.org/doi/full/10.1056/NEJMoa2022483
Moderna will start a Phase 3 study in 30,000 patients on July 27. Pfizer and BioNTech also plan to start a large study with their mRNA vaccine candidate by the end of the month. https://www.statnews.com/2020/07/14/moderna-covid19-vaccine-first-data-show-spurs-immune-response/

After mitigating multiple confounding factors, several significant associations between BCG vaccination and reduced COVID-19 deaths were observed, according to an epidemiological study published in PNAS. *Underlying mechanisms and clinical evaluation of its effectiveness need to be explored.*
https://www.pnas.org/content/early/2020/07/07/2008410117

The Vaccine Confidence ProjectTM (VCP) announced the launch of a series of public webinars on vaccines and COVID-19. The first webinar (Vaccine confidence in the time of COVID-19) will take place on 22 July. (*Thanks for the info, Anna Lucas!*)
https://www.vaccineconfidence.org/covid-19

The NIH released its COVID-19 Strategic Plan, which describes how NIH is accelerating the development of therapeutic interventions, vaccines, and diagnostics in response to the SARS-CoV-2 global pandemic. It is establishing new programmes that leverage existing capacities to advance research in five key areas: fundamental knowledge, detection and diagnosis, treatment, prevention, and health disparities. *(Thanks for the info, Anna Massandeda!)* https://www.nih.gov/sites/default/files/research-training/initiatives/covid-19-strategic-plan/coronavirus-strategic-plan-20200713.pdf

Indirect effects
According to a modelling study, deaths due to HIV, tuberculosis, and malaria over 5 years could increase in high-burden countries by up to 10%, 20%, and 36%, respectively, compared with if there was no COVID-19 pandemic.
https://www.thelancet.com/journals/langlo/article/PIIS2214-109X(20)30288-6/fulltext

ISGlobal

COVID-19 EPIDEMIC

Epidemiological situation (22/07/2020, worldometers data):

Globally:
15,122,441 confirmed cases and 620,296 deaths

- COVID-19 cases and deaths continue to increase globally, with Latin America accounting for almost half of the deaths.
- Cases in Africa are slowly but surely on the rise. South Africa, the most affected country, is currently experiencing a surge in cases (almost 400,000 confirmed cases and over 5,000 deaths).
- WHO Director-General Dr. Tedros joined Spanish leaders in an homage to those who lost their lives in the country due to COVID-19, saluting the heroic efforts of health workers and praising the government's response to reverse the virus's transmission. https://www.who.int/news-room/detail/16-07-2020-who-director-general-pays-tribute-to-spain-s-sacrifices-and-leadership-to-confront-covid-19

Confinement and Deconfinement Strategies

Spain: A total of 18,564 people have been infected since the state of alarm ended (June 21). In the last three weeks, the infections have trebled (almost 5,000 cases since Friday). 201 active outbreaks have been identified, with 2,280 associated cases.
65% of cases are from Catalonia and Aragon.
Contact tracing in Catalonia, including Barcelona, has been far from ideal. Barcelona may be heading towards another lockdown.
https://apnews.com/d175ea6f7cb41468cd19d5255908d3a7

Europe: Synchronizing intermittent lockdowns across Europe could mean half as many lockdown periods to end community transmission continent-wide. A modelling study used mobility and case data to quantify to quantify how coordinated exit strategies could delay continental resurgence and limit community transmission of COVID-19 in Europe. They find that a resurgent continental epidemic could occur up to 5 weeks earlier when well-connected countries with stringent restrictions end their interventions prematurely.
https://science.sciencemag.org/content/early/2020/07/16/science.abc5096

A study evaluated the association between physical distancing interventions and incidence of Covid-19 globally. 149 countries or regions implemented one of the five physical distancing interventions (closures of schools, workplaces, and public transport, restrictions on mass gatherings and public events, and restrictions on movement (lockdowns)). Physical distancing interventions were associated with reductions in the incidence of covid-19 globally. No evidence was found of an additional effect of public transport closure when the other four physical distancing measures were in place. https://www.bmj.com/content/370/bmj.m2743

Virus

The genomic analysis of 34 412 SARS-CoV2 sequences deposited in the GISAID database found 2 dominant subclades of the virus co-circulating in Europe and the United States derived from the Wuhan HU-1 strain isolated in China in December 2019. The authors of the pre-print study raise the (disturbing) possibility that people living in places with high prevalence of co-circulating strains may get serially infected with each variant.
https://www.medrxiv.org/content/10.1101/2020.07.13.20152959v1.full.pdf

A team investigated 80 variants and 26 glycosylation sites generated by site-directed mutagenesis. Results show that the dominant D614G alone or combined with other mutations is more infectious *in vitro*. Ablation of both N331 and N343 glycosylation at RBD drastically reduced infectivity. Ten mutations such as N234Q, L452R, A475V, V483A were markedly resistant to some mAbs. https://cell.com/cell/fulltext/S0092-8674(20)30877-1

A report in *Science* describes the cryo-EM structures of the Spike protein of SARS-CoV-2, notably the RBD pre-fusion and post-fusion conformations. Notably, the post-fusion structure is surrounded by N-glycans, which may protect it against the host immune response.
https://science.sciencemag.org/content/sci/early/2020/07/20/science.abd4251.full.pdf
This short video clearly illustrates how the SARS-CoV-2 Spike protein drives fusion between viral and cell membranes. https://www.youtube.com/watch?v=e2Qi-hAXdJo&feature=youtu.be

A major virulence factor of SARSCoVs is the nonstructural protein 1 (Nsp1) which suppresses host gene expression by ribosome association. Cryo-electron microscopy shows that Nsp1 binds to the 40S ribosomal subunit and obstructs entry to the mRNA tunnel. Thereby, Nsp1 effectively blocks RIG-I-dependent innate immune responses that would otherwise facilitate clearance of the infection.
https://science.sciencemag.org/content/early/2020/07/16/science.abc8665/tab-pdf

Transmission

The analysis of reports for 59,073 contacts of 5,706 COVID-19 index patients in South Korea (January 20–March 27, 2020) reveals that, of 10,592 household contacts, 11.8% had COVID-19. Of 48,481 non-household contacts, 1.9% had COVID-19. The analysis also suggests that older children (10-19) appear to spread disease at rates comparable to adults, though younger children may be less likely to transmit. *However, the researchers traced the contacts only of children who felt ill, so it's still unclear how efficiently asymptomatic children spread the virus.*
https://wwwnc.cdc.gov/eid/article/26/10/20-1315_article

A research team collected aerosol samples to assess the presence of infectious virus in particles sizes of >4.1 µm, 1-4 µm, and <1 µm in the environment of COVID-19 patients. The results demonstrate that SARS-CoV-2 RNA exists in respired aerosols (< 5 µm) produced during respiration, vocalization, and coughing; and that some fraction of the RNA-containing aerosols contain infectious virions.
https://www.medrxiv.org/content/10.1101/2020.07.13.20041632v1.full.pdf

A seroprevalence study across 10 diverse geographic sites in the US shows that during March to early May 2020, most persons had not been infected with SARS-CoV-2 virus. The estimated number of infections, however, was between 6 and 24 times greater than the number of reported cases, depending on the location.
https://jamanetwork.com/journals/jamainternalmedicine/fullarticle/2768834

Testing / Tracing
The FDA has authorized the first use of "pool testing" combining swab samples for Covid19 testing. This type of testing would allow to go from a half a million tests a day to potentially 5 million individuals tested per day.
https://www.statnews.com/2020/06/26/pool-testing-covid-19/

A news feature in Nature discusses SARS-CoV-2 rapid diagnostic tests with transformative potential. https://www.nature.com/articles/d41586-020-02140-8

In a population practicing physical distancing, a testing delay of more than 1 day requires the tracing delay to be at most 1 day or tracing coverage to be at least 80% to keep reproduction numbers below 1. With a testing delay of 3 days or longer, even the most efficient strategy cannot reach reproduction values below 1.
https://www.thelancet.com/journals/lanpub/article/PIIS2468-2667(20)30157-2/fulltext

A *Lancet* article describes how real-time genomic surveillance of SARS-CoV-2 in a UK hospital helped detect cryptic transmission events and identify opportunities to target infection-control interventions to further reduce health-care associated infections.
https://thelancet.com/action/showPdf?pii=S1473-3099%2820%2930562-4

Symptoms / Risk factors
Fatality rate: A report from Geneva estimates the IFR for SARS-CoV-2 at 0.64%. However, these rates will vary depending on each country's health system capacity/overload. https://www.thelancet.com/action/showPdf?pii=S1473-3099%2820%2930584-3

Compared with the average number of annual deaths in the prior 5 years, the increase in mortality in Italy between April and May 2020 was 126.4% for men and 85.4% for women. This indicates that the official count of COVID-19 deaths in Italy has substantially understated the actual increase in mortality related to the pandemic, as is the case in other countries. (*Thanks, Kurt Straif for the tip!*)
https://jamanetwork.com/journals/jamainternalmedicine/fullarticle/2768649
The same is observed for many other countries/cities, as illustrated in the Financial Times coronavirus graphs https://www.ft.com/content/a26fbf7e-48f8-11ea-aeb3-955839e06441

Histopathological changes and SARS-CoV-2 tissue tropism was documented on COVID-19 deceased patients. Findings reveal diffuse alveolar damage in the acute or organising phases, with five patients showing focal pulmonary microthrombi. Coronavirus-like particles were detected in the respiratory system, kidney, and gastrointestinal tract. https://www.thelancet.com/journals/lancet/article/PIIS0140-6736(20)31305-2/fulltext

Blood type: Data from two new studies with thousands of patients do not provide strong evidence of associations between blood group and intubation or death among COVID-19 patients.
https://www.medrxiv.org/content/10.1101/2020.04.08.20058073v1
https://link.springer.com/article/10.1007/s00277-020-04169-1
Neurological findings: A prospective cohort study in 100 healthcare workers in Germany, 28 of whom had mild to moderate COVID19 disease, reveals increased levels of serum neurofilament light chain, a marker of neuronal injury. The findings raise awareness on potential neurological damage caused by the virus.
https://link.springer.com/article/10.1007/s00415-020-10050-y

Antibodies / Immunity
The *NEJM* publishes the study (already posted as preprint) on "rapid decay of SARS-CoV-2 antibodies in persons with mild COVID-19", which measured anti-RBD IgG antibodies in 34 patients with mild symptoms at two timepoints approx. 90 days apart. The authors say the results call for caution regarding antibody-based "immunity passports," herd immunity, and perhaps vaccine durability.
https://www.nejm.org/doi/full/10.1056/NEJMc2025179?query=featured_coronavirus
However, as Florian Krammer points out in a recent twitter thread, the threshold needed for protection is not known, and a slow decline of antibodies over several months is expected. Furthermore, these studies do not consider T cell immunity.

In fact, the Krammer lab reports that the vast majority of infected individuals with mild to-moderate COVID-19 experience robust IgG antibody responses against the viral spike protein, based on a dataset of 19,860 individuals screened at Mount Sinai in New York City. They also show that titers are stable for at least three months and that anti-spike binding titers significantly correlate with neutralization of authentic SARS-CoV-2.
https://www.medrxiv.org/content/10.1101/2020.07.14.20151126v1.full.pdf

A team in Singapore demonstrated the presence of CD4 and CD8 T cells recognizing multiple regions of the nucleocaspid (NP) protein in 36 COVID-19 convalescents. They showed that SARS-recovered patients (n=23) still possess long-lasting memory T cells reactive to SARS-NP 17 years after the 2003 outbreak. They also detected SARS-CoV-2 specific T cells in a high percentage of individuals with no history of SARS, COVID-19 or contact with SARS/COVID-19 patients (n=37). These cells recognised protein fragments with low homology to "common cold" human coronaviruses but conserved amongst animal betacoranaviruses. These results suggest that infection with betacoronaviruses induces multispecific and long-lasting T cell immunity to NP.
https://www.nature.com/articles/s41586-020-2550-z

Science has published the preprint study on deep immune profiling of COVID-19 patients. A US team analyzed 125 COVID-19 patients, and compared recovered to healthy individuals using high dimensional cytometry. Integrated analysis of ~200 immune and ~50 clinical features revealed activation of T cell and B cell subsets in a proportion of patients. The analyses identified three "immunotypes" associated with poor clinical trajectories versus improving health.
https://science.sciencemag.org/content/early/2020/07/15/science.abc8511

Another study compared the single-cell transcriptional landscape of longitudinally collected peripheral blood mononuclear cells (PBMCs) from COVID-19 versus influenza A virus (IAV)-infected patients. The findings reveal distinct immune response pathways in COVID-19 and IAV patients, including increased pro-inflammatory cytokines (e.g. IL6) in the former. https://www.cell.com/action/showPdf?pii=S1074-7613%2820%2930316-2

Treatment
Interferons: The British drug company Synairgen announced promising but preliminary results for an inhaled form of interferon beta in reducing the risk of severe COVID-19. https://www.synairgen.com/wp-content/uploads/2020/07/200720-Synairgen-announces-positive-results-from-trial-of-SNG001-in-hospitalised-COVID-19-patients.pdf
In fact, a series of recent papers suggests SARS-CoV-2 disables interferons, one of the body's frontline defences against a virus and at least five studies since April have found that interferon treatment or pretreatment has a protective effect in cells and in mice infected with SARS-CoV-2. A news story in *Science* covers some of the trials, including

one in Stanford, that are testing type I or III interferons as prophylaxis or early treatment. https://www.sciencemag.org/news/2020/07/can-boosting-interferons-bodys-frontline-virus-fighters-beat-covid-19

Antibodies: A US team describes potent neutralizing mAbs recognizing non-overlapping sites, COV2-2196 and COV2-2130, that bound simultaneously to S and synergistically neutralized authentic SARS-CoV-2 virus. Passive transfer of COV2-2196 or COV2-2130 alone or combined protected mice from weight loss and lung inflammation, and rhesus macaques from SARS-CoV-2 infection.
https://www.nature.com/articles/s41586-020-2548-6

Vaccines

Encouraging results for phase 1/ 2 adenovirus-vectored vaccines: The results of two early phase COVID-19 vaccine trials are reported, one from the Jenner Institute at Oxford University with support from AstraZeneca, and the second from CanSino Biologics in Wuhan, China.
The Oxford Phase 1 ChAdOx1 nCoV-19 vaccine trial with 1077 participants showed an acceptable safety profile, with neutralizing antibody and spike protein-specific T cell responses (measured by IFN-g ELISPOT). Neutralising antibodies were generated in more than 90% of participants across different assays. A small non-randomly selected group received a second-dose after 28 days, which further boosted neutralising responses (sustained up to 56 days of observation). These results support largescale evaluation of this candidate vaccine in an ongoing phase 3 programme.
https://www.thelancet.com/journals/lancet/article/PIIS0140-6736(20)31604-4/fulltext
Another adenovirus (Ad5) vectored vaccine Phase 2 trial (CanSIno) in China also found neutralizing antibodies and T cell responses (IFN-g ELISPOT) in most people after a single dose, with a good safety profile. Older people (aged >55 years) responded less well, which means they may need a second dose.
https://www.thelancet.com/pdfs/journals/lancet/PIIS0140-6736(20)31605-6.pdf
See comment here https://www.thelancet.com/journals/lancet/article/PIIS0140-6736(20)31611-1/fulltext

The Oxford/Astra Zeneca vaccine is already being tested in Brazil, together with China's Sinovac inactivated virus vaccine. The country has now approved human trials for a third COVID-19 vaccine (mRNA vaccine co-developed by Pfizer and BioNTech).
https://www.devdiscourse.com/article/health/1138588-brazil-approves-human-trials-for-third-covid-19-vaccine

Initiative to speed-up efficacy results: The advocacy group, 1Day Sooner, has sent an open letter signed by 15 Nobel laureates and 100 other prominent researchers, ethicists, and philosophers, urging the U.S. government "to undertake immediate preparations for human challenge trials" in young, healthy people, who are less likely to suffer severe disease from COVID-19. These trials, if approved, would not be able to start before fall, once enough virus for the infections is produced and the correct dose to cause mild respiratory illness in 70% of people (as proposed by WHO) is found.
https://www.sciencemag.org/news/2020/07/controversial-human-challenge-trials-covid-19-vaccines-gain-support

Executives from five drug companies leading the vaccine race (AstraZeneca, Johnson & Johnson, Merck, Moderna, and Pfizer) are due at a US congressional hearing to talk about their progress. An article in statnews identifies six questions the panel should pose (e.g. priority populations, price, liability, large-scale production, deployment).
https://www.statnews.com/2020/07/20/covid19-vaccines-merck-moderna-congress/

Seventy-five countries submitted expressions of interest to COVAX Facility, joining up to 90 other countries which could be supported by the COVAX Advance Market Commitment (AMC). Among the group are representatives from every continent and more than half of the world's G20 economies. Together, this group of up to 165 countries represents more than 60% of the world's population. https://www.who.int/news-room/detail/15-07-2020-more-than-150-countries-engaged-in-covid-19-vaccine-global-access-facility

Nature covers a potential nanomaterial path forward for COVID-19 vaccine development. https://www.nature.com/articles/s41565-020-0737-y

Animals

Mink farms, Spain: Health authorities have ordered the culling of all 93 000 mink at a farm in eastern Spain to prevent human contagion after discovering that most of the animals had been infected with the coronavirus. The same has occurred in mink farms in The Netherlands and Denmark. https://www.reuters.com/article/us-health-coronavirus-spain-minks/spain-to-cull-93000-mink-at-a-farm-hit-by-coronavirus-idUSKCN24H28U

Indirect effects

Nature analyses ways to decarbonize conference travel after COVID-19. Biennials, regional hubs and virtual attendance can slash emissions, according to new calculations. https://www.nature.com/articles/d41586-020-02057-2

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COVID-19 EPIDEMIC

Epidemiological situation (29/07/2020, worldometers data):

Globally:
16 708 920 confirmed cases and 660 123 deaths

- The Americas region reported 53.7% of the global newly reported cases and 52.2% of newly reported deaths in the last few days, maintaining its dominance as the most severely affected region.
- The *New York Times* has published a heartbreaking photo documentary on the impact of the pandemic on the Amazonian people https://www.nytimes.com/interactive/2020/07/25/world/americas/coronavirus-brazil-amazon.html
- The cost of preventing further pandemics over the next decade by protecting wildlife and forests would equate to just 2% of the estimated financial damage caused by Covid-19. Actions include better regulation of the wildlife trade, disease surveillance and control in wild and domestic animals, ending the wild meat trade in China, and cutting deforestation by 40% in key places. https://science.sciencemag.org/content/369/6502/379

Confinement and Deconfinement Strategies

Viet Nam has closed Da Nang to tourists after 15 new locally transmitted coronavirus cases were recorded there -- the 1st in the country since April. Vietnam has recorded just over 400 COVID-19 cases and no deaths, and is considered a COVID-19 success story. https://ourworldindata.org/covid-exemplar-vietnam

In contrast, despite its initial marked success, Israel overtook the United States for most new COVID19 cases/million people. https://time.com/5868180/israel-coronavirus-weekend-shutdown/

UK, The Netherlands, Germany, Norway, Ireland, and France have advised their citizens to avoid travelling to Catalonia due to the high risk of transmission https://www.lavanguardia.com/economia/20200729/482574826473/alemania-paises-bajos-turistas-restricciones-catalunya.html

Virus

A study analyses the evolutionary history of SARS-CoV-2 using available genomic data on sarbecoviruses. The findings provide support that the SARS-CoV-2 lineage was the consequence of a direct or nearly-direct zoonotic jump from bats, and that there is no evidence that pangolins are facilitating adaptation to humans. Both SARS-CoV and SARS-CoV-2 are estimated to have diverged 40–70 years ago from currently known bat virus lineages, indicating that the lineage giving rise to SARS-CoV-2 has been circulating unnoticed in bats for decades. https://www.nature.com/articles/s41564-020-0771-4

In SARS coronaviruses, the non-structural protein 16 (nsp16), in conjunction with nsp10, methylates the 5′-end of virally encoded mRNAs to mimic cellular mRNAs, thus

protecting the virus from host innate immune restriction. A study describes the high-resolution structure of a nsp16/nsp10 heterodimer 'captured in the act' of methylating the ribose sugar of the first nucleotide of SARS-CoV-2 mRNA.
https://www.nature.com/articles/s41467-020-17496-8

A paper in *Cell* describes the 3D structure of the SARS-CoV-2 replication-transcription complex (RTC) with nsp13 helicases and identifies potential antiviral targets.
https://www.cell.com/cell/fulltext/S0092-8674(20)30941-7

Transmission
Neonates: A study with 116 deliveries by COVID-19+ mothers shows that perinatal transmission of the virus is unlikely to occur if correct hygiene precautions are undertaken, and that allowing neonates to room in with their mothers and direct breastfeeding are safe when paired with effective parental education of infant protective strategies. https://www.thelancet.com/journals/lanchi/article/PIIS2352-4642(20)30235-2/fulltext

Schools: Ten days after Israel reopened schools, the first major COVID-19 school outbreak was reported in a high school (students aged 13 to18). The outbreak started with two unlinked cases, and led to 260 infected persons overall (students, staff members, relatives and friends). The circumstances promoting infection spread involved return of teenage students to their regular classes after a 2-month closure and an extreme heatwave that led to exemption from facemasks and continuous air-conditioning. Most student cases presented with mild symptoms or were asymptomatic. https://www.eurosurveillance.org/content/10.2807/1560-7917.ES.2020.25.29.2001352#html_fulltext

Slaughterhouse: According to German researchers, coronavirus particles travelled 8 meters in a slaughterhouse's cold, stale air, shedding light on how meat plants have become global hotspots. https://www.helmholtz-hzi.de/de/aktuelles/news/news-detail/article/complete/sars-cov-2-ausbruch-in-deutschem-fleischzerlegebetrieb-uebertragungen-erfolgten-ueber-weite-distanze

Ships: A whole genome sequencing analysis of SARS-CoV-2 infections in the Diamond Princess cruise ship indicates that dissemination originated from a single introduction event before the quarantine started. Clusters could be linked to transmission through mass-gathering events in the recreational areas and direct transmission among passengers who shared cabins during the quarantine.
https://www.pnas.org/content/pnas/early/2020/07/27/2006824117.full.pdf

Modelling was used to estimate the viral load emitted by individuals breathing normally or coughing, and the concentrations expected in the simulated room at different ventilation rates. The results suggest that only few people with very high viral load pose an infection risk in poorly ventilated closed environments.
https://jamanetwork.com/journals/jamanetworkopen/fullarticle/2768712

A viewpoint in *Lancet Resp Med* reviews infectious aerosols and implications for infection control. https://www.thelancet.com/journals/lanres/article/PIIS2213-2600(20)30323-4/fulltext

In a large cohort of individuals (16,966) screened for SARS-CoV-2 by qRT-PCR, similar distributions of viral load were found in patients with or without symptoms at the time of testing, across all sub-categories examined (age, race, ethnicity, sex, resident/staff). 70.8% of residents and 92.4% of staff lacked symptoms at the time of testing, *although*

the study did not assess how many of them developed symptoms later on.
https://www.medrxiv.org/content/10.1101/2020.07.20.20157792v1

A reconstruction exercise of the full transmission dynamics of COVID-19 in Wuhan, China, estimates that 87% of the infections before March 8 were 'unascertained', potentially including asymptomatic and mild-symptomatic cases; and a R0 of 3.54 in the early outbreak. It also predicts a resurge in cases 14 days after reopening that depends on how fast the reopening was. https://www.nature.com/articles/s41586-020-2554-8_reference.pdf

A systematic review and meta-analysis on SARS-CoV-2 viral load dynamics, shedding and infectiousness concludes that: i) maximum duration of SARS-CoV-2 RNA shedding reported in URT, LRT, stool and serum was 83, 59, 35 and 60 days, respectively; ii) pooled mean duration of SARS-CoV-2 RNA shedding was positively associated with age, but not gender; iii) SARS-CoV-2 viral load in the upper respiratory tract appears to peak in the first week of illness; iv) no study to date has detected live virus beyond day nine of illness despite persistently high viral loads, indicating that detection of viral RNA cannot be used to infer infectiousness.
https://www.medrxiv.org/content/10.1101/2020.07.25.20162107v1

Nature publishes a commentary on what seroprevalence studies can and cannot tell us.
https://www.nature.com/articles/s41591-020-1018-x.pdf

Testing / Tracing
With a budget of $1.5 billion approved by US Congress, the NIH launched RADx to support the development, production scale-up, and deployment of accurate, rapid tests across the US. It aims to provide near-term solutions to increase the number of tests available by the fall of 2020, as schools and universities evaluate the safety of in-person classes and as the annual influenza season begins. In the longer term, RADx also aims to support the development and production of innovative diagnostics, with a special focus on vulnerable and underserved populations.
https://www.nejm.org/doi/full/10.1056/NEJMsr2022263

Antibody testing: A SARS-CoV-2 surrogate virus neutralization test can detect total immunodominant neutralizing antibodies targeting the RBD in the spike (S) protein. The test achieves 99.93% specificity and 95–100% sensitivity, and differentiates antibody responses to several human coronaviruses. It does not require biosafety level 3 containment, making it broadly accessible to the wider community for both research and clinical applications. https://www.nature.com/articles/s41587-020-0631-z

Contact tracing: the Johns Hopkins Bloomberg School of Public Health has launched a new free online course aimed at implementing and bolstering contact tracing programs.
https://www.coursera.org/learn/measuring-and-maximizing-impact-of-covid-19-contact-tracing/

Symptoms / Risk factors
Risk factors: In the Americas, three out of ten people – or nearly 325 million – are at increased risk of developing severe COVID-19 illness due to underlying health conditions, says the PAHO. https://www.paho.org/en/news/21-7-2020-three-out-10-people-americas-are-increased-risk-severe-covid-19-because-underlying

In an observational study of people hospitalized with COVID-19, those with high levels of C-reactive protein (an inflammation indicator) in their blood had a reduced chance of dying or being put on a ventilator when treated with steroids. But steroid treatment

more than doubled the risk of needing a ventilator or dying for people with low levels of CRP. https://www.journalofhospitalmedicine.com/jhospmed/article/225402/hospital-medicine/effect-systemic-glucocorticoids-mortality-or-mechanical

Rapid clinical whole-exome sequencing in 4 hospitals in the Netherlands allowed to describe a case series of 4 young "healthy" male patients who developed severe COVID-19 and had rare putative loss-of-function variants of X-chromosomal TLR7 associated with impaired type I and II IFN responses. The findings identify the TLR7 pathway (which recognizes ssRNA) as an inducer of type I and II IFN responses in COVID-19. https://jamanetwork.com/journals/jama/fullarticle/2768926

Of 10,021 hospitalised patients being treated in 920 different hospitals in Germany, 17% received mechanical ventilation (of whom 24% were aged 18–59 years, 22% were aged 60–69 years, 31% were aged 70–79 years, and 23% were aged ≥80 years). Twice as many men than women were in the ventilated group. The most common comorbidities were hypertension (56%), diabetes (28%), cardiac arrhythmia (27%), renal failure (23%), heart failure (20%), and chronic pulmonary disease (14%). In-hospital mortality was 22% overall. In-hospital mortality for patients with ventilation ranged from 28% in patients aged 18–59 years to 72% in patients aged 80 years or older. https://www.thelancet.com/journals/lanres/article/PIIS2213-2600(20)30316-7/fulltext

Sequelae: In the US, a multistate telephone survey of symptomatic adults who had a positive outpatient test result for SARS-CoV-2 infection, indicates that 35% had not returned to their usual state of health when interviewed 2–3 weeks after testing (20% among young adults with no chronic medical conditions).
https://www.cdc.gov/mmwr/volumes/69/wr/mm6930e1.htm?s_cid=mm6930e1_w

Heart: A study with a cohort of German patients recently recovered from COVID-19 infection, revealed cardiac involvement in 78 patients (78%) and ongoing myocardial inflammation in 60 patients (60%), independent of preexisting conditions, severity and overall course of the acute illness
https://jamanetwork.com/journals/jamacardiology/fullarticle/2768916
An analysis of autopsy cases revealed viral presence within the myocardium. Viral load >1000 copies/ µg RNA was documented in 16 of 39 patients and proinflammatory gene expression was increased in those 16 patients compared with 15 patients without any SARS-CoV-2 in the heart. However, no inflammatory cell infiltrates were observed.
https://jamanetwork.com/journals/jamacardiology/fullarticle/2768914

Lung: A *Lancet* paper describes marked lung fibrosis after severe COVID-19 in 8 patients in whom cryobiopsies were performed.
https://www.thelancet.com/journals/laninf/article/PIIS1473-3099(20)30582-X/fulltext

Mortality:
A modelling study estimates case fatality rate (CFR), symptomatic case fatality rate (sCFR) and infection fatality rate (IFR) for Hubei and six locations in Europe, including Spain. Estimates of sCFR and IFR, adjusted for bias, were similar to each other and varied less geographically than the CFR.
https://journals.plos.org/plosmedicine/article?id=10.1371/journal.pmed.1003189

An analysis of data from 169 countries shows that Covid-19 mortality rate was negatively associated with the number of Covid-19 tests per 100 people, government effectiveness score, and number of hospital beds. It was positively associated with proportion of population aged 65 or older and transport infrastructure quality score.

The authors conclude that increasing Covid-19 testing, improving government effectiveness and increasing hospital beds may attenuate Covid-19 mortality. https://www.nature.com/articles/s41598-020-68862-x

Antibodies / Immunity

Cross-reactive antibodies to S2? Using diverse assays for detection of antibodies reactive with SARS-CoV-2 spike (S), a UK team shows presence of pre-existing humoral immunity in uninfected and unexposed humans to the new coronavirus. These antibodies were mainly IgGs targeting the S2 subunit, had neutralizing activity, and were particularly prevalent in children and adolescents. They did not react with the S1 subunit or the receptor binding domain (RBD). The authors conclude that, given that antibodies to common cold coronaviruses are present in virtually all adults, the emergence of SARS-CoV-2 S-cross-reactive antibodies in a relatively small proportion (15 of 262; 5.72%) indicates additional requirements, such as random B cell receptor repertoire events or context of initial exposure or frequency of HCoV infection. This and other studies highlight the existence of potentially functionally relevant antigenic epitopes in the S2 subunit, which is conserved among cold coronaviruses (HCoVs) and SARS-CoV-2. https://www.biorxiv.org/content/10.1101/2020.05.14.095414v2.full.pdf

Epitope mapping: Epitope mapping of 19 potently neutralizing Abs isolated from 5 patients with severe disease showed they are about equally divided between those directed to the receptor-binding domain (RBD) and those to the N-terminal domain (NTD), indicating that both of these regions at the top of the viral spike are immunogenic. Several of these mAbs are promising candidates for clinical development as potential therapeutic and/or prophylactic agents against SARS-CoV-2. https://www.nature.com/articles/s41586-020-2571-7

Inflammation: A *Science* perspective discusses how aging-associated inflammation can worsen COVID-19 and what can be done to mitigate its effects. https://science.sciencemag.org/content/369/6501/256

Longitudinal immune profiling in 113 COVID-19 patients with moderate (non-ICU) and severe (ICU) disease revealed an overall increase in innate cell lineages with a concomitant reduction in T cell number. An association between early, elevated cytokines and worse disease outcomes was observed. The immune profile of patients who recovered with moderate disease was enriched in tissue reparative growth factor signature (A), while the profile for those with worsened disease trajectory had elevated levels of all four signatures identified. https://www.nature.com/articles/s41586-020-2588-y

An integrated immune analysis on 50 COVID-19 patients with different disease severity revealed a unique phenotype in severe and critical patients, consisting of a highly impaired interferon (IFN) type I response (no IFNb and low IFNa). Inflammation was driven by NFkB and characterized by TNFa and IL6 production. *(These findings were already included in a previous update, as preprint)* https://science.sciencemag.org/content/sci/early/2020/07/10/science.abc6027.full.pdf

Treatment

A humanized (mouse-derived) mAb, H014, efficiently neutralizes SARS-CoV-2 at nM level by engaging the S receptor binding domain (RBD). H014 administration reduced SARS-CoV-2 titers in the infected lungs and prevented pulmonary pathology in the hACE2 mouse model. H014 binds to RBD in open conformation and prevents attachment of SARS-CoV-2 to its host cell receptors.

https://science.sciencemag.org/content/sci/early/2020/07/22/science.abc5881.full.pdf
Using a recombinant chimeric VSV/SARS-CoV-2 reporter virus, a research team shows that functional SARS-CoV-2 S protein variants with mutations in the receptor binding domain and N-terminal domain that confer resistance to monoclonal antibodies or convalescent plasma can be readily selected *in vitro*. Notably, SARS-CoV-2 S variants that resist commonly elicited neutralizing antibodies are now present at low frequencies in circulating virus populations. Emergence of these antibody-resistant variants could limit the therapeutic usefulness of mAbs, but this can be mitigated by the use of antibody combinations that target distinct neutralizing epitopes.
https://www.biorxiv.org/content/10.1101/2020.07.21.214759v1.full.pdf

Hydroxychloroquine – 4 more nails on the coffin: A French team shows no evidence of therapeutic or prophylactic effect of HCQ or HCQ plus azithromycin in rhesus macaques infected with SARS-CoV-2. https://www.nature.com/articles/s41586-020-2558-4_reference.pdf
A multicenter, randomized, open-label, three-group, controlled trial in Brazil involving hospitalized patients with mild or moderated Covid-19 shows that the use of hydroxychloroquine, alone or with azithromycin, did not improve clinical status at 15 days as compared with standard care.
https://www.nejm.org/doi/full/10.1056/NEJMoa2019014
Results of the RECOVERY trial with hydroxychloroquine were posted. 1561 hospitalized patients randomly allocated to receive hydroxychloroquine were compared with 3155 patients concurrently allocated to usual care. HCQ was not associated with reductions in 28-day mortality but was associated with an increased length of hospital stay and increased risk of progressing to invasive mechanical ventilation or death.
https://www.medrxiv.org/content/10.1101/2020.07.15.20151852v1
Although chloroquine inhibits SARS-CoV-2 spread in kidney cell lines, it does not block SARS-CoV-2 infection of the TMPRSS2-positive lung cell line Calu-3. These results indicate that chloroquine targets a pathway for viral activation that is not operative in lung cells and is unlikely to protect against SARS-CoV-2 spread in and between patients. https://www.nature.com/articles/s41586-020-2575-3

Vaccines
A lipid-nanoparticle-encapsulated mRNA (mRNA-LNP) vaccine encoding the receptor binding domain (RBD) of SARS-CoV-2 elicited robust neutralizing antibodies against SARS-CoV-2 as well as Th1-biased cellular response in mice and non-human primates. ARCoV, developed by a Chinese team, was manufactured in liquid formulation and can be stored at room temperature for at least one week. It is currently being evaluated in phase 1 clinical trials. https://www.cell.com/cell/fulltext/S0092-8674(20)30932-6

Results for the Moderna mRNA-1273 in non-human primates show a good neutralising antibody response and a good CD4 T cell response (but low or undetectable CD8 T cell response). No viral replication was detectable in the nose of any of the eight animals in the 100-µg dose group by day 2 after challenge, and limited inflammation or detectable viral genome or antigen was noted in lungs of animals in either vaccine group (10 or 100ug). https://www.nejm.org/doi/full/10.1056/NEJMoa2024671

Moderna's mRNA vaccine candidate began its final phase 3 clinical trial yesterday—the first US vaccine to reach that milestone. A progress report will be announced once the first 50 cases of COVID-19 among the participants appear. Pfizer/BioNTech also began Phase 3 testing of its vaccine candidate on human volunteers, as well as the Oxford viral vector vaccine.
The challenge lies in landing 150,000+ volunteers who are sufficiently diverse in age, ethnicity, sex, health conditions, and other characteristics

https://www.globalhealthnow.org/2020-07/risk-covid-19-warp-speed-vaccine-trials-want-you

ISGlobal

COVID-19 EPIDEMIC

Epidemiological situation (19/08/2020, ECDC data):

Globally:
22 151 281 confirmed cases and 781 123 deaths

- Young people are leading a rise in fresh coronavirus cases across the world, with the proportion of those aged 15 to 24 who are infected rising 3-fold in about 5 months, the WHO said. The share of people aged 15-24 years rose from 4.5 to 15% between February and July.
- The United States, Brazil, India and Mexico are leading the rise in fatalities. Nearly 59 00 people are dying every 24 hours from COVID-19 on average, according to Reuters calculations based on data from the past 2 weeks. That equates to 247 people per hour, or one person every 15 seconds.
- Despite paucity of data, it appears that the virus is spreading differently and potentially with an attenuated outcome in Africa, according to a comment in *Science*. https://science.sciencemag.org/content/369/6504/624
- The worry that the pandemic would cause malaria deaths to soar does not seem to be happening, although this could be partly due to undercounting, according to our colleague Regina Rabinovich.
  https://www.sciencemag.org/news/2020/08/scientists-worried-pandemic-would-cause-malaria-deaths-soar-so-far-it-hasnt-happened

Confinement and Deconfinement Strategies
Countries in Europe and Asia are experiencing a resurgence of new cases, after restrictions were eased.

In a *NEJM* letter, Harvard epidemiologists argue that safely reopening schools full-time for all elementary school children should be a top national priority.
https://www.nejm.org/doi/full/10.1056/NEJMms2024920

The ECDC has published a technical report on COVID19 in children and the role of school settings in virus transmission. It notes that, while very few significant outbreaks of COVID-19 in schools have been documented, they do occur, and may be difficult to detect due to the relative lack of symptoms in children. Child to child transmission in schools is uncommon and not the primary cause of SARS-CoV-2 infection in children whose onset of infection coincides with the period during which they are attending school. If appropriate physical distancing and hygiene measures are applied, schools are unlikely to be more effective propagating environments than other occupational or leisure settings with similar densities of people.
https://www.ecdc.europa.eu/en/publications-data/children-and-school-settings-covid-19-transmission

Nature publishes the first of a series of editorials on key findings related to the coronavirus pandemic. This week covers how the virus was identified; the molecular details of its mechanism of infection; how it transmits between people; and the many ways in which it affects the human body.
https://www.nature.com/articles/d41586-020-02414-1

Statnews reviews what we know and we don't know about COVID-19, seven months into the epidemic. https://www.statnews.com/2020/08/17/what-we-now-know-about-covid19-and-what-questions-remain-to-be-answered/

Virus
SARS-CoV-2 variants with a 382-nucleotide deletion (Δ382) in the open reading frame 8 (ORF8) region of the genome have been detected in Singapore and other countries. A study with 278 patients (22% of which had the deletion) suggests that the variant may be associated with a milder infection.
https://www.thelancet.com/action/showPdf?pii=S0140-6736%2820%2931757-8

Transmission
Web-based surveillance of the global spread of SARS-CoV-2 during the first 11 weeks of the outbreak (Dec 31, 2019, to March 10, 2020), reveals that three-quarters of affected countries outside mainland China reported their first COVID-19 case in people who had recently travelled to an affected country—with almost two-thirds of these first cases linked to travel to Italy (27%), China (22%), or Iran (11%)-
https://www.thelancet.com/journals/laninf/article/PIIS1473-3099(20)30581-8/fulltext

A modelling study with data from the Diamond Princess cruise ship underscores the importance of implementing public health measures that target the control of inhalation of aerosols in addition to ongoing measures targeting control of large droplet and fomite transmission, not only aboard ships but in other indoor environments as well (*Thanks for tip Kurt Straif!*)
https://www.medrxiv.org/content/10.1101/2020.07.13.20153049v1

A prospective, observational cohort study in the UK and the USA with health care workers shows that front-line health care workers are at increased risk of reporting a positive COVID19 test. *(Thanks for tip Kurt Straif!*)
https://www.thelancet.com/journals/lanpub/article/PIIS2468-2667(20)30164-X/fulltext

Viral loads in asymptomatics and children:
A study with 300 individuals in a community center in South Korea shows that 36.3% were asymptomatic at the time of isolation and 21 of these (19.1%) developed symptoms during isolation. The viral load in asymptomatic individuals was similar to symptomatic patients, as was the time course.
https://jamanetwork.com/journals/jamainternalmedicine/fullarticle/2769235

An analysis suggests that children younger than 5 years with mild to moderate COVID-19 have high amounts of SARS-CoV-2 viral RNA in their nasopharynx compared with older children and adults. However, the study is limited to detection of viral nucleic acid, rather than infectious virus.
https://jamanetwork.com/journals/jamapediatrics/fullarticle/2768952

A case study of an outbreak in Ohio, where 91 people became infected in a super spreading event (church), reveals that children 6 to 16 years old are in the chain of transmission, passing SARS-CoV-2 infection on to other children as well as to adults.
https://edition.cnn.com/2020/08/05/health/ohio-church-coronavirus-spread/index.html

Testing / Tracing
The FDA has granted emergency use authorization for a saliva test which is highly sensitive. It can run approximately 90 samples in fewer than three hours in a lab.

https://www.statnews.com/2020/08/15/fda-clears-saliva-test-for-covid-19-opening-door-to-wider-testing/

Symptoms / Risk factors

Science publishes a summary of COVID19 physiopathology...
https://science.sciencemag.org/content/369/6503/510
…and of the various enduring symptoms of COVID-19, including fatigue, brain-fog, and heart damage. https://www.sciencemag.org/news/2020/07/brain-fog-heart-damage-covid-19-s-lingering-problems-alarm-scientists

A prospective cohort of COVID-19 patients followed during 12 weeks shows that most (74%) had persistent symptoms and that a more holistic approach focussing on rehabilitation and general well-being is necessary.
https://www.medrxiv.org/content/10.1101/2020.08.12.20173526v1.full.pdf

Neurological alterations: A prospective brain MRI imaging study in 60 recovered COVID19 patients finds micro-structural abnormalities in 55% of patients at 3 months, as compared with healthy controls.
https://www.thelancet.com/action/showPdf?pii=S2589-5370%2820%2930228-5
A review discusses the potential for neurotropism and mechanisms of neuropathogenesis of SARS-CoV-2, the acute and chronic neurological consequences of the infection, and potential avenues for research and therapy.
https://www.cell.com/action/showPdf?pii=S0092-8674%2820%2931070-9
The Lancet Neurology publishes a review of the diverse neurological manifestations of COVID-19 observed to date. https://www.thelancet.com/action/showPdf?pii=S1474-4422%2820%2930221-0

Risk factors:
Obesity: A UK report provides new evidence on excess weight and COVID-19
https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/903770/PHE_insight_Excess_weight_and_COVID-19.pdf
A study using the UK biobank data shows that overweight and obesity are an independent risk factor for severe COVID-19. Elevated risk was observed even at a modest weight gain. The mechanisms may involve impaired glucose and lipid metabolism. https://www.pnas.org/content/pnas/early/2020/08/10/2011086117.full.pdf
See also: https://www.acpjournals.org/doi/10.7326/M20-5677

Diabetes: Deaths in people with type 1 and type 2 diabetes rose sharply during the initial COVID-19 pandemic in England, according to a population-based cohort study. Increased COVID-19-related mortality was associated not only with cardiovascular and renal complications of diabetes but, independently, also with glycaemic control and BMI. https://www.thelancet.com/journals/landia/article/PIIS2213-8587(20)30271-0/fulltext
https://www.thelancet.com/journals/landia/article/PIIS2213-8587(20)30272-2/fulltext

Gender: A study provides further evidence that differences in immune response may explain why males are more vulnerable to covid19: female patients mounted significantly more robust T cell activation than male patients during SARS-CoV-2 infection, which was sustained in old age. Importantly, a poor T cell response

negatively correlated with patients age and was predictive of worse disease outcome in male patients, but not in female patients.
https://www.medrxiv.org/content/10.1101/2020.06.06.20123414v2

Ethnicity: Collapsing glomerulopathy in patients of African ancestry and high-risk APOL1 genotype infected with SARS-CoV-2 has been reported during the COVID-19 pandemic. This COVID-19-associated nephropathy (COVAN) may particularly impact individuals in some regions of the world, according to a comment in *Nature*.
https://www.nature.com/articles/s41581-020-0332-3.pdf

A study on COVID-19-associated multisystem inflammatory syndrome in children in the US reveals that hispanic and black patients accounted for the largest proportion (73.6%) of reported MIS-C
https://www.cdc.gov/mmwr/volumes/69/wr/mm6932e2.htm?s_cid=mm6932e2_w

Coinfections: India (Bengal) is facing an additional challenge: COVID-19 and dengue coinfections are starting to be observed in many patients, further complicating diagnosis and treatment. https://theprint.in/health/covid-dengue-co-infections-are-bengals-new-challenge-as-doctors-say-treatment-very-tricky/477020/

Viral load*: The Lancet* publishes the first report on SARS-CoV-2 viral load at diagnosis as an independent predictor of mortality in a large hospitalised cohort (n=1145). patients. https://twitter.com/erictopol/status/1291751161960083456

Antibodies / Immunity
Patients with severe COVID-19 accumulate HLA-DR-Low monocytes and immature neutrophils in blood/lungs, and calprotectin level positively correlates with neutrophil count and disease severity. The study concludes that loss of non-classical monocytes could identify high risk of severe COVID-19. https://www.cell.com/cell/fulltext/S0092-8674(20)30993-4

An analysis of the immune response over time in 113 people hospitalized with COVID19 who had moderate or severe disease revealed a maladapted immune response profile associated with severe COVID-19 and poor clinical outcome, as well as early immune signatures that correlate with divergent disease trajectories (results previously published as preprint). https://www.nature.com/articles/s41586-020-2588-y

See News and Views in *Nature* on COVID-19 and the immune response.
https://www.nature.com/articles/d41586-020-02379-1

Cross-reactive T cells:
Using human blood samples from before the emergence of SARS-CoV-2 a team from La Jolla demonstrates a range of pre-existing memory CD4 T cells that can recognise SARS-CoV-2 and common cold coronavirus epitopes with comparable affinity.
https://science.sciencemag.org/content/early/2020/08/04/science.abd3871/tab-pdf

SARS-CoV-2 S-reactive CD4+ T cells were detected in 83% of patients with COVID-19 but also in 35% of unexposed healthy donors (HD). S-reactive CD4+ T cells in HD reacted primarily to C-terminal S epitopes, which show a higher homology to spike glycoproteins of human endemic coronaviruses, compared to N-terminal epitopes.
https://www.nature.com/articles/s41586-020-2598-9
See also a comment in *Lancet* on cross-reactivity to low-pathogenic human coronaviruses https://www.thelancet.com/journals/lanmic/article/PIIS2666-5247(20)30098-7/fulltext

Evidence for long-lasting memory?
A review on T cell responses in patients with COVID-19 presents accumulating evidence on the role of T cells in disease recovery and immunological memory
https://www.nature.com/articles/s41577-020-0402-6

SARS-CoV-2 elicits robust, broad and highly functional memory T cell responses, suggesting that natural exposure or infection may prevent recurrent episodes of severe COVID-19, according to a Karolinska study now published in *Cell*. Importantly, SARS-CoV-2-specific T cells were detectable in antibody-seronegative exposed family members and convalescent individuals with a history of asymptomatic and mild COVID-19. https://www.cell.com/cell/fulltext/S0092-8674(20)31008-4

In fact, a series of new studies are starting to see encouraging signs of strong, lasting immunity, even in people that developed only mild symptoms of COVID-19, as summarised in an article in the NYT.
https://www.nytimes.com/2020/08/16/world/coronavirus-covid-19.html
These studies include:
-the above mentioned paper on T cells in mild disease
https://www.cell.com/cell/pdf/S0092-8674(20)31008-4.pdf,
-a study showing evidence for sustained mucosal and systemic antibody responses in COVID-19 patients https://www.medrxiv.org/content/10.1101/2020.08.01.20166553v1
-a study showing that recovered individuals developed SARS-CoV-2-specific IgG antibody and neutralizing plasma, as well as virus-specific memory B and T cells that not only persisted but in some cases increased over 3 months following symptom onset.
https://www.medrxiv.org/content/10.1101/2020.08.11.20171843v2
-a study showing IgG antibodies against RBD lasted longer and persisted through 75 days post-symptoms, and were highly correlated with neutralizing antibodies targeting the S protein. https://www.medrxiv.org/content/10.1101/2020.07.18.20155374v1
-a study showing that RBD- and S2-specific and neutralizing antibody titers remained elevated and stable for at least 2-3 months post symptom onset
https://www.medrxiv.org/content/10.1101/2020.08.14.20174490v1
- the REACT (REal Time Assessment of Community Transmission) study in UK, which used lateral flow tests on over 100,000 participants, detected antibodies in 96% of those who had a previous PCR-confirmed infection.
https://www.imperial.nhs.uk/about-us/news/largest-home-antibody-testing-publishes-results
- a study in macaques showing that SARS-CoV-2 infection induces germinal center responses with robust stimulation of CD4 T follicular helper cells
https://www.biorxiv.org/content/10.1101/2020.07.07.191007v1.full

Treatment
A *Science* paper describes a soluble ACE2 decoy receptor with enhanced affinity, which could be used as COVID-19 therapy.
https://science.sciencemag.org/content/early/2020/08/03/science.abc0870/tab-pdf

A multicentre, observational study shows that tocilizumab (an interleukin-6 blocking antibody) significantly reduces mortality among severe COVID19 patients as compared to propensity-matched patients.
https://www.thelancet.com/action/showPdf?pii=S2665-9913%2820%2930277-0

A short course of methylprednisolone in hospitalized patients with COVID-19 did not reduce mortality, according to a trial performed in Brazil, with ISGlobal participation *(Thanks for the tip Quique Basssat!)* https://pubmed.ncbi.nlm.nih.gov/32785710/

Vaccines
Vaccination with Oxford's ChAdOx1 nCoV-19 (prime-only and prime-boost regimen) induced a balanced Th1/Th2 humoral and cellular immune response in rhesus macaques. Reduced viral load in bronchoalveolar lavage fluid and lower respiratory tract tissue was observed in vaccinated rhesus macaques challenged with SARS-CoV-2 compared with control animals, and no pneumonia was observed in vaccinated animals. However, there was no difference in nasal shedding between both groups. Importantly, no evidence of antibody-dependent enhancement (ADE) was observed. https://www.nature.com/articles/s41586-020-2608-y

A single intranasal dose of the ChAd vaccine protects upper and lower respiratory tracts against SARS-CoV-2 in mice expressing the human ACE2 receptor. https://www.cell.com/action/showPdf?pii=S0092-8674%2820%2931068-0

One single shot of the Ad26 vaccine (Janssen) in non-human primates induced robust neutralizing antibody responses and provided complete or near-complete protection in bronchoalveolar lavage and nasal swabs following SARS-CoV-2 challenge. Vaccine-elicited neutralizing antibody titres correlated with protective efficacy, suggesting an immune correlate of protection. The optimal version of the vaccine is currently being evaluated in clinical trials. https://www.nature.com/articles/s41586-020-2607-z

Novavax announces promising phase I data for their recombinant vaccine coupled to a saponin-based adjuvant (MatrixM). Two doses of the vaccine were well tolerated and induced neutralizing antibodies in all participants and polyfunctional T cell responses. Novavax is one of the vaccines funded by operation Warp Speed. https://ir.novavax.com/news-releases/news-release-details/novavax-announces-positive-phase-1-data-its-covid-19-vaccine

Russia has declared a COVID-19 vaccine ready for use—despite a chorus of international concern that it just began Phase 3 trials last week. The vaccine, developed by the Gamaleya Institute in Moscow with assistance from Russia's Defense Ministry, uses an adenoviral vector to express the SARS-CoV-2 S protein. Russian scientists haven't published any scientific information about how the vaccine has performed in animal tests or in early-stage human studies. https://apnews.com/fcda62ad992db414d65f23b2adb78e44

Sinopharm has published results of their Phase 1/2 trial on an inactivated virus vaccine. Phase 3 trials are underway in UAE, according to the NYT vaccine tracker https://www.nytimes.com/interactive/2020/science/coronavirus-vaccine-tracker.html

Others
Infodemic: An analysis of online platforms identified 2,311 reports of rumors, stigma, and conspiracy theories related to COVID19 (February to April 2020) in 25 languages from 87 countries. Of the 2,276 reports for which text ratings were available, 1,856 claims were false (82%). http://www.ajtmh.org/content/journals/10.4269/ajtmh.20-0812
According to a report by Avaaz, Facebook is failing to keep people safe and informed during the pandemic. The top 10 misinformation sites received almost 4X more views than their reputable counterparts. 42 "super-spreader" sites garnered 28 million followers. https://secure.avaaz.org/campaign/en/facebook_threat_health/

ISGlobal

COVID-19 EPIDEMIC

Epidemiological situation (26/08/2020, ECDC data):

Globally:
23 28 539 confirmed cases and 819 756 deaths

- With the exception of the South-East Asia and Eastern Mediterranean regions, a slight decrease in the weekly case incidence was reported across WHO regions in the last seven days.
- Latin America is the current epicentre of the pandemic, with the region accounting for almost half of all deaths each day.
- Spain became the first European country to exceed 400,000 confirmed cases

Virus

A protein structural analysis in humans and other species was carried out to qualitatively assess whether amino acid changes at variable residues of ACE2 would be likely to disrupt SARS-CoV-2 spike protein binding. The results identify potential intermediate host species for SARS-CoV-2, guide the selection of animal models of COVID-19, and assist the conservation of susceptible animals both in native habitats and in human care. https://www.pnas.org/content/early/2020/08/20/2010146117

Transmission

A retrospective analysis of respiratory samples showed a 75-year-old woman, from Nottinghamshire, tested positive for SARS-CoV-2 on 21 February. The woman, who died, is believed to be the earliest community acquired case within the UK.
https://www.bbc.com/news/uk-england-nottinghamshire-53907629

A study estimates that 108,689 COVID-19 infections had occurred in the United States by March 12, despite only 1500 cases confirmed.
https://www.pnas.org/content/early/2020/08/20/2005476117

A prospective study on transmission dynamics with 100 cases shows that the attack rate was higher among the 1818 contacts whose exposure to index cases started within 5 days of symptom onset (1.0%) compared with those who were exposed later (0 cases from 852 contacts). The 299 contacts with exclusive presymptomatic exposures were also at risk (attack rate, 0.7%). Transmission was higher among household (4.6%) and nonhousehold (5.3%) family contacts than that in health care or other settings.
https://jamanetwork.com/journals/jamainternalmedicine/fullarticle/2765641

An international meeting of Biogen leaders at a Boston hotel in February led to roughly 20,000 cases of COVID-19, according to researchers.
https://www.bostonglobe.com/2020/08/25/business/biogen-conference-likely-led-20000-covid-19-cases-boston-area-researchers-say/

Children:

A study with 192 children (mean age 10.2 +/- 7 years) with suspected/confirmed SARS-CoV-2 infection shows that nasopharyngeal viral load was highest in children in the first 2 days of symptoms, significantly higher than hospitalized adults with severe disease (P = .002). Younger children had lower ACE2 expression.
https://www.jpeds.com/article/S0022-3476(20)31023-4/fulltext

About 40 million US adults who work or live with school-aged children have definite or possible risk factors for severe COVID-19 illness, according to an analysis.
https://www.acpjournals.org/doi/10.7326/M20-5413

However, the KidsCorona study conducted by Hospital Sant Joan de Deu, Barcelona, with over 2000 participants in 22 summer camps, found that the R0 in summer camps was 6x lower than that in the general community and that infected children generated few secondary cases. Keeping groups small and constant is a key issue.
https://www.sjdhospitalbarcelona.org/es/estudio-kids-corona-muestra-una-baja-tasa-contagio-los-casales-verano

A study with over 33,000 children shows a low pooled prevalence (0.65%) of positive SARS-CoV-2 test results among children who were asymptomatic and presenting for surgical or medical care at 25 hospitals across the US.
https://jamanetwork.com/journals/jamapediatrics/fullarticle/2769878

Testing / Tracing

Self-collected saliva and deep nasal swabs collected by healthcare providers are equally effective for detecting SARS-CoV-2, according to a new study with more than 1000 specimens from almost 400 volunteers at a drive-through testing site in US.
https://jcm.asm.org/content/early/2020/08/07/JCM.01824-20
Rapid tests, although less accurate, may be good enough to detect who is infectious and therefore facilitate a return to "normality", insist some public health experts.

Symptoms / Risk factors

Post-mortem analysis confirms diffuse alveolar damage, thrombosis, haemophagocytosis, and immune cell depletion as the four dominant processes related to COVID-19 mortality. Novel autopsy findings include pancreatitis, pericarditis, adrenal micro-infarction, secondary disseminated mucormycosis, and brain microglial activation. https://www.thelancet.com/journals/lanmic/article/PIIS2666-5247(20)30115-4/fulltext

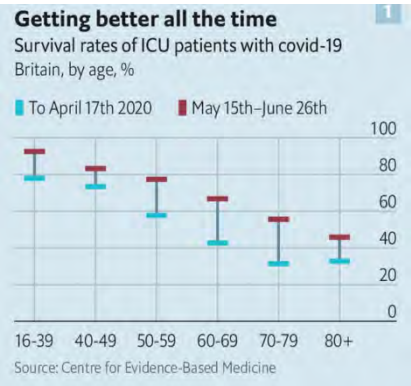
Presence of SARSCoV2 in heart muscle and endocardial cells was reported in an 11-year-old girl who died of cardiac complications from COVID19.
https://www.thelancet.com/action/showPdf?pii=S2352-4642%2820%2930257-1

A preprint study reports that immune cells (monocytes, CD4+ T cells, CD8+ T cells and B cells) are susceptible to SARS-CoV-2 infection. This was observed by *in vitro* infection of immune cells and by *ex vivo* detection of SARS-CoV-2 in peripheral blood mononuclear cells from patients with severe COVID-19. Since monocytes and lymphocytes do not express ACE2, it remains to be seen whether the virus uses an alternative entry strategy and whether this is relevant in disease progression.
https://www.biorxiv.org/content/10.1101/2020.07.28.225912v2

Pathogenic HCoVs including SARS-CoV-2 could modulate host miRNA levels by acting as miRNA sponges to facilitate viral replication and/or to avoid immune responses.
https://journals.physiology.org/doi/abs/10.1152/ajplung.00252.2020

IL-6 and TNF-α serum levels are independent and significant predictors of COVID-19 disease severity and death, according to a multiplex cytokine study by Mount Sinai researchers. The authors conclude that serum IL-6 and TNF-α levels should be considered in the management and treatment of patients with COVID-19 to stratify prospective clinical trials, guide resource allocation and inform therapeutic options. https://www.nature.com/articles/s41591-020-1051-9.pdf

An alternative and provocative way of thinking about infections like COVID-19: disease tolerance may at least partially explain why some infected people have mild symptoms or none at all, according to some scientists. https://undark.org/2020/08/24/covid-19-infection-asymptomatic/



The survival rates of ICU patients with COVID-19 in UK are drastically improving across all age categories, according to data from UK ICNARC. https://www.preprints.org/manuscript/202008.0267/v1

Obesity increases the risk of death from Covid-19 by nearly 50% and may make vaccines against the disease less effective, according to a meta-analysis using global data and commissioned for the World Bank. https://www.theguardian.com/world/2020/aug/26/obesity-increases-risk-of-covid-19-death-by-48-study-finds

More than 1,000 frontline healthcare workers reportedly have died of Covid-19 in the US, many of them immigrants and/or people of color, according to an ongoing investigation by the Guardian and KHN https://www.theguardian.com/us-news/2020/aug/26/us-health-workers-covid-19-deaths-lost-on-the-frontline

Antibodies / Immunity

A follow-up survey one month after the first seroprevalence study (SEROCOV) in the Hospital Clinic, Barcelona, shows a cumulative prevalence of 14.9% (versus 11.2% at the first survey). A decay of IgA and IgM levels was observed. https://www.medrxiv.org/content/10.1101/2020.08.23.20180125v1

Reinfection? A 33-year-old man from Hong Kong who was treated at the hospital for a mild case in March tested positive for the virus again almost five months later, when returning from Europe, but remained asymptomatic. Genomic analysis of the virus confirms that he was infected a second time. Several experts agree this is not a matter of concern: i) it is not known whether he developed neutralizing antibodies during the first infection; ii) the fact that he did not develop disease when reinfected may indicate a non-sterilizing but effective immunity, as expected; iii) the frequency of reinfections and their role in viral spread needs to be determined. https://www.sciencemag.org/news/2020/08/some-people-can-get-pandemic-virus-twice-study-suggests-no-reason-panic

See also this article on four possible scenarios regarding COVID-19 immunity: https://www.statnews.com/2020/08/25/four-scenarios-on-how-we-might-develop-immunity-to-covid-19/

T cell epitopes: An epitope mapping analysis shows that SARS-CoV-2-specific memory CD8+ T cells recurrently recognised a limited set of epitopes. Only 10% of these epitopes corresponded to the S protein, suggesting that vaccines should include other viral targets, such as ORF1ab and N protein. T cells targeting most of these immunodominant epitopes did not cross-react with the common cold coronaviruses https://www.medrxiv.org/content/10.1101/2020.07.24.20161653v2

A detailed "mapping" of NK cell responses in COVID-19 patients reveals high expression of perforin, NKG2C, and Ksp37 in patients with severe disease, reflecting increased presence of adaptive NK cells in circulation. https://immunology.sciencemag.org/content/5/50/eabd6832

Treatment

IFN: A review of 4 randomized and 11 non randomized trials suggests that JAK-inhibitor treatment is significantly associated with positive clinical outcomes regarding mortality, ICU admission, and discharge. Type I interferon treatment is associated with positive clinical outcomes regarding mortality and discharge. Additional RCTs are needed to confirm. https://www.medrxiv.org/content/10.1101/2020.08.10.20172189v1

Remdesivir: A randomized, open-label trial of hospitalized patients with moderate COVID-19 shows that patients treated with remdesivir during 5 days had a difference in clinical status as compared to standard care, although the difference was of "uncertain clinical importance". The trial involved 584 patients and 105 hospitals in the United States, Europe, and Asia. https://jamanetwork.com/journals/jama/fullarticle/2769871

Convalescent plasma: Researchers call for more rigorous clinical trials as the FDA issued an emergency use authorization for convalescent plasma. Convalescent plasma has been tested only in small trials without the statistical power to provide firm conclusions, they argue. One of the difficulties is measuring the levels of neutralizing antibodies in plasma from different donors. https://www.nature.com/articles/d41586-020-02324-2 See also: https://www.statnews.com/2020/08/23/is-convalescent-plasma-safe-and-effective /

mAbs: AstraZeneca has started a Phase I clinical trial with AZD7442 (a combination of two monoclonal antibodies) to help prevent and treat Covid-19, with the first volunteers already receiving doses. https://www.theguardian.com/business/2020/aug/25/astrazeneca-covid-19-antibody-drug-trial-volunteers-vaccine

Vaccines

Better through the nose?

A single intranasal dose of Oxford's ChAd-SARS-CoV-2-S vaccine induces high levels of neutralizing antibodies, promotes systemic and mucosal IgA and T cell responses, and almost completely prevents SARS-CoV-2 infection in both the upper and lower respiratory tracts in a mouse model expressing human ACE2. This is in contrast with intramuscular administration, which induces robust systemic immune responses and protects against lung pathology but does not confer sterilizing immunity. https://www.cell.com/cell/pdf/S0092-8674(20)31068-0.pdf

Another Ad5-vectored vaccine encoding the spike protein, given in either nasal or injected form, protected rhesus macaques from infection. Although intranasal

vaccination elicited much less systemic antibody and cellular responses than intramuscular vaccination, it conferred effective protection against SARS-CoV-2 infection. The authors say that a vaccine that can be given by nose might allow people to vaccinate themselves. https://www.nature.com/articles/s41467-020-18077-5

The University of Queensland, Australia, announced encouraging preclinical results (in hamsters) for their CEPI-funded vaccine candidate based on a molecular clamp platform (which allows generating stabilized subunit vaccines) and has started Phase I trials in volunteers. https://www.abc.net.au/news/2020-08-26/uq-covid-19-vaccine-candidate-safe-and-working-on-hamsters/12594726

Nature publishes a perspective on potential antibody-dependent enhancement of SARS-CoV-2 and the need to monitor vaccine safety very closely.
https://www.nature.com/articles/s41586-020-2538-8

The WHO has updated its draft landscape on covid-19 candidate vaccines, with 31 vaccines in human trials, including 6 in Phase 3. A 7th will start Phase 3 soon.
https://www.who.int/publications/m/item/draft-landscape-of-covid-19-candidate-vaccines

Wealthy countries have already ordered more than two billion doses of leading candidate vaccines, reflecting an "unequal scramble for the coronavirus vaccine".
https://www.nature.com/articles/d41586-020-02450-x

Others

A comment in *Nature* stresses the need to strengthen and extend networks within and between cities to make urban regions more resilient to future pandemics and other crises https://www.nature.com/articles/d41586-020-02459-2
Related to this topic, an article in *El Pais* on how neighbourhood networks in African city slums are much more efficient than government initiatives:
https://elpais.com/elpais/2020/08/10/seres_urbanos/1597051432_330539.html

The direct effect of the pandemic-driven response will be negligible, with a cooling of around 0.01 ± 0.005 °C by 2030 compared to a baseline scenario. In contrast, with an economic recovery tilted towards green stimulus and reductions in fossil fuel investments, it is possible to avoid future warming of 0.3 °C by 2050. (*Thanks for the tip, Kurt Straif!)*
https://www.nature.com/articles/s41558-020-0883-0.pdf

ISGlobal

COVID-19 EPIDEMIC

Epidemiological situation (31/08/2020, ECDC data):

Globally:
25 251 334 confirmed cases and 846 841 deaths

- India may soon pass Brazil to become the second-worst hit country, with over 3.6 million cases and 65,000 deaths https://www.cidrap.umn.edu/news-perspective/2020/08/india-surge-pushes-global-covid-19-total-higher
- In WHO's global pulse survey, 90% of countries report disruptions to essential health services since COVID-19 pandemic https://www.who.int/publications/i/item/WHO-2019-nCoV-EHS_continuity-survey-2020.1

Confinement and deconfinement strategies

In March, the Complexity Science Hub Vienna (CSH) started a comprehensive worldwide collection of governmental measures, now published. The CSH COVID-19 Control Strategies List includes information on 6,068 interventions from 56 countries: 33 European, 12 Asian, 5 South American, 2 North American, 3 African, and 1 Oceanian, plus the cruise ship Diamond Princess. The open dataset provides a valuable tool for analysing response strategies and developing preparedness plans.
https://www.nature.com/articles/s41597-020-00609-9

The US and the UK tied for last place in a poll ranking countries' handling of the pandemic, according to a Pew survey. Spain also ranked low.
https://edition.cnn.com/2020/08/27/world/global-coronavirus-attitudes-pew-intl/index.html

France extended facemask use to all of Paris, as the country experiences a steep rise in infections. https://www.reuters.com/article/us-health-coronavirus-france/france-to-make-face-masks-mandatory-everywhere-in-paris-idUSKBN25N143

Transmission

Children:
SARS-CoV-2 infections and outbreaks were uncommon in educational settings during the first month after the easing of national lockdown in England. Staff members had an increased risk of SARS-CoV-2 infections compared to students in any educational setting, and the majority of cases linked to outbreaks were in staff. The strong correlation with regional SARS-CoV-2 incidence emphasises the importance of controlling community transmission to protect educational settings.
https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/911267/School_Outbreaks_Analysis.pdf

A study in South Korea describes viral shedding in 91 pediatric patients that tested positive for SARS-CoV-2 through contact tracing or community testing, and were followed at 22 hospitals. About 22% never developed symptoms, 20% were initially asymptomatic but developed symptoms later, and 58% were symptomatic at their initial test. Duration of symptoms varied widely, from three days to nearly three weeks.

There was also a significant spread in how long children continued to shed virus and could be potentially infectious.
https://jamanetwork.com/journals/jamapediatrics/fullarticle/2770150
As pointed out in a related comment, molecular detection of virus may not necessarily correlate with infectivity.
https://jamanetwork.com/journals/jamapediatrics/fullarticle/2770149

Testing / Tracing
Virus: *Nature* publishes the first clinical validation of the specific high-sensitivity enzymatic reporter unlocking (SHERLOCK) assay using the enzyme Cas13a for the detection of SARS-CoV-2. The test has a detection limit of 42 RNA copies per reaction, is 100% specific and 100% sensitive with a fluorescence readout, and 100% specific and 97% sensitive with a lateral-flow readout. The assay should facilitate SARS-CoV-2 detection in settings with limited resources. https://www.nature.com/articles/s41551-020-00603-x

The U.S. FDA gave an emergency use authorization to Abbott Laboratories for a 15 min test that detects viral antigens and will cost 5 USD. The BinaxNOW, test uses a lateral flow technology to detect SARS-CoV-2 antigens from nasal swabs. Even if less accurate or sensitive than PCR tests, experts argue that these antigen tests can help to rapidly detect and isolate infectious people with relatively high viral loads.
https://www.sciencemag.org/news/2020/08/milestone-fda-oks-simple-accurate-coronavirus-test-could-cost-just-5

Antibodies: A head-to-head evaluation of ten point-of-care-style lateral flow assays (LFAs) and two laboratory-based ELISAs to detect anti-SARS-CoV-2 IgM and IgG antibodies starting at day 5 after symptom onset, concludes there was no standout serological assay. But four tests achieved more than 80% positivity at later time points tested and more than 95% specificity. https://www.nature.com/articles/s41587-020-0659-0

Results from over 500,000 users of the mobile App How We Feel in the US provide some insights into COVID-19 symptoms, testing and behaviour.
https://www.nature.com/articles/s41562-020-00944-2

Symptoms / Risk factors
Heart: COVID-19 causes cardiac dysfunction in up to 50% of patients. Findings in both iPSC-derived heart cells and autopsies indicate a pattern of transcriptomic and cytopathic changes associated with cardiac SARS-CoV-2 infection, including sarcomere fragmentation and loss of nuclear DNA.
https://www.biorxiv.org/content/10.1101/2020.08.25.265561v1

Brain: Mounting evidence supports an association between COVID-19 and stroke in young populations without typical vascular risk factors, at times with only mild respiratory symptoms, concludes a review in *Lancet Neurology*. Mechanisms involved include a hypercoagulable state, vasculitis, and cardiomyopathy.
https://www.thelancet.com/journals/laneur/article/PIIS1474-4422(20)30272-6/fulltext

Eyes: In a cross-sectional study, children hospitalized with COVID-19 in Wuhan, China, presented with a series of onset symptoms including fever, cough, and mild ocular manifestations, such as conjunctival discharge, eye rubbing, and conjunctival

congestion. Ocular symptoms recovered or improved eventually.
https://jamanetwork.com/journals/jamaophthalmology/fullarticle/2769877

Ethnicity: A cross-sectional study of 351 Massachusetts towns/cities found that a 10% increase in Black population was associated with a 312.3 increase in COVID-19 cases per 100,000, while a 10% increase in Latino population was associated with an increase of 258.2 cases per 100,000. Independent predictors of higher COVID-19 rates included the proportion of foreign-born non-citizens living in a community, mean household size, and share of food service workers.
https://www.healthaffairs.org/doi/full/10.1377/hlthaff.2020.01040

Multidrug-resistant *Candida auris* infections were documented in critically ill COVID-19 patients in India. https://wwwnc.cdc.gov/eid/article/26/11/20-3504_article

Fatality rate: A news feature in *Nature* reviews several studies from across the world, including one from Spain, which quantify the risk of dying from COVID-19. For every 1,000 people infected with the coronavirus who are under the age of 50, almost none will die. For people in their fifties and early sixties, about five will die — more men than women. The risk then climbs steeply as the years accrue. For every 1,000 people in their mid-seventies or older who are infected, around 116 will die.
https://www.nature.com/articles/d41586-020-02483-2
A study from Spain quantified the overall IFR between 1.1% and 1.4% in men and 0.58% to 0.77% in women,
https://www.medrxiv.org/content/10.1101/2020.08.06.20169722v1

The excess mortality in France between March and May 2020 was 25,030 deaths, mainly among people aged 65-84. This is actually lower than the 29,200 reported COVID-19 deaths during the same period. The authors propose that the 'protective' effect may concern external causes of death (such as traffic or occupational accidents), deaths related to air pollution or to other communicable diseases.
https://doi.org/10.2807/1560-7917.ES.2020.25.34.2001485

A prospective study of 651 children and young people under 19 years of age admitted to 138 hospitals in UK, concludes that severe disease was rare and death was exceptionally rare. It also indicates that children meeting the MIS-C criteria have different demographic and clinical features depending on whether they have acute SARS-CoV-2 infection (PCR positive) or are post-acute (antibody positive). Black ethnicity was significantly associated with admission to critical care.
https://www.bmj.com/content/370/bmj.m3249

Antibodies / Immunity
Another probable case of reinfection with SARS-CoV-2 is documented in a man in Nevada. In this case, the infections were separated by 40-50 days, and both were symptomatic. Genomic analysis of viral isolates at both timepoints suggests a degree of genetic discordance that 'cannot be explained reasonably through short-term in vivo evolution.' https://papers.ssrn.com/sol3/papers.cfm?abstract_id=3681489

The immunoglobulin heavy-chain variable region 3-53 gene is the most frequently used among 294 antibodies that target the receptor-binding domain (RBD) of the viral spike protein, according to a study now published in Science. These antibodies have few somatic mutations, and mostly germline-encoded residues are involved in binding to the virus's RBD. The minimal affinity maturation and high potency of these antibodies is promising for vaccine design.
https://science.sciencemag.org/content/369/6507/1119

T cell epitopes: A Hong Kong team provides a unified description of SARS-CoV-2 T cell epitopes compiled from results of 8 independent studies of convalescent COVID-19 patients, which may guide vaccine development and immunological studies. https://www.biorxiv.org/content/10.1101/2020.08.26.267724v1

Treatment

Tocilizumab: A cohort study performed in 60 Spanish hospitals including 778 COVID-19 patients with hyperinflammatory state. Results show that tocilizumab (anti IL-6 mAb) lowered the risk of intubation and/or death in these patients. Randomized trials are needed. https://www.clinicalmicrobiologyandinfection.com/article/S1198-743X(20)30492-4/fulltext

Chloroquine: A comment in *Nature Communications* highlights an international collaborative effort of independent researchers from over 80 countries, who have all come to the same conclusion—that chloroquine or hydroxchloroquine are unlikely to provide clinical benefit against COVID-19. The authors describe multiple recent studies in human organ chips and other multi-tissue *in vitro* models, mice, hamsters, and non-human primates, all of which strongly indicate the drugs do not have the efficacy suggested by earlier results obtained from *in vitro* studies with cultured cell lines. https://www.nature.com/articles/s41467-020-17907-w

Broad antiviral drug? The defensin-like peptide P9R, derived from mouse β-defensin-4, exhibited potent antiviral activity against pH-dependent viruses that require endosomal acidification for virus infection, including the enveloped pandemic A(H1N1) virus, avian influenza A(H7N9) virus, coronaviruses (SARS-CoV-2, MERS-CoV and SARS-CoV), and the non-enveloped rhinovirus. P9R significantly protected mice from lethal challenge by A(H1N1) virus and shows low possibility of leading to drug-resistance. https://www.nature.com/articles/s41467-020-17986-9

Vaccines

Moderna announced that its mRNA vaccine induced immune responses in older adults similar to those in younger participants, offering hope that it will be effective in people considered to be at high risk for severe complications from the coronavirus. The data involve Phase I results with adults above age 55 (56 to 70 and above 70) and the 100 ug dose which is being currently tested in Phase III. https://www.reuters.com/article/us-health-coronavirus-cdc-moderna/moderna-covid-19-vaccine-appears-to-work-as-well-in-older-adults-in-early-study-idUSKBN25M1Y0

The race for the vaccine is getting political and may get nasty, many experts warn. Sciencemag writes on the process and risk of releasing a vaccine too soon. https://www.sciencemag.org/news/2020/08/here-s-how-us-could-release-covid-19-vaccine-election-and-why-scares-some See also: https://www.theguardian.com/society/2020/aug/30/covid-vaccine-rush-could-make-pandemic-worse-say-scientists

Vaccine confidence: Our colleague JV Lazarus and other researchers conducted a global survey in June 2020 of 13,426 people in 19 countries to determine potential acceptance rates of a COVID-19 vaccine and factors influencing acceptance. Overall, almost 72% reported they would be very or somewhat likely to take a COVID-19 vaccine (75% in Spain). https://www.medrxiv.org/content/10.1101/2020.08.23.20180307v1

ISGlobal

COVID-19 EPIDEMIC

Epidemiological situation (07/09/2020, worldometer data):

Globally:
27,314,954 confirmed cases and 893,475 deaths

- India is setting new records for the pandemic, with over 90,000 new infections reported yesterday. Countries reporting more than 5000 newly confirmed cases in the past 24 hours include India (87,115), USA (53,813), Brazil (45,651), Spain (28,620), Argentina (10,684), France (8,975), Colombia (8,488), Mexico (6,196), Russia (5,110) and Iraq (5,036).
- The most recent WHO public health surveillance guidance asks countries to report probable cases, in addition to confirmed cases. The definition of a probable case of COVID-19 includes someone meeting clinical criteria and who is a contact of a probable or confirmed case, or a suspected case with chest imaging findings suggestive of COVID-19.
- EU countries should harmonise testing procedures and frequency to make data more comparable, says the European Parliament. There were also talks to expand the ECDC's mandate to also issue recommendations, which currently is only the competence of member states, as well as to increase its resources. https://www.europarl.europa.eu/news/en/press-room/20200827IPR85809/covid-19-eu-countries-should-harmonise-testing-procedures-and-frequency
- As of 19 Aug 2020, a total of 569 304 cases of COVID-19, including 2506 deaths, have been reported among healthcare workers, according to PAHO. Of these, 72% are female, and nurses are the most affected. file:///C:/Users/asarukhan/Downloads/2020-Aug-31-phe-epi-alert-COVID-19-healthcare-workers%20(1).pdf

Virus

A study shows that the SARS-CoV-2 ORF3b gene has premature stop codons which make it a potent interferon antagonist, suppressing type I IFN more efficiently than its SARS-CoV ortholog. In addition, the authors isolated a natural variant from two patients with severe disease (in Ecuador) with a longer ORF3b reading frame, which increases the ability to suppress interferon induction in vitro.
https://www.cell.com/action/showPdf?pii=S2211-1247%2820%2931174-8

Transmission

COVID-19 patients can exhale millions of SARS-CoV-2 RNA copies into the air per hour, according to a study in China. Exhaled breath samples had the highest positive rate (26.9%), followed by surface swabs (5.4%), and air samples (3.8%).
https://academic.oup.com/cid/advance-article/doi/10.1093/cid/ciaa1283/5898624

An analysis of a cluster of cases that occurred in a bus trip in Eastern China indicates that airborne spread of SARS-CoV-2 via air conditioning seems likely to have contributed to the high attack rate in the exposed bus.
https://jamanetwork.com/journals/jamainternalmedicine/fullarticle/2770172

Similarly, a Dutch study pinpoints the role of a ventilation system in a COVID-19 nursing home outbreak that affected just 1 of 7 wards.
https://academic.oup.com/cid/advance-article/doi/10.1093/cid/ciaa1270/5898577

The CDC reports that about a third of health workers who tested positive for SARS-CoV-2 antibodies were asymptomatic in the preceding months.
https://www.cdc.gov/mmwr/volumes/69/wr/mm6935e2.htm

Testing / Tracing
Isothermal RT-LAMP nucleic acid-based detection of SARS-CoV-2 with an additively manufactured cartridge and a smartphone-based instrument for testing can be performed at the point of sample collection. The POC system was able to distinguish positive from negative clinical samples after 30 min.
https://www.pnas.org/content/early/2020/08/27/2014739117

A story in *Science* analyses what is happening in Europe. It argues for targeting clusters of cases and superspreading events, and for identifying the source of newly detected cases (backward contact tracing) rather than, or in addition to, forward contact tracing.
https://www.sciencemag.org/news/2020/09/can-europe-tame-pandemic-s-next-wave#
This approach is particularly valuable when there is high individual-level variation in the number of secondary transmissions, as shown in a LSHTM study (that had escaped my attention) https://www.medrxiv.org/content/10.1101/2020.08.01.20166595v1

Changes in SARS-CoV-2 RNA concentrations in wastewater follows symptom onset in patients but precedes clinical test results, according to a retrospective study that used RT-qPCR to monitor virus RNA in wastewater, in Montana, US.
https://www.cell.com/action/showPdf?pii=S2666-3791%2820%2930124-5
In fact, the University of Arizona may have stopped a potential outbreak before it could spread by testing dormitory wastewater for SARS-CoV-2 RNA
https://www.sciencemag.org/news/2020/08/poop-tests-stop-covid-19-outbreak-university-arizona

Symptoms / Risk factors
Pregnant women: A systematic review and meta-analysis concludes that i) pregnant women are more likely to need intensive care treatment for covid-19 as compared to non-pregnant women, and ii) preterm birth rates are higher in pregnant women with covid-19 than in pregnant women without the disease.
https://www.bmj.com/content/370/bmj.m3320

Children: A review on why children are less susceptible to COVID-19 highlights: i) less ACE2 in respiratory tract; ii) some cross-protection by common cold coronaviruses; iii) protective Th2 responses; iv) Th2-associated eosinophilia; v) lower level of inflammatory cytokines. It also considers socioeconomic conditions.
https://www.pnas.org/content/early/2020/09/02/2012358117

Severe disease and death: SARS-CoV-2 RNA in serum at hospital admission indicates a high-risk of progression to critical disease and death, shows a study in a Swedish hospital with 106 SARS-CoV-2 RNA serum negative and 61 serum positive patients. The hazard ratios for critical disease and death were 7.2 and 8.6, respectively, for patients that were serum PCR positive (as compared to serum PCR negative).
https://academic.oup.com/cid/advance-article/doi/10.1093/cid/ciaa1285/5898271

A retrospective observational study of the first 4,000 patients hospitalized with COVID-19 in Spain provides a comprehensive view of characteristics and predictors of death in these patients. (*Thanks for sharing, Jose Maria Miro*) https://www.clinicalmicrobiologyandinfection.com/article/S1198-743X(20)30431-6/fulltext

Researchers are trying to understand whether carrying one copy of the sickle cell gene could increase the risk of severe COVID-19 or death, and help explain why COVID19 is disproportionately killing Black Americans. People with sickle cell trait can suffer from oxygen deprivation in some situations. Up to 3 million Americans are estimated to be carriers of the gene. https://www.statnews.com/2020/09/03/millions-carry-sickle-cell-trait-could-they-be-at-risk-for-severe-covid19/

A case report describes a case of a young male who developed manifestations of insulin-dependent diabetes following SARS-CoV-2 infection, in the absence of autoantibodies typical for type 1 diabetes. The authors propose that direct cytolytic β-cell damage due to SARS-CoV-2 infection occurred in this patient. The frequency of this remains to be determined, but the COVIDOM study in Germany (an epidemiological campaign foreseeing a 10-year follow up after SARS-CoV-2 infection) will help assess the long-term consequences of COVID-19 in a larger population.
https://www.nature.com/articles/s42255-020-00281-8

Long COVID: A prospective study of lung and heart complications in COVID-19 patients shows that (65%) had persistent symptoms at the time of their six-week visit; breathlessness (dyspnoea) was the most common symptom (47%), followed by coughing (15%). By the 12-week visit, breathlessness had improved and was present in 31 patients (39%); however, 13 patients (15%) were still coughing. CT scans showed 'ground glass' present in 74 patients (88%) at six weeks and 48 patients (56%) at 12 weeks. At 6 weeks, 58.5% had diastolic abnormalities.
https://www.eurekalert.org/pub_releases/2020-09/elf-cps090320.php

Counting direct and indirect deaths: *Nature* gathered figures from several databases as well as from trackers run by *The Financial Times* and *The Economist* to estimate excess deaths during the pandemic. The analysis shows that there are huge variations in excess deaths between countries- in Peru, 74% of the excess deaths are not explained by reported COVID-19 deaths while some countries, such as Bulgaria, have even experienced negative excess deaths during the pandemic so far (i.e. fewer people have died this year than expected). Excess mortality will be a mix of deaths directly caused by COVID-19, deaths maybe caused by other comorbidities, and indirect deaths caused by overstretched health services. The US recorded 20–45% more deaths from diabetes than the 5-year average and deaths from ischaemic heart disease were 6% to 29% higher than the norm. https://www.nature.com/articles/d41586-020-02497-w

Antibodies / Immunity

Antibody duration: Antiviral antibodies against SARS-CoV-2 did not decline within 4 months after diagnosis, according to a study in Iceland that measured antibodies in serum samples from 1215 persons who had recovered from SARS-CoV-2 infection, 4222 quarantined persons who had been exposed to SARS-CoV-2 and 23,452 persons not known to have been exposed. The study used six assays (including two pan-immunoglobulin assays. The authors estimate that 0.9% of Icelanders were infected with SARS-CoV-2 and that the infection was fatal in 0.3%.
https://www.nejm.org/doi/full/10.1056/NEJMoa2026116

T cell response: Virus clearance and COVID-19 survival are not associated with either SARS-CoV-2 T cell kinetics or magnitude of T cell responses, according to a study that compared T cell responses to SARS-CoV-2 S, M and N proteins in moderate, severe, and critical COVID-19 patients and unexposed donors. They also found that M-protein induces the highest frequencies of CD4+ T cells, suggesting its relevance for diagnosis and vaccination. https://www.cell.com/action/showPdf?pii=S2666-3791%2820%2930118-X

Unconventional T cells (namely, mucosal-associated invariant T cells and invariant natural killer T cells) might play a beneficial role during severe COVID-19. Patients whose circulating MAIT and iNKT cells were particularly active at the time of their admittance to the ICU were less susceptible to hypoxemia and were discharged sooner than patients whose MAIT and iNKT cells were less active.
https://rupress.org/jem/article/217/12/e20200872/152073/Phenotypical-and-functional-alteration-of

A study analysed T cell memory in 42 patients following recovery from COVID-19 (28 with mild disease and 14 with severe disease) and 16 unexposed donors, using interferon-γ-based assays with peptides spanning SARS-CoV-2. The breadth and magnitude of T cell responses were significantly higher in severe cases, while higher proportions of SARS-CoV-2-specific CD8+ T cells were observed in mild cases.
https://www.nature.com/articles/s41590-020-0782-6

CD8+ T-cell responses might serve as a more precise correlate of antiviral immunity than antibody measurements after convalescence, concludes a study that analysed CD8+ T cell responses in 26 convalescent patients and 25 healthy donors. The study identified immunodominant SARS-CoV-2 epitopes that elicit pre-existing and newly induced CD8+ T cell responses. Notably, SARS-CoV-2-specific T cells were present even in seronegative convalescent patients.
https://www.biorxiv.org/content/10.1101/2020.08.13.249433v1

In fact, a review on what we know about COVID-19 immunity stresses that memory B cells and T cells may be maintained even if there are not measurable levels of serum antibodies. https://www.nature.com/articles/s41577-020-00436-4

Nature discusses reinfections, and the three main questions that need to be addressed: how common are they; are they more or less severe than the first infection; what implications does this have for vaccines? https://www.nature.com/articles/d41586-020-02506-y

Treatment

Steroids: International clinical trials published on Wednesday confirm the hope that dexamethasone can help seriously ill patients survive Covid-19.
https://www.nytimes.com/2020/09/02/health/coronavirus-steroids-who.html
A WHO meta-analysis of 7 randomized trials that included 1703 patients of whom 647 died, 28-day all-cause mortality was lower among patients who received corticosteroids compared with those who received usual care or placebo (summary odds ratio, 0.66).
https://jamanetwork.com/journals/jama/fullarticle/2770279

A retrospective analysis with over 4,000 COVID-19 patients admitted to hospital, shows that, compared to no anticoagulants (AC), therapeutic and prophylactic AC were associated with lower in-hospital mortality and intubation. *(Thanks for the tip, Kurt Straif!)* https://www.onlinejacc.org/content/early/2020/08/24/j.jacc.2020.08.041

Vaccines
The Phase 1 results for Novavax's NVX-CoV2373, a nanoparticle vaccine composed of trimeric full-length SARS-CoV-2 spike glycoproteins and Matrix-M1 adjuvant, were published. At 35 days, it appeared to be safe, and elicited immune responses that exceeded levels in Covid-19 convalescent serum. The Matrix-M1 adjuvant induced CD4+ T-cell responses that were biased toward a Th1 phenotype.
https://www.nejm.org/doi/full/10.1056/NEJMoa2026920

The Lancet publishes phase 1 results for the Russian recombinant adenovirus-based vaccine, consisting of a prime with rAd26-S and a boost with rAd5-S 3 weeks later. The trial, with 76 healthy volunteers aged 18 to 60, also compared a lyophilised and a frozen formulation. The vaccine showed a good safety profile and induced strong humoral (i.e. neutralising abs) and cellular (CD4 and CD8) immune responses in all participants. There was no control arm.
http://www.thelancet-press.com/embargo/russiavaccine.pdf See comment: https://www.thelancet.com/journals/lancet/article/PIIS0140-6736(20)31867-5/fulltext

Sanofi and GSK are launching a large Phase 1/2 clinical trial Thursday that will take place at 11 sites across the United States. This candidate, based on recombinant proteins, is the first outside of China to use a vaccine approach for which there is already a licensed vaccine. https://www.statnews.com/2020/09/03/sanofi-gsk-covid19-vaccine-human-trials/

For an update on the current situation of vaccine trials in Africa, see this piece https://www.thelancet.com/journals/lanres/article/PIIS2213-2600(20)30401-X/fulltext

Vaccine efficacy criteria: The WHO and the FDA have recommended a vaccine efficacy (capacity to reduce the incidence of cases) of 50%. However, a paper published some weeks ago finds that the vaccine efficacy needed to stop transmission, in the absence of other preventive measures, is 70%
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7361120/

Vaccine distribution: In a policy report published in *Science*, 19 public health experts laid out an ethical framework called the *Fair Priority Model* for the distribution of COVID vaccines. Three values are particularly relevant: benefiting people and limiting harm, prioritizing the disadvantaged, and avoiding discrimination. They argue that distributing different quantities of vaccine to different countries is not discriminatory if it effectively benefits people while prioritizing the disadvantaged. This contrasts with WHO's COVAX proposal, which treats different countries identically (based on their population) rather than equitably (according to their different needs).
https://science.sciencemag.org/content/early/2020/09/02/science.abe2803

Meanwhile, the US has announced it will not join the global effort to develop and distribute a COVID-19 vaccine (COVAX)
https://apnews.com/b0c6313fca0e902b34d2ce59a6c54012

Vaccine trust: 68 % of the Spanish population is willing to get vaccinated against COVID-19, according to a poll by FECYT. Among those who hesitate, some would not want the first approved vaccine, but would get the second or third. Vaccine trust in general is still high among Spanish people: most consider they are effective in preventing disease (96%) and safe (94%). https://www.agenciasinc.es/Noticias/El-68-de-los-espanoles-esta-dispuesto-a-recibir-una-futura-vacuna-de-la-covid-19

One Health
The Wildlife Health Specialist Group (WHSG) of the International Union for Conservation of Nature (IUCN) and the World Animal Health Organisation (OIE) have recently released guidelines to minimize the risk of SARS-CoV-2 transmission from people to free-ranging wild mammals http://www.iucn-whsg.org/COVID-19GuidelinesForWildlifeResearchers

Others
If you're interested in the latest about the science of the pandemic, there's an outstanding lecture series at MIT, every Tuesday at 11.30 am, with many invited speakers who are all leaders in their respective fields, including Dr. Fauci. https://bit.ly/700Covid *(Thanks for the info, Kurt Straif!)*

ISGlobal

COVID-19 EPIDEMIC

Epidemiological situation (14/09/2020, worldometer data):

Globally:
29 049 134 confirmed cases and 924 706 deaths

- The U.N. General Assembly overwhelmingly approved a wide-ranging resolution on tackling the coronavirus pandemic, calling for "intensified international cooperation and solidarity to contain, mitigate and overcome the pandemic and its consequences." It urges U.N. member nations "to adopt a climate- and environment-responsive approach to COVID-19 recovery efforts". https://apnews.com/aa1069acfe0ced45f6baa2c3b82aa2e9

Confinement and deconfinement measures
Facing a surge with 4,000 new daily infections, Israel has imposed a three-week national lockdown to contain the spread of the virus.
https://www.bbc.com/news/world-middle-east-54134869

Senegal is among the countries that have best tackled the coronavirus. The country has only around 7 doctors per 100,000 people (vs 300 in US or UK), but has so far kept its outbreak in check with quick action, preparedness and an emphasis on testing and contact tracing. https://eu.usatoday.com/story/news/world/2020/09/06/covid-19-why-senegal-outpacing-us-tackling-pandemic/5659696002/

Virus
Mutations: The analysis of 18,514 SARS-CoV-2 sequences sampled since December 2019 finds that neutral evolution, rather than adaptive selection, can explain the rare mutations seen across SARS-CoV-2 genomes. The D614G mutation in the Spike protein has become consensus, yet there is no evidence of mutations affecting binding to the ACE2 receptor. To date, the limited diversity seen in SARS-CoV-2 should not preclude a single vaccine from providing global protection.
https://www.pnas.org/content/early/2020/08/28/2008281117
For more on the meaning of SARS-CoV-2 mutations, see this *Nature* feature.
https://media.nature.com/original/magazine-assets/d41586-020-02544-6/d41586-020-02544-6.pdf

New proteins: A high-resolution map of the SARS-CoV-2 coding regions identifies 23 new viral open reading frames (ORFs) capable of coding for previously unknown proteins. The study also finds that viral mRNAs are not translated more efficiently than host mRNAs; rather, virus translation dominates host translation due to high levels of viral transcripts. https://www.nature.com/articles/s41586-020-2739-1

Infection: A single cell transcriptome map of 28 SARS-CoV-2 and coronavirus-associated receptors across various healthy human tissues shows that intestinal goblet cells, enterocytes and kidney proximal tubule cells appear highly permissive to SARS-CoV-2, consistent with clinical data. Findings also identify non-canonical entry paths for lung and brain infections. Early embryonic and placental development are at

moderate risk of infection. https://www.cell.com/cell-reports/pdf/S2211-1247(20)31164-5.pdf

Transmission
Rapid early interventions successfully prevented early introductions of the virus into Germany and the US from taking hold, indicating that intensive testing and contact tracing could have prevented SARSCoV2 from becoming established in the US and Europe upon later introductions, according to an analysis integrating multiple information sources (air travel flow, disease incidence, viral genomics, etc.) https://science.sciencemag.org/content/early/2020/09/11/science.abc8169

The fraction of transmission from strictly pre-symptomatic infections is high (41%; 95%CI 31-50%), finds an analysis by the MRC. It confirms that most transmission occurs in the window from 2-3 days before to 2-3 days after symptom onset. https://www.medrxiv.org/content/10.1101/2020.09.04.20188516v1

A study among healthcare workers in the UK shows that seroprevalence was greatest among those working in housekeeping (34.5%), acute medicine (33.3%) and general internal medicine (30.3%), with lower rates observed in participants working in intensive care (14.8%). BAME (Black, Asian and minority ethnic) ethnicity was associated with a significantly increased risk of seropositivity. https://thorax.bmj.com/content/early/2020/08/28/thoraxjnl-2020-215414

Face masks: Recent virologic, epidemiologic, and ecologic data have led to the hypothesis that facial masking may not only protect people from infection but may also reduce the severity of disease among people who do become infected https://link.springer.com/article/10.1007/s11606-020-06067-8
Along this line, a NEJM perspective argues that face masks may provide a potential 'variolation' effect by reducing the inoculum that an exposed person inhales and thereby increase the proportion of SARS-CoV-2 infections that are asymptomatic but could confer some level of immunity.
https://www.nejm.org/doi/full/10.1056/NEJMp2026913
(Thanks for the tip, Kurt Straif and Denise Naniche!)

Testing / Tracing
A UK team repurposed automated liquid-handling infrastructure in the London Biofoundry to establish two frontline automated SARS-CoV-2 testing platforms, with a testing capacity of 2000 samples per day. The platforms can be quickly deployed and scaled. https://www.nature.com/articles/s41467-020-18130-3

Symptoms / Risk factors
As many as 1 in 100 hospitalized COVID-19 patients may experience a pneumothorax, or punctured lung, according to a multicentre observational case series https://www.cidrap.umn.edu/news-perspective/2020/09/another-possible-covid-complication-punctured-lung

Children:
Hyperinflammation in MIS-C differs from that of acute COVID-19 with respect to T-cell subsets, IL-17A (which drives Kawasaki but not MIS-C hyperinflammation) and biomarkers associated with arterial damage, according to a systems-level analyses of blood immune cells, cytokines and autoantibodies in healthy children, children with Kawasaki disease enrolled prior to COVID-19, children infected with SARS-CoV-2, and

children presenting with MIS-C. Multiple autoantibodies could be involved in the pathogenesis of MIS-C. https://www.cell.com/action/showPdf?pii=S0092-8674%2820%2931157-0
Children with COVID-19 and seasonal flu were equally likely to be hospitalized, admitted to the ICU, and require a ventilator, according to a cohort study of 315 children in a Washington DC hospital.
https://jamanetwork.com/journals/jamanetworkopen/fullarticle/2770250

Pregnant women: A prospective cohort study in Spain across 45 hospitals, with 1000 screened pregnancies (246 COVID-positive), concludes that pregnant SARS CoV2 infection increased the odds of preterm birth, premature rupture of membranes at term and neonatal intensive care unit admissions.
https://www.medrxiv.org/content/10.1101/2020.09.05.20188458v1

Obesity: A news story in Science reviews why COVID-19 is deadlier in overweight and obese people, even when young. Reasons include simple mechanics, a higher blood clotting tendency, and a reduction in number and function of immune cells.
https://www.sciencemag.org/news/2020/09/why-covid-19-more-deadly-people-obesity-even-if-theyre-young

NAIDs: A Danish study finds no association between non-steroidal anti-inflammatory drugs (i.e. ibuprofen) and 30-day mortality, hospitalization, ICU admission, mechanical ventilation, or renal replacement therapy in Danish individuals who tested positive for SARS-CoV-2. https://journals.plos.org/plosmedicine/article

Long COVID: The Guardian covers a story on long covid: more than 60.000 people in the UK may suffer from symptoms during more than three months. Some cases are mild, but others are seriously debilitating, with breathlessness and fatigue.
https://www.theguardian.com/society/2020/sep/08/60000-may-have-long-covid-for-more-than-three-months-uk-study

Antibodies / Immunity
Herd immunity: Fontanet and Cauchemez (Institut Pasteur) discuss the factors that determine herd immunity to SARS-CoV-2. They stress that the safest way to achieve it is through vaccines. https://www.nature.com/articles/s41577-020-00451-5

T cells: A study using peptide / HLA tetramers in COVID-19 patients shows a bias toward naïve, stem cell memory and central memory CD8+ T cells. rather than effector memory populations, suggesting that SARS-CoV-2 infection may compromise CD8+ T cell activation. https://www.pnas.org/content/early/2020/09/09/2015486117

Bats: An interesting, easy read on what bats can teach us about developing immunity to Covid-19 https://www.ft.com/content/743ce7a0-60eb-482d-b1f4-d4de11182fa9

Treatment
Tocilizumab: A review of observational studies with tocilizumab concludes that TCZ seems beneficial in preventing in-hospital mortality in severe, non-critically ill COVID-19 patients but that it may increase the risk of secondary infections, particularly among those admitted to ICU.
https://www.medrxiv.org/content/10.1101/2020.09.05.20188912v2

Convalescent plasma was not associated with reduction in mortality or progression to severe COVID-19 in a multicentre randomized clinical trial in India, with 464 participants. https://www.medrxiv.org/content/10.1101/2020.09.03.20187252v1
In contrast, another small study in Argentina suggests that convalescent plasma infusions can lead to an improvement in pneumonia clinical scale in COVID patients, especially before requiring mechanical ventilation.
https://www.medrxiv.org/content/10.1101/2020.09.01.20184390v1
Measurement of neutralizing antibody titres in donors could be useful in clarifying the efficacy of convalescent plasma.

mAbs: Regeneron's antiviral antibody drug has been added to the world's largest randomized trial of potential COVID-19 treatments. It is the first drug actually designed for this disease. https://www.reuters.com/article/us-health-coronavirus-regeneron-antibody/regenerons-antibody-drug-added-to-uk-recovery-trial-of-covid-treatments

Minibinders: Researchers at the Institute for Protein Design, University of Washington, used computers to design miniproteins that bind tightly to SARS-CoV-2 Spike protein. More than two million candidate proteins were designed and over 118,000 were produced and tested/improved in the lab. The most potent, with new binding modes, are capable of inhibiting infection with roughly six times more potency than the most effective monoclonal antibodies reported thus far. The size and stability of these minibinders makes it easier/cheaper to produce and scale up than mAbs.
https://science.sciencemag.org/content/early/2020/09/08/science.abd9909

Antibody cocktails: A deep mutational scanning of SARS-CoV-2 maps all amino-acid mutations, particularly in the RBD, that can escape the effect of neutralizing antibodies. The escape mutations cluster on several surfaces of the RBD that broadly correspond to structurally defined antibody epitopes. However, even antibodies targeting the same RBD surface often have distinct escape mutations. This information will help design escape-resistant antibody cocktails.
https://www.biorxiv.org/content/10.1101/2020.09.10.292078v1

Bradykinin: a new therapeutic target? A study proposes a "bradykinin storm" model, where increased bradykinin levels tie could lead to increases in vascular dilation, vascular permeability, and hypotension, explaining many coronavirus-related pathologies. The study is based on an analysis of gene expression data from cells in bronchoalveolar lavage fluid (BALF) from COVID-19 patients and proposes therapeutic intervention points that can be addressed with existing approved pharmaceuticals
https://elifesciences.org/articles/59177
See comment in
https://blogs.sciencemag.org/pipeline/archives/2020/09/08/bradykinin-and-the-coronavirus

Vaccines
BioNTech's BNT162b2 vaccine candidate, which contains a nucleoside-modified mRNA that encodes the spike glycoprotein in its prefusion conformation, elicited high levels of neutralising antibodies in rhesus macaques and strong TH1 type CD4+ and IFNγ+ CD8+ T-cell responses. A prime-boost vaccination protected macaques from lung infection upon viral challenge (and virus was only detected in nasal swabs at day 1).
https://www.biorxiv.org/content/10.1101/2020.09.08.280818v1
Pfizer BioNTech will supply 200 million doses of COVID vaccine to the EU by ends of 2020 (subject to clinical results and regulatory clearance). https://www.biopharma-reporter.com/Article/2020/09/10/EU-lines-up-deal-with-BioNTech-Pfizer-for-coronavirus-vaccine-supply

Preclinical studies in mice shows that an adenoviral vector expressing the whole-length S protein induces significantly higher neutralizing antibodies in the periphery and in the lungs, when the vaccine is administered intranasally. The vaccine by Vaxart, US is entering clinical trials.
https://www.biorxiv.org/content/10.1101/2020.09.04.283853v1

China will start phase 1 trials for a potential COVID-19 vaccine administered through a nasal spray, which contains strains of the weakened flu virus with genetic segments of the SARS-CoV-2 spike protein. https://www.foxnews.com/health/china-approves-human-trials-for-nasal-spray-coronavirus-vaccine

The phase 1 results for Russia's Sputnik vaccine, published recently in *The Lancet*, have been questioned by 26 scientists in an open letter. They point out that multiple participants report identical antibody levels, which is 'highly unlikely'.
https://www.reuters.com/article/us-health-coronavirus-russia-vaccine-let/some-scientists-spot-unlikely-patterns-in-russia-vaccine-data-letter-idUSKBN2602Q5

The UK clinical trial of AstraZeneca's vaccine has resumed. After a review of a possible adverse event that led to the pause (a woman participant who experienced symptoms consistent with transverse myelitis), Britain's regulatory agency concluded it was safe to restart. No word yet when the US trial will restart.
https://www.statnews.com/2020/09/12/astrazeneca-covid19-vaccine-trial-resumes-uk/

Nature covers the 'underdog' coronavirus vaccines that could be needed if the leading candidates fail. Some (including a Newcastle disease vector, a VSV-SARS-CoV-2 vector, and an intranasal ChAd vector) have given promising pre-clinical results but lack funding to enter clinical trials. The Gates Foundation is supporting a vaccine based on virus-like particles, which could be supplied to LMICs.
https://www.nature.com/articles/d41586-020-02583-z

Current attempts at developing a COVID vaccine should be looking at T cell responses instead of- or in addition to- antibodies, argues a UC Berkeley researcher. He cites the example of the 82-year-old yellow fever vaccine, which stimulates a long-lasting, protective T-cell response. He points out that, although most vaccine candidates are focusing on spike protein as antigen, natural infection by SARS-CoV-2 induces T cells against a broad range of epitopes, some cross-reactive with other betacoronviruses *(via Global Health Now)*
https://www.sciencedirect.com/science/article/pii/S2590136220300231

For a review on immunological considerations for COVID-19 vaccine strategies, see:
https://www.nature.com/articles/s41577-020-00434-6

Trained immunity: With the data accumulated to date, a statistical analysis concludes there is a significant correlation between universal BCG immunization and milder Covid-19. https://www.medrxiv.org/content/10.1101/2020.09.06.20189423v1.full.pdf

Vaccine distribution:
A model-informed approach to vaccine prioritization concludes that a transmission-blocking vaccine should be prioritized to adults ages 20-49y to minimize cumulative incidence and to adults over 60y to minimize mortality. For vaccines that do not block transmission, direct vaccination of adults over 60y to minimize mortality should be priority. Authors also estimate the potential benefit of using individual-level serological

tests to redirect doses to only seronegative individuals.
https://www.medrxiv.org/content/10.1101/2020.09.08.20190629v1

Vaccine confidence:
Nine pharmaceutical companies issued a joint pledge on Tuesday that they would "stand with science" and not put forward a vaccine until it had been thoroughly vetted for safety and efficacy. However, they did not rule out seeking an emergency authorization of their vaccines. https://www.nytimes.com/2020/09/08/health/9-drug-companies-pledge-coronavirus-vaccine.html
Outside researchers are calling on the drug companies to reveal more about how the trials work. https://www.nytimes.com/2020/09/13/science/coronavirus-vaccine-trials.html

Confidence in the importance, safety, and effectiveness of vaccines has fallen in some countries (including Afghanistan, Pakistan, Philippines, South Korea) and risen in others (including Finland, France, Ireland, and Italy), according to a study using data from 290 surveys between 2015 and 2019, across 149 countries, and including 284,381 individuals. Male sex and less education were associated with reduced chance of uptake. The findings highlight the importance of constant monitoring to detect emerging trends. https://www.thelancet.com/journals/lancet/article/PIIS0140-6736(20)31558-0/fulltext

Others
The financial impact of the pandemic is higher than expected: 50 to 80% of Latino and Black households in 4 major cities in US have experienced the loss of a job or a reduction in wages or work hours since the start of the pandemic, according to a NPR poll https://www.npr.org/sections/health-shots/2020/09/09/909669760/npr-poll-financial-pain-from-coronavirus-pandemic-much-much-worse-than-expected

The pandemic is creating a bigger divide between rich and poor countries. A survey for the BBC found a drop in income was reported by 69% of respondents in poorer countries, compared to 45% in richer ones. https://www.bbc.com/news/world-54106474

ISGlobal

COVID-19 EPIDEMIC

Epidemiological situation (21/09/2020, worldometer data):

Globally:
31 091 469 confirmed cases and 961 352 deaths

- India is on track to surpass the US as the worst affected country, with almost 100,000 new cases confirmed in one day (Thursday). The country has reported almost 84,000 deaths, but the real tally is suspected to be higher. https://www.npr.org/sections/coronavirus-live-updates/2020/09/17/913475045/india-is-on-track-to-surpass-u-s-as-the-country-worst-affected-by-covid-19

Confinement and deconfinement measures

Surge of cases in Europe: the number of new cases doubled in the last 2 weeks in more than half of the member states. The UK may face a second lockdown, after new cases have nearly doubled to 6,000 per day. Spain is seeing its highest number of deaths since June, especially in Madrid, where some lockdown measures have been announced. France set a record last weekend with more than 10,000 new cases in a single day and ICUs nearing capacity in cities like Bordeaux and Marseilles (*via Global Health Now*)

Virus

An article in *Science* describes a molecular pore complex that spans both membranes of the double-membrane vesicle and would allow export of SARS-CoV-2 RNA to the cytosol. https://science.sciencemag.org/content/369/6509/1395

Researchers have developed CoV-Seq, an integrated web service for fast and easy SARS-Cov-2 genome analysis and visualization.
https://www.ncbi.nlm.nih.gov/research/coronavirus/publication/32931441

Transmission

Using contact tracing data from 1,038 SARS-CoV-2 cases confirmed between 23 Jan and 28 Apr 2020 in Hong Kong, a team identified 4-7 superspreading events (notably weddings, bars and places of worship) and estimated that 19% of cases seeded 80% of all local transmission. Transmission in social settings was associated with more secondary cases than households. https://www.nature.com/articles/s41591-020-1092-0

Inflight transmission: A cluster of cases related to a 10h flight shows that seating proximity was strongly associated with increased infection risk (risk ratio 7.3). One symptomatic case generated 16 cases, 12 of them sitting nearby. At that time, the use of face masks was not mandatory on airplanes or at airports
https://wwwnc.cdc.gov/eid/article/26/11/20-3299_article

A cohort study of patients hospitalized with COVID-19 in Suizhou, China, suggests that wearing eyeglasses could protect against SARS-CoV-2 infection -the proportion of

COVID-19 inpatients who wore glasses was smaller than that in the general population. https://jamanetwork.com/journals/jamaophthalmology/fullarticle/2770872
An op-ed in the Washington Post stresses the need for more information and data to understand where transmission is occurring, but also to develop targeted messages for known high risk behavior populations. https://www.washingtonpost.com/

Testing / Tracing
Nature discusses the pros and cons of rapid antigen tests for SARS-CoV-2. In a nutshell: they can detect those who are most infectious, but need to be produced in high quantities and their use should not substitute other preventive measures. https://www.nature.com/articles/d41586-020-02661-2

MIT researchers published results for STOPCovid (version 2), a RNA- LAMP amplification combined with a CRISPR-mediated detection that can produce results in 30 minutes to an hour, with similar accuracy as the standard PCR diagnostics now used. https://www.nejm.org/doi/full/10.1056/NEJMc2026172

A UK team has developed a rapid point of care test, based on real time PCR, called CovidNudge, which requires no laboratory handling or sample pre-processing. https://www.thelancet.com/journals/lanmic/article/PIIS2666-5247(20)30121-X/fulltext#%20 (*Thanks for the tip, Kurt Straif!*)

A study measuring SARS-CoV-2 RNA concentration in wastewater in New Haven shows that it was 0–2 d ahead of SARS-CoV-2 positive test results by date of specimen collection, 1–4 d ahead of local hospital admissions and 6–8 d ahead of SARS-CoV-2 positive test results by reporting date. https://www.nature.com/articles/s41587-020-0684-z

Symptoms / Risk factors
A news feature in *Nature* reviews how COVID-19 can damage the brain. It is still not clear if and which neurological symptoms result from indirect inflammation versus direct infection by the virus. https://www.nature.com/articles/d41586-020-02599-5

A genome wide association study by 23andme reveals genetic and non-genetic associations with COVID-19 susceptibility and severity. It identifies a strong association between blood type and COVID-19 diagnosis, as well as a section on chromosome 3 (chr3p21.31) that is more strongly associated with outcome severity. https://www.medrxiv.org/content/10.1101/2020.09.04.20188318v1.full.pdf

Antibodies / Immunity
Coordinated SARS-CoV-2-specific adaptive immune responses were associated with milder disease, according to a study that analysed CD4, CD8 and neutralizing antibody responses in acute and convalescent COVID-19 patients. SARS-CoV-2-specific CD4+ and CD8+ T cells were each associated with milder disease, while scarcity of naive T cells was associated with ageing and poor disease outcomes. CXCL10 may be a biomarker of impaired T cell responses in acute COVID-19. https://www.cell.com/cell/fulltext/S0092-8674(20)31235-6

A systematic review of almost 500 manuscripts focuses on antibody-mediated immunity to SARS-CoV-2, including antibody kinetics, correlates of protection, immunopathogenesis, antigenic diversity and cross-reactivity, and population seroprevalence. https://www.nature.com/articles/s41467-020-18450-4

Treatment

Convalescent plasma:
A retrospective, propensity score–matched case–control study assessed the effectiveness of convalescent plasma therapy in 39 patients with severe or critical COVID-19 at The Mount Sinai Hospital in NYC. Oxygen requirements on day 14 after transfusion worsened in 17.9% of plasma recipients versus 28.2% of matched controls. Survival also improved in plasma recipients. Only donors with a serum IgG titer of ≥1:320 were selected. However, no correlation between donor neutralization titers and recipient outcomes were observed. https://www.nature.com/articles/s41591-020-1088-9

mAbs:
Lilly announced proof of concept data for its neutralizing antibody LY-CoV555 in COVID-19 outpatients. Hospitalization occurred in 1.7% (5/302) of LY-CoV555 patients as compared to 6% (9/150) of placebo patients. The drug was well tolerated.
https://www.prnewswire.com/news-releases/lilly-announces-proof-of-concept-data-for-neutralizing-antibody-ly-cov555-in-the-covid-19-outpatient-setting-301131785.html

Lilly also announced that baricitinib (a JAK inhibitor) in combination with remdesivir reduces time to recovery (a median of 1 day) in hospitalized patients with COVID-19, according to early results from a clinical trial involving over 1000 patients.
https://investor.lilly.com/news-releases/news-release-details/baricitinib-combination-remdesivir-reduces-time-recovery

Nanobodies: An alpaca-derived single domain antibody fragment, Ty1, specifically targets the receptor binding domain (RBD) of the SARS-CoV-2 spike and prevents ACE2 engagement. Ty1 neutralizes SARS-CoV-2 spike pseudovirus as a 12.8 kDa nanobody, which can be expressed in high quantities in bacteria.
https://www.nature.com/articles/s41467-020-18174-5

Monobodies: A Japanese team describes a high-speed *in vitro* selection of multiple high-affinity antibody-like proteins (monobodies) against various targets including the SARS-CoV-2 spike protein. One of them exhibited a high neutralizing activity against SARS-CoV-2 infection.
https://advances.sciencemag.org/content/early/2020/09/18/sciadv.abd3916

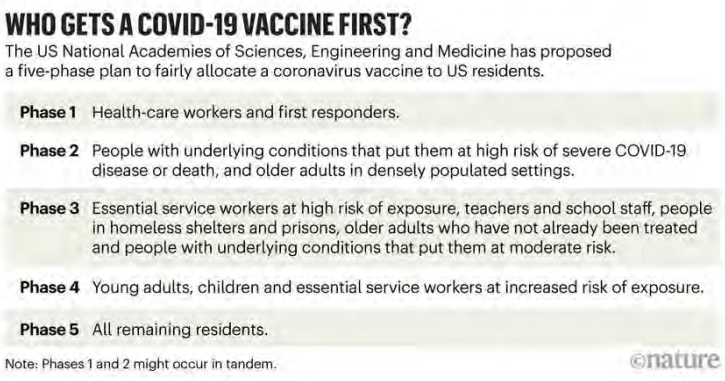
Vaccines

Moderna, Pfizer and Astra Zeneca published this week their full phase III protocols, including information on stopping rules, interim analyses, and assumptions for efficacy.
Table by Eric Topol https://twitter.com/erictopol/status/1307415684431765504

	Pfizer	Moderna	Astra-Zeneca
Sample size	30,000	30,000	30,000
Participants getting vaccine	15,000	15,000	20,000
Efficacy target	60%	60%	50%
Lower 95% CI efficacy	30%	30%	30%
Number of Events at Completion	164	151	150
Number of Interim Analyses	4	2	1
Alpha-spending function at Interim Analysis for Stopping Rule	Pocock-type	O'Brien-Fleming type	Lan-DeMets
Number of Events at 1st (or only) Interim Analysis	32	53	75

Vaccine distribution: The WHO has published its framework for the allocation and prioritization of COVID-19 vaccination. The WHO strategic advisory group will continue to update its guidance, to assign rankings to priority groups, and to include real data from vaccine trials (i.e. how effective a given vaccine is in older people).
https://apps.who.int/iris/bitstream/handle/10665/334299/WHO-2019-nCoV-SAGE_Framework-Allocation_and_prioritization-2020.1-eng.pdf

In turn, the US National Academy of Sciences has proposed a five-phase plan for US residents.



https://www.nature.com/articles/d41586-020-02684-9

Others
The CREID (Centers for Research in Emerging Infectious Diseases) network was announced 3 weeks ago by the NIH. The international network aims to detect pathogens that can jump from wildlife to the human population.
https://www.wired.com/story/the-nih-launches-a-global-hunt-for-animal-to-human-diseases/

Three new Cochrane reviews on public health measures to control SARS-CoV-2 transmission (*Thanks Kurt Straif for the info!)*
One on travel restrictions
https://www.cochranelibrary.com/cdsr/doi/10.1002/14651858.CD013717/full
One on universal screening
https://www.cochranelibrary.com/cdsr/doi/10.1002/14651858.CD013718/full
One on quarantines with or without other public health measures
https://www.cochranelibrary.com/cdsr/doi/10.1002/14651858.CD013574.pub2/full

ISGlobal

COVID-19 EPIDEMIC

Epidemiological situation (28/09/2020, worldometer data):

Globally:
33 342 965 confirmed cases and 1,002,985 deaths

- COVID-19 cases are steadily climbing in US, Canada and Europe https://www.cidrap.umn.edu/news-perspective/2020/09/covid-19-cases-climbing-us-europe-canada
- While Africa's COVID-19 cases have remained lower than projected, the pandemic has had major indirect impacts, according to a new report https://preventepidemics.org/wp-content/uploads/2020/09/PERC_RespondingtoCovidData.pdf

Confinement and deconfinement measures
An analysis published in *The Lancet* (co-signed by some of our colleagues) examines the approaches taken by nine high-income countries and regions that have started to ease COVID-19 restrictions. It concludes that the prerequisites for easing Covid-19 measures are: knowledge of infection status, community engagement, adequate public health capacity, adequate health system capacity and border controls. Many governments failed to meet the criteria necessary to avoid new waves of infection, as seen in Spain, Germany and the UK.
https://www.thelancet.com/journals/lancet/article/PIIS0140-6736(20)32007-9/fulltext

The key to South Korea's success in controlling the epidemic came from blending technology and testing like no other country, centralized control and communication—and a constant fear of failure, according to an editorial in WSJ.
https://www.wsj.com/articles/lessons-from-south-korea-on-how-to-manage-covid-11601044329

A comment in *Nature* on the role of hubris in the pandemic response points out that overconfidence in 'national specialness' has led to lack of preparedness, prevented collaboration with global health agencies and limited opportunities to learn from the experience of other countries https://www.nature.com/articles/d41586-020-02596-8

Pubs, bars and restaurants throughout England will be forced to close at 10pm and people have been told to work from home again if they can.

Catalonia (followed by the rest of Spain) will reduce the quarantine period to 10 days, as is already the case in the Netherlands. France has already reduced it to seven days and Germany may reduce it to five days.
https://english.elpais.com/spanish_news/2020-09-22/spanish-health-ministry-finalizing-agreement-with-regions-to-reduce-coronavirus-quarantine-from-14-to-10-days.html

In a special report, statnews imagines the next 15 months and what life will be like.
https://www.statnews.com/feature/coronavirus/the-road-ahead-the-next-12-months-and-beyond/

Virus

The low genetic diversity may be the Achilles heel of SARS-Co-V2, says a comment in *PNAS* https://www.pnas.org/content/pnas/early/2020/09/18/2017726117.full.pdf

A study shows that furin inhibitors block SARS-CoV-2 viral entry and viral replication, suggesting they are potential antivirals for SARS-CoV-2 infection and pathogenesis. https://www.cell.com/cell-reports/fulltext/S2211-1247(20)31243-2

Transmission

A CDC report provides evidence that younger adults contributed to community transmission of COVID-19 to older adults. Across the southern United States in June 2020, the increase in SARS-CoV-2 infection among younger adults preceded the increase among older adults by 4–15 days (or approximately one to three incubation periods). https://www.cdc.gov/mmwr/volumes/69/wr/mm6939e1.htm

A viewpoint stresses the need to better understand SARS-CoV-2 transmission dynamics in order to inform policy decisions about mitigation strategies and design targeted interventions for the settings, activities and socioeconomic factors associated with the highest risks of transmission. https://academic.oup.com/cid/advance-article/doi/10.1093/cid/ciaa1442/5910315

A systematic review found some evidence that SARS-CoV-2 infection in contacts of people with asymptomatic infection is less likely than in contacts of people with symptomatic infection.
https://journals.plos.org/plosmedicine/article?id=10.1371/journal.pmed.1003346&

A study in 4 health care facilities with hospitalized COVID-19 patients suggests that remote (more than 2 m) airborne transmission of SARS-CoV-2 is uncommon when aerosol-generating procedures have not been performed. Surface contamination was widespread, except in a room routinely cleaned with disinfectant wipes.
https://jkms.org/DOIx.php?id=10.3346/jkms.2020.35.e332

Schools, children: A concise and updated summary of what is known of COVID-19 and children concludes that although the role of children in transmission of SARS-CoV-2 remains unclear, existing evidence points to educational settings playing only a limited role in transmission when mitigation measures are in place. Therefore, school closures "should only happen if evidence exists that they help because there is plenty of evidence that they do harm".
https://science.sciencemag.org/content/early/2020/09/18/science.abd6165
A systematic review and meta-analysis including 32 studies concludes that children and adolescents under 20y had 44% lower odds of secondary infection with SARS-CoV-2 compared with adults 20 years and older. This finding was most marked in those younger than 10 to 14 years. Data were insufficient to conclude whether transmission of SARS-CoV-2 by children is lower than by adults.
https://jamanetwork.com/journals/jamapediatrics/fullarticle/2771181

Vertical transmission: An immunohistochemistry study on 101 placentas (15 of them from COVID-19 confirmed mothers) collected during the COVID-19 pandemic shows one case of placental infection and transmission to the newborn. The authors conclude that mother-to-fetus transmission of SARS-CoV-2 infection is a rare yet possible event.
https://www.thelancet.com/journals/ebiom/article/PIIS2352-3964(20)30327-3/fulltext

Along the same line, another report describes a case of congenital SARS-CoV-2 infection in an infant born via vaginal delivery to a mother with COVID-19 presenting primarily with gastrointestinal manifestations.
https://journals.lww.com/pidj/Fulltext/2020/09000/Intrauterine_Transmission_of_SARS_COV_2_Infection.32.aspx

Testing / Tracing
Combining saliva sampling with pooling is proposed as a very efficient, relatively cheap surveillance system for SARS-CoV-2.
https://www.thelancet.com/journals/lanres/article/PIIS2213-2600(20)30444-6/fulltext

Genome sequencing of sewage can provide a broader picture of prevalent circulating SARS-CoV-2 variants, shows a study performed in the San Francisco Bay area.
https://www.medrxiv.org/content/10.1101/2020.09.13.20193805v1

Dogs are being trained in several labs including France and Germany to detect COVID-19 in people, according to a story in *The Guardian*. The dogs detect molecules produced when the virus infects cells, and can correctly detect positive cases 75-85% of the time and rule out negative cases in over 80% of the time. Results are not yet peer-reviewed.
https://www.theguardian.com/world/2020/sep/25/any-breed-could-do-it-dogs-might-be-covid-testers-best-friend

During the first wave of the COVID-19 pandemic, fewer than 10% of the US adult population had detectable antibodies against SARS-CoV-2, and fewer than 10% of those with antibodies were diagnosed, according to a study that tested the plasma of 28 503 randomly selected adult patients across 1300 dialysis facilities in the US in July, 2020.
https://www.thelancet.com/journals/lancet/article/PIIS0140-6736(20)32009-2/fulltext

Symptoms / Risk factors
A study found a higher rate of gastrointestinal complications, including mesenteric ischemia, in critically ill patients with COVID-19 compared with propensity score-matched patients without
COVID-19. https://jamanetwork.com/journals/jama/fullarticle/2771160

A perspective by Eric Topol discusses how SARS-CoV-2 can cause direct and indirect damage the heart, even in patients without lung symptoms.
https://science.sciencemag.org/content/early/2020/09/23/science.abe2813

A review of 19 observational studies confirms a lack of association between angiotensin-converting enzyme inhibitor (ACEI) and angiotensin-receptor blocker (ARB) use and more severe coronavirus disease 2019 (COVID-19).
https://www.acpjournals.org/doi/10.7326/L20-1177

Children:
A study compared cytokine, humoral, and cellular immune responses in pediatric and adult patients with COVID-19 at a hospital system in New York City. Serum levels of IL-17A and IFN-γ, but not TNF-α or IL-6, were inversely related to age. Adults mounted a more robust T cell response to the viral spike protein compared to pediatric patients, suggesting that severe disease in adults is not due to a failure in adaptive immunity.
https://stm.sciencemag.org/content/early/2020/09/21/scitranslmed.abd5487

Interferon-related autoantibodies and genes: Two papers published in *Science* this week reveal that in a significant minority of patients with serious COVID-19, the interferon response is impaired by genetic flaws or by autoantibodies that attack interferon itself. Together, these two papers explain nearly 14% of severe cases.
The first study examined blood samples from 987 gravely ill patients from around the world. In 10.2% of the patients, the researchers identified antibodies that bind to and neutralize the patients' own type I interferon. None of the 663 people in a control group with mild or asymptomatic SARS-CoV-2 infection had those autoantibodies. 94% of the patients with interferon-attacking antibodies were male, suggesting it could be an X-linked recessive trait. These findings have implications for plasma donations from recovered patients.
The second study found that 3.5% of the critically ill patients harbored rare mutations in eight of 13 genes analysed, all of them involved in IFN-I responses. These findings are the 1st published results from the COVID Human Genetic Effort, an international project spanning more than 50 genetic sequencing hubs and hundreds of hospitals, in which researchers from CSIC, Spain, also participated.
https://www.sciencemag.org/news/2020/09/hidden-immune-weakness-found-14-gravely-ill-covid-19-patients

Antibodies / Immunity
A seroprevalence preprint study suggested that some regions in the Brazilian Amazon could be close to herd immunity and that this may have played a role in determining the size of the epidemic. In June, one month following the epidemic peak, 44% of the population in Manaus was seropositive for SARS-CoV-2, equating to a cumulative incidence of 52%, after correcting for the false-negative rate of the antibody test.
https://www.medrxiv.org/content/10.1101/2020.09.16.20194787v1
However, a fresh surge in cases dashes hopes that Manaus has achieved herd immunity
https://news.trust.org/item/20200927110833-uqdcv/

The German Ethics Council currently advises against Covid-19 immunity certificates, given the many uncertainties that still exist regarding immunity to the virus. (Thanks Kurt Straif for the info!) https://www.ethikrat.org/en/press-releases/2020/german-ethics-council-currently-advises-against-covid-19-immunity-certificates/

Reinfections:
The ECDC publishes a Threat Assessment Brief on reinfections with SARS-CoV-2. It reviews data on the six reported reinfections to date: all were in relatively young, immunocompetent individuals. Four were symptomatic and two were asymptomatic in the first episode. For the second infection, three were likely asymptomatic, one showed mild symptoms, one showed moderate symptoms and one required hospitalisation with oxygen support. In the six cases there has been no evidence of onward transmission to any close contacts. Testing of individuals that had a previous infection for SARS-CoV-2, if they are again exposed to a COVID-19 case, would not only inform individual case assessments but also improve the current limited evidence on re-infection risk.
https://www.ecdc.europa.eu/sites/default/files/documents/Re-infection-and-viral-shedding-threat-assessment-brief.pdf

Another reinfection case (Seattle, US) is described in a pre-print study. The findings suggest that low levels of antibodies against the D614 virus formed after primary infection in March were not protective against reinfection with the D614G spike variant acquired in July. Disease was milder upon reinfection.
https://www.medrxiv.org/content/10.1101/2020.09.22.20192443v1.full.pdf

A review on the science and medicine of human immunology discusses new strategies and technologies to directly explore the human immune system and how these approaches are facilitating the development of vaccines and therapeutics for infection, autoimmune diseases, and cancer. A good state-of-the-art read on immunology. https://science.sciencemag.org/content/369/6511/eaay4014

Treatment

mAbs: *Science* reports the isolation and characterization of two ultrapotent SARS-CoV-2 human neutralizing antibodies (S2E12 and S2M11) that protect hamsters against SARS-CoV-2 challenge. The cryo-EM structure reveals why they work so well and paves the way to using antibody cocktails that circumvent viral escape mutants. https://science.sciencemag.org/content/early/2020/09/23/science.abe3354

Among 598 human monoclonal antibodies (mAbs) from ten COVID-19 patients, 40 strongly neutralizing mAbs were identified. The most potent one (mAb CV07-209) protected hamsters from SARS-CoV-2 infection, weight loss and lung pathology. https://www.cell.com/cell/fulltext/S0092-8674(20)31246-0

Tocilizumab: Roche's phase III EMPACTA study showed tocilizumab (Actemra/RoActemra) reduced the likelihood of needing mechanical ventilation in hospitalised patients with COVID-19 associated pneumonia, although there was no statistical difference in mortality. EMPACTA is the first global phase III trial to show the drug's efficacy in COVID-19 associated pneumonia and the first with a focus on enrolling largely underserved and minority patients. https://apnews.com/1f17825984f734b19904ed2cbb7035d8

Ivermectin had no beneficial effect on the disease course over usual care in mild to moderate COVID-19 cases in a single centre study. https://www.researchgate.net/publication/344240147_Outcome_of_ivermectin_treated_mild_to_moderate_COVID-19_cases_a_single-centre_open-label_randomised_controlled_study

Of the >2,000 planned studies examining COVID-19 treatments, most have delivered little or no directly useful information, according to *Nat Med*. Exceptions include two large, adaptive trials- RECOVERY and SOLIDARITY- which combined have randomized >20,000 patients to assess the effects of several treatments on mortality, and the NIH's ACTT trial, which randomized 1,059 patients to assess the effect of remdesivir on time to disease resolution. https://www.nature.com/articles/s41591-020-1077-z

Vaccines

Novavax has started a phase 3 clinical trial in UK for its recombinant nanoparticle vaccine constructed from the full-length SARS-CoV-2 spike glycoprotein based on recombinant full-length Spike protein and the M-matrix adjuvant. Ten thousand people will take part in the trial and at least a quarter of them will be over 65, the age-group most at risk of severe Covid-19. https://www.wsj.com/articles/covid-19-vaccine-from-novavax-begins-phase-3-trial-in-u-k-11600980636

UK will host the world's first Covid-19 human challenge trials — in which young, healthy volunteers are vaccinated and then deliberately infected with coronavirus to assess the effectiveness of experimental vaccines. About 2,000 potential volunteers have

signed up for challenge studies, which should start next January. The ethics of these trials has been questioned, given there is no effective treatment if things go wrong. https://www.ft.com/content/b782f666-6847-4487-986c-56d3f5e46c0b

A comment in *The Lancet* reviews what we can expect from the first generation of COVID vaccines. It is probable that, even if effective in reducing disease, they will not reduce virus transmission to a comparable degree. Therefore, it will be important to communicate to policy makers and the general public that first-generation vaccines "are only one tool in the overall public health response and unlikely to be the ultimate solution that many expect".
https://www.thelancet.com/journals/lancet/article/PIIS0140-6736(20)31976-0/fulltext
Meanwhile, the share of Americans eager to try a first-generation coronavirus vaccine dropped significantly over the last month, according to an Axios-Ipsos survey.
https://www.axios.com/axios-ipsos-poll-coronavirus-index-vaccine-doubts-e9205f29-8c18-4980-b920-a25b81eebd84.html

Florian Krammer reviews the SARS-CoV-2 vaccines in development
https://www.nature.com/articles/s41586-020-2798-3

The WHO released guidance for Emergency Listing of COVID19 vaccines, which are stricter than those by FDA USA. Only vaccines that have undergone phase IIb or phase III studies and have received authorization from a reference NRA should be submitted for consideration.
https://www.who.int/medicines/regulation/prequalification/prequal-vaccines/WHO_evaluation_covid_vaccine/en/

A total of 156 countries (64 high-income nations, including the UK, Australia, Canada, Japan and 29 economies operating as Team Europe) have joined COVAX, in an effort to expand global access to Covid-19 vaccines. These countries represent 64% of the world population. An additional 38 countries are expected to sign soon. The US, Russia and China have not joined. So far, $700 million has been raised to pay for the vaccine in lower income countries, short of the $2 billion thought to be needed by the end of the year.
https://www.gavi.org/sites/default/files/covid/pr/COVAX_CA_COIP_List_COVAX_PR_V5.pdf
See also: https://www.sciencemag.org/news/2020/09/who-unveils-global-plan-fairly-distribute-covid-19-vaccine-challenges-await

In a speech to the General Assembly, the Russian president offered to provide UN staff the Sputnik-V vaccine https://apnews.com/6947b719b2cbbd6a06926971db82d3b2

Others
Women are 3X more likely to suffer from mental health impact during the COVID-19 pandemic, shows a survey released by the non-profit CARE *(via Global Health Now)*
https://www.care.org/wp-content/uploads/2020/09/RGA_SheToldUsSo_9.18.20.pdf

Birds: Recordings of bird songs performed during the lockdowns show that, in just a matter of weeks, sparrows' songs recovered the acoustic quality of songs sung decades ago, when city life was less noisy. https://www.sciencemag.org/news/2020/09/when-covid-19-silenced-cities-birdsong-recaptured-its-former-glory

ISGlobal

COVID-19 EPIDEMIC

Epidemiological situation (05/10/2020, ECDC data):

Globally:
35 247 104 confirmed cases and 1 038 069 deaths

- India, the USA and Brazil remain the most affected countries, accounting for over half (54.3%) of all confirmed cases globally and 48.7% of all newly confirmed cases in the past 24 hours.
- Other countries reporting more than 5000 newly confirmed cases in the past 24 hours include Spain, Argentina, France, Russia, UK, and Colombia (Oct 2)

Confinement and deconfinement measures

Europe's second wave:
Madrid (with an infection rate of 700 cases per 100,000 people) has entered a local lockdown with travel restricted to essential journeys. Bars and restaurants cannot serve after 20:00 and people cannot meet in groups larger than six. Spain's average infection rate (300 per 100,000) is the highest in all Europe.
Paris will shut all bars completely from tomorrow as the French government raises the city's coronavirus alert to maximum, following a sustained period of high infection rates. On Sunday France reported 12,565 cases of Covid-19, with an infection rate of 250 per 100,000 people and at least 30% of intensive care beds occupied.
The Czech Republic has also introduced a state of emergency as the government struggles to control a resurgence in coronavirus.
Italy has also said it will probably introduce new measures to control the virus in the coming week, as infection rates rise. https://www.bbc.com/news/world-europe-54413563

The official COVID-19 deaths are surely an underestimate, and if current trends continue, by next January the total number of deaths will reach 2.5 million. This figure could be cut to 1.8 million if every country adopts universal mask-wearing, according to LSHTM projections. https://www.nature.com/articles/d41586-020-02762-y

Transmission

Small time-window: A new analysis shows that during the early months of the COVID pandemic, the average basic reproduction number (R0) was 4.5, double that estimated initially by the WHO. At that rate, governments had just 20 days from the first reported cases to implement stringent non-pharmaceutical interventions to reduce the transmission rate to below 1.1. If the R0 remained above 2.7 for 44 days or more, as was the case in many countries, any subsequent interventions were likely to be ineffective. https://journals.plos.org/plosone/article?id=10.1371/journal.pone.0239800

India: A massive study with data from the Indian states of Tamil Nadu and Andhra Pradesh shows that reported cases and deaths have been concentrated in younger cohorts than expected from observations in higher-income countries, even after accounting for demographic differences. Case-fatality ratios spanned 0.05% at ages 5-17 years to 16.6% at ages ≥85 years. The study confirms the Pareto 80/20 rule for

SARS-CoV-2 transmission: 77% of cases did not transmit. The chances of an infected person (regardless of age) passing it on to a close contact ranged from 2.6% in the community to 9% in the household.
https://science.sciencemag.org/content/early/2020/09/29/science.abd7672

In flight: A LSHTM study identifies a cluster of COVID-19 transmissions which occurred on a 15-hour flight from Boston to Hong Kong. All four cases shared an identical viral sequence. This was in mid-February, before the use of face masks was mandatory. (*Thanks for the tip, Berta Grau!)*
https://wwwnc.cdc.gov/eid/article/26/11/20-3254_article

Two sequential studies in Italy (one in an infectious disease ward and one in emergency rooms) were unable to culture infectious virus from swabbed fomites and surfaces, supporting the notion that transmission through inanimate surfaces is less frequent than previously thought. https://www.thelancet.com/journals/laninf/article/PIIS1473-3099(20)30678-2/fulltext

Testing / Tracing

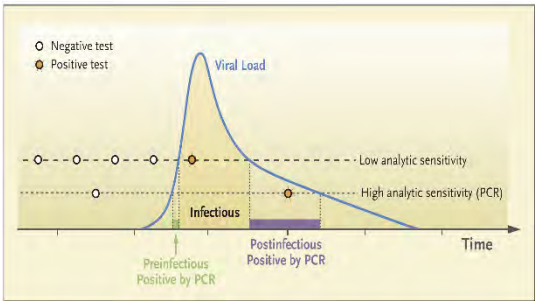
CT Threshold: A study with 3,800 qPCR positive samples found that 70% of samples with CT values of 25 or below could be cultured, compared with less than 3% of those with CT values above 35. https://academic.oup.com/cid/advance-article/doi/10.1093/cid/ciaa1491/5912603
This opens a debate on whether to add- or not- the cycle threshold (CT) value in the SARS-CoV-2 PCR report, as an indicator of how infectious that person may be.
https://www.sciencemag.org/news/2020/09/one-number-could-help-reveal-how-infectious-covid-19-patient-should-test-results

Rapid tests for LMICs: As part of the WHO-led ACT Accelerator, Abbott and SD Biosensor have agreed with the Bill and Melinda Gates Foundation to produce 120 million of rapid antigen tests to be distributed to 133 LMICs, including many in Latin America, the region hardest-hit by the pandemic in terms of fatality and infection rates.
https://www.bbc.com/news/world-54331921

A team of scientists at the Delhi-based CSIR-Institute of Genomics and Integrative Biology (IGIB) has developed an inexpensive paper-based test for coronavirus that could give fast results similar to a pregnancy test. The CRISPR-based Feluda test has 96% sensitivity and 98% specificity. https://www.bbc.com/news/world-asia-india-54338864

SalivaDirect is a highly sensitive molecular diagnostic test with a limit of detection of 6-12 SARS-CoV-2 copies/µL, according to a study performed in partnership with the National Basketball Association including over 3,700 players. High agreement between nasal swabs and saliva was found. The test, which has received Emergency Use Authorisation by the FDA, is an easy and inexpensive ($1.21-$4.39/sample) option to improve SARS-CoV-2 testing capacity.
https://www.medrxiv.org/content/10.1101/2020.08.03.20167791v2

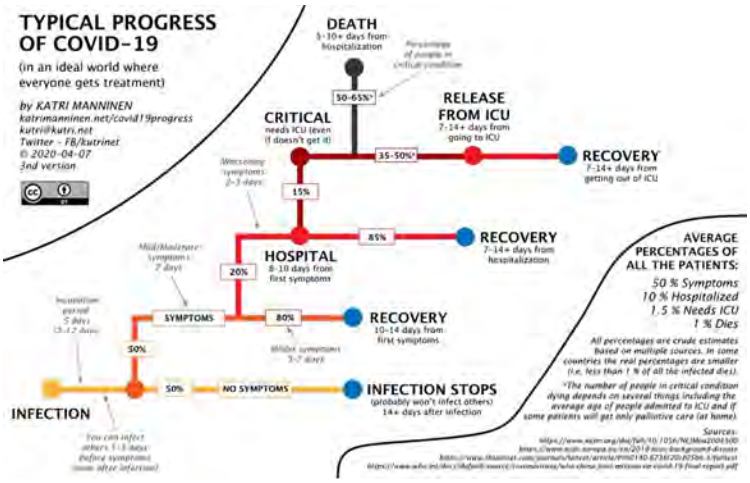
A perspective in *NEJM* stresses the need to shift from focusing on the sensitivity of a test (its ability to correctly detect small concentrations of virus in a sample) to its sensitivity to detect infections (the probability that infected persons learn they're infected in time to be isolated and prevent spread to others).
https://www.nejm.org/doi/full/10.1056/NEJMp2025631



And a *PNAS* comment argues that rapid tests at home and primary health care settings would be game changers. *However, rapid testing must be accompanied by effective contact tracing and isolation in order to make a difference.*
https://www.pnas.org/content/early/2020/09/29/2019062117

Along this line, I highly recommend this read on SARS-CoV-2 superspread cluster transmission, the importance of the dispersion measure (k), and the value of reverse contact tracing: https://www.theatlantic.com/health/archive/2020/09/k-overlooked-variable-driving-pandemic/616548/

Symptoms / Risk factors
This useful schema resumes the typical progress of COVID-19:



Cardiac arrest: In one study in Michigan, 60 (4.6%) of 1309 patients hospitalized with COVID-19 developed cardiac arrest. In another multicentre study, 701 (14%) of 5019 critically ill patients with covid-19 had in-hospital cardiac arrest. In both studies, mortality after CPR was high.
https://jamanetwork.com/journals/jamainternalmedicine/fullarticle/2771090
https://www.bmj.com/content/371/bmj.m3513

Parkinson's: A case of probable Parkinson's disease after severe SARS-CoV-2 infection is reported. Treatment with pramipexole resulted in a quick improvement according to the patient's subjective impression, as well as in clinical signs.
https://www.thelancet.com/journals/laneur/article/PIIS1474-4422(20)30305-7/fulltext

See also this perspective, which concludes that it will be important to follow up and clinically monitor COVID-19 patients, particularly those who developed specific neurological disturbances. https://www.nature.com/articles/s41531-020-00123-0

The first report of three men with spinal cord dysfunction after COVID-19 suggests that two of the cases were likely related to treatment with tocilizumab. https://www.nature.com/articles/s41394-020-00341-x

A prospective autopsy cohort study done in the Netherlands reveals an extensive systemic inflammatory response, with a continued presence of neutrophils and neutrophil extracellular traps. Few SARS-CoV-2-infected cells were present at late stages of the disease, which supports immunomodulation for the treatment of severe COVID-19. https://www.thelancet.com/journals/lanmic/article/PIIS2666-5247(20)30144-0/fulltext

A case series of multisystem inflammatory syndrome in adults associated with SARS-CoV-2 infection is described. Antibody testing was required to identify infection in one-third of 27 cases. https://www.cdc.gov/mmwr/volumes/69/wr/mm6940e1.htm?s_cid=mm6940e1_w

Data from 213 hospitals worldwide provides an estimate for mortality among patients requiring extracorporeal membrane oxygenation: mortality was 37.4% after 90 days in hospital and 39% at hospital discharge. https://www.thelancet.com/journals/lancet/article/PIIS0140-6736(20)32008-0/fulltext

Obesity: A recent metaanalysis of obesity and covid-19 estimates that people with obesity who contracted SARS-CoV-2 were 113% more likely than people of healthy weight to be hospitalized, 74% more likely to be admitted to an ICU, and 48% more likely to die. https://onlinelibrary.wiley.com/doi/full/10.1111/obr.13128

Neanderthal DNA: A recent genetic association study identified a gene cluster on chromosome 3 as a risk locus for severe COVID-19. A new study now shows that the genomic segment of ~50 kb is inherited from Neanderthals and is carried by ~50% of people in South Asia and ~16% of people in Europe today. https://www.nature.com/articles/s41586-020-2818-3

Antibodies / Immunity

Antibody diversity: Using a tool called VirScan to perform deep serological profiling, Harvard researchers revealed over 800 epitopes in the SARS-CoV-2 proteome, including 10 epitopes likely recognized by neutralizing antibodies. They used these to develop a rapid Luminex-based diagnostic tool of cross-reactivity and disease severity. https://science.sciencemag.org/content/early/2020/09/28/science.abd4250

T cell diversity- the more, the better: A new study shows that diversity of SARS-CoV-2 T cell responses was associated with mild symptoms of COVID-19, providing evidence that immunity requires recognition of multiple epitopes. These findings should guide selection of T cell epitopes for the design of multi-peptide vaccines. The study also shows that SARS-CoV-2 T cell epitopes enabled detection of post-infectious T cell immunity in 100% of COVID-19 convalescent individuals (even if they were seronegative), and revealed pre-existing T cell responses in 81% of unexposed individuals. https://www.nature.com/articles/s41590-020-00808-x

T cells – superantigen-like activation? A study shows that SARS-CoV-2 spike contains sequence and structure motifs highly similar to those of a bacterial superantigen and may directly bind T cell receptors, as in toxic shock syndrome. A skewed TCR repertoire observed in COVID-19 patients with severe hyperinflammation supports this hypothesis. Notably, other coronaviruses lack this superantigen-like motif.
https://www.pnas.org/content/early/2020/09/25/2010722117

Mucosa-associated invariant T (MAIT) cells function as pathogen sensors and can act as mediators of antiviral responses. A study shows a strong activation and profound decline of MAIT cells in severe disease, suggesting these cells are engaged in the immune response against SARS-CoV-2 and may be involved in COVID-19 immunopathogenesis.
https://immunology.sciencemag.org/content/5/51/eabe1670.full

Reinfections: India reports asymptomatic reinfection in two healthcare workers
https://academic.oup.com/cid/advance-article/doi/10.1093/cid/ciaa1451/5910388
A case study suggests that low levels of neutralizing antibodies upon the first infection may help explain a lack of protection to a second infection (which was milder).
https://www.medrxiv.org/content/10.1101/2020.09.22.20192443v1

Treatment

mAbs: Regeneron Pharmaceuticals revealed early results for its cocktail of two synthetic monoclonal antibodies that attach to the Spike of SARS-CoV-2 and block it from infecting cells. The cocktail reduced the amount of virus in nasopharyngeal swabs and alleviated symptoms more quickly, particularly in patients who were seronegative (did not have SARS-CoV-2 antibodies) and had highest viral loads at the trial's start. Eli Lilly reported similar results for its antibody cocktail two weeks ago.
https://www.sciencemag.org/news/2020/09/provocative-results-boost-hopes-antibody-treatment-covid-19
Although synthetic antibody cocktails are promising (Regeneron's drug was given to Donald Trump), many experts worry that they may only be available to a select few, given the cost and challenge of upscaling their production.

An intranasal spray developed to boost the innate immune system to fight common colds and flu reduced SARS-CoV-2 viral RNA levels in nose and throat by up to 96% when tested in ferrets. The product (INNA-051) is a TLR2/6 agonist developed by the Australian biotech Ena Respiratory, and could be used as a prophylaxis to block viral transmission and provide protection against COVID-19.
https://www.biorxiv.org/content/10.1101/2020.09.25.309914v1.full

GABA administration prevented pneumonitis in mice challenged with coronavirus mouse hepatitis virus (MHV)-1, which shares pathological features with COVID-19. The preprint study concludes that GABA-R agonists, like GABA and homotaurine, are safe, stable, inexpensive, and available worldwide, and could be promising candidates to help prevent severe illness stemming from SARS-CoV-2 infection.
https://www.biorxiv.org/content/10.1101/2020.10.04.325423v1

A brief report describes the "carnage of substandard research" during the COVID-19 pandemic. It identifies 33 papers as unsuitable for public use and either retracted, withdrawn, or noted with concern. Asia is the source of most of these manuscripts (n=19; 57.6%) with China the largest Asian subgroup (n=11; 57.9%). *(Thanks for the tip, Kurt Straif!)* https://jme.bmj.com/content/early/2020/09/09/medethics-2020-106494

Vaccines

Older adults: In a small study involving older adults (over 55y), adverse events associated with Moderna's mRNA-1273 vaccine were mainly mild or moderate. The 100-µg dose induced binding- and neutralizing-antibody titers similar to those in the 18-55 year-old group and higher than the median observed in convalescent plasma. https://www.nejm.org/doi/full/10.1056/NEJMoa2028436

Vaccine efficacy – what does it mean?: While Pfizer and the other companies with trials underway are using mild symptoms and a positive Covid-19 test as their primary end points, severe illness would probably be a better primary end point, says an article in *The Atlantic*. https://www.wired.com/story/what-does-it-mean-if-a-vaccine-is-successful/

Vaccine development updates (via *nyt coronavirus vaccine tracker*):
• Thailand's Chula Vaccine Research Center enters Phase 1 for its mRNA vaccine
• The German Center for Infection Research's MVA-based vaccine enters Phase 1.
• Inovio's Phase 2/3 clinical trial is on hold because of questions about the vaccine delivery device.

The LSHTM has developed a detailed online vaccine tracker to follow candidates as they progress through the development pipeline. https://vac-lshtm.shinyapps.io/ncov_vaccine_landscape/

Others

Air pollution and COVID-19: Long-term exposure to NO2 may enhance susceptibility to severe COVID-19 outcomes, independent of long-term PM2.5 and O3 exposure, according to a study that analysed COVID-19 case-fatality and mortality rates in the US. https://www.cell.com/the-innovation/fulltext/S2666-6758(20)30050-3
Another nationwide, cross-sectional study shows that an increase of only 1 µg/m3 in PM2.5 is associated with an 8% increase in the COVID-19 death rate.
https://projects.iq.harvard.edu/covid-pm/home *(Thanks for the tips, Joan Ballester!)*

ISGlobal

COVID-19 EPIDEMIC

Epidemiological situation (12/10/2020, ECDC data):

Globally:
37 568 843 confirmed cases and 1 077 508 deaths

- About 10% of the global population may have been infected with SARS-CoV2, according to the WHO. That's more than 20X the number of confirmed cases.

Confinement and deconfinement measures

Second wave Europe:
Europe is struggling to contain new outbreaks as just 4 countries—Germany, Finland, Cyprus, and Norway—are reporting case numbers below the European CDC's critical threshold of 20 cases per 100,000 people on a seven-day average.
France reported a record 20,000 new cases on Friday.
https://edition.cnn.com/2020/10/05/europe/ursula-von-der-leyen-self-isolates-intl/index.html

Virus

Cryo-electron tomography shows that the spike protein is flexibly connected to the viral surface by three hinges that allow it to scan the host cell surface, while shielded from antibodies by an extensive glycan coat.
https://science.sciencemag.org/content/370/6513/203

Transmission

A CDC report analysing transmission dynamics confirms previous observations: in hotspot US counties, particularly those in the South and West, percent positivity increased earliest in younger persons, followed by several weeks of increasing percent positivity among older age groups.
https://www.cdc.gov/mmwr/volumes/69/wr/mm6941e1.htm?s_cid=mm6941e1_w

A letter in *Science* stresses transmission of SARSCoV2 through aerosols (size < 100 µm). Aerosols containing infectious virus can travel more than 2 m and accumulate in poorly ventilated indoor air, leading to superspreading events. Clear guidance about the importance of moving activities outdoors, improving indoor air using ventilation and filtration, and improving protection for high-risk workers is needed.
https://science.sciencemag.org/content/early/2020/10/02/science.abf0521

A thorough *Nature* feature reviews what the data say about face masks. Baseline: there is enough evidence that they save lives. https://www.nature.com/articles/d41586-020-02801-8

A study that measured the survival rates of infectious SARS-CoV-2 on different surfaces and at different temperatures shows that SARS-CoV-2 can remain infectious for significantly longer time periods than generally considered possible (up to 28d at 20°C). Experiments however were performed in the dark (no UV light effect).
https://link.springer.com/epdf/10.1186/s12985-020-01418-7

Testing / Tracing
Rapid molecular tests: A team led by Jennifer Doudna, who shared this year's Nobel Prize in Chemistry for her co-discovery of CRISPR, developed a novel CRISPR-based diagnostic that doesn't need to preamplify coronavirus RNA. With one single guide RNA, it can detect as few as 100,000 viruses /ul. By adding a second guide RNA, it can detect as few as 100 viruses /ul. Although still less sensitive than PCR, it can give results in 5 minutes with a mobile phone readout, and can quantify the amount of virus (the intensity of the fluorescent signal is proportional to the initial amount of RNA). https://www.medrxiv.org/content/10.1101/2020.09.28.20201947v1

ELISA profiling on saliva and serum from acute and convalescent patients shows that serum and saliva IgG antibodies to SARS-CoV-2 are maintained in the majority of COVID-19 patients for at least 3 months post-symptom onset, and that IgG responses in saliva may serve as a surrogate measure of systemic immunity to SARS-CoV-2. https://immunology.sciencemag.org/content/5/52/eabe5511
Saliva could therefore be used to test both for viral RNA and for antibodies.

I recommend this NYT's simple and well-illustrated explanation on the timing of viral load, tests, symptoms, immunity, and treatment of COVID-19. https://www.nytimes.com/interactive/2020/10/05/science/charting-a-covid-immune-response.html

Symptoms / Risk factors
A study in macaques reveals critical interactions between inflammatory and thrombosis pathways leading to SARS-CoV-2 induced vascular disease: disruption of endothelium via cytokines, and involvement of complement and lung macrophage infiltration. https://www.cell.com/cell/fulltext/S0092-8674(20)31311-8

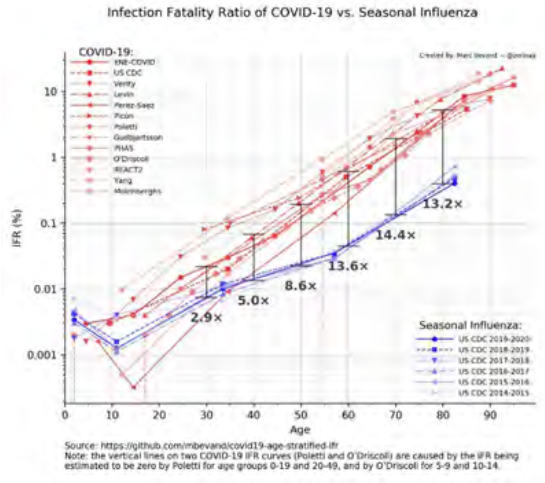
A post-mortem analysis of brains from 43 deceased COVID-19 patient concludes that neuropathological changes in these patients seem to be mild, with pronounced neuroinflammatory changes in the brainstem being the most common finding. SARS-CoV-2 could be detected in the brains of 53% of examined patients but this was not associated with the severity of neuropathological changes. https://www.thelancet.com/journals/laneur/article/PIIS1474-4422(20)30308-2/fulltext

A study shows that neutrophil proteases, which can modulate cytokine activity, may explain why some people come down with a cold and others not, and could provide therapeutic targets for respiratory syncytial virus and other respiratory infections including SARS-CoV2. https://science.sciencemag.org/content/370/6513/eaba9301

Long COVID: A good summary describes what is known about the long-term health consequences of COVID-19. The most commonly reported symptoms after acute COVID-19 are fatigue and dyspnea, followed by joint pain and chest pain. Cardiovascular, pulmonary and neurologic sequelae are also observed among recovered patients, even among those who had mild symptoms. https://jamanetwork.com/journals/jama/fullarticle/2771581

Risk factors: Being a man, having a lower income, having a lower level of education, not being married, and being born abroad in low- or middle-income countries are factors that are independently related to an elevated risk of dying from COVID-19 in Sweden, according to a population-based cohort analysing over 17,000 COVID-19 deaths. https://www.nature.com/articles/s41467-020-18926-3

This image comparing IFR of seasonal influenza vs COVID-19 across age is quite enlightening. COVID-19 mortality is significantly higher from age 35 onwards.



Antibodies / Immunity

Abnormal B cell activation: A detailed flow cytometry analysis shows that critically ill patients displayed hallmarks of extrafollicular B cell activation and high concentrations of neutralizing antibody titers. These findings suggest a pathogenic role for immune activation in certain subsets of patients. https://www.nature.com/articles/s41590-020-00814-z

Some SARS-CoV-2 antibodies may cross react with mammalian proteins (such as self-glycolipids on peripheral nerves) and could contribute to neuropathology during and after COVID-19 disease. https://www.nature.com/articles/s41577-020-00458-y

Maternally-derived abs: A study that analysed SARS-CoV-2 antibody levels in serum samples from 1,471 mother/newborn dyads found efficient transplacental transfer of SARS-CoV-2 IgG antibodies in 72 of 83 seropositive pregnant women, including those with asymptomatic infections. These finding suggest that maternal antibodies could provide neonatal protection from SARS-CoV-2 infection.
https://www.medrxiv.org/content/10.1101/2020.10.07.20207480v1

Reduced Treg? A single-cell transcriptomic analysis of >100,000 SARS-CoV-2-reactive CD4+ T cells in hospitalised vs non-hospitalised patients shows a strong cytotoxic Tfh response early in illness and reduced regulatory CD4+ T cells in the former, as compared to the latter. https://www.cell.com/cell/fulltext/S0092-8674(20)31307-6#%20

Cross-protective immunity? A study with 343 North American patients infected with SARS-CoV-2 (of which 93% required hospitalization) shows that anti-RBD IgG responses decayed slowly through 90 days with only 3 seropositive individuals seroreverting within this time period. IgG antibodies to SARS-CoV-2 RBD were strongly correlated with anti-S neutralizing antibody titers, which demonstrated little to no decrease over 75 days since symptom onset. No cross-reactivity of the SARS-CoV-2 RBD-specific antibodies with other widely circulating coronaviruses (HKU1, 229 E, OC43, NL63) was observed.
https://immunology.sciencemag.org/content/5/52/eabe0367

While another study suggests that pre-existing immune responses against endemic human coronaviruses can mitigate disease manifestations from SARS-CoV-2 infection. *(Thanks for both tips, Kurt Straif!)* https://www.jci.org/articles/view/143380

Cross-reactive T cells: Lipstich and colleagues propose four immunological scenarios for the impact of cross-reactive CD4+ memory T cells on COVID-19 severity and viral transmission, and their implications on herd immunity. Different scenarios could apply to different individuals. https://www.nature.com/articles/s41577-020-00460-4

A comment in *Nature* rightly points out that presence of SARS-CoV-2 reactive T cells in unexposed humans does not equal protective immunity. At the moment it is unclear whether these pre-existing cross-reactive T-cells ameliorate or worsen COVID-19. https://www.nature.com/articles/s41392-020-00338-w

Treatment

Remdesivir: The *NEJM* publishes the final report of the double-blind, randomized, placebo-controlled trial of intravenous remdesivir in adults hospitalized with Covid-19. Those who received remdesivir (541 patients) had a median recovery time of 10 days, as compared with 15 days for those (n=521) who received placebo. Mortality was 6.7% with remdesivir and 11.9% with placebo by day 15, and 11.4% with remdesivir and 15.2% with placebo by day 29. https://www.nejm.org/doi/10.1056/NEJMoa2007764

Remdesivir plus Baricitinib: Eli Lilly announced that fewer deaths were reported among COVID-19 patients taking a combination of its rheumatoid arthritis drug (baricitinib) and Gilead's remdesivir, as compared with patients treated with remdesivir alone (5.1% versus 7.8% at day 29). The effect was most pronounced in patients on oxygen therapy. Baricitinib could help supress the cytokine storm. https://www.reuters.com/article/us-health-coronavirus-lilly-arthritis/lillys-rheumatoid-arthritis-drug-cuts-covid-19-deaths-in-trial-data-shows-idUSKBN26T31C

Monoclonal Ab cocktails: Eli Lilly also announced preliminary results for its cocktail of two mAbs in non-hospitalised COVID-19 patients (it had previously announced promising results for a similar treatment using one antibody). A preliminary analysis shows the antibody combination significantly reduced the amount of virus in nasal swabs of patients after 11 days. The treatment also improved symptoms, according to a scored questionnaire, and resulted in less hospital visits for those who received the cocktail (0.9%) versus placebo (5.8%).
Lilly said it could have as many as 1M doses of its one-antibody treatment, LY-CoV555, by the fourth quarter of 2020, but only 50,000 doses for the combination therapy. https://www.statnews.com/2020/10/07/eli-lilly-monoclonal-antibody-cocktail-covid-19/ *There are no phase 3 clinical trial efficacy results for mAbs for the moment.*

An Italian group identified over 200 neutralizing IgG antibodies after single cell sorting of 4277 SARS–CoV–2 spike protein specific memory B cells from 14 Covid–19 survivors. Findings show that potent neutralizing antibodies are rare (1%) and recognize the RBD, followed in potency by antibodies that recognize the S1 domain, the S-protein trimeric structure and the S2 subunit. The three most potent mAbs were able to neutralize the wild type and D614G mutant viruses with less than 10 ng/mL and are potential prophylactic and therapeutic candidates.
https://www.biorxiv.org/content/10.1101/2020.10.07.328302v1

RECOVERY results: The RECOVERY trial (UK) shows that lopinavir/ritonavir (an HIV drug) is not an effective treatment for patients admitted to hospital with COVID-19. The randomised, controlled, open-label, trial included 1616 patients that received

lopinavir–ritonavir and 3424 patients that received usual care. The drug was not associated with reductions in 28-day mortality, duration of hospital stay, or risk of progressing to invasive mechanical ventilation or death.
https://www.thelancet.com/journals/lancet/article/PIIS0140-6736(20)32013-4/fulltext
The *NEJM* publishes also the final data for the UK RECOVERY trial to test hycroxychloroquine. Among patients hospitalized with Covid-19, those who received the durg did not have a lower incidence of death at 28 days than those who received usual care. https://www.nejm.org/doi/full/10.1056/NEJMoa2022926

Vaccines
China has joined the COVAX Facility. Russia and US have not.
https://www.ft.com/content/f4c6b81c-3014-4bbd-b4bd-02dd75f03fad

The White House has finally agreed to the new, stricter FDA guidelines for COVID-19 vaccines. Manufacturers are asked to provide at least 2 months of safety data before applying for an EUA, which likely means a vaccine won't be ready for wide use before election day. See the guidelines here: https://www.fda.gov/regulatory-information/search-fda-guidance-documents/emergency-use-authorization-vaccines-prevent-covid-19

EMA's human medicines committee (CHMP) has started a 'rolling review' of data for two vaccines: the Astra Zeneca/ Oxford candidate, based on a chimp adenoviral vector, and BNT162b2, the mRNA vaccine which is being developed by BioNTech in collaboration with Pfizer. The rolling reviews will continue until enough evidence is available to support a formal marketing authorisation application.
https://www.ema.europa.eu/en/news/ema-starts-second-rolling-review-covid-19-vaccine

ISGlobal

COVID-19 EPIDEMIC

Epidemiological situation (19/10/2020, ECDC data):

Globally:
40 106 965 confirmed cases and 1 114 636 deaths

- The Americas reported 37.4% of daily case numbers and 50.0% of daily deaths in the past 24 hours, maintaining its position as the most severely affected region
- COVID-19 is now the 5th-leading cause of death in Europe, where 1 million new cases were recorded in just 10 days
- China is to test 9 million people for COVID-19 this week as new outbreak emerges
- Globally, influenza activity remained at lower levels than expected for this time of the year https://www.who.int/influenza/surveillance_monitoring/updates/latest_update_GIP_surveillance/en/

Confinement and deconfinement measures
The European Union has introduced a traffic light system for travellers, with color-coded zones based on risk levels:

- Green for regions reporting < 25 new infections per 100,000 inhabitants, and test positivity below 4%
- Orange for regions reporting < 50 new infections, and test positivity over 4%, or incidence between 25 and 150 and test positivity below 4%
- Red is for regions with > 50 new infections per 100,000 inhabitants, and test positivity > 4% — or incidence > 150 per 100,000 in the past 14 days

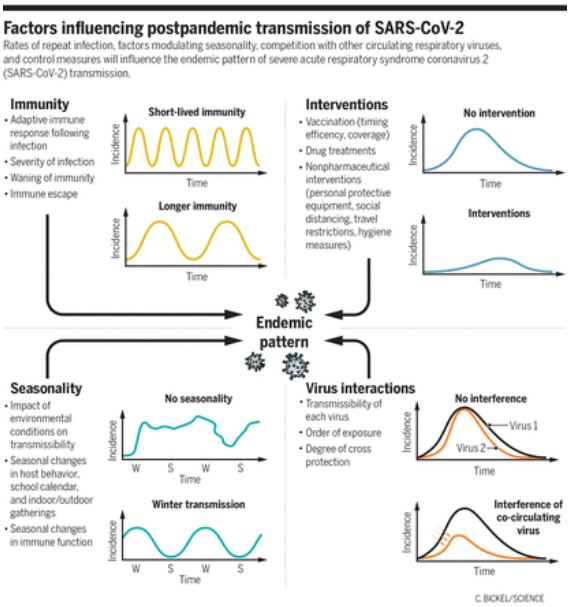
Some of Europe's latest restrictions include: Italy forbids drinking outside of restaurants and bars after 6pm. France imposed a nightly curfew in 9 cities including Paris. Wales will enter a national lockdown starting Friday. In Spain, some areas have imposed partial confinements while others have closed bars and restaurants.
The UK government's scientific advisers (SAGE) called for a short lockdown in England to halt the spread of Covid-19 already in September. They proposed an immediate "circuit breaker" as the best way to control cases. *(Thanks for the tip, Kurt Straif!)*

Barrington versus John Snow: A group of epidemiologists and public health experts have expressed grave concerns about the damaging physical and mental health impacts of the prevailing COVID-19 policies, and recommend an approach called focused protection while letting the population reach herd immunity (the Great Barrington Declaration) https://gbdeclaration.org/ This declaration has raised strong opposition, reflected in the John Snow Memorandum signed by over 4000 scientists, arguing that any pandemic management strategy relying upon immunity from natural infections for COVID-19 is flawed and will cost many lives https://www.johnsnowmemo.com/

Virus
A study in *Science* identifies commonalities among coronaviruses and highlights several shared cellular processes and protein targets that should be considered as

targets for therapeutic interventions for current and future pandemics.
https://science.sciencemag.org/content/early/2020/10/14/science.abe9403

Transmission
Reinfection, seasonality, and viral competition will shape endemic transmission patterns of SARS-CoV-2, according to an analysis in Science. Main factors influencing postpandemic transmission are illustrated here:
https://science.sciencemag.org/content/early/2020/10/13/science.abe5960



Testing / Tracing
Black Americans have to wait in average one day longer (4.4 days) for their COVID test results than whites (3.5 days), according to a survey in US with over 8,000 responders
http://www.kateto.net/covid19/COVID19%20CONSORTIUM%20REPORT%2017%20TEST%20OCT%202020.pdf

Symptoms / Risk factors
SARS-CoV-2 infects the brain choroid plexus and disrupts the blood-CSF-barrier in human brain organoids. https://www.cell.com/cell-stem-cell/fulltext/S1934-5909(20)30495-1

A study used a carbohydrate antigen microarray with over 800 individual components to profile serum anti-glycan antibodies in COVID-19 patients and healthy control subjects. Abnormally high IgG and IgM antibodies to numerous self-glycans, including gangliosides, N-linked glycans, LacNAc-containing glycans, blood group H, and sialyl Lewis X were observed in COVID-19 patients. These antibodies are known to play a role in autoimmune and neurological disorders and may help explain some of the unusual and prolonged symptoms observed in COVID-19.
https://www.biorxiv.org/content/10.1101/2020.10.15.341479v1

A systematic review comparing severe COVID-19 with other inflammatory syndromes concludes that IL6 levels are lower but several non-cytokine biomarkers, including D-dimer, C-reactive protein, and ferritin, are elevated to a similar or greater extent in patients with COVID-19 than in patients with these comparison disorders.

https://www.thelancet.com/journals/lanres/article/PIIS2213-2600(20)30404-5/fulltext

An analysis finds that, compared with other countries, the US experienced high COVID-19-associated mortality and excess all-cause mortality into September 2020.
https://jamanetwork.com/journals/jama/fullarticle/2771841

Long COVID:
An ongoing prospective longitudinal study (preprint) suggests that in a young, low-risk population with ongoing symptoms, almost 70% of individuals have impairment in one or more organs four months after initial symptoms of SARS-CoV-2 infection.
https://www.medrxiv.org/content/10.1101/2020.10.14.20212555v1.full.pdf

Risk factors:
A retrospective cohort analysis in Denmark compared 7422 individuals that tested positive for SARS-CoV-2 to a reference population of 2.2M individuals. The analysis found that patients belonging to blood group O had a lower relative risk (0.87) of SARS-CoV-2 infection (but not of hospitalization or death).
https://ashpublications.org/bloodadvances/article/4/20/4990/463793/Reduced-prevalence-of-SARS-CoV-2-infection-in-ABO

A GWAS identified a 3p21.31 gene cluster (spanning the genes SLC6A20, LZTFL1, CCR9, FYCO1, CXCR6 and XCR1) as a genetic susceptibility locus in patients with Covid-19 with respiratory failure and confirmed a potential involvement of the ABO blood-group system (higher risk in blood group A than in other blood groups and a protective effect in blood group O as compared with other blood groups).
https://www.nejm.org/doi/full/10.1056/NEJMoa2020283

Another UK group studying more than 2200 COVID-19 patients has pinned down common gene variants that are linked to the most severe cases of the disease. The GWAS identifies and replicates three novel genome-wide significant associations: at chr19p13.3 (within the gene encoding dipeptidyl peptidase 9); at chr12q24.13 (in a gene cluster encoding antiviral restriction enzyme activators), and at chr21q22.1 (in the interferon receptor gene IFNAR2). They also detect a strong signal at the known 3p21.31 locus identified in previous studies.
https://www.medrxiv.org/content/10.1101/2020.09.24.20200048v2

The recognition that NCDs are a massive contributor to COVID-19 mortality and severe illness across all age groups should be a wake-up call to accelerate preventive strategies for NCDs, with a special focus on poor and marginalised populations.
https://adc.bmj.com/content/early/2020/10/13/archdischild-2020-319923

Children: A LSHTM team analysed data of 32 different infectious diseases, 19 viral and 13 bacterial, looking for patterns in severity at different ages (case fatality and hospitalisation rates). The severity of most infectious diseases was found to be at its lowest in school-age children (5-14 years old), with the exception of dengue. Severity for many diseases rises well before old age (even in young adults >20), suggesting immune aging may start earlier than thought.
https://www.nature.com/articles/s41597-020-00668-y

Antibodies / Immunity
Antibodies:
A serological study used multiple independent assays to improve the accuracy of antibody tests in low seroprevalence communities. Results from 5882 individuals

reveals that spike RBD and S2 and neutralizing antibodies remained detectable through 5-7 months post-onset, whereas alpha-N titers diminished. Relative to mild COVID-19 cases, individuals with severe disease exhibited elevated virus-neutralizing titers and antibodies against nucleocapsid (N) and Spike RBD.
https://www.cell.com/immunity/pdf/S1074-7613(20)30445-3.pdf

T cells:
A study reveals a profound decrease of mucosal associated invariant T (MAIT) cell counts in blood of critically ill patients. These cells showed a strongly activated and cytotoxic phenotype that positively correlated with circulating pro-inflammatory cytokines, notably IL-18. The authors propose that MAIT cell phenotypes represent valuable biomarkers of disease severity and their therapeutic manipulation might prevent the inflammatory phase involved in COVID-19 aggravation.
https://www.medrxiv.org/content/10.1101/2020.08.31.20185082v1

Cross-reactivity:
A study with 17 severe COVID-19 cases shows that seasonal CoV IgG responses that did not neutralize SARS-CoV-2 were boosted well beyond detectable cross-reactivity, particularly for HCoV-OC43 spike. These findings support a 'back-boost' of poorly protective coronavirus-specific antibodies in severe COVID-19 patients that may negatively impact de novo SARS-CoV-2 immunity.
https://www.medrxiv.org/content/10.1101/2020.10.10.20210070v1

Reinfections:
The Lancet publishes the already reported case of a SARS-CoV-2 reinfection in a 25 year-old man in Nevada. Reinfection was confirmed by virus genomic sequencing and the second infection (almost two months apart) was more severe. However, antibody levels and/or T cell responses were not assessed for the first infection, so no conclusions on immunity duration can be drawn.
https://www.thelancet.com/journals/laninf/article/PIIS1473-3099(20)30764-7/fulltext
A related comment dissects what these cases mean for COVID-19 and herd immunity.
https://www.thelancet.com/journals/laninf/article/PIIS1473-3099(20)30783-0/fulltext
Another good summary on reinfections and what they mean (particularly in terms of vaccination). Bottomline: Re-infection is possible. But it's also quite rare. It may be explained by the hugely variable immune response from one person to another (no evidence of escape mutations in Spike of the re-infecting virus). Vaccination, which raises neutralizing antibodies to Spike, will likely provide a population that is even less susceptible to re-infection (although the duration and variability of the vaccine response are still not known).
https://blogs.sciencemag.org/pipeline/archives/2020/10/14/immunity-and-re-infection

Treatment
SOLIDARITY released its long-awaited interim results. None of the four treatments in the trial led by the WHO, which enrolled more than 11,000 patients in 400 hospitals around the globe, increased survival. Hope for hidroxychloroquine and lopinavir/ritonavir had already faded after results from RECOVERY. But hope remained for remdesivir and interferon beta. However, Gilead's remdesivir had no effect in reducing mortality, even after pooling data with three other clinical trials. And interferon beta, with or without lopinavir/ritonavir, did not reduce mortality either, nor did it delay the need for ventilation. Nonetheless, the trial itself is touted as an unprecedented success, given the short time to set it up and its wide scope (thanks to a

simple protocol that allowed doctors to randomize their patients to whatever study drug was available).
https://www.sciencemag.org/news/2020/10/remdesivir-and-interferon-fall-flat-who-s-megastudy-covid-19-treatments

Hong Kong is adopting the strategy of keeping patients from entering the ICU in the first place by advocating early, aggressive hospitalization and treatment, even for mild cases. This would also help interrupt community transmission and allow testing treatments early in disease. https://www.bloomberg.com/news/articles/2020-10-17/treat-covid-19-early-to-save-patients-lives-sars-veteran-urges

Convalescent plasma: A study performed in non-human primates suggests that convalescent plasma therapy is an effective strategy if donors with high level of antibodies against SARS-CoV-2 are employed and if recipients are at an early stage of disease. https://www.biorxiv.org/content/10.1101/2020.10.14.340091v1

Nature reviews potential strategies to boost immune (and vaccine) responses in older people. One promising class of anti-ageing drug are mTOR inhibitors. In the laboratory, inhibiting mTOR lengthens lifespan in animals from fruit flies to mice, and small clinical trials suggest a protective effect against severe respiratory infections in older people. Other drugs to boost immunity include the anti-inflammatory drug losmapimod which targets age-related inflammation. Some drugs are currently being tested in COVID-19. https://www.nature.com/articles/d41586-020-02856-7

Spain's CSIC joins the EU-OPENSCREEN biochemistry platform to identify new active ingredients and potential treatments for COVID-19. (*Thanks for the tip, Raul Toran!)*
https://www.csic.es/es/actualidad-del-csic/el-csic-se-une-la-infraestructura-eu-openscreen-para-investigar-en-quimica

Vaccines
Children as young as 12 to participate in Pfizer's COVID-19 vaccine trial, marking the first time under-16s have been included in any such trials in the US.
https://www.npr.org/sections/health-shots/2020/10/13/923248377/will-kids-get-a-covid-19-vaccine-pfizer-to-expand-trial-to-ages-12-and-up

Phase I/II results were published for another Chinese inactivated SARS-CoV-2 vaccine developed by the Beijing Institute of Biological Products. BBIBP-CorV is safe and well tolerated at all tested doses in two age groups (18–59 years and ≥60 years). Two-dose immunisation with 4 μg vaccine on days 0 and 21 or days 0 and 28 achieved higher neutralising antibody titres than the single 8 ug dose.
https://www.thelancet.com/journals/laninf/article/PIIS1473-3099(20)30831-8/fulltext

Russia has registered its second coronavirus vaccine. The peptide-based EpiVacCorona, developed by Novosibirsk's Vektor, is starting large-scale trials. Early trials on 100 volunteers were said to have been successful but results have not yet been made public.
https://www.themoscowtimes.com/2020/10/14/russia-approves-2nd-coronavirus-vaccine-putin-a71752

The Serum Institute of India and Bharat Biotech are expected to start Phase III clinical trials of an intranasal COVID-19 vaccine in the coming months, once they receive regulatory approval. All other candidate vaccines currently in Phase III trials are intramuscular. https://science.thewire.in/health/intranasal-covid-19-vaccine-trial-serum-institute-bharat-biotech/

A News and Views in Nature Immunology analyses what the trial results for the different candidate vaccines tell us, and what questions remain
https://www.nature.com/articles/d41586-020-02926-w

An in-depth review in *Science* on vaccine safety stresses the importance of long-term follow up of phase 3 clinical trials and concludes that, from what we know of previous vaccines, vaccine-associated enhanced disease (VAED) is highly unlikely.
https://stm.sciencemag.org/content/early/2020/10/16/scitranslmed.abe0948

Vaccine hesitancy: A 13,400-person survey in 19 countries hit hard by COVID-19, co-led by our colleague Jeffrey V Lazarus, shows that 72% of the population would likely take a vaccine when available but the remaining 28% would hesitate or refuse.
https://www.nature.com/articles/s41591-020-1124-9
Meanwhile, a poll in the US finds that the percentage of Americans that would get vaccinated as soon as a vaccine was available has fallen from 69% in mid-August to 58% earlier this month. Black Americans are the most hesitant.
https://www.statnews.com/pharmalot/2020/10/19/covid19-coronavirus-pandemic-vaccine-racial-disparities/

Socioeconomic impact
The COVID19 pandemic has cost the US an estimated $16 trillion USD, assuming it will be contained by fall of 2021. The analysis estimated cumulative financial costs related to the lost output and health reduction, by applying the technique of valuing "statistical lives". The immense financial loss from COVID-19 calls for a fundamental rethinking of government's role in pandemic preparation, with more investment in public health services and infrastructure. These investments should not be dismantled once the pandemic is over. https://jamanetwork.com/journals/jama/fullarticle/2771764

A joint statement by WHO, ILO, FAO and IFAD states that the number of undernourished people, currently estimated at nearly 690 million, could increase by up to 132 million by the end of the year; and that nearly half of the world's 3.3 billion global workforce are at risk of losing their livelihoods.
https://www.who.int/news/item/13-10-2020-impact-of-covid-19-on-people's-livelihoods-their-health-and-our-food-systems

Other
A shimmer of hope from Ebola:
Long-lasting immunity: A study with Ebola disease survivors, contacts, and negative controls revealed continuous high titre of neutralising antibodies and increased T-cell responses (for at least 14 months), which suggests long-term protective immunity in survivors. Around 10% of contacts also displayed antibodies and T cell responses, indicative of subclinical infections.
https://www.thelancet.com/journals/laninf/article/PIIS1473-3099(20)30736-2/fulltext
First approved treatment: FDA has approved Inmazeb, a cocktail of 3 monoclonal antibodies targeting the GP of the Zaire EBOV and developed by Regeneron, to treat adult and pediatric patients with Ebola. The cocktail was evaluated along with three other experimental Ebola treatments in the 2018 Congo outbreak. 33.8% of patients treated with Inmazeb died, as compared to 51% with a different treatment, at 28 days.
https://www.fda.gov/news-events/press-announcements/fda-approves-first-treatment-ebola-virus

ISGlobal

COVID-19 EPIDEMIC

Epidemiological situation (27/10/2020, ECDC data):

Globally:
43 598 033 confirmed cases and 1 160 995 deaths

- Globally, daily cases continue to increase, with countries in Europe and the Americas showing the largest increases.
- India and the USA are still the most severely affected countries in terms of cumulative case counts and daily new case confirmations.
- A total of 13 countries reported more than 10 000 cases in the past 24 hours, 9 of which were in the European region.
- A modest fraction of COVID19 economic stimulus package funds (which have surpassed USD 12 trillion worldwide) could help put the world on track to Paris Agreement goals for the climate, says a policy forum in *Science*. https://science.sciencemag.org/content/370/6514/298

Confinement and deconfinement measures
A modelling analysis of non-pharmaceutical interventions (NPIs) in 131 countries suggests they are associated with reduced transmission of SARS-CoV-2, but there is a 1 to 3-week delay in the effect of imposing or lifting restrictions on the R number. Unsurprisingly, combined measures are likely to reduce the R more than individual measures. https://www.thelancet.com/journals/laninf/article/PIIS1473-3099(20)30785-4/fulltext

To rein in the surge in cases, the Spanish government declared a national emergency yesterday with a night curfew starting at 11 pm (10 pm in Catalonia).

Victoria, Australia, declared zero COVID-19 cases today, after having 725 cases per day in the peak of wave 2, about 80 days ago.

Passengers travelling to Hong Kong and Italy from Britain's Heathrow Airport will undergo a one-hour coronavirus test before flying out of the UK, under plans to open up international travel. Passengers should book a test in advance at a cost of 80 pounds. The type of rapid test is not specified.
https://www.aljazeera.com/news/2020/10/20/uk-to-start-rapid-covid-19-tests-at-heathrow-on-tuesday-report

Virus
The spike protein mutation D614G became dominant during the COVID-19 pandemic. A study shows that D614G enhances replication on human lung epithelial cells and primary human airway tissues through improved infectivity of virions. Hamsters infected with the G614 variant produced higher infectious titers in nose and trachea, but not lungs, confirming clinical evidence that the D614G mutation enhances viral loads in the upper respiratory tract and may increase transmission. Neutralizing experiments indicate that the mutation does not reduce the efficacy of vaccines currently tested. https://www.nature.com/articles/s41586-020-2895-3

After viral Spike is cleaved in two by the host protease furin, the C terminal end of Spike 1 binds to the Neuropilin-1 receptor. Using X ray crystallography and biochemical assays, a study shows that the S1 CendR motif directly bound NRP1. Blocking this interaction using RNAi or selective inhibitors reduced SARS-CoV-2 entry and infectivity in cell culture. NRP1 thus serves as host factor for SARS-CoV-2 infection and represents a potential therapeutic target.
https://science.sciencemag.org/content/early/2020/10/19/science.abd3072/tab-pdf
A genome-scale CRISPR loss-of-function screen identifies host factors required for SARS-CoV-2 viral infection of human alveolar epithelial cells. Findings show that loss of RAB7A reduces viral entry by sequestering the ACE2 receptor inside cells and provide a valuable tool to evaluate the role of different genes in response to viral infection. https://www.cell.com/cell/fulltext/S0092-8674(20)31394-5

Transmission
SARS-CoV and SARS-CoV-2 are transmitted through the air between ferrets over more than one meter distance. Although the experiments did not discriminate between transmission via small aerosols, large droplets and fomites, these results demonstrate that SARS-CoV and SARS-CoV-2 can remain infectious while traveling through the air.
https://www.biorxiv.org/content/10.1101/2020.10.19.345363v1

So far, schools don't appear to be fuelling COVID-19 transmission, according to data emerging from random testing in the US and the UK.
https://www.nytimes.com/2020/10/22/health/coronavirus-schools-children.html

Modelling projections for the US suggests that universal mask use could save an additional 129,574 (85,284–170,867) lives from September 22, 2020 through the end of February 2021. https://www.nature.com/articles/s41591-020-1132-9

All that is known about SARS-CoV-2 transmission is summarised here:
https://science.sciencemag.org/content/370/6515/406

I recommend this brief yet very complete overview on virology, transmission and pathogenesis of SARS-CoV-2 https://www.bmj.com/content/371/bmj.m3862

Testing / Tracing
An algorithm to test multiple samples in one go, thereby reducing the total number of tests needed, has been trialled in Rwanda to screen air passengers. A single positive case could be detected even when mixed with 99 negative swab results.
https://www.nature.com/articles/s41586-020-2885-5

Singapore researchers have developed a breath test to detect COVID-19 within one minute. The Breathonix technology detects volatile organic compounds, and has achieved more than 90% accuracy in a clinical trial that involved 180 patients.
https://trak.in/tags/business/2020/10/22/this-breath-test-detects-covid-19-in-60-seconds-with-90-accuracy-find-out-how-it-works/

Symptoms / Risk factors
A new "living" high quality prediction model for COVID19 risk of hospitalization and death shows that the patients in the top 20% risk accounted for 94% of deaths. The QCOVID algorithm can dynamically recalibrated and updated as the pandemic evolves.
https://www.bmj.com/content/371/bmj.m3731

Long Covid: A study from King's College, London, using the Covid Symptom Study App, estimates that one in 20 people are sick for at least eight weeks. Old age, being female, and having more than five different symptoms in the first week, were identified as risk factors for long Covid. https://www.kcl.ac.uk/news/study-identifies-those-most-risk-long-covid

Migrants are twice as likely to contract the virus than the rest of the population, according to an OECD report. Children of migrants have also been particularly disadvantaged by school closures.
https://www.oecd.org/migration/international-migration-outlook-1999124x.htm

A CDC report finds an estimated 299,028 excess deaths occurred in the US from late January through October 3, 2020, with 198,081 (66%) excess deaths attributed to COVID-19. The largest percentage increases were seen among adults aged 25–44 years and among Hispanic or Latino persons.
https://www.cdc.gov/mmwr/volumes/69/wr/mm6942e2.htm

Antibodies / Immunity
An unbiased screen of CD8+T cell epitopes in COVID-19 patients reveals that 90% of shared epitopes are not on the Spike protein (most are on ORF1 and nucleocapsid) and that they show almost no cross-reactivity with epitopes in seasonal coronaviruses. These findings could explain the detectable but modest CD8+ T cell responses generated by vaccines targeting the S protein and provide a tool to monitor CD8+T cell reactivity in patients or vaccinated individuals.
https://www.cell.com/immunity/fulltext/S1074-7613(20)30447-7

Nature's second pandemic progress report focuses on immunity. A detailed understanding of COVID19 immunity is key to developing safe and effective vaccines.
https://www.nature.com/articles/d41586-020-02943-9

Treatment
Tocilizumab: JAMA published a trio of studies on use of the anti-IL6R antibody in COVID-19 patients with pneumonia. One large US observational study suggested some promise among critically ill patients treated in the first 2 days of ICU admission (reduced mortality).
https://jamanetwork.com/journals/jamainternalmedicine/fullarticle/2772185
Two randomized clinical trials from Italy (123 patients) and France (130 patients) found no benefit on mortality by day 28.
https://jamanetwork.com/journals/jamainternalmedicine/fullarticle/2772186
https://jamanetwork.com/journals/jamainternalmedicine/fullarticle/2772187
see also: https://www.cidrap.umn.edu/news-perspective/2020/10/studies-offer-little-hope-tocilizumab-treating-covid

Eli Lilly announced its antibody treatment does not appear to work in hospitalized patients, which is why the NIH-led trial was stopped. However, it remains confident that it helps prevent disease progression in patients that are recently diagnosed or with mild symptoms. https://www.lilly.com/news/stories/statement-activ3-clinical-trial-nih-covid19

Remdesivir: Gilead's remdesivir (Veklury) becomes first treatment to receive FDA approval for COVID-19. It as been approved to treat hospitalised COVID-19 patients aged 12y and older.

Convalescent plasma: An open label, multicentre, randomized clinical trial with 464 adults with moderate COVID-19 shows that convalescent plasma was not associated

with a reduction in progression to severe covid-19 or all cause mortality. Measurement of neutralising antibody titres in donors was not performed.
https://www.bmj.com/content/371/bmj.m3939
A clearer answer will likely come from the RECOVERY trial UK, which has enrolled the 2000th patient to compare convalescent plasma vs. usual NHS care alone. The primary outcome is 28-day mortality.

Antimalarial drugs: Artemisinins have demonstrated inhibition of SARS-CoV-2 in vitro and have anti-inflammatory effects, including inhibition of IL-6. The authors of this forum argue that there is enough evidence for launching clinical studies for ACTs, and in particular artesunate/pyronaridine, against COVID-19 infections.
https://www.cell.com/action/showPdf?pii=S1471-4922%2820%2930288-9

Vaccines
Cryo-EM and site-specific glycan analysis of one of the leading subunit vaccine candidates from Novavax confirms the structural integrity of the full-length spike protein immunogen and provides a basis for interpreting immune responses to this multivalent nanoparticle immunogen.
https://science.sciencemag.org/content/early/2020/10/19/science.abe1502

Moderna announced it has completed enrolment of 30,000 participants for the phase III trial of its mRNA-1273 vaccine. 37% are minorities.
https://www.washingtonpost.com/health/2020/10/22/vaccine-trial-moderna/

The possibility that adenoviral-based COVID-19 vaccines may leave people more vulnerable to the AIDS virus has been raised by a group of researchers based on previous bad experience with an Ad5-HIV experimental vaccine.
https://www.sciencemag.org/news/2020/10/could-certain-covid-19-vaccines-leave-people-more-vulnerable-aids-virus

For a good graphic summary of the ~200 vaccine programs of 4 different types (viral vector, genetic, protein, attenuated virus) and completion timeline of Phase 3 trials, see: https://www.wsj.com/articles/to-find-a-coronavirus-vaccine-glaxosmithkline-is-bonding-with-its-biggest-competitors-11603512029?mod=hp_lead_pos7

Lipsitch and Dean write a perspective in Science on understanding vaccine efficacy. Efficacy in high-risk groups and reduced viral shedding are two major parameters for protection.
https://science.sciencemag.org/content/early/2020/10/21/science.abe5938

The UK announced it will start human challenge trials on January to test COVID-19 vaccines, if it receives final ethical and regulatory approval. Researchers first need to determine the minimal viral dose at which most people become infected, before running the challenge trial in which healthy, young vaccinated or control volunteers are exposed to the virus. https://www.nature.com/articles/d41586-020-02821-4

Astra Zeneca announced that immune responses for its ChAd-based candidate vaccine were similar between older and younger adults, and that reactogenicity was lower in older adults https://uk.reuters.com/article/health-coronavirus-astrazeneca-vaccine/vaccine-hopes-rise-as-oxford-jab-prompts-immune-response-among-old-as-well-as-young-adults-idUSKBN27B0J1

Covid-19 vaccine trials from AstraZeneca and Johnson & Johnson will restart in the US after finding that serious illnesses in a couple of volunteers appeared not to be related

to the vaccines. https://www.statnews.com/2020/10/23/covid-19-vaccine-trials-from-astrazeneca-johnson-johnson-to-restart/

The Advisory Committee on Immunization Practices (ACIP) in US has published the scientific and ethical principles underlying its recommendations for COVID-19 vaccine allocation. https://jamanetwork.com/journals/jama/fullarticle/2772326

Mental Health

Two in five children aged 11 to 16 feel the coronavirus lockdown has made their lives worse, according to an NHS report on mental health. They said their biggest anxieties were about missing school and family and friends contracting Covid-19. https://digital.nhs.uk/data-and-information/publications/statistical/mental-health-of-children-and-young-people-in-england/2020-wave-1-follow-up

Other

The Global Health Center at the Graduate Institute of Geneva is organising a series of executive COVID-19 briefings to help guide organisations through the crisis *(Thanks for the tip, Toni Plaséncia!)* https://www.graduateinstitute.ch/covid-briefings

ISGlobal

COVID-19 EPIDEMIC

Epidemiological situation (03/11/2020, ECDC data):

Globally:
47 093 222 confirmed cases and 1 207 290 deaths

- The WHO Emergency Committee on COVID-19 has unanimously agreed that the situation still warrants a public health emergency of international concern (PHEIC). The Committee recommended an update on travel recommendations, and the need to address long-COVID. https://www.cidrap.umn.edu/news-perspective/2020/10/who-extends-covid-19-emergency-global-total-tops-45-million
- While Europe battles its second wave, Latin America has not overcome its first one and has the highest COVID-19 death rate: the region's death toll has surpassed 400,000 and more than 11 million people have been infected.
- Globally, daily confirmed case counts continued to increase this week, and the average number of daily deaths (6,100) is approaching the highest peak recorded (6,800) last April 10-16. https://www.ft.com/content/a2901ce8-5eb7-4633-b89c-cbdf5b386938
- Today's presidential election in the US will not only decide the future of the nation's COVID-19 response, but the future of various federal agencies, top officials, health care laws, and global health in general. https://www.statnews.com/2020/11/02/trump-era-science-institutions-on-the-line/

Confinement and deconfinement measures

Riots across Spain and other cities in Europe have erupted in wake of new COVID-19 restrictions. Belgium, which has the highest infection rate in Europe, has announced a new national lockdown, 2 days after Spain and Germany announced similar measures.

A news feature in *Science* points out that Europe is locking down a second time to avoid the worse, but without a long-term plan. The region should aim at eliminating the virus. https://www.sciencemag.org/news/2020/11/europe-locking-down-second-time-what-its-long-term-plan

A Stanford study links Trump rallies to more than 700 Covid deaths and 30,000 infections. https://papers.ssrn.com/sol3/papers.cfm?abstract_id=3722299

An analysis using geotracking data of 15 million smartphones per day shows that counties that voted for Trump in 2016 showed 14% less physical distancing than counties that voted for Clinton. These differences were associated with subsequent higher COVID-19 infection and fatality growth rates.
https://www.nature.com/articles/s41562-020-00977-7

Virus

A *Cell* study reports the molecular assembly of the authentic SARS-CoV-2 virus using cryoelectron tomography (cryo-ET) and subtomogram averaging (STA). Findings shed light on how the virus packs its ~30-kb-long single-segmented RNA in the ~80-nm-diameter lumen. https://www.cell.com/cell/fulltext/S0092-8674(20)31159-4

A study shows that β-coronaviruses utilize lysosomal trafficking for egress, rather than the biosynthetic secretory pathway more commonly used by other enveloped viruses. This unconventional egress is regulated by the Arf-like small GTPase Arl8b and can be blocked by the Rab7 GTPase competitive inhibitor CID1067700.
https://www.sciencedirect.com/science/article/pii/S009286742031446X
A comparative analysis of the ACE2 receptor suggests that apes and African and Asian monkeys, and some lemurs, are likely to be highly susceptible to SARS-CoV-2 infection
https://www.nature.com/articles/s42003-020-01370-w

An excellent visualisation, by National Geographic, on how SARS-CoV-2 infects and attacks the body, and how the immune system fights back:
https://www.nationalgeographic.com/magazine/2020/11/explore-how-coronavirus-attacks-the-body-and-how-the-body-fights-back/

Transmission

A novel SARS-CoV-2 variant called 20A.EU1 (S:A222V) emerged in early summer 2020, presumably in Spain, and subsequently spread to multiple locations in Europe. This and a 2nd variant, 20A.EU2 (with mutation S:S477N in the spike protein), account for the majority of recent sequences in Europe. There is no evidence for the moment that its rapid spread is due to particular properties of the virus.
https://www.medrxiv.org/content/10.1101/2020.10.25.20219063v1.full.pdf

A study reveals coronavirus can replicate in the salivary glands. Viral burden in saliva correlated with COVID-19 symptoms including taste loss. The oral cavity oral cavity therefore represents a robust site for COVID-19 infection and implicates saliva in viral transmission. https://www.medrxiv.org/content/10.1101/2020.10.26.20219089v1

A retrospective cohort study with 1,100 cases and 7,700 close contacts in Singapore shows the risk for household contacts sharing the bedroom is >5x, while speaking with a case for more than 30 min is 8X. Testing of all household contacts, including asymptomatic individuals, is warranted.
https://www.thelancet.com/journals/laninf/article/PIIS1473-3099(20)30833-1/fulltext

Genomic analysis of SARS-CoV-2 isolated from two journalists linked to the White House COVID-19 outbreak shows the viral sequences are highly similar to each other, and possess 5 distinct nucleotide mutations which make them distinct from over 160,000 publicly available sequences. This should allow to further identify cases linked to the White House superspreader event.
https://www.medrxiv.org/content/10.1101/2020.10.31.20223925v1

A good visual explanation on virus superspreading: https://vis.sciencemag.org/covid-clusters/

Testing / Tracing

An Israeli team tested 133,816 nose and throat samples by pooling either five or eight individual samples into one group sample. Using this method, the researchers required

only one-quarter of the tests they would have needed to check every sample individually. https://www.medrxiv.org/content/10.1101/2020.10.16.20213405v1

Test results from 68 people involved in the NBA basketball season shows that participants' viral levels peaked about three days after they tested positive. The researchers found that two tests given within two days can indicate whether a person's viral level is rising or falling — information that can influence treatment decisions. https://www.medrxiv.org/content/10.1101/2020.10.21.20217042v1

Kantaro's quantitative SARS-CoV-2 IgG antibody tests (co-developed with Krammer's lab) have received CE marking and are immediately available in the European Union. The test achieves 97.8% sensitivity and 99.6% specificity. It uses two virus antigens: the full-length spike protein and its receptor-binding domain (RBD). COVID-SeroKlir is configured to be most useful in a clinical setting, while COVID-SeroIndex is expected to be used for research or vaccine development. https://kantarobio.com/ce-mark-approval-granted-to-kantaro-covid-seroklir-and-covid-seroindex-quantitative-antibody-test-kits/

A US study enrolled over 30K participants to test a smartphone app that collects smartwatch and activity data, as well as self-reported COVID-19 symptoms and diagnostic testing results. A combination of symptom and sensor data was better than symptoms alone to discriminate between negative and positive individuals, suggesting continuous, passively captured data may be complementary to virus testing. https://www.nature.com/articles/s41591-020-1123-x

A Cochrane review discusses rapid, point-of-care antigen and molecular-based tests for diagnosis of SARS-CoV-2 infection. Sensitivity of antigen tests is much more variable than that of rapid molecular assays. The Xpert Xpress molecular test developed by Cepheid looks promising - 99% sensitivity, 97% specificity and results in 30 min. *(Thanks for the tip, Payam Dadvand!)*
https://www.cochranelibrary.com/cdsr/doi/10.1002/14651858.CD013705/full

Symptoms / Risk factors
A study suggests that half of patients hospitalized with COVID-19 become at least transiently positive for antiphospholipid antibodies which may lead to blood clotting. https://stm.sciencemag.org/content/early/2020/11/02/scitranslmed.abd3876

A study in Nature identifies fibroblasts as the cells that serve as the gatekeeper of the inflammatory immune response in the lungs following influenza and other respiratory infections. https://www.nature.com/articles/s41586-020-2877-5.epdf

MIS-C in Children: In June 2020, the US NIH convened a workshop of immunologists and clinicians to discuss emerging knowledge and identify key questions surrounding MIS-C. The main findings of the workshop, with a focus on immunity and genetics, are reported. https://www.nature.com/articles/s41591-020-1140-9

Disease burden: Using multiple data sources to estimate infection, hospitalization and mortality rates, an analysis concludes that the COVID-19 outbreak in Wuhan had a higher burden than the 2009 influenza pandemic or seasonal influenza in terms of hospitalization and mortality rates, and clinical severity was similar to that of the 1918 influenza pandemic. https://www.nature.com/articles/s41467-020-19238-2

Reporting of deaths from COVID-19 among those under the age of 65 is likely to be far more reliable, and can therefore give clearer insights into the underlying transmission

of the virus and better country-to-country comparisons, according to an analysis that collected age-specific COVID-19 death data from 45 countries and the results of 22 seroprevalence studies. https://www.nature.com/articles/s41586-020-2918-0

Occupational risk: A study of staff at a grocery store in US found that workers who had direct contact with customers were 5 times more likely to test positive, and a considerable portion of infections (76%) were asymptomatic at the time of testing. Those able to practice social distancing at work had lower risk of anxiety and depression. https://oem.bmj.com/content/early/2020/10/11/oemed-2020-106774.full

Air pollution: A study has concluded that long-term exposure to air pollution could be linked to 15% of global deaths from COVID-19. Researchers characterized estimated global exposure to fine particulates based on satellite data and associated it with epidemiological data. https://academic.oup.com/cardiovascres/advance-article/doi/10.1093/cvr/cvaa288/5940460

Antibodies / Immunity

A report by Krammer and colleagues shows that the vast majority of infected individuals with mild-to-moderate COVID-19 experience robust IgG antibody responses against the viral spike protein, based on a dataset of 30,082 individuals screened at Mount Sinai in New York City. Furthermore, titers are relatively stable for at least 5 months, and anti-spike binding titers correlate with neutralization of authentic SARS-CoV-2. The seroprevalence results, if extrapolated to the NYC population, mean >1.7 million infected and an IFR at 0.97.
https://science.sciencemag.org/content/early/2020/10/27/science.abd7728

A dual assay measuring antibodies against both the receptor binding domain and nucleocapsid proteins of SARS-CoV-2 reveals a 6-fold higher antibody prevalence in children than reported (0.9% vs 0.15%). The assay was performed in 15,771 children (aged 1-18 y) living in Bavaria and participating in a diabetes type 1 screening program. Almost half were asymptomatic. No correlation with type 1 diabetes was observed.
https://www.cell.com/med/fulltext/S2666-6340(20)30020-9

Antibody cross-reactivity: A study finds neutralizing activity against seasonal coronaviruses in nearly all pre-pandemic sera (from individuals with confirmed recent infection by seasonal coronaviruses), but cross-reactive neutralizing activity against SARS-CoV-2 was undetectable.
https://www.medrxiv.org/content/10.1101/2020.10.08.20209650v1.full

Cytokine storm: A study in mice shows that the combined action of TNF-α and IFN-γ induces three different types of cell death (apoptosis, pyroptosis and necroptosis) at the same time, which in turn leads to an escalating cytokine storm such as that observed in severe COVID-19. https://www.biorxiv.org/content/10.1101/2020.10.29.361048v1

Treatment

The interim results for Eli Lilly's mAb LY-CoV555 in outpatients with recently diagnosed mild or moderate Covid-19 have been published. Data show a modest effect on viral load (which is not dose-dependent) and a slight reduction in the % of patients who visited the hospital or emergency services (1.6% versus 6.3% in placebo group).
https://www.nejm.org/doi/full/10.1056/NEJMoa2029849
Lilly will provide the federal government with 300,000 doses of the treatment and is pending of a FDA emergency use authorization.

In turn, REGENERON announced positive, prospective results from an ongoing Phase 2/3 trial in the COVID-19 outpatient setting. Its antibody cocktail, REGN-COV2, significantly reduced viral load and patient medical visits by 57% (hospitalizations, emergency room, urgent care visits and/or physician office/telemedicine visits). No significant difference in efficacy between the high dose (8 g) and low dose (2.4 g) was observed. It is awaiting a EUA by the FDA. https://investor.regeneron.com/news-releases/news-release-details/regenerons-covid-19-outpatient-trial-prospectively-demonstrates
In contrast, Regeneron paused its antibody trial with severe COVID patients after interim results showed no benefit in these patients. This announcement came only days after Eli Lilly also announced it was stopping its trial in hospitalised patients. https://www.ft.com/content/42256a8d-0073-4f57-9ac4-d3cc65a8e5c0

Remdesivir: a *Science* investigation uncovers how Gilead may have deliberately hidden data before signing deals with the European Union and the US FDA (which approved the drug for use against SARS-CoV-2 some weeks ago). These decisions were not straightforward: they were taken with little data on the efficacy of the drug, and right before the SOLIDARITY results were disclosed (and of which Gilead was already aware of). “Unless more data emerge, EMA should not give the drug full approval. There are more questions than answers about the efficacy of remdesivir in hospitalized patients”, says one of the interviewees. https://www.sciencemag.org/news/2020/10/very-very-bad-look-remdesivir-first-fda-approved-covid-19-drug

Brazil’s Bolsonaro announced “a new breakthrough in the fight against COVID-19”: the antiparasitic drug nitazoxanide. However, no clinical evidence was presented and scientists are highly sceptical. https://www.sciencemag.org/news/2020/10/another-piece-populist-propaganda-critics-slam-brazilian-government-s-new-covid-19-drug

Vaccines
Three new candidates have entered phase 1 trials, including Canada’s Symvivo vaccine, based on engineered bacteria packaged into a pill, which synthetise viral Spike protein when they reach the intestine.
https://www.nytimes.com/interactive/2020/science/coronavirus-vaccine-tracker.html#symvivo

A review discusses the challenge of measuring vaccine efficacy and argues that the most important efficacy endpoint, protection against severe disease and death, is difficult to assess in phase 3 clinical trials. It also argues for the need to apply standardised, quantifiable endpoints routinely to clinical trials of COVID-19 vaccines.
https://www.thelancet.com/journals/laninf/article/PIIS1473-3099(20)30773-8/fulltext
And another comment discusses how to prepare for the vaccine, including public health messaging https://www.nature.com/articles/s41587-020-0743-5

Other
The Economist covers how COVID-19 is hindering the fight against malaria, and how health workers are “heroically adapting”. https://www.economist.com/middle-east-and-africa/2020/10/31/how-covid-19-hinders-the-fight-against-malaria

An analysis of more than 100 million Twitter messages posted worldwide during the early stages of epidemic across countries (from 22 January to 10 March 2020) shows that measurable waves of potentially unreliable information preceded the rise of COVID-19 infections, posing a serious threat to public health. As infections started to

rise, reliable information quickly became more dominant.
https://www.nature.com/articles/s41562-020-00994-6

An analysis of thousands of archival records from London, UK, reveals that plague epidemics spread much faster in the 17th century than in the 14th century. The authors discuss the potential roles of demographic and ecological factors, such as climate change or human or rat population density,
https://www.pnas.org/content/early/2020/10/13/2004904117

ISGlobal

COVID-19 EPIDEMIC

Epidemiological situation (10/11/2020, ECDC data):

Globally:
50 994 215 confirmed cases and 1 264 077 deaths

- The world has surpassed 50 million confirmed cases, with the European region accounting for 68.3% of daily case numbers and 48.8% of the daily deaths reported in the past 24 hours.
- Growth in the US is exponential, having passed 10 million cases.

Confinement and deconfinement measures

Greece announces a national 1-month lockdown to curb viral spread.

Slovakia plans to be the first country to test its whole population for SARS-CoV-2, but experts warn of logistical and technical challenges, including false-positive and false-negative results. Over 3 days, 140 951 people have been screened in a pilot test, with 5594 positive cases identified.
https://www.thelancet.com/journals/lancet/article/PIIS0140-6736(20)32261-3/fulltext

President-elect Biden names 13 experts to the COVID-19 transition advisory board, including co-chairs David Kessler (ex-FDA), Vivek Murth (ex-surgeon general) and Marcella Nunez-Smith (Yale University).
https://www.npr.org/sections/live-updates-2020-election-results/2020/11/09/933002962/president-elect-biden-names-13-experts-to-covid-19-transition-advisory-board
He has also announced the US will rejoin WHO on day one in office

Virus

A study shows that the non-structural protein 1 (Nsp1) of SARS-CoV-2 is as a major cellular pathogenicity factor. Nsp1 inhibits translation of host cell proteins by blocking the mRNA entry channel on the 40S ribosome.
https://www.sciencedirect.com/science/article/pii/S1097276520307413

Transmission

Full SARS-CoV-2 genome sequencing in Israel reveals that travellers returning from the US greatly contributed to viral spread during the country's first wave, and provides evidence for superspreader events (2-10% of infected individuals resulted in 80% of secondary infections). The initial Ro of 2.5 dropped substantially after the implementation of physical distancing measures.
https://www.nature.com/articles/s41467-020-19248-0

A prospective study of SARS-CoV-2 transmission in households (all household contacts of cases were followed daily during 7 days) is fast and silent: 35% of household contacts got infected, most within the first five days, and fewer than half showed symptoms

when first tested positive.
https://www.cdc.gov/mmwr/volumes/69/wr/mm6944e1.htm?s_cid=mm6944e1_w

Bloomberg reports on the role of schools on COVID-19 spread. Data show that school children probably are not major spreaders of COVID-19 among each other, their families, and the wider community. Rather, schools accurately reflect transmission conditions in the broader community.
https://www.bloomberg.com/news/articles/2020-11-03/testing-shows-schools-aren-t-propelling-covid-19-outbreaks

The epidemiological study performed in Southern India (and described in a previous update) has been published in Science. The study reveals superspreading predominated, with 5% of infected individuals accounting for 80% of cases. Transmission risk was observed among children and young adults, and deaths were concentrated in 50-64 year olds.
https://science.sciencemag.org/content/370/6517/691
See the superspreading events map *The Economist* has prepared:
https://www.economist.com/graphic-detail/2020/11/07/a-minority-of-people-with-covid-19-account-for-the-bulk-of-transmission

A prospective UK population-based cohort study of babies with confirmed SARS-CoV-2 infection in the first 28 days of life reveals that neonatal SARS-CoV-2 infection is uncommon, vertical transmission is possible but rare, and a high proportion of infected babies belong to minority ethnic groups.
https://www.thelancet.com/journals/lanchi/article/PIIS2352-4642(20)30342-4/fulltext

Swabbing of bank machines, shop-door handles and other frequently touched surfaces in a US city revealed that 8% of samples were positive for SARS-CoV-2 genetic material, but that material was present in small amounts. Therefore, the infection risk from touching contaminated surfaces is low. The study also found that the percentage of positive samples in one postal district peaked around 7 days before a spike in COVID-19 cases in the same district.
https://www.medrxiv.org/content/10.1101/2020.10.27.20220905v1

Testing / Tracing
A study led by Hospital Germans Trias i Pujol shows high sensitivity for Abbott's PanBio rapid antigen test to identify both symptomatic and asymptomatic individuals, particularly in samples with viral loads associated with high risk of transmission (Ct<25). Assuming a prevalence of 5%, the negative and positive predictive values were 99·6% and 81·5%, respectively.
https://www.medrxiv.org/content/10.1101/2020.10.30.20223198v1.full.pdf

Symptoms / Risk factors
An analysis of 41 consecutive post-mortem samples from individuals who died of COVID-19 reveals extensive alveolar damage, thrombosis of lung micro- and macro-vasculature, and a large number of dysmorphic pneumocytes and infected syncytia (fused cells). The long-term persistence of viral RNA in the lung could eventually explain long COVID, say the authors.
https://www.thelancet.com/journals/ebiom/article/PIIS2352-3964(20)30480-1/fulltext

Pregnancy: In an analysis of approximately 400,000 women aged 15–44 years with symptomatic COVID-19, intensive care unit admission, invasive ventilation, extracorporeal membrane oxygenation, and death were more likely in pregnant women than in nonpregnant women.
https://www.cdc.gov/mmwr/volumes/69/wr/mm6944e3.htm

Immunocomprised patients: A case report describes persistent SARS-CoV-2 infection and shedding in a female immunocompromised patient with chronic leukaemia, who shed infectious virus for up to 70 days after diagnosis. Within-host genomic evolution of the virus was observed. https://www.cell.com/cell/fulltext/S0092-8674(20)31456-2

Antibodies / Immunity
A study charting longitudinal antibody responses to SARS-CoV-2 in 92 subjects after symptomatic COVID-19 for approx. 100 days shows marked heterogeneity in antibody duration dynamics. Those with a shorter duration of symptoms had sustained antibody production, harbored increased somatic mutations in virus-specific memory B cell antibody genes, and had persistent higher frequencies of activated CD4+ T cells.
https://www.cell.com/cell/pdf/S0092-8674(20)31458-6.pdf

A study dissecting early humoral responses in hospitalised individuals shows that moderate disease is associated with a delay but ultimate convergence of IgG and that early cross-reactivity to the S2 region of Spike is linked to survival after severe disease
https://www.cell.com/cell/fulltext/S0092-8674(20)31459-8

Children with and without MIS-C had reduced neutralizing activity as compared to adult COVID-19 cohorts, indicating a distinct infection course and immune response.
https://www.nature.com/articles/s41590-020-00826-9

Pre-existing humoral immunity to SARS-CoV-2 spike glycoprotein (S)-reactive was detected by a flow cytometry-based method in SARS-CoV-2-uninfected individuals and was particularly prevalent in children and adolescents. These antibodies were predominantly IgG and targeted the S2 subunit.
https://science.sciencemag.org/content/early/2020/11/05/science.abe1107

Memory B and T cells:
A 6-month follow-up study (by Rockefeller University) in a cohort of individuals shows that the anti-SARS-CoV-2 memory B cell response evolves during the first 6 months after infection, with accumulation of Ig somatic mutations, and production of antibodies with increased neutralizing breadth and potency. The evolving immune response could be due to antigen persistence - analysis of intestinal biopsies obtained 3 months after COVID-19 onset revealed persistence of SARS-CoV-2 in the small bowel of 7 out of 14 volunteers. These findings strongly suggest that individuals who are infected with SARS-CoV-2 could mount a rapid and effective response to the virus upon re-exposure. https://www.biorxiv.org/content/10.1101/2020.11.03.367391v1

A small but key UK study has found that T cell immunity to SARS-CoV-2 is present after six months in people who had mild or asymptomatic COVID-19, suggesting they might have some level of protection for at least that time.
https://www.biorxiv.org/content/10.1101/2020.11.01.362319v1

A review on measuring immunity to SARS-CoV-2 infection analyses a selection of existing assays for measuring antibody-mediated virus neutralization and animal models of infection with SARS-CoV-2. The authors provide a framework for comparing

results and reconciling observed differences. https://www.nature.com/articles/s41577-020-00471-1

Treatment

ACE2 traps: A UCSF-led group engineered and optimized ACE2 variants that act as "receptor traps" and neutralize authentic SARS-CoV-2 infective capacity as effectively as high-affinity antibodies isolated from convalescent patients. They also bind viral spike proteins from other coronaviruses known to cause respiratory diseases. https://www.pnas.org/content/early/2020/10/21/2016093117

Nanobodies: *Science* publishes two promising studies on neutralizing nanobodies: By screening a yeast surface-displayed library of synthetic nanobody sequences, researchers developed nanobodies that disrupt the interaction between Spike and ACE2. A trivalent nanobody, mNb6-tri, displayed femtomolar affinity for Spike and picomolar neutralization of SARSCoV-2 infection. mNb6-tri retains function after aerosolization, lyophilization, and heat treatment, which enables aerosol-mediated delivery directly to the airway epithelia.
https://science.sciencemag.org/content/early/2020/11/04/science.abe3255/tab-pdf
Another team working with camelid nanobodies constructed multivalent constructs that achieved ultrahigh neutralization potency (IC50s as low as 0.058 ng/ml) and may prevent mutational escape. These thermostable Nbs can be rapidly produced in bulk from microbes and resist lyophilization, and aerosolization.
https://science.sciencemag.org/content/sci/early/2020/11/04/science.abe4747.full.pdf

The US FDA authorizes Eli Lilly's monoclonal antibody to SARS-CoV-2 (bamlanivimab) for the treatment of mild-to-moderate COVID-19 in adult and pediatric patients https://www.fda.gov/news-events/press-announcements/coronavirus-covid-19-update-fda-authorizes-monoclonal-antibody-treatment-covid-19

Treatment with an anti-TNFalpha mAb can restore "normal" ACE2 levels in patients with IBD, which might be important in the context of SARS-CoV-2 infection and potentially explain reports of reduced morbidity from COVID-19 in IBD patients treated with anti-cytokines.
https://www.sciencedirect.com/science/article/abs/pii/S0016508520353312

Vaccines

Pfizer/BioNTech announced that an early interim analysis of their phase III results suggests their mRNA vaccine was strongly effective – 90% fewer cases were observed among individuals who received two doses three weeks apart, as compared to placebo. The company cannot file for an EUA until half of the patients have been followed for at least two months after their second dose (expected to occur ends of November). No information on preventing disease versus infection is yet available.
https://www.statnews.com/2020/11/09/covid-19-vaccine-from-pfizer-and-biontech-is-strongly-effective-early-data-from-large-trial-indicate/
As statnews points out, this is also good news for all the other candidate vaccines that target Spike. https://www.statnews.com/2020/11/09/four-reasons-for-encouragement-based-on-pfizers-covid-19-vaccine-results/

New York-based Codagenix started a phase I trial for its vaccine based on an inactivated virus that has been created by introducing hundreds of mutations in the viral genome and assembled in special host cells.
https://www.nytimes.com/interactive/2020/science/coronavirus-vaccine-tracker.html#codagenix

Self-assembling protein nanoparticle immunogens elicited potent and protective antibody responses against SARS-CoV-2 in mice. The nanoparticle vaccines display 60 SARS-CoV-2 spike receptor-binding domains (RBDs) in a highly immunogenic array and induced neutralizing antibodies targeting different RBD epitopes and at ten-fold higher titers than the prefusion-stabilized spike. Their high yield and stability suggests that manufacture of the nanoparticle vaccines will be highly scalable, and clinical trials are being prepared. https://www.cell.com/cell/fulltext/S0092-8674(20)31450-1

Bahrain has granted emergency approval for the use of Sinopharm's inactivated SARS-CoV-2 vaccine candidate currently in phase III trials on frontline workers https://www.reuters.com/article/health-coronavirus-bahrain/update-1-bahrain-allows-sinopharm-covid-19-vaccine-candidate-use-in-frontline-workers-idUSL1N2HP0R0

Prophylactic nasal spray? A team from Columbia University shows that intranasal administration of a dimeric lipopeptide fusion inhibitor completely prevents SARS-CoV-2 infection in ferrets. These lipopeptides are highly stable and non-toxic and thus readily translate into a safe and effective intranasal prophylactic approach to reduce transmission of SARS-CoV-2.
https://www.biorxiv.org/content/10.1101/2020.11.04.361154v1

Other: Minks and Viral Variants

Denmark's Prime Minister announced the culling of its entire herd of 17 million mink, after detecting a viral variant that "could have reduced susceptibility to COVID-19 vaccines." So far, 5 different groups or clusters of mink variants have been found in Denmark (clusters 1-5). A specific virus from cluster 5 has been detected with 4 simultaneous changes (H69del/V70del, Y453F, I692V and M1229I) in the genes for the spike protein in 5 mink farms and in 12 patient samples. Laboratory experiments suggest this variant is slightly less susceptible to antibodies in convalescent plasma. However, no detailed information has been published and the implications in terms of transmission, clinical presentation, diagnostics, treatment, and vaccines need to be evaluated. It does mean, however, that continued mink breeding entails a risk.
https://www.statnews.com/2020/11/05/spread-of-mutated-coronavirus-in-danish-mink-hits-all-the-scary-buttons-but-fears-may-be-overblown/
See also WHO's risk assessment: https://www.who.int/csr/don/06-november-2020-mink-associated-sars-cov2-denmark/en/

ISGlobal

COVID-19 EPIDEMIC

Epidemiological situation (17/11/2020, ECDC data):

Globally:
55 154 651 confirmed cases and 1 328 537 deaths

- This week, the daily number of deaths worldwide has reached a new high: 7842 (7-day average) as compared to 6825 during the maximum peak in April.
- Europe, the US and the rest of the Americas continue to contribute to most of the newly confirmed cases and deaths in the past days.

Confinement and deconfinement measures

In the absence of vaccines and treatments, a suitable combination of non-pharmaceutical interventions is necessary to curb the spread of the SARS-CoV-2 virus. A modelling approach quantifies the impact of 6,068 hierarchically coded NPIs implemented in 79 territories, and shows that less disruptive and costly NPIs can be as effective as more intrusive, drastic, ones (such as national lockdowns).
https://www.nature.com/articles/s41562-020-01009-0

Virus

The WHO has released its plan to investigate the origins of the COVID pandemic. The search will start in Wuhan and expand across China and beyond. *Nature* reviews the challenges of this investigation. https://www.nature.com/articles/d41586-020-03165-9

Real-time conformational analysis of SARS-CoV-2 Spike indicates that antibodies can neutralise S by two different mechanisms: competition with hACE2 for binding to the receptor-binding domain (RBD) or allosteric interference with conformational changes required for entry. https://www.cell.com/cell-host-microbe/fulltext/S1931-3128(20)30618-1#%20

Two studies in *Science* show that neuropilin 1 at the cell surface greatly enhances infectivity of SARS-CoV-2 through binding to furin-cleaved Spike S1. Pathological analysis of olfactory epithelium obtained from human COVID-19 autopsies revealed that SARS-CoV-2 infected NRP1-positive cells facing the nasal cavity. The results suggest the S–NRP1 interaction as a potential antiviral target.
https://science.sciencemag.org/content/370/6518/856/tab-pdf
https://science.sciencemag.org/content/370/6518/861/tab-pdf
See related comment: https://science.sciencemag.org/content/370/6518/765.full

A case report of an immunosuppressed patient shows that the virus mutated quickly in the person's body. https://www.nejm.org/doi/10.1056/NEJMc2031364

Experiments in primary human cells and animal models suggests that the D614G substitution enhances SARS-CoV-2 infectivity, competitive fitness, and transmission.
https://science.sciencemag.org/content/early/2020/11/11/science.abe8499

Testing / Tracing
A comparison of seven commercial SARS-CoV-2 rapid point-of-care antigen tests, performed by C. Dorsten and colleagues, shows that the sensitivity range of most tests overlaps with viral loads typically observed during the first week of symptoms (i.e. when individuals are most infectious). These tests could therefore enable rapid decision making in various areas of healthcare and public health.
https://www.medrxiv.org/content/10.1101/2020.11.12.20230292v1.full.pdf

Transmission
Using cell phone data and mobility networks, researchers mapped the hourly movements of 98 million people from neighborhoods. The model predicts that a small minority of "superspreader" places (mainly restaurants, gyms, cafes, houses of worship) account for a large majority of infections and that restricting occupancy at these places is more effective than general lockdowns. https://www.nature.com/articles/s41586-020-2923-3

A study of an outbreak on an aircraft carrier (USS T Roosevelt), with a crew of 4,779, shows quick spread facilitated by close quarters and 47% of those who tested positive never developed symptoms. https://www.nejm.org/doi/full/10.1056/NEJMoa2019375
Another study with over 1,800 marine recruits who were supervised during 2 weeks at a closed college campus shows that transmission clusters occurred within platoons even with masks, social distancing and symptom monitoring. Most recruits who tested positive were asymptomatic, and no infections were detected through daily symptom monitoring. https://www.nejm.org/doi/full/10.1056/NEJMoa2029717

A transmission model combining epidemiological and mobility data shows that marked, asynchronous reductions of the basic reproductive number occurred throughout the US in association with social distancing and other control measures. If these measures had been implemented 1-2 weeks earlier, up to 59,000 deaths could have been averted.
https://advances.sciencemag.org/content/early/2020/11/05/sciadv.abd6370

Italian researchers claim to have detected SARS-CoV-2 antibodies in asymptomatic individuals involved in a lung cancer screening program as early as September 2019.
https://journals.sagepub.com/doi/10.1177/0300891620974755

In a recent update, the CDC seems to acknowledge a role of masks in self-protection, while the German RKI still sees no such evidence *(Thanks for the tip, Kurt Straif!)*
https://www.cdc.gov/coronavirus/2019-ncov/more/masking-science-sars-cov2.html

Symptoms / Risk factors
An analysis of 12,066 hospitalized patients from the Spanish registry SEMI-COVID-19 identified 4 phenotypic clusters which predicted the in-hospital prognosis of clinical outcomes. Those presenting cold-like symptoms and loss of smell and taste had a better prognosis. https://www.mdpi.com/2077-0383/9/11/3488

TMPRSS2 protein are co-expressed in some pancreatic ducts, but not in beta cells of the human pancreas, making it unlikely that the isolated reports of type 1 diabetes after SARS-CoV-2 infection are due to direct viral infection. https://www.cell.com/cell-metabolism/fulltext/S1550-4131(20)30601-X

A systematic review of SARS-CoV-2 related Multisystem Inflammatory Syndrome in 655 children concludes that although most children required intensive care and

immunomodulatory therapies, favorable outcomes were reported on the majority with low-mortality rates.
https://journals.lww.com/pidj/Fulltext/2020/11000/A_Systematic_Review_of_Multisystem_Inflammatory.3.aspx

A seroprevalence study in Kenya reveals an average prevalence of 5.6% (174/3098), indicating that SARS-CoV-2 exposure is more extensive than indicated by case-based surveillance. The "sharp contrast" between antibody prevalence and COVID-19 deaths hints that the virus's effects are dampened in Africa.
https://science.sciencemag.org/content/early/2020/11/11/science.abe1916

Long Covid: In one study with 128 participants recovered from COVID-19, 50% reported persistent fatigue up to 10 weeks after initial symptoms. There was no association between COVID-19 severity and post-viral fatigue.
https://journals.plos.org/plosone/article?id=10.1371/journal.pone.0240784

A retrospective study using electronic health records from 62,354 patients diagnosed with COVID-19, shows that 20% were diagnosed with a psychiatric disorder within 3 months. Anxiety, depression and insomnia were the most frequent mental health problems. https://www.thelancet.com/journals/lanpsy/article/PIIS2215-0366(20)30462-4/fulltext

Antibodies / Immunity
An analysis using peptide-MHC class I tetramer technology suggests that pre-existing and induced SARS-CoV-2-specific CD8+T cells represent major determinants of immune protection in mild SARS-CoV-2 infection. Virus-specific CD8+ T cells were detectable in convalescent individuals who were seronegative for anti-SARS-CoV-2 antibodies targeting spike (S) and nucleoprotein (N).
https://www.nature.com/articles/s41591-020-01143-2

A study indicates that COVID-19 patients are less inflamed than influenza patients. Up-regulation of IL-6, GCSF, IL-1RA, and MCP1 predicted death from acute respiratory failure among COVID-19 patients but were not statistically higher than influenza patients. Single-cell transcriptional profiling was concordant with profound suppression in interferon signalling among COVID-19 patients.
https://advances.sciencemag.org/content/early/2020/11/13/sciadv.abe3024

A test developed by Adaptive Biotechnologies could facilitate the study of SARS-CoV-2 specific T cell responses in people exposed to the virus. The test is based on detecting public TCR sequences specific for the 11 most immunogenic antigens the team has previously identified. https://www.nytimes.com/2020/11/10/health/t-cell-test-coronavirus-immunity.html

Treatment
Patients who received inhaled interferon beta-1a (developed by Synairgen) had greater odds of improvement and recovered more rapidly from SARS-CoV-2 infection than patients who received placebo, according to a randomised, double-blind, placebo-controlled phase 2 trial involving adults admitted to hospital with COVID-19.
https://www.thelancet.com/journals/lanres/article/PIIS2213-2600(20)30511-7/fulltext

Artificial intelligence analyses have identified baricitinib, a JAK inhibitor, as a potential drug for COVID-19. In vitro experiments and a small trial in patients shows that JAK

inhibition reduces SARS-CoV-2 liver infectivity and modulates inflammatory responses to reduce morbidity
and mortality.
https://advances.sciencemag.org/content/early/2020/11/13/sciadv.abe4724/tab-pdf

A Stanford University team will test whether nasal drops that contain chicken antibodies to SARS-CoV-2 can offer temporary protection. The IgY antibodies are harvested from egg yolks of chickens immunized with Spike. No preclinical data is available yet. A first trial in Australia will test safety before an efficacy trial is launched in the US. https://www.sciencemag.org/news/2020/11/can-nose-full-chicken-antibodies-ward-coronavirus-infections

A study describes the design, validation, and optimization of de novo hACE2 decoys to neutralize SARS-CoV-2. The best decoy, CTC-445.2d, potently neutralized SARS-CoV-2 infection in vitro and protected Syrian hamsters from a subsequent lethal SARS-CoV-2 challenge. Since the decoy replicates the spike protein target interface in hACE2, it is intrinsically resilient to viral mutational escape.
https://science.sciencemag.org/content/early/2020/11/04/science.abe0075

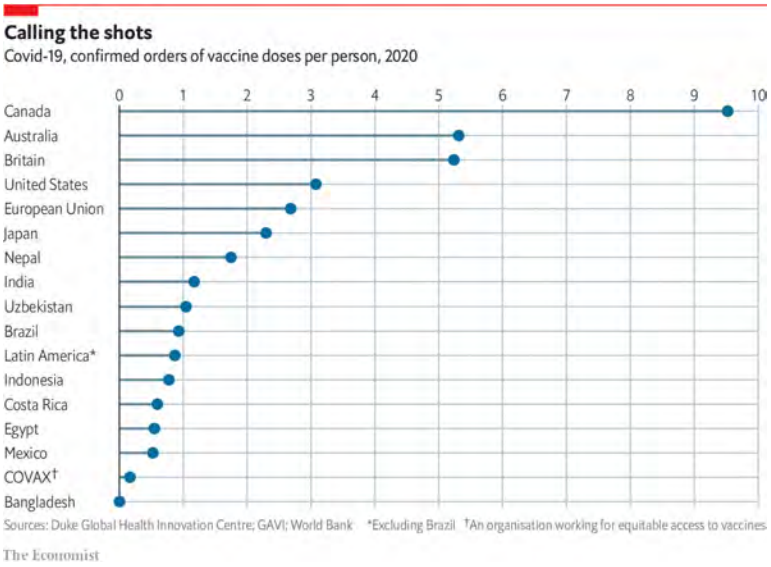
Researchers from UC Irvine produced yeast with the ability to continuously hypermutate antibodies. This allowed them to evolve high-affinity nanobodies against SARS-CoV-2 by iteratively growing and enriching yeast cells that bind antigen. After 3-8 of these cycles saw ~580-fold and ~925-fold improvements in binding affinities and pseudovirus neutralization potencies, respectively. This technology would allow to streamline antibody generation in rapid response to current and future viral outbreaks.
https://www.biorxiv.org/content/10.1101/2020.11.11.378778v1

A study aimed at optimising the use of convalescent plasma shows that higher antibody levels were observed in men, in older donors and in those who had been hospitalised.
https://www.eurosurveillance.org/content/10.2807/1560-7917.ES.2020.25.45.2001754

Vaccines
Moderna's first interim analysis for its mRNA vaccine candidate indicates an efficacy of 94.5%. The analysis was based on 95 cases, of which 90 cases of COVID-19 were observed in the placebo group versus 5 cases observed in the mRNA-1273 group (cases confirmed two weeks after last shot). Eleven severe cases occurred, all of them in the placebo group. By the end of 2020, Moderna expects to have approximately 20 million doses of mRNA-1273 for the U.S. It remains on track to manufacture 500 million to 1 billion doses globally in 2021. In contrast to the Pfizer vaccine, the Moderna vaccine can be kept at refrigerator temperatures for a month.
https://investors.modernatx.com/news-releases/news-release-details/modernas-covid-19-vaccine-candidate-meets-its-primary-efficacy

Janssen is starting a major trial in UK to test whether two doses of its adenoviral-vectored vaccine protect better than one. https://www.bbc.com/news/health-54951650

Wealthy nations representing just 13 percent of the world's population have already reserved more than half (51 percent) of the promised doses of leading COVID-19 vaccine candidates, says an Oxfam report. Even if all five vaccines succeed, 61% of the world's population will not have a vaccine until at least 2022.
https://www.oxfam.org/en/press-releases/small-group-rich-nations-have-bought-more-half-future-supply-leading-covid-19



A webinar organised by BMJ on "COVID-19: Known unknowns" will take place on 20th November *(Thanks for the tip, Kurt Straif!)* https://t.co/XsWuDwc3MF?amp=1

Other: more on mink

Scientists who have reviewed data from Denmark's mink-related variants say the mutations aren't particularly concerning because there is little evidence that they allow the virus to spread more easily among people, make it more deadly or will jeopardize therapeutics and vaccines https://www.nature.com/articles/d41586-020-03218-z

In the Netherlands, whole genome sequencing of outbreaks on 16 mink farms and the humans living or working on these farms concludes that the virus was initially introduced from humans, circulated widely among mink, and was then transmitted back to humans. 68% of tested mink farm residents, employees or contacts had evidence of SARS-CoV-2 infection. No unique mutations were observed (in contrast to cluster 5 in Denmark).
https://science.sciencemag.org/content/sci/early/2020/11/09/science.abe5901.full.pdf

ISGlobal

COVID-19 EPIDEMIC

Epidemiological situation (24/11/2020, ECDC data):

Globally:
59 307 493 confirmed cases and 1 397 672 deaths

- The global daily reported cases and deaths continue to grow, with countries in the European and the Americas regions still showing the largest increases.

Testing / Tracing

The first COVID-19 diagnostic self-test at home has been approved by the U.S. FDA. It is a molecular (LAMP-based) diagnostic test that can provide results in 30 minutes or less, and would cost around 50USD. https://www.npr.org/sections/coronavirus-live-updates/2020/11/17/936055284/fda-approves-first-at-home-coronavirus-test

Public Health England and the University of Oxford show lateral flow tests are accurate and sensitive enough to be used in the community, including for asymptomatic people. Of the 40 tested, the Innova SARS-CoV-2 Antigen Rapid Qualitative Test is nearing completion of the evaluation process, with an overall sensitivity of 76.8% for all PCR positive individuals but over 95% for individuals with high viral loads.
https://www.ox.ac.uk/news/2020-11-11-oxford-university-and-phe-confirm-lateral-flow-tests-show-high-specificity-and-are

A modelling study shows that effective screening depends largely on frequency of testing and the speed of reporting, and is only marginally improved by high test sensitivity. This means that screening should prioritize accessibility, frequency, and sample-to-answer time; whereas analytical limits of detection should be secondary.
https://advances.sciencemag.org/content/early/2020/11/20/sciadv.abd5393.1

Results of the city-wide SARS-CoV-2 nucleic acid screening programme conducted in Wuhan between May 14 and June 1, 2020 are reported. All city residents aged six years or older were eligible and 9,899,828 (92.9%) participated. No new symptomatic cases and 300 asymptomatic cases were identified. The prevalence of SARS-CoV-2 infection in Wuhan was therefore very low five to eight weeks after the end of lockdown.
https://www.nature.com/articles/s41467-020-19802-w

Transmission

A systematic review and meta-analysis of SARS, SARS-CoV-2 and MERS viral load and shedding dynamics concludes that although SARS-CoV-2 RNA shedding in respiratory and stool samples can be prolonged, duration of viable virus is relatively short-lived. SARS-CoV-2 titres in the upper respiratory tract peak in the first week of illness.
(Thanks Kurt Straif for the tip!)
https://www.thelancet.com/journals/lanmic/article/PIIS2666-5247(20)30172-5/fulltext

Symptoms / Risk factors

Obesity: A prospective serology-based cohort analysing the effect of BMI on SARS-CoV-2 infection and disease, suggests obesity is not linked to an increased risk of SARS-CoV-2 infection; that symptom phenotype is strongly influenced by obesity; and that despite evidence of obesity-associated immune dysregulation in severe COVID-19, there is no evidence of a muted or suppressed immune response in non-severe infections.
https://www.medrxiv.org/content/10.1101/2020.11.11.20229724v1.full.pdf

Another study analysing data from the UK Biobank shows that people who are genetically predisposed toward obesity or high levels of "bad" cholesterol (LDL) are at increased risk (15% and 58% respectively) of contracting COVID-19. People with a positive SARS-CoV-2 test were more likely to be older, male, impoverished, and had a higher prevalence of heart and metabolic risk factors.
https://geneticobesitynews.com/2020/11/19/higher-covid-infection-risk-seen-in-genetic-predisposition-to-obesity-bad-cholesterol/

Children: A study in three children with symptomatic COVID parents shows that children can mount an immune response to SARS-CoV-2 without virologic confirmation of infection - all family members had salivary anti-SARS-CoV-2 antibodies, predominantly IgA. These findings raise the possibility that immunity in children can prevent the establishment of SARS-CoV-2 infection.
https://www.nature.com/articles/s41467-020-19545-8

Antibodies / Immunity

The largest prospective study to date, performed with 12,219 HCWs (1246 of them positive for antibodies), shows that a prior SARS-CoV-2 infection that generated antibody responses offered protection from reinfection for most people in the six months following infection.
https://www.medrxiv.org/content/10.1101/2020.11.18.20234369v1

Another study among HCWs of Barcelona's Hospital Clinic (led by our colleague Carlota Dobaño) showed that SARS-CoV-2-specific IgGs remain stable for at least three months, while IgAs and IgMs decay. https://academic.oup.com/jid/advance-article/doi/10.1093/infdis/jiaa696/5974123

Breast milk from COVID-19 recovered women contain significant amounts of SARS-CoV-2 specific IgA antibodies, most of them neutralizing, which may protect babies from infection https://www.cell.com/iscience/fulltext/S2589-0042(20)30932-9

The 'COVID Warriors' study (UK) reports results for the second round of testing in a large longitudinal survey of antibody responses in children (aged 2-15). With almost 1,000 participants, the seroprevalence was of 7.7% (not substantially different from the first testing, two months before). The results indicate that antibody titres in children exposed to SARS-CoV-2 remain at a detectable level for at least 62 days, with some antibody titres increasing over time (consistent with data in adults).
https://www.thelancet.com/action/showPdf?pii=S1473-3099%2820%2930884-7

Memory B and T cells: A study analysed multiple compartments of circulating immune memory to SARS-CoV-2 in 185 COVID-19 cases, including 41 cases at > 6 months post-infection. Spike IgG was relatively stable over 6+ months. Spike-specific memory B cells were more abundant at 6 months than at 1 month. SARS-CoV-2-specific CD4+ T cells and CD8+ T cells declined with a half-life of 3-5 months. These results suggest immunity to SARS-Cov-2 could last several months, even years.
https://www.biorxiv.org/content/10.1101/2020.11.15.383323v1

A longitudinal assessment of individuals recovered from mild COVID-19 shows SARS-CoV-2-specific IgG antibodies, neutralizing plasma, memory B and memory T cells that persisted for at least three months, and IgG memory B cells that even increased over time. Additionally, SARS-CoV-2-specific memory lymphocytes exhibited characteristics associated with potent antiviral function. https://www.cell.com/cell/fulltext/S0092-8674(20)31565-8

A review in *Science Immunology* sheds light on the "known unknowns" of pre-existing and acquired T cell responses in relation to acute and convalescent SARS-CoV-2 infection. https://immunology.sciencemag.org/content/5/53/eabe8063

Cross-reactivity: A study analysing hCOV-specific antibodies in sera collected before the COVID-19 pandemic indicates that most individuals possessed hCoV-reactive antibodies before the pandemic and around 23% of them possessed non-neutralizing antibodies that cross-reacted with SARS-CoV-2 spike and nucleocapsid proteins. These cross-reactive antibodies were not associated with protection against SARS-CoV-2 infections or hospitalizations, but paradoxically they were boosted upon SARS-CoV-2 infection. https://www.medrxiv.org/content/10.1101/2020.11.06.20227215v1

Reinfections: According to BNO's COVID-19 reinfection tracker, there are 26 confirmed (genetically proven) cases and 572 suspected cases of reinfection worldwide. https://bnonews.com/index.php/2020/08/covid-19-reinfection-tracker/

Treatment

Monoclonal antibodies: Pairs of antibodies may be more effective than single antibodies at preventing and treating COVID-19, according to a study that tested human monoclonal antibodies (hu-mAbs) in a Syrian hamster model and in a mouse-adapted model of SARS-CoV-2 infection. Results also suggest that binding to activating Fc receptors enhances the antibodies' protective capacity. https://rupress.org/jem/article/218/3/e20201993/211549/Antibody-potency-effector-function-and

Regeneron's antibody treatment (casirivimab and imdevimab administered together) has been granted EUA by the FDA for the treatment of mild to moderate COVID-19 in adults and pediatric patients (12 years of age or older). https://www.fda.gov/news-events/press-announcements/coronavirus-covid-19-update-fda-authorizes-monoclonal-antibodies-treatment-covid-19

Remdesivir: In revised guidance, the WHO has recommended against using remdesivir to treat hospitalized COVID-19 patients because current evidence does not prove it improves patient outcomes. https://www.statnews.com/2020/11/19/who-recommends-against-remdesivir-covid-19/

Vaccines

AstraZeneca/Oxford: Phase 2/ 3 trial results for AstraZeneca's vaccine ChAdOx1 show it is better tolerated in older adults than in younger adults and has similar immunogenicity across all age groups after a boost dose. No T cell responses were measured and no efficacy results are reported. https://www.thelancet.com/journals/lancet/article/PIIS0140-6736(20)32466-1/fulltext

Interim results for the phase 3 trial of the vaccine (AZD1222) were announced based on 131 infections, 30 of them in the vaccine group and 101 in the control group (saline or

meningitis shot). One dosing regimen (with n=2,741) showed vaccine efficacy of 90% when given as a half dose, followed by a full dose one month apart. The other regimen, two full doses one month apart, (n=8,895) showed 62% efficacy. Combined, the average efficacy was 70%. There was some evidence for lower levels of asymptomatic infection, according to the press release. https://www.astrazeneca.com/media-centre/press-releases/2020/azd1222hlr.html
Apparently, the half-dose was a lucky mistake! https://www.reuters.com/article/us-health-coronavirus-astrazeneca-dosing/dosing-error-turns-into-lucky-punch-for-astrazeneca-and-oxford-idUSKBN28327Q
The differences in efficacy between the full and half dose are presently not known but could be due to immunity against the adenoviral vector, induced upon the first shot https://blogs.sciencemag.org/pipeline/archives/2020/11/23/oxford-az-vaccine-efficacy-data
The HumanVaccineProject (HVP) has published a newsletter on these results, with comments from our colleague Carlota Dobaño: *(Thanks Carlota for the tip!)* https://www.humanvaccinesproject.org/newsletters/

Sinovac: Phase 1/ 2 results for Sinovac's inactivated vaccine candidate against COVID-19 (CoronaVac) were published: the low dose was safe and well-tolerated. Neutralising antibodies were induced in all vaccinated volunteers, albeit at lower levels than those observed in convalescent patients. Phase 3 trials are already underway. https://www.thelancet.com/journals/laninf/article/PIIS1473-3099(20)30843-4/fulltext

Pfizer/BioNTech has submitted an Emergency Use Authorization to the FDA. The Advisory committee will meet on December 10 to discuss the request.
The Infectious Disease Society of America stresses that even if an EUA is granted, clinical trials and data collection must continue. Measures that include wearing masks, frequent handwashing, maintaining physical distance, and restricting the size of gatherings will remain crucial. https://www.idsociety.org/news--publications-new/articles/2020/idsa-response-to-pfizer-eua-app/

Other: more on mink farms
An analysis of published SARS-CoV-2 genomes isolated from minks in different countries identified 23 recurrent mutations (including three nonsynonymous mutations in the Spike RBD) that independently emerged at least four times but are only very rarely observed in strains circulating in humans. These results point to ongoing adaptation of SARS-CoV-2 to a new host, which may also have happened in humans before the first SARS-CoV-2 genomes were sequenced. https://www.biorxiv.org/content/10.1101/2020.11.16.384743v1

Data from SARS-CoV-2 spread in Denmark's mink farms has been published. Full-length virus genome sequencing revealed novel virus variants in mink which subsequently appeared within the local human community. https://wwwnc.cdc.gov/eid/article/27/2/20-3794_article

Following a review of the evidence on mink variants in Denmark, the ECDC and WHO concluded that the risk for the population at large was not increased but stressed the importance of surveillance at the human-animal interface and rapid exchange of information to track possible viral changes that could be of concern. https://www.thelancet.com/pdfs/journals/laninf/PIIS1473-3099(20)30912-9.pdf

ISGlobal

COVID-19 EPIDEMIC

Epidemiological situation (01/12/2020, ECDC data):

Globally:
63 245 164 confirmed cases and 1 469 469 deaths

- Last week saw the first decline in newly-reported COVID-19 cases globally since September, due to a decrease in cases in Europe, according to the WHO https://www.who.int/director-general/speeches/detail/who-director-general-s-opening-remarks-at-the-media-briefing-on-covid-19---30-november-2020
- However, cases are still increasing in most other regions, and gains can easily be lost, especially with the holiday season coming up, warns WHO DG Tedros.
- The USA continues to show uncontrolled transmission.

Virus

Origin: *The Lancet* Covid-19 Commission's task force on the origins of the virus was announced this week, and will be led by Peter Daszak, bat virus researcher and president of EcoHealth Alliance. Apart from analysing all available evidence, the task force will seek to interview researchers in China to attempt to understand where and how the virus originated. However, unlike the WHO mission, it will not work on the ground from China.
https://www.scmp.com/news/china/science/article/3111691/where-did-covid-19-originate-these-virus-sleuths-are-assessing

Mutations: At this stage, there is no evidence for significantly more transmissible lineages of SARS-CoV-2 due to recurrent mutations, according to an analysis that developed a phylogenetic index to quantify the relative number of descendants in sister clades with and without a specific allele. https://www.nature.com/articles/s41467-020-19818-2

Cell entry: A study shows that cholesterol 25-hydroxylase (CH25H) -an interferon-stimulated gene with broad antiviral activities- and its enzymatic product (25HC), are potent inhibitors of SARS-CoV-2 replication. Internalized 25HC accumulates in the late endosomes and potentially restricts fusion of SARS-CoV-2 spike protein to the membrane, via blockade of cholesterol export.
https://www.pnas.org/content/early/2020/11/24/2012197117

Testing / Tracing

A pilot study led by Hospital Sant Joan de Deu, Barcelona, with over 2,000 participants, shows that direct RT-qPCR on self-collected raw saliva is a simple, rapid, and accurate method that can be scaled up for enhanced community-wide SARS-CoV-2 screening. Saliva sampling is easier and reduces the risk of aerosols.
https://www.medrxiv.org/content/10.1101/2020.11.19.20234245v2

The FDA granted an EUA for COVID-SeroKlir, Kantaro's robust semi-quantitative antibody test that measures anti-SARS-CoV-2 antibody levels. Kantaro partnered with

Bio-Techne to manufacture and distribute the test. The underlying technology was developed by Dr. Florian Krammer and colleagues at Mount Sinai.
https://www.fda.gov/media/144009/download

Metagenomic next-generation sequencing (mNGS) using cell-free DNA from body fluids enables high-specificity, unbiased pathogen detection (including SARS-CoV-2) and may accelerate clinical decisions. https://www.nature.com/articles/s41591-020-1105-z

Transmission
Combining epidemiological analysis with deep viral genome sequencing during the first wave of infections in Austria enabled the reconstruction of superspreading events and a map of tourism-related viral spread originating from Austria in spring 2020. The findings reveal a low-frequency mutation that progressed to fixation within the infection chain. Furthermore, validated infector-infectee pairs allowed to determine an average transmission bottleneck size of 10^3 SARS-CoV-2 particles.
https://stm.sciencemag.org/content/early/2020/11/20/scitranslmed.abe2555.full

Serologic testing of US blood donations suggests that SARS-CoV-2 may have been introduced into the United States prior to January 19, 2020. 7,389 samples were tested, of which 106 were reactive to SARS-CoV-2 by pan Ig and 1/90 (1.1%) had SARS-CoV-2 S1-specific Ig. However, potential cross-reactivity to human common cold coronaviruses (at least in some samples) cannot be ruled out.
https://academic.oup.com/cid/advance-article/doi/10.1093/cid/ciaa1785/6012472

Symptoms / Risk factors
Loss of smell: Single-cell RNA-seq analysis shows that sustentacular cells, which maintain the integrity of olfactory sensory neurons, express ACE2 and TMPRSS2, providing a potential 'entry door' for SARS-CoV-2 into a sensory system in direct connection with the brain. https://www.cell.com/iscience/fulltext/S2589-0042(20)31036-1
Another study shows that SARS-CoV-2 induces acute anosmia and ageusia in golden Syrian hamsters, both lasting as long as the virus remains in the olfactory epithelium and the olfactory bulb. Furthermore, olfactory mucosa sampling in COVID-19 patients presenting with persistent loss of smell reveals the presence of virus transcripts and of SARS-CoV-2-infected cells, together with protracted inflammation.
https://www.biorxiv.org/content/10.1101/2020.11.18.388819v1.full#ref-12

A review of Parkinson cases related to SARS-CoV-2 concludes no substantiated causality. https://www.thelancet.com/journals/laneur/article/PIIS1474-4422(20)30442-7/fulltext

An analysis identifies a consensus pattern within the Spike glycoprotein which is also present in in many proteins involved in coagulation processes. This cysteine-rich EGF-like domain could be involved in the mechanisms leading to coagulopathy and cell-fusion in COVID-19 disease. https://www.nature.com/articles/s41420-020-00372-1

Antibodies / Immunity
A longitudinal analysis of antibody responses conducted on a prospective cohort of COVID-19 patients shows that individuals with mild or asymptomatic infection experienced an insignificant decay in neutralizing activity that persisted six months

after symptom onset or diagnosis. The study was performed at the IGTP, Barcelona. https://www.biorxiv.org/content/10.1101/2020.11.22.389056v2

T cells: An analysis of T cells recognising common cold coronaviruses and SARS-CoV-2 in pre-exposed or COVID-19 patients identifies low avidity CD4+T cell responses as a hallmark of severe COVID-19. The findings also argue against a protective role for CCCoV reactive T cells in SARS-CoV-2 infection.
https://www.cell.com/immunity/fulltext/S1074-7613(20)30503-3

Regarding T cell responses, this review summarises what is known of SARS-CoV-2 cross-reactive T cells. https://www.nature.com/articles/s41590-020-00838-5

Beyond B and T cells: A multi-omics analysis identifies responses of megakaryocytes, erythroid cells and plasmablasts as hallmarks of severe COVID-19 trajectories. The findings may help develop biomarkers and targeted treatments of patients with COVID-19. https://www.cell.com/immunity/fulltext/S1074-7613(20)30504-5

Mucosal immunity: A perspective article argues that there is a significant role for mucosal immunity and for secretory as well as circulating IgA antibodies in COVID-19. It also discusses how mucosal immunity can be exploited for beneficial diagnostic, therapeutic (particularly vaccines), or prophylactic purposes.
https://www.frontiersin.org/articles/10.3389/fimmu.2020.611337/full
In RSV infection, for example, neutrophilic inflammation in the airway at the time of pathogen exposure predisposes individuals to symptomatic infection.
https://science.sciencemag.org/content/370/6513/eaba9301

Treatment

HCQ: Postexposure therapy with hydroxychloroquine does not prevent SARS-CoV-2 infection or symptomatic COVID-19, according to a cluster-randomized trial with over 2500 healthy contacts of COVID cases (trial led by O. Mitja).
https://www.nejm.org/doi/full/10.1056/NEJMoa2021801?query=featured_home
In turn, the European Medicine Agency (EMA)'s safety committee (PRAC) has recommended updating the product information for all chloroquine or hydroxychloroquine-containing medicines following a review of all available data that confirmed a link between the use of these medicines and the risk of psychiatric disorders and suicidal behaviour. The review was prompted by a report from the Spanish Medicines Agency (AEMPS) of six cases of psychiatric disorders in patients with COVID-19 who were given higher than authorised doses of hydroxychloroquine.
https://www.ema.europa.eu/en/news/meeting-highlights-pharmacovigilance-risk-assessment-committee-prac-23-26-november-2020

Convalescent plasma: A randomized trial of convalescent plasma for the treatment of Covid-19 severe pneumonia showed no benefit. The trial was performed in Argentina, with 228 patients assigned to receive convalescent plasma and 105 to placebo. Specific SARS-CoV-2 IgG antibody titer was measured in each convalescent plasma pool before transfusion and was above 1:800 in all cases. No difference in clinical outcomes or mortality was observed.
https://www.nejm.org/doi/full/10.1056/NEJMoa2031304?query=featured_home

Oxygen: As Peter Piot and John Nkengasong point out in Global Health Now, 9 in 10 hospitals in low- and middle-income countries don't have access to the equipment that they need to diagnose and treat oxygen deficiency. As a result, only 20% of patients who need oxygen receive it. https://www.globalhealthnow.org/2020-11/medical-oxygen-key-fighting-covid-19-pneumonia-and-next-respiratory-pandemic

Vaccines

The Sputnik V vaccine by Gamaleya Institute has reported efficacy of 91.4%, based on a second interim analysis with 39 infections (8 in vaccinated group, 31 in control group) among the almost 19,000 participants. The two-dose scheme begins with an Ad26-spike shot and is followed by a booster shot 21 days later with Ad5-spike (to avoid immune responses that could lower the efficacy of the second shot).
https://sputnikvaccine.com/newsroom/pressreleases/second-interim-analysis-of-clinical-trial-data-showed-a-91-4-efficacy-for-the-sputnik-v-vaccine-on-d/
Also: https://www.sciencemag.org/news/2020/11/more-data-its-covid-19-vaccine-russia-institute-offers-new-evidence-success

Moderna announced final phase 3 results for its vaccine candidate, showing 94% efficacy (a total of 196 cases of symptomatic Covid-19 in the 30,000-volunteer study, with 185 cases in placebo group and 11 in vaccine group). There were 30 cases of severe Covid-19 and 1 death in the placebo group of the study, and none in the vaccine group. It has applied for an EUA to the US FDA, and for a conditional marketing authorization from the European Medicines Agency.
https://www.statnews.com/2020/11/30/moderna-covid-19-vaccine-full-results/

Oxford/AstraZeneca announced its vaccine will undergo a new global trial to test the new dosing regime in a larger group of people, including those over 55 years of age (this age group was not included in those receiving the half-full regime by mistake). The timeline for regulatory approval and rollout of the vaccine in the UK and Europe should not be affected, they say. The full, peer-reviewed data would be published in the Lancet medical journal at the weekend.
https://www.theguardian.com/world/2020/nov/26/scrutiny-grows-over-oxford-universityastrazeneca-vaccine

D Burton and E Topol discuss the probability that COVID-19 vaccines induce stronger immunity than that induced upon natural infection.
https://www.nature.com/articles/s41591-020-01180-x

ISGlobal

COVID-19 EPIDEMIC

Epidemiological situation (08/12/2020, ECDC data):

Globally:
67 965 261 confirmed cases and 1 557 616 deaths

- This week, the number of COVID-19 patients in US hospitals passed 100,000 for the first time. The overall weekly hospitalization rate is at its highest point since the beginning of the pandemic, with steep increases in adults aged 65 years and older.
- Europe and the Americas region represent over 83% of both newly confirmed cases and newly reported deaths in the past 24 hours. In the Western Pacific region, Japan and South Korea are reporting a high incidence of cases.

The Lancet publishes some thoughts from the annual Lancet–Chinese Academy of Medical Sciences conference—held virtually last week. Issues covered the East Asian exceptionalism, the importance of being transparent about uncertainty, the physical, social and psychological long-term consequences, vaccine distribution, and humanitarian aspects, among others.
https://www.thelancet.com/journals/lancet/article/PIIS0140-6736(20)32584-8/fulltext

Virus
The nucleocapsid protein of SARS-CoV-2, which surrounds the viral genome, is produced at high levels within infected cells, enhances the efficiency of viral RNA transcription, and is essential for viral replication. A study shows that efficient transcription of viral RNA depends on liquid-liquid phase separation by the nucleocapsid protein in the cytoplasm, and proposes how this key step in viral replication can be inhibited. https://www.nature.com/articles/s41467-020-19843-1

A study exploring the coding potential of negative-strand RNA intermediates of SARS-CoV-2 found several putative ORFs and one new functional SARS-CoV-2 protein-coding loci which codes for a protein with alpha-helical structure (named Avo1) and is conserved in RaTG13 bat coronavirus. Avo1 contains a unique SREBP2 binding site which is associated with the "cytokine storm".
https://www.biorxiv.org/content/10.1101/2020.11.27.400788v1

A clustering analysis of > 1,900 SARS-CoV-2 genomes from around the world, over time, consistently identified 6 types of strains. Type VI haplotype, characterised by four single nucleotide variations (SNVs) including Spike D614G, has become the dominant one, suggesting a possible fitness gain. Later SNVs have emerged with strong allelic associations, forming new subtypes. Authors conclude that SNVs are an important consideration for SARS-CoV-2 classification and surveillance.
https://www.pnas.org/content/pnas/117/48/30679.full.pdf

Testing / Tracing

Rapid nucleic tests without amplification:

An amplification-free nucleic acid immunoassay, implemented on a lateral flow strip, can detect SARS-CoV-2 RNA in less than one hour. The assay uses DNA probes that bind to the regions in ORF1ab, envelope protein (E) and nucleocapsid (N), and a fluorescent-nanoparticle-labelled monoclonal antibody that binds to double-stranded DNA–RNA hybrids. The assay achieved sensitivities of 100% and specificities of 99% for both saliva and nasopharyngeal swabs. The commercial kit has been approved by the Chinese NMPA and has been given the CE certification.
https://www.nature.com/articles/s41551-020-00655-z

J. Doudna and her team publish in *Cell* their amplification-free CRISPR-Cas13a assay for the direct detection of SARS-CoV-2 from a nasal swab, which can be read with a mobile phone reader device. The assay has the potential to enable rapid, low-cost POC screening for SARS-Cov-2. https://www.cell.com/cell/fulltext/S0092-8674(20)31623-8

Transmission

In a global analysis of where SARS-CoV-2 transmission takes place, households show the highest transmission rates (with a secondary attack rate of 21.1%), says a report from the Imperial College London COVID-19 Response Team. The report also reveals that the chance of an asymptomatic infected person infecting a close contact was 3.5%, which was approximately a quarter of the 12.8% chance for a symptomatic infected person infecting a close contact. https://www.imperial.ac.uk/news/209673/covid-19-spread-different-social-settings-imperial/

A study with 68 NBA players performed a prospective longitudinal RT-qPCR testing to measure their viral RNA trajectories. On average, viral RNA concentrations peaked rapidly, regardless of symptoms (2.7 days after first detection). However, the viral clearance period was shorter for asymptomatic individuals (6.7 days) than for symptomatic individuals (10.5 days).
https://www.medrxiv.org/content/10.1101/2020.10.21.20217042v2
Together, these findings raise hopes that the current vaccines, which reduce the number of symptomatic cases, may also help reduce viral transmission

A German study concludes that 20 days after becoming mandatory, face masks reduced the number of new infections by around 45%.
https://www.pnas.org/content/early/2020/12/02/2015954117

A study estimating ratio of imported versus local cases in over 100 countries concludes that stringent travel restrictions might have little impact on epidemic dynamics except in countries with low COVID-19 incidence and large numbers of arrivals from other countries, or where epidemics are close to tipping points for exponential growth.
https://www.thelancet.com/journals/lanpub/article/PIIS2468-2667(20)30263-2/fulltext

A study using blood donor samples from Manaus shows that by June, one month after the epidemic peak, 44% of the population had detectable IgG antibodies. Correcting for cases without a detectable antibody response and antibody waning, the authors estimate a 66% attack rate in June, rising to 76% in October.
https://science.sciencemag.org/content/early/2020/12/07/science.abe9728

Symptoms / Risk factors
Cytokine storm is an umbrella term encompassing several disorders of immune dysregulation that can lead to multiorgan failure, and is an important feature in severe COVID-19. A review article describes in detail what is known on clinical and pathophysiological features of cytokine storms resulting from treatments, autoimmunity, pathogens, and COVID-19, as well as current and potential treatments. https://www.nejm.org/doi/full/10.1056/NEJMra2026131

The Centro Nacional de Epidemiología in Spain has published the country's lethality ciphers for the first pandemic wave: the infection fatality risk was 1.1% to 1.4% in men and 0.6% to 0.8% in women. It increased sharply after age 50, ranging from 11.6% to 16.4% in men aged 80 or more and from 4.6% to 6.5% in women aged 80 or more. These results confirm that fatality from covid-19 was greater than that reported for other common respiratory diseases, such as seasonal influenza.
https://www.bmj.com/content/371/bmj.m4509

A deep and time resolved molecular characterization of COVID-19 disease progression (performed with 86 diagnostic markers at 687 sampling points and 139 hospitalised patients) reveals a proteome profile in blood that could help predict which patients will need oxygen or ventilator support. The test has been validated in a further 24 severely ill patients, where it correctly predicted the outcome for 18 of 19 of those who survived and for five of five patients who died.
https://www.medrxiv.org/content/10.1101/2020.11.09.20228015v1.full.pdf

A news feature in *Nature* focuses on the high prevalence of delirium in severe COVID-19 patients and the potential risk of developing dementia later on.
https://www.nature.com/articles/d41586-020-03360-8

A case report describes two identical male twins who live together and developed COVID-19 simultaneously. They were attended by the same medical team. One developed severe disease and the other mild illness.
https://www.acpjournals.org/doi/10.7326/L20-1207

Immunocompromised patients may shed viable virus for at least 2 months, according to a study with 20 cancer patients who received stem cell transplants or CAR T-cells
https://www.nejm.org/doi/full/10.1056/NEJMc2031670

Antibodies / Immunity
Asynchronous responses:
Analysis of temporal IFN and inflammatory cytokine patterns in 32 moderate-to-severe COVID-19 patients with pneumonia reveals that IFN type I and III production were diminished and delayed, and pro-inflammatory cytokines (TNF, IL6, IL8) were produced before IFNs in in all patients. This pattern contrasts with what is observed in patients with pneumonia by influenza (where IFN production precedes pro-inflammatory cytokines). Higher type III IFN levels in patients with COVID-19 correlated with lower viral load and faster viral clearance. These data point to an untuned antiviral response in COVID-19, contributing to persistent viral presence, hyperinflammation and respiratory failure. https://www.nature.com/articles/s41590-020-00840-x

Cell has published the study from the La Jolla group demonstrating that COVID-19 patients, especially at elder ages, suffered the most when the immune components (CD4, CD8 T cells and antibodies) were asynchronous. The worst cases of COVID-19 had low levels of CD8+ killer T cells and CD4+ T helper cells. Scarcity of naïve T cells in

elderly people may be a risk factor for severe disease, and CXCL10 may be a biomarker of impaired T cell responses.
https://www.sciencedirect.com/science/article/pii/S0092867420312356

A longitudinal analysis of 983 longitudinal plasma samples from 79 hospitalized COVID-19 patients and 175 SARS-CoV-2-infected outpatients and asymptomatic individuals shows higher ratios of IgG antibodies targeting S1 or RBD domains of spike compared to nucleocapsid antigen in outpatients who had mild illness versus severely ill patients. Antibody responses in acute illness were insufficient to predict inpatient outcomes. https://immunology.sciencemag.org/content/5/54/eabe0240

Cross-reactivity: An analysis of antibody genes expressed by memory B cells across ages and anatomical locations indicates that, consistent with serological reports, pre-pandemic children had class-switched convergent clones to SARS-CoV-2, enriched in cross-reactive clones for seasonal coronaviruses, while adults showed few such clones in blood or lymphoid tissues.
https://www.biorxiv.org/content/10.1101/2020.12.01.407015v1

Treatment
A ribonucleoside analogue inhibitor of influenza viruses, MK-4482/EIDD-2801, was repurposed for use against SARS-CoV-2. Therapeutic treatment of infected ferrets twice a day significantly reduced the SARS-CoV-2 load in the upper respiratory tract and completely suppressed spread to untreated contact animals. The drug, which can be given orally, is currently in Phase 2/3 clinical trials.
https://www.nature.com/articles/s41564-020-00835-2

Researchers from the gene therapy field are developing with Regeneron a nasal spray containing an adeno-associated virus (AAV) which delivers genetic instructions to nose and throat epithelial cells so they can directly produce SARS-CoV-2-specific antibodies. This could be particularly attractive for people with weakened immune systems or who need rapid protection. The spray is currently being tested on animals.
https://medicalxpress.com/news/2020-12-scientists-nasal-covid-.html

The WHO Solidarity Trial Consortium has published its final results. The trial tested four repurposed drugs - remdesivir, hydroxychloroquine, lopinavir, and interferon beta-1a — in patients hospitalized with Covid-19. It recruited a total of 11,330 patients from 405 hospitals in 30 countries across the world between March 22 and Oct 4, 2020. All 4 drugs had little or no effect on hospitalized patients with Covid-19, as indicated by overall mortality, initiation of ventilation, and duration of hospital stay.
https://www.nejm.org/doi/full/10.1056/NEJMoa2023184

Another randomised clinical multicentre trial among persons with recent exposure shows no meaningful effect of hydroxychloroquine as postexposure prophylaxis to prevent SARS-CoV-2 infection. https://www.acpjournals.org/doi/10.7326/M20-6519

ANTICOV is a large clinical trial launched in Africa to study whether cheap, available drugs can prevent mild COVID-19 cases from becoming severe. The trial (in which ISGlobal participates) aims to recruit thousands of patients in 13 African countries. It hopes to test a long list of drugs, including the hepatitis C drug sofosbuvir, the antiparasitic drugs nitazoxanide and ivermectin, and colchicine, which is used to treat gout. The fact that the combination drug lopinavir/ritonavir and hydroxychloroquine will be the first tested is “raising some eyebrows”.
https://www.sciencemag.org/news/2020/12/first-its-kind-african-trial-tests-common-drugs-prevent-severe-covid-19

see also: https://dndi.org/research-development/portfolio/anticov/

Vaccines
Moderna published immunogenicity data for its mRNA vaccine 119 days after the first vaccination (90 days after the second vaccination) in 34 healthy adult participants. Binding and neutralizing antibodies declined slightly over time, particularly in those aged over 55, but they remained elevated in all participants 3 months after the booster vaccination. A follow-up analysis to assess safety and immunogenicity in the participants for a period of 13 months is ongoing.
https://www.nejm.org/doi/full/10.1056/NEJMc2032195
Moderna plans to start evaluating its vaccine on children ages 12-17 (Pfizer has already started).

The interim analysis for the Oxford /AstraZeneca vaccine has been published, with data from 11636 participants (7548 in the UK, 4088 in Brazil). In participants who received two standard doses (most were 6-12 weeks apart), vaccine efficacy was 62·1% (27 vs 71 cases), and of 90% for those who received a low dose followed by a standard dose (3 vs 30 cases). There is not enough efficacy data yet for adults older than 55 years-old. In total, there were ten cases hospitalised for COVID-19, all in the control arm; two were classified as severe COVID-19, including one death. Data from more than 20,000 participants shows a good safety profile. https://marlin-prod.literatumonline.com/pb-assets/Lancet/pdfs/S0140673620326611.pdf

The UK becomes the first country in the world to approve the Pfizer/BioNTech mRNA COVID-19 vaccine for widespread use. It will start to be rolled-out next week. The first 800,000 doses should arrive in the coming days and will be used to vaccinate elderly people in care homes. https://www.bbc.com/news/health-55145696 . A 90-year old lady was the first to receive the vaccine on Monday.

Sao Paolo has announced it will start vaccinating its 46 million residents with the Chinese developed CoronaVac. Vaccination will start Jan 25 and the first to receive it will be healthcare professionals, people over 60 years old, and the indigenous population. https://www.aljazeera.com/economy/2020/12/7/bbsao-paolo-sets-first-date-in-latin-america-to-start-vaccination

FDA scientists endorse Pfizer /BioNTech vaccine ahead of the agency's panel on December 10, where it will vote on granting an EUA. In their document, they state that the two-dose vaccine was "highly effective" in preventing symptomatic Covid-19, and that the data "suggest a favorable safety profile." The data also suggest that the vaccine may begin preventing some Covid-19 cases after the first dose. The oldest participant who received the Pfizer vaccine in the Phase 3 trial was 89-years-old.
https://www.statnews.com/2020/12/08/fda-scientists-endorse-highly-effective-pfizer-biontech-covid-19-vaccine-ahead-of-key-panel/

Pfizer /BioNTech has said it will only be able to roll out half of the promised doses by the end of this year (50M instead of 100M) due to supply-chain hurdles. The company is setting up two final assembly and distribution centers: one in Michigan, US, and one in Belgium, Europe. https://www.wsj.com/articles/pfizer-slashed-its-covid-19-vaccine-rollout-target-after-facing-supply-chain-obstacles-11607027787

The Advisory Committee on Immunization Practices (ACIP) voted 13-1 to recommend that both health care workers and residents of long-term care facilities be first to receive the COVID-19 vaccine. The next phase of priority vaccinations could focus on essential workers such as educators, food and agriculture workers, utility workers,

police, firefighters, corrections officers, and transportation employees. People aged 65 and older (about 53 million) and adults with high-risk medical conditions would be next. https://edition.cnn.com/2020/12/01/health/cdc-acip-covid-19-vaccine-recommendation-vote/index.html
An interesting article by H Branswell explains the reasons why one person voted against prioritizing long-term care residents.
https://www.statnews.com/2020/12/03/cdc-advisory-panels-lone-dissenter-on-why-long-term-care-residents-shouldnt-receive-covid-19-vaccine-first/

A story in *Science* stresses the need to prepare the public for vaccine side effects
(Thanks for sharing, Carlota Dobaño!)
https://science.sciencemag.org/content/370/6520/1022.full

Vaccine trials and placebo recipients: ethics vs the need for evidence
A WHO Ad Hoc Expert Group publishes a perspective on why placebo-controlled vaccine trials are still needed. They argue that as long as vaccine supplies are limited, it is ethically appropriate to continue blinded follow-up of placebo recipients in existing trials and to randomly assign new participants to vaccine or placebo. The opportunity to obtain reliable evidence about longer-term effects would be destroyed by early unblinding and immediate vaccination of participants assigned to placebo. Even when effective vaccines have been deployed in some locations, countries with limited or no access to a known effective vaccine could still ethically permit placebo-controlled trials of vaccines of potential relevance to them (f.ex. one-dose versus two-dose vaccines). This would increase the likelihood of reliably identifying multiple vaccines with favorable benefit–risk profiles and earn broad public trust.
https://www.nejm.org/doi/full/10.1056/NEJMp2033538
This is backed by another policy forum in *Science*, which underlines that there is a difference between vaccine trials with participants and clinical trials with patients. Researchers should thus ensure that any plans to conduct placebo-controlled trials remain ethically appropriate given current evidence. In other words, is the trial's risk-benefit profile still acceptable? (consider social value and risk to participants); and do participants consent? One proposal is to continue the blinded, placebo-controlled trial with a guarantee that individuals in the placebo arm will receive an efficacious vaccine once their participation in the study is completed.
https://science.sciencemag.org/content/early/2020/12/02/science.abf5084
The NYT publishes an article on the subject, with an interesting proposal by Dr. Fauci, who defends the ethical obligation of giving the vaccine to people in the placebo group. Vaccine makers could give everyone who got the placebo the vaccine, while also giving everyone who got the vaccine the placebo. None of the trial participants would know which order they got the doses. Then, the 2 groups could be compared to see if immunity in both groups faded as quickly.
https://www.nytimes.com/2020/12/02/health/covid-vaccine-placebo-group.html

Good news for influenza vaccines:
A vaccine that induces immune responses to a wide spectrum of influenza virus strains and subtypes has produced strong and durable responses in Phase 1 clinical trials. The chimeric HA vaccine, directed at the stalk domain of the HA protein, which is more conserved, broadly neutralizes diverse influenza virus strains in both animal models and humans. https://www.nature.com/articles/s41591-020-1118-7

Other
ORCHESTRA, a three-year H2020 research project aimed at connecting cohorts in Europe to rapidly inform public health and vaccine strategies on COVID-19, was launched this week. The project is led by Prof. Evelina Tacconelli of the University of Verona and involves 26 partners (37 when considering the wider network) from 15

countries (Argentina, Belgium, Brazil, Congo, France, Gabon, Germany, India, Italy, Luxemburg, Netherlands, Romania, Slovakia, Spain, Venezuela). Our colleague Elisa Sicuri is participating in one of the WPs. (*Thanks for the tip, Elisa Sicuri!)*
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15 12 2020

¿Circulando antes de lo pensado? Un equipo italiano detectó material genético del SARS-CoV-2 en un frotis de garganta tomado de un niño de 4 años a inicios de diciembre 2019, unos tres meses antes de que se confirmara el primer caso en Italia. El pequeño no había viajado, lo cual sugiere que el virus circulaba fuera de China antes de lo pensado.

¿Impacto sobre la fertilidad masculina? Un pequeño estudio con biopsias de testículo obtenidas de pacientes con COVID-19 muestra que el virus puede infectar células germinales y afectar la producción de espermatozoides. Este hallazgo sugiere que el virus podría afectar la fertilidad masculina.

Una calculadora de riesgo de mortalidad: Un equipo de la Johns Hopkins University desarrolló una calculadora 'online' para estimar el riesgo de mortalidad por COVID-19 para la población de EEUU según una serie de factores sociodemográficos y condiciones de salud.

Empleos de alto riesgo: Entre marzo y julio del 2020, el personal sanitario en el Reino Unido tuvo un riesgo 7 veces mayor de enfermar gravemente por COVID-19, comparado con personal no-esencial. El riesgo fue incluso mayor (8 veces) para aquellos que no eran de raza blanca. Las y los trabajadores sociales y de educación también tuvieron un riesgo mayor (1.8 veces) comparado con personas que realizan trabajos no esenciales, según el análisis.

Más sobre tratamiento
Un antibiótico no aporta beneficio: El ensayo clínico RECOVERY del Reino Unido encontró que la azitromicina no aporta ningún beneficio a pacientes hospitalizados con COVID-19. Los resultados preliminares no muestran diferencias en mortalidad, avance de la enfermedad, o duración de la hospitalización entre el grupo tratado y el grupo control.

Más sobre vacunas
Pfizer /BioNTech: Esta semana se publicaron los resultados finales de fase 3 para la vacuna de Pfizer-BioNTech. Dos dosis de la vacuna, espaciadas de 21 días, fueron seguras y eficaces al 95% contra la COVID-19. La eficacia fue similar en personas de diferentes edades, sexo, etnicidad, masa corporal o condiciones crónicas de salud. Hubo 10 casos de COVID-19 grave tras la primera dosis, 9 de ellos en el grupo placebo y uno en el grupo vacuna. Los efectos secundarios más frecuentes fueron dolor en el sitio de inyección, cansancio y dolor de cabeza. La incidencia de efectos adversos graves fue muy baja y similar entre el grupo placebo y el grupo vacuna. Se seguirá haciendo un seguimiento de seguridad a las y los participantes durante dos años.

¿Combinando vacunas? Muy pronto, podría comenzar un ensayo para averiguar si combinando diferentes vacunas contra la COVID-19 se puede obtener una mayor protección que con dos dosis de la misma. AstraZeneca probará una dosis de su vacuna con una segunda dosis de la de Pfizer. Esta estrategia mixta busca inducer respuestas celulares y humorales (de anticuerpos) más fuertes que con un solo tipo de vacuna. AtraZeneca también anunció que exploraría combiner su vacuna con la Sputnik V del Instituto Gamaleya (que usa vectores adenovirales diferentes).

Malas noticias para dos candidatas: Sanofi ha sufrido un contratiempo con su vacuna a base de proteína recombinante, que desarrolla en colaboración con GSK, debido a un problema en la dosificación que resultó en un menor nivel de anticuerpos generados por personas mayores. Esto significa que, si se aprueba, la vacuna no podría empezar a distribuirse antes de la segunda mitad del 2021.

La Universidad de Queensland en Australia ha decidido suspender el desarrollo de su vacuna a base de proteína recombinante tras encontrar que las personas vacunadas desarrollan anticuerpos que podrían dar resultados falsos positivos en los tests para el VIH. Esto se debe a que la vacuna incluye un pequeño fragmento derivado de una proteína del VIH que sirve para estabilizar la proteína *Spike* del SARS-CoV-2.

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Evidence of early circulation? An Italian team found SARS-CoV-2 RNA in a throat swab collected from a child in early December 2019, around 3 months before the first identified coronavirus disease case in Italy. The child had not travelled, so this finding raises the possibility that the virus was circulating outside China earlier than thought.

Impact on male fertility? A small study on testis biopsies from COVID-19 patients reveals the virus can infect germ cells and affect the production of spermatozoids. These findings raise the possibility that the virus may affect male fertility.

A mortality risk calculator: A Johns Hopkins University team generated an online risk calculator for COVID-19 mortality based on sociodemographic factors and pre-existing health conditions for the US population. The model can identify relatively small fractions of the population that might experience a disproportionately large number of deaths, and could help set priorities for allocating early COVID-19 vaccines.

High-risk occupations: In the period between March and July, UK health care workers had a seven-fold higher risk of becoming severely sick from COVID-19 than non-essential workers, and this risk was even higher (8-fold) if they were non-white. Social and education workers were also at higher risk (1-8-fold) as compared to non-essential workers, according to the analysis.

More on treatment
No benefit for an antibiotic: The UK RECOVERY trial found no benefit from azithromycin in patients hospitalised with COVID-19. The preliminary analysis shows no significant difference in mortality, disease progression or length of hospital stay between treated and control groups.

More on vaccines
Pfizer /BioNTech: The final Phase 3 results for the Pfizer-BioNTech vaccine were published this week. The two doses, given 21 days apart, were safe and 95% effective against COVID-19. Similar vaccine efficacy was observed in groups of different age, sex, ethnicity, body mass index or underlying health conditions. Ten cases of severe COVID-19 occurred after the first dose, 9 of them in placebo recipients and one in a vaccine recipient. Short-term side effects including pain at the injection site, fatigue, and headache were frequent. The incidence of serious adverse events was very low and similar in both groups. Safety monitoring of participants will continue for 2 years.

Mixing vaccines? A trial may start soon to find out whether mixing COVID vaccines gives better protection than 2 doses of the same one. AstraZeneca will test combining one shot of its vaccine with a second shot of Pfizer's vaccine. This heterologous prime-boost approach seeks to induce stronger cellular and humoral responses than with one single type of vaccine. It will also explore combining its vaccine with Gamaleya's Sputnik V vaccine (which uses different adenoviral vectors).

Bad news for two vaccine candidates: Sanofi has suffered a setback in the development of their recombinant protein-based vaccine it is developing with GSK, after detecting a

lower response in older adults due to a dosing problem in their formulation. This means that, if approved, it will not be deployed before the second-half of 2021.

The University of Queensland has decided to end the development of its recombinant protein vaccine after finding that vaccinated volunteers developed antibodies that could give false HIV-positive results. This is because the vaccine included a small “molecular clamp”, derived from a protein of HIV, to stabilise the SARS-CoV-2 Spike protein.

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COVID-19 EPIDEMIC

Epidemiological situation (22/12/2020, ECDC data):

Globally:
confirmed cases and deaths

-

Confinement and deconfinement measures
UK situation

Virus
Variants:
UK variant: A new variant that has rapidly spread in the UK harbors 17 mutations, of which 9 are in the Spike protein (deletion 69-70, deletion 144, N501Y, A570D, D614G, P681H, T716I, S982A, D1118H). Preliminary analyses estimate that this new variant has the potential to increase the reproductive number (R) by 0.4 or greater with an estimated increased transmissibility of up to 70%. There is no indication at this point of increased infection severity associated with it. Preliminary results suggest the double deletion could be less susceptible to neutralising antibodies. A few cases with the new variant have to date been reported by Denmark and the Netherlands and Belgium. In South Africa, a lineage separate from the UK variant that also has the N501Y mutation has also been also associated to increased transmission.
https://www.ecdc.europa.eu/en/publications-data/threat-assessment-brief-rapid-increase-sars-cov-2-variant-united-kingdom
https://www.sciencemag.org/news/2020/12/mutant-coronavirus-united-kingdom-sets-alarms-its-importance-remains-unclear
The UK New and Emerging Respiratory Virus Advisory Group (NERVTAG) has "moderate confidence" that the VUI-202012/01 variant demonstrates a substantial increase in transmissibility compared to other variants. There are currently insufficient data to draw any conclusions on:
-Underlying mechanism of increased transmissibility
-Disease severity: 4 deaths in around 1000 cases have been identified but more information is needed
-Antigenic escape: The location of the mutations in the RBD raises the possibility that this variant is antigenically distinct from prior variants. Four probable reinfections have been identified amongst 915 subjects with this variant but further investigation is needed. https://khub.net/documents/135939561/338928724/SARS-CoV-2+variant+under+investigation%2C+meeting+minutes.pdf/962e866b-161f-2fd5-1030-32b6ab467896?t=1608470511452

G614 variant: An article in *NEJM* summarises what is known of the SARS-CoV-2 G614 variant. Bottom-line: there is strong genetic and molecular evidence for enhanced fitness of the variant over ancestral strains, providing strong support for its role in facilitating global spread. The SARS-CoV-2 G614 variant did not cause more severe disease than the ancestral strain in hamsters, a finding that supports current findings in humans. Fortunately, the variant is as sensitive to neutralization by serum

specimens as the D614 strain and thus may allay fears that it could escape vaccine-elicited immunity. https://www.nejm.org/doi/full/10.1056/NEJMcibr2032888

A preprint study suggests SARSCoV2 RNA retrotranscribe and integrate to our genome, which could why some people persistently produce viral RNA after recovery. https://www.biorxiv.org/content/10.1101/2020.12.12.422516v1

An analysis of the SARS-CoV-2 genome reveals a possible host-microRNA-mediated interaction between the 3′-UTR shared by betacoronaviruses and human microRNA hsa-miR-1307-3p which could result in weakened host immune responses. This interaction could represent a therapeutic target. https://msphere.asm.org/content/5/6/e00754-20

Testing / Tracing

A $30, 20-minute at-home COVID-19 over-the-counter test has been approved by the FDA. The tests will soon be available at drugstores. https://apnews.com/article/over-the-counter-home-coronavirus-test-ac070f4d42d9d7eacc486c9bed4ccaa0

A multiplex serological assay was developed to measure IgG and IgM antibody responses to seven SARS-CoV-2 spike or nucleoprotein antigens, two antigens for the nucleoproteins of the 229E and NL63 seasonal coronaviruses, and three non-coronavirus antigens. Findings show that, 1 year after infection, a four-antigen multiplex assay can increase sensitivity to 96·4% and, at the population level, allows estimation of seroprevalence levels under 2%. https://www.thelancet.com/journals/lanmic/article/PIIS2666-5247(20)30197-X/fulltext

Transmission

A study in Singapore suggests that people with asymptomatic COVID-19 are infectious but might be less infectious than symptomatic cases: the incidence of COVID-19 among close contacts of a symptomatic index case was 3·85 times higher than for close contacts of an asymptomatic index case. https://www.thelancet.com/journals/lancet/article/PIIS0140-6736(20)32651-9/fulltext

At least 10% of the Spanish population (over 4.5M people) has been exposed to SARS-CoV-2, according to results from the fourth phase of the national seroprevalence study (ENE-COVID). This is almost the double than the prevalence observed ends of June. Results also indicate that 40% of cases still go undetected. Highest seroprevalence was observed among HCW (17%), women carers (16.3%), women cleaners (13.9%), women in socio-sanitary jobs (13.1%) and migrants (13%).

A seroprevalence study of SARS-CoV-2 infection in Geneva shows that over 1/5th of Geneva residents (22%) has virus-specific antibodies. The study also shows a higher than expected prevalence of infection among children over 6 (23%). The less exposed were children under 6 (15%) and adults over 65 (10-14%). The most exposed were those aged 18 to 35 (27-28%). https://www.hug.ch/medias/communique-presse/covid-19-immunite-population-genevoise-double-six

Symptoms / Risk factors

A cohort-based analysis (8.26 million adults) estimates a 4-fold increased risk for COVID-19–related hospitalization and a 10-fold increased risk for COVID-19–related

death in persons with Down syndrome, a group that is currently not strategically protected. https://www.acpjournals.org/doi/full/10.7326/M20-4986

The COVID-19 pandemic was associated with increases in all-cause mortality among US adults aged 25 to 44 years from March through July of 2020. 38% of these excess deaths were attributed directly to COVID-19.
https://jamanetwork.com/journals/jama/fullarticle/2774445

By October, COVID-19 became the third cause of death in the USA for persons aged 45 and older. Between November and December, it has become the first cause of death (daily mortality rates for heart disease and cancer, which for decades have been the 2 leading causes of death, are approximately 1700 and 1600 deaths per day, respectively; versus over 3000 for COVID-19 between November and December 2020).
https://jamanetwork.com/journals/jama/fullarticle/2774465
The USA, which constitutes 4% of the globe's population, has contributed to 19% of the global total of deaths (as of 14 Dec 2020).

A retrospective cohort study in France comparing outcomes for patients hospitalised for COVID-19 and patients hospitalised for influenza shows that in-hospital mortality was higher in patients with COVID-19 (16.9%) than in patients with influenza (5.8%), with a relative risk of death of 2.9.
https://www.thelancet.com/journals/lanres/article/PIIS2213-2600(20)30527-0/fulltext

Long Covid: A comment in Lancet signed by members of the UK doctors #longcovid group explains that long COVID guidelines need to reflect lived experience.
https://www.thelancet.com/journals/lancet/article/PIIS0140-6736(20)32705-7/fulltext

Antibodies / Immunity
Quantity vs quality: A study comparing humoral immune responses and clinical outcomes in 113 SARS-CoV-2-infected patients of varying severity reveals that neutralization potency (i.e. the quality of anti-RBD IgG antibodies irrespective of the quantity) was significantly diminished in severely ill patients. The data support a role for IgM and IgA antibodies in contributing to SARS-CoV-2 neutralization, despite their transient nature in serum. The authors also show that COVID-19 sera neutralize D614 and G614 variants, but not a highly-homologous bat coronavirus (WIV1-CoV).
https://www.cell.com/cell/fulltext/S0092-8674(20)31685-8

More on immune dysregulation: A study performed single-cell RNA sequencing (scRNA-seq) to analyse the transcriptome of peripheral blood mononuclear cells from healthy (n=3) and COVID-19 patients with moderate disease (n = 5), acute respiratory distress syndrome (ARDS, n = 6), or recovering from ARDS (n = 6). Findings indicate defective antigen presentation and interferon responsiveness in monocytes from ARDS patients, as well as suppression of genes involved in cytotoxic activity of NK and CD8 cells. The study indicates that dysregulation of both the innate and adaptive immune responses may be contributing to a more severe disease course.
https://www.cell.com/cell-reports/fulltext/S2211-1247(20)31579-5

Treatment
mAb cocktails: An interim analysis of a double-blind clinical trial shows that the REGN-COV2 antibody cocktail reduced viral load, with a greater effect in patients

whose immune response had not yet been initiated or who had a high viral load at baseline. https://www.nejm.org/doi/full/10.1056/NEJMoa2035002

Vaccines

Codagenix and the Serum Institute of India announced they will start Phase 1 trials for COVI-VAC, a single-dose intranasal, live attenuated vaccine against SARS-CoV-2. It was developed using synthetic biology. The trial will be conducted in London. https://www.prnewswire.com/news-releases/codagenix-and-serum-institute-of-india-announce-commencement-of-first-in-human-trial-of-covi-vac-a-single-dose-intranasal-live-attenuated-vaccine-for-covid-19-301191756.html/

The FDA granted emergency use authorization to Moderna's mRNa COVID-19 vaccine for adults aged 18 or older, following recommendation by an advisory panel (20 votes yes, one abstention). Efficacy in preventing confirmed COVID-19 occurring at least 14 days after the second dose of vaccine was 94.1.0%, with 11 COVID-19 cases in the vaccine group and 185 COVID-19 cases in the placebo group. All severe cases (30) occurred in the placebo group. There are 450 more cases of disease that are being analysed and the data should soon be available. Nearly 16% of participants in the vaccine arm of the trial developed grade 3 adverse effects. There were no anaphylactic or severe hypersensitivity reactions with close temporal relation to the vaccine. Moderna unveiled a plan to offer volunteers who received placebo in its clinical trial the vaccine, although this point remains controversial.
https://www.fda.gov/media/144434/download

Two papers provide a more detailed description of immune responses to the AstraZeneca/ Oxford vaccine. A single dose of the vaccine induced a Th1-biased response characterized by IFN-γ and TNF-α cytokine secretion by CD4+ T cells and antibody production predominantly of IgG1 and IgG3 subclasses. CD8+ T cells, of monofunctional, polyfunctional and cytotoxic phenotypes, were also induced.
https://www.nature.com/articles/s41591-020-01179-4
Anti-spike neutralizing antibody titers, as well as Fc-mediated functional antibody responses were substantially enhanced by a booster dose of vaccine. IgG, IgA, IgM levels were not higher than convalescent patients as reported for mRNA vaccines.
https://www.nature.com/articles/s41591-020-01194-5

A nice overview of mRNA technology is provided by *Science*
https://www.sciencemag.org/news/2020/12/messenger-rna-gave-us-covid-19-vaccine-will-it-treat-diseases-too

Other

Wild minks: On December 13, the US Department of Agriculture reported that a wild mink in Utah tested positive for the coronavirus. A genetic analysis of the virus suggested the wild mink picked it up from a nearby mink farm, perhaps via wastewater from the farm. https://promedmail.org/promed-post/?id=20201213.8015608

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