



TRENDS-in-MEDICINE

BULLETIN: UPDATE ON CORONAVIRUS

March 22, 2020
by Lynne Peterson

Be careful, be safe, and be well.

Based on the latest data available as of 6 pm on March 22, 2020, this is the newest information about the SARS-CoV-2 virus and the disease it causes, Covid-19. Your news is saturated with coronavirus news, so this bulletin is an attempt to highlight the key things you need to know *from the last few days*. If there are topics you would like to see addressed in future coronavirus bulletins, please email us at trendsmed@gmail.com.

The U.S. is now fourth in the world in terms of the number of Covid-19 cases, and it is still in the escalation phase. The situation in Italy is especially concerning because the fatality rate is at least double the rate in China and three times the top rate that the U.S. Centers for Disease Control and Prevention (CDC) estimated as likely for the U.S.

Two good sources for Covid-19 numbers:

U.S. <https://covidtracking.com/data/>

Worldwide <https://coronavirus.jhu.edu/map.html>

Worldwide Covid-19 Statistics						
Country	As of March 18			As of March 22 (just 4 days later)		
	Cases	Deaths	Fatality rate	Cases	Deaths	Fatality rate
Worldwide	217,242	8,704	4.0%	335,972	14,632	4.4%
China	81,137	3,130	3.9%	81,407	3,265	4.0%
Italy	35,713	2,978	8.3%	59,138	5,476	9.3%
Spain	13,176	638	4.8%	28,768	1,772	6.2%
U.S.	9,249	145	1.6%	33,276	417	1.3%
Germany	12,327	28	0.2%	24,873	94	0.4%
Iran	17,061	1,135	6.7%	21,638	1,685	7.8%
U.K.	>2,600	104	4.0%	5,741	282	4.9%

U.S. Covid-19 Statistics (as of March 22)			
State	Cases	Deaths	Fatality rate
New York	15,168	114	0.8%
Washington	1,793	94	5.2%
California	1,554	29	1.9%
New Jersey	1,914	20	1.0%
Michigan	1,035	8	0.8%
Florida	830	13	1.6%
Louisiana	837	20	2.4%
Illinois	1,058	9	0.9%
Massachusetts	646	5	0.8%

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Some of the things that the U.S. data currently suggest or show:

- ~10% of people tested for coronavirus are testing positive.
- 10%-13% of people testing positive for Covid-19 are being hospitalized.
- As expected, ~80% of the deaths are in elderly people, particularly the elderly with a comorbid condition.
- The fatality rate in the U.S. – and in every state except Washington – is far below the rates in Italy, even early in the outbreak there, and, in fact, lower than most of the world (except South Korea and Germany).
- Data continue to indicate that men are more likely to die from Covid-19 than women.

Other tidbits to consider:

- A study by researchers at the University of Minnesota estimated that if Covid-19 reaches levels seen in other countries, there could be 6 seriously ill patients for every **hospital bed**, unrealistically assuming all hospital beds would be available.
- How to know when you have Covid-19: The usual symptoms are fever, dry cough, and shortness of breath; but a study, published in the *American Journal of Gastroenterology*, found that almost half of hospitalized patients in Hubei, China, had gastrointestinal (GI) **symptoms** as well or as the primary symptoms.
- How to know when a patient's **Covid-19 is over**: No symptoms (including no fever) and 2 negative tests 24 hours apart.
- A Chinese study, published in *Nature Medicine*, found that 9 of 10 Chinese children who got Covid-19 had only mild symptoms, but – and it is a big but – **fecal tests** showed that children continued to be positive for Covid-19 even after their nose and throat swab tests were negative, suggesting that rectal swab testing should be used to determine the quarantine duration for pediatric infections.
- Seattle is turning a soccer field into a **field hospital**, and New York City is turning the Javits Center into a field hospital.
- *Unresolved issue*: Can you take **ibuprofen** or a corticosteroid if you think you have Covid-19? France's health minister joined the chorus of experts warning against use of these drugs, saying they could make the infection worse. He recommended paracetamol (acetaminophen in the U.S.) instead. However, the World Health Organization (WHO) tweeted that it “does not recommend against the use of ibuprofen.”

Governmental actions/notices/news

- The primary approach being used across the U.S. (and in many other countries) is **social distancing**. Eight states (California, Connecticut, Delaware, Illinois, Louisiana, New Jersey, New York, and Ohio) have issued **stay-at-home orders** of one type or another for the whole state.
 - **New York** accounts for 46% of all diagnosed Covid-19 cases in the U.S., and New York City is 62% of the New York state total. Gov. Andrew Cuomo said 35% of the New York City hospitalizations were in people age >70, even though they are only 10% of the New York City population.
 - **President Trump**:
 - **Closed the border with Mexico**, so now both the northern and southern borders are closed except for trade and essential travel.
 - Said there will *not* be a **national quarantine**.
 - Authorized physicians to **practice across state lines**.
 - Approved a **major disaster declaration** for New York and Washington state. California has made a similar request, and the President said he would expedite that request.
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- Activated the **National Guard** in New York, California, and Washington state – under the control of the governors but at the expense of the federal government, through the Federal Emergency Management Administration (FEMA). President Trump emphasized that this is *not* martial law.
- FEMA is providing **field hospitals** to New York (4 large), California (8 large), and Washington state (3 large and 4 small). In addition, thousands of personal protection gear items have been and are being shipped to those states, with more on the way. FEMA will not be providing any direct aid to individuals at this point in time.
- Said he isn't going to *require private industry* to produce needed medical equipment through the Defense Production Act, though he has activated his authority to do that – unless private industry doesn't do it voluntarily. However, he said that so far industry has been stepping up and volunteering to make what's needed. Honeywell, 3M, General Motors, and more. He called it the “greatest mobilization of the industrial base since World War II.”
- Warned people and companies against price gouging warning, “...or we will come for you.”
- Congress is poised to pass a \$2 trillion **economic stimulus**/relief package, but details are still being ironed out.
- A declaration granting “covered persons” **liability immunity** from “any claim of loss caused by, arising out of, relating to, or resulting from the manufacture, distribution, administration, or use of medical countermeasures” against Covid-19 was signed by Health and Human Service Secretary Alex Azar. This is retroactive and applies from February 4, 2020, to October 1, 2024.
- New York Gov. Cuomo has been doing such a good job with his daily briefings about coronavirus that there is talk of him displacing both former Vice President Joe Biden and Sen. Bernie Sanders as the **Democratic nominee** for president.
- **Pharma reps** are trying to use digital tools to reach doctors since they can't visit them.
- White House Trade Adviser Peter Navarro said the President is expected to sign an executive order aimed at relocating **medical supply chains** from abroad to the U.S.
- The U.S. Surgeon General flatly said there should be no “**play dates**” that get kids together during school closures.
- Four U.S. Senators – Sen. Richard Burr (R-NC), Sen. Dianne Feinstein (D-CA), Sen. James Inhofe (R-OK), and Sen. Kelly Loeffler (R-GA) – profited by **selling stock** before the coronavirus-fueled stock market crash, though all deny insider trading, a Senate ethics investigation is likely.

Elective surgery

Elective surgery is increasingly being canceled/postponed, and U.S. government officials are calling for even more elective procedures to be avoided. And it is not just hospitals that are postponing elective procedures. Ambulatory surgery centers (ASCs) are postponing elective surgeries. The Ambulatory Surgery Center Association (ASCA) says a surgery may be deemed urgent and necessary if the treating physician decides that a months-long delay would increase the likelihood of significantly worse morbidity or prognosis for the patient. ASCA also is advising ASCs that they may need to be prepared for the possibility that hospitals will need to shift necessary surgeries to them.

Even dentists are being asked to cancel/postpone procedures – and to donate their N95 masks.

In the U.K., hospitals were told to postpone all non-urgent elective operations through April 15 for a period of at least three months.

Insurance

America's Health Insurance Plans (AHIP), an insurance lobbying group, said there is no plan to waive copays, deductibles, and other fees for coronavirus **treatment**. Public Citizen called AHIP out for this, calling it “outrageous” that insurers plan

to profit from the treatment of coronavirus victims, warning, “If costs are waived for tests, but not for treatment, people who test positive for the coronavirus may not be able to afford treatment and will continue to infect others.”

President Trump said that health insurers had agreed to “waive all copayments for coronavirus treatments, extend insurance coverage to these treatments, and to prevent surprise medical billing.” But the industry later clarified that insurers planned to waive out-of-pocket costs for coronavirus testing, not treatments.

The American Medical Association issued a new CPT code for testing.

Testing

The FDA took a number of steps designed to make testing more available, including:

- Granting emergency use authorization (EUA) to a number of SARS-CoV-2 tests, including tests from: Abbott, GenMark Diagnostics, Hologic, LabCorp, Quest, and Quidel.
- Granting EUA for the first point-of-care diagnostic test for coronavirus – **Danaher/Cepheid’s Xpert Xpress SARS-CoV-2 test**, which provides results in ~45 minutes and operates on the company’s automated GeneXpert Systems – of which there are 23,000 worldwide and 5,000 (mostly in hospitals) in the U.S. It is expected to be about a week before this is actually in use in labs.
- Giving states the ability to authorize laboratory-developed tests.
- Saying private companies can begin [marketing](#) coronavirus test kits directly to the public. The FDA will review the accuracy of test data submitted by the manufacturers retroactively. FDA Commission Stephen Hahn, MD, admitted this approach has risk but said it is warranted by the severity of the pandemic. Among the companies that plan to launch at-home coronavirus tests that can be purchased online soon are: Everlywell; and Nurx and its partner Molecular Testing Labs.

Vice President Pence said, “We should be caught up on the testing backlog by the middle of the week [March 25-26].”

One potential hold-up has been the supply of reagents, but Qiagen said it would quadruple its reagent production in six weeks.

Several other tests have been submitted to the FDA for EUA, including:

- BioGX and Becton Dickinson’s co-developed Covid-19 assay, which runs on the BD Max system.
- DiaSorin Molecular, which is developing its Simplexa COVID-19 Direct Assay with a \$679,000 grant from the Biomedical Advanced Research and Development Authority (BARDA).
- E25Bio, which is developing a fast diagnostic test.
- Qiagen, which got \$598,000 from BARDA to support development of a version of its QIAstat-Dx Respiratory Panel to differentiate SARS-CoV-2 from 21 other common respiratory pathogens.
- Mesa Biotech, which got \$561,330 from BARDA to develop and launch its SARS-CoV-2 point-of-care test that provides results in 30 minutes.

Transmission

- Craig Smith, MD, surgeon-in-chief at **New York**-Presbyterian Hospital/Columbia University Medical Center, sent a [memo](#) to colleagues that read, in part: “One week ago I was optimistic that our health care systems could avoid being overwhelmed, even as we began eliminating elective surgery...To think we could mimic Italy seemed risible a week ago.”
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Not today...It has also become obvious that the virus has breached our Department walls, and we can expect to hear about increasing numbers of infected Department colleagues. It should be no surprise if these infections appear in clusters associated with the care of infected patients. This underlines the importance of deploying providers strategically to minimize the chance of incapacitating all or most of one subspecialty because of illness and quarantine.”

- The Surgeon General and WHO both insist that Covid-19 is not spread through the mail.
- Newly-identified people infected/under quarantine for Covid-19 include:
 - President Trump and Vice President Pence have both tested negative.
 - German Chancellor Angela Merkel was exposed, has not tested positive, but is in a 14-day self-quarantine.
 - Sen. Rand Paul (R-KY) tested positive and is self-quarantining.
- *Can you get Covid-19 from swimming in a pool if another swimmer has Covid-19?* Ambassador Deborah Birx, MD, the White House Coronavirus Response Coordinator, said, “It is in saliva...So, keep your distance in a pool.”

Treatment

There are now two FDA approved drugs with clinical data showing they are effective in Covid-19 patients. Both trials are small, but at least there are data. The question is whether patients will be able to get these drugs because it means the doctor would have to prescribe them off-label unless the patient’s hospital is participating in a trial, and the willingness of doctors to do that is not at all clear. Yes, they should be studied in clinical trials, but if there is no trial in a patient’s hospital, should that patient be denied either/both of these drugs?

■ **Hydroxychloroquine** (Sanofi’s Plaquenil and generics), an old anti-malarial + the antibiotic azithromycin (Pfizer’s Zithromax, Z-Pak), which are generic and have FDA approval for other indications. There are data from a small French trial by a well-respected French doctor showing 100% efficacy in mild-to-moderate Covid-19 patients. President Trump has been touting this, and Bayer has donated 3 million doses to the U.S. The patient dose of hydroxychloroquine to treat Covid-19 is 600 mg/day.

https://drive.google.com/file/d/186Bel9RqfsmEx55FDum4xY_I1WSHnGbj/view

Mylan, Novartis, Apotex, and Teva have also volunteered to donate supplies of hydroxychloroquine or chloroquine.

President Trump said New York asked to be first to have access, and use there is supposed to start in some sort of registry or trial on March 24, 2020.

Asked what patients have to lose with using this, Thomas Frieden, MD, former head of the CDC, said, “Absolutely we should figure out if this has an impact.” Like Anthony Fauci, MD, director of the National Institute of Allergy and Infectious Diseases (NIAID), he is pushing for studying it in trials. But, again, what about patients where no trial is available?

The Illinois Pharmacists Association tweeted on March 22 that they are “disturbed by the current actions of prescribers that are inappropriately prescribing medicines such as hydroxychloroquine, chloroquine, and azithromycin without valid patient-provider relationship or reasonable medical rationale.”

However, the availability of chloroquine and hydroxychloroquine may be a problem for a while. According to numbers from Premier:

- **Chloroquine:** From January 2019 through February 2020, hospitals ordered an average of 149 units/month of chloroquine (~75 units ordered every two weeks). From March 1-17, 2020, 2,357 units were ordered – a 3,000% spike vs. typical demand.

- **Hydroxychloroquine:** The average monthly units ordered for this was 8,800 from January 2019 through February 2020, or ~4,400 units ordered every two weeks. From March 1-17, 2020, orders total 16,110 ordered – a 260% spike vs. typical demand.

Premier said that to manage this spike in demand, all the major wholesale distributors recently put hydroxychloroquine and chloroquine on allocation, which means ordering is restricted to historic purchasing volumes in order to protect the supply chain and prevent hoarding.

However, Premier noted that the spike started *before* the allocations went into place, which means that many healthcare providers may already have large quantities on hand that they can use to treat patients. However, it is not known if the right quantity is in the right location. Premier suggested that wholesalers work with the group purchasing organizations (GPOs) and their members to ensure the supply gets to providers who need it most – the hospitals treating Covid-19 patients.

Once those supplies are depleted, Premier said re-ordering will be capped at historic levels. Since these are older drugs not typically used in the acute-care setting, historic purchasing has been low. Premier warned that replenishments will not match current demand.

Now the good news, in addition to the tablets being donated by Bayer, Teva said it would donate millions of tablets of hydroxychloroquine and chloroquine tablets either to hospitals or to the federal government. And Premier pointed out that both of these drugs are older, relatively inexpensive solid oral dose drugs, which means their manufacturing is far less complicated than it is for other drugs.

For chloroquine, there is currently a single manufacturer producing products. However, four additional manufacturers reportedly have approval from the FDA to make it. For hydroxychloroquine, there are 10 suppliers with FDA approval, but not all of them are currently manufacturing it. Premier said it is “hard at work” trying to persuade manufacturers to either increase production or re-enter markets they have abandoned.

■ **Roche’s Actemra (tocilizumab, RoActemra in Europe)**, an anti-IL-6. A 20-patient Chinese study is in pre-print which found that severe/critical Covid-19 patients given this drug in addition to routine therapy had their fever return to normal, 75% lowered their oxygen intake (with one patient needing no oxygen). CT scans shows that lung lesion opacity resolved in 19 patients. Nineteen of the 20 patients were discharged an average of 13.5 days post-treatment, and the others are recovering well.

<http://chinaxiv.org/abs/202003.00026>

Roche is planning to start a global Phase III trial in April in 330 patients with Covid-19 in collaboration with BARDA.

There are also other anti-IL-6s, and at least two companies reportedly have started an anti-IL-6 trial:

- **Sanofi and Regeneron Pharmaceuticals’ Kevzara (sarilumab)** – A trial reportedly is underway somewhere.
- **EUSA Pharma’s Sylvant (siltuximab)** – An observational study in underway in Bergamo, Italy, for treating patients with severe Covid-19.

Other investigational therapies to watch:

- **AIM ImmunoTech’s Ampligen (rintatolimod)**, a mismatched double stranded polymer of RNA (dsRNA) – an antiviral – which is approved in some countries to treat chronic fatigue syndrome.
 - **Merck KGaA’s Rebif (interferon beta-1a)** – The company has donated samples of this multiple sclerosis drug to French researchers who want to try it to see if this anti-inflammatory will ease Covid-19 symptoms.
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- **Regeneron Pharmaceuticals** hopes to have a two-antibody cocktail ready for administration to at-risk people before exposure, either as a vaccine or as a treatment for those already infected.
- A Johns Hopkins University researcher is working on a treatment, outlined in a paper in *The Journal of Clinical Investigation*, that uses antibodies from the blood plasma or serum of people who have recovered from Covid-19 to boost the immunity of newly infected patients and those at risk of contracting the disease.

https://hub.jhu.edu/2020/03/13/covid-19-antibody-sera-arturo-casadevall/?mc_cid=d4cedee418&mc_eid=48ecfba1b6

What doesn't work: Johnson & Johnson is warning that there is no evidence its HIV drug Prezista (darunavir) is effective in Covid-19.

Vaccines

About 20 companies are reportedly working on a SARS-CoV-2 vaccine. Here are 13 of them:

- **BioNTech's BNT-162** – The company is collaborating with Fosun Pharma to test this mRNA vaccine in China, starting in April. BioNTech also plans to test the vaccine in Europe and the U.S. through a collaboration with Pfizer, which will co-develop and distribute it outside China.
- **CanSino Biologics** is collaborating with the Academy of Military Medical Sciences' Institute of Biotechnology in China on a recombinant coronavirus vaccine and was given regulatory permission by Chinese authorities to start human testing.
- **CaroGen** which announced development of its *AVIDIO*/SARS-CoV-2 recombinant vaccine in collaboration with scientists from Yale University School of Medicine.
- **Chongqing Zhifei Biological Products**, in collaboration with the Institute of Microbiology at the Chinese Academy of Sciences, started animal studies in February 2020.
- **Codagenix** is working on a live-attenuated vaccine in India.
- **CureVac** got a grant of up to \$88 million from the European Commission to scale up production of its mRNA vaccine.
- **GlaxoSmithKline** is collaborating with Clover Biopharmaceuticals on a vaccine, Covid-19 S-Trimer.
- **Inovio Pharmaceuticals' INO-4800** – This DNA vaccine for MERS is being developed for Covid-19 in collaboration with Beijing Advaccine Biotechnology and GeneOne Life Science, with Phase I trials planned for the U.S. and China.
- **Johnson & Johnson** hopes to begin human clinical trials on a COVID-19 vaccine in early November 2020.
- **Migal Research Institute** in Israel, which had been developing a coronavirus vaccine for chickens, is now modifying it for humans. Human trials are expected to start in a few months.
- **Moderna Therapeutics' mRNA-1273**, which is working with NIAID, on an mRNA vaccine. It started Phase I healthy volunteer testing in the U.S. this month.
- **Novavax** plans to start clinical trials in spring 2020 with its vaccine, derived from the coronavirus spike protein, boosted by its Matrix-M adjuvant.
- **Vir Biotechnology** is collaborating with Wuxi Biologics in China on a vaccine.

Impact on drug development (*unrelated to diagnosis/treatment of Covid-19*)

Among the delays in development of drugs unrelated to Covid-19 because of coronavirus:

- Both the FDA and ICER postponed indefinitely all meetings through at least the end of April. That likely means drug/device approval delays.
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- **ADDEX THERAPEUTICS' [dipraglurant](#)** – The pivotal trial (Study 301) of this mGluR5-negative allosteric modulator to treat levodopa-induced dyskinesia in Parkinson's disease patients was "postponed" with no new start date announced.
- **Albuterol [inhalers](#)** – The American College of Allergy, Asthma, and Immunology (ACAAI) noted that certain areas of the country are experiencing shortages of these devices – and expects the situation to worsen – because hospitals are switching to albuterol inhalers in lieu of nebulizers because of a concern that using nebulizers on Covid-19 patients could spread the virus in the hospital's air.
- **IVERIC BIO's [Zimura \(avacincaptad pegol\)](#)** – A second Phase II trial of this C5 inhibitor for geographic atrophy (GA) secondary to dry age-related macular degeneration (AMD) was delayed due to Covid-19.
- **PROVENTION BIO's [teplizumab \(PRV-031\)](#)** – The global Phase III PROTECT trial of this anti-CD3 in newly diagnosed Type 1 diabetes was temporarily paused because of Covid-19.

Unanswered questions

- ? *Can people get Covid-19 more than once?*
- ? *Are there long-term effects from getting Covid-19, even mild Covid-19? A [study](#) of CT scans of 112 passengers who were on the Diamond Princess cruise ship, published in **Radiology: Cardiothoracic Imaging**, found that symptomatic patients had a higher prevalence of lung opacities and airway abnormalities vs. asymptomatic patients, but how long does it last? Is some damage permanent? Do severe patients develop pulmonary fibrosis if they survive?*
- ? *Does Covid-19 threaten the blood supply? Are blood banks testing donors or the blood they donate?*

