TRENDS-in-MEDICINE

# BULLETIN: UPDATE ON CORONAVIRUS 4/27

April 27, 2020
by Lynne Peterson

**Be careful, be safe, and be well.**

The SARS-CoV-2 virus and Covid-19, the disease it causes, continue to have much of the world on pause, but there are small signs of the beginning of the end. In the U.S. and most of Europe, the rate of Covid-19 cases appears to have peaked/plateaued and, in some places, started a slow decline. Countries, states, and localities are starting to try to figure out how to safely get their economy restarted again. However, it is clear that this will not be quick, and there will be no sudden return to the old normal.

**Worldwide**, nearly 3 million people have been infected with the coronavirus. In the **United States**, total cases are nearly 1 million, or 32% of the worldwide total. The virus has now killed 202,846 people worldwide, with 27% of those (53,755) in the U.S., which is more than 11 times the number of deaths in China from the virus. (*See charts on Pages 17-19*)

Among the countries we are monitoring, the highest mortality rate is in France (14.0%), and only slightly behind that are the U.K. (13.6%), Italy (13.5%), and Spain (10.2%). This has been bringing up the worldwide mortality rate, which is now 7.0%. Sweden, which didn't order a lockdown, has a similar mortality rate (12.1%) to the other European countries, so it may have been spared some economic pain without increasing mortality.

On a per capita basis, for the countries followed:

- The ***case rate*** increased slightly to 0.04% worldwide and is highest in Spain at 0.48%, followed in order by Spain, Italy, France, and the U.K. The U.S. is better than Italy or Spain but worse than France or the U.K. The case rate is lowest in Germany and Sweden, but Sweden has been increasing.
- The ***case fatality rate*** per 100,000 people has been slowly but steadily climbing everywhere (except China, whose numbers continue to be suspect). In the last 10 days, it has doubled in the U.S. to 16, which is still less than Sweden (22). Spain is the highest at 49, and Germany is lowest at 7.1.

The key chart (#4 on Page 18) – the increase in cases per day, which offers a look at progress toward flattening the curve – shows:

- Worldwide, there appears to be an undulating plateau at a little more than 80,000 new cases per day. Spain appears to have plateaued at ~4,300 new cases/day, the U.K. is floating at ~5,000 new cases/day, and Italy appears to be coming down slowly.
- The U.S. doesn't appear to have peaked or flattened. Over the last 10 days the additional cases per day have gone from ~33,000 to >47,000.

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In the U.S.

- **New York** and **New Jersey** together account for 41% of all U.S. cases and 42% of all deaths in the country. New York Gov. Andrew Cuomo said his state appears to have plateaued but the new cases per day chart do not support that. They have been increasing the past five days.
- **Louisiana** and **Washington** state appear to have their outbreaks in control, but there remain concerns about **Illinois** and **Massachusetts.**

Some things to pay particular attention to in this report include:

- The U.S. fatality rate is likely to exceed the modelers' estimates.
- A worldwide backlash is developing against China.
- Face masks are becoming increasingly mandatory in public.
- Transmission appears to be more of a problem in confined spaces – and in nursing homes, which are still problematic.
- Experts are increasingly predicting a second wave of Covid-19 this fall, and if it coincides with the flu, the situation could be "difficult." (*See Page 6*)
- New indications about possible temporary reservoirs for the virus in the body (eye and testes). (*See Page 7*)
- Elective surgeries are getting restarted, at least a little.
- Be careful about mixing fatality rates based on case reports and rates based on prevalence estimated from antibody tests; it is apples and oranges. (*See Page 11*)
- There is still no really promising data on any treatment under investigation, but there were some mixed data on two agents – Regeneron Pharmaceuticals and Sanofi's Kevzara (sarilumab) and Gilead Sciences' remdesivir – and some negative data on hydroxychloroquine. (*See Pages 13-14*)
- Despite the desire for a vaccine, it may not be available as fast as experts would like. (*See Vaccine Timing on Page 16*)

## The world

### Australia

– Sydney tried re-opening two of its beaches for exercise only (no sitting), but that experiment lasted for only a few days before they were shut down again because of large crowds of people sitting on those beaches.

### China

- The Covid-19 **death toll** in Wuhan was raised by 50% with no explanation. But no one outside of China seems to believe China's number for Covid-19 cases or deaths in Wuhan or elsewhere. American Enterprise Institute estimates the true number of Covid-19 cases in China is, conservatively, 2.9 million.
- The director of the **Biosafety Level 4 lab** in Wuhan, where it is believed the SARS-CoV-2 virus accidentally escaped, starting the current pandemic, strongly denied the virus came from his lab.
- Nobel laureate Luc Montagnier, MD, PhD, a French virologist and the co-discoverer of the AIDS virus, and two colleagues believe SARS-CoV-2 has been manipulated, containing elements of HIV and malaria that could not have arisen naturally. However, suggestions that the virus was man-made or man-manipulated were dismissed by Anthony Fauci, MD, director of the U.S. National Institute of Allergy and Infectious Diseases (NIAID), who said, "There was a study recently where a group of high-quality evolutionary virologists looked at the sequences in bats as they evolve, and the mutations it took to get to this point is totally consistent with a jump from animal to human."
- There is a growing call for China to have to pay for its role in the coronavirus spread. What "pay" means is unclear, but there has been a call in the U.S. for new legislation that would allow Covid-19 victims to sue a foreign government,

which is not currently legal. President Trump said there should be "**consequences**" if Beijing was knowingly responsible for the pandemic.

### France

- At least 1,081 of the 1,746 sailors on the **aircraft carrier** Charles de Gaulle have Covid-19. The outbreak on the ship apparently started after sailors had shore leave in Brest.
- Monitoring **wastewater** may be one way to detect a second wave of Covid-19 early. French researchers reported that they detected a rise and fall in SARS-CoV-2 concentration in sewage that paralleled the current outbreak in Paris, and they suggested this may be an inexpensive, non-invasive early warning marker.
- The government banned online sale of **nicotine** products – patches, gum – and limited their sale in pharmacies after French researchers reported that their data suggest that smokers have a statistically significant lower rate of contracting Covid-19. Trials of nicotine as a preventive are being planned in France.

### Germany

- **Face masks** are becoming mandatory across the country.
- German Chancellor Angela **Merkel** warned, "We are at the beginning of the pandemic…We cannot return to life before the pandemic. Our everyday lives will be different."

**Japan** – Cases have spiked, leading the government to declare a **national emergency**. In Hokkaido, for example, a lockdown seemed to control the virus well, but when the lockdown was lifted, a second wave hit, and the city was locked down a second time. And Tokyo hospitals are reportedly overwhelmed. There was a report in ***Japan Today*** of a case where an ambulance carrying a man with Covid-19 symptoms had to search for hours to find an available hospital. Finally, the 81st hospital tried accepted him.

**Sweden** – The government did *not* do a forced lockdown, and the case-fatality rate is 12.1% with the per capita rate 0.18% (vs. 0.04% globally and 0.28% for the U.S.). But the country reportedly is near achieving herd immunity status, at least in the capital, Stockholm.

### U.K.

- Total deaths for this outbreak were predicted to top at 23,791 (down from >37,000 previously), but that was before the Office for National Statistics (ONS) reported the coronavirus death toll in England and Wales is 40% higher than government data (13,121 deaths by April 10 vs. the government tally of 9,288).
- Prime Minister Boris Johnson is expected to return to work (part-time) on April 27.

## United States

The **U.S. fatality rate** that the University of Washington's Institute for Health Metrics and Evaluation (IHME) predicted was originally 100,000-240,000 (at best), but that has been progressively lowered due to the effects of mitigation (stay-at-home orders). The lowest estimate was 60,308 (range 30,188-175,965), but that has gone up now to 65,976 – the first increase since they started reporting. The 60,000 figure did seem too low since the U.S. is already at more than 53,000 deaths, but is 66,000 high enough?

Ambassador Deborah Birx, MD, the White House Coronavirus Response Coordinator, said earlier this week, "Across the U.S…we do see improvement across all the large metro areas – even in Rhode Island and Connecticut. Detroit is doing quite well with declines now. New Orleans is nearly back to baseline. We continue to see outbreaks in nursing homes and confined spaces." More recently, she added that they are still worried about Boston and Chicago.

- President Trump proposed a **three-phase plan for governors to follow to re-open the economy**, county-by-county and state-by-state. Before starting each phase, there are gating requirements that have to be met. In short, the key *new* things opened in each phase are:
  - ***Gating 1:*** *Downward trend for 14 days, hospitals have capacity, robust testing available.*
  - **Phase One:** Gatherings <10, gyms open, large venues open with social distancing, outpatient elective surgeries allowed.
  - ***Gating 2:*** *Same as Gating 1 plus no rebound in Phase 1.*
  - **Phase Two:** Gatherings <50, non-essential travel resumes, schools and organized youth activities resume, bars open with limited standing, inpatient elective surgery allowed.
  - ***Gating 3:*** *Same as Gating 1 plus no rebound in Phase 2.*
  - **Phase Three:** Vulnerable individuals can go out, no limit on gathering size, unrestricted staffing of worksites, visits to senior living facilities and hospitals allowed, bars can increase standing capacity.

  *For more details see chart on Page 19.*

  With this approach, all states would go through each phase, but states will be on different timetables. And how long a state is in each phase will vary. One expert has estimated that, for most states, Phase 1 will last a few weeks, Phase 2 will last 12-18 months (yikes!), and Phase 3 really requires a vaccine.

  What the President did not offer was any estimate of how long each of these phases is likely to last. And Americans are already getting tired of stay-at-home orders. There have been **protests** in dozens of states, including Alabama, Arizona, California, Colorado, Florida, Idaho, Illinois, Kansas, Kentucky, Michigan, Minnesota, Missouri, Montana, New Mexico, New York, North Carolina, Ohio, Oregon, Pennsylvania, Tennessee, Texas, Utah, Virginia, Washington, and Wisconsin.

  In actual practice, some governors have already started loosening restrictions without following the President's 3-step plan.

  - **Florida.** Gov. Ron DeSantis opened beaches in northeastern Florida, and that appears to be going well so far. For example, Duval County beaches were opened for limited hours (6-11 am and 5-8 pm) for walking (no sitting), swimming, surfing, taking care of pets, and fishing. The mayor of Jacksonville said, "Five percent of those tested are positive in our area…Our hospitalizations are fairly flat and stable and have been for quite some time…This is not Spring Break…This is simply people out, moving around in a safe way."
  - **Georgia**, on the other hand, opened businesses widely, including tattoo parlors, hair salons, and massage parlors (among other businesses) across the state, even over the objection of some mayors. President Trump said, "I disagree with him…Maybe you wait a little longer until you are in Phase 2…I would keep it [shutdown] a little longer, but I told him I totally disagree."

- **Disinfectants.** President Trump also caused an outcry among doctors and other experts when he questioned whether a disinfectant could be injected or used internally to kill the virus as it does on surfaces. They were quick to warn that disinfectants cannot be used that way, that ingesting or injecting a disinfectant is dangerous. And Reckitt Benckiser, which makes Lysol, issued a warning not to ingest Lysol or any other disinfectant. The President later tried to say that he was being sarcastic with reporters, but the replay of his comments didn't support that claim. The President cut the next daily White House Task Force briefing short and hasn't held a briefing since then.

- **Social distancing guidelines.** The President's social distancing guidelines were initially for 15 days, then another 30 days, and now the President said he may extend them longer, to early summer.

- **Economic relief.** With 26.5 million Americans now out of work, mostly because of Covid-19, the Senate and House both approved a Phase 3.5 relief plan, another $484 billion. It includes $321 billion for the small businesses through the paycheck protection program (PPP), with $120 billion of this for the smallest businesses. There is also $75 billion for hospitals, $25 billion for testing, and $60 billion for economic disaster loans. President Trump signed the legislation on April 23rd.

  The glitch was that when the list of companies that got PPP loans in the first tranche was released there were large colleges (e.g., Harvard and Stanford), companies, and franchisees on the list that raised eyebrows. **Harvard** got a lot of bad publicity but said it would not accept the money. Other companies that may face negative publicity for getting a loan – and who could see the government attempt a claw back – include **Conformis**, the orthopedic company. Basically, any public company is likely to generate bad publicity by getting a PPP loan.

  A Lending Tree survey of >1,200 small business owners found that only 5% of the companies surveyed had gotten a PPP loan in the first tranche, though 60% had applied for funding.

  The process of applying is not as easy as the politicians make it sound. They tell people that there is only a two-page form that needs to be completed. What they don't mention are the multitude of documents that must accompany this form. One truly small business owner said she had to prepare and file 12 separate documents, and she had to get an accountant to prepare them because they were complicated. Then, her first application was not fully processed in time by the first lender (her large accounting firm's recommendation), and she had to start over with her community bank for the second attempt. That required more documents. The community bank worked hard to get all the documents correctly packaged, even working on weekends. She is hopeful the loan will go through in the second tranche. This may be one reason most of the loans so far have gone to larger small businesses.

- **Food supply.** Five meat packing plants have had to shut down because of Covid-19 outbreaks among workers, but industry officials say there isn't expected to be a meat (or other food) shortage in the U.S.

- The **military travel ban** was extended to June 30, 2020.

  - The **USNS Comfort** is leaving New York harbor and returning to Norfolk. After treating just 159 patients, it is no longer needed there.

  - The **USS Roosevelt** may get its captain back. Navy leaders recommended that Capt. Brett Crozier, who was relieved of duty for a leaked letter complaining about Covid-19 aboard the aircraft carrier – and who himself got Covid-19 – be reinstated. So far, 866 sailors on the ship have contracted Covid-19.

- **Nursing homes.** The U.S. coronavirus problem really started with a nursing home (Washington state), and nursing homes have remained an issue. About 11,000 of the people who died from Covid-19 were nursing home patients across 36 states though more than half were in New Jersey and New York.

  - Dr. Birx said nursing homes are still seeing outbreaks.

  - Barbara Ferrer, PhD, MPH, director of Public Health in Los Angeles, said that the "vast majority" of Covid-19 deaths were in skilled nursing facilities – 39% of all deaths. She said, "It is very difficult in nursing homes to contain the outbreaks…Many employees work in multiple sites…and once they are infected [they can spread it] – and now we know they can be infected without symptoms. We do have more nursing homes with 5-6 infected…but many nursing homes have only 1 or 2 infected."

  - Some states – including New York – require nursing homes and long-term care facilities to take recovering Covid-19-positive patients.

  - Seema Verma, administrator of the Centers for Medicare and Medicaid Services (CMS), said her agency has a strategy, announcing a new effort around nursing home transparency, "We are requiring nursing homes to report to patients and

their families if there are cases of Covid-19 inside the nursing home. We are also requiring them to report directly to CDC [Centers for Disease Control and Prevention] when they have cases of Covid-19."

- The Veterans Administration also is deploying teams to help in nursing homes.
- A study, published in the ***New England Journal of Medicine***, found that infection-control strategies that focus only on symptomatic residents are not sufficient to prevent transmission of Covid-19 because more than half the residents who tested positive were asymptomatic at the time of the test.

■ **Whistleblower.** Rick Bright, PhD, director of the Biomedical Advanced Research and Development Authority (BARDA) and acting Deputy Assistant Secretary in the Office of the Assistant Secretary for Preparedness and Response (ASPR), Department of Health and Human Services (HHS) – and a vaccine specialist – was reassigned to head up coronavirus testing at the National Institutes of Health (NIH).

Dr. Bright said he plans to file a whistleblower complaint, charging he was demoted because he questioned the potential of hydroxychloroquine to treat Covid-19. He said, "I am speaking out because to combat this deadly virus, science – not politics or cronyism – has to lead the way."

Gary Disbrow, PhD, Dr. Bright's former deputy at BARDA, has taken over as the acting director of BARDA. Dr. Bright hired the same lawyer that Christine Blasey Ford used in her accusations against now Supreme Court Justice Brett Kavanaugh, Debra Katz.

*Asked about Dr. Bright*, President Trump said he had never heard of him.

## A second wave?

Robert Redfield, MD, director of the CDC, said that if there is a second wave of Covid-19 in Fall 2020, it could be worse than the current wave *because* it could coincide with the winter flu season. So, there will be a concerted effort to vaccinate people for the flu this fall.

- President Trump said the virus "might not come back in a second wave, and if it does come back it will be in smaller doses that we can contain…We will be watching for it, but it is also possible it won't come back."
- Dr. Birx said, "I don't know if it will be worse. This has been very bad…What happened in New York was very bad…I believe we will have an early warning signal." However, she later added, "That's why we didn't stop any ventilator orders. It is important to have a comprehensive stockpile for the fall."
- NIAID's Dr. Fauci said, "In the fall we will be much, much better prepared to do containment…It will be complicated by influenza season."

A makeshift hospital is being constructed by the Army Corps of Engineers in the Washington DC convention center. Why now, when Covid-19 cases have peaked and are on the way down? Gen. Todd Semonite, head of the Army Corps of Engineers, said, "We don't know if it is coming back in the fall, so it is a good reserve." *That pretty much says there won't be any conferences, medical or otherwise, at the convention center the rest of this year.*

■ **Contact tracing.** Minimizing any second wave, experts insist, will require three things – beside flu shots – testing, contact tracing, and isolation. Tests are becoming more available, so the big hurdle will be the contact tracing. This is the traditional way the CDC investigates a disease outbreak, but the initial wave of Covid-19 was so big, so fast, and so geographically spread out that not a lot of contact tracing could be done. For the next coronavirus wave, assuming there is one, contact tracing will be key.

- Massachusetts is recruiting 1,000 people to be contact tracers.

- New York Gov. Andrew Cuomo said he will need a "tracing army." Former New York City Mayor Michael Bloomberg volunteered to help recruit that army, developing the first-ever testing-tracing-isolation program and doing it on a tristate basis – New York, New Jersey, and Connecticut.

■ **Blood supply.** The FDA has said that SARS-CoV-2 isn't a threat to the blood supply because it is a respiratory virus and not transmitted in blood – and because blood banks don't take donations from people with symptoms of Covid-19. But potential donors are not tested for the virus. And, there really hasn't been any testing reported to show that the virus cannot be transmitted through blood if an asymptomatic infected person donates blood. Now, a Chinese study, published in the journal ***Blood Transfusion*** – a peer-reviewed journal, not a pre-print – raises questions again.

The authors indicated that China is screening blood donations for SARS-CoV-2 in Hubei province, where the Covid-19 outbreak was worst. They wrote, "Although there is no evidence that Covid-19 can be transmitted through blood or blood products, the nucleic acid-based detection of SARS-CoV-2 has been added to the blood screening process in Wuhan and other cities of Hubei province to minimize the possible risks."

In addition, blood donated in Hubei "has to be registered on the information management system and needs to be followed up until the expiry date of the blood products; this has facilitated the isolation or urgent recall of blood products donated by individuals with suspected SARS-CoV-2 infection. Proactive measures such as the temporary isolation of blood for 14 days after collection and delaying its release for clinical use have also been taken in areas seriously affected by Covid-19."

■ **Reservoir?** Earlier in the coronavirus pandemic, Francis Collins, MD, PhD, director of the NIH, said researchers just don't know yet whether SARS-CoV-2 hides in a reservoir in the body long-term like HIV or shorter term with Ebola (where it can be found in semen and in the eye for up to a year). There still is no answer to this question, but data are building that the coronavirus is not restricted to the lungs as most experts initially insisted, and may be behaving more like Ebola in this regard. For instance, there are now reports that SARS-CoV-2 can be found in eyes and testes.

- **Testes.** A 68-patient pre-print study, conducted in Mumbai, India, suggests that the testes may be able to harbor the coronavirus because the ACE2 receptor, to which SARS-CoV-2 binds, is plentiful in testicular tissue. This is still a preliminary finding, and there are questions of how the coronavirus gets to the testes since it is not supposed to travel in the bloodstream, and there are no data on the virus in semen in testicular-positive men. However, this would help explain why men are more likely than women to catch and to die from Covid-19. And it would raise questions about (1) possible sexual transmission through seminal fluid and (2) the efficacy of any vaccine.
- **Eyes.** Italian researchers reported in the ***Annals of Internal Medicine*** on a woman whose coronavirus infection was present in eye fluids, possibly at contagious levels, and eye samples continued to show positivity long after nasal swabs turned negative.

## U.S. states and cities

Dr. Birx said there is still concern about Boston and Chicago, but New Orleans is doing well.

■ California – San Francisco and a number of counties are requiring people age >2 to wear a face mask in public.

■ Hawaii is paying to send tourists home who don't observe the state's mandatory 14-day quarantine for new arrivals. The statewide stay-at-home order was extended to May 31.

■ Massachusetts – Officials in Salisbury, a beach town, voted to refuse to turn on water for the ~300 currently unoccupied seasonal homes to prevent the owners from coming there, at least through May 15.

■ Michigan

- The governor slightly loosened her *very* strict stay-at-home order but extended it to May 15.

- Henry Ford Health System has been reporting its Covid-19 statistics each day, and there were some interesting numbers. Over the past 9 days, on average:
  - ✓ 37% of the people they tested were positive for Covid-19, but the number positive appears to be decreasing slightly in the past few days (to 34%)
  - ✓ Hospital stays were 9.8 days (up from an average of 8 days on April 16)
  - ✓ Average ICU stays were 9.9 days (up from an average of 9 days on April 16)

■ New York

- New York City canceled early summer concerts and festivals.
- Gov. Cuomo
  - ✓ Issued an executive order allowing marriage licenses to be able to be issued online – and for marriage ceremonies to be able to be conduced by video.
  - ✓ Started a rolling (and continuing) release of non-violent prisoners over age 50 with ≤90 days to serve on their sentence.
  - ✓ Urged Covid-19 survivors to donate plasma for use in convalescent plasma treatments of other Covid-19 patients.
  - ✓ Continued his plea for more federal funds for states, like his, hard hit by Covid-19. Senate Majority Leader Mitch McConnell suggested Congress should pass legislation instead that would allow states to go bankrupt. That prompted this response from Gov. Cuomo: "I dare you to pass a bill allowing states to file bankruptcy…and see what happens to the stock market…New York [is] the No. 1 state in donating to the federal pot, Kentucky is the No. 3 state in taking from the federal pot. They take out more than they put in every year."
  - ✓ Predicted post-Covid-19 will be different, saying, "The question shouldn't be: When do we re-open? The question should be: Let's use this crisis, this time…to re-imagine what we want society to be…Wow, we went thru hell, but look what we learned and look at how much better we made it…Stop saying re-open and say re-imagine."
  - ✓ Said, "We showed we can control the beast…and slow the infection rate…We will have to make sure we keep that beast under control."

■ Texas – All schools will be closed through the end of the school year. The governor formed a statewide Strike Force, re-opened state parks (but only for groups of ≤6, and stores are starting to open, first with retail-to-go.

■ Washington – Boeing brought back 27,000 workers.

## Elective surgery

Several governors are not waiting to meet the President's Reopening Plan criteria to allow some hospitals – in areas with little or no Covid-19 – to resume elective surgeries. New York Gov. Cuomo, for instance, said he would allow hospitals not dealing with Covid-19 and who are hurting from lack of procedures, to resume elective surgery. And Vice President Pence called on states to resume elective surgery as soon as safe. Hospitals are anxious to start doing elective surgeries – their bread and butter – again, but it is likely to be gradual.

Interestingly, before the coronavirus, outpatient procedures outnumbered inpatient procedures (53% vs. 47%) across the U.S. What are those procedures most likely to be? Before Covid-19, the most common procedures were:

- Outpatient – eye, ear, nose, mouth, pharynx, male genital, endocrine, and skin.
- Inpatient – cardiovascular, respiratory, urinary, hemic, and lymphatic.

Among the 20 states moving ahead with elective surgeries – at least in some hospitals and to some extent – are: Alaska, Arizona, Arkansas, California, Colorado, Indiana, Iowa, Minnesota, Nebraska, Oklahoma, Oregon, Pennsylvania, South Dakota, Tennessee, Texas, Utah, Vermont, Virginia, Washington, and West Virginia.

CMS issued recommendations for elective procedures to be done in the President's Phase 1. And several medical groups issued guidelines for restarting elective procedures, including a joint statement – a Roadmap for Resuming Elective Surgery after COVID-19 Pandemic – by the American College of Surgeons, American Society of Anesthesiologists, Association of periOperative Registered Nurses, and the American Hospital Association. They prioritized these specialties: cancer, organ transplants, cardiac, and trauma.

## Drug shortages

- **Antibiotics.** Nine drug companies reported shortages of azithromycin. Premier said demand jumped 150% after President Trump touted its use with hydroxychloroquine to treat Covid-19.
- **Controlled substances.** The Drug Enforcement Administration (DEA) lifted three restrictions on hospitals and clinics during the coronavirus pandemic:
  - Allowing DEA-registered dispensers (including medical practices, pharmacies, and hospitals) to exceed the 5% limit on distribution of controlled substances.
  - In some cases permitting hospital/clinic satellite sites to handle controlled substances.
  - Allowing narcotic treatment programs to accept deliveries without signing for them.
- **Compounding.** The FDA is temporarily allowing registered outsourcing facilities to compound 13 frequently used hospital drugs (e.g., anesthetics and analgesics) to give them flexibility to respond to demand for drugs to treat intubated Covid-19 patients.
- **Dialysis drugs.** About 20% of coronavirus patients in the ICU require dialysis, often for weeks, and that is raising concern about a potential shortage of dialysis fluids. The Federal Emergency Management Agency (FEMA), the FDA, and CMS have been discussing potential emergency use authorizations (EUAs) to allow importation of more dialysis fluids, and Fresenius Medical Care and Baxter said they would help hospitals get additional supplies and dialysis machines.
- **Imports from India.** At least 50 manufacturing facilities in India have been shut down, including a Sun Pharmaceuticals site, and others have cut production. For example, Dr. Reddy's Laboratories is reportedly operating at 15% capacity at two sites, Abbott is operating at ≤30% capacity, and Cadila is operating at 35% capacity.
- **Tracking shortages.** The European Medicines Agency (EMA) instituted a fast track monitoring system designed to prevent shortages of drugs used for treating Covid-19 patients. Under this system, each pharmaceutical company appoints a single contact person who will report to EMA and national competent authorities on all current and anticipated shortages in drugs used to treat Covid-19 patients.

## Medical supplies

The first big shortages in the U.S. were personal protective equipment (PPE) and ventilators, but as the administration repeatedly points out, no Americans have been denied a ventilator who needed one. Soon, the national stockpile will have 110,000 ventilators, enough that President Trump said the U.S. will be loaning ventilators to Mexico, France, Italy, Honduras, Indonesia, and maybe even Germany. The PPE supply also has been improving steadily.

Then came a shortage of tests, but that also is starting to get handled. More than 5 million people have been tested for Covid-19 in the U.S., and the numbers are steadily increasing. There are still spot shortages of swabs and collection cups,

but production of those items is ramping up. President Trump said he was invoking the Defense Production Act (DPA) to help an undisclosed swab company build more production lines.

- **Other supply news:**
  - **Masks** – The FDA issued an EUA that makes it easier for companies to make masks to be used by the general public and healthcare personnel, provided the masks meet the requirement of the EUA.
  - **Hill-Rom's MetaNeb**, an intrapulmonary-percussive ventilation device for use by Covid-19 patients to reduce their time in ICU and on a ventilator, was granted an EUA.
  - **Sterilucent's HC 80TT**, a hydrogen peroxide sterilizer, for decontaminating N95 masks was granted an EUA for up to 10 cycles per respirator.
  - **Stryker's Sterizone VP4**, a sterilizer that can decontaminate ~20 N95 respirators (or similar masks) per cycle, was granted an EUA.
  - **Vent Multiplexor's Vent Multiplexor**, a ventilator sharing device that allows two people to share one ventilator, was granted an EUA.
  - **Vomaris' V.Dox** – The company is seeking accelerated approval for masks that don't just keep the virus from getting through but actually kill the virus. The masks have embedded microcell batteries that create electricity when moisture is detected.
- **Ventilator maintenance.** Typically, manufacturers have strict service/repair contracts with hospitals for maintenance of these devices, and that maintenance is generally performed every 6 months or 2,000 hours of operation. Questions are being raised about whether manufacturers will be able to service all the ventilators in the country during the pandemic, but contracts generally prevent third-party servicers to work on complex equipment, even during this pandemic. So, this is a potential problem on the horizon.

## Diagnostic testing

Testing supplies are the new shortage, but a multitude of tests have been approved, and more are on the horizon. FDA Commissioner Stephen Hahn, MD, said the Agency is working with >400 test developers on diagnostic and antibody tests, plus 220 labs have begun patient testing with their own validated tests.

- **Abbott's ID NOW** – The company warned that this rapid (5-13 minute) diagnostic test can have false negatives if a special solution is used to move or store patient samples. Instead, patient swabs should be put directly into the device to get accurate results.
- Among the other Covid-19 *diagnostic* tests that have recently been granted an EUA:
  - **Boston Children's Hospital's RT-PCR test**
  - **Exact Sciences' RT-PCR test**
  - **LabCorp's Pixel, a home sample collection Covid-9 test kit.** With this RT-PCR test, a patient is sent a kit, uses a swab to collect a nasal sample, and then mails the sample back to LabCorp for processing. However, a patient has to have a physician's prescription to get the test kit in the first place.
  - **Mayo Clinic's RT-PCR test**
- In other testing news:
  - **Behold.ai** was granted a CE Mark by the EMA for its artificial-intelligence-run chest x-ray diagnosis algorithm that should help speed up triaging of patients suspected of having Covid-19.

- **Mobidiag's Novodiag**, a Covid-19 RT-PCR test, which delivers results in ~1 hour, was granted an EUA in Finland and was submitted to regulators in the U.K., France, and Sweden.
- **PathoFinder's RealAccurate Quadruplex Corona-plus RT-PCR kit**, which can detect both SARS-CoV-2 and Middle East Respiratory Syndrome (MERS) coronavirus, was granted a CE Mark by the EMA. The test takes 2 hours for results.
- **Saliva.** A pre-print study found that saliva swabs – which are easier than nasal swabs – is a good alternative to nasal swabs in detecting SARS-CoV-2, with greater sensitivity and consistency throughout the course of infection. *Remember, the Rutgers saliva test got an EUA earlier this month.*
- **Seegene's Allplex 2019-nCoV Assay**, an RT-PCR test. It was also given a CE Mark by the EMA.
- **Tangen Biosciences** got a $696,000 grant from BARDA to develop a SARS-CoV-2 point-of-care molecular diagnostic test that provides results within an hour.

## Antibody (serology) testing

Serology tests measure whether someone has antibodies to SARS-CoV-2, which indicates they have been exposed to the virus and may have had Covid-19, even asymptomatically. There are false negatives and false positives with the antibody tests. So far, the FDA has issued at least five EUAs for antibody tests and has applications for more than 100 more. All of these EUA tests were "self-validated," which means the company did its own testing, but that testing has not been confirmed (validated) by the FDA.

**The immunity question.** Makers of unvalidated tests are required to make it clear to users that the tests are not validated, and the FDA said it is cracking down on companies that don't make it clear or who make unsubstantiated claims. And the Agency is warning doctors and consumers on interpretation of the tests, saying there is no evidence that antibodies are protective, though theoretically they are expected to be.

In fact, both the FDA and the World Health Organization (WHO) have issued warnings about making assumptions that people who test antibody (IgG) positive have immunity to Covid-19. *Serial* testing of people who are antibody-positive is needed before immunity can be determined, not a single positive antibody test.

- WHO said, "There's no evidence serological tests can show whether a person has immunity or is no longer at risk of becoming reinfected."
- The FDA recently issued a warning – a Dear Healthcare Provider letter – about the limitations of serological tests for SARS-CoV-2, and FDA Commissioner Dr. Hahn issued a separate statement. The key points in those statements:
  - ✓ None of the tests are ***diagnostic*** of Covid-19 – that they can't confirm a person has Covid-19 or exclude someone from having Covid-19.
  - ✓ Letter: "Experience with other viruses suggests that individuals whose blood contains antibodies associated with SARS-CoV-2 infection – provided they are recovered and not currently infected with the virus – may be able to resume work and other daily activities in society."
  - ✓ Dr. Hahn: "We don't yet know that just because someone has developed antibodies, that they are fully protected from reinfection, or how long any immunity lasts." This raises a question: *Do antibody-positive individuals need to be tested for active infection before returning to work?*

**Using the tests for prevalence studies.** **The question is what value the prevalence studies offer.** Two prevalence studies – one in California and another in New York – have been done, and they both show that significantly more people are positive than diagnostic studies show. And some officials have said that this lowers the mortality rate. That is both true and untrue. It is true that if asymptomatic people are picked up and added to the positive pool, the number of deaths will be a smaller

percentage of the total. However, that prevalence fatality rate can't be compared to the mortality rates being cited for counties, state, and countries around the world because they use case fatality rates, not prevalence fatality rates.

- In a **Los Angeles County** prevalence study of 863 people given a serology test for Covid-19, 4.1% (range 2.8%-5.6%) of undiagnosed people were found to have antibodies for Covid-19. If that were applied to the population of the county, it would translate to 221,000-442,000 adults who may have been infected at some point, which is up to 55 times more people than currently show up in the case count.

  LA's Dr. Ferrer said that reinforces the need for people to stay at home and observe physical distance requirements because many, many people are positive who may not be showing any symptoms, adding, "We need to assume at any point in time, we could be infected by anyone we come in contact because they could be infected…That means distancing, masks, and stay home."

  Interestingly, more men than women (6% vs. 2%) were positive, and more whites than Latinos (7% vs. 2.5%). But age was not a big discriminator (2.4% of age 18-34 and 4.3% of age ≥55). Dr. Ferrer's spin on the results was: That means 95% of Angelinos have not been infected…If the denominator is 300,000 and not 12,000, mortality drops from 4.5% to 0.1%-0.2%…That is still more deaths than from influenza."

- A **New York** antibody study tested 3,000 people randomly at grocery stores and shopping locations in 19 counties in the state. Preliminary results showed that 13.9% were positive for Covid-19. If that were extrapolated to the 19.4 million population of the state, it would mean that at least 2.7 million New Yorkers have been infected with the virus. It would also drop the *prevalence* fatality rate to 0.6%. There were variations by location in positivity: 21.2% among New York City participants, 11.7% in Westchester County, and 16.7% on Long Island but only 3.6% across the rest of the state.

**Validation.** The FDA now wants to get all the tests validated – and make it easier to do so – so that accurate assessments can be assured. To speed this process up, the FDA is collaborating with the National Cancer Institute (NCI), the National Institute of Allergy and Infectious Diseases (NIAID), and the Centers for Disease Control and Prevention (CDC) to establish a capability at NIH for evaluating serological tests *for developers*. This will include tests already available for use, as well as tests not yet on the market where additional validation data are needed to support an EUA. These performance assessments for serological tests will begin soon, with results expected quickly.

The newest EUAs for serology tests are:

- **Chembio Diagnostic Systems**' DPP COVID-19 IgM/IgG System.
- **DiaSorin** got ~$180,000 from BARDA to develop a serology test that can deliver results within 45 minutes. It has already been released in Italy.
- **Eurofins Technologies** has both an EUA from the FDA and a CE Mark from the EMA for an ELISA antibody test.
- **Ortho Clinical Diagnostics**' VITROS Immunodiagnostic Products Anti-SARS-CoV-2 Total Reagent Pack.
- **Roche's Elecsys Anti-SARS-CoV-2 serology test** has a CE Mark and was submitted to the FDA for an EUA. It is expected to be available in CE Mark countries in early May.

## Treatments

There currently are **no** approved therapeutics for Covid-19, but FDA Commissioner Dr. Hahn said there are 72 trials underway in the U.S., with another 211 in the planning stages.

There are also investigational therapies that address a particular aspect of Covid-19, such as hyperbaric oxygen for patients with severe pneumonia, perhaps preventing complications and helping with recovery.

- **Anti-IL-6/6R**
  - A perspective, published in the journal ***Science*** – co-authored by Carl June, MD, an immunologist at the University of Pennsylvania known for his work on CAR T therapies – explains the rationale for anti-IL-6/IL-6R drugs. He makes a compelling case for why they should work. Roche and Regeneron Pharmaceuticals (with Sanofi) have trials ongoing of their agents.
  - Regeneron Pharmaceuticals and Sanofi's Kevzara (sarilumab) – Based one preliminary analysis of the 47 patients in the Phase II portion of the ongoing, placebo-controlled Phase II/III trial of this IV anti-IL-6R in hospitalized Covid-19 patients, the independent data monitoring committee recommended that the drug only be used at a higher dose (400 mg) and only in critical (ventilator, high-flow oxygenation, or ICU) patients, and the study protocol for both the Phase II and Phase III portions of the trial is being amended to end both testing in severe patients and use of the lower dose (200 mg).

    In the Phase II portion

    - ✓ Sarilumab met the primary endpoint, rapidly lowering CRP, but the effect was greater in severe patients (-79% with 400 mg and -77% with 200 mg vs. -21% with placebo).
    - ✓ In a pre-specified, exploratory analysis, sarilumab had no notable benefit when severe and critical patients were pooled together, and there were *negative* trends for most outcomes in the severe patients vs. positive trends for all outcomes in critical patients.
      - – 36% of low-dose patients died vs. 23% of high-dose patients and 27% of placebo patients.
      - – 53% of high-dose patients were discharged vs. 39% of low-dose patients and 41% of placebo patients.
    - ✓ In a separate analysis by the companies, the negative trends with the severe patients seen in Phase II patients was not seen in Phase III patients.
    - ✓ Results from the Phase III portion of the trial are expected by June 2020.
    - ✓ A second Phase III trial outside the U.S. will also be amended in the same way. Those results are expected in 3Q20.

- **Convalescent plasma.** The FDA launched its own website aimed at encouraging patients who recovered from Covid-19 to donate plasma for use in convalescent plasma treatment of the virus. The website guides patients to local blood or plasma collection centers where they can *discuss* eligibility and schedule an appointment to donate.

- **DPP4 inhibitors.** A commentary, published in ***Diabetes Research and Clinical Practice***, suggests that the anti-inflammatory effects of these Type 2 diabetes drugs could help diabetic patients manage Covid-19 immune overreaction.

- **Gilead Sciences' remdesivir** – People are so anxious for results that tidbits of data are being reported as news. Among those tidbits:
  - **Negative news.** WHO briefly posted data from one of the two randomized trials in China of this antiviral. That trial had been stopped early (with 237 of the planned 453 patients) because enrollment was too slow due to the requirement that patients enrolling not have taken anything else prior. The data, while inconclusive, did not show a benefit to remdesivir: After 1 month, 13.9% of remdesivir patients died vs. 12.8% of control patients.
  - **Trial ended.** The second randomized trial in China was "suspended" because there were no longer patients with Covid-19 in China to enroll.
  - **Positive news.** *Unofficial* data from one site (the University of Chicago Medicine) in a Phase III trial in the U.S. showed that only two of their 125 (113 with severe disease) patients enrolled died. All patients got daily infusions of remdesivir. An investigator said, "We have seen people come off ventilators a day after starting therapy. So, in that realm, overall our patients have done very well…Most of our patients are severe and most of them are leaving at six

days, so that tells us duration of therapy doesn't have to be 10 days. We have very few that went out to 10 days, maybe three."

- **Positive animal news.** A pre-print study on ***bioRxiv*** on remdesivir in 12 rhesus macaques by Gilead and researchers at NIH showed that early treatment (IV daily for 3 days starting 12 hours after being infected) reduced symptoms and lung damage vs. untreated monkeys. The conclusion: These data support early remdesivir treatment initiation in Covid-19 patients to prevent progression to severe pneumonia. *Remember, this is an infused drug, so to be useful, it has to work in trials of hospitalized patients, which means either moderate or severe patients, since mild patients generally are not hospitalized.*

■ **Hydroxychloroquine (HCQ)**

- **Negative news #1.** In pre-print results on ***medRxiv*** from an open-label, 150-patient trial of standard of care ± this malaria drug (given 200 mg for 3 days, then 800 mg/day), Chinese researchers found no difference in the 28-day coronavirus negative conversion rate (85.4% vs. 81.3%) or in alleviation of symptoms. However, a post hoc analysis found a significant reduction in symptoms when the confounding effects of antiviral agents were removed. Yet, adverse events were significantly higher with HCQ (30% vs. 8.8%), and 2 HCQ patients had a serious adverse event.
- **Negative news #2.** A 368-patient Veterans Administration non-randomized, retrospective study missed both primary endpoints, finding that severe Covid-19 patients did not benefit from HCQ, either alone or in combination with azithromycin, with no reduction in either risk of death or mechanical ventilation vs. supportive care. In fact, the rate of death was higher with HCQ:
  - ✓ **Ventilation rate:** 13.3% HCQ alone, 6.9% for HCQ + azithromycin, and 14.1% for supportive care.
  - ✓ **Death rate:** 17.8% for HCQ alone (HR 2.61), 22.1% for HCQ + azithromycin (HR 1.14), and 11.4% for standard of care.
- **Novartis** got the green light from the FDA to start a 440-patient trial of HCQ in hospitalized Covid-19 patients.
- The **FDA** issued a Drug Safety Communication saying it is concerned that hydroxychloroquine and chloroquine are being used inappropriately to treat non-hospitalized patients with Covid-19 or to prevent that disease. The FDA noted that both drugs have known side effects, including serious and potentially life-threatening heart rhythm problems, which are in the label for the approved uses (malaria, lupus). The EUA for these drugs was for their *temporary* use only in hospitalized patients with Covid-19 when clinical trials are not available or participation is not feasible.

  FDA Commissioner Dr. Hahn added, "While clinical trials are ongoing to determine the safety and effectiveness of these drugs for Covid-19, there are known side effects of these medications that should be considered. We encourage healthcare professionals making individual patient decisions to closely screen and monitor those patients to help mitigate these risks."
- The **European Medicines Agency** issued a "reminder" that chloroquine and HCQ are known to potentially cause heart rhythm, and those could be exacerbated by combining either of the drugs with other medications, such as azithromycin. The EMA advises doctors to carefully monitor their patients on these drugs, but it does not advise against their use.
- A **panel of 50 medical experts**, convened by the National Institutes of Health, recommended against use of HCQ either alone or with azithromycin outside of a clinical trial – the same advice the FDA has given. The panel also did not endorse use of any other therapy outside of a clinical trial. And the panel recommended against use of HIV drugs because of negative clinical trial data and the potential for harm.

■ **KD Pharma and SLA Pharma's EPAspire (eicosapentaenoic acid free fatty acid, EPA-FFA)** – The companies are starting a study of this fish oil to see if it can improve the prognosis of Covid-19 patients by reducing the inflammatory immune response in the lungs.

- **PharmaMar's Aplidin (plitidepsin)** – The company is seeking regulatory approval from Spain's Spanish Medicines and Healthcare Products Agency for a Phase II trial of two doses of this multiple myeloma drug (an EF1A inhibitor, given IV BID) as a treatment for pneumonia in Covid-19 patients.

- **University of Pittsburgh** researchers are using artificial intelligence to help test various combinations of drugs in Covid-19 simultaneously, hoping to quickly identify an effective drug or combination of drugs.

- **Vanda Pharmaceuticals** is collaborating with the University of Illinois at Chicago on identification of novel antivirals to treat Covid-19.

**Key Coronavirus Treatments in Development**

| Company | Target | Product name | Stage | Target Covid-19 patients |
|---|---|---|---|---|
| Airway Therapeutics | recombinant human protein | AT-100 | preclinical | N/A |
| Amgen and Adaptive Biotechnologies | antiviral | -- | preclinical | prophylactic or treatment |
| AstraZeneca | SGLT2 | Farxiga (dapagliflozin) | Phase III | patients with comorbid conditions |
| CalciMedica | CRAC channel inhibitor | CM-4620-IE | 60-patient, open-label Phase II | severe Covid-19 pneumonia before ARDS |
| CytoDyn | CCR5 antagonist | leronlimab | 75-patient Phase II | mild-to-moderate respiratory complications |
| Gilead Sciences | antiviral | remdesivir | Numerous Phase II and III trials ongoing. Compassionate use halted | varies by trial from moderate to severe patients. Results from Phase III in severe patients due in May 2020 |
| Merck | antiparasitic | ivermectin | preclinical and Phase I | patients with lung injury from ventilator |
| PharmaMar | EF1A inhibitor | Aplidin (plitidepsin) | ready to start Phase II | pneumonia in Covid-19 patients |
| Regeneron Pharmaceuticals and Sanofi | anti-IL-6R | Kevzara (sarilumab) | 400-patient Phase II/III | severe Covid-19 |
| Regeneron Pharmaceuticals | -- | none yet | preclinical | -- |
| Roche | anti-IL-6 | Actemra (tocilizumab) | Phase III | Hospitalized Covid-19 patients with severe pneumonia |
| Takeda, CSL Behring, Biotest, and Octapharma | polyclonal hyperimmune globulin | TAK-888 (convalescent plasma) | N/A | Patients at high risk for infection |
| Vanda Pharmaceuticals | NK1 receptor antagonist | tradipitant | Phase III ODYSSEY VLY-686-3501 | Covid-19 patients with pneumonia (neurogenic inflammation of the lungs) |
| Vir Biotechnology and (a) WuXi Biologics, (b) Biogen, and (c) Generation Bio | antibody | N/A | preclinical | N/A |

## Vaccines

- **Mutations.** A Chinese pre-print study on ***medRxiv*** found that the SARS-CoV-2 virus has mutated into at least 30 different genetic strains. The researchers found that some of the most aggressive strains of the virus were able to generate 270 times the viral load of the weakest strains, and the aggressive strains killed human cells fastest. *If confirmed, this has significant implications for any vaccine.*

- **BCG.** Three pre-print studies found that the incidence of Covid-19 is lower in countries where the Bacille Calmette-Guerin (BCG) tuberculosis vaccine is routinely used vs. where it is not used. However, the World Health Organization cautioned against use of the vaccine as a preventive for Covid-19, saying that could cause a shortage of the vaccine for neonates.

- **WHO** convinced Sir Andrew Witty, former CEO of GlaxoSmithKline, to temporarily leave his positon as president/CEO of UnitedHealth Group's Optum, to co-lead the WHO's Covid-19 vaccine program.

- **Vaccine demand.** GlaxoSmithKline CEO Emma Walmsley predicted that one vaccine may not be enough to meet demand in Covid-19, saying, "The world's going to definitely need more than one vaccine when you think about demand in this hugely challenged global health crisis."

- **Timing.** Clarivate, an analytics company, used artificial intelligence to conclude that (a) it will be at least 5 years for either the Moderna Therapeutics' mRNA-1273 or Inovio Pharmaceuticals' INO-4800 vaccine to get full regulatory approval, and (b) neither vaccine has a high probability of success. Clarivate gave Moderna a probability of success and a time window of 5.2 years; Inovio's vaccine got a 15% probability of success with a window of 5.5 years. *The question is whether either is safe enough for an EUA, which would shorten the timeline.*

  *What if the first vaccine to market is a Chinese-developed vaccine?* Former FDA Commissioner Scott Gottlieb, MD, expressed concern about the quality of a Chinese vaccine.

- **Vaccine development.** NIH and the Foundation for the NIH announced a public-private partnership – Accelerating Covid-19 Therapeutic Interventions and Vaccines (ACTIV) – with the FDA, HHS, CDC, the EMA, numerous biopharmaceutical companies, and others. The goal is to speed up development of a Covid-19 vaccine and treatment options. ACTIV will develop a collaborative framework for prioritizing vaccine and drug candidates, streamlining clinical trials, coordinating regulatory processes, and/or leveraging assets among all partners.

- Among the **companies working on a vaccine** for SARS-CoV-2 (and there are >70 vaccine candidates in development) are:
  - BioNTech and Pfizer ex-China (BioNTech and Shanghai Fosun Pharmaceutical Group in China) – This vaccine was cleared to start human trials.
  - Dynavax and University of Queensland, Australia
  - GlaxoSmithKline, separately, with (a) University of Queensland, (b) Clover Biopharmaceuticals, (c) Vir Biotechnology, and (d) Sanofi
  - Heat Biologics and University of Miami
  - Imperial College, London
  - Inovio Pharmaceuticals' INO-4800
  - Johnson & Johnson
  - Medicago
  - Moderna Therapeutics' mRNA-1273 – in Phase I but Phase II could start soon.
  - Novavax
  - Oxford University's ChAdOx1 nCoV-19, an adenovirus vaccine vector – This is in a Phase I trial.
  - Sanofi
  - Sinovac Biotech is starting Phase I trials in China. In a preclinical study in macaque monkeys, the vaccine was protective.
  - Vaxart
  - China National Pharmaceutical Group/Wuhan Institute of Biological Products – starting Phase I trials in China.

**Unanswered questions** (*Items will remain on this list until answered.*)

? When someone develops **antibodies** to the coronavirus, how long are those antibodies protective – months, years, a lifetime? Antibody testing may help get this answer. Watch the results from the Beaumont Health antibody study.

? Are the **neurological symptoms/effects** reversible in some, all, most patients?

? Do people with lupus or rheumatoid arthritis who are taking **hydroxychloroquine** (Sanofi's Plaquenil) have a lower rate of getting Covid-19? The Medicare or Kaiser databases should be able to answer it, but no one has offered those data yet.

? Has SARS-CoV-2 **mutated**? Chinese researchers suggest it has, but are there differences between the virus in Europe and in the U.S.? If so, how will this affect vaccine development?

| #1A Worldwide Covid-19 Statistics – Daily Cases | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Country | April 16 | | | April 17 | | | April 18 | | | April 19 | | | April 20 | | |
| | Cases | Deaths | Fatality rate | Cases | Deaths | Fatality rate | Cases | Deaths | Fatality rate | Cases | Deaths | Fatality rate | Cases | Deaths | Fatality rate |
| Worldwide | 2,182,734 | 147,384 | 6.8% | 2,243,512 | 154,209 | 6.9% | 2,347,875 | 161,402 | 7.2% | 2,404,071 | 165,522 | 6.9% | 2,476,916 | 170,297 | 6.9% |
| **U.S.** | **672,246** | **33,318** | **5.0%** | **701,475** | **37,054** | **5.3%** | **735,287** | **39,090** | **5.3%** | **759,467** | **40,679** | **5.4%** | **786,968** | **42,308** | **5.4%** |
| Spain | 184,948 | 19,315 | 10.4% | 190,839 | 20,002 | 10.5% | 195,944 | 20,453 | 10.4% | 198,674 | 20,453 | 10.3% | 200,210 | 20,852 | 10.4% |
| Italy | 168,941 | 22,170 | 13.1% | 172.434 | 22,745 | 13.2% | 175,925 | 23,227 | 13.2% | 178,972 | 23,660 | 13.2% | 181,228 | 24,114 | 13.3% |
| France | 147,113 | 17,942 | 12.2% | 149,130 | 18,703 | 12.5% | 152,978 | 19,349 | 12.6% | 154,098 | 19,744 | 12.8% | 156,480 | 20,292 | 13.0% |
| U.K. | 103,093 | 13,729 | 13.3% | 109,769 | 14,607 | 13.3% | 115,317 | 15,498 | 13.4% | 121,172 | 16,095 | 13.3% | 125,856 | 16,550 | 13.1% |
| Germany | 138,369 | 4,105 | 3.0% | 141,397 | 4,352 | 3.1% | 143,779 | 4,543 | 3.2% | 145,742 | 4,642 | 3.2% | 147,065 | 4,862 | 3.3% |
| Sweden | 12,990 | 1,816 | 14.0% | 13,216 | 1,522 | 11.5% | 13,740 | 1,541 | 11.2% | 14,276 | 1,558 | 10.9% | 14,777 | 1,580 | 10.7% |
| China | 83,760 | 4,636 | 5.5% | 83,783 | 4,636 | 5.5% | 83,805 | 4,636 | 5.5% | 83,817 | 4,636 | 5.6% | 83,828 | 4,636 | 5.5% |

Source: https://coronavirus.jhu.edu/map.html www.statista.com/statistics/1102203/cumulative-coronavirus-cases-in-sweden/

| #1B Worldwide Covid-19 Statistics – Daily Cases | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Country | April 21 | | | April 22 | | | April 23 | | | April 24 | | | April 25 | | |
| | Cases | Deaths | Fatality rate | Cases | Deaths | Fatality rate | Cases | Deaths | Fatality rate | Cases | Deaths | Fatality rate | Cases | Deaths | Fatality rate |
| Worldwide | 2,563,384 | 177,415 | 6.9% | 2,624,465 | 183,120 | 7.0% | 2,721,354 | 191,231 | 7.0% | 2,790,986 | 195,920 | 7.0% | 2,896,746 | 202,846 | 7.0% |
| **U.S.** | 824,438 | 45,039 | 10.4% | 840,476 | 46,611 | 5.5% | 886,709 | 50,243 | 5.7% | 890,524 | 51,017 | 5.7% | 938,072 | 53,755 | 5.7% |
| Spain | 204,178 | 21,282 | 10.4% | 208,389 | 21,717 | 10.4% | 213,024 | 22,157 | 10.4% | 219,764 | 22,524 | 10.2% | 223,759 | 22,902 | 10.2% |
| Italy | 183,957 | 24,648 | 13.4% | 187,327 | 25,085 | 13.4% | 189,973 | 25,549 | 13.4% | 192,994 | 25,969 | 13.5% | 195,351 | 26,384 | 13.5% |
| France | 159,299 | 20,829 | 13.1% | 157,135 | 21,373 | 13.6% | 158,183 | 21,856 | 13.8% | 159,495 | 22,278 | 14.0% | 161,664 | 22,648 | 14.0% |
| U.K. | 130,175 | 17,378 | 13.3% | 134,638 | 18,151 | 13.5% | 138,078 | 18,738 | 13.6% | 144,635 | 19,566 | 13.5% | 149,569 | 20,381 | 13.6% |
| Germany | 148,453 | 5,086 | 3.4% | 150,648 | 5,315 | 3.5% | 153,129 | 5,611 | 3.7% | 154,545 | 5,723 | 3.7% | 156,513 | 5,877 | 3.8% |
| Sweden | 15,322 | 1,765 | 11.5% | 16,004 | 1,937 | 12.1% | 17,273 | 2,129 | 12.3% | 17,567 | 2,152 | 12.3% | 18,177 | 2,192 | 12.1% |
| China | 83,861 | 4,636 | 5.5% | 83,868 | 4,636 | 5.5% | 83,800 | 4,636 | 5.5% | 83,885 | 4,636 | 5.5% | 83,908 | 4,636 | 5.5% |

| #2A Worldwide Per Capita *Case* Rate | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Country | Population | April 14 | April 15 | April 16 | April 17 | April 18 | April 19 | April 20 | April 21 | April 22 | April 23 | April 24 | April 25 |
| Worldwide | 7,577 million | 0.03% | 0.03% | 0.03% | 0.03% | 0.03% | 0.03% | 0.03% | 0.03% | 0.03% | 0.04% | 0.04% | 0.04% |
| **U.S.** | 330 million | **0.18%** | **0.19%** | **0.20%** | **0.21%** | **0.22%** | **0.23%** | **0.25%** | **0.25%** | **0.25%** | **0.27%** | **0.27%** | **0.28%** |
| Spain | 47 million | 0.36% | 0.38% | 0.39% | 0.41% | 0.42% | 0.42% | 0.43% | 0.43% | 0.44% | 0.45% | 0.47% | 0.48% |
| Italy | 60 million | 0.27% | 0.28% | 0.28% | 0.28% | 0.29% | 0.30% | 0.31% | 0.31% | 0.31% | 0.32% | 0.32% | 0.33% |
| France | 67 million | 0.21% | 0.20% | 0.22% | 0.22% | 0.23% | 0.23% | 0.24% | 0.24% | 0.23% | 0.24% | 0.24% | 0.24% |
| U.K. | 67 million | 0.13% | 0.15% | 0.15% | 0.16% | 0.17% | 0.18% | 0.19% | 0.19% | 0.20% | 0.21% | 0.22% | 0.22% |
| Germany | 83 million | 0.16% | 0.16% | 0.17% | 0.17% | 0.17% | 0.18% | 0.18% | 0.18% | 0.18% | 0.18% | 0.19% | 0.19% |
| Sweden | 10 million | 0.11% | 0.12% | 0.13% | 0.13% | 0.14% | 0.14% | 0.14% | 0.15% | 0.16% | 0.17% | 0.18% | 0.18% |
| China | 1,386 million | 0.006% | 0.006% | 0.006% | 0.0006% | 0.006% | 0.006% | 0.006% | 0.006% | 0.006% | 0.006% | 0.006% | 0.006% |

| #2B Worldwide Per Capita *Fatality* Rate: Deaths per 100,000 People | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Country | Population | April 14 | April 15 | April 16 | April 17 | April 18 | April 19 | April 20 | April 21 | April 22 | April 23 | April 24 | April 25 |
| Worldwide | 7,577 million | 1.7 | 1.8 | 1.9 | 2.0 | 2.1 | 2.2 | 2.2 | 2.3 | 2.4 | 2.5 | 2.6 | 2.7 |
| **U.S.** | 330 million | 8 | **9** | **10** | **11** | **12** | **12** | **13** | **14** | **14** | 15 | 15 | 16 |
| Spain | 47 million | 39 | 40 | 41 | 43 | 44 | 44 | 44 | 45 | 46 | 47 | 48 | 49 |
| Italy | 60 million | 35 | 36 | 37 | 38 | 39 | 39 | 40 | 41 | 42 | 43 | 43 | 44 |
| France | 67 million | 24 | 26 | 27 | 28 | 29 | 29 | 30 | 31 | 32 | 33 | 33 | 34 |
| U.K. | 67 million | 18 | 19 | 20 | 22 | 23 | 24 | 25 | 26 | 27 | 28 | 29 | 30 |
| Germany | 83 million | 4.2 | 4.6 | 4.9 | 5.2 | 5.5 | 5.6 | 5.9 | 6.1 | 6.4 | 6.8 | 6.9 | 7.1 |
| Sweden | 10 million | 10 | 12 | 18 | 15 | 15 | 16 | 16 | 18 | 19 | 21 | 22 | 22 |
| China | 1,386 million | 0.24 | 0.24 | 0.33 | 0.46 | 0.46 | 0.46 | 0.46 | 0.46 | 0.46 | 0.46 | 0.46 | 0.46 |

| #3A U.S. Covid-19 Statistics – Daily Cases | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| State | April 16 | | | April 17 | | | April 18 | | | April 19 | | | April 20 | | |
| | Cases | Deaths | Fatality rate | Cases | Deaths | Fatality rate | Cases | Deaths | Fatality rate | Cases | Deaths | Fatality rate | Cases | Deaths | Fatality rate |
| California | 26,182 | 890 | 3.4% | 27,528 | 985 | 3.6% | 28,963 | 1,072 | 3.7% | 30,333 | 1,166 | 3.8% | 30,978 | 1,208 | 3.9% |
| Florida | 22,897 | 646 | 2.8% | 24,119 | 699 | 2.9% | 25,269 | 754 | 3.0% | 25,996 | 781 | 3.0% | 26,660 | 806 | 3.0% |
| Illinois | 25,733 | 1,072 | 4.2% | 27,575 | 1,134 | 4.1% | 29,160 | 1,259 | 4.3% | 30,357 | 1,290 | 4.2% | 31,508 | 1,349 | 4.3% |
| Louisiana | 22,532 | 1,156 | 2.1% | 23,118 | 1,213 | 5.2% | 23,580 | 1,267 | 5.4% | 23,928 | 1,296 | 5.4% | 24,523 | 1,328 | 5.4% |
| Massachusetts | 32,181 | 1,245 | 3.9% | 34,403 | 1,404 | 4.1% | 36,372 | 1,560 | 4.3% | 38,077 | 1,706 | 4.5% | 38,077 | 1,706 | 4.5% |
| Michigan | 29,263 | 2,093 | 7.2% | 30,023 | 2,227 | 7.4% | 30.791 | 2,308 | 7.5% | 31,424 | 2,391 | 7.6% | 32,000 | 2,468 | 7.7% |
| New Jersey | 75,317 | 3,518 | 4.7% | 78,467 | 3,840 | 4.9% | 81,420 | 4,070 | 5.0% | 85,301 | 4,202 | 4.9% | 88,806 | 4,377 | 4.9% |
| **New York** | **222,284** | **12,292** | **5.5%** | **229,642** | **12,822** | **5.6%** | **236,732** | **13,362** | **5.6%** | **242,786** | **13,869** | **5.7%** | **247,512** | **14,347** | **5.8%** |
| Washington | 11,290 | 567 | 5.0% | 11,618 | 583 | 5.0% | 11,829 | 603 | 5.1% | 12,085 | 624 | 5.2% | 12,286 | 634 | 5.2% |

Source: https://covidtracking.com/data/

| #3B U.S. Covid-19 Statistics – Daily Cases | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| State | April 21 | | | April 22 | | | April 23 | | | April 24 | | | April 25 | | |
| | Cases | Deaths | Fatality rate | Cases | Deaths | Fatality rate | Cases | Deaths | Fatality rate | Cases | Deaths | Fatality rate | Cases | Deaths | Fatality rate |
| California | 33,261 | 1,268 | 3.8% | 35,396 | 1,354 | 3.8% | 37,369 | 1,469 | 3.9% | 39,254 | 1,562 | 4.0% | 41,137 | 1,651 | 4.0% |
| Florida | 27,495 | 856 | 3.1% | 28,309 | 910 | 3.2% | 28,832 | 979 | 3.4% | 30,174 | 1,031 | 3.4% | 30,839 | 1,075 | 3.5% |
| Illinois | 33,059 | 1,468 | 4.4% | 35,108 | 1,565 | 4.5% | 36,934 | 1,688 | 4.6% | 39,658 | 1,795 | 4.5% | 41,777 | 1,874 | 4.5% |
| Louisiana | 24,854 | 1,405 | 5.7% | 25,258 | 1,473 | 5.8% | 25,739 | 1,540 | 6.0% | 26,140 | 1,601 | 6.1% | 26,512 | 1,644 | 6.2% |
| Massachusetts | 41,199 | 1,961 | 4.8% | 42,944 | 2,182 | 5.1% | 46,023 | 2,360 | 5.1% | 46,023 | 2,360 | 5.1% | 53,348 | 2,730 | 5.1% |
| Michigan | 32,967 | 2,700 | 8.2% | 33,966 | 2,813 | 8.3% | 35,291 | 2,977 | 8.4% | 36,641 | 3,085 | 8.4% | 37,203 | 3,274 | 8.8% |
| New Jersey | 92,387 | 4,753 | 5.1% | 95,865 | 5,063 | 5.3% | 99,989 | 5,368 | 5.4% | 102,196 | 5,617 | 5.5% | 105,523 | 5,863 | 5.6% |
| **New York** | **251,690** | **14,828** | **5.9%** | **257,216** | **15,302** | **5.9%** | **263,460** | **15,740** | **6.0%** | **271,590** | **16,162** | **6.0%** | **282,143** | **16,599** | **5.9%** |
| Washington | 12,494 | 652 | 5.2% | 12,494 | 682 | 5.5% | 12,494 | 692 | 5.5% | 12,753 | 711 | 5.6% | 12,977 | 723 | 5.6% |

# The most important chart

| #4 Watching for When the Coronavirus Curve Flattens - *APRIL 2020 - World and U.S. (*Additional* CASES each day, not total cases) | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| Location | April 16 | April 17 | April 18 | April 19 | April 20 | April 21 | April 22 | April 23 | April 24 | April 25 |
| Worldwide | 110,506 | 60,778 | 104,363 | 56,196 | 72,845 | 86,468 | 61,081 | 96,889 | 69,632 | 105,760 |
| China | 358 ** | 23 | 22 | 12 | 11 | 33 | 7 | 32 | 85 | 23 |
| Spain | 4,289 | 5,891 | 5,105 | 2,730 | 1,536 | 3,968 | 4,211 | 4,635 | 6,740 | 3,995 |
| Italy | 3,786 | 3,493 | 3,491 | 3,047 | 2,256 | 2,729 | 3,370 | 2,646 | 3,021 | 2,357 |
| U.K. | 3,577 | 6,676 | 5,548 | 5,855 | 4,684 | 4,319 | 4,463 | 3,440 | 6,557 | 4,934 |
| **U.S.** | **32,582** | **29,229** | **33,812** | **24,180** | **27,501** | **37,470** | **16,038** | **46,233** | **3,815†** | **47,548** |
| California | 1,758 | 1,346 | 1,435 | 1,370 | 645 | 2,283 | 2,135 | 1,973 | 1,885 | 1,883 |
| Florida | 386 | 1,222 | 1,150 | 727 | 664 | 835 | 814 | 523 | 1,342 | 665 |
| Illinois | 1,140 | 1,842 | 1,585 | 1,197 | 1,151 | 1,551 | 2,049 | 1,826 | 2,724 | 2,119 |
| Louisiana | 581 | 586 | 462 | 348 | 595 | 331 | 404 | 481 | 401 | 372 |
| Massachusetts | 2,263 | 2,222 | 1,969 | 1,705 | 0† | 3,122 | 1,745 | 3,079 | 0† | 7,325 |
| Michigan | 1,204 | 760 | 768 | 633 | 576 | 967 | 999 | 1,325 | 1,350 | 562 |
| New Jersey | 4,287 | 3,150 | 2,953 | 3,881 | 3,505 | 3,581 | 3,478 | 4,124 | 2,207 | 3,327 |
| **New York** | **8,505** | **7,358** | **7,090** | **6,054** | **4,726** | **4,178** | **5,526** | **6,344** | **8,130** | **10,553** |
| Washington | 596 | 328 | 211 | 256 | 201 | 208 | 0† | 0† | 259 | 224 |

* This is the metric watch to find when the curve flattens. **High due to inclusion of Wuhan deaths at home †Likely due to late reporting

| #5 Death Toll Increases - APRIL 2020 - World and U.S. (*Additional* DEATHS, not total deaths) | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| **Location** | **April 16** | **April 17** | **April 18** | **April 19** | **April 20** | **April 21** | **April 22** | **April 23** | **April 24** | **April 25** |
| Worldwide | 9,718 | 6,825 | 7,193 | 4,120 | 4,775 | 7,118 | 5,705 | 8,111 | 4,689 | 6,926 |
| China | 1,280† | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Italy | 525 | 575 | 491 | 433 | 454 | 554 | 427 | 464 | 420 | 415 |
| Spain | 503 | 687 | 451 | 0 * | 454 | 366 | 773 | 587 | 367 | 378 |
| U.K. | 835 | 978 | 710 | 597 | 455 | 828 | 474 | 587 | 828 | 815 |
| **U.S.** | **2,333** | **3,736** | **2,036** | **1,589** | **1,629** | **2,731** | **1,572** | **3,632** | **774** | **2,738** |
| California | 61 | 95 | 87 | 94 | 42 | 60 | 86 | 115 | 93 | 89 |
| Florida | 37 | 53 | 55 | 27 | 25 | 50 | 54 | 69 | 52 | 44 |
| Illinois | 124 | 62 | 125 | 31 | 59 | 119 | 97 | 123 | 107 | 79 |
| Louisiana | 53 | 57 | 54 | 29 | 32 | 77 | 68 | 67 | 61 | 43 |
| Massachusetts | 137 | 159 | 156 | 146 | 0* | 255 | 221 | 178 | 0* | 370 |
| Michigan | 172 | 134 | 81 | 83 | 77 | 232 | 113 | 164 | 108 | 189 |
| New Jersey | 362 | 322 | 230 | 132 | 175 | 376 | 310 | 305 | 249 | 266 |
| **New York** | **706** | **630** | **540** | **507** | **478** | **481** | **474** | **438** | **422** | **437** |
| Washington | 26 | 16 | 211 | 256 | 10 | 18 | 30 | 10 | 19 | 12 |

*** likely reporting was delayed** **† Wuhan data updated**

| President Trump's Plan for Re-Opening the Economy | | | |
|---|---|---|---|
| **Gating before Phase One** | **Phase One** | **Phase Two** | **Phase Three** |
| Downward trend for 14 days in both Covid-19 cases and flu cases | All vulnerable individuals continue to shelter-in-place | All vulnerable individuals continue to shelter-in-place | Vulnerable individuals can resume public interactions, carefully |
| Downward trend in positive tests as a percent of total tests for 14 days | Everyone maintains physical distancing in public | Everyone maintains physical distancing in public | Low-risk individuals should consider minimizing time spent in crowded environments |
| Hospitals have the ability to treat all patients without crisis care | No gatherings of >10 people | No gatherings of >50 people | |
| Robust testing program in place for at-risk healthcare workers, including antibody testing | Minimize non-essential travel | Non-essential travel can resume | Non-essential travel allowed |
| **Gating before Phase Two** | Businesses encourage telework, return to work in phases, and common areas closed | Businesses encourage telework and common areas closed | Unrestricted staffing of worksites |
| Satisfy the gating criteria a second time and no rebound in Phase 1 | Businesses strongly consider special accommodations for vulnerable personnel | Businesses strongly consider special accommodations for vulnerable personnel | |
| **Gating before Phase Three** | Schools and organized youth activities remain closed | Schools and organized youth activities can resume | Schools and youth activities open |
| Satisfy the gating criteria a third time and no rebound in Phase 2 | No visits to senior living facilities and hospitals | **No visits** to senior living facilities and hospitals | Visits to senor living facilities allowed |
| | Large venues (theaters, sit-down dining, sporting venues, houses of worship) can resume with ***strict*** social distancing | Large venues can resume with ***moderate*** social distancing | Large venues can operate with limited physical distancing |
| | Gyms can open with social distancing | Gyms remain open with social distancing | Gyms remain open |
| | Bars remain closed | Bars may operate with diminished standing-room occupancy | Bars may increase standing-room occupancy |
| | Elective surgeries can resume on an outpatient basis only | Elective surgeries can resume on an outpatient and inpatient basis | Elective surgeries continue |