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BULLETIN: UPDATE ON CORONAVIRUS 5/31

May 31, 2020
by Lynne Peterson

Be careful, be safe, and be well.

The number of cases in the U.S. today (1,775,125) of Covid-19, the disease caused by the SARS-CoV-2 virus, is more than triple what it was 51 days ago. The U.S. now has almost as many cases as existed in the entire world on April 11, 2020: 1,777,517. (*See charts on Pages 19-20-21*)

Given the variations in the way countries record cases, the best way to compare locations is not cases or per case deaths but ***per capita fatalities***. (*See chart 2B on Page 20*) Looking at it that way:

- **Europe**, with ~741 million people, has had 1.8 million cases of Covid-19 and >173,454 deaths, for a per capita mortality rate of 23 per 100,000 people. The highest per capita mortality rate has been in Belgium (82 per 100,000 people). The mortality rate per 100,000 has stabilized in Italy (55), France (43), Spain (58), and Germany (10), but the rates in the U.K. (57) and Sweden (44) are still increasing slowly but steadily.
- The **U.S.**, with ~330 million people, also has had 1.8 million cases and 103,906 deaths, a per capita *mortality* rate of 31 per 100,000 people. This is higher than Europe overall, but lower than most of the key countries we monitor.
- **BRIC** – The per capita fatality rate is continuing to increase in all of these countries (Brazil, Russia, India) except China.

Another important way to follow mortality is to look at ***new deaths per day***. (*See chart 4B on Page 21*) From this, it is apparent that over the last 8 days:

- Worldwide, deaths are holding pretty steady at about 4,000/day, so improvements in some areas of the world are being offset by worsening in other areas.
- In Europe: Spain appears under control, and Italy is improving, but the U.K. is still getting worse.
- The U.S is mostly holding steady, with ups and downs, but no steady trend downward. Most states are also holding relatively steady, with the exception of New York and Texas, which have improved a little.
- Deaths in China have been virtually non-existent for weeks, with an occasional one-day tiny spike (if the data are believable).

Since the peak of Covid-19 cases has passed in the U.S. and Europe, countries and states are re-opening; the focus now is turning to the other hot spots: Brazil, which is No. 1 in the world, and Russia, at No. 2. Russia has an extraordinarily low mortality rate, with just 1.1% of today's total of 405,843 positive cases dying, which compares to fatality rates of 6.2% worldwide, 6.0% in Brazil, 5.9% in the U.S., and 15.4% in France.

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Why is the rate so low in Russia? There are several possible explanations, including:

- There could be more deaths than the government is reporting.
- The Covid-19 death definition does not include people who are Covid-19-positive but die from another reason, such as a heart attack, but even if all additional excess deaths per month were added, the rate would still be only about 2%.
- The percentage of the population that are age ≥65 (14.7%) is lower than in France (20.0%) and the U.S. (15.8%), but not that much lower, and significantly higher than in Brazil (8.9%).
- There are significantly fewer old people living in nursing homes or assisted living facilities in Russia.
- Russia has done millions of tests, which could boost the number of asymptomatic Covid-19 patients.
- Maybe Russian hospitals learned from problems elsewhere.

With this background, there are currently four things getting the most attention:

1. Whether **re-opening** countries and states will result in a new spike in cases. Some increase is generally expected, but the question is whether that will spiral out of control.
2. Whether there will be **another wave** – and even possibly several disease waves.
3. Whether a **vaccine** can be developed quickly that actually works. There is a massive effort underway but no guarantee that a vaccine will be successful and/or safe.
4. Whether a preventive or curative **treatment** can be identified or developed.

What could become a major problem for the re-opening in the U.S. is the loss of social distancing in major cities across the country because of the riots that have been occurring after the death of George Floyd, a black man in Minneapolis, under the knee of a white police officer, was captured on video. Will there be a spike in Covid-19 cases/deaths after the large protests – violent and non-violent – occurring everywhere?

The world

WHO

- There are now at least 62 countries calling for a probe into the World Health Organization's Covid-19 response.
- President Trump announced that the U.S will pull out of WHO, accusing it of protecting China in the coronavirus pandemic and of not making the changes the U.S recommended. It isn't clear whether the President needs Congressional approval to fully withdraw.

China – People in Beijing no longer are required to wear a mask outdoors to protect against the spread of Covid-19.

India – The number of cases are still low for a country of 1.4 billion people, and the per capita rate is almost as low as China (<1%), and the death rate is also less than 1 in 100,000. However, the total number of cases is now approaching 200,000, putting it at No. 10 in the world. So, it bears watching.

Italy – Shops, restaurants, and church services restarted on May 15, and gyms, swimming pools, and sports centers opened May 25. Travel restrictions will be lifted on June 3, allowing visitors in and out of the country with no quarantine period. It's a risk the prime minister said was necessary or "we will never be able to start up again."

Japan – The prime minister lifted the Covid-19 state of emergency. The country, with a population of 126 million, has had only 16,651 cases and 858 deaths. Mexico has a comparable population, but almost five times as many cases and ten times as many deaths.

United States

- **Hawaii** – Extended its 14-day room quarantine for anyone traveling there on pain of fine or expulsion.

- **Michigan** – The state has been hard hit by the virus, but there are some signs things are improving. Henry Ford Hospital is an 877-bed hospital in the center of the state's most affected area, Detroit. The hospital reports almost daily numbers, and since it first started testing for Covid-19, more than 7,300 people have tested positive. Over the last couple of weeks, the average Covid-19 patient length of stay has stayed relatively stable at an average of 12 days; ICU days likewise have remained stable at an average of 15 days, but the number of new patients diagnosed positive has dropped in half to about 21/day.

- **North Carolina** – The Republican convention is scheduled for August 24-27 in Charlotte, but the location is now in doubt. President Trump has threatened to move the convention to another state unless there is no requirement for social distancing or masks. The governor countered with a proposal for a scaled back event, and the President said that was not acceptable. Look for some resolution to this standoff over the next week.

- **Texas** – Texas Supreme Court Justice Debra Lehrmann – and her husband, Greg – tested positive for the virus.

- **Who is dying?** Nationwide ~43% of Covid-19 deaths were nursing home/assisted-living/long-term care facilities residents. With ~2 million people living in one of the ~15,600 nursing home in the U.S. or a long-term care facility, that translates to ~2.2% of those residents dying from Covid-19, so the risk to an individual long-term care resident is ~1 in 50. The numbers of Covid-19-related deaths vary, depending on who is providing the data, but by state it looks like this:
  - Rates are highest in Minnesota (81%), Rhode Island (77%), Ohio (70%), Vermont (70%), and Pennsylvania (69%). But this is not just a U.S. problem: in Sweden the rate is 45%.
  - **Florida** – Nearly half (44%) of the Covid-19 deaths in the state (1,001 of 2,400) are people in nursing homes and long-term care facilities.
  - **Illinois** – 42% of the 5,083 people who died as of May 27.
  - **Massachusetts** – Of the 6,547 deaths as of May 27, nearly two-thirds (62% or 4,041) were residents of a nursing home or rest home.
  - **Michigan** – Of the 5,334 deaths in the state as of May 27, 23% were residents of a nursing home or long-term care facility in one count, but another count showed that as of May 22, 47% of the deaths were nursing home/assisted living facility (ALF) residents.

- **Travel**
  - President Trump extended the travel ban to include Brazil, denying entry to non-Americans who have been in that country in the past two weeks.
  - *Is flying safe?* Maybe more than you think. You might get the virus from another passenger, even one wearing a mask (remember masks are very leaky), but the air circulating in the plane is probably safer than you knew. According to Joseph Allen, DSc, MPH, an assistant professor of exposure assessment science at Harvard's T.H. Chan School of Public Health, the ventilation system requirement for airplanes meet the levels recommended by the CDC for use with Covid-19 patients in airborne infection isolation rooms. Airplanes do 10-12 air changes/hour. The minimum target for a hospital isolation room is 6/hour for existing facilities and 12/hour for new facilities. Airplanes also use the same HEPA air filter as isolation rooms.

Dr. Allen's focus would be on improved safety at airports: mandatory masks, increased ventilation, touchless bathrooms, temperature screening, more hand sanitizer stations. He also suggests that airlines change the way they handle boarding and discontinue meal and drink service.

- **Restrictions.** According to an analysis by WalletHub, a personal finance website, the states with the most Covid-19 restrictions (from masks to travel) are (in order): Illinois, Rhode Island, District of Columbia, Massachusetts, and Vermont. The states with the fewest restrictions are: South Dakota, Wisconsin, Idaho, Missouri, and Utah.

- **Patient attitudes.** A survey in mid-May 2020 of 1,189 adults by the Kaiser Family Foundation (KFF) on the impact of Covid-19 on decisions about healthcare among U.S. patients found:
  - 48% of patients said they or someone in their household had postponed/skipped medical care due to the pandemic.
  - 11% said they or a family member's health worsened because of postponing/skipping care due to Covid-19.
  - 68% of those who delayed care (32% of all adults) expect to get the delayed care in the next three months.
  - 1% said they will not get care.
  - 2% said they will not get care for >1 year.

- **Hospitalized patients and nursing home residents.** Before the coronavirus pandemic, the advice was that every hospitalized patient – and every nursing home resident – should have an advocate. Being a hospitalized patient or a nursing home resident is dis-empowering, but in the era of Covid-19 safety measures, family and friends are barred from both hospitals and nursing homes. You can't get in even wearing a mask and gloves. So, there is no loved one to help monitor care, to help prevent accidents, errors, or mistreatment. It would be nice to believe none of those things happen in hospitals and nursing homes, but that is just not true.

  Here is a real case example: The ambulance takes your husband away. You follow by car to the hospital where your temperature is checked, and you are shown an outside bench where you can sit (for hours). After a while (a long while), a nurse comes out to hear what information you can provide about your loved one – who does not know his medications and gets his medical history wrong all the time. But the nurse isn't taking notes and doesn't have a chart with him.

  The local hospital is now part of the Cleveland Clinic system, but the doctors are the same ones that have failed your family in the past, so you are deservedly nervous. And while the nurse says they can access your husband's Cleveland Clinic records, it isn't easy for them to do that, so they simply don't do it. You can pull those records up on your laptop, but the emergency room staff doesn't have them. And you can't give the information to them because you can't get in.

  Eventually, you go home to wait. Good news: they put your loved one in an ER room with a telephone. He calls – every 15 minutes or so. That helps because you can tell him things to ask, and he can ask your questions.

  They are running tests, and more tests, and more tests. At long last, the ER doctor comes in to discuss the case with your husband, and he is on the phone with you, so he makes the doctor talk to you. You find out that one of the tests they did was incorrect; they did only one part of it, and when you point this out to the doctor, he hems and haws. But he didn't repeat it correctly.

  They decide to keep your husband overnight and do more tests in the morning. He is doing much better, but they need to find the cause of the problem that brought him to the hospital, so they are moving him to a regular room. That generates a call to you from registration, which, of course, has the wrong information about his doctors – all of whom are true Cleveland Clinic doctors at the Cleveland Clinic in Weston FL. You correct that information, and order a ban on the cardiologist who, before the Cleveland Clinic affiliation, told you not to go to the Cleveland Clinic because they were just

money grubbers. And a ban on the cardiologist in the same practice who yelled at you and walked out of the room when you asked an appropriate question about your mother-in-law's testing. In fact, a ban on everyone in that cardiology practice.

More good news: Your husband doesn't have his cell phone with him, but there is a phone in his room, and he continues to call every 15 minutes. On one call he tells you he refused a medication because it was not what he usually takes, but the nurse comes in while he is talking to you, and you are able to clear up the confusion. The hospital is out of his usual medication, and this is an acceptable substitution. But she did not explain any of that to him when she first tried to give it to him.

Better news: The next morning the hospitalist checks on your husband, and he has a long conversation with you on the phone while he is in your husband's room. He is on the same page as you, and he recognizes the shortcoming of the ER test, and repeats it correctly. You are more comfortable, but still very worried about your lack of access.

Best news: Your husband will be fine and can get out the next morning. He has a non-life-threatening problem that can now be handled outpatient because none of the potential deadly causes appear to be involved. And the hospital's infection control procedures were very, very good, so you (and he) are not overly worried that he caught Covid-19 in the hospital.

Now: ***Imagine if this were your spouse, your mother, your grandmother***. You drop your loved one off at the hospital, and you may be entirely out of the loop, where the best you can do is pray or cross your fingers. It's like dropping your loved one in a black box and having to just wait and see how it comes out.

In addition, with the travel bans and difficulty in traveling, taking your loved one to the "best" hospital for whatever condition may arise could be impossible. If you live in Minnesota, you can probably drive to the Mayo Clinic; if you live in Ohio, you can probably drive to the main campus Cleveland Clinic; and if you live in Texas, you can probably make it to MD Anderson Cancer Center. But if these are the major medical centers that you would normally choose for your family, you may have to settle for local (and possibly if not probably) inferior care, lack of access to clinical trials, and lack of access to investigational therapies. That's really scary.

Please take a moment and really think about how you would feel if this happened to you. It may change how you feel about lockdowns.

Transmission

- A study in China found that 25 of 172 people who tested positive for Covid-19, were treated in the hospital, and then discharged developed symptoms again within 7-10 days post-discharge. These repeaters did not infect their immediate contacts. However, the researchers suggested that additional testing should be performed to be sure patients are actually clear of the virus when released, "It is probable that two negative RT-PCR tests – 24 hours apart – may not be sufficient for clearance." Instead, they recommended two negative RT-PCR tests taken over 48 hours.
- Other Chinese researchers suggested that released patients should be strictly supervised (quarantined) for at least two weeks after discharge.
- A U.K researcher estimated that ~10% of cases lead to 80% of the spread of Covid-19. And Swiss researchers estimated that SARS-CoV-2 has higher transmissibility than SARS or MERS. *Where are people getting Covid-19?* The Swiss researchers said it is much more likely in an enclosed space than outside. Japanese and Chinese researchers came to the same conclusion. The Japanese study found the risk of infection indoors is almost 19 times higher than outdoors.

What is a dangerous environment?

- Meatpacking plants because large numbers of people work closely together in a loud environment with a low temperature, which helps the virus survive.
- Places where people shout (bars) or sing (churches).

■ Data from Arkansas suggest some places where residents there *aren't* getting sick during the early days of that state's re-opening. In one snapshot from the state, here is how business exposure looked: 1% of cases from barber shops, 0.8% from restaurants, 0.7% from churches, 0.5% from daycare centers, and 0.2% from gyms. The big site in that state: meatpacking plants.

Diagnostic testing

The **FDA**:

- Updated the requirements for molecular diagnostics companies seeking an emergency use authorization (EUA) for their SARS-CoV-2 diagnostic test. As part of the validation process, companies must now include the use of actual positive samples.
- Suspended testing of patient samples collected at home through the Seattle Coronavirus Assessment Network (SCAN), which has been getting technical assistance from the Bill and Melinda Gates Foundation. The tests will be able to resume after the test gets an EUA.
- Partnered with **Aetion** on real-world data analytics for Covid-19 to explore the natural history of the disease, treatment and diagnostic patterns, and identification of patient characteristics.

Among the Covid-19 *diagnostic* tests that recently got an EUA from the FDA are:

- **1drop**'s 1copy Covid-19 qPCR multi-kit
- **Avera Institute for Human Genetics**' SARS-CoV-2 assay
- **Biocollections Worldwide**'s SARS-CoV-2 assay
- **BioCore**'s 2019-nCoV Real Time PCR Kit
- **bioMérieux/BioFire Diagnostics**' Respiratory Panel 2.1, which can differentiate and detect SARS-CoV-2 and 21 other bacterial and viral respiratory pathogens in ~45 minutes
- **Bio-Rad Laboratories**' SARS-CoV-2 Droplet Digital PCR test
- **Cedars-Sinai Medical Center**'s SARS-CoV-2 RT-PCR assay
- **Color**'s SARS-CoV-2 LAMP Diagnostic Assay, which uses loop-mediated isothermal amplification technology
- **Everlywell**'s Covid-19 Test Home Collection Kit, allows people to collect their own nasal swab samples
- **Exact Sciences**' SARS-CoV-2 test
- **Express Gene Molecular Diagnostics Laboratory**'s Express Gene 2019-nCoV RT, a PCR diagnostic panel
- **Genedrive**'s Genedrive 96 SARS-CoV-2 Kit
- **GeneMatrix**'s NeoPlex Covid-19 Detection Kit, for use in high-complexity CLIA-certified labs
- **Gnomegen**'s COVID-19-RT-qPCR Detection Kit

- **HiberGene Diagnostics**' rapid Covid-19 test (with positive results in 30 minutes and negative results in an hour)
- **IDEXX Laboratories/Opti Medical Systems**' Opti SARS-CoV-2 RT-PCR test kit, which can deliver results in 3.5 hours
- **One Health Laboratories**' SARS-CoV-2 RT-PCR test
- **P23 Labs**' TaqPath SARS-CoV-2 test
- **Sansure Biotech**'s Novel Coronavirus Nucleic Acid Diagnostic Kit
- **Seasun Biomaterials**' AQ-TOP Covid-19 Rapid Detection Kit
- **Sherlock Biosciences** was granted an EUA for a CRISPR diagnostic test, and the test, which takes about an hour, may be the most accurate test yet. Sherlock is working with an undisclosed partner on scale-up.
- **SolGent**'s DiaPlexQ
- **SpectronRx**'s Hymon SARS-CoV-2 test kit
- **Thermo Fisher Scientific**
  - ✓ Applied Biosystems TaqPath Covid-19 Combo Kit was granted an expanded EUA, allowing the test to be run on certain configurations of the QuantStudio 5 and QuantStudio 7 Flex real-time PCR instruments
  - ✓ MagMAX viral/pathogen II nucleic acid isolation kit, for use by laboratories
- **University of Tennessee Health Science Center**'s UTHSC/UCH SARS-CoV-2 RT-PCR assay

The European Medicines Agency (EMA) granted a CE-IVD Mark to some additional tests, including:

- **Advanced Biological Laboratories**' UltraGene Combo2Screen, which delivers results in 2 hours
- **Altona Diagnostics**' RealStar SARS-CoV-2, a real-time PCR kit for research use only
- **Eurofins Technologies**' GSD NovaPrime SARS-CoV-2 test, a multiplex assay that can deliver results within 2 hours
- **NeuMoDx'** SARS-CoV-2 assay, a multiplex RT-PCR SARS-CoV-2 test that can deliver results in 80 minutes
- **Ortho Clinical Diagnostics**' VITROS Immunodiagnostic Products Anti-SARS-CoV-2 Total Reagent Pack and Calibrators

Diagnostic tests on the horizon include:

- **Danaher/Beckman Coulter** is getting an additional $2.3 million from the Biomedical Advanced Research Development Authority (BARDA) to support development of a sepsis detection algorithm for use in Covid-19 patients.
- The U.S. military's Defense Advanced Research Projects Agency (DARPA) and **Fluidigm** reportedly are helping Mount Sinai, Duke University, and Princeton University develop an epigenetic test for pre-infectious SARS-CoV-2 carriers. It's a blood-based microfluidics test that could detect the presence of the virus as early as 24 hours after infection – long before people show symptoms and even before the person is likely able to spread the virus to others.
- **Johnson & Johnson/Janssen** is partnering with **Alveo Technologies** on development of an at-home test for viral infectious diseases, including respiratory syncytial virus and coronavirus.
- **Pictor** was given a $300,000 grant by New Zealand's Ministry of Business, Innovation, and Employment to develop a fast SARS-CoV-2 test that can deliver results within an hour and which can simultaneously detect biomarkers associated with various stages of infection.

Antibody (serology) testing

The problem with antibody tests is that they provide a good picture for epidemiologists but are not really useful (yet) for individuals because it still is not clear what a positive antibody test means for immunity, if any. However, there is starting to be some suggestion (not proof) that there may be some immunity from Covid-19 antibodies. A study by researchers at Beth Israel Deaconess Medical Center in laboratory monkeys found that antibodies do provide protection, whether they are triggered by an infection or a vaccine. But that is in monkeys, not humans.

Meanwhile, there is a growing number of antibody tests getting either an EUA from the FDA or a CE Mark from the EMA, and there are more than 180 in development.

The latest approved antibody tests include:

- **Biomerica**'s COVID-19 IgG/IgM Rapid Test for detecting antibodies to the SARS-CoV-2 coronavirus was granted a CE Mark.
- **CeGaT**'s Corona Antibody Test, which claims nearly 99% accuracy for negative samples and >95% accuracy for positive samples, was granted a CE Mark.
- **GenScript Biotech Europe**'s cPass-SARS-CoV-2 Surrogate Virus Neutralization test kit was granted a CE-IVD Mark.
- **PerkinElmer/Euroimmun**'s Covid-19 antibody test was cleared for use by certain laboratories certified to perform high-complexity tests.

■ In other antibody testing news:

- The FDA released a list of 28 Covid-19 antibody tests that are no longer allowed to be sold in the U.S. after their manufacturers voluntarily withdrew the tests or failed to apply for an EUA.
- **Thermo Fisher Scientific** is collaborating with WuXi Diagnostics and the Mayo Clinic on development of an open-platform Covid-19 ELISA antibody test.
- The U.K. government contracted with **Abbott** to supply its IgG antibody tests to the National Health Service.
- Health Canada authorized **Abbott's Architect** SARS-CoV-2 IgG antibody tests.
- In France, **Eurobio Scientific** will distribute **NG Biotech**'s Covid-19 NG-Test IgG-IgM rapid antibody tests (~15 minutes) to nursing homes and healthcare providers.

Antigen tests

The FDA issued an EUA for the first Covid-19 antigen test, a new category of tests that quickly detect fragments of proteins found on or within the virus by testing samples collected from the nasal cavity using swabs. The EUA was issued for Quidel's Sofia 2 SARS Antigen FIA for use in high and moderate complexity CLIA-certified labs as well as for point-of-care testing by facilities operating under a CLIA Certificate of Waiver.

What do antigen tests do? They are fast and less expensive than diagnostic or antibody tests. They are designed for ***rapid*** detection of the SARS-CoV-2 virus, usually in just minutes. However, antigen tests may not detect all active infections. They are very specific for the virus but are not as sensitive as RT-PCR tests. This means that positive results from antigen tests are highly accurate, but there is a higher chance of false negatives.

Treatments

■ **Gene therapy and Covid-19.** The World Orphan Drug Congress Europe sponsored an *industry* webinar on gene therapy and Covid-19. Among the points the speakers made:

- Some clinical trials have run into major delays, averaging about 6 months.
- Marketing of some approved therapies is deliberately being delayed by the sponsor.
- There is plenty of capital available, but there may be more impact on companies with a short capital runway and a lack of news flow.
- Covid-19 does not appear to be delaying regulatory reviews or approvals.
- There may be downward pricing pressure on gene therapies.
- Companies need to adjust to supply chain delays, but lessons learned on how to buy Covid-19 supplies can be applied to cell and gene therapy supplies.
- Post-Covid-19 there may be more harmonization, more working together, and more cooperation between industry and regulators.

Sander van Deventer, MD, PhD, executive vice president of research and product development at uniQure:

✓ "There has been less effect on gene therapy than other sectors…because we are not immediately dependent on consumer demand and the associated revenues. We don't fund operations from income…and investors in biotech are used to working with loss-making companies."

✓ He said the Dutch government has a "very strict" regulatory approach, and gene therapy approvals can take years, but "when the Dutch government found out it would be years before [a Covid-19 adenovirus vaccine] could be approved, they actually overnight changed regulations we have been discussing for the last 20 years."

Thomas Bols, head of government affairs and public policy, EMEA and APAC, at PTC Therapeutics, said:

✓ European regulators have delayed setting policy for the coming years "because they are working almost exclusively on the Covid-19 crisis…and older dossiers are being put on hold because they are learning a lot from Covid-19…New initiatives learned from Covid-19 are taking priority over more classical health policy initiatives being developed before the crisis.

✓ "The price of cell and gene therapies was already a point of discussion [before Covid-19] to the point of being controversial…Now that we are going to more of a recession…and governments are spending millions on healthcare and the economy, I could see the price of gene therapies becoming more commoditized.

✓ "There are some negative elements, but overall the future looks reasonably bright for this sector.

✓ "On review times, both the FDA and the EMA are really making a huge effort to speed things up…I'm not saying they cut corners, but where things can be done quicker…[But] the European Commission is adamant that this is temporary.

✓ "There is a very distinct shortage in knowledge on how to set up and operate viral vector manufacturing for cell therapies…CMOs [contract manufacturing organizations] are expanding, but they are learning right along with [their customers]."

Lance Weed, an industry consultant and former vice president of operations at uniQure, said:

✓ "[Supply chains] have a lot longer response time…We are seeing weeks of delay…There are also quality control testing delays due to staffing issues at the test site, a lack of reagents…and a lack of gowning supplies."

- ✓ He also warned that vendor support can be delayed – particularly by travel restrictions – which could impact calibration vendors, water systems, cleaning staff for the clean room, etc."
- ✓ *Asked about the outlook for disposable equipment or whether companies will go back to stainless steel systems*, he said, "With the proper supply chain and planning, you can still maintain single-use disposables…If you were doing large quantity production, that would drive you to stainless steel…I don't think the industry will move back to stainless steel any time soon…All manufacturers [suppliers] have really been upping their quality game to make sure you get what you order in good workable condition, and I think they are expanding their capabilities…So, even though you may be experiencing some shortages now, I don't see single-use manufacturing being a bottleneck…I think it will be more on the capabilities of the CMOs."

Gilead Sciences' remdesivir

- The preliminary results of the ongoing trial that led to an EUA for this antiviral were published in the ***New England Journal of Medicine***. The mortality data were slightly different (7.1% vs. 11.9% but still not significant). And the drug worked best in patients on oxygen, so there are no data on using it earlier.
- Remdesivir was approved by the U.K.'s Medicines and Healthcare products Regulatory Agency (MHRA) to treat severely ill Covid-19 patients in the National Health Service through the Early Access to Medicines Scheme to use of unlicensed drugs in emergency situations.

Hydroxychloroquine (HCQ)

- President Trump finished his two-week course of HCQ and has stopped taking it. No one knows if it did any good, but he didn't appear to suffer any negative side effects.
- France banned the use of HCQ by hospitals to treat Covid-19.
- A study presented at the American Society of Clinical Oncology (ASCO) virtual meeting, which looked at the impact of Covid-19 on cancer patients, also shed a little light on HCQ use in cancer patients. Jeremy Warner, MD, an oncologist from Vanderbilt-Ingram Cancer Center, reported that an analysis of 928 cases of Covid-19 in cancer patients at 104 institutions in the U.S. and Canada found:
  - ✓ About 20% of patients (~180) who were given HCQ + azithromycin had a significant increased risk of death, but in the ~10% of patients (~90) who got hydroxychloroquine alone, there was *no* increase in mortality.
  - ✓ Only two patients got HCQ as part of a clinical trial; the rest got it off-label. About 10% were taking HCQ at the time they presented to the hospital with Covid-19.
  - ✓ Dr. Warner said, "Taking hydroxychloroquine alone was not a significant risk factor [for mortality], once we adjusted for other factors…The combination showed a three-fold increased risk of dying within 30 days for any cause…That is the adjusted odds ratio…and the confidence interval was pretty narrow."
  - ✓ Asked for his opinion, ASCO president Howard Burris, III, MD, said, "We need to wait for a randomized clinical trial to understand the real risk:benefit [of HCQ]."
- WHO halted a trial of HCQ in Covid-19 due to safety concerns.
- NIAID is funding an ~2,000-patient Phase IIb trial testing HCQ + azithromycin to treat Covid-19. The trial will be run by the AIDS Clinical Trials Group (ACTG), which is funded by NIAID.
- An observational study of ~15,000 Covid-19 patients by researchers at Brigham and Women's Hospital, published in ***The Lancet***, found no benefit to HCQ with or without azithromycin vs. a database of 81,000 controls. The study also suggested an increased risk of serious cardiac problems and increased mortality with the combination.

- An observational, retrospective meta-analysis of a WHO database with >21 million adverse event case reports from more than 130 countries from 1967-2020, published in ***Circulation***, found that the combination of HCQ and azithromycin is potentially lethal in Covid-19 patients.
  - ✓ 76,822 adverse event reports were associated with HCQ alone, and in 28.4% of those cases (21,808), HCQ was suspected to be associated with the adverse event.
  - ✓ 89,692 adverse event reports were associated with azithromycin alone, and in 60.8% of those cases (54,533), azithromycin was suspected to be associated with the adverse event.
  - ✓ 607 adverse event reports reported were associated with the combination of both medications.
  - ✓ There was significantly greater reporting of prolonged-QT (LQT) and/or ventricular tachycardia including Torsades-de-Pointes (TdP/VT) for each drug individually in the suspected cases vs. all other medications.
  - ✓ HCQ was significantly associated with the development of conduction disorders and heart failure.
  - ✓ Azithromycin monotherapy was associated with more reports of LQT and/or TdP/VT than HCQ alone (0.8% vs. 0.3%).
  - ✓ The combination of HCQ + azithromycin was associated with a greater reporting of LQT and/or TdP/VT than either medication alone (0.6% vs. 1.5%, respectively).
  - ✓ Deaths for TdP/VT cases was 8.4% with HCQ and 20.2% with azithromycin vs. 0 and 5.4% for LQT without TdP/VT with HCQ and azithromycin, respectively.
  - ✓ The researchers concluded, "Reports of potentially lethal acute cardiac proarrhythmogenic effects [promoting irregular heart rhythms] have been described mainly with azithromycin but also with hydroxychloroquine. Their combination yielded an even stronger signal. Hydroxychloroquine was also associated with potentially lethal heart failure when exposure was prolonged over several months."

■ **Merck MSD** has thrown its hat into the treatment ring with a deal with **Ridgeback Biotherapeutics** for the exclusive worldwide rights to an early-stage oral antiviral, EIDD-2801, which has passed safety in a Phase I study and has shown potent antiviral activity against *multiple* coronavirus strains, including SARS-CoV-2 and MERS.

■ Among ***other therapies*** on the long list of drugs in development to treat Covid-19 are:

- **ACE inhibitors** – UnitedHealth Group is sponsoring a virtual clinical trial to see if these anti-hypertensives can help in the treatment of high-risk Covid-19 patients. The study comes after Yale School of Medicine researchers analyzed data on 10,000 people in UnitedHealth plans who were taking ≥1 anti-hypertensive. They found that Medicare Advantage members taking an ACE inhibitor had a 40% reduction in the risk of hospitalization due to Covid-19, but there was no mortality benefit.
- **Aldeyra Therapeutics**
  - ✓ **ADX-629** – The company is expected to submit an IND [investigational new drug] application to the FDA in June 2020 for this RASP inhibitor as a treatment for the respiratory complications (cytokine storm) that Covid-19 patients sometimes experience.
  - ✓ **ADX-1612** – The company is seeking an IND for this HSP90 inhibitor to conduct trials in Covid-19 treatment.
- **Atea Pharmaceuticals' AT-527** – The FDA approved the IND application for this oral direct-acting antiviral (DAA) – an oral purine nucleotide prodrug that is also being studied to treat hepatitis C virus (HCV) – clearing the way for an 180-patient Phase II trial in adults in the hospital (or a hospital-affiliated facility) with moderate Covid-19 and ≥1 risk factor for a poor outcome (obesity, hypertension, diabetes, or asthma).

The trial will test two regimens – 550 mg QD on Day 1 then 550 mg BID for 9 days or 550 mg BID on Day 1 then 550 mg BID for 9 days – plus standard of care. The primary endpoints are need for mechanical ventilation at Day 14 and the percent of patients with treatment-emergent adverse events at Day 14. Interestingly, the trial is limited to patients age 45-80.

- **Fujifilm's Avigan (favipiravir)**
  - ✓ Russia's Ministry of Health approved this antiviral, an oral flu drug, for use in Covid-19 patients.
  - ✓ India's Drug Controller General gave approval for clinical trials in India by Strides Pharma.
- **Lilly and Junshi Biosciences' CB6** – The companies are planning a first-in-human trial of this antibody for prevention of Covid-19 after it showed an ability to boost development of neutralizing antibodies and decrease viral levels by ~3-logs in rhesus monkeys.
- **Nikkiso** – Research in combination with the University of Miyazaki found that the company's deep ultraviolet light LED weakened SARS-CoV-2, reducing its infection capacity by >99.9%.
- **Roche's Actemra (tocilizumab)** – Roche is partnering with Gilead Sciences to test a combination of this anti-IL-6 with remdesivir in a 450-patient Phase III trial in Covid-19 patients with severe pneumonia. This is in addition to the large montherapy trial Roche is running by itself.

Vaccines

A lot of hopes are pinned on a vaccine (or vaccines), but an AP-NORC poll of 1,056 American adults in mid-May found that 49% would get a vaccine if one were developed, 31% were unsure, and 20% would not get a vaccine.

The pharma viewpoint. In what may be a first, the heads of four major pharmaceutical companies did a virtual press conference with about 130 journalists, sponsored and moderated by the International Federation of Pharmaceutical Manufacturers & Associations (IFPMA), to talk about Covid-19 vaccine research and development.

Among the key points to come out of this session:

- ✓ Industry is collaborating way more than usual.
- ✓ Glass vials are a bottleneck, and pharma wants to be able to use larger (5-10 dose) vials.
- ✓ Pharmas are not giving up their patents or intellectual property on vaccines.
- ✓ Pricing will be at cost as long as there is a pandemic, but once the pandemic is declared over by WHO, that price will increase (at least in developed countries).
- ✓ Phase III trials may not be able to be done in the U.S. and Europe because of declining cases there. Instead, they may need to be done in South America or South Africa.

■ **Thomas Cueni, director general of IFPMA**, cautioned:

- "While we should give our undivided attention to ending the Covid-19 pandemic, we must not fall into the trap of forgetting the need for ongoing immunization efforts to continue as well as being very vigilant in tracking any future virus.
- "There are quite a number of [bottlenecks]. The challenge is daunting…We may need 15 billion doses…We have been successful in flattening the curve, so it is challenging to do the trials and extremely challenging to scale up…This is a huge investment, and the investment is at-risk at a time when we don't know which vaccine will work…We will not have sufficient quantities on Day 1."

- **Emma Walmsley, CEO of GlaxoSmithKline**, said:
  - There are 4 principles to the development of a Covid-19 vaccine: a working partnership, taking a truly global approach, a commitment to access, and a focus on future pandemic preparedness.
  - GSK has made its vaccine adjuvant broadly available with partners in North America, Europe, and Asia and has committed to supplying 1 billion doses of the adjuvant in 2021.
- **Albert Bourla, DVM, PhD, chairman/CEO of Pfizer**, said:
  - "The only rival is the virus right now.
  - "The reason we have chosen an mRNA vaccine…was because we already had a two-year collaboration with BioNTech, and they are mastering this technology…and they are also working on a flu vaccine. We feel that right now we have enough expertise…and the technology was offering speed…because with mRNA you can do in weeks things that can take months with other technology.
  - "We started without a contract…exchanging materials…and eventually signed a contract…I hope the technology will be proven effective.
  - "We are in clinical trials in humans in the U.S. and Europe…The first phase [Phase I] will be completed in June…we will have enough data to proceed to Phase II and Phase III very rapidly. Eventually, we aim to make a study of a large number – 20,000-30,000 people…We do have experience running very large trials…The largest was in the Netherlands with 80,000 people…And we will move very fast.
  - "It is critical, if you want supply, you have to be able to manufacture at-risk.
  - "If things go well and the stars are aligned, we will have…enough evidence of safety and efficacy that we – and the FDA and the EMA – can feel comfortable to have a vaccine by the end of October [2020]."
- **Pascal Soriot, executive director/CEO of AstraZeneca** (which is partnered with the University of Oxford), said:
  - He recognized the potential threat of Covid-19 early, "I was on video 3-4 times a week with our team in China…and we saw this was something very different."
  - He noted that AstraZeneca is working on an antibody, a BTK inhibitor, collaborating with GSK, and was attracted by the Oxford vaccine because "it was technology that was tested before…and the Oxford group was very advanced…We finished Phase I/II last week and should see results soon…Oxford announced the start of a Phase II/III trial in the U.K. in 10,000 volunteers.
  - "We will start a 30,000-patient study in the U.S. in July or so…We are moving full speed like everyone else…The good thing is we are testing multiple technologies…Maybe 1-2-3 technologies will work, but we have to give it several shots because we don't know which one will work."
  - *Asked if he would consider human challenge trials*, Soriot said, "We talked about it internally, but it is much too early. The technical issues are yet to be resolved…and the protocol still needs to be resolved. At some point, it may be done, but it is still too early. We still have an opportunity to show efficacy in the 'normal way.'
  - "The problem is we are all running against time…In Europe, the disease is declining…It is still going in the U.K. and the U.S., but very soon the disease intensity will be low, and it will become difficult…If the disease gets to a low level, it may be that challenge studies will be needed."
- **Paul Stoffels, MD, vice chairmen of the executive committee and chief scientific officer for Johnson & Johnson**, said:
  - "We published validated animal models [recently]…Now, we are doing real challenge studies to validate…to determine if a single dose is sufficient or if it needs a prime boost.

- "It is important to look at how to up-scale this…That is a massive parallel project…I can proudly say we are in place to deliver 1 billion vaccines next year…We plan to start in early September.
- "We plan to do two large Phase III studies…Hopefully, they can be done in the North. If not, we may have to go to the South…South Africa, Brazil, and maybe other countries…It has to be global, and we have to address massive quantities and equitable access.
- "We can bring two subcutaneous vaccines…I'm sure everyone is working on that…but to get to GAVI countries [Gavi, the Vaccine Alliance is a public-private global health partnership], you need to be able to make it reasonable.
- "We hope to have vaccine efficacy data early next year.
- "The regulators deserve a big thank you…They work with us all day, hours…Now, it is exceptional.
- "It is a race against the virus, not against each other."

■ *Asked about scaling up manufacturing:*

- Pfizer's Dr. Bourla said, "We have already started preparing materials, clearing licenses, installing new lines…Typically we are producing in single-dose vials, but we are exploring with governments if it would be more convenient to have 5- or 10-dose vials. If this could be…acceptable and practical, I think we can resolve a significant part of the bottleneck."
- AstraZeneca's Soriot said, "We are committed to manufacturing a billion doses…We also need to commit to responsible pricing…and to just-in-case, not just-in-time manufacturing…We [also] need to make sure the route to market and allocation is effective…We need to reach the people who need it the most because they are most exposed or the most vulnerable."

■ *Asked about making a profit on a Covid-19 vaccine:*

- GSK's Walmsley said, "We don't expect a profit during this period because we want to invest any short-term profit in pandemic preparedness and in donations, significant volumes of donations, to the developing world…We are one of the biggest suppliers to GAVI."
- J&J's Dr. Stoffels said, "Fill and finish…is a big bottleneck now…Getting to 5-10 in a vial is probably [the answer]."
- AstraZeneca's Soriot said, "The challenge is not making the vaccine but to fill the vials. There are not enough vials in the world…So, we are looking at 5-10 doses per vial…There are a limited number of glass vials…We have a supply-chain focus on the U.S., another for Europe, and another for Asia…and we are doing it at no profit…This is what a healthy pharmaceutical industry can do…The whole industry is stepping in in different ways. That is what we can do."

■ *Asked about plans for a Phase III efficacy trial*, AstraZeneca's Soriot said, "Our focus is on speed, not haste. We are not concealing results…The disease is declining, at least in the Northern Hemisphere…Our focus is on a Phase III in the U.K, another Phase III in the U.S. with 30,000 volunteers…We are also doing studies in South Africa and Brazil…And if that works, we want to be able to supply it."

■ *Asked if they would participate in a global distribution scheme:*

- GSK's Walmsley said, "We are absolutely committed to access…The easiest way to get 50 billion doses as fast as we can, collectively…This is, in many ways, a collective effort."
- Pfizer's Dr. Bourla said, "What will be the challenge is that every national government would like the vaccine for themselves…The reality is that governments will try to exercise all the leverage they have to be among the first, and I'm afraid we will be caught in the middle…I'm thinking very carefully about what would be the best way to make sure [that doesn't happen]."

- *What is the definition of the pandemic period for which vaccines will be supplied on a non-profit basis?* J&J's Dr. Stoffels said, "For the majority of countries, it will be when WHO declares it over…The allocation problem will be significantly less than if we wait 6-9 months on volume commitments. Speed is of the essence here…Save the high-risk groups first, and later the entire population."
- *Since the U.S provided $1.2 billion, will it get your Oxford vaccine first?* AstraZeneca's Soriot said, No.
- *When the first vaccine is proven safe and effective, will the runner-up players continue to pursue development of their own candidates?* Yes.
- *Who will be the first to bring a vaccine to market?* Pfizer's Dr. Bourla said, "Who is first is irrelevant…Everyone wants to be first. We need and hope everyone will be successful."
- *How important is it to know the source of the virus, whether it was from a wet market?* J&J's Dr. Stoffels said, "At this moment it doesn't matter. We have to solve this disease very quickly. We will find out later…This is not the first coronavirus creating a challenge…We knew what to do. Going forward we need to study what other coronaviruses have a similar pattern, so we can be prepared."
- *Have you signed contracts with individual governments for delivery of first supplies?* Pfizer's Dr. Bourla said, "No. We are in discussions with many governments on delivery…We are not taking money from any government to advance our vaccine efforts…We do that because we believe we can move faster if we don't have to involve a third party. No contract has been signed, but we are in discussions with multiple governments."
- *Will you join WHO's voluntary patent pool?* No. AstraZeneca's Soriot said, "IP [intellectual property] is a fundamental part of our industry, and if you don't protect IP, then there is no incentive for anyone to innovate. What is important is for companies to provide product at cost in a pandemic." GSK's Walmsley added, "IP is absolutely fundamental to our industry. Whether it is HIV or vaccines, there is not enormous evidence that IP is a barrier to access." Pfizer's Dr. Bourla agreed, saying, "It is nonsense and dangerous…487 biotechs or other companies reached out to Pfizer in 6 weeks to request help. The risk we are taking are billions of dollars, and the chances are still not very good…To say, they are going to take your IP I think is dangerous."
- *Is GSK, the largest vaccine maker, not making a coronavirus vaccine, just an adjuvant, because of losses on other vaccines?* Walmsley said, "In January it was obvious this will be an enormous global problem. The question was what we could uniquely bring. There are more than 200 vaccine candidates. Should GSK increase the probability of the success of multiple vaccines by offering our adjuvant broadly to any credible candidate? We felt what only we could bring was adjuvant technology that was a boost to multiple other candidates."
- *How many vaccines are needed for the world?* J&J's Dr. Stoffels said, "We need several because up to 15 billion vaccine [doses] may be needed. Five to 10 will definitely be needed to save the whole world."
- *How expensive will the vaccines be?* Pfizer's Dr. Bourla said, "Typically, industry prices are based on value. That is not possible in a pandemic. I don't know the price. I never thought about it."
- *Will you charge royalties on your technology?* AstraZeneca's Soriot said, "We said we would not charge royalties during a pandemic…They will be relatively inexpensive. No one talks of the cost of testing. It costs about $50 to do one PCR test…and think of the cost savings by not having to test so often."
- *If SARS-CoV-2 just disappears, how much will industry have invested in vain?* AstraZeneca's Soriot said, "I don't know…I suspect hundreds and hundreds of millions of dollars…and a lot of time." Pfizer's Dr. Bourla added, "The cost for us so far is $2 billion, most of it front-loaded in the first year. And that doesn't include salaries, just out of pocket costs on top of our people."
- *Why can't the glass vial makers just make more vials?* J&J's Dr. Stoffels said, "At the moment they are."

This **list of vaccines** expands and updates what we have already mentioned. The WHO has proposed creation of a voluntary pool that would collect intellectual property rights as well as regulatory test information and other data related to developing SARS-CoV-2 vaccines, treatments, and diagnostics.

A number of **different approaches** are being tried to create a vaccine. In fact, there are at least 10 vaccines in clinical trials and another 115 in preclinical evaluation. All of them have pros and cons. All (or none) of them may work: recombinant-protein based vaccines, replicating and non-replicating viral vector-based vaccines, DNA vaccines, and mRNA vaccines, live attenuated vaccines, and inactivated virus vaccines.

It is important to understand that a first-generation coronavirus vaccine **likely won't be like a sterilizing measles vaccine**, once and done for life and totally preventing the disease. Rather, a coronavirus vaccine may be more like a flu vaccine, reducing the risk of getting Covid-19 and reducing the severity of symptoms in someone who gets the virus, not necessarily preventing infection entirely.

A good question is whether the coronavirus vaccines will **prevent the spread of the virus by an infected person**. Neutralizing antibodies may protect against severe Covid-19, but they may not protect against infection in the upper airways. Vincent Munster, PhD, chief of the virus ecology unit at NIAID's Rocky Mountain Laboratories, said a vaccine that mitigates the severity of Covid-19 would still be a significant contribution, "If we push the disease from pneumonia to a common cold, then I think that's a huge step forward."

The **WHO is not too optimistic** about a SARS-CoV-2 vaccine, cautioning that the virus may never go away and that the world will have to learn to live with it. Michael Ryan, MD, WHO's emergencies director, compared it to HIV, saying, "HIV has not gone away, but we have come to terms with the virus…This virus may become just another endemic virus in our communities, and this virus may never go away."

Former FDA Commissioner **Scott Gottlieb**, MD, told CNBC, "We might have [a vaccine] available in the fall for emergency use authorization for certain populations, and we'll certainly have the doses by the end of the year. I just don't think we'll have the data to support widespread inoculation at that point."

The **European Medicines Agency** has commissioned independent research on preparing for real-world monitoring of Covid-19 vaccines once they are authorized in the European Union. The ACCESS (vACcine Covid-19 monitoring readinESS) will be led by Utrecht University, which will be the coordinator of the EU Pharmacoepidemiology and Pharmacovigilance Research Network, a public/academic partnership of 22 European research centers. Once on the market, approved vaccines will be monitored closely by the EMA and its Pharmacovigilance Risk Assessment Committee (PRAC).

The **leading vaccine projects** include:

- **AstraZeneca' AZD-1222** (Oxford University's ChAdOx1 nCoV-19), a recombinant viral vector vaccine.
- **CanSino Biologics, Ad5-nCoV**, a recombinant adenovirus-based vaccine. This Chinese company's vaccine is in Phase II. Data from a 195-patient Phase I trial conducted in Wuhan, China, were published recently in ***The Lancet***, showing the vaccine was "tolerable and immunogenic" at Day 28 post-vaccination. Adverse events included headache, fatigue, fever, and muscle pain – nothing unexpected. This vaccine is distinguished from Moderna's vaccine in that:
  - Both antibody and T cell responses were observed by Day 14, while Moderna was rather evasive on quantities of antibodies and on T cells, saying T cell tests are "complicated finicky assays."
  - The CanSino Phase II trial is testing the vaccine in some people age >60, but Moderna is not testing it in the elderly.

- Both companies dropped the highest dose used in Phase I.
- The CanSino Phase I results have been published in a peer-reviewed journal, and Moderna's have not.

CanSino is also collaborating with Precision NanoSystems on an mRNA vaccine, which will give it two shots on goal. CanSino has the rights in Asia (except Japan), and Precision has them everywhere else. The company also is planning a Phase I/II trial in Canada.

- **CureVac's unnamed vaccine**, an mRNA vaccine. The company reported that a low dose (2 µg) of its vaccine generated "high levels" of virus-neutralizing titers in animal models. A Phase I/IIa trial is expected to start in June 2020. CureVac, which got $30 million in funding from the Coalition for Epidemic Preparedness Innovations (CEPI), estimated it could produce "several hundred million" doses at its facility in Germany.

- **Inovio Pharmaceuticals' INO-4800**, a DNA vaccine. The company estimates it can make 1 million doses by the end of 2020, with additional capacity by Richter-Helm. In preclinical data, published in ***Nature Communications***, INO-4800 generated neutralizing antibodies on three different assays and generated "high levels" of T cells specific to the spike protein on the surface of SARS-CoV-2.

- **Johnson & Johnson and Emergent BioSolutions**, an Ad2 vector vaccine. The effort got $456 million from BARDA. J&J estimates it could produce 300 million doses/year in 2020, 600-900 million in 1Q21, and up to 1 billion/year by the end of 2021. J&J said it plans to sell its vaccine ***at cost*** (at least initially).

- **Merck MSD** is late to the game, but it…
  - Is buying **Themis Bioscience** and will apply its vaccine expertise to Themis' measles vector platform. The obvious goal: a one-and-done vaccine as with measles. For Themis the deal means the ability to scale up. Merck plans to start testing a Covid-19 vaccine sometime in 2020. Merck also has a memorandum of understanding with CEPI about the need to make the vaccine "accessible to those who need it, including low-income, middle-income, and high-income countries, based on the medical need."
  - Is collaborating with non-profit IAVI on another vaccine candidate that uses the same recombinant vesicular stomatitis virus (rVSV) technology that Merck used in its Ebola Zaire vaccine. This vaccine, too, is expected to start clinical trials this year. And this vaccine got a small amount of funding ($38 million) from BARDA.

- **Moderna Therapeutics' mRNA-1273**, an mRNA vaccine (as its name implies). Moderna got $530 million from BARDA. Lonza will handle manufacturing. Anthony Fauci, MD, director of the National Institute of Allergy and Infectious Diseases (NIAID), recently said he is "cautiously optimistic about the vaccine," but it is important to remember that NIAID is partnered on this vaccine, so Dr. Fauci is not exactly a neutral party.

  After the interim Phase I data were released, the company said there were three Grade 3 adverse events with the high dose, so that dose was not going forward. One of those 3 patients has come forward and described his adverse events: a fever of 103 degrees, flu-like symptoms, nausea, vomiting, fainted, and generally feeling as sick as he'd ever felt.

  Why emphasize this since that dose (250 mg) has been discontinued? Because a Moderna official previously said that elderly patients may need a much higher dose than younger people. So, if the 25 mg dose fails and 100 mg is required for everyone under age 65, there wouldn't be the capability to boost the dose for the elderly.

- **Novavax's NVX-CoV-2373**, a recombinant protein vaccine. The company said it is scaling up production and was on track to be able to manufacture 100 million doses by the end of 2020. Then, it bought Praha Vaccines, a Czech manufacturer, and decided to collaborate with Serum Institute of India, which will add capacity for ≥1 billion doses/year.

- **Pfizer and BioNTech's BNT-162**, an mRNA vaccine.

- **Sanofi**
  - Is collaborating with **GlaxoSmithKline** on developing a vaccine (no candidate ready yet). Sanofi got $30 million from BARDA (small potatoes compared to the $1.2 billion BARDA gave AstraZeneca) to support this project.
  - Is collaborating with Translate Bio on an mRNA vaccine.
- **Shionogi/UMN Pharma** is developing a vaccine by reprogramming the genes of a baculovirus – a pathogen that only infects arthropods (e.g., insects and spiders). Using insects, Shionogi said it could be manufactured in eight weeks.
- **Sinovac Biotech's PiCoVacc**, a formaldehyde inactivated vaccine with alum adjuvant. This Chinese company plans to produce 100 million doses/year and will build a new production facility in Beijing.

#1A Worldwide Covid-19 Statistics – Daily Cases												
Country	May 22			May 23			May 24			May 25		
	Cases	Deaths	Fatality rate	Cases	Deaths	Fatality rate	Cases	Deaths	Fatality rate	Cases	Deaths	Fatality rate
Worldwide	5,213,483	338,225	6.5%	5,311,089	342,105	6.4%	5,407,613	345,059	6.4%	5,495,061	346,232	6.3%
U.S.	**1,600,723**	**95,972**	**6.0%**	**1,622,670**	**97,087**	**6.0%**	**1,643,246**	**97,720**	**5.9%**	**1,662,302**	**98,218**	**5.9%**
Spain	234,824	28,628	12.2%	235,290	28,678	12.2%	235,772	28,752	12.2%	235,900	26,834	11.4%
Italy	228,658	32,616	14.3%	229,327	32,735	14.3%	229,858	32,785	14.3%	230,158	32,877	14.3%
France	182,015	28,218	15.5%	182,036	28,218	15.5%	182,709	28,370	15.5%	183,067	28,460	15.5%
U.K.	255,544	36,475	14.3%	258,504	36,757	14.2%	260,916	36,875	14.1%	262,547	36,996	14.1%
Germany	179,710	8,228	4.6%	179,986	8,261	4.6%	180,328	8,283	4.6%	180,600	8,309	4.6%
Sweden	32,809	3,925	12.0%	33,188	3,992	12.0%	33,459	3,998	11.9%	33,843	4,029	11.9%
China	**84,081**	**4,638**	**5.5%**	**84,084**	**4,638**	**5.5%**	**84,095**	**4,638**	**5.5%**	**84,102**	**4,638**	**5.5%**
India	124,794	3,728	3.0%	131,920	3,869	2.9%	138,536	4,024	2.9%	144,950	4,172	2.9%
Mexico	62,527	6,989	11.2%	65,856	7,179	10.9%	68,620	7,394	10.8%	71,105	7,633	10.7%
Russia	326,448	3,249	1.0%	335,882	3,388	1.0%	344,481	3,541	1.0%	353,427	3,633	1.0%
Brazil	330,890	21,048	6.4%	347,398	22,013	6.3%	363,211	22,666	6.2%	374,898	23,473	6.3%

https://coronavirus.jhu.edu/map.html www.worldometers.info/coronavirus/country/uk/
www.statista.com/statistics/1102203/cumulative-coronavirus-cases-in-sweden/

#1B Worldwide Covid-19 Statistics – Daily Cases												
Country	May 26			May 27			May 28			May 29		
	Cases	Deaths	Fatality rate	Cases	Deaths	Fatality rate	Cases	Deaths	Fatality rate	Cases	Deaths	Fatality rate
Worldwide	5,589,626	350,453	6.3%	5,693,066	355,653	6.2%	5,813,919	360,389	6.2%	5,931,963	365,051	6.2%
U.S.	**1,680,913**	**98,913**	**5.9%**	**1,699,933**	**100,442**	**6.1%**	**1,721,750**	**101,617**	**5.9%**	**1,747,087**	**102,836**	**5.9%**
Spain	236,259	27,117	11.5%	236,259	27,116	11.5%	237,906	27,119	11.4%	238,564	27,121	11.4%
Italy	230,555	32,955	14.3%	231,139	33,072	14.3%	231,732	33,142	14.3%	232,248	33,229	14.3%
France	182,847	28,533	15.6%	183,038	28,599	15.6%	186,364	28,665	15.4%	186,924	28,717	15.4%
U.K.	266,599	37,130	13.9%	268,619	37,542	14.0%	270,508	37,919	14.0%	272,607	38,243	14.0%
Germany	181,200	8,372	4.6%	181,524	8,428	4.6%	182,196	8,470	4.6%	182,922	8,504	4.6%
Sweden	34,440	4,125	12.0%	35,088	4,220	12.0%	35,727	4,266	11.9%	36,476	4,350	11.9%
China	**84,102**	**4,638**	**5.5%**	**84,106**	**4,638**	**5.5%**	**84,106**	**4,638**	**5.5%**	**84,123**	**4,638**	**5.5%**
India	150,973	4,344	2.9%	158,333	4,534	2.9%	165,799	4,711	2.8%	174,020	4,981	2.9%
Mexico	74,560	8,134	10.9%	78,023	8,597	11.1%	81,400	9,044	11.1%	84,627	9,415	11.1%
Russia	362,342	3,807	1.1%	370,680	3,968	1.1%	379,051	4,142	1.1%	387,623	4,374	1.1%
Brazil	391,222	24,512	6.3%	411,821	25,598	6.2%	438,238	25,598	5.8%	465,166	27,878	6.0%

#2A Worldwide Per Capita *Case* Rate									
Country	Population	May 22	May 23	May 24	May 25	May 26	May 27	May 28	May 29
Worldwide	7,577 million	0.07%	0.08%	0.07%	0.07%	0.07%	0.08%	0.08%	0.08%
U.S.	330 million	**0.49%**	**0.49%**	**0.50%**	**0.50%**	**0.51%**	**0.52%**	**0.52%**	**0.53%**
Spain	47 million	0.50%	0.50%	0.50%	0.50%	0.50%	0.50%	0.51%	0.51%
Italy	60 million	0.38%	0.38%	0.38%	0.38%	0.38%	0.39%	0.39%	0.39%
France	67 million	0.27%	0.27%	0.27%	0.27%	0.27%	0.27%	0.28%	0.28%
U.K.	67 million	0.38%	0.39%	0.39%	0.39%	0.40%	0.40%	0.40%	0.41%
Germany	83 million	0.22%	0.22%	0.22%	0.22%	0.22%	0.22%	0.22%	0.22%
Sweden	10 million	0.33%	0.33%	0.33%	0.34%	0.34%	0.35%	0.36%	0.36%
China	**1,386 million**	**0.006%**	**0.006%**	**0.006%**	**0.006%**	**0.006%**	**0.006%**	**0.006%**	**0.006%**
India	1,353 million	0.006%	0.01%	0.01%	0.01%	0.01%	0.01%	0.01%	0.01%
Mexico	126 million	0.05%	0.05%	0.05%	0.06%	0.06%	0.06%	0.06%	0.07%
Russia	145 million	0.23%	0.23%	0.24%	0.24%	0.25%	0.26%	0.26%	0.27%
Brazil	210 million	0.16%	0.17%	0.17%	0.18%	0.19%	0.20%	0.21%	0.22%

This is a really important chart for comparing locations

#2B Worldwide Per Capita *Fatality* Rate: Deaths per 100,000 People									
Country	**Population**	**May 22**	**May 23**	**May 24**	**May 25**	**May 26**	**May 27**	**May 28**	**May 29**
Worldwide	7,577 million	4.5	4.5	4.6	4.6	4.6	4.7	4.8	4.8
U.S.	330 million	**29**	**29**	**30**	**30**	**30**	**30**	**31**	**31**
Spain	47 million	61	61	61	57	58	58	58	58
Italy	60 million	54	55	55	55	55	55	55	55
France	67 million	42	42	42	42	43	43	43	43
U.K.	67 million	54	55	55	55	55	56	57	57
Germany	83 million	10	10	10	10	10	10	10	10
Sweden	10 million	39	40	40	40	41	42	43	44
China	**1,386 million**	**0.33**	**0.33**	**0.33**	**0.33**	**0.33**	**0.33**	**0.33**	**0.33**
India	1,353 million	0.28	0.29	0.30	0.31	0.32	0.34	0.35	0.37
Mexico	126 million	0.6	0.6	0.6	0.6	0.6	0.7	0.7	0.7
Russia	145 million	2	2	2	3	3	3	3	3
Brazil	210 million	10	10	11	11	12	12	12	13

# 3A US. Covid-19 Statistics – Daily Cases												
State	**May 22**			**May 23**			**May 24**			**May 25**		
	Cases	**Deaths**	**Fatality rate**	**Cases**	**Deaths**	**Fatality rate**	**Cases**	**Deaths**	**Fatality rate**	**Cases**	**Deaths**	**Fatality rate**
California	88,444	3,630	4.1%	90,631	3,708	4.1%	92,710	3,774	4.1%	94,558	3,795	4.0%
Florida	**49,451**	**2,268**	**4.6%**	**50,127**	**2,312**	**4.6%**	**50,867**	**2,316**	**4.6%**	**51,746**	**2,331**	**4.5%**
Georgia	41,218	1,785	4.3%	42,132	1,811	4.3%	42,838	1,824	4.3%	43,344	1,830	4.2%
Illinois	105,444	4,715	4.5%	107,796	4,790	4.4%	110,304	4,856	4.4%	112,017	4,884	4.4%
Louisiana	36,925	2,668	7.2%	37,040	2,668	7.2%	37,169	2,690	7.2%	37,809	2,690	7.1%
Massachusetts	90,889	6,228	6.9%	91,662	6,304	6.9%	92,675	6,372	6.9%	93,271	6,416	6.9%
Michigan	53,913	5,158	9.6%	54,365	5,223	9.6%	54,679	5,228	9.6%	54,881	5,240	9.5%
New Jersey	152,719	10,985	7.2%	153,104	11,081	7.2%	154,154	11,133	7.2%	155,092	11,144	7.2%
New York	**358,154**	**23,195**	**6.5%**	**359,926**	**23,282**	**6.5%**	**361,515**	**23,391**	**6.5%**	**362,764**	**23,488**	**6.5%**
Texas	52,268	1,440	2.8%	53,449	1,480	2.8%	54,509	1,506	2.8%	55,971	1,527	2.7%
Washington	19,117	1,044	5.5%	19,265	1,050	5.5%	19,585	1,055	5.4%	19,828	1,061	5.4%

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

# 3B US. Covid-19 Statistics – Daily Cases												
State	**May 26**			**May 27**			**May 28**			**May 29**		
	Cases	**Deaths**	**Fatality rate**	**Cases**	**Deaths**	**Fatality rate**	**Cases**	**Deaths**	**Fatality rate**	**Cases**	**Deaths**	**Fatality rate**
California	96,733	3,814	3.9%	98,980	3,884	3.9%	101,697	3,973	3.9%	103,886	4,068	3.9%
Florida	**52,255**	**2,338**	**4.5%**	**52,634**	**2,400**	**4.6%**	**53,285**	**2,446**	**4.6%**	**54,497**	**2,495**	**4.6%**
Georgia	43,730	1,871	4.3%	44,421	1,907	4.3%	45,070	1,962	4.4%	45,670	1,974	4.3%
Illinois	113,195	4,923	4.3%	114,306	5,083	4.4%	117,455	5,270	4.5%	117,455	5,270	4.5%
Louisiana	38,054	2,701	7.1%	38,497	2,722	7.1%	38,802	2,740	7.1%	38,802	2,766	7.1%
Massachusetts	93,693	6,473	6.9%	93,693	6,473	6.9%	94,895	6,640	7.0%	95,512	6,718	7.0%
Michigan	55,104	5,266	9.6%	55,608	5,334	9.6%	56,014	5,372	9.6%	56,621	5,406	9.5%
New Jersey	155,764	11,191	7.2%	156,628	11,339	7.2%	157,815	11,401	7.2%	158,844	11,531	7.3%
New York	**363,836**	**23,564**	**6.5%**	**364,965**	**23,643**	**6.5%**	**366,733**	**23,722**	**6.5%**	**368,284**	**23,780**	**6.5%**
Texas	56,560	1,546	2.7%	57,921	1,562	2.7%	59,776	1,601	2.7%	61,006	1,626	2.7%
Washington	20,065	1,070	5.3%	20,181	1,078	5.3%	20,406	1,095	5.4%	20,764	1,106	5.3%

#4A Watching for When the Coronavirus Curve Flattens - *MAY 2020 - World and U.S. (*Additional* CASES each day, not total cases)								
Location	**May 22**	**May 23**	**May 24**	**May 25**	**May 26**	**May 27**	**May 28**	**May 29**
Worldwide	111,059	97,606	96,524	87,448	94,565	103,440	120,853	118,044
China	18	3	11	7	0	4	0	17
Spain	1,787	466	482	128	359	0	1,647	658
Italy	652	669	531	300	397	584	593	516
U.K.	3,298	2,960	2,412	1,631	4,052	2,020	1,647	2,099
U.S.	**23,576**	**21,947**	**20,576**	**19,056**	**18,611**	**19,020**	**21,817**	**25,337**
California	2,247	2,187	2,079	1,848	2,175	2,247	2,717	2,189
Florida	776	676	740	879	509	379	651	1,212
Georgia	813	914	708	506	386	691	649	600
Illinois	2,758	2,352	2,508	1,713	1,178	1,111	3,149	0
Louisiana	421	115	129	640	245	443	305	0
Massachusetts	805	773	1,013	596	422	0	1,202	617
Michigan	403	452	314	02	223	504	406	607
New Jersey	1,247	385	1,050	938	672	864	1,187	1,029
New York	**1,696**	**1,772**	**1,589**	**1,249**	**1,072**	**1,129**	**1,768**	**1,551**
Texas	945	1,181	1,060	1,462	589	1,361	1,855	1,230
Washington	146	148	320	243	257	116	125	358

* This is the metric to watch to find when a curve flattens or spikes occur

This may now be the most important chart

#4B The New Key Measure - MAY 2020 - World and U.S. (*Additional* DEATHS each day, not total deaths)									
Location	**May 22**	**May 23**	**May 24**	**May 25**	**May 26**	**May 27**	**May 28**	**May 29**	**8-day Average**
Worldwide	5,301	3,880	2,954	1,173	4,221	5,200	4,736	4,662	4,016
China	18	0	0	0	0	0	0	0	2
Spain	--	50	74	82	283	0	3	2	71
Italy	130	119	50	92	78	117	72	87	93
U.K.	351	282	128	134	134	412	377	324	268
U.S.	**1,270**	**1,115**	**633**	**498**	**695**	**1,529**	**1,175**	**1,219**	**1,017**
California	88	78	66	21	19	70	89	95	66
Florida	46	44	4	15	7	62	46	49	34
Georgia	31	26	13	6	41	36	55	12	28
Illinois	108	75	66	28	39	160	187	0	83
Louisiana	39	0	22	0	11	21	18	26	17
Massachusetts	80	76	68	44	57	0	167	78	71
Michigan	39	65	5	12	26	68	38	34	36
New Jersey	142	96	52	11	47	148	62	130	86
New York	**112**	**87**	**109**	**97**	**76**	**79**	**79**	**58**	**87**
Texas	21	40	26	21	19	16	38	25	26
Washington	7	6	5	6	9	8	17	11	9