[4] Anti-viral and vaccine update

The development of anti-viral medications and vaccines is typically a lengthy and complex process involving randomized trials, control groups, large populations and a variety of steps designed to demonstrate both efficacy and safety for broad public use. In this section, we walk through some history on anti-viral development, the latest news on anti-viral progress on COVID-19 and then do the same for vaccines. We then discuss the potential for convalescent plasma, and take a deep dive into the Chloroquine controversy.

**Anti-virals**

Let’s start with a discussion of anti-virals, and some challenges to keep in mind:

- Viruses reproduce by hijacking the host’s own biological machinery. Having very few of their own enzymes and proteins, they typically present few opportunities for specific drugs to target.
- That might explain why **only 90 anti-virals were ever approved for final use** from 1963 to 2016 out of the thousands proposed in scientific literature (see chart below). And even this number overstates reality since some single agents are counted more than once for each virus they cover, several have been withdrawn due to lack of efficacy, and others are rarely prescribed at all.
- These challenges might also explain the lack of anti-viral success against **Ebola**, for which numerous therapies were tested (chloroquine, favipiravir, brincidofovir, monoclonal antibodies, remdesivir, antisense RNA and convalescent plasma). Ultimately, none proved to be effective despite some agents showing success in non-human primates.

**History of antiviral drug development**

Number of approved drugs

![Graph showing the number of approved antiviral drugs](chart.png)

In a paper published in mid April in the Journal of the American Medical Association, the authors concluded that “currently, there is no evidence from randomized clinical trials that any potential therapy improves outcomes in patients with either suspected or confirmed COVID-19, and there are no clinical trial data supporting any prophylactic therapy”¹. The paper analyzed the 291 clinical trials underway at the time, including those not yet recruiting, recruiting, active, or completed. Their conclusion may change as the results of clinical trials underway become known, but is a reminder that many press reports floating around in March 2020 had overstated the potential for certain drugs.

**Update on the latest anti-viral trials underway**

The “Solidarity” trial has been launched by the WHO, and will determine the effectiveness of remdesivir, chloroquine, lopinavir-ritonavir and lopinavir-ritonavir-interferon beta-1a. While such trials can take years to design and conduct, the Solidarity trial may reduce the timeline by 80% by conducting a single global clinical trial. Similar efforts include the “Recovery” trial in the UK and the “Remap-Cap” trial conducted by the University of Pittsburgh. In addition, the US NIH announced the “Accelerating COVID-19 Therapeutic Interventions and Vaccines” partnership (ACTIV), a collaborative effort with 16 pharmaceutical companies to prioritize vaccine and drug candidates and streamline clinical trials.

**Chloroquine/hydroxychloroquine**

A complete mess. See pages 7 and 8.

**Remdesivir (anti-viral).** There are multiple trials underway to determine if remdesivir is safe and effective against COVID-19. Gilead admitted that partial results were posted to the web “by mistake”, did not show efficacy (more people died in the remdesivir group than in the control group) and that the study was terminated due to a lack of patients. A study involving 12 rhesus macaque monkeys did have a control group and showed positive results from Remdesivir (lower virus amounts, less lung damage), but apes are apes. Gilead’s study of 2,400 severe patients and 1,600 mild patients will be much more informative.

**Lopinavir/ritonavir (anti-viral).** Despite in vitro success against other coronaviruses, there is no published in vitro data for lopinavir/ritonavir in SARS-CoV-2, and likely a limited role for this combination. In a randomized clinical trial published in the New England Journal of Medicine, there were no differences in clinical improvement, viral clearance, or mortality for antiviral treatment versus standard care.

**Ribavirin (anti-viral).** Studies suggest limited value. Ribavirin treatment of SARS yielded inconclusive results, which were also associated with substantial toxicity that included hemolytic anemia in 60% of patients.

**Oseltamivir (anti-viral).** This influenza drug has no documented activity against SARS-CoV-2 in vitro

**Tocilizumab (immuno-modulator).** This monoclonal antibody, approved by the FDA for treatment of rheumatoid arthritis and for cytokine release syndrome, has yielded success but in small numbers of patients with severe COVID cases. In China, tocilizumab is included in COVID-19 treatment guidelines, and randomized clinical trials are underway in China including COVID patients with with severe pneumonia.

**Corticosteroids (immuno-modulator) could decrease inflammatory responses in the lungs, but could also lead to delays in viral clearance and increases in secondary infection risk. Guidelines: avoid corticosteroids, since potential harms and lack of proven benefit mean they usually should not be used outside of randomized clinical trials.

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¹ “Pharmacologic Treatments for Coronavirus Disease 2019 (COVID-19)”, James Cutrell, MD, Division of Infectious Diseases and Geographic Medicine, Department of Medicine; and James Sanders, PhD, Department of Pharmacy, University of Texas Southwestern Medical Center, Dallas, April 13, 2020
Special focus: how might anti-viral medications actually work against COVID-19?

- Some drugs may function as both an anti-viral medication (which interrupts various steps of the viral lifecycle inside cells), and/or as an immuno-modulator.
- The latter might be very important, since many people that are dying from COVID-19 are suffering from sudden multiple organ failure. Doctors don’t know yet if that’s because of the viral infection itself, or because of immune system damage caused by a “cytokine storm”. Some drugs being tested are used for auto immune disorders to prevent the cascade of inflammatory damage that accompany them. As a result, it’s possible they inhibit the replication of the virus, and might prevent further immune system damage which causes organ failure.
- More trials are required until we know for sure; there was a lot of excitement about certain anti-virals for use against Ebola which didn’t end up showing any efficacy once trials were done, and now it looks like AbbVie’s Kaletra does not work well against COVID-19 either.
- To be clear, anti-virals are generally administered to people that are already infected. It is still unclear if they will be able to be widely used prophylactically by people that have a high likelihood of having been infected, such as healthcare workers exposed to heavy viral loads in the workplace, and family members of infected individuals.
- Anti-virals have the potential to substantially reduce mortality rates and decrease complications. It is also still unclear if they can significantly slow the rate of infection and hospitalization since they will largely be administered to hospitalized patients. And to be clear, anti-virals do not materially change the rate of whatever community transmission is taking place; vaccines are needed for that.

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One possibility is that patients are dying from “cytokine storm syndrome”, a large, rapid release of cytokines into the blood as a result of viral infections or immunotherapy. From oncology doctors at Washington University in St. Louis: “we believe that there is increasing evidence that cytokine storm syndrome is occurring co-incident with the progressive pneumonia and in severe cases may be driving the pathology and increasing the risk of death above and beyond what would be expected by the viral infection by itself.”

Vaccines

The goal of creating a vaccine to combat an infectious disease appears to have decent odds, at least when compared to success rates of other clinical trials.

However, a COVID-19 vaccine is not a foregone conclusion. The world is still searching for an HIV vaccine; just last month, yet another large-scale HIV vaccine study failed to show efficacy, and no vaccine has been developed for any human coronavirus. First some background, then details on specific vaccine candidates:

- Scientists have to figure out which part of the SARS-CoV-2 virus to target for the vaccine. Its “spike protein” is being used by many candidates, but could result in worse outcomes due to a phenomenon known as “antibody dependent enhancement” (ADE). In ADE, virus clearance pathways typically used by the body’s immune system are hijacked by the virus and end up enhancing viral infection instead. That’s why human clinical trials are vital to the vaccine approval process. The good news is that two front-running vaccine candidates (Oxford and Sinovac) see no sign of ADE in animal studies.

- In recent decades, it has generally taken several years for vaccines to be tested and approved. However, this timeline has been improving. It took 20 months for a SARS vaccine to reach human testing (it was never completed since the virus was eradicated first through non-pharmaceutical intervention), it took only six months to move to testing for Zika virus, and Moderna entered coronavirus testing in humans for its mRNA-1273 vaccine in just two months (animal testing was completely skipped).

- **RNA/DNA vaccines, recombinant protein vaccines and cell culture-based vaccines are all options being examined.** RNA/DNA vaccines and viral vector vaccines are the most novel and aim to leverage the body’s ability to generate the immunogenic (antibody-provoking) protein. The body would then generate antibodies against the protein to provide protection. To be clear, no RNA/RNA vaccines have been approved to date. Cell culture-based vaccines are the incumbent technology in which the immunogenic protein is generated outside the body in vitro, and injected into the body.

- The genetic sequence of SARS-CoV-2 and its various mutations have been identified in **record time.** Once the right animals are found for vaccine testing (ferrets might work, and a recent study from the University of Pittsburgh showed antibody responses in mice), toxicity tests in animals often take 3-6 months. After that, Phase I, II and III trials are needed to demonstrate safety and efficacy in humans.

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3 Sources include Derek Lowe’s *Science Translational Medicine*, Johns Hopkins and “SARS-CoV-2 vaccines: status report”, Fatima Amanat and Florian Krammer, Graduate School of Biomedical Sciences and Dep’t of Microbiology, Icahn School of Medicine at Mount Sinai, March 2020
• **Phase II trials** typically focus on efficacy in different populations (age, gender, pre-existing health conditions and range of medications being taken), all with different dosing schedules, and are designed to set the stage for larger Phase III runs. Some steps can be accelerated by running a lot of simultaneous trials instead of sequential ones, but not all of them

• **Scaling up vaccine production can be challenging.** Even for influenza vaccines, for which many production facilities exist, demand in the case of a pandemic could exceed production capacity. Live-attenuated virus, inactivated virus, recombinant protein, and nucleic acid vaccines all entail completely different production and distribution methods; a commitment by the Gates Foundation to fund 7 vaccine factories at once could help accelerate the timetable

• A COVID-19 vaccine would have to be deployed widely across the globe in all populations. The **safety bar for mass vaccination** of this type would likely be very high, particularly since the individual case mortality rate is thought to be relatively low in parts of the population.

Here’s some detail on specific vaccine candidates:

• **J&J** announced a very ambitious timetable for a COVID-19 vaccine that uses the same technology platform as their Ebola vaccine (which took 5 years to complete). This platform is also used by J&J for its Zika, RSV, and HIV vaccine candidates which are currently in Phase 2 or Phase 3 trials. J&J aims to begin Phase I trials in September 2020 with production as early as spring 2021. They have reportedly identified a lead vaccine candidate (with two backups)

• **Sanofi and GlaxoSmithKline** have accelerated development of a vaccine based on the delivery of SARS-CoV-2 spike proteins into humans, a process designed to engender an antibody response. Their existing Flu-Blok process (approved in 2013) would work as follows: take the genetic sequence of the SARS-CoV-2 virus, splice it into an insect virus and wait for cells from insects (moths, actually) to generate SARS-CoV-2 spike proteins, which are injected into humans. An “adjuvant” of organic chemicals is added to provoke an even stronger immune response (small amounts of aluminum, for example, have been used in vaccines since the 1930’s for this reason). Sanofi/GSK have announced the following timetable: testing in humans in the second half of 2020, and filing for regulatory approval by the second half of 2021. Unlike RNA/DNA vaccine development, applying the Flu-Blok approach to COVID-19 relies on more proven vaccine technology

• **Oxford University** announced a very aggressive timetable for development of a vaccine based on a chimpanzee virus that is altered to be harmless to humans, and which includes genetic components coding for the SARS-CoV-2 spike proteins. As with the other vaccine ideas cited above, the spike proteins of the virus are expected to provoke the body’s immune system into generating the necessary antibodies. Oxford’s Jenner Institute hopes to produce one million doses by the fall if current clinical trials are successful (6,100 volunteers have been recruited into a randomized trial)
  o The Serum Institute of India, one of the world’s largest vaccine companies, actually announced that they will produce 40 million of Oxford’s vaccines now, even before trials are completed
  o The Oxford vaccine was reportedly successful when used against 6 rhesus macaque monkeys

• **CanSino’s** adenovirus vector vaccine, which uses a live unrelated virus to deliver the DNA needed for generation of SARS-CoV-2 proteins (such vector vaccines have been used in human trials for HIV, influenza, Ebola, tuberculosis, and malaria, but none have been approved yet)
- **BioNTech’s mRNA vaccine candidates** (four in total, in partnership with Pfizer) which have been given approval in Germany for use in Phase VII trials

- A **Sinovac/Dynavax** partnership on the development of inactivated virus vaccine with an adjuvant. Sinovac announced in April that their vaccine produced antibodies in rats, mice and rhesus monkeys; appear to work against ten different mutational strains of the virus; and that they did not see any evidence of antibody dependent enhancement described on page 4

- **Moderna RNA and Inovio DNA vaccine candidates.** As mentioned above, these vaccines aim to engineer RNA and DNA to enter human cells which would then generate virus proteins. A new ingenious approach that has not yet been approved for use. Inovio also plans to develop a new delivery approach (through the skin via a handheld device) which will require additional regulatory approvals

- **The entire BCG vaccine thesis is highly questionable; see pages 9-10**

### Convalescent plasma

Houston Methodist Hospital was the first to receive approval from the FDA to use “convalescent plasma” (or “convalescent sera”) to treat infected patients and vulnerable populations. Step 1: collect serum from recovered patients that contain virus-neutralizing antibodies, and step 2: infuse it into other COVID-19 patients. This approach was used during the Victorian era before antibiotics to treat meningitis and pneumonia (by injecting bacteria into horses and harvesting horse serum). High frequency convalescent plasma is currently used to treat immuno-deficient individuals against pathogens like measles and mumps.

**Like antivirals and vaccines, convalescent plasma applied to COVID-19 will require clinical trials to demonstrate efficacy.** In addition, it would not confer long-term immunity (antibody half-lives are just 30 days), and thus would at best provide a temporary benefit for some period of weeks. However, that might be sufficient when dealing with a pandemic wave of infection over a short period. Convalescent plasma might be difficult to scale and runs the risk of transmission of other undiscovered viruses but could be a vital tool in certain high-risk cases.

More background⁴:

- The largest convalescent plasma study from the SARS era involved the treatment of 80 patients in Hong Kong. Patients treated before day 14 had improved prognosis defined by discharge from hospital before day 22, consistent with the notion that earlier administration is more likely to be effective

- In the 2009–2010 H1N1 influenza virus pandemic, convalescent plasma was used to treat individuals with severe infection requiring intensive care. The serum-treated individuals manifested reduced respiratory viral burden, inflammatory cytokine responses and mortality

- Risks include inadvertent infection with another infectious disease agent and reactions to serum constituents, including immunological reactions such as serum sickness. Screens for blood-borne pathogens and blood type matches of donors and recipients can reduce this risk, in principle

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⁴ “The convalescent sera option for containing COVID-19”, Arturo Casadevall, Department of Molecular Microbiology and Immunology, Johns Hopkins School of Public Health, March 13, 2020
The collapse of chloroquine

Remdesivir, ivermectin (an FDA-approved anti-parasitic drug) and chloroquine (a widely-used anti-malarial and autoimmune drug) were shown in recent studies to reduce COVID-19 viral loads in cell cultures with low levels of toxicity to the cell. That’s what is shown in the chart on the left; but remember, these are cell cultures and not live trials, there are no successful vaccines to-date against any of the coronaviruses, and there are numerous drugs that were promising in vitro for other infectious diseases and which failed in clinical studies.

The controversy started with widespread media reports of positive results from a March study from France that combined hydroxychloroquine (HCQ) and azithromycin (a “Z-pack”). The chart above (right) made the rounds on the internet very quickly. However, it is now clear that this French study:

- was a non-randomized trial with only 36 patients, and had no discussion of outcomes
- excluded 6 recipients that were not discussed, some of whom of required ventilation and/or died
- started out with higher viral loads in the control group than in the infected patients, which could explain why the control group showed higher infected rates at the conclusion of the study
- imputed more than 1/3 of the control group virus tests rather than measuring them
- sourced its treatment group (unlike the control group) from a single medical center
Unlike the French study, there have been other randomized HCQ and chloroquine studies *with control groups*:

- The Shanghai Public Health Clinical Center found no benefits from HCQ when comparing the control group to the treatment group.

- A study from Renmin Hospital of Wuhan University *did* find improvements in “time to clinical recovery” and in pneumonia severity vs the control group when using HCQ.

- A Brazilian study initially planned to enroll 440 severely ill patients to test two doses of chloroquine (450 mg twice a day for one day and then one a day for four more days, and 600 mg twice a day for 10 days). When 25% of patients in the group developed heart rhythm problems (trends suggested that more deaths were occurring in that group as well), scientists halted that part of the study.

- After two more failed HCQ trials, American biotech pioneer William Haseltine (known for his groundbreaking work on HIV/AIDS and the human genome) concluded that “hydroxychloroquine had no beneficial effect on disease progression or viremia of patients hospitalized for COVID according to two controlled trials from France and China. Both found that hydroxychloroquine induced dangerous heart rhythm abnormalities. The French study recommended against the use of the drug for patients hospitalized for COVID-19.”

- The US Veterans Administration reported no benefits and higher death rates for hospitalized COVID-19 patients treated with HCQ when compared to the control group.

Finally, on April 19, an NIH panel recommended against the use of HCQ and azithromycin to treat COVID patients. The panel also recommended against the use of lopinavir/ritonavir or other HIV protease inhibitors due to negative clinical trial data, and also recommended against using interferon because it appeared to make patients with SARS and MERS worse.

**Bottom line:** *results from large-scale randomized clinical trials are the only viable path to an antiviral solution, and there is no guarantee that one will be found.*

*Sources available upon request*
The highly questionable premise that the BCG vaccine is a driver of COVID severity

Some healthcare professionals have advanced the premise that the BCG vaccine (a tuberculosis vaccine given to children) somehow explains regional differences in COVID severity. In epidemiology, mathematical biology and medical communities, there’s a LOT of BCG skepticism:

- The WHO has stated that there is no medical evidence to support the BCG thesis.
- The BCG vaccine is used more widely in less developed, younger countries. As severity of COVID-19 is strongly linked to age, population distributions (or vaccines other than BCG) may be much better ways to explain cross-country differences. It’s also an odd time to draw conclusions about cross-country BCG impacts since the virus is now rising more sharply in parts of the developing world that use it.
- Chinese healthcare professionals said they did not see any variation in COVID infection or mortality rates based on BCG vaccination histories.
- Tuberculosis is a bacteria while SARS-CoV-2 is a virus, raising questions as to why a BCG vaccine would work in the first place.
- Some studies supporting the BCG concept didn’t incorporate population heterogeneity, actual vaccination rates or differences in response rates among individuals.
- The key flaw: many BCG studies are derived from quick and dirty cross-country comparisons, and are prone to biases that “confuse the public.” They compare groups rather than individuals, and are much less helpful in identifying what may cause or prevent disease. Cross-country comparisons are simple and don’t require a lot analysis, but are prone to “ecological fallacy” (just because you observe a correlation between average exposure and outcomes does not mean that individuals with greater exposures have a higher/lower risk of disease). We already have in hydroxychloroquine a “stunning example of policy decisions made on the basis of weak evidence.”

If that’s not enough for you, see the chart on the next page.

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5 “Bacille Calmette-Guérin (BCG) vaccination and COVID-19”, WHO Science Brief, April 12, 2020

6 The Imperial College of London has made it clear in their research that % of symptomatic cases requiring hospitalization, % of hospitalized cases requiring critical care and case fatality rates closely track age distributions.

7 Epidemiologist Salim Karim, Columbia University Mailman School of Public Health, Adjunct Professor of Medicine at Weill Medical College of Cornell University

8 “Coronavirus and the tuberculosis vaccine”, Dr. M. Noon, University of Goettingen, April 21, 2020

9 “A Skeptic’s Guide To Ecologic Studies During A Pandemic”, Madhukar Pai, Canada Research Chair in Translational Epidemiology & Global Health, McGill University, April 22, 2020
Let’s make it even simpler. Consider reported COVID deaths per million people as a function of BCG vaccine policy (assuming that reported deaths in developing economies are accurate, which is a big “if”). Yes, as shown in the chart, there’s a cluster of low death rates in countries with long-standing BCG vaccine policies [group 1]. But analytically, the entire BCG thesis falls apart in my view for the following three very simple reasons:

- The number of countries that “never had a widespread BCG vaccine policy” [group 6] is extremely small, and its dispersion is very wide.
- There are a lot of countries that no longer use the BCG vaccine but only terminated it after 1970 [group 3]. In other words, anyone over the age of 50 in these countries had the BCG vaccine, and many of these countries have high COVID death rates anyway (e.g., France, Spain). Why?
- There’s also a cluster of countries that only instituted BCG vaccine policies after 1970, and their COVID death rates are low as well [group 5]. If that’s the case, how were their older people protected if they didn’t get the vaccine??

Given the unknowable complexity of the body’s immune system, it’s impossible to predict if the BCG vaccine will or won’t work against COVID-19, and any clinical trials conducted will be interesting to watch. I sure hope it works, like every other idea proposed. But to me, the BCG thesis so far is very sloppy science.
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