MAY 12, 2020

RA CAPITAL'S COVID-19 MAP:
Insights into a Coordinated Response Strategy

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For more information about RA Capital's COVID-19 coverage, please visit:
www.racap.com/covid-19

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INTRODUCTION

The world is now embarking on a massive initiative to fight COVID-19. Hundreds of companies, non-profits, academic institutions, and government agencies are playing a part in an effort that some have compared to the Manhattan Project. The US government calls its own portion of this effort Operation Warp Speed.

When executing on a large-scale, multi-pronged initiative, it is essential to have an overview of the totality of the ongoing work. If each individual vaccine or drug or test is a chess piece, then one needs to see the chessboard as a whole. Lists of all the programs fall short in conveying the interdependencies and opportunities for using different technologies together or in a particular sequence.

Our team has created a map that captures many of the major ongoing technology development efforts in the world to solve our COVID-19 crisis. The goals of the map are to not only lay out the competitive landscape of a given space, but to also reveal strategic insights that emerge when looking at the space in its totality. Historically, such technology landscape maps of cancer, auto-immune disorders, diabetes, and other diseases have guided our own investment of time and money into what we believed to be the most important projects. We hope that this map will be of use to BARDA, CEPI, and other grant-giving organizations as they consider the best uses of their resources, and we are making it available to the global community in the hopes that it allows leaders to formulate strategies to make the most of all the ongoing work.

As one example, today there is considerable funding going to vaccines that focus the immune response on just the viral spike protein. While that is logical, it leaves us all undiversified in our vaccine development strategy. We would argue that at least some funding should go towards vaccines that rely on inactivated and attenuated virus.

On the treatment side, while remdesivir is authorized for emergency use to treat patients with serious COVID-19, it is in short supply, difficult to manufacture, and must be given intravenously (IV). But there are related drugs in testing whose probabilities of success are informed by remdesivir's. Some of these are oral and may be easier to manufacture. Remdesivir's success thus far should spark a shift in resources to make the most of those other programs.

Meanwhile, the map teaches us that we should be thinking ahead further: are there enough syringes and needles to meet an undoubtedly unprecedented demand for a COVID-19 vaccine? Who should receive the limited doses of COVID-19 vaccine that may become available in late 2020 or early 2021? What drugs might work best in combination, or in what sequence? Will there be knock-on effects from COVID-19 that we need to prepare for, such as a surge in demand for flu vaccine; America normally only procures enough doses for half the population – should we put in a larger order now? How do we ensure that everyone can access COVID-19 treatments and vaccines? COVID-19 has accelerated all facets of drug and vaccine R&D and regulation. Only by looking at the big picture can we see the gaps in our vaccination and treatment strategies. Only by looking at the big picture can we more quickly anticipate where to shift resources when a project fails (there will be failures along the way). And only by looking at the big picture can we judge how to make the most of any success.

Below, you will find many of our key insights around vaccine, therapeutics, and diagnostic development that we have gleaned from looking at the big picture.

VACCINES

The vaccine programs that were first to reach clinical testing are considered difficult to manufacture at scale. Therefore, the vaccines that reach the market sooner than others might not be the ones that will necessarily be produced in sufficient amounts to meet the world's needs. Some of the vaccines that may be among the first scaled to billions of doses may not be able to be re-dosed every year if it turns out that we need to get seasonal booster shots. Some vaccines might be more readily combined with flu vaccines than others, which would be useful if we do someday need to give regular booster shots and want to avoid having to give people

two injections. So, the various vaccine programs may serve different purposes. The earliest ones to market might only benefit front-line workers; the first to scale to high levels of production will unlock the global economy; the ones that can be readily re-dosed and combined with flu vaccine may take a bit longer to develop but help keep SARS-CoV-2 permanently in-check.

mRNA

Vaccines that deliver mRNA encoding SARS-CoV-2 Spike antigen could be among the first to be approved, but most companies working with this technology can only manufacture them on the scale of a few kilograms. The most important two questions for those programs are how much mRNA will be required to generate an immune response and will the vaccines require more than one dose. If two doses are required (e.g. at least 50ug each, which Moderna suggests is likely), then those programs will initially serve to vaccinate tens of millions of people per month globally. But if some of these programs need only a single 5ug dose, then mRNA could quickly vaccinate hundreds of millions of people per month by the end of 2020 or by early 2021. We will know what doses are needed within a few months: trials for vaccines by CureVac, BioNTech, Moderna, and others should read out by fall 2020.

Adenoviral Vectors

Johnson & Johnson (J&J) is scaling up production of its adenoviral-vector-based COVID-19 vaccine and plans on initially delivering hundreds of millions of doses, with capacity to make 1 billion doses/year sometime in 2021. However, J&J is not yet in the clinic. Their trials will likely start this fall. But in late April, the University of Oxford ambitiously launched a controlled trial of a similar adenoviral vaccine in over 1000 people. This will tell us how good such a vaccine could be, point to an effective dose, and indicate whether it needs to be boosted with a second dose. The Oxford vaccine might scale up more slowly than J&J's but it will give us a sense of how well and how efficiently J&J's might work. In the event that it only needs to be given once and at a low dose, then we might speculate that J&J's manufacturing capacity will stretch to vaccinate many more people than originally planned. However, there is also a risk that a second dose of Oxford's adenoviral vaccine does not work as well because our immune systems generate antibodies against the viral vector in response to the first dose (a problem particular to vectorized vaccines). In that case, we could possibly boost with a different vaccine.

Exploring Combinations

Combining an adenoviral vaccine for the prime dose and other vaccines for the boost dose might even maximize vaccine production capacity due a vaccine phenomenon known as fractional dosing in which the booster dose can sometimes be much lower than the initial priming dose. So rather than using 1B adenoviral doses to vaccinate 500M people twice and 500M doses of a protein-based (or mRNA-based) vaccine to vaccinate 250M people twice for a total vaccination of 750M people, we might vaccinate 1B people with a combination of one dose of the adenoviral vaccine and a half-dose of the protein-based vaccine. The various large-scale vaccine groups should be collaborating on joint animal studies with a goal of exploring these "heterologous prime-boost" human studies. To our knowledge, such collaborations are not yet ongoing.

Protein Antigens and Combinations with Flu Vaccines

We will eventually have options that are more conventional than mRNA or viral-vector vaccines. Novavax, for example, will start trials in May 2020 of two doses of its nanoparticle vaccine. With enough investment, they might be able to scale up production considerably. Behind Novavax is Sanofi, which unlike all the other companies mentioned so far, is one of the world's few large vaccine manufacturers (Sanofi has support from GlaxoSmithKline, another large vaccine player, which has contributed a novel but proven adjuvant to Sanofi's effort). Sanofi sells conventional flu vaccines and is now working on a protein subunit version of the SARS-CoV-2 vaccine. That vaccine will be slow to market but is potentially the easiest to scale using tried and true methods. Depending on the adjuvant, it could also be combined with Sanofi's existing flu vaccine, allowing for streamlined global distribution over the long run. It makes sense for governments and payers to think now about how and

how much they would want to pay for a combination flu/SARS-CoV-2 vaccine versus just the individual parts. Making sure that people get the flu shot is going to be critical to minimizing false alarms from people getting the flu but scaring themselves and others into thinking it is COVID-19.

Vaccines and Antibody Tests

When we do have a vaccine, we need to anticipate that antibody tests of the future need to be able to tell the difference between antibodies from a vaccine and antibodies from an infection. We have both of these kinds of tests and need to make sure that the right ones are deployed and used at the right time in synchrony with vaccines to track the vaccines' real-world effectiveness. We will also need antibody tests that can accurately tell when a person has been reinfected; that is possible by looking for IgM antibodies, though those suffer from poor specificity (high false-positive rate). Better IgM tests are required if we hope to be able to detect rates of reinfection without having to use PCR to catch each reinfection (especially since reinfections might be milder or even asymptomatic in patients with some immunity after a vaccination or first infection).

Passing the Safety Hurdle

Hanging over the whole vaccine field are several questions about COVID-19 vaccine safety and efficacy. We all want to know if they will work in humans, and we know that several vaccines have been able to generate antibodies in animals that protect those animals from infection. We also know that these first few experiments have not observed a phenomenon called "enhanced disease" in which a vaccine helps the virus infect certain immune cells and leads to worse outcomes. However, before we can be sure these vaccines do not cause enhancement, it would be good to know that we can somehow induce enhancement in animals. Several laboratories are trying to do this (e.g. use an intentionally poorly prepared vaccine to cause enhancement). As soon as one does, that will allow everyone to compare their vaccines in this model. It will be essential that these preclinical studies are published as quickly as possible so that the field can learn from them.

Monitoring for Antigenic Drift (that would require updating vaccines)

Based on sequencing of SARS-CoV-2 from patients all over the world, we are seeing the emergence of mutations in the Spike protein, including the critical Receptor Binding Domain (RBD) that we consider the virus' greatest point of vulnerability to antibodies. It is feared that if the RBD changes too much, then our vaccines will stop working against these new strains. This phenomenon of antigen drift is one way the flu evolves slightly away from our vaccines each season, requiring us to update flu vaccines to keep them effective. Therefore, we need vaccine manufacturers to regularly test whether the antibodies their vaccines generate can neutralize these new RBD-mutated strains. If they detect waning efficacy, we need them to start working on updated versions of their vaccines. Reporting these findings to the public would go a long way towards reassuring the public that news of new strains with feared mutations in the RBD region does not mean that vaccines will not work.

Just in case: Preparing for Potential Challenge Studies

There is a complex relationship between social distancing and vaccine development. On the one hand, social distancing helps to flatten the curve until we get a vaccine. On the other hand, unless there is a certain rate of new infections in the tested population (i.e. the "attack rate", such as 2% of people getting infected each month), it is impossible to demonstrate that a vaccine actually works to prevent real-world infections. Therefore, it will be important for vaccine developers to be able to run studies wherever in the world there are high rates of infections.

Some have suggested testing vaccines on volunteers who are willing to then let themselves be exposed to the virus to see if the vaccine protected them (so-called "challenge studies"). However, we currently neither know the right dose of virus to simulate an infection in the real world nor do we have a supply of the virus that would be considered suitable for such a trial. It probably makes sense to solve those two problems quickly in case it turns out that most countries in the world have flattened their curves by this fall to such an extent that vaccine trials are undoable. Regardless

of their feasibility, the ethics of doing such challenge studies are unclear and also require study.

Making doses of remdesivir and any other proven antiviral therapeutics available to such volunteers in challenge studies would provide an added level of safety. After all, the point of a vaccine is primarily to prevent an infection. Volunteers could be vaccinated, exposed to virus, and then tested every day or two to catch an infection early. Anyone infected can be started right away on a therapeutic, lowering the risks to volunteers and making such a trial ethically more acceptable.

THERAPEUTICS

Drugs can help infected people recover more quickly, with fewer symptoms and reduced chance of death. Safe and effective therapies to treat COVID-19 and its symptoms can help bridge the way to widely available vaccines (likely in late 2021). Understanding what kinds of treatments might be on the horizon can help prioritize resources and anticipate future challenges, directing efforts to help plug gaps in our collective COVID-19 response. Once we know what types of drugs are showing signs of working, we can redouble our efforts to find the best among them and the best ways to use them. Such incremental improvements have turned good older types of drugs into much better newer ones, as we've seen with blood pressure medications and insulins. This same kind of iterative, incremental innovation can be accelerated to address COVID-19 if we look a few moves ahead.

Our COVID-19 arsenal can be split into two general buckets: drugs that attack SARS-CoV-2 itself, either by preventing it from getting inside our cells or disrupting replication once it is in there; or drugs that prevent or limit the damage the virus can inflict, by protecting vital organs or properly calibrating our immune responses – prodding an underactive immune response or dampening an overactive one that is doing more harm than good.

Antivirals – Repurposed and Novel

The first generation of drugs being tested for COVID-19 are those that are already on the market or were being developed to treat other viral infections, such as flu or hepatitis C. Gilead's polymerase inhibitor remdesivir, originally developed to fight Ebola, has already been proven to work to some extent and now has Emergency Use Authorization for the treatment of hospitalized COVID-19 patients. We will likely know by June or July whether any other repurposed drugs are effective against COVID-19. Especially promising are oral polymerase inhibitors; they work in the same way as remdesivir but are more convenient. Some of them may even be easier to manufacture. The challenge with these drugs is twofold: they may differ in their ability to get to the lungs and the potency with which they work on SARS-CoV-2.

Behind these repurposed drugs are those specially developed to target SARS-CoV-2, most prominently monoclonal antibodies. Antibodies are similar to antibiotics and antivirals in that resistance is possible. If the virus' Spike protein mutates in the region that an antibody binds to, then the antibody may lose its ability to bind to the virus. Regeneron is developing a cocktail of antibodies, much like we use a cocktail of antivirals to manage HIV and cure hepatitis C. In case a virus has one mutation that prevents one antibody from binding, then the other antibodies in the cocktail will still neutralize the virus. But there are a number of companies that are, at least initially, only testing one antibody in the clinic. They should consider collaborating to create multi-antibody cocktails, similarly to how HIV pioneers created combination pills to treat HIV.

One challenge with all novel drugs is that making them at scale might turn out to be harder than proving that they work. As we have seen with remdesivir, initial supply must be rationed. It is important that the discovery or approval of an effective drug does not prompt an uncontrolled easing of social distancing. Premature celebrations or overconfidence will lead to more infections than our drug supply can accommodate.

Further complicating the question of supply is whether drugs that each are partially effective would be best used together or individually. If we have 250,000 courses each of remdesivir and a similarly effective

antibody, should we treat 500,000 people with one of the drugs or should we treat 250,000 people with both? Remdesivir is only about 30% effective in terms of shortening the time to discharge from the hospital and it appears to reduce the chance of dying by about the same. An antibody might offer similar efficacy alone, but together maybe they would 95% effective. We need to answer these questions with clinical trials to make sure we get the most benefit from our early batches of proven drugs. For example, that means making sure that remdesivir is available at hospitals that are studying therapeutic antibodies and that antibodies are tested at hospitals that have access to remdesivir.

Some groups are working on generating polyclonal antibodies in animals. But they need a SARS-CoV-2 vaccine with which to vaccinate the animals so that they develop antibodies. Yet vaccine companies are focused on making vaccines, not helping other groups generate polyclonal antibodies for therapy. Still, it would be ideal if some of the companies that have had success making batches of their vaccines could collaborate with groups developing polyclonal antibodies in cows and horses to see if those might be a source of therapeutic antibodies before monoclonal antibodies come to market. Realistically, those would be only a few months apart at this point, so if this work does not start right away, then we may as well wait for monoclonal antibodies, which will be in clinical testing in 3Q20 and could plausibly come to market in 4Q20, about the same time as the first low-scale vaccines and about four to six months before we estimate some of the large-scale vaccines become available.

Taming inflammation and Efficient Development Strategies

There are many drugs that could potentially mitigate the severe symptoms of COVID-19 by preventing a patient's immune system from overreacting and causing more harm than good (these drugs are typically used to treat rheumatoid arthritis and other autoimmune disorders and therefore are all being repurposed). The trouble with the immune system is that we really do not understand it well enough to calculate the odds of any one of these drugs working. It therefore makes sense that we are taking a "throw everything at the wall" approach to treating this cytokine storm. However, especially as we get the rate of infection under some control, we need to think carefully about how we test these drugs in the context of fewer severely ill patients. Repeatedly searching for the particular circumstances where any one drug might work, as we have seen the world do with hydroxychloroquine, a generic drug that initially seemed promising before failing in multiple studies, is inefficient.

It is critical to learn from early trials and accept when a drug does not seem to work. We should carefully allocate the finite supply of patients (at facilities that can run high-quality trials) to other drugs that might have a better chance of working. This is less of a problem with antiviral drugs since those can always be tested in milder patients. But drugs meant to treat severe disease will face enrollment constraints. Like a hundred cars trying to get through an intersection without a system, no one makes progress. But if we are systematic, we can avoid a traffic jam and test the most promising candidates as quickly as possible.

How we prioritize which drugs get tested when patients are in short supply is a key question. If one IL-6 inhibitor fails, we might argue that it makes sense to run one more IL-6 inhibitor trial because of how plausible it is to believe that this mechanism should work to rein in cytokine storm. But if that second one fails, then all IL-6 inhibitors should be deprioritized in favor of other approaches. We can work our way through the various categories laid out on the map systematically, instead of judging each drug by its own trial.

PLANNING FOR ACCESS

We hope you agree that it is inspiring to see how humanity has mustered its technological know-how in response to this crisis. We have long seen this level of ingenuity and determination applied to hundreds of other diseases that represent urgent unmet needs – our team has made over 100 maps spanning hundreds of disease areas covering thousands of companies and technologies. We are certainly heartened to see what science can do to ease human suffering, if we continue to invest in biomedical progress.

Today, COVID-19 is an urgent unmet need for all of us that has revealed the major gaps in America's healthcare system, particularly early in the crisis when insurance plans started to deny coverage of testing and care that the CDC was recommending. In response to outcries and recognizing that patients disregarding guidelines due to out of pocket costs was a threat to public health, insurance plans and the government have patched up some of those holes. Tests are now generally well covered and the federal government has vowed to cover the costs of care of millions of uninsured Americans. We now need to likewise secure affordable access future vaccines, drugs, and tests for the long run, beyond the current crisis.

We should also remember that cancer, diabetes, and countless other diseases are a personal COVID-like crisis for all those who suffer from them and their families. The reforms we consider for COVID-19 are the reforms we should consider for every disease and for all of healthcare. With proper insurance, biomedical innovation can offer America great value and remain affordable to each of us when we become patients in need of care.

RACAPITAL

NAVIGATING A TECHATLAS MAP

MOST TECHATLAS MAPS ARE STRUCTURED IN A SIMILAR WAY:

Start at the center to learn some of the basics about the disease and how the map is structured. In this case, we teach that the major goals are prevention and treatment. Then follow the branches outwards, a bit like a "choose your own adventure" story, to learn about different approaches to achieving each goal. We teach in the nodes what might make one approach better than another to guide your choice.

Similar technologies are grouped together. That allows us to spot when data from one program changes the probabilities of success for related programs.

At the end of each branch, you get to the specific programs.
IN THESE ENDNODES, YOU'LL FIND:

SPONSOR: The name of the company or companies (sometimes universities) working on the technology (i.e. drug/vaccine/test).

STAGE: Stage of development (in case of drugs, we use a mouse icon to indicate that it's still preclinical and a person icon to indicate that clinical studies have started).

TRIAL DESIGN:
If a clinical study has started, we indicate with "RCT" if the trial is randomized and controlled, which is important because uncontrolled trials are hard to interpret and learn from, so we're primarily focused on RCT data to know whether a drug really works.

ROUTE OF ADMINISTRATION:
Whether the drug is given orally, IV, or via some other way.

TECHNOLOGY NAME:
Some programs have special designations that their sponsors refer to.

DATA DATE:
When we expect to see data from a clinical study

FOR DRUGS:

REPURPOSED/NOVEL:
Some drugs were already available or in development to treat something else when COVID-19 struck and could be repurposed into testing for COVID-19 quickly. If the Repurposed icon is not illuminated, that means the drug is Novel, which means it likely will take longer to start clinical studies.

THERAPEUTIC vs PROPHYLAXIS:
We illuminate the corresponding icon to indicate whether a drug is being tested to treat infected patients or to prevent exposed people from becoming ill.

IN HOSPITAL OR POTENTIALLY OUT-PATIENT:
We illuminate an icon to teach whether a drug is likely to be limited to the hospital setting for various reasons or might be available at a pharmacy.

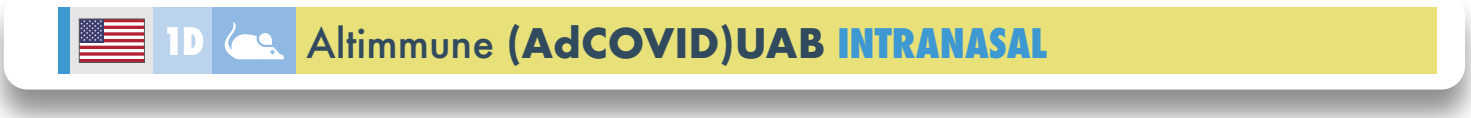
FOR VACCINES:

 # OF DOSES: Most vaccines will need to be given as a two-dose course (2D) but there is a chance that some might work with only one dose (1D).

GEOGRAPHY: Because some companies working on vaccines may prioritize their home regions (possibly because they are receiving grants from local agencies), we include a flag to indicate what region a company is based in. Where there are collaborations, we indicate the flags for each of the companies.

UPDATES:

With each update, we will highlight any changes since the previous update. This will include new programs being added, new Map structures being added, and updated Milestones.



THE MAP ALSO HAS MANY OTHER INFOGRAPHICS DESIGNED TO TEACH:

- how long it will take to develop vaccines and drugs,
- how quickly courses of various vaccines will become available,
- how COVID-19 progresses from the point of infection and when certain antibodies start showing up that diagnostic tests can detect,
- basic protective measures and how they work to flatten the curve,
- how the virus replicates and what that means for vaccine development.