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BREAKING THE COVID-19 CURVE: WHY WE ARE OPTIMISTIC ON VACCINES AND THERAPEUTIC ANTIBODIES

SEPTEMBER 8, 2020

Multiple vaccines may warrant Emergency Use Authorization (EUA) in Q4:20 due to political pressure, but the durable immunity data needed for full approval will be a more difficult hurdle.

Market opportunity for vaccines is significant from $3B in FY21 and $4.3B in FY23. Government agreements secured ~3B doses globally. We view PFE/BNTX as most promising.

We project GILD's Veklury revenue of $3.6B, $2.1B, $1.4B, $1.0B, and $750MM for 2020-'24.

Antibody therapy may have prophylactic and therapeutic roles. Competitive space could reach $2.9B in FY21 and $1.1B in FY24. REGN/RHHBY's cocktail is regimen to beat.

Yaron Werber, M.D.
646 562 1415
yaron.werber@cowen.com

Leo Ai, Ph.D.
646 562 1419
leo.ai@cowen.com

Steve Scala, R.Ph., CFA
617 946 3923
steve.scala@cowen.com

Phil Nadeau, Ph.D.
646 562 1336
phil.nadeau@cowen.com

Joshua Jennings, M.D.
646 562 1333
josh.jennings@cowen.com

Boris Peaker, Ph.D., CFA
646 562 1377
boris.peaker@cowen.com

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Yaron Werber, M.D.
646 562 1415
yaron.werber@cowen.com

Leo Ai, Ph.D.
646 562 1419
leo.ai@cowen.com

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617 946 3923
steve.scala@cowen.com

Phil Nadeau, Ph.D.
646 562 1336
phil.nadeau@cowen.com

Joshua Jennings, M.D.
646 562 1333
josh.jennings@cowen.com

Boris Peaker, Ph.D., CFA
646 562 1377
boris.peaker@cowen.com

SECTOR NOTE

BREAKING COVID-19 CURVE WITH VACCINES & ANTIBODIES - AHEAD OF THE CURVE SERIES

THE COWEN INSIGHT

One or more vaccines may be approved for emergency use in Q4:20, but access for general population is the more relevant economic catalyst and likely to occur in H1/mid-'21. Antibody therapies will have major role supplementing vaccines. We expect both modalities to generate significant revenue in FY21 ($3B and $2.9B, respectively). PFE/BNTX's vaccine and REGN/RHHBY's cocktail are most promising.

Transitioning From the End of the Beginning to the Beginning of the End

A return to normalcy and its associated economic recovery hinges on successful prophylactic and therapeutic treatments for COVID-19. Though much of the political focus has been on the potential for regulators to grant Emergency Use Authorization (EUA) to one or more vaccine candidate before the presidential election in November, we believe investors should focus on the timing of full approval and the subsequent rollout to the general population.

Recent reports noted that the four leading COVID-19 vaccine makers will issue a statement reaffirming their commitment not to file for EUA until they have sufficient clinical data from ongoing Phase 3 studies. This could delay the EUA timing to after the election and into year-end.

Based on the neutralizing antibody (nAb) and T cell data in the early trials and initial manufacturing capacity, we believe at least one EUA in Q4:20 is likely and will allow vaccination of the most vulnerable patients first (e.g., people with ≥2 co-morbid conditions, hospitalized and nursing home patients in regions with high case counts). While this is a positive for society, we do not expect it to be a catalyst for economic activity (though the market is likely to welcome it as a sign that vaccine trials are on track for success).

ACIP Sets Stage For Vaccine Rollout – Vote Expected On September 22 Ahead of VRBP Advisory Committee Meeting On October 22

Based on the CDC's Advisory Committee on Immunization Practices (ACIP) initial recommendation following its public hearing on August 26 about the plan for vaccine rollout, the first phase will offer vaccination to 25-26M people while the second phase will extend that to 45-50% of the U.S. population. Phase 3 will roll out to another 40-45% of the population. A vote on this interim prioritization scheme is expected on September 22 for approval ahead of CBER's Vaccine & Related Biological Products (VRBP) advisory committee meeting scheduled for October 22 to discuss COVID-19 vaccines.

What We Don't Know Can Hurt Us – Key Question Is Sustainability Of Protection After The Initial Early Period Post Vaccination

Data from patients who have recovered from COVID-19 show that nAb levels against the virus peak within 3 months and then decrease. This naturally raises the question of whether developing an effective vaccine is possible. The key question for full approval of COVID-19 vaccines is whether the duration of immunity will be sustainable after the first 3 months.

This is critical because when nAb levels fall, there is a risk for vaccine dependent enhancement (VDE) (aka antibody dependent enhancement or ADE). Meaning that the vaccine-generated antibodies become insufficient to confer protection but theoretically can facilitate viral entry into immune cells and lead to increased severity among infected patients compared to placebo by helping the virus infect the person.

While we believe that the risk of VDE is relatively low (our base case is that vaccines are generally tolerable and safe), the need to prove safety beyond the initial few months will translate to full FDA approval no sooner than Q1:21.

FDA's 50% Efficacy Threshold for COVID-19 Vaccines Balances Achievability and Usefulness

As outlined in a guidance document in June 2020, the FDA will require vaccine trials to show >50% efficacy above placebo in the primary endpoint, with the lower bound of the confidence interval above 30%. These thresholds were chosen based on the belief that they are high enough for consumers to agree to take a vaccine yet not so onerous that developers would need years to refine their candidates. In comparison, many approved vaccines have demonstrated far higher efficacy, such as measles (97% effective), pertussis (85%), HPV (90%), and polio (99%). But these vaccines took over a decade or more to develop. The flu vaccine, which is 50% effective in a good year (only 29% effective in the 2018-'19 flu season), provides perhaps a more reasonable benchmark.

We Believe Multiple Vaccines Will Clear 50% Efficacy Hurdle for Full FDA Approval in Q1:21

Phase 1 and 2 vaccine studies have consistently generated nAb titers in excess of convalescent sera, including the candidates from Moderna, Pfizer/BioNTech, AstraZeneca/Oxford and Novavax, among others. We view the FDA efficacy requirement for approval as highly achievable since the common primary endpoint among the ongoing Phase 3 studies is prevention of symptomatic COVID-19 cases. Though the higher bar of prevention of infection (aka full protective immunity) is preferable, prevention of symptomatic cases is sufficient given the urgent societal need.

In line with our base case, Dr. Anthony Fauci stated in early August that a vaccine could end up being only 50-60% effective. In addition, Moderna has powered their Phase 3 trial to achieve 60% efficacy over placebo. We believe that 50-60% efficacy, when combined with some persistent protective public health measures (masks are unlikely go away for the time being) and the current level of herd immunity (not fully known but may be in the 10-20% range in several regions), will be sufficient to provide confidence to return to normal activity.

One risk to this view is the potential for public distrust of vaccines and low levels of inoculation if the approval process is viewed as too politicized and rushed; this is even more reason for the FDA to wait for at least 6 months of data before issuing an approval.

The FDA advisory panel meeting on October 22 to discuss COVID-19 vaccines will be a key event to watch, particularly regarding clarification and/or updates regarding the requirements for full approval.

Allocation to the General Population Not Likely Until Q2/Mid-'21 Given Overall Need

Post approval, vaccines are expected to be rolled out in phases according to the Advisory Committee on Immunization Practices (ACIP) recommendations. Based on the expected ACIP framework for allocation, we expect a vaccine to be available for high-risk populations immediately after Q1:21 approval, followed by distribution to the general population in Q2/mid-'21.

Using influenza vaccine penetration as a guide, we estimate peak penetration in increased risk individuals to be ~65%, with peak penetration in the remaining population to be ~30%.

Despite Pricing Pressure, We See Vaccines Peaking At $4.3B in FY21 With $20B In Cumulative Sales Over Several Years

Vaccines are likely to be significant profit drivers despite low initial pricing based on sizable opportunity and potential for the virus to be a recurring annual threat. Thus far, the U.S. government has secured 800M initial doses (though not all vaccines may succeed) with contracts ranging from $4 to $20 per dose. While it is possible that future pricing will be higher (Moderna has made the case for $32-$37 per dose of its vaccine for "smaller-volume" agreements but just agreed to sell 100M doses for $1.5B excluding another $955M in funding from BARDA), there will be bipartisan pressure to keep prices down, especially for drug makers that have accepted development funding.

Our base case scenario assumes a bolus of vaccine sales in FY21-24, generating peak US and EU vaccine revenue of $4.3B in FY21 before declining to $600M in FY26. The total of vaccine sales in FY21-FY33 is estimated to be $20B.

Initial Pivotal Vaccine Data Expected Q4:20, We Believe Pfizer/BioNTech Vaccine Is The Most Promising Candidate So Far

Moderna, Pfizer/BioNTech, AstraZeneca/Oxford, Inovio, CanSino, Sinovac, and Sinopharm are currently in Phase 2/3 or Phase 3 clinical trials and we expect interim data from each in Q4:20. As of September 4, Pfizer/BioNTech enrolled >25,000 of 30,000 volunteers in its Phase 3 study while Moderna enrolled ~21,000 out of 30,000. Moderna recently noted that it will slow down enrollment to ensure that it will enroll enough diverse patients to be representative of the general population.

We view Pfizer/BioNTech's mRNA vaccine candidate BNT162b2 as the current leader based on strong evidence of both nAb titers and T cell response. Moderna's mRNA-1273 vaccine demonstrated strong nAb titers but had a somewhat disappointing CD8+ T cell response, especially compared to its preclinical data. Oxford/AZN's viral vector vaccine AZD1222, on the other hand, showed an encouraging T cell response but a less robust nAb response.

One important disadvantage of mRNA vaccines is the requirement for cold storage, which could be a significant hurdle to global access and could slow distribution. We envision that only specialized clinics and practices will be able to offer these vaccines by virtue of the need to store them in special coolers or freezers. Moderna has the slight edge in regard to this issue as their vaccine candidate requires -20 degrees Celsius for distribution and can be stored at -5 degrees Celsius for up to 7 days. On the other hand, the candidate from Pfizer/BioNTech requires distribution at -80 degrees Celsius and can only be stored for 24 hours at -5 degrees Celsius, though they are working to develop a formulation that would not require such frigid temperatures.

Vaccine Manufacturing Capacity Potential of ~1.3B Doses in FY20 and 8B Doses in FY21, Though Not All Programs Will Be Successful

Total industry manufacturing capacity has the potential to be ~1.3B doses in FY20 and 8B doses in FY21 by using the low end of company guidance. Even if these production levels are not reached (since not all the programs in development will be successful), we believe there will be enough supply to meet demand based on our expected vaccine penetration.

Neutralizing Antibody Therapies Will Fill the Gaps Around Vaccines

Antibody therapies will start generating data in late September and into the fall. Data from Regeneron/Roche will be first to read out. We believe EUA is possible before YE '20 or in early '21. We expect these antibodies will be used in 3 different ways:

1. high-risk patients who do not get a robust immune response from vaccines (aka elderly and immunosuppressed patients),
2. for prophylaxis in people who were exposed but have not been vaccinated (neutralizing antibodies may offer immediate protection while vaccines may take too long to work), and
3. as a therapeutic after diagnosis early during infection.

As monoclonal antibodies have a relatively long half-life, a single dose of antibody therapy might last up to 2-3 months. In some cases, half-life extended antibodies might last up to 6 months, which will be ideal for prophylaxis.

We Expect Multiple Antibody Therapies To Be Successful – Regeneron/Roche's Antibody Cocktail Is The Most Promising Strategy

Several companies, such as Regeneron/Roche, Eli Lilly/Abcellera/Junshi, Vir/GSK, AstraZeneca, Celltrion, Amgen, BeiGene/Singlomics, and AbbVie, are currently in the race for developing neutralizing antibodies against SARS-CoV-2 for prophylactic and therapeutic uses. Eli Lilly/Abcellera/Junshi and Regeneron/Roche have advanced their programs into pivotal trials. Celltrion, Vir/GSK, and AstraZeneca entered the clinic in July/August.

These companies are using different approaches to develop the antibody therapies, such as single antibody vs two antibody cocktail, IV injection vs SQ/IM injections, targeting receptor binding domain (RBD) vs. targeting other regions of the spike protein, identifying candidates from plasma of convalescent patients vs from genetically humanized mice, etc.

We consider Regeneron/Roche's REGN-COV2 cocktail strategy as the most promising. The cocktail is composed of two antibodies that bind two distinct epitopes on the RBD of spike protein. It is expected to enhance the potency and avoid resistance due to viral mutation based on preclinical data.

We Expect Initial Clinical Data In September - Pivotal Data Expected By YE:20

Regeneron/Roche plan to report initial data from the treatment trials by the end of September. Vir/GSK, Celltrion, and AstraZeneca also have plans to report pivotal data by YE:20.

Companies such as Lilly, Vir/GSK, Celltrion, and BeiGene/Singlomics also announced plans to start new prevention/treatment trials in H2:20.

We anticipate that antibody therapy will be effective for a short period of time, given prior experience with Ebola and other coronaviruses. We note that the key is the durability of immunity as recent data showed that nAb titers drop rapidly after 3 months of symptom onset in recovered COVID-19 patients. Hence, we envision that use for prophylaxis will require repeated dosing.

Interim Data Could Lead To EUA For Antibody Therapy Around YE:20 – We Assume Wide Adoption To Start In The High-Risk Population In FY21

We think it is possible that the FDA will give emergency use authorization (EUA) to one or more antibody therapies upon initial pivotal data with 2-3 months of follow-up around YE:20.

Recall, the FDA provided EUA for convalescent plasma therapy in late August based on underwhelming retrospective data despite many concerns, likely fueled by political pressure.

We anticipate that the FDA will likely require 1-5 years follow-up of efficacy and safety for the full approval based on prior experience of the Ebola vaccine.

Upon the EUA, we envision that the initial uptake will be in the high-risk populations, such as people in senior homes, immune-compromised people, households of diagnosed patients, and healthcare workers.

Antibody Therapy As Prophylaxis Is a Lucrative Opportunity With Estimated Peak Sales Of ~$1.7B In FY21

In the prophylaxis segment, we estimate launch in early FY21 with a conservative price of $125 per dose in the US and $75 per dose in EU (60% of the US price). We assume that people will require 2 doses of prophylaxis per year on average. We project the peak global sales to be ~$1.7B in FY21 with 10% penetration in the high-risk people who are not vaccinated.

Using Neutralizing Antibodies As Therapeutics Is a $1.2B Opportunity But With Potential Upside

We anticipate that the pricing for antibody therapies will be set by milligrams, syringe, or vial size. Hence there will be a different price point for prophylaxis and therapeutic uses. We anticipate that the per dose price might be higher for treatment compared with prophylaxis as a higher dose is likely needed for antibody treatment to elicit stronger antiviral responses in the symptomatic patients.

We project sales to peak at ~$1.2B in FY21 with 30% penetration in the symptomatic COVID-19 patients (hospitalized and non-hospitalized patients) at a price of $750 per patient in the US and $450 per patient in EU (6X of the prophylaxis cost on the per dose basis).

We Model Total Antibody Sales To Peak At $2.9B In FY21 Based On Our Base Case Assumptions – REGN/RHHBY's REGN-COV2 Could Reach $1.5-$2B in FY21 – AZN's AZD7442 Started Phase 1 In Late Aug

Based on our base case assumptions, we project total antibody sales to reach the peak of ~$2.9B in FY21, then decline to ~$270-280M in FY27 and roughly stabilize at that level

onward. We anticipate that Regeneron/Roche could garner $1.5-$2B of that market in FY21 with their antibody cocktail.

We estimate the total of antibody sales in FY21-FY33 to reach $10B. In our view, antibody cocktails from REGN/RHHBY REGN-COV2 (in the lead with data in late Sept) or AZN 's AZD7442 (started Phase 1 in late Aug) will dominate this segment.

Antibody Manufacturers Are Scaling Up Their Production Capacity To Meet The High Demand – We Estimate Tens Of Millions Of Doses Will Be Needed By 2021

Overall, we estimate the annual demand in the US will be ~156k treatment doses for hospitalized patients, ~4.4M treatment doses for non-hospitalized symptomatic patients, and ~87M preventative doses for the high-risk population in FY21.

Multiple antibody companies have already started to scale up their manufacturing capacity due to the high unmet need. We anticipate that these companies will have the capacity of collectively delivering tens of millions of doses in 2021.

We See A Solid Opportunity For Gilead's Veklury With $3.6B Peak Sales In FY20

We see an opportunity for drugs, such as Gilead's Veklury (remdesivir), that target COVID-19 disease at different stages. Based on the reported data, antiviral drugs tend to have more success in mild to moderate patients, while immunosuppressants might be more effective in the severe to critical patients.

This is consistent with the hypothesis that antiviral therapy will be more effective in the early stage of the infection while viral replication is the primary driver, and immunosuppression will be more effective in the late stage of the disease when hyperactive immune responses drive the pathology.

We expect Veklury to remain part of the standard of care for hospitalized patients for the foreseeable future, but we project that the number of hospitalized patients will decline after the first effective vaccine is launched. Our model assumes that happens in 2021. Based upon these assumptions, we project Veklury revenues of $3.6B, $2.1B, $1.4B, $1.0B, and $750MM for 2020-'24.

BREAKING THE COVID-19 CURVE: WHY WE ARE OPTIMISTIC ABOUT VACCINES AND THERAPEUTIC ANTIBODIES

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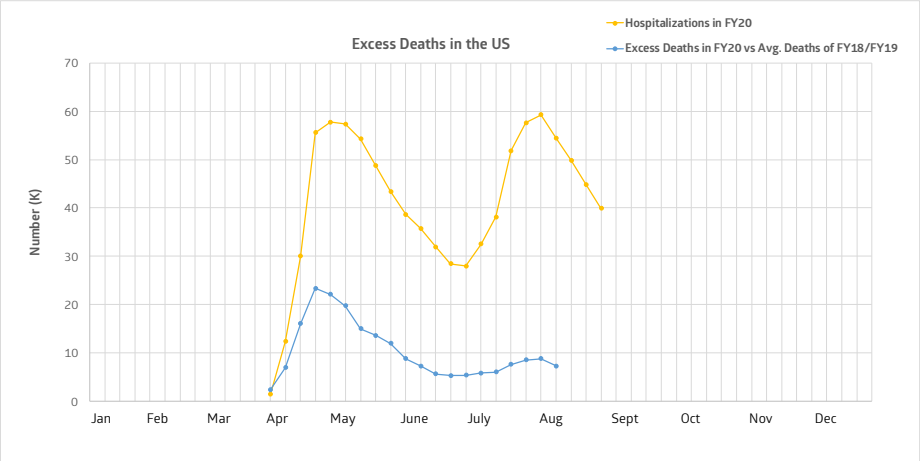
Transitioning From Bending To Breaking The Curve

The formula for bending the curve has been validated at this point—social distancing, masks, washing hands, etc. We have also seen improvements in outcomes as our health care system becomes more experienced and better equipped at handling COVID-19 patients, as evidenced by the moderation of excess deaths since June despite the recent spike in cases and hospitalizations.

Recent Spike Of Cases/Hospitalizations In July/August Has Not Led To An Increase In Excess Deaths



Source: Cowen and Company, CDC

Tracking excess deaths is a useful way to account for potential underreporting of COVID-19 deaths outside of the hospital.

We believe the lack of a surge in excess deaths in July/August in conjunction with the spikes of cases and hospitalizations was due to better clinical care and the fact that the spike was primarily driven by a rapid growth of infections in young people.

To go from bending the curve to breaking the curve, we will need the successful development of vaccines and therapeutics that have the ability to prevent or diminish the severity of COVID-19 disease. We expect the number of hospitalized patients and excess deaths to decrease significantly over time as vaccines and antibody therapies become widely available.

Another Wave Possible But Should Subside As Vaccines Are Launched In Early/H1:21

It is possible that we will see another case resurgence in the US and Europe as schools resume and people go back indoors when the cooler weather arrives. But we are optimistic that the pandemic will get under control in early/H1:21 when vaccines are launched that should both reduce the rate and severity of infections.

Vaccines and Therapeutic Antibodies for COVID-19

Vaccines Vs Neutralizing Antibodies: Friends Or Frenemies?

Vaccines should be available for emergency use in Q4:20, high-risk populations in Q1:21 and the general population in Q2/mid-'21.

With the potential for further case spikes on the horizon and reclosing the economy off the table, the urgency for expeditious development of vaccines and therapeutics has never been higher. We are optimistic that multiple vaccine candidates will prove safe and effective, with lessons from past vaccines informing strategies to mitigate the risk of antibody-dependent enhancement (ADE). Vaccines should be available for emergency use in Q4:20, high-risk populations in Q1:21 and the general population in Q2/mid-'21. Antibody therapies will beat vaccines to market but will be highly competitive and their utility will suffer once vaccines become available.

Nevertheless, we see a role for both modalities as vaccines are not likely to confer full immunity, and patients will benefit from quick onset, passive immunity with a neutralizing antibody upon exposure. Alternatively, patients who are likely to see a weak immune response from a vaccine (e.g. elderly, nursing home residents, immunocompromised individuals) could benefit from getting a prophylactic dose of a neutralizing antibody.

Road to Recovery Goes Through Vaccines and Therapeutic Antibodies

If reopening the economy after the prolonged shutdown was the end of the beginning, then the successful development of vaccines and therapeutic antibodies has the potential to be the beginning of the end.

The confidence for consumers to resume any semblance of a pre-virus level of activity will require vaccines or therapeutics that can be used prophylactically to prevent spread or at least mitigate disease severity. Drugs like Gilead's Veklury (remdesivir), which may decrease the length of hospitalization and modestly improve the need for oxygen therapy, certainly represent progress but will do little to assuage the public fear of contracting the virus. True confidence will require safe and effective vaccines or therapeutics that can be used prophylactically to prevent spread, and effective oral or subcutaneous (SQ) therapies that would be used upon diagnosis in the outpatient setting to prevent spread and reduce hospitalizations.

Vaccine Development Is In Hyperdrive And Will Have Bumps

As biopharma companies are progressing at a historic pace, including several with unproven technologies, there may likely be a high rate of failure among the over 150 vaccine candidates currently being studied. But that is ok and should in fact be expected and encouraged. The good news is that government and public funding in the U.S. and Europe and motivated regulatory agencies is expediting the time to market without sacrificing safety. More so, these funding sources are willing to partake in the risk associated with starting production months before final results are confirmed.

Based on current progress, we expect at least one vaccine to be available for emergency use in Q4:20 (potentially in Nov/Dec) and multiple vaccines available for high-risk populations (such as elderly, nursing home residents, immunocompromised and patients with diabetes, high cardiovascular risks and renal failure), healthcare workers and those whom have been exposed in Q1:21. Inoculation of the general public will likely not begin until Q2/mid-'21, thereby giving us some roadmap as to when economic recovery will start.

A risk to the timing of the economic recovery pivots on the timelines for manufacturing scale up, but companies are making faster than expected progress on that front with several billion doses possible by the end of 2021 from Pfizer/BioNTech, Moderna, JNJ, AstraZeneca/Oxford University, Novavax, and GSK among others.

Importantly, there could be a bottleneck in production if the raw materials become difficult to source. We estimate that hundreds of millions or even billions of doses will be needed since it is unlikely for the world to reach herd immunity in the next 1-2 years at the current infection rate.

mRNA Vaccine Candidates Lead The Pack, Pfizer/BioNTech's BNT162b Most Promising Candidate So Far

With persistent hotspots around the world and potentially a 2-dose vaccine regimen required, we expect there will be multiple vaccines (likely of different types) approved in order to address the enormous worldwide need. The early data supports mRNA, viral vector and protein subunit vaccines as potentially successful modalities.

Should a SARS-CoV-2 mutation require updated vaccines in the future, mRNA vaccines can be updated immediately once the new viral genome is sequenced.

As a group, we believe the mRNA vaccines are the current leaders. Candidates from Moderna and Pfizer/BioNTech have been among the quickest to enter clinical trials owed to their rapid construction and generic manufacturing process. Candidates of other modalities are mostly set to complete their pivotal trials after these 2 mRNA vaccines (with exception of AstraZeneca/Oxford's AZD1222), which we expect will result in a higher bar for their approval.

In addition to their rapid development, mRNA vaccines have multiple advantages and relatively few disadvantages relative to other vaccine modalities.

Key Question Is Timing Of Vaccine Approval

There are many reports of the growing "politicization" of the vaccine approval process in the U.S. amidst the Presidential elections in November. While President Trump announced that a vaccine will be approved by that point, it is not clear whether data will be ready to support Emergency Use Authorization (EUA) or accelerated approval based on surrogate markers (such as neutralizing antibody and/or T cell levels) that will be measured in the early period (first 3 months) after immunization.

The key question for full approval is the sustainability of immunity in the period following the first 3 months when neutralizing antibody levels typically fall.

However, the key question for full approval is the sustainability of immunity in the period following the first 3 months when neutralizing antibody levels typically fall. At that period, the risk for vaccine dependent enhancement (VDE) (aka antibody dependent enhancement or ADE) rises as these neutralizing titers fall.

What is encouraging is that companies such as AstraZeneca announced in early September their commitment to patient safety and noted that they are not in a rush to getting a vaccine approved prematurely.

Pfizer/BioNTech noted that they can start the submission for approval to FDA as early as in October based on interim data from the ongoing Phase 3 studies. Pfizer also iterated their commitment to not filing before they have the required data.

A common announcement from several companies that are participating in Operation Warp Speed is expected imminently regarding their position not to file prematurely despite the heightened political pressure.

In our view, it will likely take into late '20 or early '21 for a vaccine to be approved and available in the supply channels.

In terms of vaccine allocation, the National Academy of Medicine has outlined an ethical framework based on lessons learned from prior mass vaccination campaigns as well as the allocation of scarce medical resources during the COVID-19 pandemic. The authors recommend a phased approach to vaccine apportionment, with best efforts made to

complete each phase before proceeding to the next. The ACIP held a public hearing on August 26 about the plan for vaccine rollout. A vote on this interim prioritization scheme is expected on September 22 for approval ahead of CBER's Vaccine & Related Biological Products (VRBP) advisory committee meeting scheduled for October 22 to discuss COVID-19 vaccines.

Ethical Framework For Equitable Allocation of COVID-19 Vaccine

	Phase 1	Phase 2	Phase 3	Phase 4
Groups	**Phase 1a:** ▪ High-risk workers in health care facilities ▪ First responders **Phase 1b:** ▪ People with underlying conditions that put them at significantly higher risk ▪ Older adults living in congregate settings	▪ Workers in essential industries at high-risk of exposure ▪ Teachers and school staff ▪ People with underlying conditions that put them at moderately higher risk ▪ Older adults not in Phase 1 ▪ People and staff in shelters, prisons or group homes	▪ Young adults ▪ Children ▪ Workers in essential industries not in Phase 1 or 2	▪ Anyone not in Phase 1-3
Estimated Proportion of U.S. Population	Phase 1a: 5% Phase 1b: 10%	30-35%	40-45%	5-15%

Source: National Academies of Sciences, Engineering, and Medicine 2020. Discussion Draft of the Preliminary Framework for Equitable Allocation of COVID-19 Vaccine. Washington, DC: The National Academies Press; Cowen and Company

Justified Optimism Based on Early Vaccine Data

In an era of unprecedented scientific progress bred out of necessity amid a pandemic, early vaccine data has surpassed initial expectations. Phase 1 and 2 vaccine studies have consistently generated neutralizing antibody (nAb) titers in excess of convalescent sera reference values, including the candidates from Moderna, Pfizer/BioNTech, AstraZeneca/Oxford and Novavax, among others. In addition, the vaccines appear to have favorable tolerability, including in the elderly population.

We are optimistic that vaccines will protect against symptomatic infection in the early period (at least 2-3 months) post-vaccination.

Based on the robust nAb responses, as well as some preliminary T cell data, we are confident that some degree of immunity will be provided in the early period (at least 2-3 months) post-vaccination; the most likely level of immunity, in our view, is for protection against symptomatic COVID-19 disease. Full protective immunity, meaning prevention of infection completely, is a much higher bar and thus less likely.

What We Don't Know Can Hurt Us – Key Question Is Sustainability Of Protection After The Initial Early Period Post Vaccination

There is currently no way to predict efficacy beyond the initial post-vaccination period. While we can reasonably surmise that the peak nAb levels (occurring within a few weeks of administration) will be sufficient for immune protection, only Phase 3 trials can shed light on the exact antibody threshold that confers protection.

Ph3 trials cannot be rushed as we must test outcomes once antibody titers have waned to sub-neutralizing concentrations.

As antibody levels naturally wane over time, it remains to be seen how individuals with sub-neutralizing antibody concentrations will fare. The presence of antibodies that are insufficient to neutralize the virus can potentially be worse than having no antibodies at all, a phenomenon known as antibody-dependent enhancement (ADE).

In our view, positive interim data from the early period (<3 months) of a Phase 3 trial is important but not sufficient for full approval. The most critical data will come several months after vaccination when individuals with sub-neutralizing antibody titers are exposed to the virus. The WHO, for example, has requested vaccine efficacy for a

Data on memory B and T cells is currently lacking.

minimum of 6 months in order to properly assess durability and lack of harm. The hope is that memory B and T cells will be present to reignite the immune system upon exposure to the virus.

We Expect Multiple Vaccines Will Be Approved To Address The Worldwide Need

Confidence in being asymptomatic or minimally symptomatic will be sufficient for resumption of normal activity.

The common primary endpoint among the ongoing Phase 3 studies is prevention of symptomatic COVID-19 cases. Preventing seroconversion (which would include asymptomatic cases) is a secondary endpoint and will be examined in only a subset of trials. As mentioned above, we are confident that multiple trials will be successful in this primary endpoint. Though full protective immunity is the pinnacle achievement, prevention of symptomatic cases is sufficient given the urgent societal need.

The downside to partial protection from a vaccine is the potential to still infect others, specifically unvaccinated individuals. If contagiousness is at least somewhat diminished in a vaccinated individual that seroconverts, then the non-vaccinated population will derive benefit from widespread inoculation (i.e., herd immunity).

We Believe Scenario 2 Is the Most Likely Outcome Among Successful Vaccine Candidates And Will Allow Accelerated Economic Recovery

	Possible Vaccine Effectiveness Scenarios				
	Scenario 1	Scenario 2	Scenario 3	Scenario 4	Scenario 5
Level of immunity	Full protective immunity	Protection against symptomatic disease	Protection against symptomatic disease	Protection against severe disease	No protection
Risk of becoming infectious to others	Negligible	Decreased	Unchanged	Unchanged	Unchanged
Vaccinated individuals will be comfortable resuming activity	+++	++	++	+	
Non-vaccinated individuals will benefit from herd immunity	+++	+			

Source: Cowen and Company

We Believe Pfizer/BioNTech Vaccine Is The Most Promising Candidate So Far

Among the vaccines that have been first to publish data, we view Pfizer/BioNTech's BNT162b as the current leader based on strong evidence of both nAb titers and T cell response. Moderna's mRNA-1273 demonstrated strong nAb titers but had a somewhat disappointing CD8+ T cell response, especially compared to its preclinical data. Oxford/AZN's vaccine (AZD1222), on the other hand, showed an encouraging T cell response, but a less robust nAb response. Though the significance of CD8+ activity for protective immunity remains unknown, it is helpful at this stage to compare across the vaccines in development. Novavax's NVX-CoV2373 is certainly in the hunt after demonstrating very impressive nAb titers, however CD8+ activity was not assessed, and the company is behind in development (Phase 3 trial is planned to start in October).

Due to lack of standardization in the assays used, comparing the early data across different studies is inherently difficult. Reference to convalescent serum provides a useful benchmark, though not all studies include this data. Of note, the FDA cutoff for use of convalescent plasma therapy is nAb titers of ID_{50} ≥160.

Early Data Across Different Vaccine Trials

Vaccine	mRNA-1273			BNT162b1			AZD1222		NVX-CoV2373		Ad5-nCoV		CoronaVac				Unnamed	
Developer(s)	Moderna			Pfizer/BioNTech			AstraZeneca/Oxford		Novavax		CanSino		Sinovac				Sinopharm/Wuhan Inst	
Modality	mRNA vaccine (full S protein, modRNA)			mRNA vaccine (RBD subunit, modRNA)			ChAdOx1-vectored vaccine (full S protein)		Protein subunit vaccine (trimeric full S protein)		Ad5-vectored vaccine (full S protein)		Inactivated whole-virus				Inactivated whole-virus	
Dose Regimen	25ug (Day 1, 28)	100ug (Day 1, 28)	250ug (Day 1, 28)	10ug (Day 1, 21)	30ug (Day 1, 21)	100ug (Day 1)	$5x10^{10}$vp (Day 1)	$5x10^{10}$vp (Day 1, 28)	5ug + MM1 (Day 0, 21)	25ug + MM1 (Day 0, 21)	$5x10^{10}$vp (Day 1)	$1x10^{11}$vp (Day 1)	3ug + alum (Day 0, 14)	3ug + alum (Day 0, 28)	6ug + alum (Day 0, 14)	6ug + alum (Day 0, 28)	5ug + alum (Day 0, 14)	5ug + alum (Day 0, 21)
n	15	15	15	12	12	12	533	10	29	28	129	253	120	120	120	120	42	42
nAb Response (live SARS-CoV-2)																		
Magnitude (IC_{50})				Convalescent Serum: 94			No CS reference				No CS reference		Convalescent Serum: 164				No CS reference	
Time post final vaccine dose																		
0 or 1 day	-	-	-	13	29	10	-	256	-	-			-	-	-	-	-	-
7 or 8 days	-	-	-	168	267	10	-	-	-	-			-	-	-	-	-	-
14 or 15 days	-	-	-	180	437	-	-	372	-	-			28	-	35	-	121	247
21 or 22 days	-	-	-	-	-	33	-	-	-	-			-	-	-	-	-	-
28 or 29 days	-	-	-	-	-	-	201	-	-	-	18	20	24	~46	~29	65	-	-
Magnitude (IC_{80})	Convalescent Serum: 158						No CS reference											
Time post final vaccine dose																		
0 or 1 day	-	-	-	-	-	-	-	70	-	-	-	-	-	-	-	-	-	-
7 or 8 days	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
14 or 15 days	340	654	-	-	-	-	-	136	-	-	-	-	-	-	-	-	-	-
28 or 29 days	-	-	-	-	-	-	51	-	-	-	-	-	-	-	-	-	-	-
Magnitude (IC_{99})									Convalescent Serum: 984									
Time post final vaccine dose																		
0 or 1 day	-	-	-	-	-	-	-	-	103	126	-	-	-	-	-	-	-	-
7 or 8 days	-	-	-	-	-	-	-	-	3906	3305	-	-	-	-	-	-	-	-
nAb Response (pseudotype virus)																		
Magnitude (IC_{50})	Convalescent Serum: 109						Convalescent Serum: ~400				No CS reference							
Time post final vaccine dose																		
0 or 1 day	12	18	21	-	-	-	-	163	-	-	-	-	-	-	-	-	-	-
7 or 8 days	106	256	374	-	-	-	-	334	-	-	-	-	-	-	-	-	-	-
14 or 15 days	112	344	332	-	-	-	-	451	-	-	-	-	-	-	-	-	-	-
28 or 29 days	81	232	270	-	-	-	88	-	-	-	55	61	-	-	-	-	-	-
Magnitude (IC_{80})	Convalescent Serum: 43																	
Time post final vaccine dose																		
0 or 1 day	10	10	12	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
7 or 8 days	53	121	158	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
14 or 15 days	60	154	141	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
28 or 29 days	39	110	121	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
PBMC or CD4+ T-Cell Response																		
Magnitude (IFNγ spots/million PBMCs)																		
Time post final vaccine dose																		
0 or 1 day	-	-	-	-	-	-	-	529	-	-	-	-	-	-	-	-	-	-
7 or 8 days	-	-	-	~720 across doses 1-50ug			183	445	-	-	-	-	-	-	-	-	-	-
14 or 15 days	-	-	-	-	-	-	856	-	-	-	-	-	-	-	-	-	-	-
28 or 29 days	-	-	-	-	-	-	554	614	-	-	100	110	-	-	-	-	-	-
56 or 57 days	-	-	-	-	-	-	424	-	-	-	-	-	-	-	-	-	-	-
CD8+ T-Cell Response																		
Magnitude (IFNγ spots/million PBMCs)																		
Time post final vaccine dose																		
7 or 8 days	-	-	-	~500 across doses 1-50ug			-	-	-	-	-	-	-	-	-	-	-	-

vp= viral particles; MM1 = Matrix-M1 adjuvant; alum = aluminum hydroxide adjuvant

Source: Cowen and Company

Cold Storage Supply Requirements For mRNA Vaccines Will Limit Number Of Sites That Can Offer These Modalities – Moderna Has The Edge Over Pfizer/BioNTech

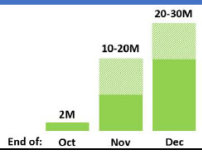
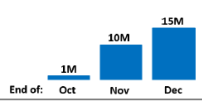
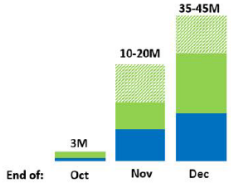
mRNA vaccines require cold-chain storage which is a significant hurdle to global access. Within the group, however, there are variable distribution requirements. The candidates from Pfizer/BioNTech require distribution at -80 degrees Celsius, though they are working to develop a formulation that would not require such frigid temperatures. They can also only be stored at 5 degrees Celsius for up to 24 hours.

Moderna's vaccine candidate, on the other hand, possesses a less onerous requirement for distribution (-20 degrees Celsius) and storage (can be stored at 5 degrees Celsius for up to 7 days). mRNA-1273 is also likely easier to handle as it does not require using a diluent to reconstitute the vaccine prior to injection.

As a result, we envision that only specialized clinics and practices will be able to offer these vaccines by virtue of the need to store them in special coolers or freezers.

Planning Around Vaccines With Cold Storage Supply Requirements:

Pfizer/BioNTech's BNT162b2 Fits Into Candidate "A" Profile, Moderna's mRNA-1273 Fits Into Candidate "B" Profile

Scenario	Cumulative Doses available	Distribution requirements	Administration
1. **Vaccine candidate A** is the first to demonstrate safety & efficacy		• **Shipped direct at --70-80°C** on dry ice, to be used within 10 days	• Vaccine can be stored at 2-8°C for 24 hours • 6 hour shelf life at room temperature • Unique diluent / kit requirements • Only shippable to large admin sites
2. **Vaccine candidate B** is the first to demonstrate safety & efficacy		• **Central distro capacity at -20°C,** may be stored for months at -20°C	• Vaccine can be stored at 2-8°C for 7 days • 6 hour shelf life at room temperature
3. Vaccine candidates A and B demonstrate safety & efficacy		• As above	• Administration site considerations as above • Complexity increases significantly if sites are administering 2 products with different requirements and differing dose schedules

Source: CDC Presentation, August 2020

mRNA Vaccines Offer Superior Advantages Over Other Vaccine Modalities

Other than their need for cold storage, mRNA vaccines have multiple advantages and relatively few disadvantages relative to other vaccine modalities.

Pros and Cons Based on Vaccine Modality

Modality • Developers	Pros					Cons				
	Rapid vaccine construction	No handling of infectious material	Amplification*	Can be used in immunocompromised subjects	History of approved vaccines	Risk of genomic integration	Requires specialized administration	Requires cold chain storage	Requires adjuvant	Preexisting antibodies to vector possible
DNA Vaccine • Inovio • Genexine	✓	✓	✓	✓	X	✓	✓	X	X	X
mRNA Vaccine • Moderna • Pfizer/BioNTech • CureVac • Translate Bio/Sanofi	✓	✓	✓	✓	X	X	X	✓	X	X
Viral Vector (Replicating) • Merck	X	X	✓	X	✓	✓	X	X	X	✓
Viral Vector (Non-replicating) • AstraZeneca/Oxford • CanSino • Johnson & Johnson	X	X	✓	✓	X	✓	X	X	X	✓
Whole Virus (Inactivated) • Sinovac/Dynavax • Sinopharm • IMBCAMS**	X	X	X	X	✓	X	X	X	X	X
Protein Subunit • Novavax/Emergent Bio • Clover/Dynavax/GSK • Sanofi/GSK	X	✓	X	✓	✓	X	X	X	✓	X
Virus-like Particles • Medicago/GSK	X	✓	X	✓	✓	X	X	X	X	X

*Amplification = # of protein antigen molecules produced per molecule of vaccine delivered
**IMBCAMS = Institute of Medical Biology at the Chinese Academy of Medical Sciences

Source: Cowen and Company

If Significant SARS-CoV-2 Mutations Occur, Genetic Vaccines Will Be Best Equipped To Rapidly Produce An Updated Vaccine

Genetic vaccines have a distinct advantage over other modalities in terms of turnaround time if/when a new vaccine is required due to viral escape. These vaccines are engineered to introduce genetic material (DNA or mRNA) that codes for a protein (whole protein or subunit part of the whole protein) that will then circulate in the body. Production of a reengineered vaccine can begin immediately as the only requirement is for the genetic sequence of the updated target protein be entered into a computer.

Thus, if a SARS-CoV-2 strain requires an updated vaccine, the genetic vaccine developers (Moderna, Pfizer/BioNTech) that produce a successful vaccine with their current version will be best positioned to grab market share in the future.

FDA Guides 50% Efficacy Hurdle for Vaccines Though Likely To Be A Moving Target

The FDA has guided that >50% efficacy over placebo will be needed for approval.

The FDA recently published guidance on clinical trial design for COVID-19 vaccine studies, which requires the primary efficacy endpoint point estimate to be >50% above placebo with a lower bound of the appropriately alpha-adjusted confidence interval of >30%. We believe this bar could be elevated in the future if any vaccine candidates demonstrate very strong data, though at first regulators will be incentivized to approve multiple vaccines to meet demand. By comparison, the WHO has called for 70% efficacy with a lower bound of 50% for at least 6 months.

By comparison, the WHO has called for 70% efficacy with a lower bound of 50% for at least 6 months.

Thus far, most pivotal studies are enrolling 30,000 subjects per study except JNJ announced plans to commence in late September a 60,000 subject pivotal study to massively overpower to boost the chance for success. Moderna has shared that its Phase 3 COVE trial (n=~30,000) commenced in July and is powered to demonstrate a 60% improvement over placebo for the primary endpoint of prevention of symptomatic confirmed COVID-19 disease.

During a recent client conference call that we hosted, when asked if the FDA would consider approval for a vaccine that does not meet the 50% threshold but has a confidence interval with a lower bound that is still above 30%, our consultant noted that this scenario would be unlikely but should warrant approval if other vaccines are producing data in the same range. The FDA figures that for a trial size of ~30,000 participants, it would be hard to miss the 50% level but still hit the 30% lower bound criteria. Larger studies with over 100,000 participants could potentially have a primary efficacy endpoint estimate in the 40% range and a confidence interval with a lower bound above 30%.

In contrast to vaccines failing to meet the FDA guidance, our consultant believes that the bar could be elevated if any vaccine candidates demonstrate very strong data. In a scenario where one vaccine shows efficacy that is 80% above placebo while another vaccine is 55% above placebo (assuming both meeting the confidence interval criteria and safety is comparable), our consultant believes the FDA may approve both vaccines at first while supply remains limited and having multiple vaccines would be helpful from a global health perspective. However, once supply is no longer constrained, 80% would become the new bar for approval.

FDA Signals It May Not Need An AdCom For COVID-19 Vaccine But Won't Cut Corners

The FDA appears to be leaning toward forgoing an advisory committee meeting for the first SARS CoV-2 vaccine and using the emergency use authorization (EUA) prior to the submission of a full BLA. At the same time the agency is making it clear that the review process will still rely on standards of evidence analogous to a full BLA.

The agency delivered that message indirectly at the CDC & ACIP meeting on July 29. The FDA is clearly trying to run a fine line between making it clear they are moving as fast as humanly possible while also making it clear that they are not cutting corners or bowing to political pressure.

The FDA is planning to hold an advisory panel meeting on October 22nd to discuss COVID-19 vaccines.

See Cowen's WRG note on this here.

Several Companies Have Entered Pivotal Studies, Initial Data Expected Q4:20

Moderna, Pfizer/BioNTech, AstraZeneca/Oxford, Inovio, Sinovac, and Sinopharm are currently in Phase 2/3 or Phase 3 clinical trials. The primary endpoint across the trials (though Sinopharm design not explicit) is the number of PCR confirmed symptomatic COVID-19 cases in the treatment arm vs placebo arm. Secondary efficacy endpoints are less consistent across the studies, but several will evaluate the frequency of severe cases and antibody titers.

Pivotal Study Designs Of The Five Most Advanced Vaccine Candidates

Vaccine	BNT162b2	AZD1222	mRNA-1273
Developer(s)	Pfizer/BioNTech	AstraZeneca/Oxford	Moderna
Modality	mRNA	Adenoviral Vector	mRNA
Current Phase	Ph2/3	Ph2/3	Ph3
Trial ID	NCT04368728	NCT04400838	NCT04470427
n	30,000	10,260	30,000
Population	Age 18 to 85 without immunocompromised state or unstable medical condition	Age 5 and above without immunocomprised state or severe disease	Age 18 and above without immunocomprised state or unstable medical condition
Study Arms/Dose	BNT162b2 (2 doses of 30 µg, IM) vs. placebo	AZD1222 (1-2 doses 5 x 10^{10} vp, IM) vs placebo	mRNA-1273 (2 doses of 100 µg, IM) vs. placebo
Primary Endpoint	Confirmed symptomatic COVID-19 cases (up to 2 yrs)	Confirmed symptomatic COVID-19 cases (6 months)	Confirmed symptomatic COVID-19 cases (up to 2 yrs)
Secondary Endpoints	▪ Confirmed COVID-19 cases (by CDC-defined symptoms) ▪ Confirmed severe COVID-19 cases ▪ SAEs by 6 months	▪ SAEs by 6 months ▪ IFN-gamma (T-cell) response to S protein ▪ Ab titers to S protein (seroconversion rate) ▪ nAb titers to live/pseudotype SARS-CoV-2	▪ Severe COVID-19 cases ▪ Infection by SARS-CoV-2 ▪ SAEs by 2 years ▪ nAb and S-protein specific binding Ab titers
Estimated Initial Data Readout	October-20	October-20	December-20

Vaccine	CoronaVac	Unnamed
Developer(s)	Sinovac	Sinopharm/Wuhan Inst
Modality	Inactivated Whole Virus	Inactivated Whole Virus
Current Phase	Ph3	Ph3
Trial ID	NCT04456595	ChiCTR2000034780
n	8,870	15,000
Population	Healthcare workers age 18 and above without immunocompromised state or unstable medical condition	Age 18 and above without immunocomprised state or unstable medical condition
Study Arms/Dose	CoronaVac (2 doses of 3 or 6 µg, IM) vs placebo	Unnamed vaccine (2 doses of 5 µg, IM) vs placebo
Primary Endpoint	Confirmed symptomatic COVID-19 cases (up to 1 yr)	"Protective efficacy against COVID-19"
Secondary Endpoints	▪ Confirmed severe COVID-19 cases ▪ Cell mediated immune response by 1 month ▪ SAEs by 1 year	▪ Severe COVID-19 cases ▪ Ab titers against SARS-CoV-2 at 2 weeks ▪ SAEs by 1 year
Estimated Initial Data Readout	October-20	Q4:20

Source: Cowen and Company

Interim Data Readouts In Q4:20 Should Lead To EUA in Late '20 Or Early '21 Due To Political Pressure

Given the political backdrop, there will be pressure on FDA to provide emergency use authorization (EUA) to one or more vaccines around the time of the election. *The New York Times* reported in early September that the Centers for Disease Control and Prevention (CDC) has been reaching out to states to prep them ahead of a potential vaccine rollout by November 1st.

Based on enrollment in the Phase 3 studies thus far, the interim data will include an average duration of follow-up of <3 months. As mentioned above, we believe there will be signal for efficacy during this early window. As a result, the agency may feel compelled to give EUA at that time.

Pfizer/BioNTech And Moderna Are Most Likely To Get EUA First – AstraZeneca Takes A Stand On Patient Safety

Pfizer/BioNTech and Moderna are likely to get EUA first. AstraZeneca takes a stand in support of patient safety.

As of September 4, Pfizer/BioNTech enrolled >25,000 of 30,000 volunteers in its Phase 3 study while Moderna enrolled ~21,000 out of 30,000 in its Phase 3 study. These two vaccines are the most likely to get EUA first.

Interestingly, in early September, AstraZeneca made two public announcements iterating their intention to expand their global Phase 3 studies to 50,000 volunteers and

continue to enroll the 30,000 Phase 3 study in the U.S. In addition, the company voiced its commitment to patient safety and to following responsible drug development practices to ensure that a vaccine is not offered until it was tested adequately. These statements were in response to press reports alleging that their vaccine is also likely to get EUA based on initial Phase 1/2 data from a European study.

Hard Clinical Endpoints Will Be Needed To Support Full Approval

Vaccines should be available for emergency use as early as in late Q4:20, high-risk populations in Q1:21, and the general population in Q2/mid-'21.

For full approval, it is likely that at least 6 months of follow-up will be necessary in our view. This will hopefully provide sufficient data on the outcomes of vaccinated individuals exposed to SARS-CoV-2 after initial nAb levels have waned. We believe this will be a Q1:21 event.

Confidence that vaccination is not likely to exacerbate disease will be key as consumers weigh the decision of whether to get the vaccine. This long-term risk is a distinct consideration from the short-term tolerability concern (typically measured in the days to weeks post-vaccination) that has been addressed in Phase 1 and 2.

If a vaccine is approved in Q1:21, distribution will be based on the ACIP allocation framework as mentioned above. Based on availability, inoculation of the general population will likely begin in Q2/mid-'21. The timeframe could be accelerated if multiple vaccines receive approval.

In addition to interim data from pivotal studies, Q4:20 will be filled with catalysts for many of the most advanced programs.

Upcoming Milestones And Manufacturing Expectations For Vaccine Candidates

Modality	Vaccine Name	Developer(s)	Immunologic Target	Current Phase	Potential News	Estimated Timing	Manufacturing Expectations
mRNA	mRNA-1273	Moderna	Full S protein	Ph3	Complete Phase 3 Enrollment Initial Phase 3 Data Regulatory Approval	September-20 December-20 Q1:21	500M to 1B doses per year in 2021
	BNT162b2	Pfizer/BioNTech	Full S protein	Ph2/3	Complete Phase 2/3 Enrollment Initial Phase 3 Data Regulatory Approval	September-20 October-20 Q1:21	100M doses by YE20, 1.3B doses in 2021
	CVnCoV	CureVac	Full S protein	Ph1	Phase 1 Data	Sept/Oct-20	Hundreds of millions of doses in 2020, scaling up to billions by 2022
	Unnamed	Translate Bio/Sanofi	Full S protein	Preclinical	Start Phase 1 Trial Regulatory Approval	Q4:20 H2:21	90-360M doses annually by H1:21
DNA	INO-4800	Inovio	Full S protein	Ph1	Start Phase 2/3 Trial Phase 2/3 Data	September-20 Q1:21	1M doses by YE20, >100M doses in 2021
	GX-19	Genexine	Full S protein	Ph1/2	Phase 1 Data	September-20	No specific guidance
Adenoviral	AZD1222	AstraZeneca/Oxford	Full S protein	Ph2/3	Phase 3 Data Regulatory Approval	October-20 Q4:20	400MM doses in Sept (at-risk), >1B doses in 2021
	Ad5-nCoV	CanSino	Full S protein	Ph3	Initial Phase 3 Data	December-20	100-200M doses per year in 2021
	Ad26.COV2-S	Janssen Pharma	Full S protein	Ph1/2	Phase 1 Data Start Phase 3 Trial	September-20 September-20	500M doses in 2020, 1B doses in 2021
Replicating Viral Vector	V591 (Measles vector)	Merck	Undisclosed DNA cargo	Preclinical	Start Phase 1 Trial	Q3:20	No specific guidance
	V590 (rVSV vector)	Merck	Full S protein	Preclinical	Start Phase 1 Trial	H2:20	No specific guidance
Inactivated Virus	Unnamed	Wuhan Inst/Sinopharm	Whole virus	Ph3	Phase 3 Data Regulatory Approval (China)	Q4:20 YE:20	200M doses per year
	BBIBP-CorV	Beijing Inst/Sinopharm	Whole virus	Ph3	Phase 3 Data Regulatory Approval (China)	Q4:20 YE:20	200M doses per year
	CoronaVac	Sinovac	Whole virus	Ph3	Initial Phase 3 Data Complete Phase 3 Study	October-20 February-21	100M doses per year
	Unnamed	Inst of Med Biol at Chinese Acad of Med Sciences (IMBCAMS)	Whole virus	Ph2	Phase 2 Data Start Phase 3 Trial	H2:20 Unknown	No specific guidance
Protein Subunit	NVX-CoV2373	Novavax/Emergent Bio	Full S protein	Ph1/2	Start Phase 3 Trial Initial Phase 3 Data	October-20 December-20	100M doses in 2020, >1B doses in 2021
	SCB-2019	Clover/GSK/Dynavax	Full S protein	Ph1	Phase 1 Data	September-20	Hundreds of millions of doses in 2021
	Unnamed	Sanofi/GSK	Protein Subunit	Ph1/2	Phase 1/2 Data Start Phase 3 Trial Regulatory Approval	December-20 December-20 H1:21	100M doses in 2020, >1B doses by mid-2021
	MVC-COV1901	Medigen/Dynavax	S-2P protein	Preclinical	Start Phase 1 Trial	September-20	Dynavax able to supply 600M to 1.2B doses of adjuvant per year
Virus-Like Particles	CoVLP	Medicago/GSK/Dynavax	Plant-derived VLP	Ph1	Phase 1 Data Start Phase 2/3 Trial Regulatory Approval	September-20 October-20 H1:21	100M doses by YE:21, 1B doses annually by 2023

Source: Cowen and Company

Despite Pricing Pressure, Vaccines Should Be Major Profit Drivers At Least For The Next Few Years – Key Question Is Whether That Will Be Sustainable

Even before any official pricing was announced, companies developing vaccines were already feeling pressure to keep prices low to allow broad use across the world. This has been especially true for companies collaborating with non-profit entities such as BARDA, NIAID, CEPI, and others. Health and Human Services Secretary Alex Azar has said that if the government co-funded private research or development of a vaccine, "we would ensure there's access to the fruits of that, whether vaccine or therapeutics." In the same vein, 46 Congressional Democrats signed a letter to President Trump in February looking to prevent any private company from having an exclusive license on a successful coronavirus vaccine in order to ensure affordable pricing and access.

Two companies, AstraZeneca and JNJ, have stated that their vaccines will be offered at-cost during the pandemic's emergency period (prices may be raised in the future). An executive from Sanofi commented that the price of its vaccine will likely be below €10. EpiVax's CEO has also stated that the company is not looking to make a profit, only to cover costs.

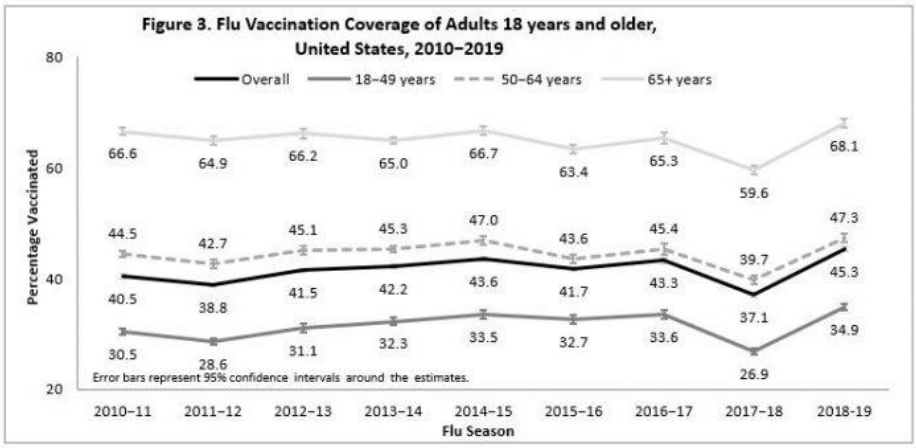
Thus far, the U.S. government has secured 800M initial doses (though not all vaccines may succeed) with contracts ranging from $4 to $20 per dose (see table further in the report).

Vaccine Market Could Reach $4.3B At Peak Globally – Expecting A Sustainable Sizable Market Assuming COVID-19 Becomes A Circulating Virus

The COVID-19 pandemic does not appear to be letting up in the near term. In the long run, we expected SARS-CoV-2 to enter the pantheon of chronically circulating viruses and will require periodic vaccines (with frequency depending on durability).

Compliance with the influenza vaccine is a useful benchmark in forecasting penetration for COVID-19 vaccines with the caveat that the COVID-19 pandemic has been far more disruptive to everyday life, and its vaccine will likely garner equal or more interest if the public trusts the veracity of safety data. Overall, 45.3% of adults ≥ 18 years of age received vaccination for influenza in the 2018-19 season, with a higher rate in adults > 65 years of age (68.1%).

Overall Rate of Flu Vaccination In Adults Over The Last 10 Years Is Typically In Mid-40s%



Source: CDC

We estimate a higher penetration for COVID-19 vaccines among older individuals and those with health conditions that increase risk for severe disease. In the US, we estimate there are ~53M individuals over the age of 65 and ~62M individuals with pertinent health conditions that are below age 65. The combined ~115M individuals represent the number of people in the U.S. at increased risk for severe COVID-19 and should be among the first tranche of vaccine distribution. In the EU, we estimate the increased risk population to be ~174M individuals (~1.5x the US). We believe the increased risk group will achieve a higher penetration rate (peak 65%) than the remaining population (peak 30%).

Market Opportunity For Vaccines Is Significant Assuming Need For Annual Vaccination

Vaccines are likely to be significant profit drivers despite low initial pricing based on sizable opportunity and potential for the virus to be a recurring annual threat. Thus far, the U.S. government has secured 800M initial doses (though not all vaccines may succeed) with contracts ranging from $4 to $20 per dose. While it is possible that future pricing will be higher (Moderna has made the case for $32-$37 per dose of its vaccine for "smaller-volume" agreements but just agreed to sell 100M doses for $1.5B excluding another $955M in funding from BARDA), there will be bipartisan pressure to keep prices down, especially for drug makers that have accepted development funding.

Total U.S. Funding For Vaccine Development Has Reached Over $10B, Paying Btw $4-$20/Dose

US Government Vaccine Funding					
Company	Supply Agreement ($MM)	Doses (MM)	$/Dose	Development Funding ($MM)	Total ($MM)
Sanofi/GSK	$2,042	100	$20.42	$30	$2,072
Pfizer/BioNTech	$1,950	100	$19.50	$0	$1,950
Novavax	$1,600	100	$16.00	$0	$1,600
Moderna	$1,525	100	$15.25	$955	$2,480
JNJ	$1,000	100	$10.00	$456	$1,456
AstraZeneca	$1,200	300	$4.00	$0	$1,200
Merck	$0	-	-	$38	$38
Total	**$9,317**	**800**		**$1,479**	**$10,796**

Source: Cowen and Company

Outside of the US, the financial terms of agreements between governments and individual companies have been less transparent. Though over 2B doses have been secured, these initial orders are unlikely to be highly profitable based on comments from companies such as AstraZeneca and JNJ.

Ex-US Supply Agreements Have Secured Over 2B Doses

Global Government Vaccine Funding (Ex-US)				
Company	Supply Agreement (MM)	Doses (MM)	$/Dose	Additional Dose Option (MM)
EU				
AZN	$843	300*	$2.81	100
	-	300**	-	100
SNY/GSK	-	300	-	-
JNJ	-	200	-	-
UK				
AZN	-	100	-	-
SNY/GSK	-	60	-	-
NVAX	-	60	-	-
PFE/BNTX	-	30	-	-
JNJ	-	30	-	22
China				
AZN	-	100	-	200
Japan				
NVAX	-	250	-	-
AZN	-	120	-	-
PFE/BNTX	-	120	-	-
JNJ	-	TBD	-	-
MRNA	-	40	-	-
South Korea				
NVAX	-	TBD	-	-
Brazil				
AZN	$356	100	$3.56	-
Australia				
AZN	-	25	-	-
Total		**2,135**		**422**

*Deal with Inclusive Vaccines Alliance (IVA), spearheaded by Germany, France, Italy and the Netherlands

**Deal with European Comminssion, $396M down payment, otherwise terms undisclosed

Source: Cowen and Company

Our Base Case Scenario Assumes A Bolus Of Vaccine Sales In FY21-24

In our base case scenario (Scenario 3 in the chart below), we assume

1. vaccines will be priced at $15 per dose in the US and $10 per dose in the EU;
2. vaccines will see a bolus of sales upfront in FY21-FY24, and
3. vaccine penetration will reach the peak at 65% in the high-risk population and 30% in the remaining population in FY22-FY23, then decline significantly to 10% and 3% in the respective populations in FY25.

We think the market could be sizable on a global bases assuming that vaccinations are given annually.

Based on Scenario 3, the total US and EU vaccine revenue will peak at $4.3B in FY21 and decline to $600M in FY26. The total of vaccine sales in FY21-FY33 is estimated to be $20B.

In Scenario 1 and 2, we assume the same peak penetrations. But, in Scenario 1, we assume a steady growth of vaccine penetration to its peak in FY33. In Scenario 2, we assume the same penetrations in FY21-23 as in Scenario 3, but a much slower tapering onwards.

For both Scenarios 1 and 2, the total of vaccine sales in FY21-FY33 is estimated to be $44B-$45B.

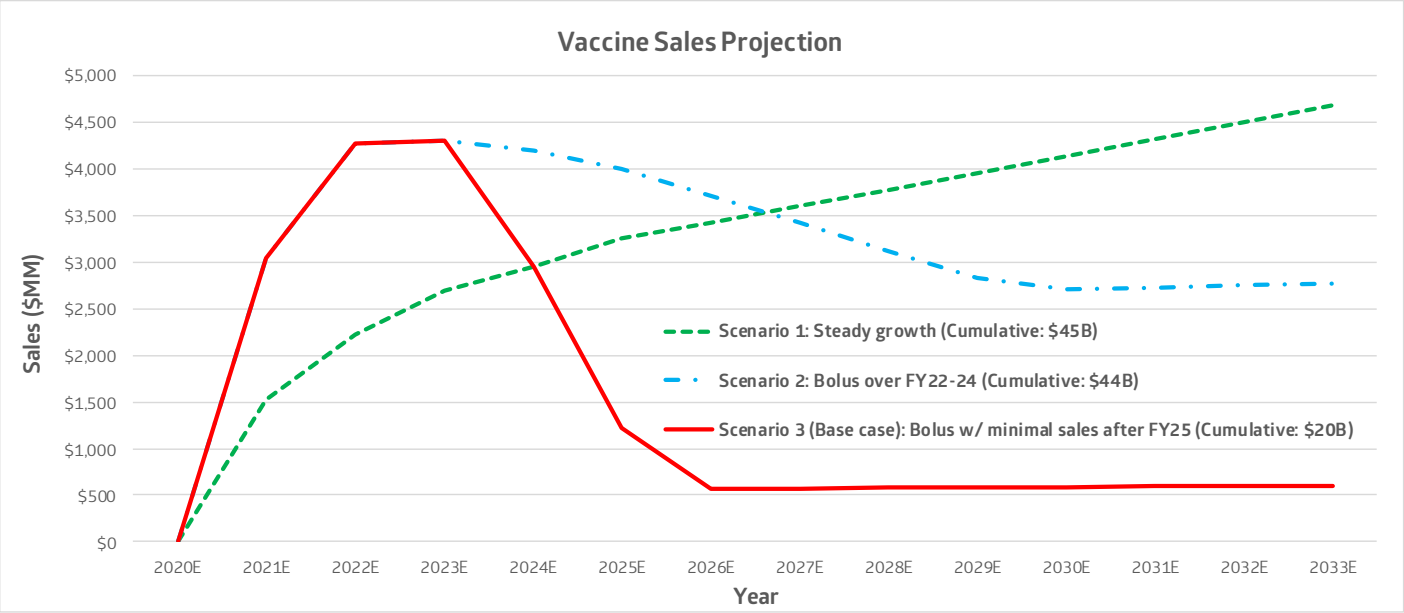
COVID-19 Vaccines Represent A Large Opportunity Depending On The Number Of Successful Candidates And Future Pricing

Vaccine Market Scenario 3

	2020E	2021E	2022E	2023E	2024E	2025E	2026E	2027E	2028E	2029E	2030E
US population	329,731,335	332,698,917	335,693,207	338,714,446	341,762,876	344,838,742	347,942,291	351,073,771	354,233,435	357,421,536	360,638,330
Growth rate		*1%*	*1%*	*1%*	*1%*	*1%*	*1%*	*1%*	*1%*	*1%*	*1%*
% of population 65 years of age and over	*16.0%*	*16.0%*	*16.0%*	*16.0%*	*16.0%*	*16.0%*	*16.0%*	*16.0%*	*16.0%*	*16.0%*	*16.0%*
US population 65 years of age and over	52,757,014	53,231,827	53,710,913	54,194,311	54,682,060	55,174,199	55,670,767	56,171,803	56,677,350	57,187,446	57,702,133
% of population 20-64 years of age	*58.5%*	*58.5%*	*58.5%*	*58.5%*	*58.5%*	*58.5%*	*58.5%*	*58.5%*	*58.5%*	*58.5%*	*58.5%*
US population 20-64 years of age	192,892,831	194,628,866	196,380,526	198,147,951	199,931,283	201,730,664	203,546,240	205,378,156	207,226,560	209,091,599	210,973,423
% of population 20-64 years of age with increased risk	*32.0%*	*32.0%*	*32.0%*	*32.0%*	*32.0%*	*32.0%*	*32.0%*	*32.0%*	*32.0%*	*32.0%*	*32.0%*
US population 20-64 years of age with increased risk	61,725,706	62,281,237	62,841,768	63,407,344	63,978,010	64,553,813	65,134,797	65,721,010	66,312,499	66,909,312	67,511,495
Total number of increased risk individuals	114,482,720	115,513,064	116,552,682	117,601,656	118,660,071	119,728,011	120,805,563	121,892,813	122,989,849	124,096,757	125,213,628
% of total US population	*34.7%*	*34.7%*	*34.7%*	*34.7%*	*34.7%*	*34.7%*	*34.7%*	*34.7%*	*34.7%*	*34.7%*	*34.7%*
Total number of non-increased risk individuals	215,248,615	217,185,853	219,140,526	221,112,790	223,102,806	225,110,731	227,136,727	229,180,958	231,243,587	233,324,779	235,424,702
% of total US population	*65.3%*	*65.3%*	*65.3%*	*65.3%*	*65.3%*	*65.3%*	*65.3%*	*65.3%*	*65.3%*	*65.3%*	*65.3%*
Increased risk individuals vaccinated	0	46,205,226	75,759,243	76,441,076	53,397,032	17,959,202	12,080,556	12,189,281	12,298,985	12,409,676	12,521,363
Vaccine penetration	*0%*	*40%*	*65%*	*65%*	*45%*	*15%*	*10%*	*10%*	*10%*	*10%*	*10%*
Non-increased risk individuals vaccinated	0	54,296,463	65,742,158	66,333,837	44,620,561	22,511,073	6,814,102	6,875,429	6,937,308	6,999,743	7,062,741
Vaccine penetration	*0%*	*25%*	*30%*	*30%*	*20%*	*10%*	*3%*	*3%*	*3%*	*3%*	*3%*
Price	$15	$15	$15	$15	$15	$15	$15	$15	$15	$15	$15
% change		*0%*	*0%*	*0%*	*0%*	*0%*	*0%*	*0%*	*0%*	*0%*	*0%*
Total US Vaccine Revenue ($MM)	**$0**	**$1,508**	**$2,123**	**$2,142**	**$1,470**	**$607**	**$283**	**$286**	**$289**	**$291**	**$294**
EU population	517,579,449	521,720,085	525,893,846	530,100,996	534,341,804	538,616,539	542,925,471	547,268,875	551,647,026	556,060,202	560,508,684
Growth rate	*1%*	*1%*	*1%*	*1%*	*1%*	*1%*	*1%*	*1%*	*1%*	*1%*	*1%*
% of population 65 years of age and over	*20.0%*	*20.0%*	*20.0%*	*20.0%*	*20.0%*	*20.0%*	*20.0%*	*20.0%*	*20.0%*	*20.0%*	*20.0%*
EU population 65 years of age and over	103,515,890	104,344,017	105,178,769	106,020,199	106,868,361	107,723,308	108,585,094	109,453,775	110,329,405	111,212,040	112,101,737
% of population 15-64 years of age	*65.0%*	*65.0%*	*65.0%*	*65.0%*	*65.0%*	*65.0%*	*65.0%*	*65.0%*	*65.0%*	*65.0%*	*65.0%*
EU population 15-64 years of age	336,426,642	339,118,055	341,831,000	344,565,648	347,322,173	350,100,750	352,901,556	355,724,769	358,570,567	361,439,131	364,330,644
% of population 15-64 years of age with increased risk	*21.0%*	*21.0%*	*21.0%*	*21.0%*	*21.0%*	*21.0%*	*21.0%*	*21.0%*	*21.0%*	*21.0%*	*21.0%*
EU population 15-64 years of age with increased risk	70,649,595	71,214,792	71,784,510	72,358,786	72,937,656	73,521,158	74,109,327	74,702,201	75,299,819	75,902,218	76,509,435
Total number of increased risk individuals	174,165,485	175,558,809	176,963,279	178,378,985	179,806,017	181,244,465	182,694,421	184,155,976	185,629,224	187,114,258	188,611,172
% of total EU population	*33.7%*	*33.7%*	*33.7%*	*33.7%*	*33.7%*	*33.7%*	*33.7%*	*33.7%*	*33.7%*	*33.7%*	*33.7%*
Total number of non-increased risk individuals	343,413,965	346,161,276	348,930,567	351,722,011	354,535,787	357,372,074	360,231,050	363,112,899	366,017,802	368,945,944	371,897,512
% of total EU population	*66.4%*	*66.4%*	*66.4%*	*66.4%*	*66.4%*	*66.4%*	*66.4%*	*66.4%*	*66.4%*	*66.4%*	*66.4%*
Increased risk individuals vaccinated	0	70,223,523	115,026,131	115,946,340	80,912,708	27,186,670	18,269,442	18,415,598	18,562,922	18,711,426	18,861,117
Vaccine penetration	*0%*	*40%*	*65%*	*65%*	*45%*	*15%*	*10%*	*10%*	*10%*	*10%*	*10%*
Non-increased risk individuals vaccinated	0	86,540,319	104,679,170	105,516,603	70,907,157	35,737,207	10,806,932	10,893,387	10,980,534	11,068,378	11,156,925
Vaccine penetration	*0%*	*25%*	*30%*	*30%*	*20%*	*10%*	*3%*	*3%*	*3%*	*3%*	*3%*
Price	$10	$10	$10	$10	$10	$10	$10	$10	$10	$10	$10
% change		*0%*	*0%*	*0%*	*0%*	*0%*	*0%*	*0%*	*0%*	*0%*	*0%*
Total EU Vaccine Revenue ($MM)	**$0**	**$1,528**	**$2,142**	**$2,159**	**$1,480**	**$614**	**$283**	**$286**	**$288**	**$290**	**$293**
Global Vaccine Revenue ($000s)	**$0**	**$3,036**	**$4,265**	**$4,301**	**$2,951**	**$1,221**	**$567**	**$572**	**$577**	**$581**	**$586**

Source: Cowen and Company

COVID-19 Vaccines Represent A Large Opportunity – Our Base Case Scenario 3 Projects Peak Sales Of $4.3B In FY23



Source: Cowen and Company

Based on the sensitivity analyses of our base case (Scenario 3), we project vaccine sales to peak at $4.3B in FY23 if the vaccine is priced at $15 per patient in the U.S. and $10 per patient in EU (~60% of U.S. price).

Sensitivity Table For Potential Vaccine Prices (vs Our Baseline Assumption of $15/Dose In US And $10/Dose In Europe)

		Price/Dose In The US					
	Sales ($MM)	**$5**	**$10**	**$15**	**$20**	**$25**	**$30**
	2020	$0	$0	$0	$0	$0	$0
	2021	$1,012	$2,024	$3,036	$4,048	$5,060	$6,072
Year	**2022**	$1,422	$2,843	$4,265	$5,686	$7,108	$8,529
	2023	$1,434	$2,867	$4,301	$5,735	$7,168	$8,602
	2024	$984	$1,967	$2,951	$3,934	$4,918	$5,901
	2025	$407	$814	$1,221	$1,627	$2,034	$2,441

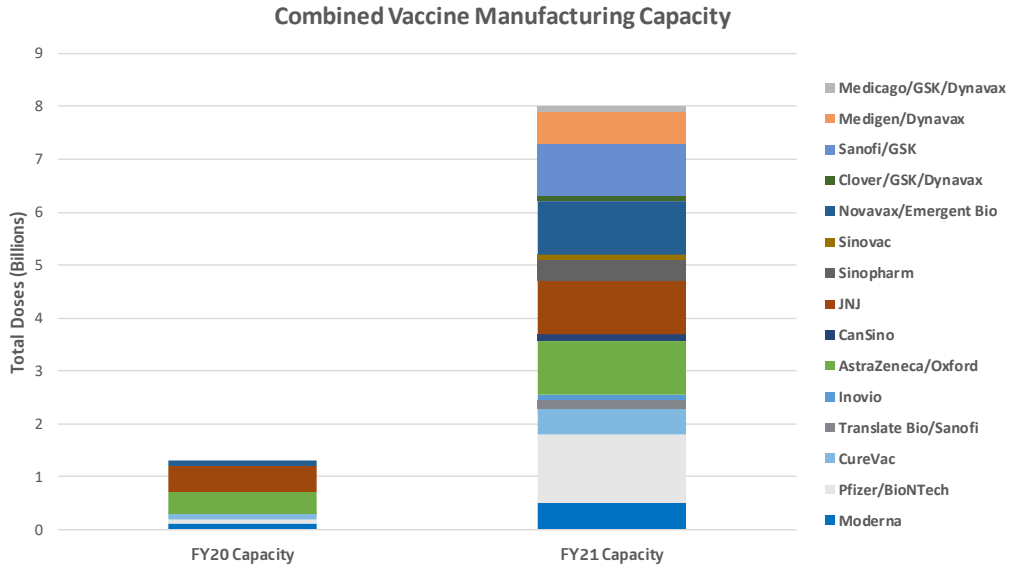
Source: Cowen and Company

Potential Industry-Wide Vaccine Manufacturing Capacity of ~1.3B Doses in FY20 and 8B Doses in FY21, Though Not All Programs Will be Successful

We estimate potential industry manufacturing capacity to be ~1.3B doses in FY20 and 8B doses in FY21 by using the low end of company guidance (when available) and not including companies that have given no specific guidance (i.e. Merck and Genexine). These estimates assume that companies can meet their projections and that all programs will be approved.

In our view, not all the programs in development will be successful, and there will likely be some delays to reach projections of manufacturing capacity. Among the leaders in development thus far, we have confidence in Moderna, Pfizer/BioNTech, AstraZeneca, and JNJ meeting their estimated production capacities if their candidates are successful.

Potential Manufacturing Capacity of ~1.3B Doses in FY20 and 8B Doses in FY21 From 15 of the Leading Developers



Source: Cowen and Company, Company reports

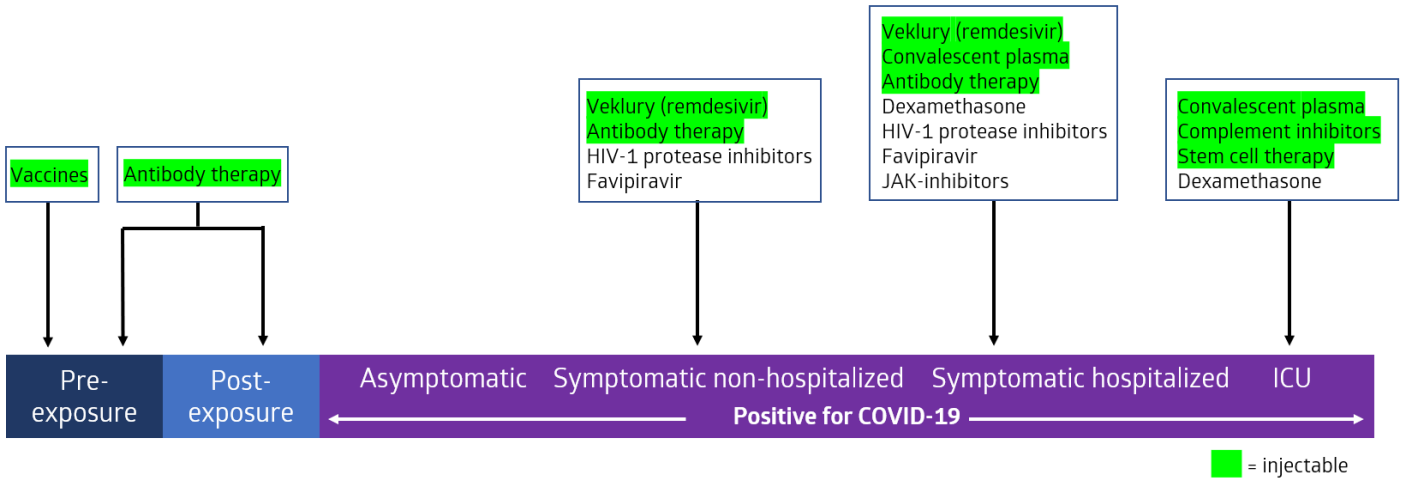
We See A Solid Opportunities For Gilead's Veklury With $3.6B Peak Sales In FY20

Many drugs with different mechanisms are being tested as vaccines, prophylaxis, or treatments for COVID-19. We see opportunities for these drugs at different COVID-19 disease stages.

Based on the reported data, antiviral drugs tended to have more success in mild to moderate patients, while immunosuppressants might be more effective in the severe to critical patients.

This is consistent with the hypothesis that antiviral therapy will be more effective in early stage of the infection while viral replication is the primary driver and immunosuppression will be more effective in late stage of the disease, when hyperactive immune responses drive the pathology.

Opportunities Exist For Different Drugs During The Course Of COVID-19



Source: Cowen and Company

We Project Peak Global Veklury Revenue of $3.6B In 2020

On May 1, 2020, Veklury (remdesivir) was granted an emergency use authorization (EUA) by the FDA for the treatment of hospitalized patients with severe COVID-19. The EUA was granted based on the top-line data from the NIAID-led study of remdesivir in addition to the Gilead-sponsored SIMPLE-severe study. On August 29, Veklury's EUA was expanded to include all patients hospitalized with COVID-19, regardless of whether they are receiving supplemental oxygen or mechanical ventilation, based on data from the SIMPLE-moderate study. An NDA for Veklury was filed in August 2020.

Veklury has been priced at $390 per vial for U.S. government healthcare programs and for the governments of developed countries (to avoid the need for price negotiation on a country-by-country basis), translating to $2,340/patient for a 5-day treatment course. U.S. private insurance companies will pay ~33% more at $520/vial or $3,120/patient in total for a 5-day treatment course.

We expect Veklury to remain part of the standard of care for hospitalized patients for the foreseeable future, but we project that the number of hospitalized patients will decline after the first effective vaccine is launched. Our model assumes that happens in 2021. Based upon these assumptions, we project remdesivir revenue of $3.6B, $2.1B, $1.4B, $1.0B, and $750MM for 2020-24.

Global Veklury COVID-19 Revenue Model

	2020E	2021E	2022E	2023E	2024E	2025E
US population	330,487,927	333,462,318	336,463,479	339,491,650	342,547,075	345,629,999
Growth rate	*1%*	*1%*	*1%*	*1%*	*1%*	*1%*
% Of Population Diagnosed With COVID-19	*2%*	*3%*	*2%*	*1%*	*1%*	*1%*
Number Of Diagnosed U.S. COVID-19 Cases (K)	7000	9000	5047	3395	2213	2169
% Hospitalized	*13%*	*13%*	*13%*	*13%*	*13%*	*13%*
Number Of Hospitalized U.S. COVID-19 Cases (K)	910	1170	656	441	288	282
% Remdesivir Penetration	*110%*	*47%*	*55%*	*60%*	*60%*	*60%*
Number Of U.S. COVID-19 Cases On Remdesivir (K)	1000	549	359	264	173	169
Price Per Treatment Course ($)	$2,750	$2,730	$2,785	$2,840	$2,897	$2,955
U.S. Remdesivir Revenue ($MM)	$2,750	$1,500	$1,000	$750	$500	$500
EU population	517,579,449	521,720,085	525,893,846	530,100,996	534,341,804	538,616,539
Growth rate	*1%*	*1%*	*1%*	*1%*	*1%*	*1%*
% Of Population Diagnosed With COVID-19	*1%*	*1%*	*0%*	*0%*	*0%*	*0%*
Number Of EU COVID-19 Cases (K)	4400	3000	2192	1370	1370	1370
% Hospitalized	*13%*	*13%*	*13%*	*13%*	*13%*	*13%*
Number Of Hospitalized COVID-19 Cases (K)	572	390	285	178	178	178
% Remdesivir Penetration	*64%*	*66%*	*60%*	*60%*	*60%*	*60%*
Number Of EU COVID-19 Cases On Remdesivir (K)	363	256.4	170.9	106.8	106.8	106.8
Price Per Treatment Course ($)	$2,340	$2,340	$2,340	$2,340	$2,340	$2,340
EU Remdesivir Revenue ($MM)	$850	$600	$400	$250	$250	$250
Worldwide Veklury Revenue ($MM)	**$3,600**	**$2,100**	**$1,400**	**$1,000**	**$750**	**$750**

Source: Cowen and Company

Antibody Therapy Will Play A Critical Role Adjunctive To Vaccines – Antibodies Are Promising But Must Be Given Early Upon Exposure

COVID-19 vaccines are expected to elicit durable protection which is critical to breaking the curve and restarting economies globally. Vaccine development is now at a historic pace support by government funding in the US and to a lesser extent in Europe.

However, the ability of vaccines to elicit high responses and durable immunity is still uncertain and there are concerns about risks of antibody-dependent enhancement (ADE) associated with vaccines. More so, it is expected that the elderly and patients who are immunocompromised are less likely to benefit from a vaccine as they are less likely to mount a robust immune response.

Antibody therapy should come in time to play a critical role as it can help people who may not get a good vaccine response, as prophylaxis following exposure, or will be used as a treatment for COVID-19 patients. Candidates are being developed by companies like Regeneron/Roche using established technology that was used to develop therapies to treat other diseases, such as MERS and Ebola. Other companies such as GSK/Vir, Lilly, AstraZeneca, Amgen, AbbVie, Abcella, Junshi, and Celltrion have also joined the race.

At this point, only Regeneron/Roche (phase 3 data expected in late Sept) and AstraZeneca (phase 1 commenced in late Aug) are testing a cocktail of antibodies. Lilly plans to develop a cocktail soon.

Neutralizing Antibodies As Treatment IV For Hospitalized And High-Risk Patients Or As Prophylaxis SQ

We expect antibody therapies to be given intravenously (IV) or subcutaneously (SQ) to hospitalized or particularly high-risk non-hospitalized individuals, which could support a higher price point. Additionally, those modalities are being developed as prophylaxis for people who have been exposed to COVID-19 or have a high chance of being exposed.

Antibody Therapies Can Be Used For Prophylaxis To Prevent Infections Or Hospitalizations And For Treatment In Diagnosed Patients

Antibody modalities hold promise given historical successes in Ebola and MERS. We think antibody therapeutics have the potential to help people who will not benefit from vaccines and/or be used as a supplement for prevention after exposure.

Neutralizing antibodies have the potential to confer passive immunity and immediate protection against COVID-19. They may be used as prophylaxis to prevent infection or hospitalization and as treatment for patients with positive diagnosis.

As monoclonal antibodies have a relatively long half-life, a single dose of antibody therapy might last up to 2-3 months. In some cases, half-life extended antibodies might last up to 6 months, which will be ideal for prophylaxis.

Several Companies Are In The Antibody Pursuit

Several companies, such as Regeneron/Roche, Eli Lilly/Abcellera/Junshi, Vir/GSK, AstraZeneca, Celltrion, Amgen, BeiGene/Singlomics, and AbbVie, are currently in the race for developing neutralizing antibodies against SARS-CoV-2 for prophylactic and therapeutic uses.

Eli Lilly/Abcellera/Junshi and Regeneron/Roche have advanced their programs into pivotal trials. Celltrion, Vir/GSK, and AstraZeneca also entered the clinic in July/August.

Multiple Antibody Therapy Programs Will Have Initial Data In H2:20 – Many Upcoming Milestones And Catalysts In H2:20/H1:21

Company	Approach	Candidate	Target	Regimen	IC_{50}	Fc Domain Modification	Platform/ Source	Clinical Status	Catalyst/Milestone	Manufacturing Capacity By 2020	Manufacturing Capacity By 2021
Eli Lilly/ AbCellera/ Junshi	Single antibody and antibody cocktail	LY-CoV555 (Human IgG1)	Spike protein	IV	NA	LALA mutation being investigated	DARPA Pandemic Prevention Platform	Ph1 in hospitalized pts started on 6/1 BLAZE-1 Ph2 in mild to moderate pts started on 6/17 BLAZE-2 Ph3 prevention trial started on 8/3	To report efficacy data from BLAZE-1 in Q4:20 To start a Ph3 treatment trial in the coming weeks	Several hundred thousand doses by YE:20	Not disclosed
		JS016	RBD	IV	36 ng/ml	LALA mutation to minimize FcγR activation and Fc - mediated toxicity	Convalescent COVID-19 patients	Ph1 in healthy subjects started on 6/8 and reported positive topline safety data with no DLE as of 7/12	To start a Ph1b trial in non-severe COVID-19 patients and Ph2/3 trials in severe and critical patients soon		
		A third candidate	SARS-CoV-2 (not spike protein	NA	NA	NA	NA	NA	Might be combined with LY-CoV555 and/or JS016		
Regeneron/ Roche	Two-antibody cocktail	REGN-COV2 (REGN10987 + REGN10933)	Spike protein	IV for treatment, SC for prevention	37-42 pM	No modification	Convalescent COVID-19 patients or genetically-humanized mice (VelociMab)	The first 2 adaptive Ph1/2/3 treatment studies in hospitalized and non-hospitalized patients started on 6/11 and moved to the Ph2/3 on 7/6 Ph3 prevention study started on 6/30	To report initial data from the treatment trials in September	70k-300k potential treatment doses or 420k- 1,300k prevention doses as early as end of summer	1M doses per month by FY21 by Regeneron and ≥3.5X globally with Roche collaboration
Celltrion	Single antibody and two-antibody cocktail	CT-P59	SARS-CoV-2	NA	NA	NA	Convalescent COVID-19 patients	Ph1 in healthy volunteers started in UK in mid July; Global Phase 1 in mild COVID-19 patients started in August	To complete Ph1 in healthy volunteers by Q3:20; To start further global Phase 2 and 3 prevention and treatment trials soon and have pivotal data by YE:20	NA	Mass-production to cover up to 5M patients a year by H1:21
Vir/GSK	Single antibody	VIR-7831/ VIR-7832 (Human IgG1)	SARS-CoV-2	NA	79 ng/ml for S309	One mutation to extends the half-life and potentially a second mutation to enhance binding to activating receptors	Modified from S309, human IgG1 isolated from a convalescent SARS patient	Ph2/3 of VIR-7831 started in August	To report initial data from Ph2/3 of VIR-7831 by YE:20 To start a Ph2 of VIR-78312 in H2:20. Both will be tested as prophylaxis and treatment	Hundreds of thousands of doses by YE:20	Tens of millions of doses by FY21
Amgen/ Adaptive	NA	NA	NA	NA	NA	NA	Convalescent COVID-19 patients	NA	NA	NA	NA
AstraZeneca/ Vanderbilt Univ.	Two-antibody cocktail	AZD7442 (AZD8895 +AZD1061)	SARS-CoV-2	IV and IM	15-4,000 ng/mL	YTE mutation for half-life extension	Convalescent COVID-19 patients or genetically-humanized mice via YTE technology platform	Ph1 started in late August	Likely to have initial data in Q4:20	NA	1M doses to start as early as H1:21
BeiGene/ Singlomics	Single antibody and a potential two-antibody cocktail	DXP-593 and DXP-604	SARS-CoV-2	NA	1.2 ng/ml and 15 ng/mL	NA	Convalescent COVID-19 patients	NA	To start a placebo-controlled Ph1 trial in September; To start a global Phase 1/2 trial in mild-to-moderate COVID-19 by early October	NA	NA
AbbVie/ Harbour/ Utrecht U/ Erasmus Med Center	Single antibody	47D11	SARS-CoV-2		61 ng/ml	NA	From genetically-humanized mice (Harbour's H2L2 Harbour mice)	Not started yet	NA	NA	NA

Source: Cowen and Company

We Expect Multiple Antibody Therapies To Be Successful – Regeneron/Roche's Antibody Cocktail Is The Most Promising Strategy

These companies are using different approaches to develop the antibody therapies, such as single antibody vs two antibody cocktail, IV injection vs SC/IM injections, targeting receptor binding domain (RBD) vs. targeting other regions of the spike protein, identifying candidates from plasma of convalescent patients vs from genetically humanized mice, etc.

Companies also modified the Fc domain of antibodies to enhance the antibody's half-life and reduce the risk of antibody-dependent enhancement (ADE).

We consider Regeneron/Roche's cocktail strategy as the most promising. The cocktail is composed of two antibodies that bind two distinct epitopes on the RBD of spike protein.

It is expected to enhance the potency and avoid resistance due to viral mutation based on preclinical data.

Regeneron/Roche And Lilly Are Leading The Pack Given Their Advanced Clinical Programs And Cocktail Strategies

We think Eli Lilly/Abcellera/Junshi and Regeneron/Roche are in the lead. These two companies have the most advanced clinical programs supported by strong preclinical data.

More so, Regeneron/Roche is studying an antibody cocktail directly while Eli Lilly/Abcellera/Junshi have three candidates that can be potentially combined to fight viral mutation.

We Expect Initial Clinical Data In September - Pivotal Data Expected By YE:20

Regeneron/Roche plan to report initial data from the treatment trials by the end of September. Vir/GSK, Celltrion, and AstraZeneca also have plans to report pivotal data by YE:20.

Companies, such as Lilly, Vir/GSK, Celltrion, and BeiGene/Singlomics, also announced plans to start new prevention/treatment trials in H2:20.

We anticipate that antibody therapy will be effective for a short period of time, given prior experience with Ebola and other coronaviruses. We note that the key is the durability of immunity as recent data showed that nAb titers drop rapidly after 3 months of symptom onset in recovered COVID-19 patients. Hence, we envision that use for prophylaxis will require repeated dosing.

Interim Data Could Lead To EUA For Antibody Therapy Around YE:20 – We Assume Wide Adoption To Start In The High-Risk Population In FY21

We think it is possible that the FDA will give emergency use authorization (EUA) to one or more antibody therapies upon initial pivotal data with 2-3 months of follow-up around YE:20.

Recall, the FDA provided EUA for convalescent plasma therapy in late August based on underwhelming retrospective data despite many concerns, likely fueled by political pressure.

We anticipate that the FDA will likely require a 1-5 years follow-up of efficacy and safety for the full approval based on prior experience of the Ebola vaccine.

Upon the EUA, we envision that the initial uptake will be in the high-risk populations, such as people in senior homes, immune-compromised people, households of diagnosed patients, and healthcare workers.

Antibody Therapies Have Received Less Funding Support

Antibody therapies have not benefited from government funding to the same extent as vaccines. In the US, only Regeneron's antibody therapy, REGN-COV2, has received $450M from BARDA for secured supplies so far. In EU, Regeneron's REGN-COV2, has not received any federal funds.

Government Funds For Therapeutics In The U.S.

US Government Therapy Involvement						
Company	Contract ($MM)	Development Funding ($MM)	Total ($MM)	Doses	$/Dose	Milestones
REGENERON	$450	$0	$450	70K-300K treatment doses and 420K-1,300K preventative dosages	N/A	To manufacture a fixed number of bulk lots by Q3 in addition to fill/finish and storage
GILEAD	$1,566	$0	$1,566	100% of the projected Remdesivir production in July (94.2K treatment courses), 90% in August (174.9K), and 90% in September (232.8K)	$3,120	To supply >500K treatment courses through September
Total	**$2,016**	**$0**	**$2,016**			

Source: Cowen and Company, Company reports

Government Funds For Therapeutics In EU

EU Government Therapy Involvement						
Company	Contract (€MM)	Development Funding (€MM)	Total (€MM)	Doses	$/Dose	Milestones
REGENERON	€ 0	€ 0	€ 0			
GILEAD	€ 63	€ 0	€ 63	Treatment doses of ~30K patients to cover the current needs over the next few months	$3,120 per dose in the US	To submit the final reports of the Remdesivir studies to the EMA by December 2020 as part of the conditions to be fulfilled
Total	**€ 63**	**€ 0**	**€ 63**			

Source: Cowen and Company, Company reports

Antibody Therapy Will See Meaningful Uptake As Both Prophylaxis And Treatment

We see a lucrative market opportunity of antibody therapy for both prophylaxis and therapeutic treatment.

We recently saw case resurgences in the US and many EU countries. The pandemic is still not under control in Latin America and some part of Asia. There is a huge demand globally for prophylaxis to protect people from the COVID-19 infection as many countries and regions have started to gradually reopen.

More so, the total global cases have reached 27M with daily cases still trending up. In the US, the COVID-19 hospitalizations hit the record high in several states recently. Therefore, we think antibody therapy will also play an important role for COVID-19 treatment.

Prophylaxis Is A Lucrative Market Opportunity - Enough Room For Multiple Players

In the pre-exposure prophylaxis setting, we see high demand in groups with increased risk due to COVID-19, even after vaccines are developed. This includes healthcare workers, patients with hypertension or diabetes, and elderly people of ≥65 years old.

In the US, we estimate that there are ~17M healthcare workers, ~77M patients with hypertension or diabetes who are 20-64 years old, and ~41M elderly people who are ≥65 years old. Considering that a portion of this high-risk population would have been infected by the time antibody therapies become available, we estimate that the total market opportunity in this setting is 114M people in 2020. The market size is larger because family members who are in close contact with COVID-19 patients might need prophylaxis as well. We estimate that the EU market size is ~175M people, which is ~1.5X of the US market size.

We anticipate that antibody therapies will likely be approved in 2021 due to the slower-than-expected enrollment. Given that vaccines will likely be approved in Q4:20/H1:21, we think the market opportunity for antibody therapy as prophylaxis will become smaller as people get vaccinated. We conservatively assume that people at higher risk will not take prophylaxis once vaccinated.

Based on our base case assumptions on vaccine penetration (Scenario 3), we model the market opportunity of prophylaxis to grow from 69M people in FY21 to 102M people in FY25 in the US and from 105M people in FY21 to 154M people in FY25 in EU.

Recall, convalescent sera data showed that ~20% of recovered patients have low to undetectable level of neutralizing antibody. Based on prior experience with other coronavirus, we estimate that people will likely need to take vaccines every year to maintain effective protection. This suggests that antibody therapy, as an adjunctive regimen, will also be used once a year in people who respond to vaccines. In people who do not respond well to vaccines or who cannot take vaccines (such as elderly and the immuno-compromised), antibody therapy might be used more than once a year.

Recall, these monoclonal antibodies for RSV only have a half-life of ~3 weeks. Hence monthly injections were needed during RSV seasons to maintain a prophylactic level.

More so, our consultant also believes the post-viral immune response will be heterogeneous with ~10% of people developing short term immunity (months), others with immunity that will last about 1 year, and some with lifelong immunity based on data from MERS. As it is difficult to predict which bucket an individual will enter ahead of time, we anticipate a portion of recovered patients might still consider taking antibody therapy for pre-exposure prophylaxis as a precaution.

In the post-exposure prophylaxis setting, antibody therapy will also play an important role in people who have recent exposure to the virus.

Therefore, we believe there is enough room for multiple antibody therapy players given the high global demand for prophylaxis.

Treatment Is A Relatively Smaller Market – We Think The Opportunity May Diminish Over Time

In the therapeutic treatment setting, we consider the symptomatic COVID-19 patients, including both non-hospitalized and hospitalized patients, as the beachhead market for antibody therapies. We note that patients with severe COVID-19 are usually hospitalized for observation and supportive care.

Based on the forecast from Institute for Health Metrics and Evaluation (IHME) in July, we conservatively estimate that there will be a total of ~4.5M diagnosed cases in H2:20 and ~7.7M diagnosed cases in 2021 in the US. We assume 60% of the cases will be symptomatic, translating to ~4.6M symptomatic cases in 2021. Recall, CDC estimates that 35% of the cases are asymptomatic in May 2020, translating to 65% of symptomatic cases. We think the proportion of symptomatic cases will decline year over year due to vaccines and prophylaxis. Based on CDC's best estimate of 3.4% for symptomatic case hospitalization ratio, we calculate that there will be ~156k hospitalized patients. We estimate that there will be ~2.6M people diagnosed with COVID-19 (~1.5M symptomatic cases) in EU in 2021, which is ~33% of cases in the US.

Given the recent resurgence of new cases in many states, we think this estimate is conservative.

We think that the market opportunity for antibody treatment is relatively smaller compared with prophylaxis. Notably, we anticipate that this treatment market opportunity may diminish over time as vaccines/prophylaxis become widely available. This is because that vaccines and prophylaxis are expected to protect people from getting infected, or at least lower the severity of potential COVID-19 infection. Therefore, we anticipate that the number of patients with symptoms severe enough to require antibody treatment will decrease over time.

We model the market opportunity of treatment will decline from ~4.6M patients in FY21 to ~546k patients in FY25 in the US and from 1.5M patients in FY21 to 182k patients in FY25 in EU.

We Anticipate That COVID-19 Vaccines Will Likely Be Priced Low

The final cost of a vaccine will be driven by the production cost, which is affected by many factors including the vaccine technology and its manufacturing process, the availability and cost of ingredients, and the dosing regimen. Multiple large pharma companies noted that vaccines could be priced as low as ~$10 per dose. Many vaccine developers have also promised to price a viable vaccine fairly.

Recall, respiratory-virus vaccines, such as Afluria and Prevnar, cost roughly $400-800 per person, assuming 2-4 doses are needed each season.

Given government funding and the essentiality of the vaccines, we think that vaccines will likely be priced much lower than this level. Vaccine developers are facing government pressure to offer the vaccines at a low price to allow global access. Many of those companies are collaborating with the government and have received government funding for their vaccine development. Countries like the US and China will likely take political actions to ensure that the vaccines will be affordable and accessible globally. Notably, a few large pharmas have commented that they expect to charge $3-25 per dose for their potential vaccine products. CanSino also noted recently that the Chinese government might be taking control of pricing and supply as well as exports to lower the profit margin of its vaccine products.

Therefore, we do not expect vaccine to be a huge money maker, especially for companies that received government funding for their vaccine development.

More so, we anticipate that manufacturers might adopt different pricing models based on situations in different countries, such as the income-level and the local competition.

It Is Unlikely For Antibody Therapies To Compete With Vaccines On Price – We Anticipate Antibody Therapies Will Not Be Priced High

In comparison, antibody therapies will most likely be given intravenously or subcutaneously, which makes it unlikely to be very cheap in our view. Of note, oral prophylaxis drugs, such as Relenza and Tamiflu, are priced at about $71-168 per person while Synagis (an antibody for respiratory syncytial virus, RSV) costs >$3K-6K per person, assuming that 1-2 doses are needed each season.

But the cost of antibodies is estimated to be in the range of $50-500/gram, translating to $10-100/dose assuming 200 mg per dose, which is protective dose in adults based on existing therapies. We assume the treatment dose will be 6-10X higher than the protective dose. Therefore, antibody manufactures theoretically can price it low if they are willing to do so.

Recall, we anticipate that antibody therapies could be approved in Q4:20 and play a critical role. We think that manufacturers will likely price antibody therapies fairly for ethical reasons. More so, some of the manufacturers also received federal funds, which will have influence on the pricing of antibody therapies.

However, we anticipate that antibody therapies might be launched ahead of vaccines and could be used adjunctively to vaccines later, we think it is unlikely that antibody manufactures will price antibody therapies very low to compete against vaccines.

Prophylaxis Is A Lucrative Opportunity With Estimated Peak Sales Of ~$1.7B In FY21

Our sensitivity analyses suggest that prophylaxis is a much bigger opportunity than treatment.

In the prophylaxis segment, we estimate launch in early FY21 with a conservative price of $125 per dose in the US and $75 per dose in EU (60% of the US price). We assume that people will require 2 doses of prophylaxis per year on average. We project the peak global sales to be ~$1.7B in FY21 with 10% penetration in the high-risk people who are not vaccinated.

Of note, family members who are in close contact with COVID-19 patients are not included in our estimates. More so, we conservatively model two doses per year as some companies anticipate that their antibody candidates can provide an immunity of up to 6 months. People who do not respond well to a vaccine or who cannot take a vaccine might need multiple prophylaxis doses a year. More so, many antibody therapies are expected to have a half-life of ~ one month, and therefore need to be dosed monthly. We consider these as an upside to our estimates.

Prophylaxis Represents A Lucrative Opportunity

Prophylaxis Market

	2020E	2021E	2022E	2023E	2024E	2025E	2026E	2027E	2028E	2029E	2030E
US population	329,731,335	332,698,917	335,693,207	338,714,446	341,762,876	344,838,742	347,942,291	351,073,771	354,233,435	357,421,536	360,638,330
Growth rate		*1%*	*1%*	*1%*	*1%*	*1%*	*1%*	*1%*	*1%*	*1%*	*1%*
% of population 65 years of age and over	*16.0%*	*16.0%*	*16.0%*	*16.0%*	*16.0%*	*16.0%*	*16.0%*	*16.0%*	*16.0%*	*16.0%*	*16.0%*
US population 65 years of age and over	52,757,014	53,231,827	53,710,913	54,194,311	54,682,060	55,174,199	55,670,767	56,171,803	56,677,350	57,187,446	57,702,133
% of population 20-64 years of age	*58.5%*	*58.5%*	*58.5%*	*58.5%*	*58.5%*	*58.5%*	*58.5%*	*58.5%*	*58.5%*	*58.5%*	*58.5%*
US population 20-64 years of age	192,892,831	194,628,866	196,380,526	198,147,951	199,931,283	201,730,664	203,546,240	205,378,156	207,226,560	209,091,599	210,973,423
% of population 20-64 years of age with increased risk	*32.0%*	*32.0%*	*32.0%*	*32.0%*	*32.0%*	*32.0%*	*32.0%*	*32.0%*	*32.0%*	*32.0%*	*32.0%*
US population 20-64 years of age with increased risk	61,725,706	62,281,237	62,841,768	63,407,344	63,978,010	64,553,813	65,134,797	65,721,010	66,312,499	66,909,312	67,511,495
Total number of increased risk individuals not vaccinated	114,482,720	69,307,838	40,793,439	41,160,579	65,263,039	101,768,810	108,725,007	109,703,532	110,690,864	111,687,082	112,692,265
% of total US population	*34.7%*	*20.8%*	*12.2%*	*12.2%*	*19.1%*	*29.5%*	*31.2%*	*31.2%*	*31.2%*	*31.2%*	*31.2%*
Individuals taken prophylaxis	0	6,930,784	4,079,344	3,292,846	3,915,782	3,053,064	2,174,500	1,097,035	1,106,909	1,116,871	1,126,923
Prophylaxis penetration	*0%*	*10%*	*10%*	*8%*	*6%*	*3%*	*2%*	*1%*	*1%*	*1%*	*1%*
Price/dose	$125	$125	$125	$125	$125	$125	$125	$125	$125	$125	$125
% change		*0%*	*0%*	*0%*	*0%*	*0%*	*0%*	*0%*	*0%*	*0%*	*0%*
Avg. number of doses per year		2	2	2	2	2	2	2	2	2	2
Total US Prophylaxis Revenue ($MM)	**$0**	**$866**	**$510**	**$412**	**$489**	**$382**	**$272**	**$137**	**$138**	**$140**	**$141**
EU population	517,579,449	521,720,085	525,893,846	530,100,996	534,341,804	538,616,539	542,925,471	547,268,875	551,647,026	556,060,202	560,508,684
Growth rate	*1%*	*1%*	*1%*	*1%*	*1%*	*1%*	*1%*	*1%*	*1%*	*1%*	*1%*
% of population 65 years of age and over	*20.0%*	*20.0%*	*20.0%*	*20.0%*	*20.0%*	*20.0%*	*20.0%*	*20.0%*	*20.0%*	*20.0%*	*20.0%*
EU population 65 years of age and over	103,515,890	104,344,017	105,178,769	106,020,199	106,868,361	107,723,308	108,585,094	109,453,775	110,329,405	111,212,040	112,101,737
% of population 15-64 years of age	*65.0%*	*65.0%*	*65.0%*	*65.0%*	*65.0%*	*65.0%*	*65.0%*	*65.0%*	*65.0%*	*65.0%*	*65.0%*
EU population 15-64 years of age	336,426,642	339,118,055	341,831,000	344,565,648	347,322,173	350,100,750	352,901,556	355,724,769	358,570,567	361,439,131	364,330,644
% of population 15-64 years of age with increased risk	*21.0%*	*21.0%*	*21.0%*	*21.0%*	*21.0%*	*21.0%*	*21.0%*	*21.0%*	*21.0%*	*21.0%*	*21.0%*
EU population 15-64 years of age with increased risk	70,649,595	71,214,792	71,784,510	72,358,786	72,937,656	73,521,158	74,109,327	74,702,201	75,299,819	75,902,218	76,509,435
Total number of increased risk individuals not vaccinated	174,165,485	105,335,285	61,937,148	62,432,645	98,893,309	154,057,796	164,424,979	165,740,379	167,066,302	168,402,832	169,750,055
% of total EU population	*33.7%*	*20.2%*	*11.8%*	*11.8%*	*18.5%*	*28.6%*	*30.3%*	*30.3%*	*30.3%*	*30.3%*	*30.3%*
Individuals taken prophylaxis	0	10,533,529	6,193,715	4,994,612	5,933,599	4,621,734	3,288,500	1,657,404	1,670,663	1,684,028	1,697,501
Prophylaxis penetration	*0%*	*10%*	*10%*	*8%*	*6%*	*3%*	*2%*	*1%*	*1%*	*1%*	*1%*
Price/dose	$75	$75	$75	$75	$75	$75	$75	$75	$75	$75	$75
% change		*0%*	*0%*	*0%*	*0%*	*0%*	*0%*	*0%*	*0%*	*0%*	*0%*
Avg. number of doses per year		2	2	2	2	2	2	2	2	2	2
Total EU Prophylaxis Revenue ($MM)	**$0**	**$790**	**$465**	**$375**	**$445**	**$347**	**$247**	**$124**	**$125**	**$126**	**$127**
Global Prophylaxis Revenue ($MM)	**$0**	**$1,656**	**$974**	**$786**	**$934**	**$728**	**$518**	**$261**	**$264**	**$266**	**$268**

Source: Cowen and Company

Based on the price sensitivity analyses for the base case scenario, we project prophylaxis sales to reach peak sales of $1.7B in FY21 at a price of $125/dose in the US and $75/dose in EU.

Price Sensitivity For Prophylaxis Relative To Our Base Case Of $125/Dose

		Price/Dose In The US						
	Sales ($MM)	**$50**	**$75**	**$100**	**$125**	**$150**	**$175**	**$200**
Year	**2020**	$0	$0	$0	$0	$0	$0	$0
	2021	$663	$994	$1,325	$1,656	$1,988	$2,319	$2,650
	2022	$390	$585	$780	$974	$1,169	$1,364	$1,559
	2023	$314	$472	$629	$786	$943	$1,101	$1,258
	2024	$374	$561	$748	$934	$1,121	$1,308	$1,495
	2025	$291	$437	$583	$728	$874	$1,020	$1,165

Source: Cowen and Company

Treatment Is A Smaller Opportunity With Potential Upside

In the treatment segment, we think it's going to be hard for antibody manufacturers to have different antibody therapy prices for prophylaxis and treatment. We think it will be most likely that the unit price will be set (i.e. by milligrams, by syringe, or by bottle). We anticipate that the per dose price might be higher for treatment compared with prophylaxis as a higher dose is likely needed for antibody treatment to elicit stronger antiviral responses in the symptomatic patients.

We project sales to peak at ~$1.2B in FY21 with 30% penetration in the symptomatic COVID-19 patients (hospitalized and non-hospitalized patients) at a price of $750 per patient in the US and $450 per patient in EU (6X of the prophylaxis cost on the per dose basis).

Of note, the retail price of dexamethasone is $39 on average. Recall, dexamethasone recently showed promise in treating COVID-19 patients by reducing mortality by one-third in ventilated patients (HR 0.65; P = 0.0003) and by one-fifth in patients on oxygen but not ventilated (HR 0.80; P = 0.0021).

Gilead Veklury (remdesivir) was recently priced at $390 per vial, which equates to $2,340 per patient for all governments in the developed world based on current treatment patterns of a 5-day treatment course with 6 vials. US insurers will pay $3,120 and countries in the developing world will get greatly reduced prices through generic manufacturers. Recall, Veklury showed accelerated recovery in moderate and severe hospitalized patients in the SIMPLE & NIAID studies.

We anticipate that the market opportunity in this segment will become smaller over time as the vaccines and prophylaxis are expected to prevent more people from getting infected or lower the severity of the infection.

Antibody Treatment Is A Smaller Opportunity And We Expect The Market To Diminish Over Time

Treatment Market

	2020E	2021E	2022E	2023E	2024E	2025E	2026E	2027E	2028E	2029E	2030E
US patients diagnosed with COVID-19	4,500,000	7,650,000	4,972,500	3,232,125	2,100,881	1,365,573	887,622	576,955	375,020	243,763	158,446
Growth rate		*70%*	*-35%*	*-35%*	*-35%*	*-35%*	*-35%*	*-35%*	*-35%*	*-35%*	*-35%*
% of patients with symptoms (hospitalized + non-hospitalized)	*65%*	*60%*	*55%*	*50%*	*45%*	*40%*	*37%*	*34%*	*31%*	*28%*	*25%*
Total number of patients with symptoms	2,925,000	4,590,000	2,734,875	1,616,063	945,397	546,229	328,420	196,165	116,256	68,254	39,612
Individuals taken treatment	0	1,377,000	820,463	404,016	189,079	92,859	45,979	23,540	11,626	6,825	3,961
Treatment penetration	*0%*	*30%*	*30%*	*25%*	*20%*	*17%*	*14%*	*12%*	*10%*	*10%*	*10%*
Price	$750	$750	$750	$750	$750	$750	$750	$750	$750	$750	$750
% change		*0%*	*0%*	*0%*	*0%*	*0%*	*0%*	*0%*	*0%*	*0%*	*0%*
Total US Treatment Revenue ($MM)	**$0**	**$1,033**	**$615**	**$303**	**$142**	**$70**	**$34**	**$18**	**$9**	**$5**	**$3**
EU patients diagnosed with COVID-19	1,500,000	2,550,000	1,657,500	1,077,375	700,294	455,191	295,874	192,318	125,007	81,254	52,815
Growth rate		*70%*	*-35%*	*-35%*	*-35%*	*-35%*	*-35%*	*-35%*	*-35%*	*-35%*	*-35%*
% of patients with symptoms (hospitalized + non-hospitalized)	*65%*	*60%*	*55%*	*50%*	*45%*	*40%*	*37%*	*34%*	*31%*	*28%*	*25%*
Total number of patients with symptoms	975,000	1,530,000	911,625	538,688	315,132	182,076	109,473	65,388	38,752	22,751	13,204
Individuals taken treatment	0	459,000	273,488	134,672	63,026	30,953	15,326	7,847	3,875	2,275	1,320
Treatment penetration	*0%*	*30%*	*30%*	*25%*	*20%*	*17%*	*14%*	*12%*	*10%*	*10%*	*10%*
Price	$450	$450	$450	$450	$450	$450	$450	$450	$450	$450	$450
% change		*0%*	*0%*	*0%*	*0%*	*0%*	*0%*	*0%*	*0%*	*0%*	*0%*
Total EU Treatment Revenue ($MM)	**$0**	**$207**	**$123**	**$61**	**$28**	**$14**	**$7**	**$4**	**$2**	**$1**	**$1**
Global Treatment Revenue ($MM)	**$0**	**$1,239**	**$738**	**$364**	**$170**	**$84**	**$41**	**$21**	**$10**	**$6**	**$4**

Source: Cowen and Company

Of note, our estimate is based on the following assumptions: 1) the average of daily new cases will be ~25k/day in H2:20 in the US; 2) the annual cases will be ~7.7M in FY21, which decrease by 35% year over year from FY22 onward due to vaccination and prophylaxis; 3) the protection provided by vaccines may last for ~1 year.

We think that there are still many unknowns that could substantially change our estimates, such as the magnitude of the second wave, the progress of vaccine development, and the durability of immunity. We see an upside to our estimate if there is a bigger second wave or the immunity lasts less than a year.

Based on our price sensitivity analyses, we project treatment sales to reach the peak of ~$1.2B in FY21 at a price of $750 per patient in the US and $450 per patient in EU.

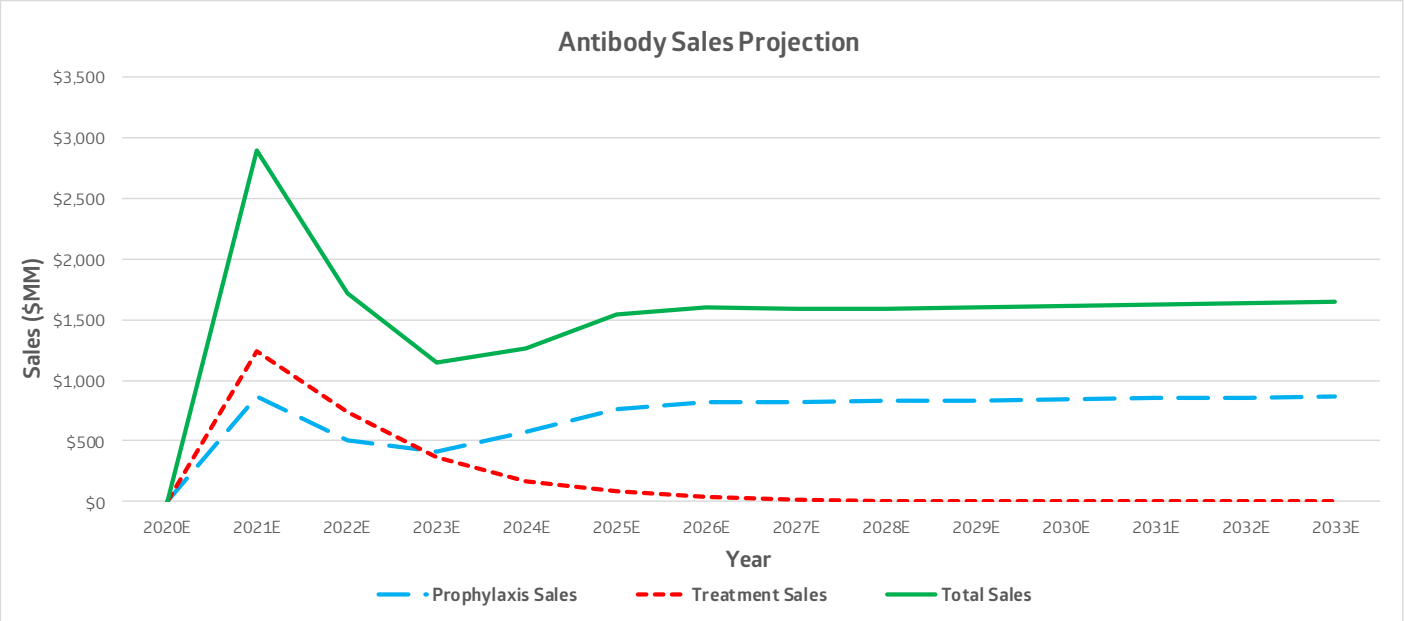
Price Sensitivity For Treatment Relative To Our Base Case Of $750/Patient

		Price/Patient In The US						
	Sales ($MM)	**$300**	**$450**	**$600**	**$750**	**$900**	**$1,050**	**$1,200**
Year	**2020**	$0	$0	$0	$0	$0	$0	$0
	2021	$496	$744	$991	$1,239	$1,487	$1,735	$1,983
	2022	$295	$443	$591	$738	$886	$1,034	$1,181
	2023	$145	$218	$291	$364	$436	$509	$582
	2024	$68	$102	$136	$170	$204	$238	$272
	2025	$33	$50	$67	$84	$100	$117	$134

Source: Cowen and Company

In total, we project antibody sales to reach the peak of $2.9B in FY21, then decline to $270-280M in FY27 and roughly stabilize at that level onwards. We estimate the total of antibody sales in FY21-FY33 will reach $10B (prophylaxis: $7B and treatment: $3B).

Antibody Sales Are Expected To Peak At ~$2.9B In FY21



Source: Cowen and Company

Antibody Manufacturers Are Scaling Up Their Production Capacity To Meet The High Demand – We Estimate Tens Of Millions Of Doses Will Be Needed By 2021

Overall, we estimate that the annual demand in the US will be ~156k treatment doses for hospitalized patients, ~4.4M treatment doses for non-hospitalized symptomatic patients, and ~69M preventative doses for the high-risk population in FY21.

Our consultant noted that many antibody companies develop their own cell lines with some developed lower titer (<2 g/L) and some developed high titer (>10 g/L) cell lines. To scale up the antibody production to meet the high demand, antibody manufacturers need to either optimize their manufacturing process (i.e. downstream cell culture process and the upstream purification process) or free up the capacity in a facility for dedicated COVID-19 antibody production.

Our consultant also noted that that the industry average is 15-20 batches/year and many companies can easily scale up their capacity to 200-250 batch/year if they free up the production lines of other drugs for COVID-19 antibody production.

Recall, multiple antibody companies have already started to scale up their manufacturing capacity due to the high unmet need. We anticipate that these companies will have the capacity of collectively delivering tens of millions of doses in 2021.

Antibody Therapy Timelines And Manufacturing Capacity

Company	Approach	Candidate	Clinical Status	Catalyst/Milestone	Manufacturing Capacity By 2020	Manufacturing Capacity By 2021
Eli Lilly/ AbCellera/ Junshi	Single antibody and antibody cocktail	LY-CoV555 (Human IgG1)	Ph1 in hospitalized pts started on 6/1 BLAZE-1 Ph2 in mild to moderate pts started on 6/17 BLAZE-2 Ph3 prevention trial started on 8/3	To report efficacy data from BLAZE-1 in Q4:20 To start a Ph3 treatment trial in the coming weeks	Several hundred thousand doses by YE:20	Not disclosed
		JS016	Ph1 in healthy subjects started on 6/8 and reported positive topline safety data with no DLE as of 7/12	To start a Ph1b trial in non-severe COVID-19 patients and Ph2/3 trials in severe and critical patients soon		
		A third candidate	NA	Might be combined with LY-CoV555 and/or JS016		
Regeneron/ Roche	Two-antibody cocktail	REGN-COV2 (REGN10987 + REGN10933)	The first 2 adaptive Ph1/2/3 treatment studies in hospitalized and non-hospitalized patients started on 6/11 and moved to the Ph2/3 on 7/6 Ph3 prevention study started on 6/30	To report initial data from the treatment trials in September	70k-300k potential treatment doses or 420k- 1,300k prevention doses as early as end of summer	1M doses per month by FY21 by Regeneron and ≥3.5X globally with Roche collaboration
Celltrion	Single antibody and two-antibody cocktail	CT-P59	Ph1 in healthy volunteers started in UK in mid July; Global Phase 1 in mild COVID-19 patients started in August	To complete Ph1 in healthy volunteers by Q3:20; To start further global Phase 2 and 3 prevention and treatment trials soon and have pivotal data by YE:20	NA	Mass-production to cover up to 5M patients a year by H1:21
Vir/GSK	Single antibody	VIR-7831/ VIR-7832 (Human IgG1)	Ph2/3 of VIR-7831 started in August	To report initial data from Ph2/3 of VIR-7831 by YE:20 To start a Ph2 of VIR-78312 in H2:20. Both will be tested as prophylaxis and treatment	Hundreds of thousands of doses by YE:20	Tens of millions of doses by FY21
Amgen/ Adaptive	NA	NA	NA	NA	NA	NA
AstraZeneca/ Vanderbilt Univ.	Two-antibody cocktail	AZD7442 (AZD8895 +AZD1061)	Ph1 started in late August	Likely to have initial data in Q4:20	NA	1M doses to start as early as H1:21
BeiGene/ Singlomics	Single antibody and a potential two-antibody cocktail	DXP-593 and DXP-604	NA	To start a placebo-controlled Ph1 trial in September; To start a global Phase 1/2 trial in mild-to-moderate COVID-19 by early October	NA	NA
AbbVie/ Harbour/ Utrecht U/ Erasmus Med Center	Single antibody	47D11	Not started yet	NA	NA	NA

Source: Cowen and Company, Company reports

Gilead's Veklury (Remdesivir) Is The First Therapeutic To Gain Emergency Use Authorization For COVID-19 In The U.S.

Gilead's Veklury (remdesivir; aka GS-5734) is a nucleotide analogue initially developed as a treatment for the Ebola and Marburg viruses. It was later shown to have activity against coronaviruses such as MERS and SARS and more recently was shown to be effective against SARS-CoV-2 in preclinical models. Several clinical studies to date have shown remdesivir to be effective in the treatment of hospitalized patients with COVID-19, and remdesivir was granted emergency use authorization (EUA) for hospitalized patients with severe COVID-19 symptoms by the FDA on May 1, 2020. The EUA was subsequently expanded on August 28 to include all hospitalized patients with COVID-19. Gilead announced on August 10, 2020 that it had filed an NDA for remdesivir for the treatment of patients with COVID-19.

Recently Completed Phase 3 Studies Support Veklury's Activity

On February 26, 2020, Gilead announced the initiation of two multinational Phase 3 studies to evaluate remdesivir for the treatment of adult patients hospitalized with COVID-19. The SIMPLE-severe study was initially designed to enroll n=400 patients with severe COVID-19 to be randomized 1:1 to receive a 5-day or 10-day course of treatment of intravenous remdesivir. The SIMPLE-moderate study was initially designed to enroll n=600 patients with moderate COVID-19 to be randomized 1:1:1 to receive either a 5-day or 10-day course of intravenous remdesivir or standard of care alone. The SIMPLE-severe study was subsequently expanded to enroll an additional 5.6K patients, and the SIMPLE-moderate study was modified to enroll an additional 1.0K patients.

Select Clinical Studies Of Remdesivir In COVID-19

Data Source		Target Enrollment	Moderate Hospitalized Patients	Severe Requiring Oxygen	Critical Intubated Patients	Placebo or Standard of Care included?	Key Question
REMDESIVIR MONOTHERAPY							
China	Randomized, double-blind	n = 453 (237 enrolled)	–	✓	–	P	1. Is remdesivir a safe and effective treatment for COVID-19 patients?
China	Randomized, double-blind	n = 308 (74 enrolled)	✓	–	–	P	
NIH NIAID	Randomized, double-blind	n = 1,053	✓	✓	✓	P	
GILEAD	Randomized, open label	n = 600[2]	✓	–	–	SoC	2. Is a 5-day treatment course as effective as a 10-day course?
GILEAD	Randomized, open label	n = 400[3]	–	✓	–	–	
REMDESIVIR COMBINATION THERAPY							
NIH NIAID	Randomized, double-blind combination with Baricitinib	n = TBD	✓	✓	✓	SoC	3. Can combination therapies improve outcomes?

Source: Gilead Q1:20 Earnings Slides

The Gilead-sponsored studies were designed to augment several trials of remdesivir that had already been initiated at the time, including two placebo-controlled studies conducted in China's Hubei province led by the China-Japan Friendship Hospital and a placebo-controlled study led by NIAID.

Positive NIAID-Led Study Suggests Remdesivir Is Active And Will Have A Role In Treatment

On April 29, 2020, Dr. Fauci, the director of the NIAID, made a statement to the press detailing topline results from the randomized, placebo-controlled NIAID-led study of remdesivir in patients with COVID-19. Results from the ACTT-1 study were subsequently published in the *NEJM* on May 22, 2020.

The study enrolled n=1,063 patients hospitalized with COVID-19 and evidence of lower respiratory tract involvement. Patients were randomized 1:1 to receive either a 10-day course of treatment with remdesivir or placebo. On April 27, the data and safety monitoring board conducted an interim analysis and recommended an early unblinding of the results of the study due to an indication that patients in the remdesivir arm were achieving improvement in time to recovery. Interim data from n=1,059 patients were available at the interim analysis. On the primary endpoint of time to recovery (either discharged or hospitalized but not requiring supplemental oxygen or ongoing medical care), remdesivir treatment led to a statistically significant 32% improvement vs. placebo (median 11 days vs. 15 days, p<0.001). Mortality was also numerically lower for patients treated with remdesivir vs. placebo, though the difference was not statistically significant (HR=0.70; 95% CI, 0.47 to 1.04). The Kaplan-Meier estimates of mortality by 14 days were 7.1% for patients who received remdesivir and 11.9% for patients who received placebo.

Remdesivir continued to demonstrate a favorable safety profile. Serious AEs were seen in 21% of patients treated with remdesivir vs. 27% of patients treated with placebo. Grade ≥3 AEs were observed in 29% of patients given remdesivir vs. 33% of patients given placebo. NIAID is now conducting a 1,032-patient Phase 3 combination study of remdesivir with Lilly/Incyte's JAK inhibitor baricitinib in hospitalized patients with COVID-19 (ACTT-II, NCT04401579). According to clinicaltrials.gov, as of July 15, 2020, this study had completed enrollment at n=1,034 patients.

We discussed remdesivir's results with a COVID KOL on an investor call following release of the top-line data. He thinks the available information suggests that remdesivir has anti-viral activity against the SARS-CoV-2 virus with an acceptable safety profile, and therefore it is likely to have a role in the treatment of patients hospitalized for COVID-19. Nonetheless, he thinks that remdesivir has moderate (not dramatic) benefits in the time to disease recovery and progression of the disease. Nonetheless, as there are few other therapies with proven benefit, he suggests that remdesivir will be first-line therapy for hospitalized patients. He is hopeful that remdesivir will eventually be used as part of combination regimens that will produce more meaningful benefits.

SIMPLE-Severe Study Suggests 5-Day And 10-Day Courses Of Remdesivir Have Equivalent Efficacy In Severe COVID-19 Patients

In April 29, Gilead announced top-line results from the first open-label Phase 3 SIMPLE study of remdesivir in patients with severe COVID-19. Data were subsequently published in the *NEJM* on May 27. The study enrolled n=397 patients who were randomized 1:1 to receive either 5 or 10 days of treatment with IV remdesivir (200mg on the first day and 100mg per day thereafter). At baseline patients had radiologic evidence of pneumonia and either oxygen saturation of ≤94% on room air or receiving supplemental oxygen, excluding patients on ECMO or mechanical ventilation. The study was previously expanded to enroll an additional 5.6K patients, including those on mechanical ventilation.

The primary endpoint of the study is clinical status at day 14, assessed using a 7-point scale. The scale is 1 - death, 2 - hospitalized, on invasive mechanical ventilation or extra

corporeal membrane oxygenation (ECMO), 3 - hospitalized, on non-invasive mechanical ventilation or high flow oxygen devices, 4 - hospitalized, requiring low flow supplemental oxygen, 5 - hospitalized, not requiring supplemental oxygen - requiring ongoing medical care, 6 - hospitalized, not requiring supplemental oxygen - no longer requiring ongoing medical care, and 7 - not hospitalized.

At baseline, the 5-day and 10-day groups were balanced in terms of demographic characteristics, but not baseline disease characteristics. More patients in the 10-day group vs. the 5-day group had a clinical status of (2) at baseline (5% vs. 2%) and more patients had a clinical status of (3) at baseline (30% vs. 24%). This led to a statistically significant difference in clinical status at baseline (p=0.02).

Overall, 65% (n=129/200) and 54% (n=107/197) of patients in the 5-day and 10-day group, respectively achieved clinical improvement of ≥2-points on the 7-point scale at day 14. After adjusting for the imbalance in clinical status at baseline, there was no difference in the distribution of clinical status at day 14 for patients randomized to the 5-day or 10-day treatment groups (p=0.14).

The median time to clinical improvement was 10 days and 11 days for patients given the 5-day and 10- day treatment course of remdesivir, respectively. At day 14, a majority of patients in both groups were discharged from the hospital: 60% (n=120/200) of patients in the 5-day group and 52% (n=103/197) of patients in the 10-day group (p=0.44). Day 14 mortality rates were 8% (n=16/200) and 11% (n=21/197) in patients treated for 5-days and 10-days, respectively (p=0.70).

Efficacy Outcomes From The SIMPLE-Severe Study Of Remdesivir In Severe COVID-19

Outcome, n (%)	RDV for 5 Days (n=200)	RDV for 10 Days (n=197)
Subjects with Recovery	140 (70%)	116 (59%)
≥ 2-pt Improvement in Ordinal Scale	129 (65%)	107 (54%)
Discharge	120 (60%)	103 (52%)
Death	16 (8%)	21 (11%)
Duration of hospitalization from Day 1, median (IQR)	7 (6-10)	8 (5-10)
Total duration of hospitalization, median (IQR)	10 (8-13)	10 (8-13)

Source: Gilead Q1:20 Earnings Slides

Gilead indicated that outcomes differed by geography and provided data excluding patients treated in Italy. Ex-Italy, at day 14 the rate of clinical improvement across both arms was 64% (n=205/320), the rate of discharge was 61% (n=196/320), and the overall mortality rate was 7% (n=23/320).

Gilead also provided data from an exploratory analysis of the impact of earlier treatment on outcomes. Patients who received treatment within 10 days of symptom onset appeared to have superior outcomes vs. patients who received treatment >10 days after symptom onset. Across both treatment arms, by day 14, 62% of patients who received early treatment were discharged from the hospital vs. 49% of patients who received later treatment.

Safety was similar in both groups. Serious AEs were observed in 21% of patients in the 5-day group and 35% of patients in the 10-day group. Grade ≥3 AEs were observed in 30% of patients in the 5-day group and 43% of patients in the 10-day group. Remdesivir

appeared sufficiently safe and well-tolerated. The most common AEs in the 5-day and 10-day treatment arms were nausea (10% and 9%), acute respiratory failure (6% and 11%), increased ALT (6% and 8%), and constipation (7% in both groups).

In our consultant's opinion, data from Gilead's first Phase 3 SIMPLE trial in patients with severe COVID-19 continue to suggest remdesivir is sufficiently safe to be used to treat SARS-CoV-2. Moreover, patients treated with a 5-day course of RDV appeared to have similar outcomes to those treated for 10 days, suggesting a shorter duration of treatment should be sufficient for at least some patients. Early data point toward trends in improved outcomes for patients who receive RDV earlier in their disease course (within 10 days of symptom onset). Given the lack of a control arm in the first SIMPLE study, our consultant finds it difficult to discern the true impact of RDV on disease progression, and therefore he thinks the data are not conclusive on their own in proving remdesivir's benefit.

Chinese Studies Were Inconclusive Due To Early Termination

Initially the two Chinese studies of remdesivir had intended to enroll n=308 moderate COVID-19 patients (NCT04252664) and n=453 patients with severe disease (NCT04257656). In early April 2020, the moderate study was suspended after having enrolled only n=74 patients due to effective control of COVID-19 in China. The severe study was terminated after having enrolled only n=237 patients. Results from the severe study were published in *The Lancet* on April 29, 2020.

The study enrolled n=237 patients with severe COVID-19 who were randomized 2:1 to receive 10-days of treatment with remdesivir or placebo. While remdesivir failed to improve time to clinical improvement vs. placebo (HR=1.23), an analysis of patients who received treatment within 10 days of symptom onset demonstrated numerically faster time to improvement (HR=1.52).

We would note that, in the Chinese study, the median time to clinical improvement was 21.0 days in patients given remdesivir vs. 23.0 days for patients given placebo. This is substantially slower than the median time to clinical improvement observed in the Phase 3 SIMPLE study conducted by Gilead, in which patients treated with remdesivir for 10 days experienced clinical improvement at a median of 11 days. In the Chinese study, day-28 mortality was 14% (n=22/158) for patients treated with remdesivir and 13% (n=10/78) for patients given placebo. AEs were balanced between arms (66% for RDV vs. 64% for placebo), and the rate of discontinuations was low (12% for RDV vs. 5% for placebo).

Full data from the failed Chinese study of remdesivir reaffirm remdesivir's safety profile and corroborate the trend observed in the SIMPLE study toward improved outcomes for patients who receive early treatment. Our consultants believe these results are in keeping with the underlying biology of the disease - that the virus is the main driver early in the disease course before inflammation becomes paramount. Antivirals are expected to be useful shortly after symptom onset whereas anti-inflammatory mechanisms are thought to be required later. Our KOL is not overly concerned by the trial's missed primary endpoint as it was stopped early due to insufficient enrollment; it may have been underpowered to determine an effect of remdesivir on disease progression.

Remdesivir Data In Moderate COVID-19 Continue To Support Use, Lead To Expansion Of FDA's EUA

On June 1, 2020, Gilead announced top-line results from the second of the two Phase 3 SIMPLE trials of remdesivir in patients with COVID-19. Results were published in *JAMA*

in August 2020. This study was conducted in hospitalized patients with moderate COVID-19 who had pneumonia but no reduction in oxygen saturation level.

In the initial portion of the study, n=596 patients were randomized to receive either a 5-day treatment course of remdesivir, a 10-day treatment course of remdesivir, or standard of care alone. The study was previously expanded to enroll up to an additional 1K moderate COVID-19 patients.

The primary endpoint of the study is the odds ratio of improvement in clinical status vs. SOC on day 11, assessed via a 7-point ordinal scale. According to clinicaltrials.gov, the scale is 1 - death, 2 - hospitalized, on invasive mechanical ventilation or extra corporeal membrane oxygenation (ECMO), 3 - hospitalized, on non-invasive mechanical ventilation or high flow oxygen devices, 4 - hospitalized, requiring low flow supplemental oxygen, 5 - hospitalized, not requiring supplemental oxygen - requiring ongoing medical care, 6 - hospitalized, not requiring supplemental oxygen - no longer requiring ongoing medical care, and 7 - not hospitalized.

The 5-day course of remdesivir successfully differentiated from SOC on the primary endpoint, as patients treated with 5-day remdesivir were 65% more likely to achieve clinical improvement vs. SOC on day 11 (OR=1.65; p=0.017). Though patients treated with the 10-day course of remdesivir were numerically more likely to achieve clinical improvement on day 11 vs. SOC, the level of improvement failed to achieve statistical significance (OR=1.35; p=0.18).

The 5-day course of remdesivir led to a higher proportion of patients achieving a ≥1-point improvement in clinical status vs. SOC on day 11 (76% vs. 66%; p=0.026). There were also numerical improvements for both remdesivir groups vs. SOC on the proportion of patients who experienced clinical worsening (5-day RDV: 3%, 10-day RDV: 6%, SOC: 11%) or death (5-day RDV: 1%, 10-day RDV: 2%, SOC: 2%), though these were not statistically significant.

Remdesivir continues to appear sufficiently safe and well-tolerated. The most common AEs in the 5-day remdesivir, 10-day remdesivir, and SOC arms were nausea (10%, 9%, 3%), diarrhea (6%, 5%, 7%), hypokalemia (5%, 7%, 2%), and headache (5%, 5%, 3%). The rate of grade ≥3 AEs was 10%, 12%, and 12% and the rate of serious AEs was 5%, 5%, and 9% for patients randomized to 5-day remdesivir, 10-day remdesivir, and SOC, respectively.

We are encouraged that the 5-day course of treatment with remdesivir has shown a statistically significant improvement vs. SOC on clinical improvement in patients with moderate COVID-19. These data corroborate the previous results of the NIAID-led study of remdesivir and continue to indicate that remdesivir is sufficiently safe and active, supporting its use in the treatment of hospitalized patients with COVID-19.

The SIMPLE moderate study had recruited patients with more moderate disease than either the SIMPLE severe study or the NIAID-led study. As our consultants had postulated that the efficacy of remdesivir would be greater when used earlier in the course of the disease, we suspect some investors may have expected markedly better outcomes in the moderate study compared to the prior studies. In fact, patients treated with 5-day remdesivir were 65% more likely to achieve clinical improvement vs. SOC on day 11. Nonetheless, remdesivir's benefits in treating COVID-19 continue to look relatively modest, even in the more moderate population. Only 10% more patients achieved a ≥1-point improvement in clinical status vs. SOC on day 11 (76% vs. 66%), and the 10-day treatment course failed to differentiate from SOC on the primary endpoint. Therefore, while the data continue to support use, it is also clear that other agents and

combination regimens will be needed to further improve outcomes for hospitalized patients.

Our physician consultant had previously raised a concern that, with the initial analysis having only ~200 patients per arm, the SIMPLE moderate study may have been somewhat underpowered given the moderate magnitude of remdesivir's benefit. Data from the 1K patient extension study may further clarify the potential benefit of remdesivir generally, and the 10-day treatment course more specifically. Data from the expansion will be shared in the next couple of months.

On August 28 the FDA expanded remdesivir's EUA based on the SIMPLE Moderate study results to include all hospitalized patients regardless of whether they are receiving supplemental oxygen or mechanical ventilation.

We Project Peak Global Veklury Revenue of $3.6B In 2020

On May 1, 2020 remdesivir was granted an emergency use authorization (EUA) by the FDA for the treatment of hospitalized patients with severe COVID-19. The EUA was granted based on the top-line data from the NIAID-led study of remdesivir in addition to the Gilead-sponsored SIMPLE-severe study. Under the EUA, the 10-day regimen is recommended for patients on mechanical ventilation or ECMO and the 5-day regimen is recommended for all other patients, though treatment can be extended to 10 days in patients who do not improve after 5 days of treatment.

On August 29 remdesivir's EUA was expanded to include all patients hospitalized with COVID-19, regardless of whether they are receiving supplemental oxygen or mechanical ventilation. An NDA for remdesivir was filed in August 2020.

On June 30, 2020, Gilead disclosed that, with the last of the 250K donated treatment courses of remdesivir being shipped, it would begin recording remdesivir (Veklury) revenue and that its price had been set at $390 per vial for governments of developed countries. Gilead expects most patients will receive a 5-day treatment course requiring 6 vials, which results in a total cost per patient of $2,340. The decision to implement flat pricing was taken to avoid the need for price negotiation on a country-by-country basis. In the U.S., while government healthcare programs will be able to purchase remdesivir at the $390/vial price, private insurance companies will pay ~33% more at $520/vial or $3,120/patient in total for a 5-day treatment course.

Gilead has indicated that by early October 2020, manufacturing should be sufficient to meet real-time global demand. Though Gilead anticipates that more than 2MM doses of remdesivir will be produced in 2020, much will be available only very late in Q4:20. Gilead's guidance calls for 1-1.5MM treatment courses to be sold during H2:20. We expect remdesivir to remain part of the standard of care for hospitalized patients for the foreseeable future, but we project that the number of hospitalized patients will decline after the first effective vaccine is launched. Our model assumes that happens in 2021. Based upon these assumptions, we project remdesivir revenue of $3.6B, $2.1B, $1.4B, $1.0B, and $750MM for 2020-24.

Admittedly, any projections are likely to be imprecise as there is much uncertainty as to how the treatment paradigm will evolve with hundreds of therapeutics and vaccines in development. Moreover, the number of patients who will be hospitalized for COVID-19 in future years cannot be known with any real precision in light of the prospects for effective vaccines and treatments, herd immunity, and/or continued social distancing. We will continue to re-evaluate our projections as the pandemic and treatment paradigm evolve.

Global Veklury COVID-19 Revenue Model

	2020E	2021E	2022E	2023E	2024E	2025E
US population	330,487,927	333,462,318	336,463,479	339,491,650	342,547,075	345,629,999
Growth rate	*1%*	*1%*	*1%*	*1%*	*1%*	*1%*
% Of Population Diagnosed With COVID-19	*2%*	*3%*	*2%*	*1%*	*1%*	*1%*
Number Of Diagnosed U.S. COVID-19 Cases (K)	7000	9000	5047	3395	2213	2169
% Hospitalized	*13%*	*13%*	*13%*	*13%*	*13%*	*13%*
Number Of Hospitalized U.S. COVID-19 Cases (K)	910	1170	656	441	288	282
% Remdesivir Penetration	*110%*	*47%*	*55%*	*60%*	*60%*	*60%*
Number Of U.S. COVID-19 Cases On Remdesivir (K)	1000	549	359	264	173	169
Price Per Treatment Course ($)	$2,750	$2,730	$2,785	$2,840	$2,897	$2,955
U.S. Remdesivir Revenue ($MM)	$2,750	$1,500	$1,000	$750	$500	$500
EU population	517,579,449	521,720,085	525,893,846	530,100,996	534,341,804	538,616,539
Growth rate	*1%*	*1%*	*1%*	*1%*	*1%*	*1%*
% Of Population Diagnosed With COVID-19	*1%*	*1%*	*0%*	*0%*	*0%*	*0%*
Number Of EU COVID-19 Cases (K)	4400	3000	2192	1370	1370	1370
% Hospitalized	*13%*	*13%*	*13%*	*13%*	*13%*	*13%*
Number Of Hospitalized COVID-19 Cases (K)	572	390	285	178	178	178
% Remdesivir Penetration	*64%*	*66%*	*60%*	*60%*	*60%*	*60%*
Number Of EU COVID-19 Cases On Remdesivir (K)	363	256.4	170.9	106.8	106.8	106.8
Price Per Treatment Course ($)	$2,340	$2,340	$2,340	$2,340	$2,340	$2,340
EU Remdesivir Revenue ($MM)	$850	$600	$400	$250	$250	$250
Worldwide Veklury Revenue ($MM)	**$3,600**	**$2,100**	**$1,400**	**$1,000**	**$750**	**$750**

Source: Cowen and Company

Developing A Vaccine For Novel Virus – Literally An Operation Warp Speed

COVID-19 Has Already Outpaced Prior Coronavirus Outbreaks Due To Long Infectious Period Even Following Resolution Of Symptoms

The current COVID-19 pandemic represents the third and most severe outbreak of coronavirus since the turn of the century. The 2002-'03 spread of SARS lasted ~7 months, included >8,000 confirmed cases of infection and caused 774 deaths across 26 countries. The more recent outbreak of MERS in 2012 had a high case fatality rate (CFR) of ~35% but was much narrower in scope. Stemming from its high transmissibility and prolonged period of infectiousness, estimated to range from 8-37 days in data from Wuhan, the SARS-CoV-2 virus has spread rapidly and has already surpassed 27M confirmed cases globally. Strict containment efforts have effectively slowed the spread, providing time for health care systems to decompress and for society to formulate a plan for a new normal.

Data Indicates Resurgence Is Likely With Containment Efforts Eased

Work from Harvard's School of Public Health has projected that a second wave (with several thereafter) is unavoidable without indefinite social distancing until a vaccine is available. According to their model, easing of social distancing prior to a vaccine leads to widespread infection (>50% of the population) within a short period of time; the rapidity depends on whether social distancing is intermittently reinstated or abandoned. The contagion would only stop when herd immunity is reached.

R_0 = the expected number of cases generated by one case assuming the entire population is susceptible

R_e = the expected number of cases generated by one case accounting for mitigating factors (e.g. masks) and the presence of non-susceptible hosts

Due to social and economic pressures, it is clear that society is not prepared to remain under lockdown until a vaccine is available, with many countries currently navigating the reopening process despite persistent cases. We have seen the effective reproduction number (R_e) go below 1 in many places during lockdown (viral spread eventually extinguishes when each infected person transmits to <1 other person), only to return above 1 with reopening. Without reinstituting lockdown measures, we expect cases to remain elevated over time with various hotspots emerging, though we likely will not revert back to the rampant transmission seen during March/April (when infectivity was essentially at R_0) due to increased awareness and precautions such as frequent hand washing, masks, 6 ft distancing, limitations on venue capacity, etc., as well as rising immunity in society.

In the face of ongoing resurgence without the prospect of reinstituting lockdown measures likely, health care companies are working around the clock to create a vaccine or therapeutic that can dramatically reduce R_e and mitigate spread. Governments around the world, especially the US, are attempting to expedite the process through riskless financing and regulatory streamlining.

Current Population Immunity Likely Low – Far From Herd Immunity Levels

If we will need >50% of the population to be resistant to achieve herd immunity (lower if there is heterogeneous susceptibility though there is no definitive evidence of this thus far), screening studies are the best way to estimate disease prevalence and know how close we are. Molecular testing, until only recently, has been geared to those with symptoms given limited capacity and thus that total confirmed case count is a vast underestimate of true cases. Serologic testing holds the key to defining the proportion of the population that has been exposed to SARS-CoV-2, with the caveat that work still needs to be done to determine the reliability of immunity in individuals with antibodies present. However, there is also some evidence that asymptomatic individuals do not mount detectable antibody responses but may still develop some form of immunity

which could result in significant undercounting. Nonetheless, it appears that seroconversion rates are still well below the threshold required for herd immunity.

Serologic testing was performed as a screening tool in Santa Clara County, California and found a population prevalence of 2.5-4.2%. While this is still very far away from herd immunity levels, it was 50 to 85 times higher than the number of confirmed cases at the time.

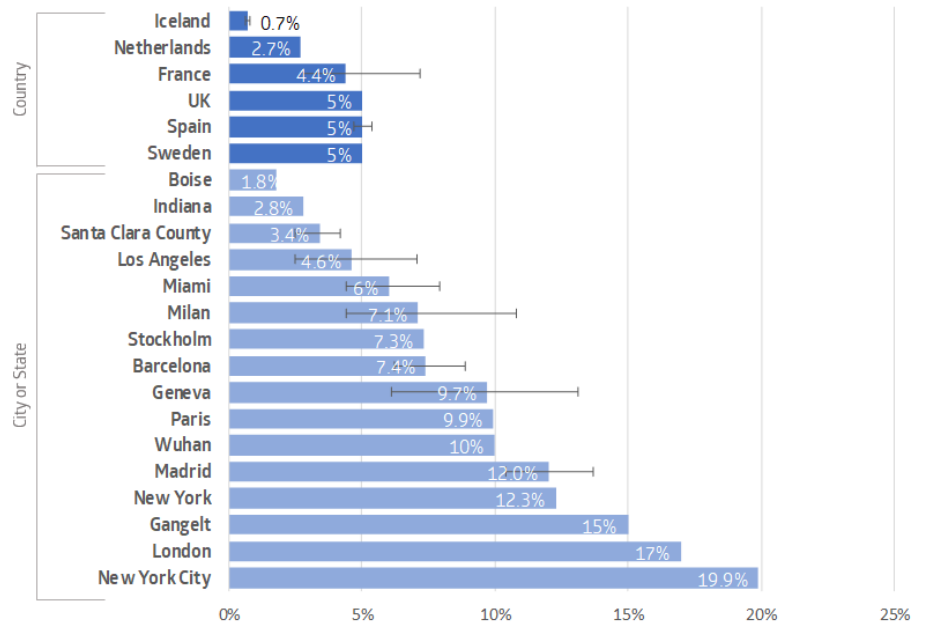
Serological testing shows that herd immunity rates are highly variable ranging from 0.7% in Iceland to 19.9% in New York City

Random testing done by New York State of approximately 15,000 people at grocery stores and shopping locations found antibodies in 12.3% of those tested, with a higher rate among those in NYC at 19.9%. This result is in line with the previously performed sampling of pregnant women in NYC that showed an antibody prevalence of 15%.

The highest reported prevalence was in a Boston homeless shelter population which revealed 36% of residents had acquired COVID-19, though this is a particularly vulnerable population and does not represent the likely prevalence in the region.

Testing done by Amgen/DeCode Genetics in Iceland showed herd immunity rates of 0.6-0.8% since the outbreak and a study in Gangelt, Germany showed a 15% rate in the hardest hit area of that country.

Estimated Percentage of the Population With Antibodies to SARS-CoV-2



Source: Cowen and Company, American Enterprise Institute

With herd immunity far away based on available seroprevalence studies, the global population remains highly vulnerable to a second wave and a highly effective vaccine or therapeutic will save lives if developed in time.

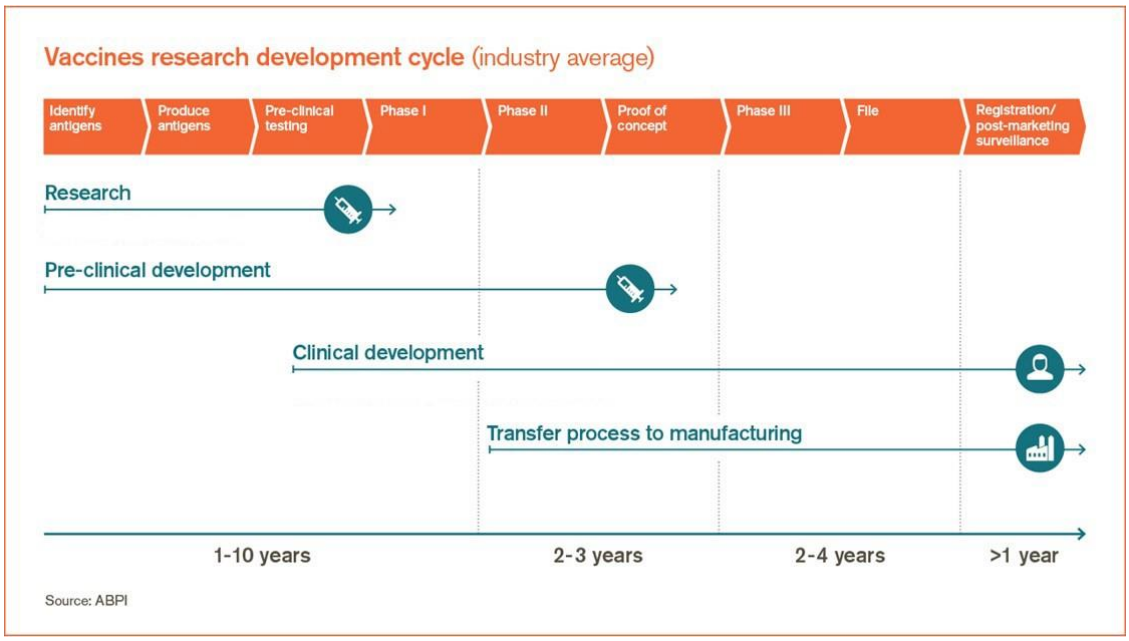
Traditionally Vaccines Take A Long Time and Have a High Failure Rate

With vaccine development in hyperdrive to shorten the timetable, the risk of failure among potential candidates is heightened. Even under 'normal' circumstances from 2006-2015, the success rate for the 238 vaccine candidates starting in Phase 1 was only

16.2%. The success rate for SARS-CoV-2 will likely be lower than 16.2% given the novelty of the virus and the rapid pace of vaccine development. The good news is that there are 176 COVID-19 vaccine candidates in development as of early September, and we only need a few to be successful in development.

No vaccine has ever been produced in less than several years; the process is characteristically slow due to the rigorous tasks of antigen selection, antigen production (via various modalities), preclinical testing, clinical dosing studies, toxicity analysis, antibody measurements, assessment of safety/efficacy upon infectious exposure, assessment of duration of protection, understanding stability/storage characteristics, optimizing manufacturing process, obtaining regulatory approval, and widespread distribution.

Average Timeline for Vaccine From Development to Market



Source: GSK, ABPI

One of the greatest challenges in vaccine development, and part of the reason for the high failure rate, is that the early measures of safety and antibody development in a Phase 1 trial are not necessarily predictive of the clinical response in a Phase 3 trial. A Phase 1 trial typically evaluates for toxicity at escalating vaccine dosages (short-term adverse reactions to the drug, not related to viral exposure post-vaccine) and development of new antibodies to the virus as confirmation that the vaccine is immunogenic. Thus, a vaccine that is immunogenic with acceptable toxicity will advance to further trials.

In contrast, late phase clinical trials evaluate how vaccinated individuals fare over time, most importantly when exposed to the target virus. It is common for the antibodies generated from a vaccine to be insufficient to provide immunity. In the worst-case scenario, the antibodies not only fail to be protective but instead augment the viral illness, a phenomenon known as immune enhancement (more details to follow below).

Operation Warp Speed Provides Jet Fuel To Bringing A Vaccine To The Market Quickly

Tagged "Operation Warp Speed," the U.S. government has targeted its resources toward select companies in order to pull forward manufacturing. The stated aim of the operation is to deliver 300M doses of a safe, effective vaccine by January 2021. As of the time of this report, over $10B has been committed to seven companies deemed most likely to produce a successful vaccine against SARS-CoV-2. The seven companies are Moderna, Sanofi/GSK, Pfizer/BioNTech, Novavax, JNJ, AstraZeneca/Oxford University and Merck.

7 Companies Selected Through Operation Warp Speed Have Been Allocated Over $10B

Modality	Vaccine Name	Developer(s)	Total US Gov't Contracts/Funding ($MM)	Current Phase	Potential News	Estimated Timing	Manufacturing Expectations
mRNA	mRNA-1273	Moderna	$2,480	Ph3	Complete Phase 3 Enrollment Phase 3 Data Regulatory Approval	September-20 December-20 Q1:21	500M to 1B doses per year in 2021
	BNT162b2	Pfizer/BioNTech	$1,950	Ph2/3	Complete Phase 2/3 Enrollment Phase 3 Data Regulatory Approval	September-20 October-20 Q1:21	100M doses by YE20, 1.3B doses in 2021
Adenoviral	AZD1222	AstraZeneca/Oxford	$1,200	Ph2/3	Phase 3 Data Regulatory Approval	October-20 Q4:20	400MM doses in Sept (at-risk), >1B doses in 2021
	Ad26.COV2-S	Janssen Pharma	$1,456	Ph1/2	Ph 1 Data Start Phase 3 Trial	September-20 September-20	500M doses in 2020, 1B doses in 2021
Replicating Viral Vector	V591 (Measles vector)	Merck	$38	Preclinical	Start Phase 1 Trial	Q3:20	No specific guidance
	V590 (rVSV vector)	Merck	⇧	Preclinical	Start Phase 1 Trial	H2:20	No specific guidance
Protein Subunit	NVX-CoV2373	Novavax/Emergent Bio	$1,600	Ph1/2	Start Phase 3 Trial Initial Phase 3 Data	October-20 December-20	100M doses in 2020, >1B doses in 2021
	Unnamed	Sanofi/GSK	$2,072	Ph1/2	Phase 1/2 Data Start Phase 3 Trial Regulatory Approval	December-20 December-20 H1:21	100M doses in 2020, >1B doses by mid-2021
			Total: $10,796				

Source: Cowen and Company

Under normal circumstances, mass production would wait until clinical results prove successful in order to avoid taking losses on the inventory if the results due not pan out. The time from successful trial results to large-scale product availability can be several months. The government's plan is to fund production while clinical trials are still underway (and assume any losses on wasted product if the trials fail) so that the vaccines are ready for distribution as soon as possible.

Protective Immunity Requires Antibody-Mediated Viral Neutralization

Antibodies develop as part of the body's adaptive immune response to infection. In response to a virus, antibodies against the epitopes on multiple virus proteins will be produced. A subset of these antibodies will have the ability to neutralize the virus, meaning they block viral infectivity. Antibody-mediated neutralization occurs through blockage of viral entry to host cells and/or post-entry viral replication. The affinity of neutralizing antibodies to bind to the target viral epitope and the accessibility of that epitope will together determine the potency of neutralization.

$PRNT_{50}$ Neutralization Assay Is The Gold Standard For Quantifying Immune Responses To Vaccines - Pseudovirus Assays Are Safer to Perform

$PRNT_{50}$ is the lowest concentration of serum able to reduce the number of live SARS-CoV-2 plaques by at least 50%

The titer of neutralizing antibodies against a given virus can be quantified by the plaque reduction neutralization test (PRNT), the gold standard for detecting and measuring neutralizing antibodies. In this test, a serum sample (or a laboratory-created antibody solution) is mixed with a viral suspension and incubated. If the serum can reduce the number of viral plaques (regions of infected cells) by at least 50% compared to the control (serum free virus) then the serum is diluted, and the test is repeated. Dilution is continued until the serum is no longer able to reduce the number of plaques by 50%.

The lowest (most dilute) concentration of serum able to achieve the 50% threshold of plaque reduction is designated as the $PRNT_{50}$ value.

Instead of using live virus, pseudovirus neutralization assays use a surrogate benign virus that has been given the SARS-CoV-2 envelope to mimic cell entry

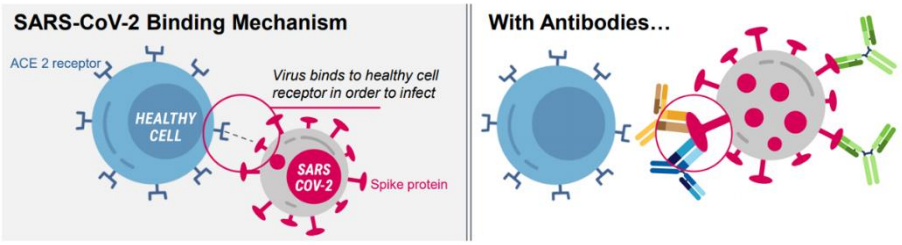
Pseudovirus neutralization assays are not considered the gold standard but are often used in clinical studies due to ease of use. In this assay, a benign virus is artificially given the SARS-CoV-2 envelope but not the genes to create the envelope. This pseudovirus will thus have the ability to infect host cells in the same fashion as live SARS-CoV-2 but is safe because it does not have the capacity to produce additional SARS-CoV-2 envelope proteins after infection. The pseudovirus does carry a recombinant luciferase gene (rLuc) that allows visual determination if viral entry/replication has occurred. The pseudovirus is combined with a serum sample to test if serum antibodies are able to neutralize against host cell entry. Cell cultures with reduced luminescence are deemed to have an effective neutralizing antibody titer.

Receptor Binding Domain (RBD) of the S Protein Appears To Be the Holy Grail For SARS-CoV-2 Antibody Targets

With SARS-CoV-2, just like with SARS-CoV, the virus attaches to the human angiotensin-converting enzyme 2 (ACE2) receptor for host cell entry and infection. Binding to the ACE2 receptor is facilitated by the receptor-binding domain (RBD) of the spike glycoprotein (S) on the surface of each coronavirus. Once bound, a conformational change in the S protein occurs to enable membrane fusion with the host cell. ACE2 receptors are abundant on lung and small intestine epithelia, making them the likely entry sites for coronaviruses in humans.

Neutralizing antibodies to the S protein are ones that bind to the RBD and prevent the virus from binding to ACE2. Importantly, the mere presence of an antibody that binds to the RBD does not necessarily mean the virus will be prevented from binding to ACE2 as factors such as concentration, specificity and affinity will determine if the antibody will achieve neutralization.

Neutralizing Antibodies In Sufficient Concentration Prevent SARS-CoV-2 From Binding To Host Cells



Source: Regeneron

Antibody-Dependent Enhancement (ADE) Occurs When Anti-Virus Antibodies Are Not Neutralizing And Actually Help The Virus Enter The Host Cell

Antibodies that attach to the virus but fail to inhibit cell attachment and entry are considered non-neutralizing since the virus is still able to infect host cells. An antibody may be non-neutralizing because it binds to a viral epitope not involved in cell attachment (i.e. not the RBD of the S protein) or because the antibody is present in a sub-neutralizing concentration. Unfortunately, non-neutralizing antibodies are not always innocuous. Instead, non-neutralizing antibodies have the potential to cause

antibody dependent enhancement (also referred to as vaccine enhancement if the non-neutralizing antibodies were created due to the vaccine) upon re-exposure to the virus.

Non-Neutralizing Antibodies Can Lead to Antibody-Dependent Enhancement

Antibody-dependent enhancement (ADE) is a paradoxical phenomenon in which pre-existing non-neutralizing antibodies enable the virus to infect immune cells via an alternative pathway (the ACE2 receptor is not present on immune cells). Thus, prior exposure to viral antigens (either through infection or vaccine) is a prerequisite for ADE.

The virus is not able to penetrate into immune cells on its own. However, when non-neutralizing antibodies bind to the virus, the virus-antibody complex can use the Fc domain of the antibody to bind to the Fc receptors (FcRs) of the immune cells which leads to uptake. FcRs are expressed on several different immune cells, including monocytes, macrophages, and B cells. The activated FcRs also lead to a signaling cascade (with input from RNA sensing Toll-like receptors TLR3, TLR7 and TLR8 activated by exposure to viral RNA) that upregulates pro-inflammatory cytokines and downregulates anti-inflammatory cytokines, causing severe systemic inflammatory symptoms.

Initial data suggests that there are 7-10 epitopes on the spike protein that can confer complete neutralization and there are 2x as many sites that do not confer full neutralization when targeted with an antibody.

Dengue Virus Is Notorious For Increased Severity With Reinfection Due to ADE

Heterotypic viruses, of which Dengue virus (DENV) is a well-known example, carry a high risk of ADE. There are four serotypes of DENV. After infection with one serotype, neutralizing antibodies to that serotype may bind but fail to neutralize a different serotype. While it is possible to have cross-neutralizing antibodies from the primary infection in sufficient concentration to provide immunity from other serotypes, the titer of neutralizing antibody can wane over time to a point where they do not confer sufficient protection (by comparison, homotypic protection is long-lasting).

When only non-neutralizing antibodies against DENV are present (including antibodies that have the potential to be neutralizing but are at a sub-neutralizing concentration), a patient infected for the second time with DENV will typically suffer a more severe illness compared to the primary infection as a consequence of ADE with entry of the antibody-virus complex into phagocytic cells via the FcR pathway. Thus, in the case of DENV, it is worse to have non-neutralizing antibodies than none at all.

Strong evidence for ADE can be seen in infants born to mothers that have antibodies to DENV. Passive immunity from maternal antibodies wane to sub-neutralization levels within the first few months of life but will persist in the infant during the first year of life. Infection with DENV within the ~8-9 months window with non-neutralizing antibodies carries an increased risk of severe disease.

Further proof of ADE in DENV was seen in a long-term pediatric study by Katzelnick et al. that measured antibody titers and observed protection with high antibody titers but higher risk for severe disease with suboptimal antibody titers.

The history of vaccine development for DENV provides useful lessons about ADE as the world pursues a vaccine for SARS-CoV-2. It took nearly six decades for a DENV vaccine to be developed despite a dire need (according to the WHO, there are an estimated 100-400 million DENV infections each year), and yet the vaccine remains problematic. A retrospective analysis of the first DENV vaccine developed by Sanofi revealed a higher

risk of severe disease in individuals that were seronegative at the time of vaccination, understood to be a result of ADE. Currently, the vaccine is limited to individuals who have had at least 1 documented DENV infection previously (since they are at risk for ADE even without a vaccine).

ADE Has Also Been Seen with SARS-CoV

In studies of mice vaccinated with viral vectors encoding either the S protein or the nucleocapsid (N) protein of SARS-CoV performed by Yasui et al, the N-protein immunized mice experienced severe ADE. The mice with ADE exhibited high expression of T cell activators (IFN-γ, IL-2, IL-4 and IL-5), pro-inflammatory cytokines (IL-6 and TNF-α), and pro-inflammatory chemokines (CCL2 and CCL3), while having low expression of anti-inflammatory cytokines (IL-10 and TGF-β). In a related fashion, the N-protein immunized mice also demonstrated severe lung pathology with increased infiltration of neutrophils and eosinophils compared to S-protein immunized mice.

In a hamster model, a SARS-CoV vaccine enhanced infection of B cell lines upon infection. These results were confirmed using a human cell line of promonocytes. Here, concentrated antibodies against the S protein neutralized SARS-CoV, however when diluted to lower concentrations, the same antibodies actually facilitated infection.

Modifications to the SARS-CoV vaccine, such as production of only the RBD of the S protein rather than the entire S protein, led to desired protection without evidence of ADE in further animal studies. However, due to lack of funding once SARS was no longer spreading, the vaccine never made it to human trials.

Learning From The Past- How The Current Vaccines Can Avoid Immune Enhancement

According to our KOLs, the best mitigating factor in avoiding ADE is a robust neutralizing antibody response. The problem lies in defining the threshold for the neutralizing antibody titer that will provide protective immunity. With a novel coronavirus strain, there is no historical data to rely on.

$PRNT_{50}$ concentrations from serum samples of patients who have recovered from COVID-19 provide a reference point for antibody titers. These reference values serve as a preliminary benchmark for Phase 1 vaccine study results; if the antibody response to a vaccine appears in line with the level seen in recovered patients, then the vaccine is on the right track. The antibody titers of recovered patients can be thought of as a surrogate for immunity while awaiting true immunity testing (i.e. Phase 3 clinical trials).

The antibody levels in recovered patients are only a reference point because it cannot be assumed that such a level confers immunity. Perhaps the patient had a sufficient concentration for neutralization at the time of recovery, however at the time of the blood test the concentration had waned to a sub-neutralization concentration (as an example, in the Phase 1 trial for Moderna, the convalescent serum from recovered patients that was used as a benchmark was drawn 30-60 days post-infection). There have been several reports, including from South Korea, of patients experiencing reinfection; these patients initially tested positive, then tested negative (via molecular testing) post-recovery, but then tested positive again at a later date. It remains unclear if this represents true reinfection or if the negative test was a false negative.

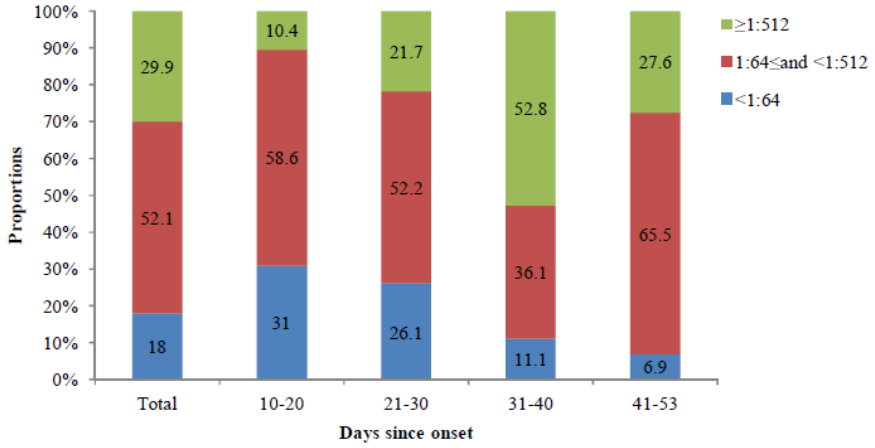
In Phase 3 trials, a population with likely exposure will be vaccinated and conclusively demonstrate the neutralizing antibody titer required for immunity and avoidance of ADE. By measuring antibody titers periodically, study investigators will be able to correlate titer levels with protection and ADE (if it occurs).

For now, with vaccines still in the preclinical or early clinical stages, convalescent serum from recovered patients will remain the best proxy for the neutralizing antibody titers needed for immunity. The more robust neutralizing antibody response, the better; if vaccine A elicits a higher $PRNT_{50}$ titer than vaccine B, then vaccine should be considered more promising assuming all else is equal (delivery, durability, safety, etc.).

Neutralizing Antibody Titers Variable In Recovered Patients

Another issue for early stage vaccine trials using convalescent sera as a comparison is the wide range of antibody responses exhibited by recovered patients. In one study of 70 recovered patients in China, neutralizing antibody titers were measured serially to better understand the dynamics of the immune response. The study found that the peak titers levels occurred on day 31-40 after symptom onset, with 52.8% of patients having a titer of 1:512 or above during that time. The remainder of patients had a less robust response with 36.1% and 11.1% having a day 31-40 titer of within 1:64 to 1:512 and less than 1:64, respectively. When adjusted for patient factors, there was a trend for a higher antibody titer in individuals with more severe symptoms (P=0.023).

Distribution of Neutralizing Antibody Titers in 70 COVID-19 Patients at Different Times Since Symptom Onset



Source: Wang et al., *Clin Infect Dis* 2020

Given the heterogeneity of antibody responses and the change over time, using convalescent sera titers as a surrogate for protection in vaccine studies is problematic. It is not clear what part of the neutralizing antibody titer range in recovered patients should be used for comparison; perhaps antibody responses that fall within the range are not sufficient, and we will discover in later trials that only the high end of the titer range confers protection. We will not know the answers until pivotal studies have been completed.

T Cell Patterns Can Also Provide A Framework For Vaccine Developers

The pattern of CD4+ and CD8+ T cell response in COVID-19 disease has recently been characterized in studies out of Germany (the Charité University Hospital in Berlin) and the US (La Jolla Institute for Immunology) by examining the serum of recovered patients. Identifying the natural immune response to the virus can help in vaccine strategy and in the selection of immunological endpoints for vaccine trials.

The German and US studies found CD4+ T cells reactive to the SARS-CoV-2 spike glycoprotein in 83% and 100% of COVID-19 patients, respectively. Beyond the spike protein, the US study found T cell recognition of the M and N proteins, which are likely co-dominant as each was recognized in 100% of patients, and several additional structural antigens.

Taken together, this data identifies several antigens that can potentially be targeted in a vaccine toward the goal of mimicking the natural T cell response after infection. Since vaccine development began well before T cell data was available, the best use right now could be as a correlate of protection (similar to neutralizing antibody titers) and potentially down the road if vaccine efficacy is lacking and additional antigen targets are needed.

Interestingly, the two studies also found that many people never inflicted with COVID-19 had T cell reactivity to the virus. In the German study, 34% of SARS-CoV-2 naïve healthy donors had CD4+ T cells reactive to the spike protein. The La Jolla study expanded its search to antigens beyond the spike protein and found reactive T cells in ~40-60% of unexposed individuals. The significance of these cross-reactive T cells is unclear at this point but may be the key to understanding the wide range of COVID-19 disease manifestations, including the high rate of asymptomatic individuals.

Overactivation Of Th2 Relative To Th1 Has Been Associated With Poor Outcomes In Respiratory Viral Infections

There is evidence that some patients with severe COVID-19 disease experience Th2 (aka type 2) immunopathology, a form of immune enhancement that is distinct from ADE. Th2 immunopathology refers to dysregulation of the T cell response toward overactivation of the Th2 pathway which causes an allergic-type response through activation of IgE antibody producing B cells, mast cells and eosinophils. The desired immune response for a viral infection is via the Th1 (aka type 1) pathway which is mediated by macrophages and cytotoxic T cells.

Overactivation of Th2 relative to Th1 has been associated with poor outcomes in respiratory viral infections. Eosinophils are believed to play a particularly important role due the potent proinflammatory function, including activation of IL-6, a key mediator of "cytokine storm" in fatal cases.

A predisposition of the immune system toward a Th2 response has been shown to be more likely in patients with cancer, immunodeficiency, autoimmune disorders, congestive heart failure, chronic obstructive pulmonary disease and hepatic cirrhosis, all known conditions suppressive to Th1 immunity.

Th2 immunopathology can occur even in the presence of a sufficient neutralizing antibody concentration to block viral cell entry. In a preclinical study by Tseng et al., mice vaccinated against SARS-CoV exhibited Th2 immunopathology even though no virus was detected on day two after challenge in most animals. Importantly, the immunopathologic reaction was reduced when using a S protein vaccine compared to a whole virus vaccine. It has been hypothesized that the augmentation of the Th2 response may be linked to antibodies against the nucleocapsid (N) protein.

RSV Vaccine Trials Represent Tragic Lessons In Vaccine Development Related to Th2 Immunopathology

One of the best-known examples of vaccine enhancement occurred in a U.S. trial in the 1960's for a vaccine against respiratory syncytial virus (RSV), a leading cause of lower respiratory tract infections in children worldwide. Young children were given an

inactivated RSV vaccine and developed severe disease upon exposure to the virus, with many requiring hospitalizations. Subsequent animal studies confirmed vaccine enhancement attributable to a Th2-type immunopathologic reaction.

With lessons learned from RSV and other viruses (such as measles), Th2-biased immune responses are now a known cause of vaccine associated enhanced respiratory disease (VAERD) believed to be related to immune complex deposition in lung tissue. As such, current vaccine developers pay careful attention to the balance of Th1 vs Th2 response when vaccinated individuals are exposed to the target virus.

In the preclinical work by Moderna for example (see section on Moderna later in the report), Ig subclass and T cell cytokine data were measured to assess Th1 vs Th2 response to SARS-CoV-2 infection in mice vaccinated with mRNA-1273.

Adjuvant For Vaccines Is An Important Determinant of Eliciting Th1 vs Th2 Responses

Adjuvants are added to a vaccine to enhance and direct the immune response. Aluminum salts (referred to as 'alum') were the only adjuvant for over 70 years and have an excellent safety record. With the addition of novel adjuvants to the market over time, alum is mainly now used in vaccines consisting of inactivated toxins or recombinant proteins. The role of alum within these vaccines is to:

1. absorb viral antigens and elute them following inoculation, and

2. act as a mild irritant in order to recruit leukocytes to the site of injection and thereby enhance the immune response.

Alum characteristically promotes a Th2 response and thus is not ideal for pathogens that would be best targeted by the Th1 pathway.

There are now new adjuvants have been developed to achieve a Th1 skewed response (to be discussed later in the report).

Frequency of Vaccine Administration Will Depend on Durability of Antibodies and Mutation Rate of Virus

After SARS-CoV-2 vaccines become available, it is unknown how often repeat inoculation will be necessary. The frequency of administration will depend on two factors:

1. the durability of neutralizing antibodies, and

2. the mutagenicity of the virus.

As mentioned above, sub-neutralizing concentrations of neutralizing antibodies not only fail to be protective but can be harmful by facilitating ADE. Thus, once the minimum effective titer of neutralizing antibodies is established, booster shots can be given as needed to keep titers above that threshold. Data from clinical trials will elucidate how rapidly the neutralizing antibody concentration wanes over time and thereby how often booster shots are needed.

Assuming the majority of the population is vaccinated in mid to late '21, we expect manufacturing capacity to be able to handle demand for future doses (in 2022 and beyond) needed for waning immunity based on the current ramp.

SARS-CoV-2 Mutates Relatively Slowly In the S Protein Via Genetic Drift – Suggesting That Vaccines And Antibodies Should Be Effective

Viral escape (also referred to as antigenic escape) refers to the ability of viral mutations to render previously neutralizing antibodies ineffective. In the case of influenza, new vaccines are needed annually for flu season due to the high mutation rate (aka antigen shift); with such a high mutation rate, there is bound to be at least one in a key location even if the majority of mutations are irrelevant to the ability of the neutralizing antibodies to be effective.

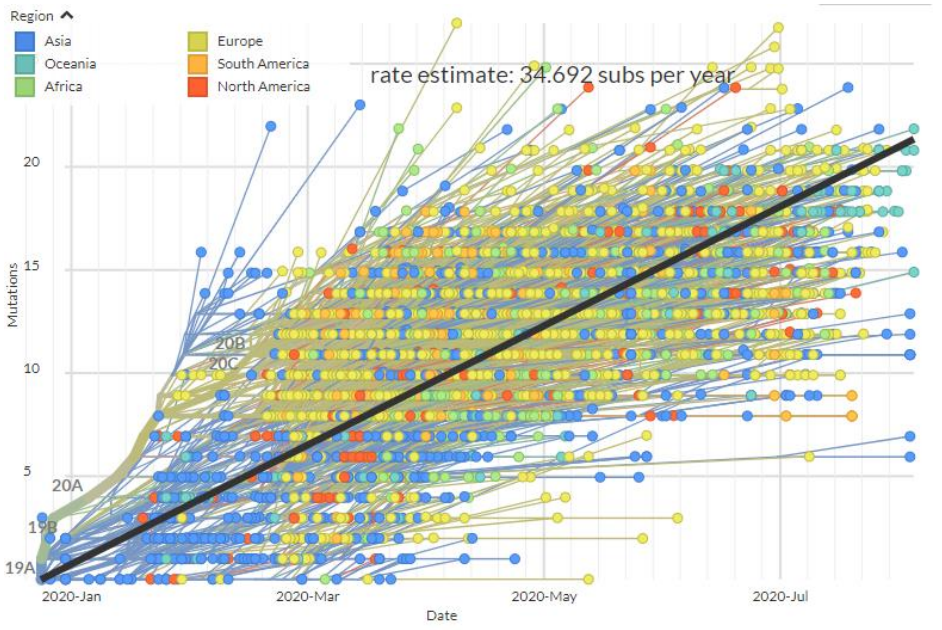
The mutagenicity of SARS-CoV-2 will determine how often vaccines (or antibody cocktails) need to be updated (distinct from vaccine booster shots which are repeat doses of the same vaccine). Unlikely influenza, the SARS-CoV-2 virus mutates more slowly via antigen drift which may not necessarily require a new vaccine for each season.

As we will discuss, mRNA vaccines have a distinct advantage over other modalities in terms of turnaround time if/when a new vaccine is required due to viral escape.

Mutagenesis Appears To Be Significantly Slower Than Influenza

Biostatistical analyses of SAR-CoV-2's mutagenic profile are ongoing, and predictive conclusions from these studies shift frequently; however, they remain essential to the development of a viable vaccine or antibody therapy. Collective analyses from the Bedford lab at Nextstrain project an average of about 35 mutations per year in the antigen expression profile of the virus, which is roughly in line with other coronavirus strains. By comparison, influenza has an average of almost 50 mutations per year.

Virologists Now Predict ~35 Mutations Per Year in SARS-CoV-2 (Up From ~25/year Previously)



Source: NextStrain, GISAID

A study out of Wuhan, China, that examined samples from eleven patients claims to have seen thirty-three strains of SARS-CoV-2 (including 19 novel strains), which showed

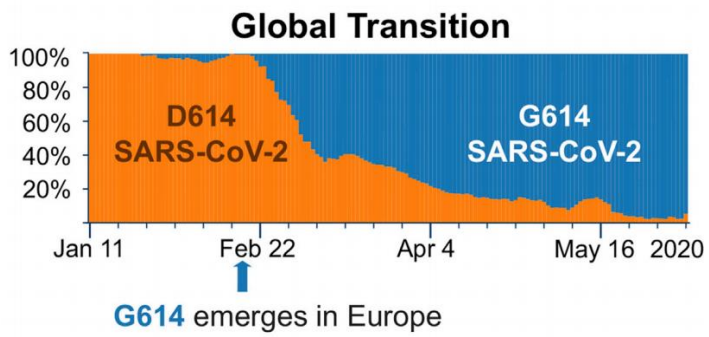
varying viral loads when tested in vitro. Importantly, the study suggests that select mutations in the virus may confer additional pathogenicity. Broad sequencing in Iceland detected five strains originating from the UK and mainland Europe.

New Mutation Emerged With a Dominant Strain That Is More Infectious But Is Not More Pathogenic

The G614 form of SARS-CoV-2 has become the dominant strain due to higher infectivity but is not more pathogenic.

A recent study by Korber et al. published in *Cell* showed that a SARS-CoV-2 variant carrying G614 form of the S protein has replaced D614 as the most prevalent form in the global pandemic. The G614 variant was found to be dominant by dynamically tracking the variant frequencies. The statistically significant consistency of the pattern across national, regional and municipal levels suggests that the G614 variant may have a fitness advantage.

Global Transition From The D614 to G614 Form The SARS-CoV-2 S Protein



Source: Korber et al., *Cell* 2020

While the G614 variant appears to significantly boost infectivity, there does not appear to be a significant difference in pathogenicity or mortality associated with the mutation. Continued screening/documentation of novel mutations in SARS-CoV-2 will be essential for therapies targeting these proteins both during development and post-approval to assess for viral escape.

Putting all the data together, we believe the rate of mutation in key surface antigens targetable by a vaccine or antibody therapy will be considerably slower than the flu and these targets would not be expected to drastically shift frequently. In addition, the homology of the spike protein between SARS-CoV and SARS-CoV-2 likely reflects evolutionary constraint given the critical function of this protein in host cell invasion. As a result, antigens in the S protein are less likely to have a consequential mutation.

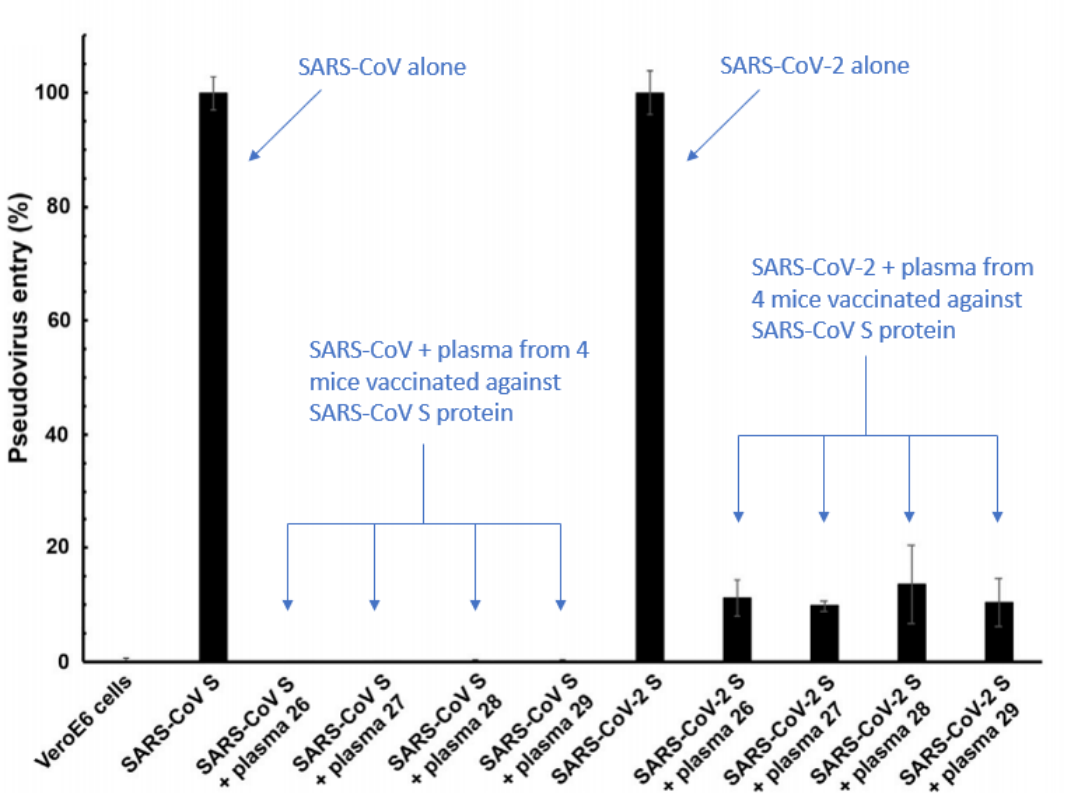
Spike Protein Likely Under Evolutionary Constraint

The SARS-CoV-2 S protein is comprised of two functional subunits (S1 and S2). The S1 subunit binds to the ACE2 receptor (the RBD is on the distal portion of the S1 subunit) while the S2 subunit is responsible for fusion of the viral and cellular membranes. In the prefusion confirmation, S1 and S2 are non-covalently bound. The two subunits are cleaved during the cell invasion process.

The amino acid sequence of the S protein is 76% similar between SARS-CoV and SARS-CoV-2. The S2 subunit is more conserved than the S1 subunit. In a study by Walls et al., the sera of 4 mice immunized with the S protein from SARS-CoV was able to reduce SARS-CoV-2 cell entry by 90%. The ability of SARS-CoV polyclonal antibodies to inhibit S

protein mediated cell entry for SARS-CoV-2 demonstrates the structural conservation of the S protein between the two viruses.

A 90% Reduction In SARS-CoV-2 Cell Entry After Addition of Plasma From Mice Vaccinated Against SARS-CoV Spike Protein



Source: Walls et al., *Cell* 2020

The conservation of the S protein provided the foundation for the design of vaccines and therapeutics for SARS-CoV-2. Given the urgent need, vaccine development was initiated by multiple companies shortly after the SARS-CoV-2 genome was sequenced in January 2020. As a result, developers did not have the benefit of convalescent serum analysis as this data only became available recently. The spike protein was the agreed target among experts given its vital role in cell entry and the clear importance based on evolutionary positive selection.

COVID-19 Cases Are Still Spiking In The Summer But Herd Immunity Might Be Unachievable - Vaccine And Therapeutics Are Needed To Bend The Curve

Impact Of Weather With Humidity On Transmission Is Marginal As The Number Is Not Slowing Down During The Summer, Raising Concerns About The Second Wave

It was hoped that viral transmission could be blunted by the warmer weather with higher humidity during the summer months. However, this theory has fallen flat as daily new cases are still setting all records, especially in the US, Latin America, and India. At the same time, many European and Asian countries are also reporting case resurgences.

Without a widely available vaccine or therapeutic treatment, a potential second wave of COVID-19 infections this winter poses a serious risk and could lead to more deaths than the first wave. This is because the healthcare system is already nearing or reaching capacity with a backlog of patients requiring treatment in many regions as we face another potential outbreak of annual seasonal flu.

Updated Clinical Data In The US Showed A Decline Of Case Fatality Rate (CFR) vs Stable CFR Rates In China And Italy

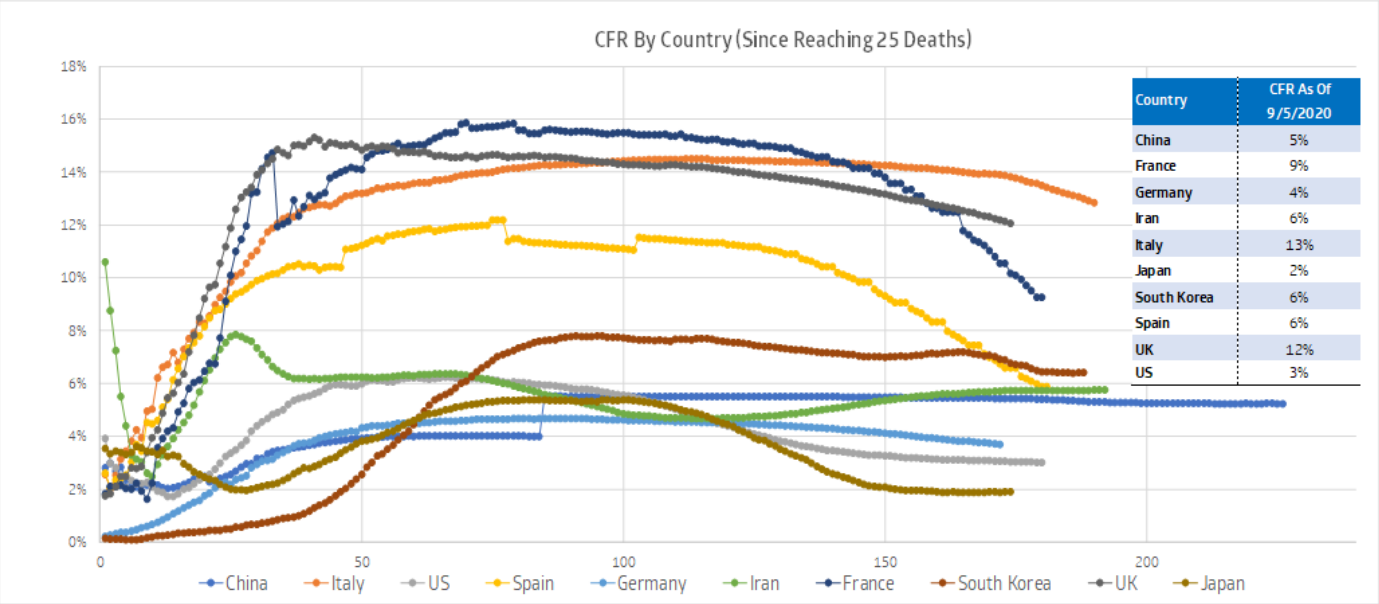
Italy was the first European country to be affected by COVID-19 with >276K confirmed total cases and >35K deaths to date. Based on early outcome data, Italy has a higher mortality rate than the US or China. This appears to be based on a combination of an older population that have a high rate of antibiotic resistance and where ~28% are smokers. More so, the rapid rise in cases overwhelmed Italy's healthcare system, contributed to worse outcomes. Of note, the median age in Italy of those who have died is ~80 years while only 1% of the deaths have been detected in patients <50 years.

Similar outcomes were also seen in the US. The data from the CDC for patients who died with COVID-19 during February 12–May 18, 2020 shows that ~80% of deaths were aged ≥65 years (88% in Italy) and 3% of deaths were aged ≤ 44 years, consistent with the data of February 12–March 16, 2020.

Additionally, consistent with reports describing the characteristics of deaths in persons with COVID-19 in the US and China, ~3/4 of deaths had one or more underlying medical conditions reported (76%) or were aged ≥65 years (75%).

Notably, the case fatality rate (CFR = total deaths/total confirmed cases) has been stable at ~13-14% in Italy and ~4-5% in China in the last 3 months. In comparison, the CFR has been declining in the US, Spain, and Japan in the past 2 months.

CFR Is Declining In Some Countries Largely Due To Rapid Growth Of New Cases



Country	CFR As Of 9/5/2020
China	5%
France	9%
Germany	4%
Iran	6%
Italy	13%
Japan	2%
South Korea	6%
Spain	6%
UK	12%
US	3%

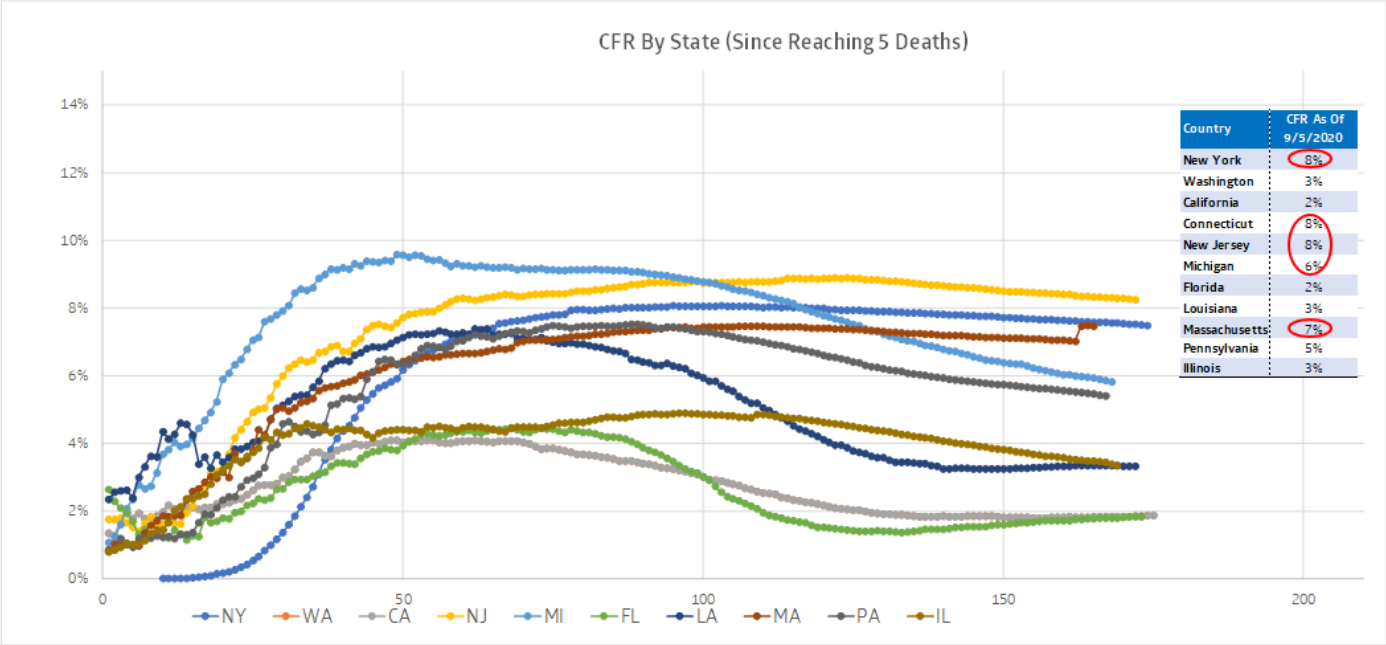
Source: JHU CSSE, Cowen and Company

Decline Of CFR In Many Regions Is Largely Driven By The Spike Of Infections In Young People

We think that the rapid growth of infections in young people was the main driver of the recent decline of CFR in many regions. As countries and regions started to gradually reopen in May and June, masking and social distancing measures were not strictly followed.

This trend can be clearly seen in some hotspot states in the US with the fastest growth of new cases. Many states reported significant growth of cases in younger people, leading to the closure of bars and the ban of large gatherings in several states, such as California, Florida, and Texas.

Recent Decline Of CFR In Many US States Is Primarily Driven By Rapid Growth Of Infection In Young People



Source: JHU CSSE, Cowen and Company

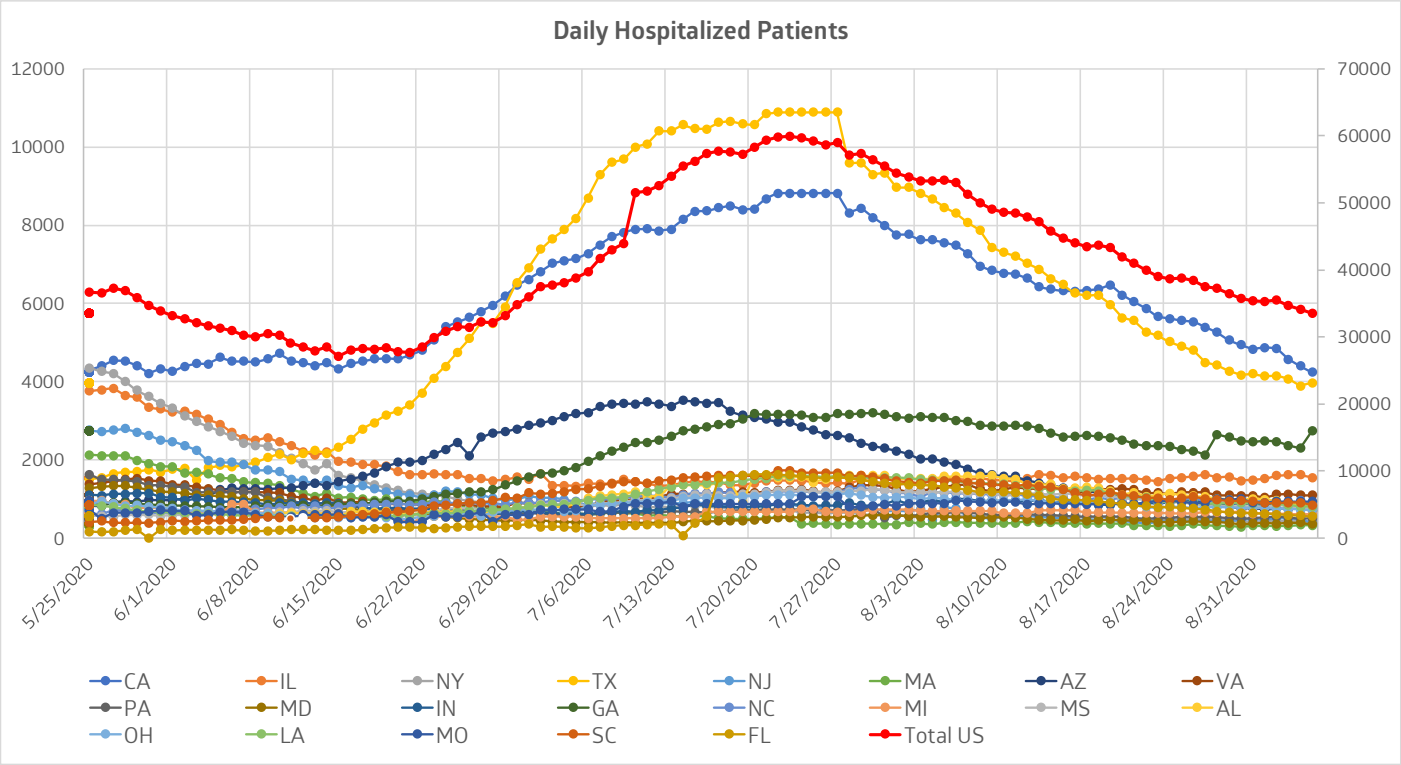
We Anticipate That The CFR In These Regions Will Increase Soon

Due to the rapid growth of hospitalizations in July, hospitals in many regions were reaching their capacity, which likely contributed to the clinical outcomes.

Importantly, we expect the CFR to go back up soon in some regions. This is because there is an approximately 4-week time lag between case diagnosis and deaths. Encouragingly, due to the implementation of new measures, daily cases have stabilized in many states.

Encouragingly, after local governments imposed new measures, many states are seeing stabilization of new cases and declining hospitalizations, which is expected to lead to improved clinical outcomes.

Hospitalizations In Some Hotspot States Are Declining



Source: JHU CSSE, Cowen and Company

Data Shows That The Excess Deaths Have Been Moderating Since June

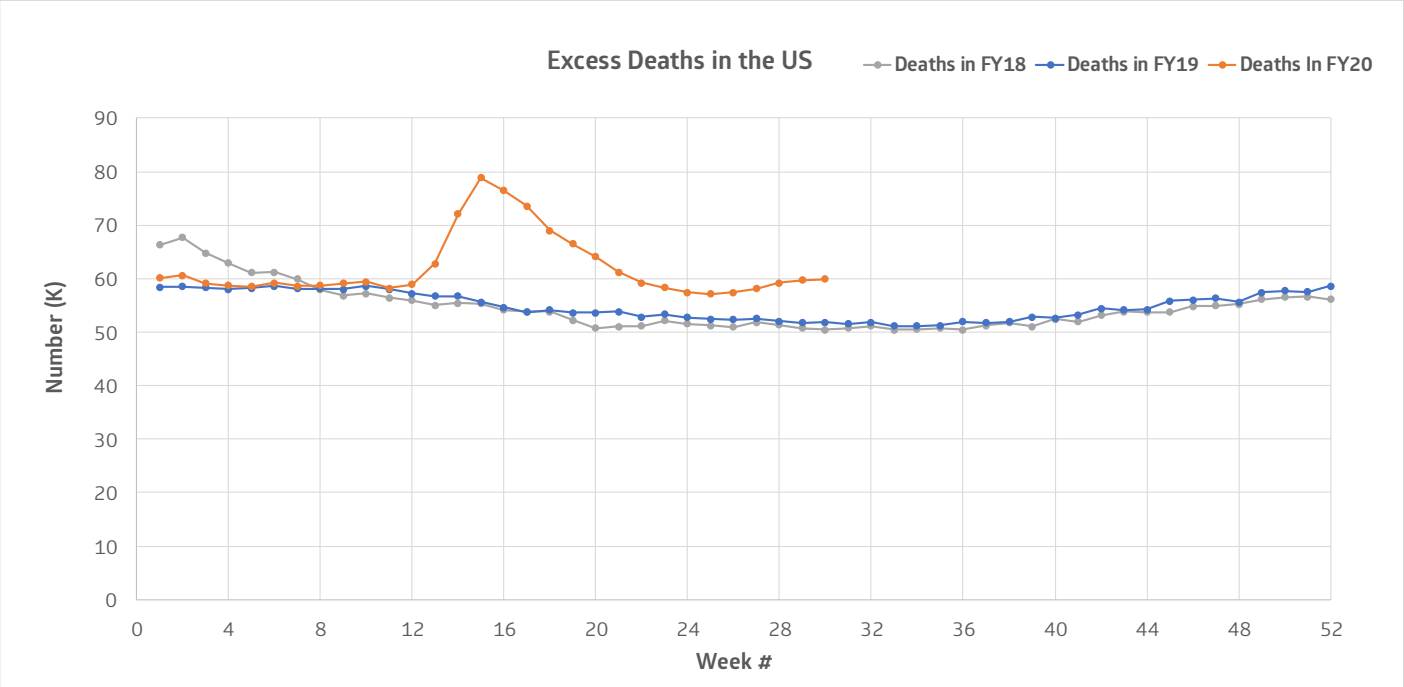
We used data from the CDC to compare the all-cause mortality in FY20 to that of FY18/FY19. The data shows that the COVID-19 pandemic caused a sharp increase of deaths between March and June in FY20. The weekly number of deaths peaked at ~79K in mid-April, which was ~42% higher than the historical number in FY18 and FY19.

From week ending February 29th through the week ending August 8th, the cumulative number of excess fatalities is >200K, underlining the impact of COVID-19 within this period.

Encouragingly, we see that the deaths have been moderating since June. In the week ending August 8th, the number of deaths was ~14% higher than the historical number.

There is a lag in issuing death certificates. But the data encouragingly shows that the death burden due to this pandemic had moderated substantially. This might also be due to better clinical care as the natural course of the illness is now better understood.

Data Shows That The Excess Deaths Have Been Moderating Since June



Source: CDC, Cowen and Company

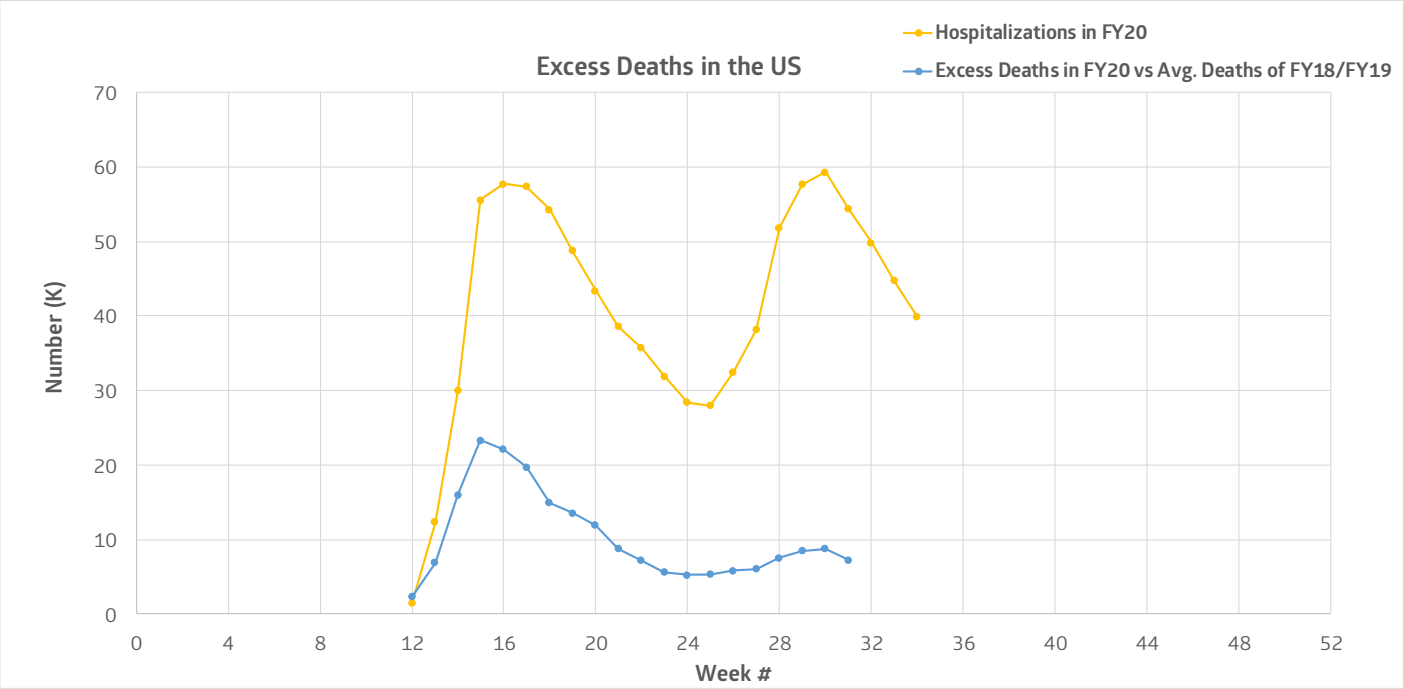
Recent Spikes Of Cases/Hospitalizations Do Not Seem To Cause A Similar Surge Of Excess Deaths

Importantly, the recent spikes of daily cases and hospitalizations in July-August did not seem to result in a similar surge of excess deaths.

We think that it is in part due to the fact that the recent spike was primarily driven by a rapid growth of infections in young people. Although the infected young people might still get hospitalized due to their symptoms, the fatality rate among them is low.

We anticipate that the reopening of schools and drop in the temperature in the fall likely will lead to an increased number of infections. It is important for young people to continue to follow social distancing measures and wear masks so that they will not cause unnecessary transmission of the virus into the general population, especially the high-risk population.

Recent Spikes Of Cases/Hospitalizations In July/August Do Not Seem To Cause A Rapid Increase Of Excess Deaths



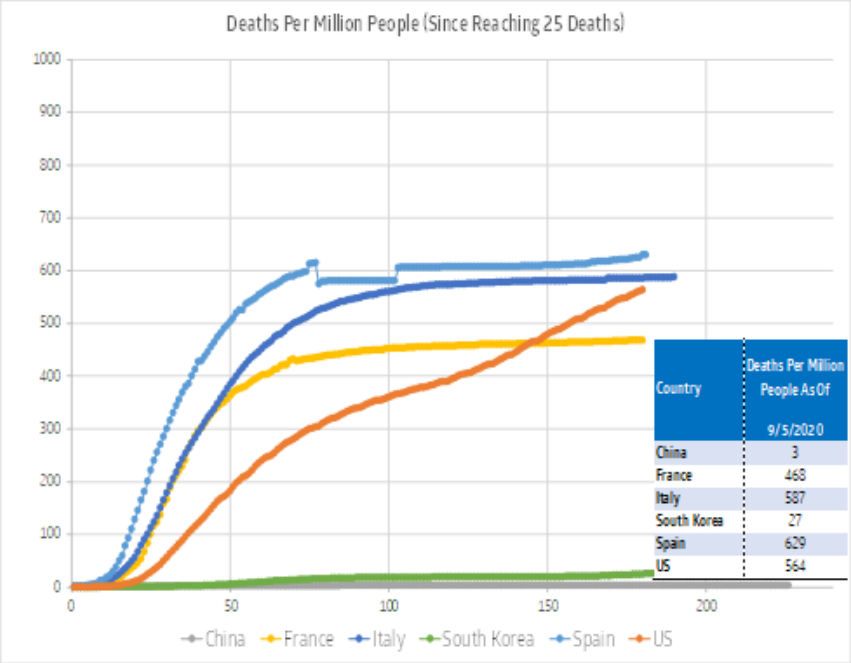
Source: CDC, Cowen and Company

While The Number Of Cases Is Still Growing Rapidly, US Is Lower Than EU In Terms Of Mortality Rate Per Million

As of August 3, the US has reported over 4.6M confirmed cases, which is much greater than China's ~88K and Italy's ~248K. However, the 4% case fatality rate in the US remains low. The CFR rate in the US is among the lowest in the EU and Asian countries.

Importantly, the mortality rate per million people in the US of 463 deaths per million people is lower than many EU countries, such as Italy (581 deaths per million people), and Spain (608 deaths per million people), but significantly higher than some Asian countries, such as China (3 death per million people) and South Korea (6 death per million people).

Deaths Per Million People In The US Is Lower Than Some EU Countries



Source: JHU CSSE, Cowen and Company

A New Study Showed Antibody Immunity Fade In Only Months, Suggesting Herd Immunity Might Be Unachievable – We Await More Data From Large Studies

A study out of King's College London recently published on *medRxiv* (not peer reviewed yet) suggests that immunity to COVID-19 may last only months. The researchers repeatedly tested 96 COVID-19 patients for antibodies between March and June and found that levels of neutralizing antibody (nAb) peaked ~ 3 weeks post onset of symptoms (POS) and then rapidly fade away.

Of note, researchers consider the ID50 levels of 50-200, 201-500, 501-2000, and >2000 as low, medium, high, and potent nAb titers.

Importantly, researchers found that while 60% of patients produced "potent" nAb titers following COVID-19 infection, only 17% had the same level of potency at the end of the 3-month period.

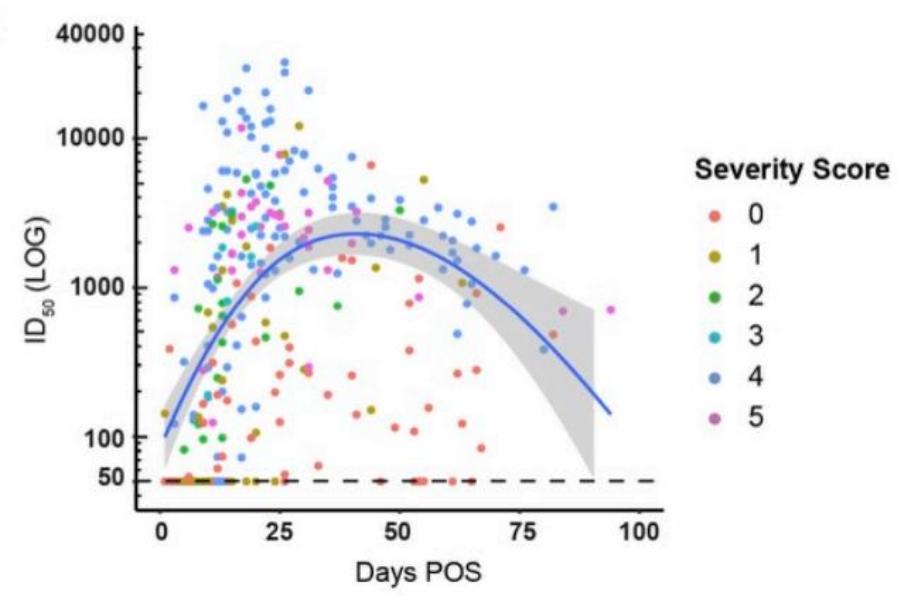
Encouragingly, data showed that antibody levels were higher and lasted longer in people who had more severe disease with some milder cases having undetectable antibody levels at the end of the 3 months. Notably, high nAb titers (>1000) were found in some asymptomatic patients.

This longitudinal study of antibody responses in COVID-19 has the longest follow-up time we have seen so far. We think this study calls into question whether a durable "herd immunity" can be achieved either through a vaccine or through community spread of the virus. As protective antibodies may wane quickly with time, data from this study suggests that the virus could potentially re-infect people repeatedly.

With that said, it remains unclear to what degree nAb titer correlates with immunity. Whether T cells provide some level of protection is also to be determined.

Overall, we await more data from large studies to better understand the correlates of immunity. The new findings are important and will help with development of vaccines and antibody therapies.

Levels Of Neutralizing Antibody Titer In Patients Are Enhanced By Disease Severity, But Wane With Time



Source: Seow et al, *medRxiv,* 2020

Sweden's Herd Immunity Strategy Questionable As It Leads To More Cases And Unnecessary Deaths

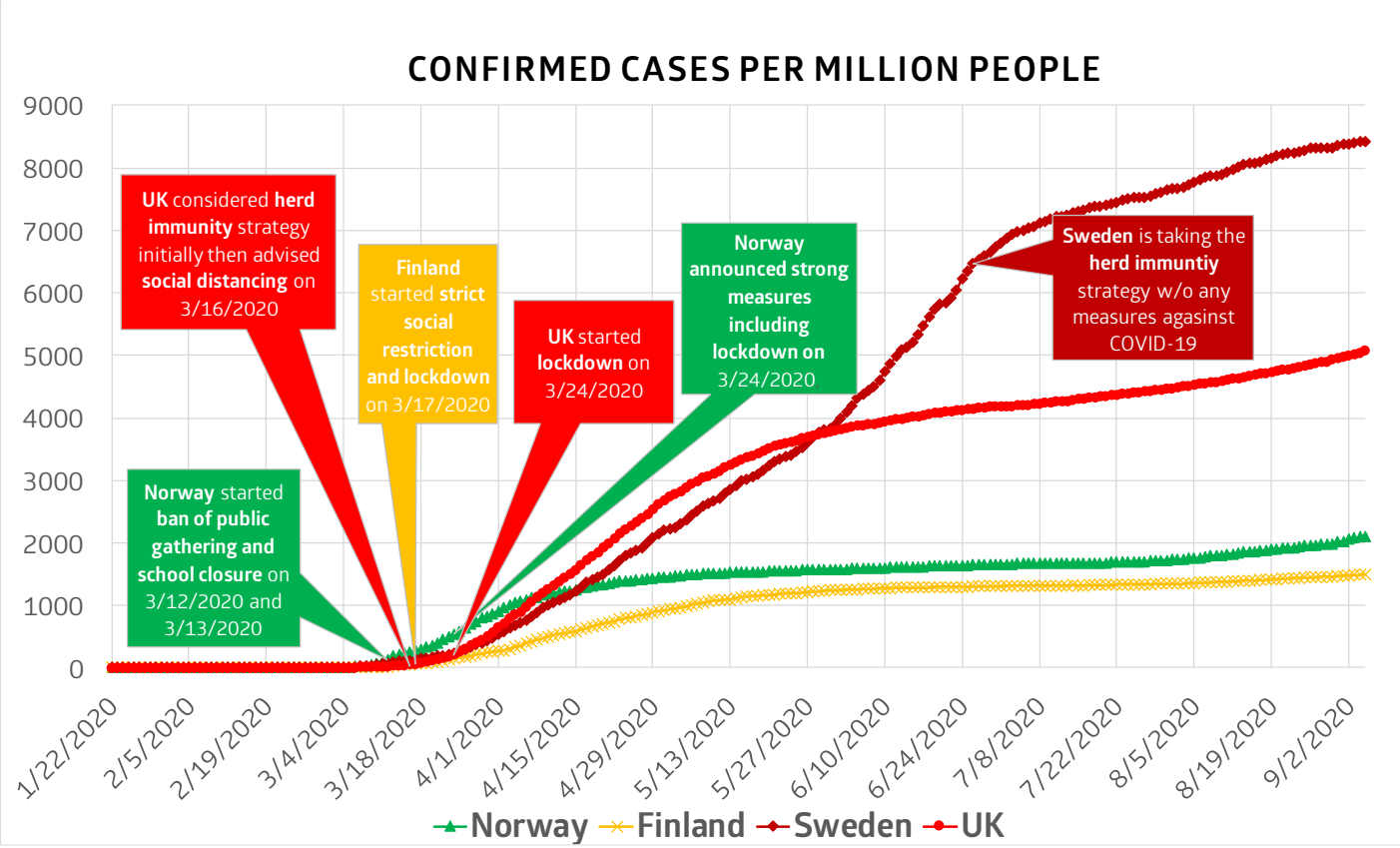
Sweden has adopted a strategy for COVID-19 that bucked the trend. The strategy was to implement no containment measures and get to herd immunity as quickly as possible. Initially, that strategy garnered some kudos given that outcomes initially did not look that different from other countries where strict containment (at grave economic costs) were implemented.

However, sentiment is now changing driven by updated outcomes data in that country. Whereas the herd immunity strategy has been controversial initially (but looked like it might just work), more recent data is leading to widespread criticism and leading the government to change course.

Data from March through July suggests that the country saw a lot more new infections and deaths compared with neighboring countries. The data showed that earlier during the pandemic, Sweden did not implement any lockdown measures. It led to a spike in daily cases and deaths that culminated in a death rate that is among the highest in Europe for its population of ~10 million. For example, Sweden's cases per million and deaths per million are significantly higher than Norway and Finland.

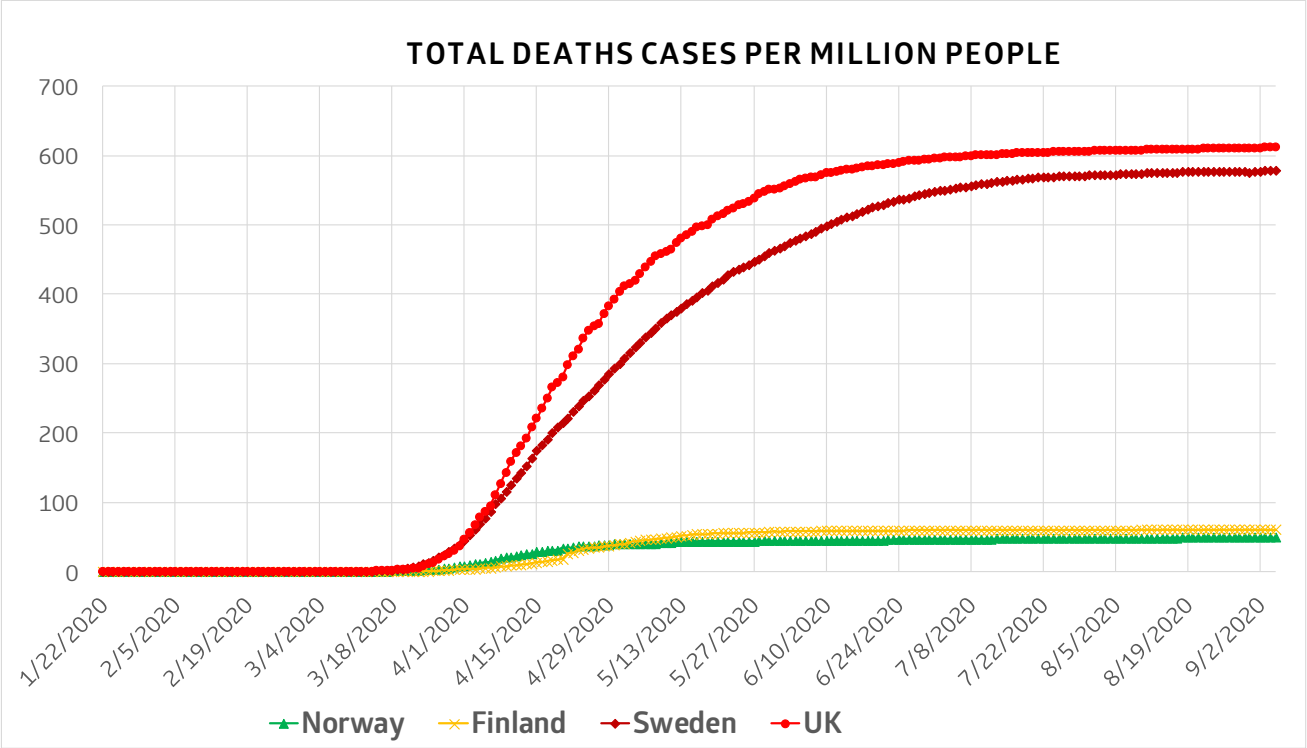
Importantly, thousands of Swedish people over the age of 70 died. Around half of those deaths occurred at care homes, which may have been avoidable.

Norway/Finland Adopted Strict Social Restrictions – Sweden Taking Heard Immunity – UK Reacted Too Late



Source: JHU CSSE, Cowen and Company

Sweden's Total Number Of Death Per Million People Is Significantly Higher Than Norway And Finland



Source: JHU CSSE, Cowen and Company

Sweden's Recent Decline Of Case Fatality Rate (CFR) Is Largely Due To A Rapid Growth Of Infections In Young People

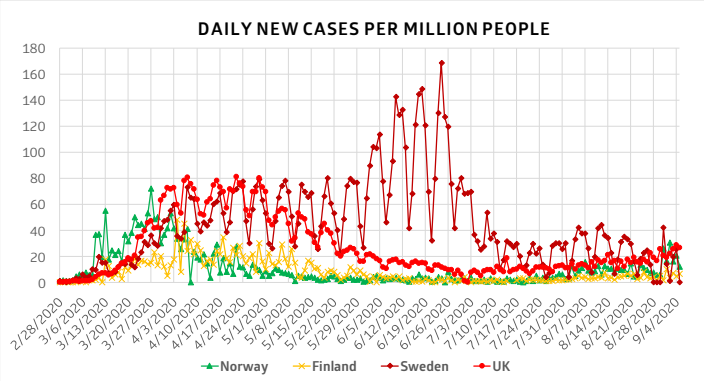
A recent decline of CFR was seen in Sweden. The coincidence of low mask-wearing compliance and low death rate does not mean masks don't work as this is a classic example of correlation not causation.

We note that the recent decline of CFR is largely driven by a rapid growth of infections in young people due to the lack of social distancing measures. We saw a similar CFR decline in many countries and regions, which started to gradually reopen in May and June. In these countries and regions, masking and social distancing measures were not strictly followed.

This is because there is an approximately 4-week time lag between case diagnosis and deaths. The rapid growth of new cases artificially takes down the CFR in those countries, such as Spain and France. More so, young COVID-19 patients tend to have less severe symptoms and have a much lower mortality rate that will lower the CFR when daily new cases stabilize. We expect the CFR in Sweden to go back up soon as new measures are implemented.

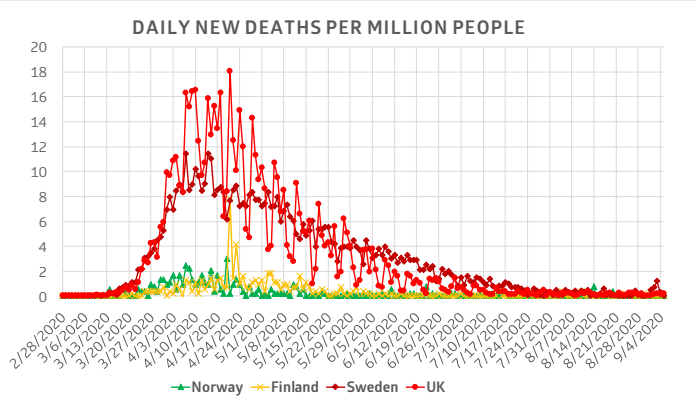
Of note, other factors could also affect the CFR in a certain country or region, such as population density, age structure, how people are mixing with others, and hospital capacity.

Sweden's Herd Immunity Strategy Leads To More Daily COVID-19 Cases



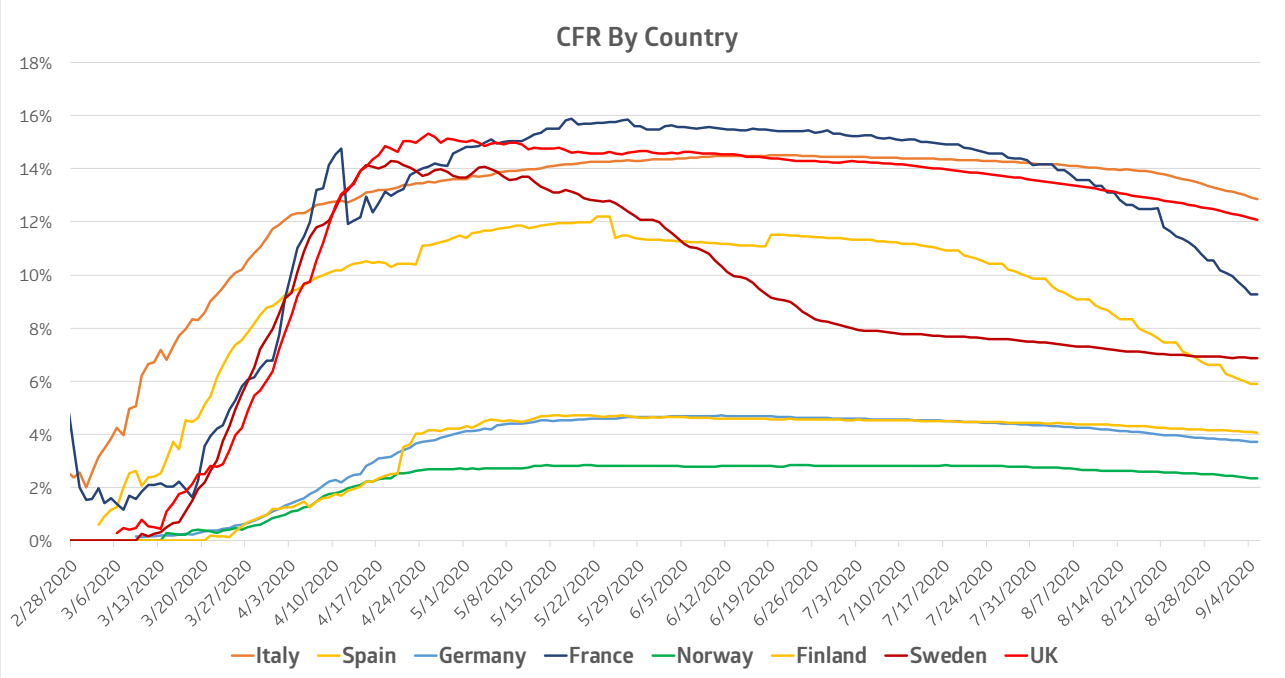
Source: JHU CSSE, Cowen and Company

Norway/Finland's Adoption Of Strict Restrictions Seemed To Result In Much Better Outcomes



Source: JHU CSSE, Cowen and Company

Sweden's Recent Decline Of CFR Is Largely Due To A Rapid Growth Of New Cases Started In June



Source: JHU CSSE, Cowen and Company

Swedish Government Now Moving To Implement New Lockdowns

Now, the Swedish government has recommended voluntary social distancing and protective equipment like masks. The Swedish government also banned large gatherings and asked people to avoid non-essential travel, work from home, and to isolate if they

were unwell. In early August, the Swedish media reported that the country's government was seeking more powers to implement a lockdown and change the containment status.

Recall, recent studies suggest that achieving herd immunity may not be possible without a vaccine. A study out of King's College London recently published on medRxiv (not peer reviewed yet) suggests that immunity to COVID-19 may last only months. Importantly, the data showed that while 60% of patients produced "potent" nAb titers following infection, only 17% had the same level of potency at the end of the 3-month period.

Importantly, First Ever Officially Documented Case Of COVID-19 Re-infection Suggests Immunity Might Not Be Durable

Researchers at HKU recently reported that they have documented the world's first case of COVID-19 re-infection. The 33-yo patient was cleared of COVID-19 and discharged from a hospital in April and tested positive again after returning from Spain in August.

The HKU researcher team reported in *Clinical Infectious Diseases* that the virus strain that caused the second infection was "clearly different" from the first one. It suggests that the SARS-CoV-2 virus could persist in the global environment like other coronaviruses associated with common cold.

In fact, many countries reported cases of COVID-19 re-infections. These findings suggest that the immunity after natural infection might not be durable.

Therefore, a durable herd immunity is unlikely to be achievable and people who recovered from COVID-19 might still want to wear masks and follow social distancing measures to avoid re-infection and spreading of the SARS-CoV-2 virus.

More so, this suggests that vaccination or antibody therapy should still be considered for patients recovered from COVID-19.

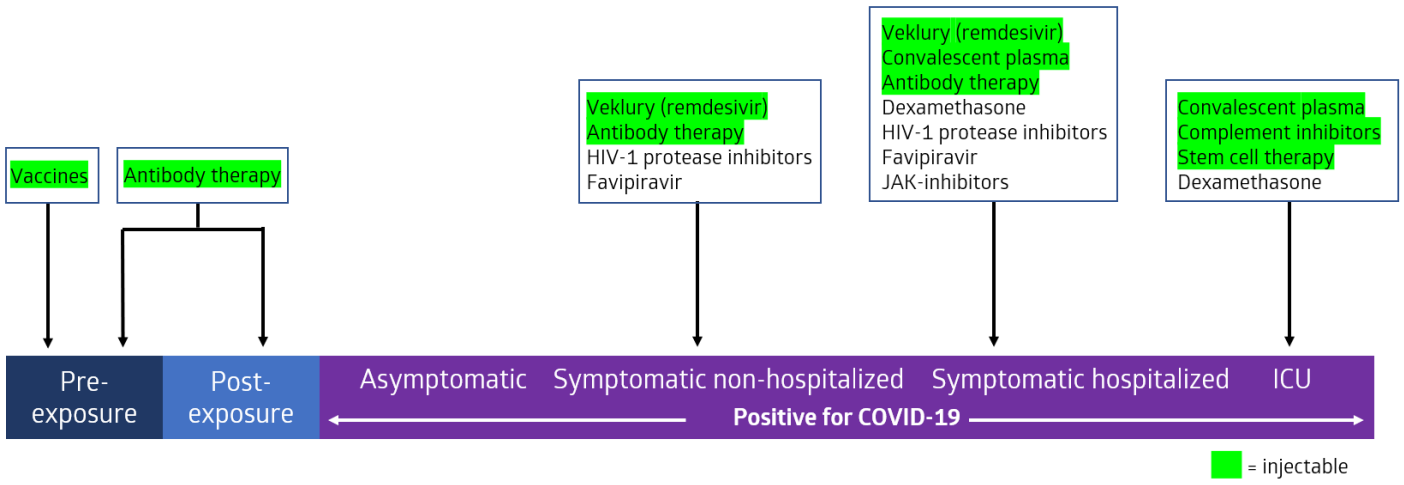
We See Opportunities For Different Regimens At Different Disease Stages

The world is in desperate need of solutions to slowing the spread of COVID-19 and treating the infected patients. Many drugs with different mechanisms are being tested as vaccines, prophylaxis, or treatments for this novel coronavirus that causes COVID-19. We see opportunities for these drugs at different COVID-19 disease stages.

Based on the reported data, the antiviral drug tended to be more effective in mild to moderate patients, while immunosuppressants tended to have more success in the severe to critical patients.

This is consistent with the hypothesis that antiviral therapy will be more effective in early stage of the infection while viral replication is the primary driver and immunosuppression will be more effective in late stage of the disease, when hyperactive immune responses drive the pathology.

Opportunities Exist At Different Stages Of The COVID-19 Disease



Source: Cowen and Company

Antibody Therapies Have Not Benefited From Government Funding To The Same Extent As Vaccines – Regeneron Is First To Announce Antibody Contract With BARDA

Different from vaccines, only limited funds have been allocated globally to conduct studies and secure the supply of COVID-19 therapeutics for prevention and treatment of COVID-19 at the present time.

In the US, only Regeneron's antibody therapy, REGN-COV2, and Gilead's antiviral drug, remdesivir, have received federal funds for secured supplies so far.

On June 29, the Department of Health and Human Services (HHS) announced an agreement with Gilead to secure large supplies of remdesivir for the US through September, allowing hospitals in the US to purchase the drug in amounts allocated by HHS and state health departments. Based on the agreement, HHS has secured more than 500K treatment courses of remdesivir for the US hospitals through September. This represents 100% of Gilead's projected production for July (94.2K treatment courses), 90% of production in August (174.9K treatment courses), and 90% of

production in September (232.8K treatment courses), in addition to an allocation for clinical trials. The cost of remdesivir is expected to be $3,120 per treatment course for a typical patient. The price will be $2,340 per treatment course for patients on government-sponsored insurance and for those in other countries with national health care systems.

On July 7th, Regeneron announced that the company has signed a $450M agreement with the Biomedical Advanced Research and Development Authority (BARDA) and the Department of Defense (DoD) Joint Program Executive Office for Chemical, Biological, Radiological and Nuclear Defense to manufacture and supply REGN-COV2, as part of Operation Warp Speed. The agreement supports the immediate manufacturing scale-up of the product if clinical trials are successful and the FDA grants Emergency Use Authorization (EUA) or product approval. This manufacturing deal with the BARDA and the DoD estimates that 70K to 300K treatment doses or 420K to 1.3M prevention doses of REGN-COV2 could be available by September.

Government Funding For Therapeutics In The US

US Government Therapy Involvement						
Company	**Contract ($MM)**	**Development Funding ($MM)**	**Total ($MM)**	**Doses**	**$/Dose**	**Milestones**
REGENERON	$450	$0	$450	70K-300K treatment doses and 420K-1,300K preventative dosages	N/A	To manufacture a fixed number of bulk lots by Q3 in addition to fill/finish and storage
GILEAD	$1,566	$0	$1,566	100% of the projected Remdesivir production in July (94.2K treatment courses), 90% in August (174.9K), and 90% in September (232.8K)	$3,120	To supply >500K treatment courses through September
Total	**$2,016**	**$0**	**$2,016**			

Source: Cowen and Company, Company reports

In EU, Regeneron's REGN-COV2, has not received any federal funds. Gilead's remdesivir, has received €63M from EMA for treatment doses of ~30K patients to cover the current needs over the next few months. Notably, Gilead needs to submit the final reports of the remdesivir studies to the EMA by Dec. 2020 as part of the conditions to be fulfilled.

Government Funding For Therapeutics In EU

EU Government Therapy Involvement						
Company	Contract (€MM)	Development Funding (€MM)	Total (€MM)	Doses	$/Dose	Milestones
REGENERON	€ 0	€ 0	€ 0			
GILEAD	€ 63	€ 0	€ 63	Treatment doses of ~30K patients to cover the current needs over the next few months	$3,120 per dose in the US	To submit the final reports of the Remdesivir studies to the EMA by December 2020 as part of the conditions to be fulfilled
Total	**€ 63**	**€ 0**	**€ 63**			

Source: Cowen and Company, Company reports

What Degree of Immunity Can We Expect From A SARS-CoV-2 Vaccine?

At this time, there is no human data as to whether infection with SARS-CoV-2 results in protective immunity against re-exposure and, if so, in what proportion of individuals. Serologic testing for antibodies to SARS-CoV-2 is useful in determining exposure within a population but having antibodies does not indicate protective immunity. As an example, individuals with HIV typically have high antibody levels yet these antibodies do not prevent or clear the disease.

While we await prospective studies in recovered COVID-19 patients to determine potential reinfection risk, we can look to animal models for clues.

Rhesus Macaque Model Demonstrates Protection Against SARS-CoV-2 Rechallenge at 35 Days

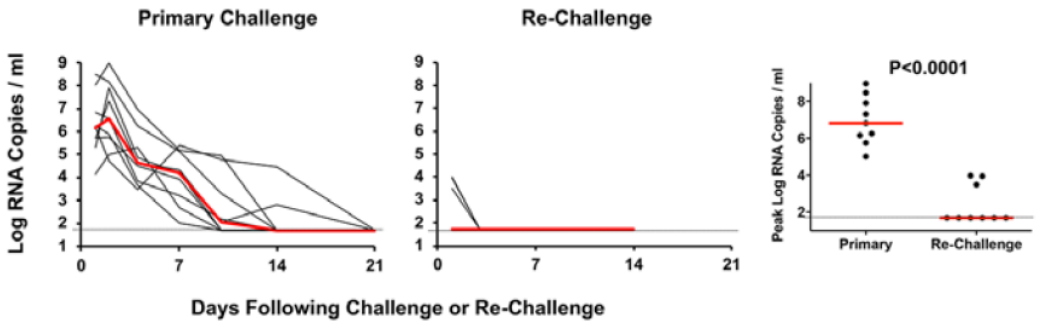
In a study at Harvard by Chandrashekar et al, nine rhesus macaques were infected with SARS-CoV-2, given time to achieve viral clearance (35 days), and then were rechallenged with the virus. Viral loads were measured via bronchoalveolar lavage (BAL) and nasal swab following initial infection and after rechallenge.

As a benchmark, FDA guidelines for convalescent plasma therapy recommend neutralizing antibody titers of ≥1:160

The initial infection with SARS-CoV-2 resulted in a median neutralizing antibody titer of approximately 1:100 with a range of 1:35 to 1:326 by live virus neutralization assay and 1:83 to 1:197 by pseudovirus neutralization assay. Recall, the neutralizing antibody titer is reported as the highest dilution of the serum that can still inhibit 50% of viral colonies in the assay.

Recall, the live virus neutralization assay assesses the ability of serum antibodies to reduce SARS-CoV-2 growth (measured as plaque reduction), whereas the pseudovirus assay uses a benign virus that has the SARS-CoV-2 envelope integrated into its surface (but not into the genome). Live assays are the gold standard for quantifying immune responses to vaccines but require significant biohazard measures and are more laborious compared to pseudovirus assays which are safer and faster.

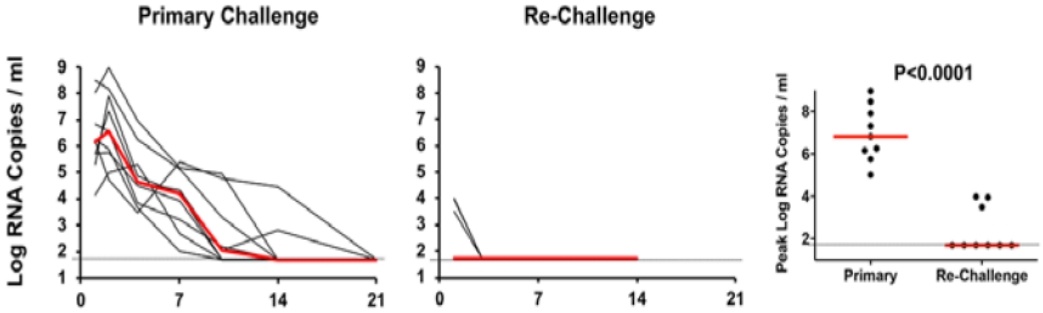
Viral Loads Following SARS-CoV-2 Rechallenge in Rhesus Macaques Assessed in Bronchoalveolar Lavage (BAL)



Source: Chandrashekar et al., *Science,* 2020

Upon re-challenge, there was a >5 log_{10} reduction in the median viral load in BAL samples (P<0.0001) and a >1.7 log_{10} reduction in the median viral load in nasal swab samples (P=0.0011) compared with the primary infection.

Viral Loads Following SARS-CoV-2 Rechallenge in Rhesus Macaques Assessed in Nasal Swabs



Source: Chandrashekar et al., *Science* 2020

The larger reduction in viral load upon rechallenge exhibited in the lung compared to the nose can be explained by the superior penetration of immune cells in pulmonary tissue. In addition to reduced viral loads, little or no clinical disease was observed in the animals following rechallenge.

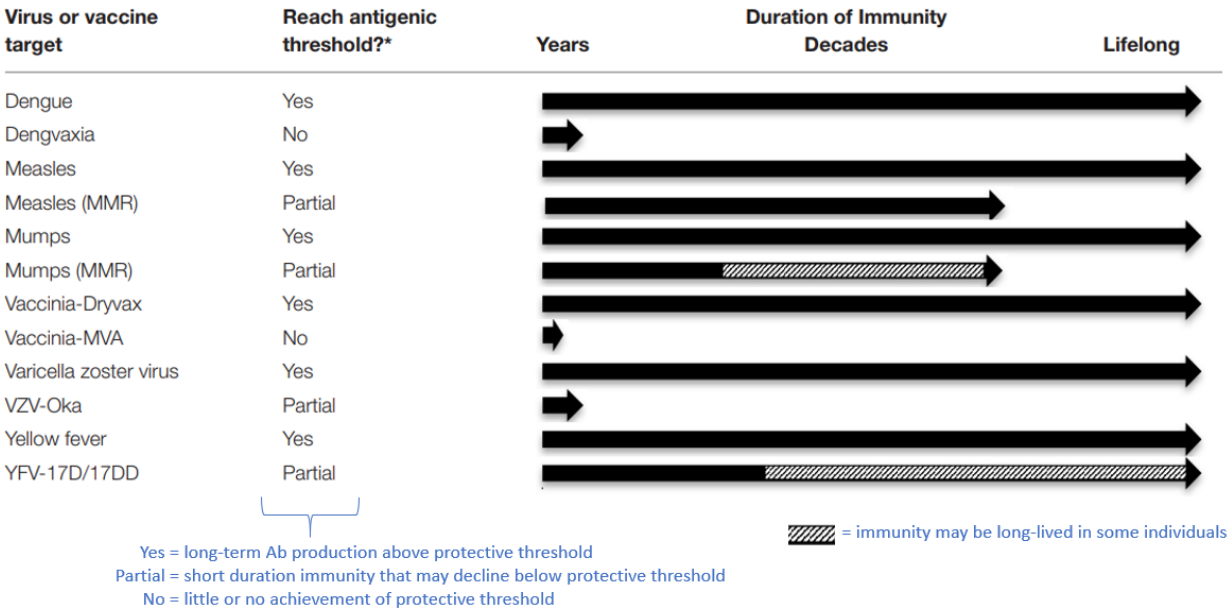
The significant reduction in viral load, particularly in the lungs, and lack of signs of clinical disease are reflective of protective immunity. Given that all animals in the study demonstrated protection from reinfection, the study investigators were unable to determine the neutralizing antibody titer that correlates with protection.

Looking To Other Viruses For Insight Into Durability of Immunity

Though reassuring that protective immunity is possible post-infection, the rhesus macaque data only evaluated re-exposure 5 weeks after infection, a time when antibody titers are near their peak. To get a sense of how long protective immunity may last, we can look to data from other viruses.

The durability of antibody responses after infection or vaccination is highly variable across different viruses. The structural biology of the antigen appears to be a key determinant of durability, with multivalent protein antigens typically leading to longer immunity compared to monovalent antigens.

Examples of Immunity Generated From Wild-type Viruses vs. Live-attenuated Vaccines



Source: Slifka et al. *Frontiers in Immunology* 2019

There Is A Strong Correlation Between Neutralization Titer And S-RBD-Specific IgG Titers

Recall, the receptor binding domain (RBD) of the coronavirus S protein is critical for viral entry. Prior data from SARS-COV, MERS, and SARS-COV-2 showed that infected hosts generate antibodies that target the virus S protein. Preclinical studies also showed that IgG directed against the S protein has *in vitro* virus neutralizing activity. Therefore, antibodies targeting the RBD domain of SARS-CoV-2 are thought to be potentially neutralizing.

Encouragingly, the first randomized, placebo-controlled (RCT) study by Li et al. showed a significant correlation between the SARS-CoV-2 viral neutralization titer and the S-RBD–specific IgG titer (r = 0.622, p=0.03).

Recall, neutralizing antibody titer (PRNT50) is defined as the reciprocal of the highest test serum dilution for which the virus infectivity is reduced by 50% when compared with the control.

This study well characterized the S receptor binding domain (RBD)–specific IgG antibody titer for convalescent plasma products as < 1:160, 1:160, 1:320, 1:640, 1: 1280, or ≥ 1:1280. The study only used plasma units with high titers of S-RBD–specific IgG antibody (≥ 1:640). This suggests that the potential benefits correlated with high viral neutralizing antibody titer.

Recall, the FDA guidelines recommend use of neutralizing antibody titers of ≥1:160 and consider a titer of 1:80 as acceptable if an alternative matched unit is not available.

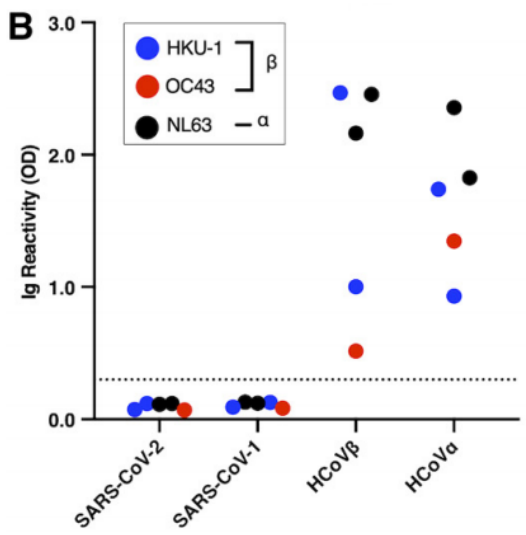
Another Study Confirms Strong Correlation Between Anti-S Protein And Neutralizing Antibodies Titers

A separate study by Premkumar et al. published in *Science Immunology* also showed a strong correlation between the levels of RBD-binding antibodies and SARS-CoV-2 neutralizing antibodies.

We think this is encouraging as it suggests that RBD-binding antibody titer may be used as a good surrogate for neutralizing antibody titer in clinical practice. Recall, it is difficult to perform neutralizing antibody assays, especially the gold standard PRNT assays, as it is relatively cumbersome, time-intensive (few days), and requires a higher biosafety level (BSL-3).

The data showed that researchers tested early convalescent sera from people with laboratory confirmed viruses and showed that SARS-CoV-2 RBD has high sensitivity and specificity for serology. None of the immune sera from people exposed to recent HCoV infections cross-reacted with the recombinant RBD of SARS-CoVs. The sensitivity of the assay was high (98% and 81% respectively for Ig and IgM) for specimens collected 9 days or more after symptom onset.

RBD-Binding Antibody Has Robust Specificity For SARS-CoVs-1 & -2



Source: Premkumar et al, *Science Immunology*, 2020

RBD-Binding Antibody Assay Has High Sensitivity For Ig And IgM For Specimens Collected 9 Days Or More After Symptom Onset

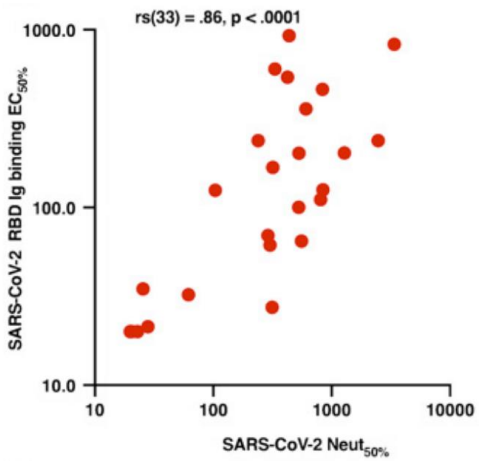
Post symptom onset	SARS-CoV-2		HCOVβ	
	Ig	IgM	Ig	IgM
1-4 days	0/5	0/5	5/5	0/5
7-8 days	8/14	6/14	13/13	0/13
9-16 days	24/25	20/25	23/23	0/23
17-43 days	33/33	27/33	33/33	0/33

Source: Premkumar et al, *Science Immunology*, 2020

RBD-Binding Antibody Titer Is A Good Surrogate For Neutralizing Antibodies Titer

Importantly, data also suggested a strong correlation between the levels of RBD-binding antibodies and levels of SARS-CoV-2 neutralizing antibodies in patients. As assessed by the Spearman test (ρ=0.86, $p<0.0001$), the researchers showed a significant correlation between the total RBD-binding Ig (total immunoglobulin) antibodies and levels of neutralizing antibodies in SARS-CoV-2 patients (n=50).

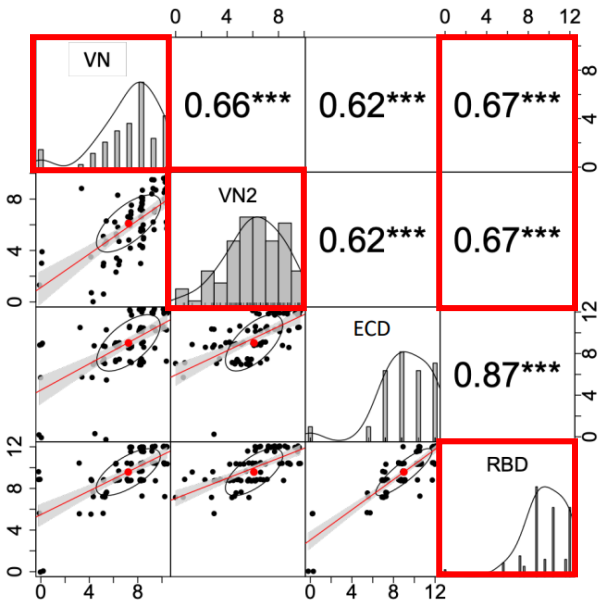
Magnitude Of Total RBD-Binding Ig Antibody Strongly Correlated With Levels Of Neutralizing Antibodies In SARS-CoV-2 Patients



Source: Premkumar et al, *Science Immunology,* 2020

Another study by Salazar et al. published on *bioRxiv* (not peer reviewed) also showed a strong positive correlation (Pair-wise Pearson correlation test, p<0.001) between anti-RBD and anti- ectodomain (ECD) plasma IgG ELISA titers and levels of neutralizing antibodies as assessed by two different neutralization assays (VN: assay 1 for log2 of reciprocal titers; VN2: assay 2 for log2 of IC50 value) in plasma and serum samples from recovered SARS-CoV-2 patients (n=68).

Anti-RBD Plasma IgG Titers Showed A Strong Correlation With Neutralizing Antibody Levels



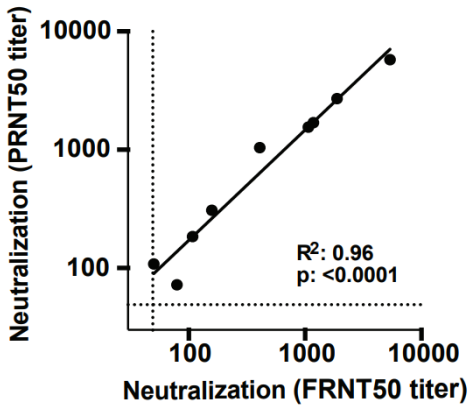
Source: Salazar et al. *bioRxiv,* 2020

Early Data Showed High Antibody Titers And Strong Correlation Between RBD-Specific IgG Titer And Neutralizing Antibody Titer In Recently Infected Patients

Another recent study by Suthar et al. published on *medRxiv* (not peer reviewed) demonstrated evidence of the potency of neutralizing antibodies via a novel focus reduction neutralization titer (FRNT) assay using VeroE6 cells. The neutralization potency (n = 44, 3-30 days after symptom onset) was measured by the reduction in virally infected foci. The study showed a very strong positive correlation between the FRNT assay and the standard plaque reduction neutralization titer (PRNT) assay (R^2 = 0.96, p<0.0001, n=9).

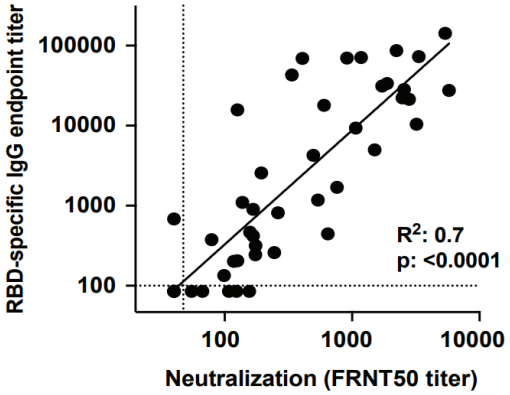
Encouragingly, the study provided further validation that RBD-specific antibody titers can be used as a surrogate of neutralization potency in acutely infected COVID-19 patients (R^2 = 0.7, p<0.0001). Notably, the researchers observed viral neutralization activity in 40 out of 44 samples from acutely infected COVID-19 patients. Of note, antibody response is expected to be high at ~30-day post symptom onset based on data from prior SARS-CoV and MERS-CoV studies. The fact that 4 out of 44 samples have non-detectable viral neutralization activity indicates that some patients might not develop strong antibody responses after infection.

$FRNT_{50}$ Assay Strongly Correlates With The Standard $PRNT_{50}$ Assay



Source: Suthar et al., *medRxiv,* 2020

RBD-specific IgG Titers Showed A Strong Correlation With Neutralization Titers Based On The $FRNT_{50}$ Assay



Source: Suthar et al., *medRxiv,* 2020

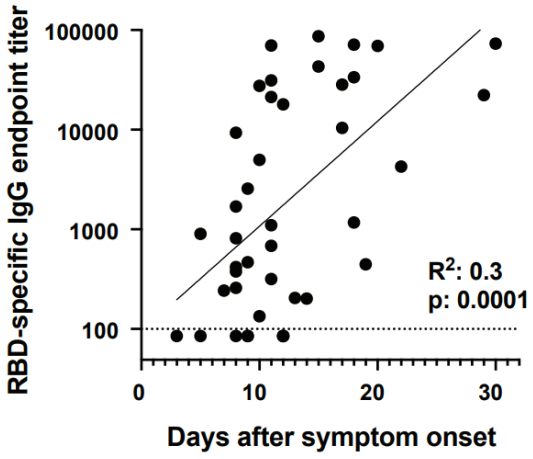
Importantly, the study by Suthar et al. showed that both RBD-specific and neutralizing antibody responses occur rapidly after SARS-CoV-2 infection (6 days after infection) and both RBD-specific IgG titers and neutralizing antibody titers reached a high level 30 days after symptom onset. More so, there appears to be positive correlation between RBD-specific IgG and neutralizing antibody titer levels and number of days after symptom onset.

Studies Have Been Too Short To Answer Correlation To Durability Of Antibody Titers

The findings of Suthar et al. are consistent with prior findings for SARS and MERS. But we note that the study was based on plasma samples of different COVID-19 patients collected at different time within the 3-to-30-day period post symptom onset. Therefore, it is not time-series data over a period of time for each patient.

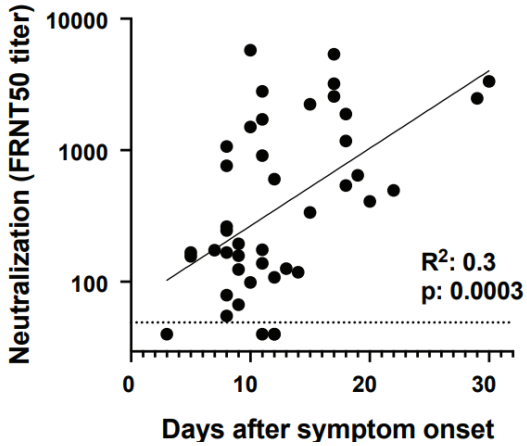
Notably, the conclusions were only based on limited data within a very short period after symptom onset. The kinetics of antibody responses and correlates of protection over a longer period are still unknown.

RBD-specific IgG Titer Reached A High Level In Patients Within 30 Days After Symptom Onset



Source: Suthar et al., *medRxiv,* 2020

Neutralizing Antibody Titer Also Reached A High Level In Patients Within 30 Days After Symptom Onset



Source: Suthar et al., *medRxiv,* 2020

But Correlates Of Protection And Durability Of Immunity Remain Unknown

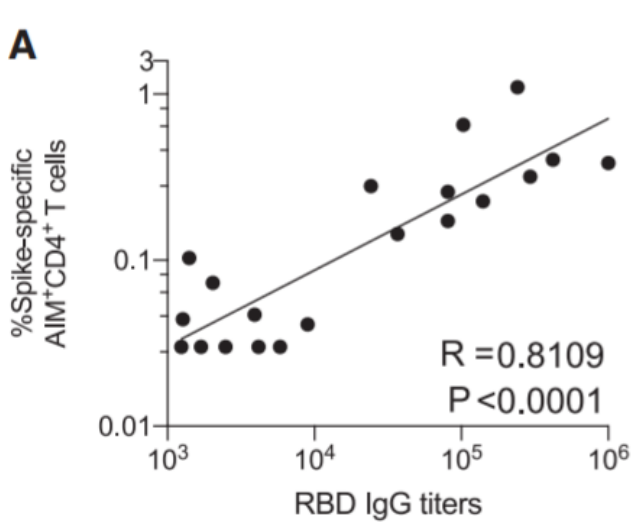
Early data has shown that the antibody responses within 30 days of symptom onset are robust, but uncertainty remains about what constitutes a protective immune response, what level of the response is needed for protection from infection vs. severe disease, and how long can the protection last.

A study by Grifoni et al. published in *Cell* reported that T cell responses are also correlated with neutralizing antibody responses. Investigators found that spike-specific CD4+ T cell responses were robust and correlated well with the magnitude of the anti-spike RBD IgG titers (R=0.81, p<0.0001). As expected, the non-spike SARS-CoV-2-specific CD4+ T cell response did not correlate as well with anti-spike RBD IgG titers.

Data Shows That CD4+ And CD8+ Cells Were Identified In COVID-19 Patients

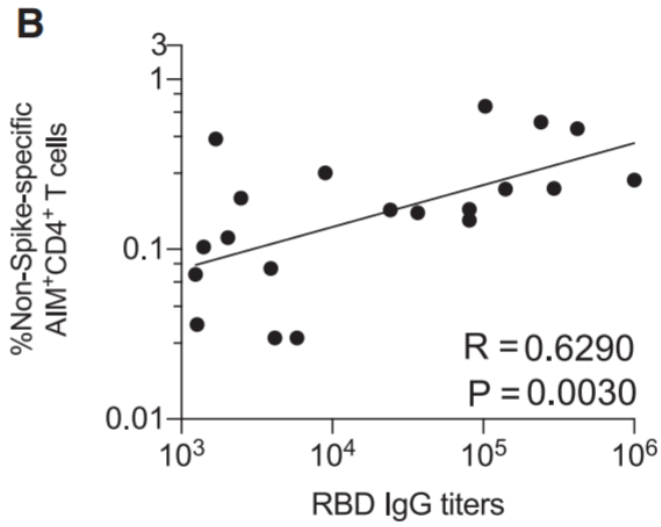
More so, circulating SARS-CoV-2-specific CD8+ and CD4+ T cells were identified in 70% and 100% of COVID-19 convalescent patients, respectively.

Neutralization Antibody Titers Correlate Well With Spike-specific CD4+ T Cell Responses



Source: Grifoni et al., *Cell,* 2020

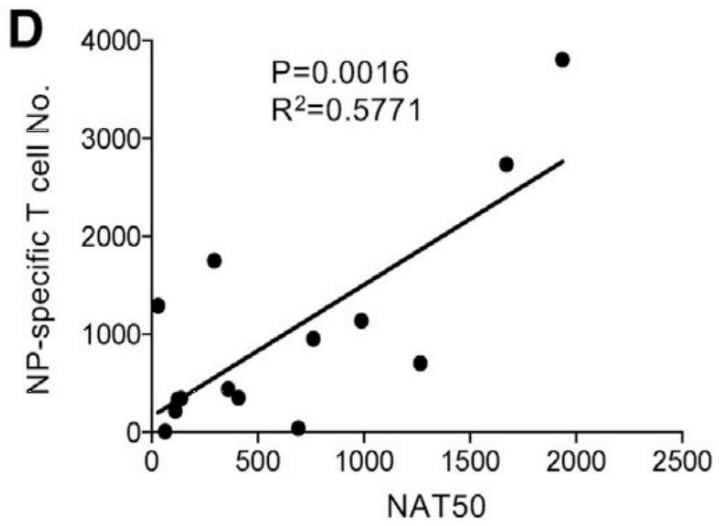
Neutralization Antibody Titers Did Not Correlate Well With Non-spike-specific CD4+ T Cell Responses



Source: Grifoni et al., *Cell,* 2020

Notably, a recent study by Ni et al. published in *Immunity* showed that neutralizing antibody titers (NAT_{50}) significantly correlated with the numbers of virus nucleocapsid protein (NP) specific T cells in COVID-19 convalescent individuals (R^2=0.577, p=0.0016; n=14), suggesting that both B and T cells participate in immune-mediated protection to viral infection. Previous studies of SARS patients also showed that ~90% had functional, virus-neutralizing antibodies and ~50% had strong T-lymphocyte responses.

Neutralization Antibody Titers Correlate With The Numbers Of Virus-Specific T cells



Source: Ni et al., *Immunity,* 2020

Importantly Emerging Data Suggests That Antibody Titers Wane Over Time

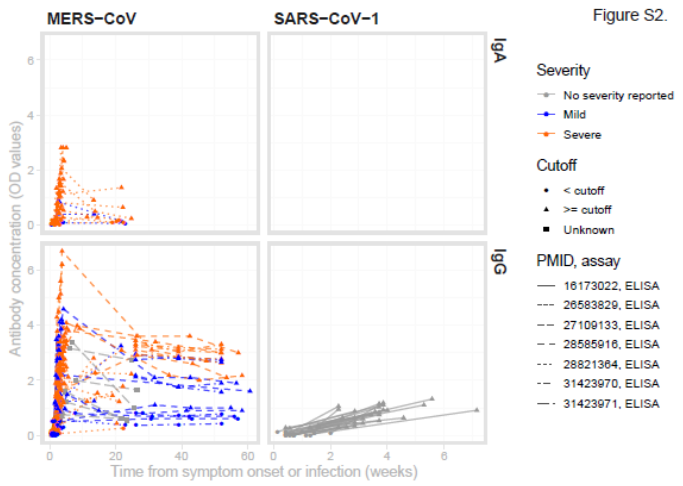
Prior studies of other human coronaviruses showed that antibody levels waned overtime and antibody kinetics post infection varied significantly between patients. Most strikingly, recent reports from China showed that younger patients had fewer antibodies with 10-20% of symptomatic patients having little or no-detectable antibody. More so, limited data from prior human challenge studies also suggested that protection after infections may last only 1 or 2 years.

Historical SARS And MERS Data Provide Insights About Antibody Kinetics And Correlates Of Protection - But Again Suggest Titers Wane

A recent review article by Huang el al. published on *medRxiv* (not peer reviewed) summarized available data of SARS-CoV-2 and other human coronaviruses to provide some insights regarding antibody kinetics and correlates of protection. The researchers found that prior infection might induce immunity against new infection, at least for a certain period, and cross-reactivity of pre-existing antibodies to other coronaviruses could provide cross-protection. However, such cross-reactivity also raised concerns about potential ADE.

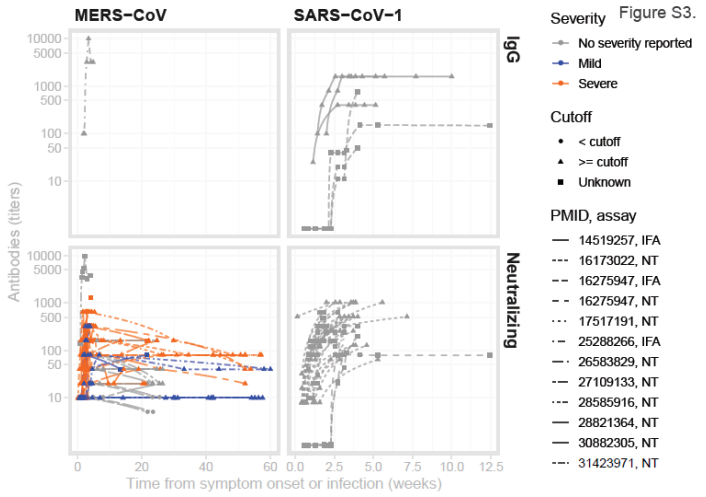
Importantly, the data showed that levels of IgG and neutralizing antibody titer waned overtime but are typically detectable up to at least a year.

Studies Of SARS/MERS Showed Levels of IgG Waned Overtime



Source: Huang el al. *medRxiv,* 2020

Studies Of SARS/MERS Showed Antibody Titers Decayed Overtime

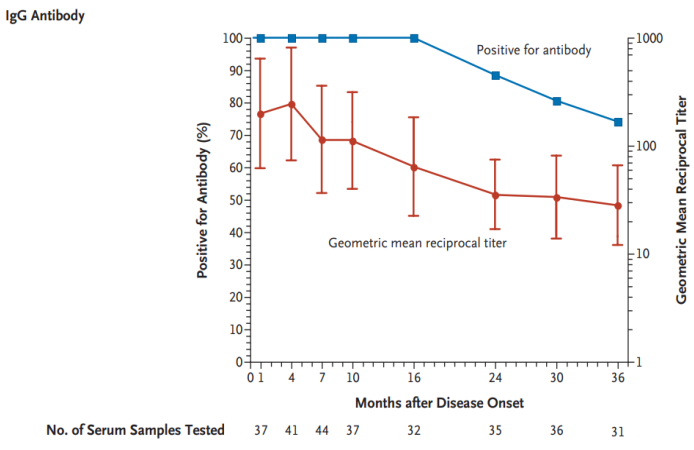


Source: Huang el al. *medRxiv,* 2020

Data From SARS-CoV-1 Infection Shows Titers Peak At 4 Months Then Wane – But Still Detectable In Most Patients At 36 Months

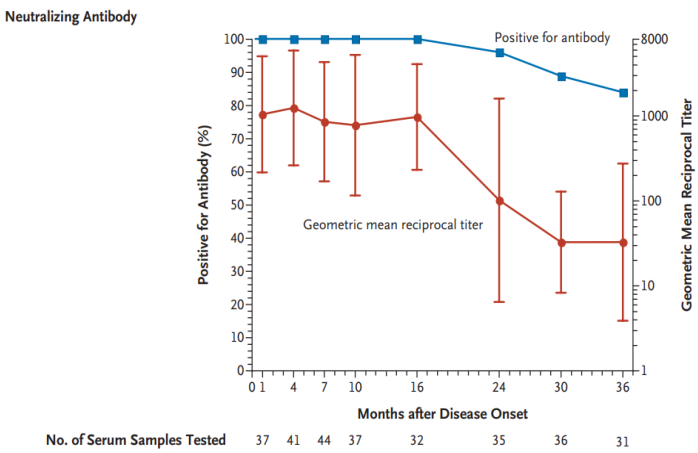
Of note, few studies reported antibody titer data over a course of ≥2 years after disease onset. Only one study by Cao et al. published in *NEJM* reported data of a SARS-CoV-1 antibody titer over the course of 3 years (n=37). The study showed that titers for both IgG and neutralizing antibodies peaked at month 4 and waned thereafter. The study showed 74% and 84% of patients had detectable levels of IgG and neutralizing antibodies at month 36, respectively.

74% Of Samples Were Positive For IgG Antibody And Geometric Mean Reciprocal Titers Was ~1:30 In SARS Patients At Year 3



Source: Cao et al., *NEJM,* 2020

84% Of Samples Were Positive For IgG antibody And Geometric Mean Reciprocal Titers Was ~1:30 In SARS Patients At Year 3



Source: Cao et al., *NEJM,* 2020

Studies With HCoV Show That Re-Infection Is Possible But With Lower Severity

Characterization of a correlate of protection requires studies to measure immune responses prior to virus exposure and over a period post infection. Few studies reported such data so far. Several studies with HCoV re-challenge showed that serum IgG, IgA, and neutralizing titer provide correlates of protection from infection.

However, repeat human challenge experiments with single HCoV also suggested that patients can be re-infected with the same HCoV one year after the first challenge, with possible lower severity of symptoms.

Studies Showed Possible Correlates Of Antibody Immunity And Protection Against CoV Infection

Authors	Year Of Study	Country/ Region	Study Type	Participants	Virus	Key findings
Reed *et al*	1984	UK	Challenge experiment	Adults (n=18)	HCoV-229E, HCoV-OC43	• Re-challenged (n = 6) volunteers who had been experimentally infected 8-12 months previously. On the first challenge, all 6 developed symptoms and detectable virus and 5 of 6 experienced significant rise in titer. In the second season, 0/6 experienced illness, detectable virus or significant rise in titer. • Re-challenged (n=12) volunteers with heterologous virus (not identical to first experimental infection) 8-14 months after first infections. 7/12 developed cold symptoms
Cohen *et al*	1991	UK	Challenge experiment	Adults (n=54)	HCoV-229E	• Challenge study focused on psychological-stress and its impact on response to experimental infection with coronavirus. • Suggested that was associated with risk but lacks details broken out for just coronavirus. serological status (having above or below median value)
Barrow *et al*	1990	UK	Challenge experiment	Adults (n=53)	HCoV-229E	• Found lower proportions of individuals with high neutralizing titer experienced 'significant colds' upon viral challenge than individuals with low titer.

Source: Huang el al. *medRxiv,* 2020, Cowen and Company

Types of SARS-CoV-2 Vaccines

Regardless of the modality employed, the intention of all vaccines is to expose the body to a foreign antigen that will not cause disease but will induce an immune response that is sufficient to protect from future infection. Whether a vaccine includes a weakened form of the virus itself, fragments of key proteins, or the genetic material needed to create key proteins, a robust humoral and cellular immune response is the goal.

The array of vaccine modalities in development for COVID-19 include multiple novel technologies that are yet to produce a licensed vaccine, including DNA, mRNA and non-replicating viral vector vaccines. Though these novel approaches do not have the track record of modalities such as whole-virus and replicating viral vector vaccines, they may offer advantages in terms of development speed, manufacturing scale up and/or safety in immunocompromised individuals.

Pros and Cons Based on Vaccine Modality

Modality • Developers	Pros					Cons				
	Rapid vaccine construction	No handling of infectious material	Amplification*	Can be used in immunocompromised subjects	History of approved vaccines	Risk of genomic integration	Requires specialized administration	Requires cold chain storage	Requires adjuvant	Preexisting antibodies to vector possible
DNA Vaccine • Inovio • Genexine	✓	✓	✓	✓	X	✓	✓	X	X	X
mRNA Vaccine • Moderna • Pfizer/BioNTech • CureVac • Translate Bio/Sanofi	✓	✓	✓	✓	X	X	X	✓	X	X
Viral Vector (Replicating) • Merck	X	X	✓	X	✓	✓	X	X	X	✓
Viral Vector (Non-replicating) • AstraZeneca/Oxford • CanSino • Johnson & Johnson	X	X	✓	✓	X	✓	X	X	X	✓
Whole Virus (Inactivated) • Sinovac/Dynavax • Sinopharm • IMBCAMS**	X	X	X	X	✓	X	X	X	X	X
Protein Subunit • Novavax/Emergent Bio • Clover/Dynavax/GSK • Sanofi/GSK	X	✓	X	✓	✓	X	X	X	✓	X
Virus-like Particles • Medicago/GSK	X	✓	X	✓	✓	X	X	X	X	X

*Amplification = # of protein antigen molecules produced per molecule of vaccine delivered
**IMBCAMS = Institute of Medical Biology at the Chinese Academy of Medical Sciences

Source: Cowen and Company

Genetic Vaccines Employ Novel Technologies To Quickly Design And Produce Vaccines At Massive Scale – mRNA Vaccines Are In the Lead Position

Genetic vaccines (such as mRNA or DNA vaccines) employ part of the virus' genetic code to induce immunity in the host. These vaccines are engineered to introduce genetic material that codes for a protein (whole protein or subunit part of the whole protein) that will then circulate in the body. The immune system will then recognize that whole or protein subunit as foreign and mount an immune response against it. This vaccine is novel and has not yielded any approvals yet.

mRNA Vaccines: Encode the instructions to make viral proteins (which the body will then form antibodies against). Uses a system such as a liposome for delivery into the host. There are currently no approved mRNA vaccines for humans. Moderna and Pfizer/BioNTech are the leaders and both showed promising proof of concept in term of

inducting neutralizing antibodies and T cell responses. Of those, we view Pfizer/BioNTech to have the better data.

DNA Vaccines: Plasmid DNA is delivered into cells. The cells use the DNA to create mRNA which will guide the assembly of viral proteins (which the body will then form antibodies against). There are currently no approved DNA vaccines for humans, but they have been approved for veterinary cases. Inovio is a leader in this area.

Viral-Vector Based Vaccines Are Highly Promising But Face Some Challenges Due to Prior Exposure to Adenovirus (AAV), Elderly And Patients With High Antiviral Titers

In this approach, a gene from the target virus is added to virus being used as a vector (e.g. adenovirus). The vector is then able to enter cells and deliver the gene to create a protein coding for the antigenic part of the target virus. As the adenovirus is not able to replicate (since one of its genes was replaced), this approach is safe as it protects against undesired viral replication.

Importantly, this strategy does not require use of an adjuvant and promotes a robust cytotoxic T cell response to eliminate virus-infected cells. This approach is in clinical trials for HIV and Ebola. JNJ and AstraZeneca/Oxford University are the leaders in this modality.

Whole-Virus Vaccines (Inactivated and Live Attenuated) Are Validated Modalities But Production Is Slow

This modality uses an inactivated or weakened virus that is unable to cause disease. This is the most common form of vaccine in use today (examples include influenza, chickenpox, measles, mumps and rubella). The benefit of this approach is that it can induce a quick and strong immune response and is commonly used in combination with an adjuvant for improved immunogenicity. The downside is that creating these vaccines is slow and requires months to grow each batch of viruses. Sinovac/Dynavax is the leader in this space.

Protein-Based Vaccines Employ Traditional Modalities And Require Adjuvants To Boost Immune Response

Protein-based vaccines use a viral protein or a protein fragment to elicit an immune response in the host. These vaccines commonly used in combination with an adjuvant for improved immunogenicity.

Virus-Like Particle Vaccines: These modalities contain pieces of viral proteins to illicit immune response. As they do not contain live virus, they harbor no risk of causing disease but are still immunogenic. Medicago/GSK is the leader in this space.

Recombinant Protein-Based Vaccines: Viral proteins are created in other cells (e.g. yeast) and then purified. This type of vaccine can use a whole or protein fragments. The proteins are manufactured using recombinant technologies. This approach has been employed for vaccines that include shingles and hepatitis B. GlaxoSmithKline (GSK) and Sanofi are the leaders in this space.

There Are Multiple Vaccine Programs In Development – mRNA Vaccines Are In The Lead

There are currently more than >30 vaccines against SARS-CoV-2 in clinical trials with several more expected to start in the coming months. Moderna was the first to begin in-human trials in March and was the first to start a Phase 3 study in July.

Upcoming Milestones And Manufacturing Expectations For Vaccine Candidates

Modality	Vaccine Name	Developer(s)	Immunologic Target	Current Phase	Potential News	Estimated Timing	Manufacturing Expectations
mRNA	**mRNA-1273**	Moderna	Full S protein	Ph3	Complete Phase 3 Enrollment Initial Phase 3 Data Regulatory Approval	September-20 December-20 Q1:21	500M to 1B doses per year in 2021
	BNT162b2	Pfizer/BioNTech	Full S protein	Ph2/3	Complete Phase 2/3 Enrollment Initial Phase 3 Data Regulatory Approval	September-20 October-20 Q1:21	100M doses by YE20, 1.3B doses in 2021
	CVnCoV	CureVac	Full S protein	Ph1	Phase 1 Data	Sept/Oct-20	Hundreds of millions of doses in 2020, scaling up to billions by 2022
	Unnamed	Translate Bio/Sanofi	Full S protein	Preclinical	Start Phase 1 Trial Regulatory Approval	Q4:20 H2:21	90-360M doses annually by H1:21
DNA	**INO-4800**	Inovio	Full S protein	Ph1	Start Phase 2/3 Trial Phase 2/3 Data	September-20 Q1:21	1M doses by YE20, >100M doses in 2021
	GX-19	Genexine	Full S protein	Ph1/2	Phase 1 Data	September-20	No specific guidance
Adenoviral	**AZD1222**	AstraZeneca/Oxford	Full S protein	Ph2/3	Phase 3 Data Regulatory Approval	October-20 Q4:20	400MM doses in Sept (at-risk), >1B doses in 2021
	Ad5-nCoV	CanSino	Full S protein	Ph3	Initial Phase 3 Data	December-20	100-200M doses per year in 2021
	Ad26.COV2-S	Janssen Pharma	Full S protein	Ph1/2	Phase 1 Data Start Phase 3 Trial	September-20 September-20	500M doses in 2020, 1B doses in 2021
Replicating Viral Vector	**V591 (Measles vector)**	Merck	Undisclosed DNA cargo	Preclinical	Start Phase 1 Trial	Q3:20	No specific guidance
	V590 (rVSV vector)	Merck	Full S protein	Preclinical	Start Phase 1 Trial	H2:20	No specific guidance
Inactivated Virus	**Unnamed**	Wuhan Inst/Sinopharm	Whole virus	Ph3	Phase 3 Data Regulatory Approval (China)	Q4:20 YE:20	200M doses per year
	BBIBP-CorV	Beijing Inst/Sinopharm	Whole virus	Ph3	Phase 3 Data Regulatory Approval (China)	Q4:20 YE:20	200M doses per year
	CoronaVac	Sinovac	Whole virus	Ph3	Initial Phase 3 Data Complete Phase 3 Study	October-20 February-21	100M doses per year
	Unnamed	Inst of Med Biol at Chinese Acad of Med Sciences (IMBCAMS)	Whole virus	Ph2	Phase 2 Data Start Phase 3 Trial	H2:20 Unknown	No specific guidance
Protein Subunit	**NVX-CoV2373**	Novavax/Emergent Bio	Full S protein	Ph1/2	Start Phase 3 Trial Initial Phase 3 Data	October-20 December-20	100M doses in 2020, >1B doses in 2021
	SCB-2019	Clover/GSK/Dynavax	Full S protein	Ph1	Phase 1 Data	September-20	Hundreds of millions of doses in 2021
	Unnamed	Sanofi/GSK	Protein Subunit	Ph1/2	Phase 1/2 Data Start Phase 3 Trial Regulatory Approval	December-20 December-20 H1:21	100M doses in 2020, >1B doses by mid-2021
	MVC-COV1901	Medigen/Dynavax	S-2P protein	Preclinical	Start Phase 1 Trial	September-20	Dynavax able to supply 600M to 1.2B doses of adjuvant per year
Virus-Like Particles	**CoVLP**	Medicago/GSK/Dynavax	Plant-derived VLP	Ph1	Phase 1 Data Start Phase 2/3 Trial Regulatory Approval	September-20 October-20 H1:21	100M doses by YE:21, 1B doses annually by 2023

Source: Cowen and Company, Company reports

mRNA Vaccines Are Novel But Offer Rapid Development Time And Manufacturing Scale Up – Initial Data Is Highly Encouraging

As a platform, mRNA therapies have the potential to transform vaccine development, as well as treat genetic disorders caused by protein or gene dysfunction. Moderna, and BioNTech are the leaders in the field are currently investigating mRNA vaccines against several common and rare infectious diseases.

There are several advantages for mRNA vaccines including:

1. use of the cell's own machinery to product natural, fully functional proteins
2. no handling of infectious material
3. restoration of gene expression without entering the cell nucleus or changing the genome
4. rapid development from target selection to product candidate
5. rapid scale up of production due to generic manufacturing process, and
6. amplification (each mRNA molecule will produce more than one protein molecule).

If this novel modality is successful, the ability to rapidly develop mRNA vaccines to nearly any viral target will enable future preparedness for any significant mutations to SARS-CoV-2 and for the next pandemic.

The risks in creating an mRNA vaccine for SARS-CoV-2 include the lack of validation of the technology; thus far, no mRNA vaccines have been approved for use.

Since mRNA technology does not have the track record of classic vaccine modalities, there are several unknowns including the stability of mRNA in an immune-stimulated environment (since mRNA is immunogenic) and whether other drugs could decrease its potency.

mRNA vaccine candidates require cold-chain storage which is a significant hurdle to global access for the vaccine.

Additionally, mRNA vaccine candidates require cold-chain storage which is a significant hurdle to global access for the vaccine. For example, Translate Bio's product requires transport at -80 degrees Celsius (-110 degrees Fahrenheit) and they are working to develop a formulation that would not require such frigid temperatures. Moderna's vaccine candidate, on the other hand, has a more convenient temperature requirement of 5 degrees Celsius (41 degrees Fahrenheit).

Optimization of the Lipid Nanoparticle Delivery Mechanism Could Provide Differentiation Among mRNA Vaccines

Recent advances in the delivery system of mRNA provide the foundation for successful candidates. In particular, optimization of lipid nanoparticles (LNPs) for intramuscular (IM) delivery has led to improved tolerability and augmentation of immune responses. Each company has its own proprietary LNP technology which plays an important role in differentiating its platform from competitors.

Various RNA Modifications Have Set The Stage For Success By Enhancing Stability

The RNA itself has also been improved over time through modifications to the chemical composition of the molecules post-synthesis. These modifications have the potential to alter function and stability. As an example, 'mRNA capping' is a process that involves methylation of a guanine nucleotide found on the five-prime (5') end of the mRNA and enhances efficiency for protein production. Further improvements in protein translation have been achieved through incorporation of modified nucleosides such as pseudouridine and 1-methylpseudouridine.

Both mRNA-1273 and BNT162b2 use nucleoside-modified RNA (modRNA) which encode for the full pre-fusion S protein. The candidate from Translate Bio/Sanofi has not been disclosed at this time.

Moderna Is Ahead of the Pack But Not Looking The Best

mRNA Vaccines in Development

Modality	Vaccine Name	Developer(s)	Immunologic Target	Current Phase	Potential News	Estimated Timing	Manufacturing Expectations
mRNA	**mRNA-1273**	Moderna	Full S protein	Ph3	Complete Phase 3 Enrollment Initial Phase 3 Data Regulatory Approval	September-20 December-20 Q1:21	500M to 1B doses per year in 2021
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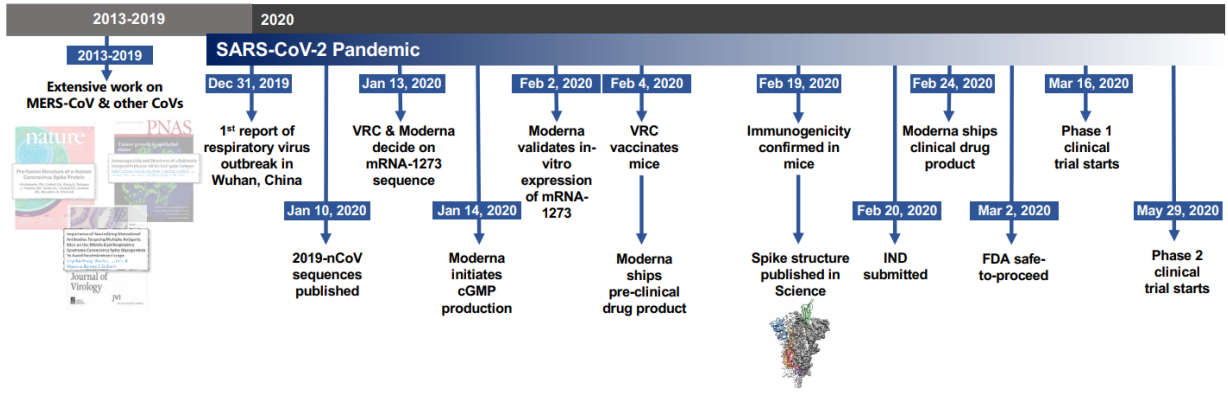
	Unnamed	Translate Bio/Sanofi	Full S protein	Preclinical	Start Phase 1 Trial Regulatory Approval	Q4:20 H2:21	90-360M doses annually by H1:21

Source: Cowen and Company

In collaboration with National Institute of Allergy and Infectious Diseases (NIAID), Moderna's vaccine (mRNA-1273) is currently the furthest in development among competitors. The company started vaccine development as soon as the viral genome was published by China in January. Phase 1 data was published in *NEJM* in July. Phase 3 studies commenced in July and we expect data around December based on the current rate of enrollment wherein some reports suggest that enrollment is proceeding slower than expected.

Timeline For mRNA-1273's Progression To Clinical Trials



Source: Corbett et al., *bioRxiv preprint* 2020, Moderna

Moderna's Zika and CMX Vaccines Provided Proof of Concept for Utility of mRNA To Induce Immunity

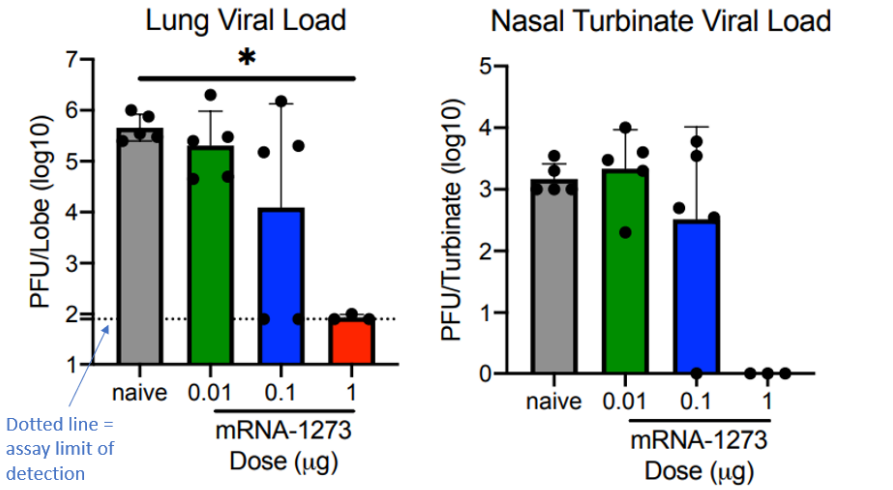
With their proprietary lipid nanoparticle (LNP) used for delivery of mRNA into cells, Moderna provided proof of concept with their H10/H7 influenza vaccine by meeting the FDA threshold of a HAI titer of 1:40 for flu vaccines. They are also developing vaccines for Zika and CMV. The mRNA technology gives them the ability to create complex antigens through encoding multimeric proteins that the body will create, present via antigen presenting cells (APCs) such as dendritic cells, and then form antibodies against.

This method ensures the conformational formation of the protein will mimic the natural virus, a feat that is sometimes difficult for ex-vivo protein injections.

mRNA-1273 Provides Promising Preclinical Proof of Concept For SARS-CoV-2 With Robust Neutralizing Antibody Titers

Moderna's mRNA-1273 encodes for the full S protein (pre-fusion stabilized) which produces the protein in the same confirmation as the native virus. Thus far, the company has released partial Phase 1 results and preclinical data in mice. In the preclinical study, published in preprint form on bioRxviv, mice were immunized at weeks 0 (prime) and 3 (boost) with either 0.01, 0.1 or 1 µg of mRNA-1273 and then challenged with mouse-adapted SARS-CoV-2 at 13 weeks post-boost. The 1 µg dose effectively protected against SARS-CoV-2 infection and the lungs and noses of the mice.

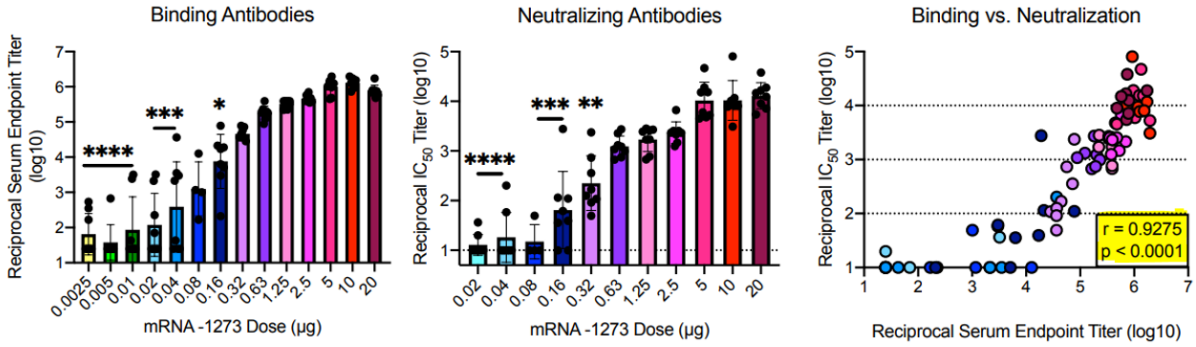
At 13 weeks Post-Boost, 1 µg Dose of mRNA-1273 Protects Mice From SARS-CoV-2 Infection



Source: Corbett et al., *bioRxiv preprint* 2020, Moderna

Neutralizing antibody titers demonstrated a potent dose-dependent response and correlated well with binding antibody titers ($r=0.9275$, $p<0.0001$). This correlation is important since it is much easier to perform assays that measure binding antibody titers than neutralizing antibody titers.

Dose-Dependent mRNA-1273-Elicited Antibody Responses and Strong Correlation Between Binding and Neutralization Titers



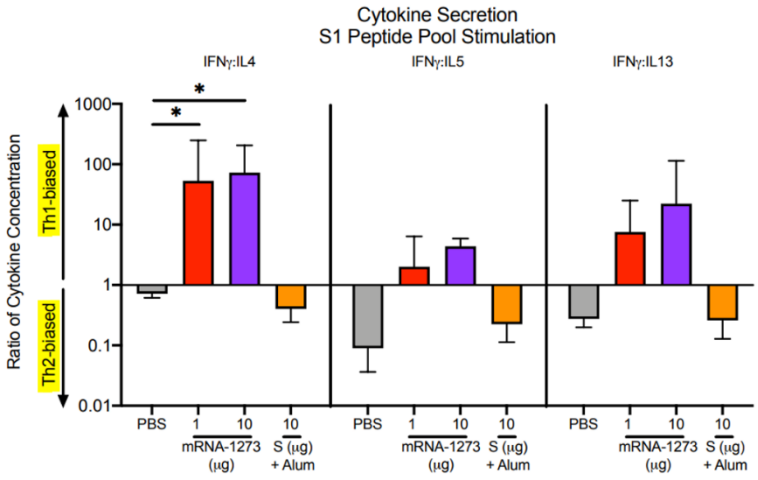
Source: Corbett et al., *bioRxiv preprint* 2020, Moderna

Mean neutralizing titers after prime-boost regimen with the 1 µg dose ranged from 1:89 to 1:1,115, depending on the mouse strain.

Preclinical Data Shows Encouraging Th1 Response While Sparing Th2 Activity

The study also evaluated the balance of Th1 and Th2 responses given the known risk of disease enhancement associated with a Th2-biased response (discussed previously in this report). To assess for a Th1 vs Th2 response, Ig subclass and T cell cytokine data were measured in response to SARS-CoV-2 infection in mice vaccinated with mRNA-1273. As a comparison arm, some mice were instead vaccinated with S protein adjuvanted with alum. The results demonstrated that mRNA-1273 vaccinated mice exhibited a Th1-biased response (which is desirable), whereas the S protein adjuvanted with alum led to a Th2-biased response (which is not desirable as can raise the chance for immune enhancement).

mRNA-1273 Elicited a Th1 Skewed Response Relative to S Protein Adjuvanted with Alum



Source: Corbett et al., *bioRxiv preprint* 2020, Moderna

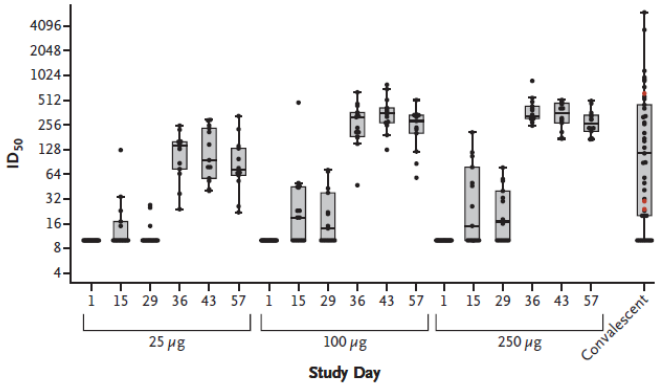
First Published Data For Moderna's Vaccine Show Promising Antibody Titers – But Raised Questions About CD8 T Cell Response

The prime/boost regimen used in the preclinical study was similar to the regimen tested in the Phase 1 trial which included 45 subjects vaccinated with either 25, 100 or 250 µg of mRNA-1273 on day 1 and day 29. Partial results from the Phase 1 study were released in May 2020 and full results were published in NEJM in July 2020. The study revealed that the vaccine induced dose-dependent increases in binding antibody titers, high levels of neutralizing antibody (nAb) relative to convalescent serum and a manageable safety profile, providing support for its 100 µg dose for the upcoming Phase 3.

$PRNT_{80}$ is the lowest concentration of serum able to reduce the number of live SARS-CoV-2 plaques by at least 80%

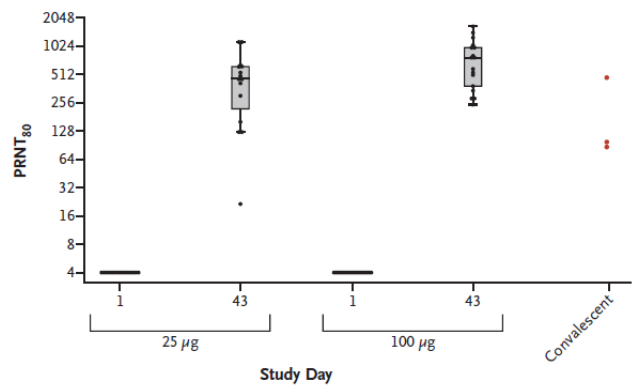
In the study, nAb titers were measured by 2 separate assays as there is currently no standard across studies. The geometric mean nAb titer for the 100 µg dose cohort was 654 on day 43 as measured by $PRNT_{80}$ assay (which was 4.1x reference convalescent sera [n=3]) and 232 on day 57 as measured by pseudovirus neutralization assay (PsVNA) ID_{50} (which was 2.1x reference convalescent sera [n=38]). The small number of convalescent sera samples with $PRNT_{50}$ assays (n=3) relates to the difficulty of performing the test.

Neutralizing Ab Response As Measured By PsVNA ID_{50}



Source: Moderna, *NEJM*

Neutralizing Ab Response As Measured By Live Virus $PRNT_{80}$



Source: Moderna, *NEJM*

mRNA-1273 Is Competitive with Pfizer/BioNTech's BNT162b1 But Induces A Lower Nab Titer

We view the nAb response of Moderna's 100 µg prime-boosted vaccination (2 doses given 28 days apart) as similar to Pfizer/BioNTech's BNT162b1 (also prime-boost strategy with doses given 21 days apart), though direct comparisons are difficult due to different assays and different time points.

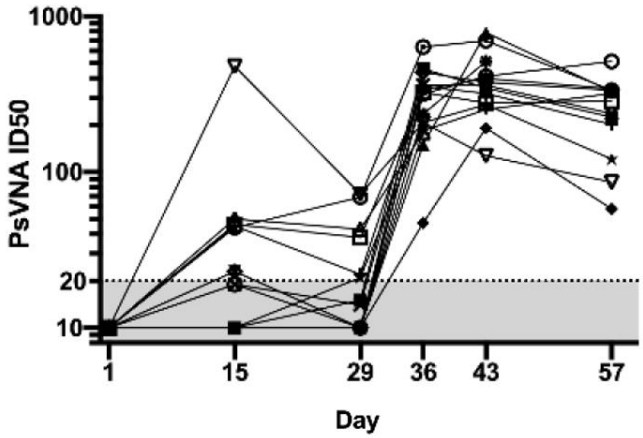
Pfizer/BioNTech's BNT162b1 geometric mean nAb titer on day 28 (7 days after the second 30µg dose) reached 267 (2.8x the mean in convalescent sera). Of note, it is not easy to compare across studies because of the difference in the assays and unequal follow-up time.

Durability May Be A Concern For mRNA-1273 Given Drop In Titers From Day 43 to 57

Durability is a key question for all vaccines attempting to confer immunity against a novel virus, but perhaps even more so with a new technology such as an mRNA-based vaccine. Isolating our view to the 100 µg dose (since this is the dose that will be used in

the Phase 3 trial), we see that the nAb geometric mean ID_{50} on day 43 was 344 and then there was a significant drop to 232 on day 57.

Time Course Of nAb Response in the 100 µg Dose Group (Prime Dose on Day 1, Boost on Day 29; Geometric Mean ID_{50} of 344 on Day 43 and 232 on Day 57



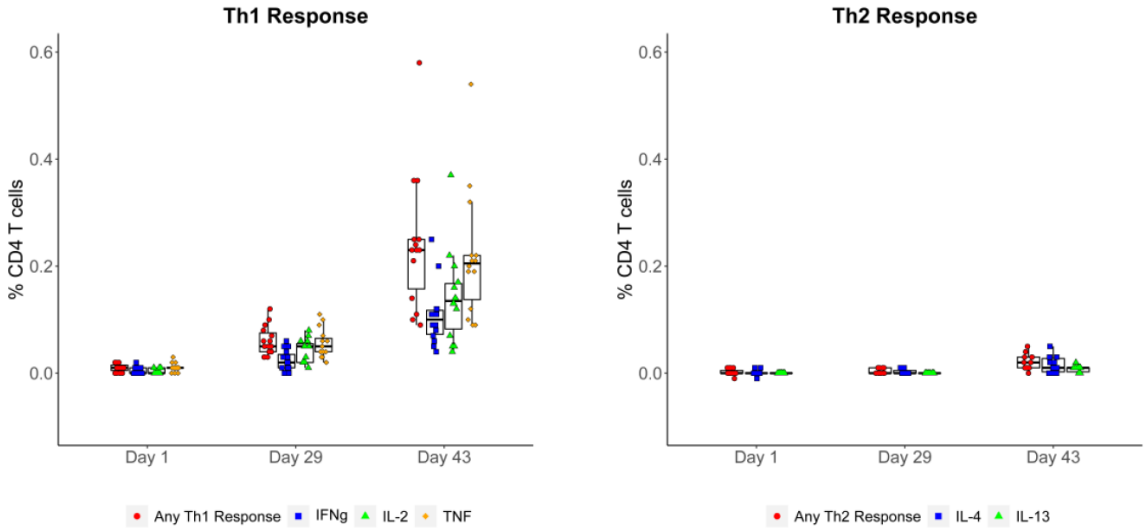
Source: Moderna, *NEJM*

Since we do not currently know what nAb titer correlates with immune protection (only Phase 3 trials can identify the correlate of protection level), one potential benchmark for titer levels is the FDA guideline of nAb titers of ID_{50} ≥160 for convalescent plasma therapy. Moderna's data showed 3 of the 15 subjects treated with 100 µg dose dropped below 160 within 4 weeks after the booster dose.

Th1 Response Is Encouraging As Reduces Risk For ADE But Lackluster CD8 T Cell Response Somewhat Disappointing in Phase 1 Study

In terms of T cells, mRNA-1273 demonstrated a favorable Th1 skew in the CD4 response, which is an important finding that makes vaccine enhancement less likely.

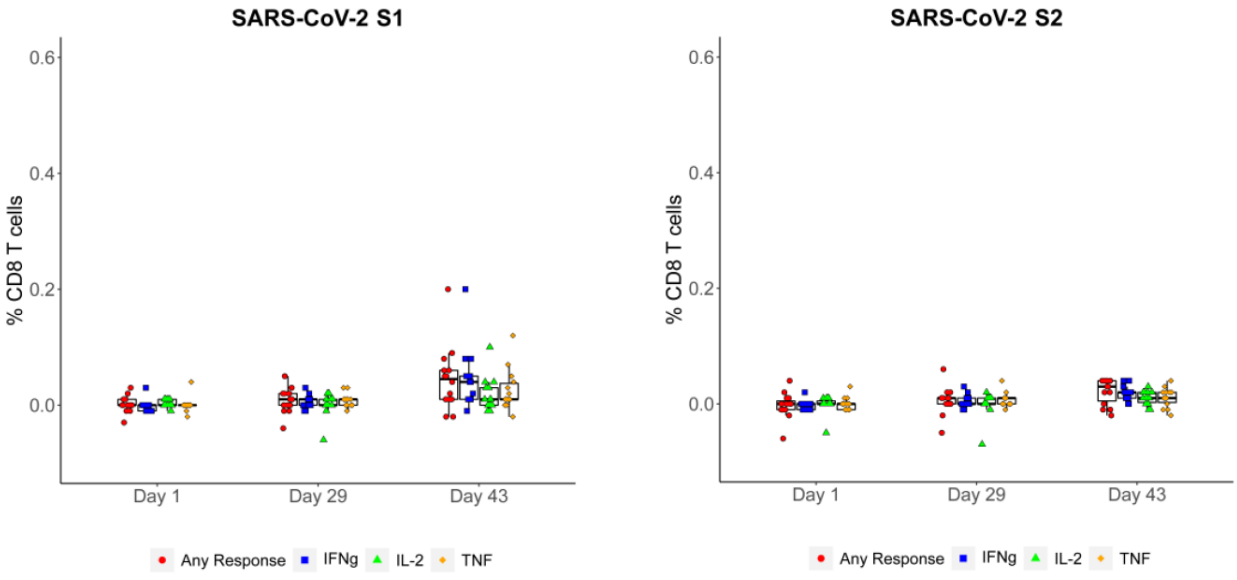
Skewed Th1 Response Seen Based on Frequencies of CD4+ T cells Producing The Indicated Cytokines After Stimulation with S2 Subunit Peptide Pool



Source: Moderna, *NEJM*

The low level CD8 response was somewhat disappointing, especially compared to Moderna's preclinical data, though the relevance of CD8 levels for protective immunity in the presence of high nAb titers remains unknown.

Frequencies of CD8+ T cells Producing The Indicated Cytokines After Stimulation with S1 Subunit Peptide Pool (Left) or S2 Subunit Peptide Pool (Right)

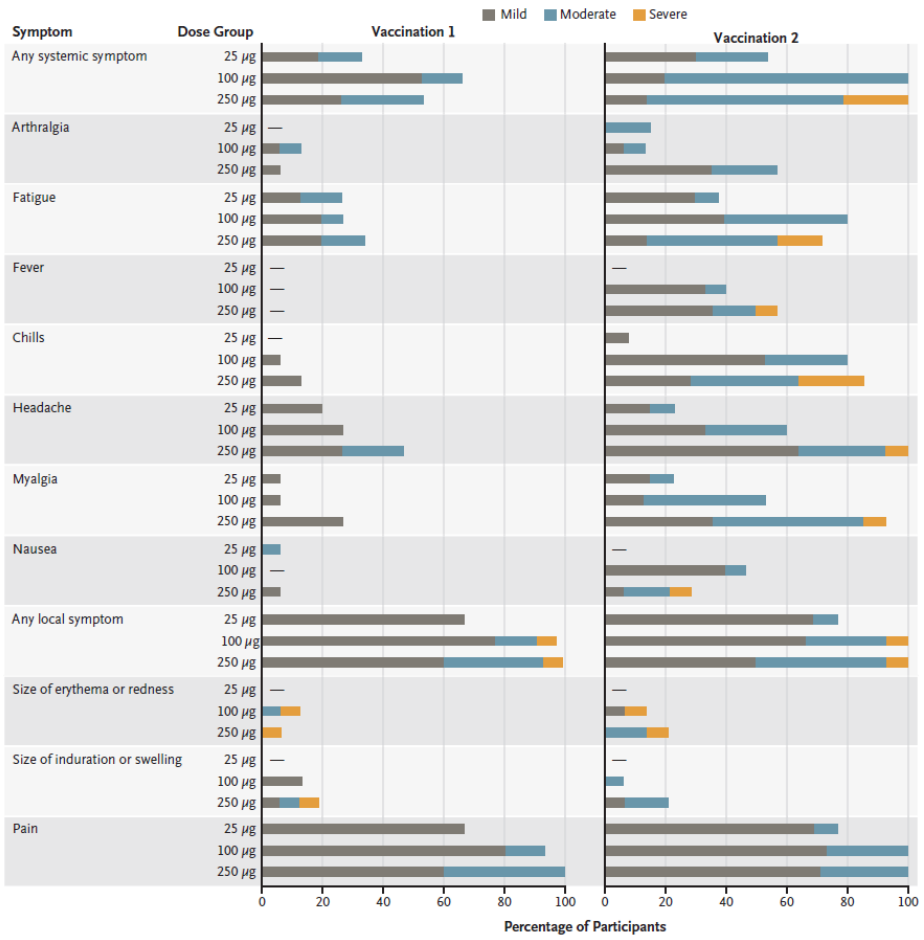


Source: Moderna, *NEJM*

Vaccine Generally Well Tolerated at the 100 µg Dose

Adverse events (AEs) were generally transient and mild/moderate in severity at 100µg dose. However, given the frequency of AEs, there is reason to be concerned about the tolerability in an older, high-risk population.

AEs Were Mild/Moderate In Severity At 100µg Dose, But Most Notable At 250µg Dose



Source: Moderna, *NEJM*

Enrollment Completed In Phase 2

Overall, we think the promising immune response of mRNA-1273 provides further validation of the mRNA-based technology.

Enrollment is complete for Moderna's Phase 2 trial which will test a 50 and 100 µg dose.

Phase 3 COVE Study Commenced In July – Data Is Likely In December

The Phase 3 COVE trial (n=~30,000) commenced in July and is powered to demonstrate a 60% improvement over placebo for the primary endpoint of prevention of symptomatic confirmed COVID-19 disease.

The Phase 3 COVE trial (n=~30,000) commenced in July and is powered to demonstrate a 60% improvement over placebo for the primary endpoint of prevention of symptomatic confirmed COVID-19 disease. Recall, the FDA recently has published new guidelines on safety and efficacy for COVID-19 vaccines, looking for an effectiveness of at least 50% higher than placebo with a 30% threshold at the lower end of the confidence interval.

Data will be reviewed on an ongoing basis by an independent monitoring committee led by the NIH. The trial is expected to have interim analyses after 53 and 106 events, prior to a final event-driven analysis at ~151 events.

As of September 4, the COVE trial enrolled 21,411 of the target 30,000 participants.

In terms of defining symptomatic confirmed COVID-19 disease, the study uses the following criteria:

1. At least two systemic symptoms such as fever, chills, myalgia, headache, sore throat, new olfactory/taste disorder(s), OR
1. at least one respiratory symptom such as cough, shortness of breath, or difficulty breathing, OR
2. clinical or radiologic evidence of pneumonia, AND
3. at least one PCR positive NP swab, nasal swab, saliva or respiratory sample

Key secondary endpoints include prevention of severe COVID-19 disease (as defined by the need for hospitalization) and prevention of infection by SARS-CoV-2 regardless of symptomology (will capture asymptomatic cases).

Phase 3 COVE Study Design

Vaccine	mRNA-1273
Developer(s)	Moderna
Modality	mRNA
Current Phase	Ph3
Trial ID	NCT04470427
n	30,000
Population	Age 18 and above without immunocomprised state or unstable medical condition
Study Arms/Dose	mRNA-1273 (2 doses of 100 µg, IM) vs. placebo
Primary Endpoint	Confirmed symptomatic COVID-19 cases (up to 2 yrs)
Secondary Endpoints	▪ Severe COVID-19 cases ▪ Infection by SARS-CoV-2 ▪ SAEs by 2 years ▪ nAb and S-protein specific binding Ab titers
Estimated Initial Data Readout	December-20

Source: Cowen and Company

Moderna Is Planning 500M-1B Annual Capacity Depending On The Final Dose (50µg or 100µg)

In terms of production, the company has stated that they will be able to supply 500M to 1B doses per year at the 100 µg dose (that total reflects the partnership with Lonza). With the final regimen likely to require 2 doses, Moderna will be able to vaccinate up to 500M individuals. Funding from BARDA supported the planning/execution for the Phase 2 and 3 studies and will also support the scale-up of mRNA-1273 manufacturing.

To date, Moderna has received $955M from BARDA ($483M in April, $472M in July) and entered into a supply agreement with the U.S. government in August for $1.525B to deliver an initial 100M doses (translating to $15.25/dose). In total, the U.S. government has committed $2.48B for early access to mRNA-1273.

Moderna has made the case for $32-$37 per dose of its vaccine for "smaller-volume" agreements in the future.

Moderna Engaging With European Commission To Supply 80M Doses Across Europe

In late August, Moderna announced conclusion of advanced talks with the European Commission to supply 80M doses of mRNA-1273 to Europe. The agreement provides for the option to purchase an additional 80M doses for a total of up to 160M doses. Pricing was not disclosed.

BioNTech/Pfizer Behind In Starting Pivotal Trial But Looking Most Promising So Far

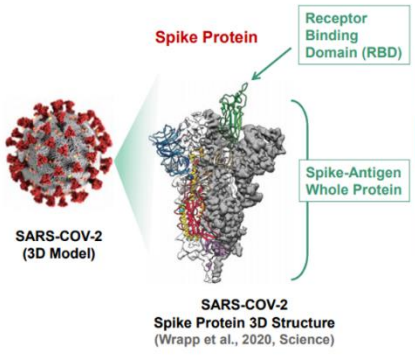
mRNA Vaccines in Development

Modality	Vaccine Name	Developer(s)	Immunologic Target	Current Phase	Potential News	Estimated Timing	Manufacturing Expectations
mRNA	mRNA-1273	Moderna	Full S protein	Ph3	Complete Phase 3 Enrollment Initial Phase 3 Data Regulatory Approval	September-20 December-20 Q1:21	500M to 1B doses per year in 2021
	BNT162b2	Pfizer/BioNTech	Full S protein	Ph2/3	Complete Phase 2/3 Enrollment Initial Phase 3 Data Regulatory Approval	September-20 October-20 Q1:21	100M doses by YE20, 1.3B doses in 2021
	CVnCoV	CureVac	Full S protein	Ph1	Phase 1 Data	Sept/Oct-20	Hundreds of millions of doses in 2020, scaling up to billions by 2022
	Unnamed	Translate Bio/Sanofi	Full S protein	Preclinical	Start Phase 1 Trial Regulatory Approval	Q4:20 H2:21	90-360M doses annually by H1:21

Source: Cowen and Company

Similar to Moderna, BioNTech and Pfizer are collaborating on a LNP-encapsulated SARS-CoV-2 mRNA vaccine. There are 4 mRNA-based vaccines are in parallel development with slightly different properties.

BNT162 Variants: Targeting SARS-CoV-2 Spike-Protein and RBD



Variant	Target	RNA construct	Immunization
162a1	RBD subunit	uRNA	prime/ boost
162b1	RBD subunit	modRNA	prime/ boost
162b2	2P-mutated full spike protein	modRNA	prime/ boost
162c2	2P-mutated full spike protein	saRNA	single injection

Source: BioNTech

BNT162b1 (Modified RNA For RBD Subunit) Vaccine Provides Proof of Concept – But Version 162b2 (Modified RNA For Full Spike Protein) Is Advancing Toward Pivotal Studies

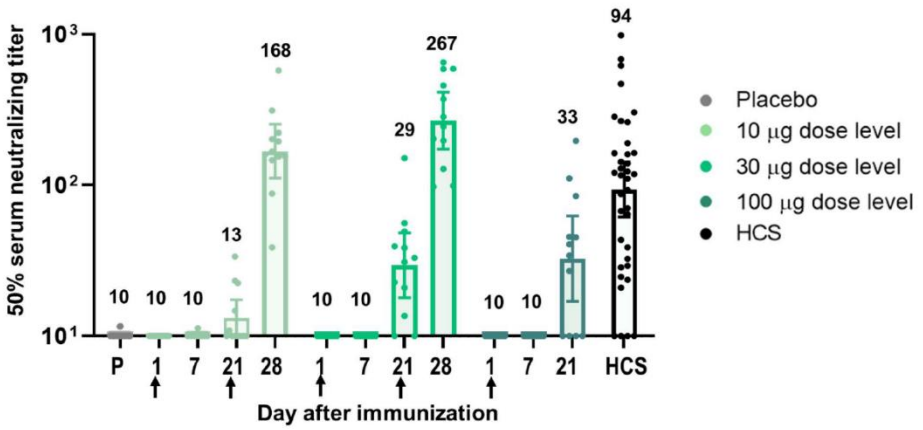
Data from the two simultaneous Phase 1/2 trials for the BNT162b1 candidate (one in the US, one in Germany) have been recently published. These trials included healthy adults age 18-55 for the dose escalation portion, with the plans to expand the age range to include subjects up to age 85 after providing initial evidence of safety and immunogenicity.

The companies selected to advance BNT162b2, a modified RNA vaccine targeting the full spike protein into the pivotal Phase 2/3 study.

Early Data From US Trial Confirms Immunogenicity and Tolerability

In the US Phase 1/2 study of BNT162b1, Pfizer/BioNTech reported that the vaccine was immunogenic with dose-dependent RBD-binding IgG concentrations and SARS-CoV-2 neutralizing titers after a prime-boost regimen. Geometric mean neutralizing titers of 168 (at 10 µg dose) and 267 (at 30 µg dose) at day 28 (7 days after dose 2) reached 1.8- to 2.8-fold that of a panel of convalescent human sera. All subjects who received 10 or 30 µg of BNT162b1 had significantly elevated RBD-binding IgG antibodies w/ geometric mean concentrations (GMCs) of 4,813 and 27,872 units/ml which are 8- and 46.3-times the GMC of 602 units/ml in a panel of 38 sera of convalescent pts.

50% SARS-CoV-2 Neutralizing Geometric Mean Titers (GMTs)



Source: Mulligan et al., *medRxiv* 2020, Pfizer/BioNTech

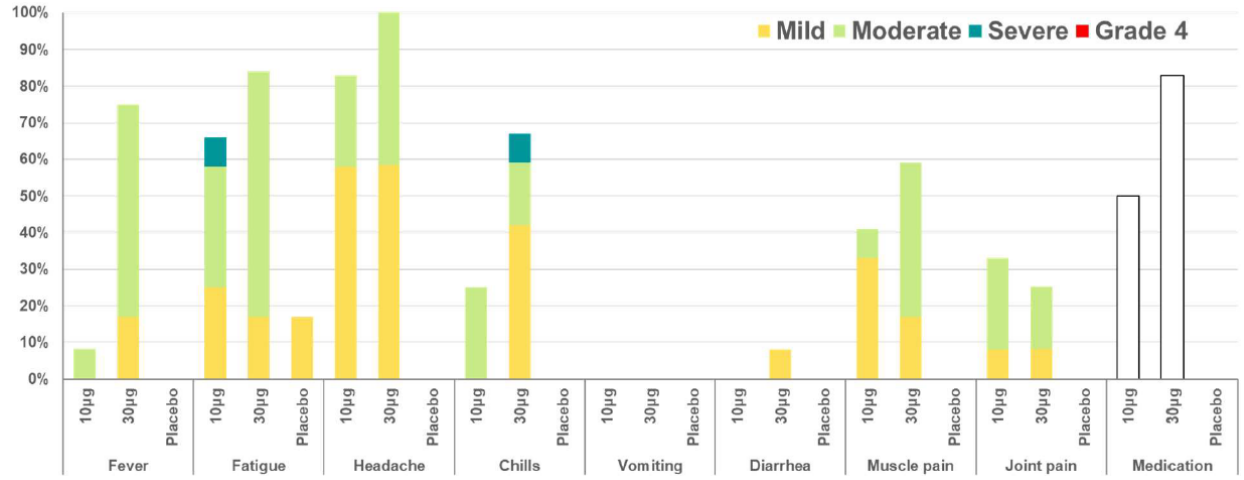
We think the early data is positive as it showed dose-dependent antibody responses along with promising tolerability. Recall, the FDA guidelines recommend use of neutralizing antibody titers of ≥160 for convalescent plasma therapy and consider 80 as acceptable if an alternative matched unit is not available.

BNT162b1 Shows Encouraging Safety At Desired Doses – Identifies Good Therapeutic Window

In terms of tolerability, the study showed dose-dependent side effects, including fevers, fatigue, headache and chills, which were more common at the 30 µg dose than the 10 µg dose. There was one severe AE in the 10 µg dose group and one in the 30 µg dose

group. Of note, the 100 µg dose cohort had multiple severe AEs reported after the prime dose and investigators elected not to pursue the boost dose in that group.

Systemic Events and Medication Use After Second Vaccination (Boost) For 10 µg and 30 µg Dose Levels



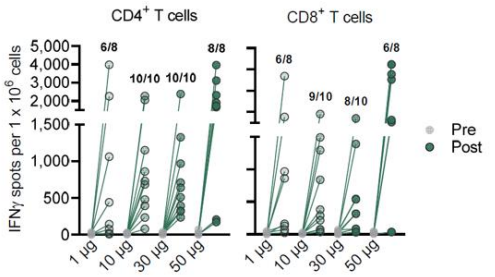
Source: Mulligan et al., *medRxiv* 2020, Pfizer/BioNTech

BNT16b1 Shines By Showing Robust CD4+ and CD8+ Responses

Results from the second Phase 1/2 trial for BNT162b1 that was completed in Germany were published in medRxiv (not peer reviewed). The novel information gained from this second study is in the T cell response to the vaccine which was measured using direct *ex vivo* IFNγ ELISpot with peripheral blood mononuclear cells (PBMCs).

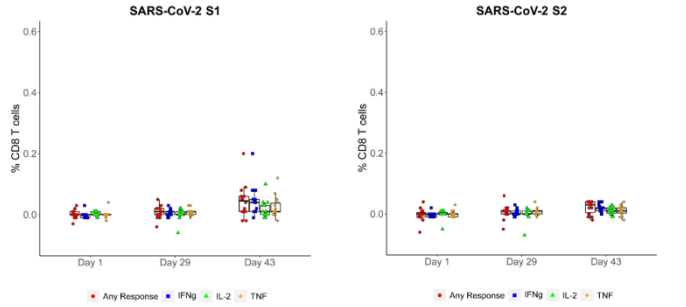
In the study, prime-boost dosing (with doses ranging from 1 to 50µg given on day 1 and day 22) elicited robust CD4+ and CD8+ T cell responses on day 29 (7 days after boost), with 34 of 36 (94%) of subjects mounting RBD-specific CD4+ responses, and 29 of 36 (81%) of subjects mounting RBD-specific CD8+ responses. This compares favorably to Moderna's mRNA-1273 (figures below) which had a somewhat disappointing CD8+ response, though it is difficult to compare across studies due to different assays and different time points.

BNT162b1: Frequency and Magnitude of T Cell Response



Source: Mulligan et al., *medRxiv* 2020, Pfizer/BioNTech

mRNA-1273: Frequency of CD8+ T cells Producing Indicated Cytokines (100µg Dose Group)



Source: Moderna, *NEJM*

Of note for BNT162b1, the magnitude of induced CD4+ and CD8+ T cells was similar across the dose range. This is a surprising finding as historical vaccine studies (prior to COVID-19) have demonstrated a direct relationship between antigen dose and T cell response magnitude (though this does not speak to the quality of the T cells as lower antigen doses have been associated with increased CD4 T cell memory development).

Pfizer/BioNTech Take The Lead Among Vaccines Candidates

With strong data for both nAb titers and T cell response, we view the vaccine from Pfizer/BioNTech as the current leader among vaccine candidates. Moderna's mRNA vaccine demonstrated strong nAb titers but had a somewhat disappointing T cell response. Oxford/AZN's vaccine, on the other hand, showed an encouraging T cell response, but a less robust nAb response.

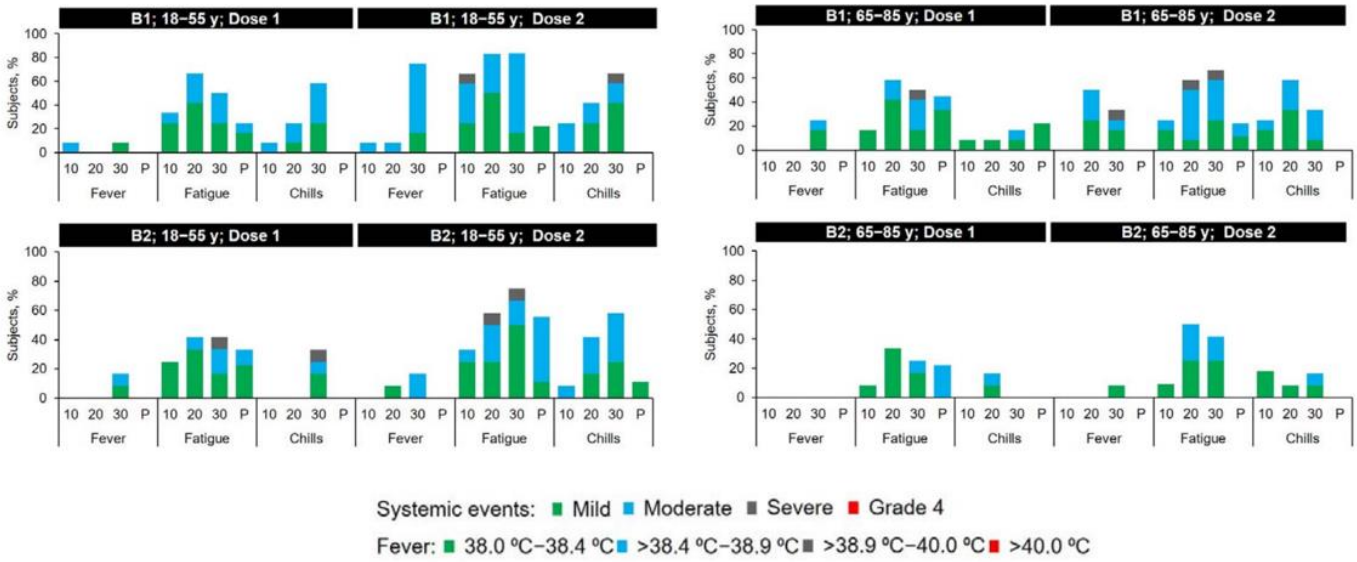
BNT162b2 Was Selected For Phase 2/3 Development Due To Better Safety And Coverage Of The Full S Protein

The BNT162b2 candidate was selected for the Phase 2/3 global trial from among the four vaccine candidates in testing, despite the Phase 1 data publications centering around BNT162b1. The selection was announced in July based on the companies' evaluation of the totality of the data from the preclinical and clinical studies. While BNT162b1 encodes for the receptor binding domain (RBD) of the SARSCoV-2 spike protein, BNT162b2 encodes an optimized SARS-CoV-2 full-length spike protein antigen.

The data for BNT162b2 was subsequently published in August in *medRxiv* and confirmed the claims that the b2 candidate elicited similar dose-dependent neutralizing GMTs to the b1 candidate and these levels were comparable to or higher than reference convalescent serum. The study also corroborated the previous claims that BNT162b2 was associated with less systemic reactogenicity.

In the study, subjects were stratified by age (18-55 cohort and 65-85 cohort) and given 10, 20, 30 or 100 µg in a prime-boost regimen of either BNT162b1 or BNT162b2. In terms of systemic events within 7 days, the BNT162b2 candidate was associated with a milder reactogenicity profile, particularly in older adults.

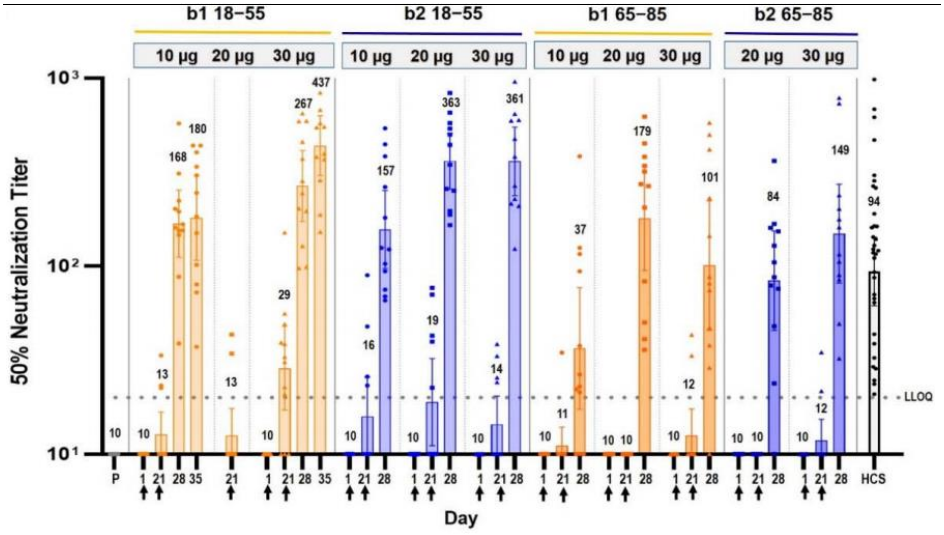
BNT162b2 Demonstrated An Improved Tolerability Profile Compared to BNT162b1, Particularly In Older Adults



Source: Walsh et al., *medRxiv* 2020, Pfizer/BioNTech

In terms of immunogenicity, the neutralizing antibody responses were similar between the two candidates. In the younger cohort receiving the 30 µg dose, the 50% neutralizing GMT one week after the booster dose was 267 for BNT162b1 and 361 for BNT162b2. Notably, both candidates elicited lower titers in the older cohort (~0.4x the younger cohort) with neutralizing GMTs of 101 for BNT162b1 and 149 for BNT162b2. All groups achieved mean titers above the level of reference convalescent serum (94).

Both Candidates Generated Similar Neutralizing Ab Response (With Lower Titers In Older Adults)



Source: Walsh et al., *medRxiv* 2020, Pfizer/BioNTech

Decreased immunogenicity in older adults is a general concern in vaccine development and will be something to watch closely in pivotal studies.

BNT162b2 elicited T cell responses against the RBD and against the remainder of the spike glycoprotein that is not contained in BNT162b1. Pfizer/BioNTech believe that immune recognition of more spike T cell epitopes may have the potential to generate more consistent responses across diverse populations and in older adults.

Phase 2/3 Safety And Efficacy Study Started in July 2020 – Plan To Seek Approval As Early As October 2020

Pfizer/BioNTech initiated a Phase 2b/3 trial in July 2020. Similar to Moderna's Phase 3 study, the study will enroll an estimated 30,000 subjects ages 18-85. BNT162b2 will be tested at the 30 µg dose level in a 2 dose regimen. As of September 5, the trial enrolled over 25,000 of the target 30,000 subjects.

The primary endpoints will be prevention of COVID-19 in those who have not been infected, and prevention of COVID-19 regardless of prior COVID-19 infection. Secondary endpoints include prevention of severe COVID-19 in those groups. The primary efficacy analysis will be an event-driven analysis based on the number of symptomatic cases.

Pfizer/BioNTech could commence filing for Emergency Use Authorization (EUA) as early as October depending if the event rate is sufficient to hit the >50% efficacy bar vs placebo

Pfizer's CEO Albert Bourla stated that the company expects to know if the vaccine works by late October 2020 and will plan to file with the FDA soon thereafter.

By the end of October, the study will have 4 months of safety and efficacy data. If the event-rate in the placebo arm is high enough, the data has the potential to be sufficient to demonstrate the >50% efficacy over placebo that the FDA has outlined and warrant emergency use authorization (EUA). Of note, additional safety data will still be important to monitor in the subsequent months prior to a full approval as the risk of immune enhancement increases once the initial nAb titers have waned.

Manufacturing Capacity Should Provide For 100M By YE:20 and 1.3B+ Doses By YE:21

The companies have estimated they will be able to manufacture up to 100M doses by YE:20 and 1.3B+ doses by YE:21.

In July, they announced an agreement with U.S. government for an initial order of 100 million doses for $1.95 billion with the option to acquire up to 500 million additional doses. This computes to $19.50 per dose and thus $39 total for the prime-boost regimen being employed in the pivotal trial.

Recall that this program was included in Operation Warp Speed but Pfizer did not receive any BARDA funding prior to this recent supply agreement with the U.S. government. In Europe, BioNTech received €100MM in loans from the European Investment Bank (EIB) but otherwise did not receive any EU assistance.

While $19.50 is near the top of the range for vaccine pricing at the current time, the lack of significant financial support should provide the opportunity for Pfizer/BioNTech to seek higher prices in future years when the world is no longer in crisis.

Translate Bio/Sanofi Is A Distant Third But Sanofi Highlighted Translate Bio's Manufacturing Capacity

mRNA Vaccines in Development

Modality	Vaccine Name	Developer(s)	Immunologic Target	Current Phase	Potential News	Estimated Timing	Manufacturing Expectations
mRNA	mRNA-1273	Moderna	Full S protein	Ph3	Complete Phase 3 Enrollment Initial Phase 3 Data Regulatory Approval	September-20 December-20 Q1:21	500M to 1B doses per year in 2021
	BNT162b2	Pfizer/BioNTech	Full S protein	Ph2/3	Complete Phase 2/3 Enrollment Initial Phase 3 Data Regulatory Approval	September-20 October-20 Q1:21	100M doses by YE20, 1.3B doses in 2021
	CVnCoV	CureVac	Full S protein	Ph1	Phase 1 Data	Sept/Oct-20	Hundreds of millions of doses in 2020, scaling up to billions by 2022
	Unnamed	Translate Bio/Sanofi	Full S protein	Preclinical	Start Phase 1 Trial Regulatory Approval	Q4:20 H2:21	90-360M doses annually by H1:21

Source: Cowen and Company

Translate Bio and Sanofi are currently in preclinical testing of the mRNA vaccine and hope to begin human trials in Q4:20. The LNP is internally developed by Translate Bio and has been used for other viral targets. In terms of the antigen that the mRNA will encode, they are currently looking a number of different constructs including full-length S protein (pre-fusion) as well as specific epitopes. The lead program is the full-length S protein (just like Moderna) based on its high immunogenicity and crucial involvement in cell entry.

Translate Bio is confident in their platform, noting the culmination of many small optimizations over time, including the ability to encode immunostimulatory sequences to help drive immune response. In addition, the company has been scaling up their manufacturing capabilities and boosting their purification capacity at scale.

The companies have not yet disclosed details about their vaccine compound such as whether it is nucleoside-modified RNA (modRNA) and whether it will encode the full pre-fusion S protein or only the RBD subunit.

Phase 1 Studies With Sanofi Should Commence In Q4:20 – Filing Possible in H2:21 Depending On Competitive Landscape – Projecting 90-360MM Dose Capacity By H1:21

If clinical trials begin in Q4:20 as the companies hope, the earliest regulatory approval would likely be H2:21, assuming an accelerated pathway. In terms of production, they have demonstrated the ability to produce mRNA vaccines in 100g and even 250g batches. By running multiple batches per month, they hope to achieve 90-360MM doses annually by H1:21.

DNA Vaccines Are Still Not Validated

DNA vaccines share many of the same advantages as mRNA vaccines, such as rapid construction, generic manufacturing, amplification, and the avoidance of handling infectious material. Just like mRNA vaccines, DNA vaccines are also new technologies and there are currently no approved candidates despite years of research.

DNA vaccines also carry two unique disadvantages compared to mRNA candidates. First, some require specialized tools for intradermal administration. This requirement is related to the need for DNA vaccines to enter an extra membrane (the nucleus) compared to mRNA and as a result necessitates additional technology for stability. Inovio's INO-4800, for example, uses its trademarked CELLECTRA 2000 device to administer the vaccine intradermally.

Second, DNA vaccines have a theoretical risk of integrating into the host chromosome which can be oncogenic. Multiple studies have demonstrated this risk is low and integration does not occur at relevant levels. Of note, viral vector vaccines carry the same theoretical risk since they also transmit genetic material into the nucleus.

Inovio Pharmaceuticals' MERS Vaccine Provide Some Validation But Platform Needs To Prove Itself

DNA Vaccines in Development

Modality	Vaccine Name	Developer(s)	Immunologic Target	Current Phase	Potential News	Estimated Timing	Manufacturing Expectations
DNA	INO-4800	Inovio	Full S protein	Ph1	Start Phase 2/3 Trial Phase 2/3 Data	September-20 Q1:21	1M doses by YE20, >100M doses in 2021
	GX-19	Genexine	Full S protein	Ph1/2	Phase 1 Data	September-20	No specific guidance

Source: Cowen and Company

Inovio's INO-4800 is the only DNA vaccine candidate currently in clinical trials for COVID-19. The company started design of the vaccine using their proprietary DNA medicine platform shortly after the SARS-CoV-2 genetic sequence was published.

Inovio has experience with coronavirus vaccines, with their MERS vaccine making it to a Phase 2a trial (with the plan to have the vaccine be available for emergency use as a stockpile after Phase 2 testing). Phase 1/2a data against MERS-CoV demonstrated near-100% seroconversion and neutralization from a similarly designed vaccine INO-4700.

INO-4800 Employs Optimized DNA Plasmids To Produce The S Protein

INO-4800 is composed of optimized DNA plasmids that are delivered directly into cells through the use of Inovio's proprietary hand-held smart devices (intradermal or intramuscular) that use a brief electrical pulse to reversibly open small pores in the cell to allow the plasmids to enter. Once within the cell, the DNA instructs the cell to produce the target antigen (in this case the S protein) which will ultimately elicit an immune response.

Preclinical Data Provides Initial Neutralizing Antibody And T Cell Responses

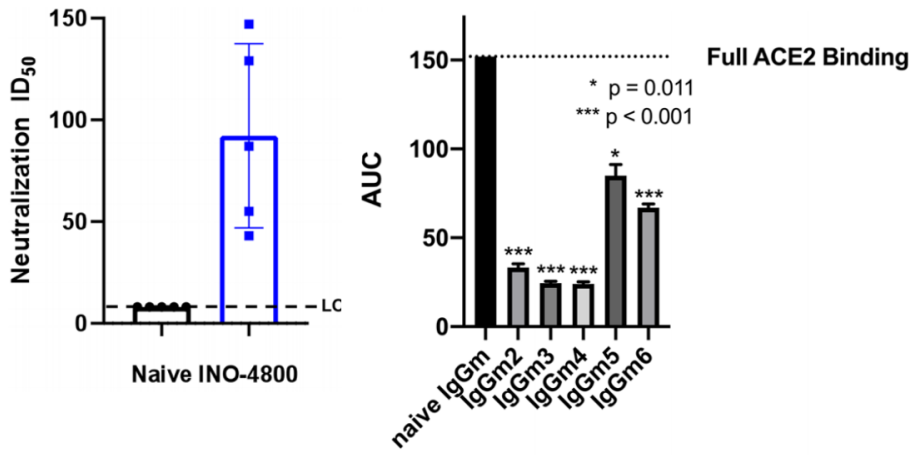
Preclinical data for INO-4800 has demonstrated neutralizing antibody and T cell immune responses against coronavirus SARS-CoV-2 in mice and guinea pigs. Three separate neutralization assays confirmed the strong response including:

1. an assay using live SARS-CoV-2 viruses,

2. a pseudo-virus assay (where another virus displays the SARS-CoV-2 S protein), and

3. a novel high-throughput surrogate neutralization assay that measures the ability of antibodies to block the S protein from binding to the host ACE2 receptor.

INO-4800 Vaccinated Mice Demonstrate Strong Neutralizing Antibody Response and Inhibition of Viral Binding to ACE2 Receptor



5 mice were vaccinated on day 0 and day 14, serum samples collected 7 days post-boost

Source: Smith et al., *Nature Communications* 2020, Inovio

Awaiting Publication of Phase 1 Data In Healthy Volunteers – Phase 2/3 To Start in September

Inovio released interim data in late June from Phase 1 trial of 40 healthy volunteers 18 to 50 years of age. The information was distributed via press release as publication in a peer-reviewed medical journal is planned in the near future. The company states that the Phase 1 data demonstrates INO-4800 is generally well-tolerated and generated an immune response, though detailed data was not shared.

According to the *New York Times*, Inovio is currently being sued by one of its manufacturers for technology theft and by shareholders for exaggerating its progress on the vaccine. In addition, the company has claimed to be part of Operation Warp Speed but is not on the list of selected companies.

A Phase 2/3 efficacy trial is planned to start in September (previously guided for July/August) pending regulatory approval.

Inovio Guides 1M Doses Possible By YE'20, >100M Doses in 2021

The company has expanded its manufacturing capacity with the help of the Coalition for Epidemic Preparedness Innovations (CEPI) funding and plans to produce one million doses by YE 2020 for additional trials and emergency use. They hope to generate over 100M doses in 2021.

Whole-Virus Vaccines Are Validated And Approved For Many Infectious Diseases

Whole-virus vaccines, either with inactivated or attenuated virus, are a validated vaccine development approach and represent the most common form of vaccine in use today (examples include influenza, chickenpox, measles, mumps and rubella). By providing the whole virus, the developer does not have to determine which antigens are most important for immunity and instead allows the host to build a broad immune response against the key targets. The weakened virus is often given in combination with an adjuvant for improved immunogenicity.

Since the virus is given in a weakened form, it is unable to cause disease. However, laboratory workers do have to deal with infectious material during the development process, which is a disadvantage of this modality.

Another disadvantage to whole-virus vaccines, especially compared to genetic vaccines (DNA and mRNA), is that the development process is slow and requires months to grow each batch of viruses. As a result, if/when there are future significant genetic changes to SARS-CoV-2 that require a new vaccine, creating an updated whole-virus vaccine is essentially like starting from scratch.

In contrast, genetic vaccines can be produced much faster by incorporating the new genetic code of the virus (with any new mutations) and efficiently producing the vaccine using the routine manufacturing methods.

Sinovac Early Data Demonstrate Weak Neutralizing Antibody Response

Whole-Virus Vaccines in Development

Modality	Vaccine Name	Developer(s)	Immunologic Target	Current Phase	Potential News	Estimated Timing	Manufacturing Expectations
Inactivated Virus	**Unnamed**	Wuhan Inst/Sinopharm	Whole virus	Ph3	Phase 3 Data Regulatory Approval (China)	Q4:20 YE:20	200M doses per year
	BBIBP-CorV	Beijing Inst/Sinopharm	Whole virus	Ph3	Phase 3 Data Regulatory Approval (China)	Q4:20 YE:20	200M doses per year
	CoronaVac	Sinovac	Whole virus	Ph3	Initial Phase 3 Data Complete Phase 3 Study	October-20 February-21	100M doses per year
	Unnamed	Inst of Med Biol at Chinese Acad of Med Sciences (IMBCAMS)	Whole virus	Ph2	Phase 2 Data Start Phase 3 Trial	H2:20 Unknown	No specific guidance

Source: Cowen and Company

Sinovac's CoronaVac Fails To Reach Neutralizing Antibody Titers of Convalescent Plasma In Early Data

Sinovac published its Phase 1/2 data on its inactivated virus vaccine candidate, CoronaVac in *medRxiv*. In the trial, subjects were given a prime-boost regimen of either 3 or 6 µg of the vaccine (both with alum) or placebo on a Day 0,14 schedule or Day 0,28 schedule.

Neutralizing antibody titers were measured 28 days after the second vaccine dose and ranged from 24 to 65 among the different dosages and schedules. For comparison, convalescent serum tested by the same method in the same laboratory had an average neutralizing antibody titer of 164.

There is currently no data for Sinovac's vaccine in combination with Dynavax's CpG 1018 adjuvant.

CoronaVac Has Two Phase 3 Studies In Progress, Expect Initial Data In October

Sinovac currently has two Phase 3 trials underway for CoronaVac:

4. The first study launched in Brazil in July and plans to include 9,000 subjects.
5. The second study launched in Indonesia in early August and will enroll up to 1,620 subjects. The study is planned to last 6 months.

We have guarded expectations for the initial Phase 3 data in October based on the Phase 1/2 data. Perhaps the immune response will be strong if the adjuvant is changed from alum to CpG 1018. Based on clinicaltrials.gov, it is not clear which adjuvant was chosen for the Phase 3 study.

If Successful, Sinovac Expects To Produce 100MM Doses Per Year

Indonesia's state-run pharmaceutical company, Bio Farma, has agreed to produce 100 million doses of CoronaVac if the vaccine is successful. As mentioned above, Indonesia is also a site for one of the Phase 3 trials. Sinovac and Bio Farma were natural partners as the companies share a similar vaccine production program.

Dynavax Hopes CpG-1018 Adjuvant Will Boost COVID-19 Vaccine Potency; Several Collaborations Ongoing

Dynavax has developed and actively markets Heplisav, a potential best-in-class vaccine for Hepatitis B. The adjuvant used in Heplisav is CpG 1018, an oligonucleotide sequence containing cytosine phosphoguanine (CpG) motifs. With CpG 1018 having received FDA approval, Dynavax has outlined a strategy to make it a broadly used adjuvant, ultimately incorporated into a number of vaccines. Dynavax's COVID-19 focused collaborations are perhaps the most rapidly advancing manifestations of this strategy.

CPG 1018 Drives Increased Antibody Titers And Bolsters Th1 Response

Oligodeoxynucleotides (ODN) with unmethylated CpG motifs essentially mimic the genetic material of bacteria and viruses. The motifs trigger downstream signaling through interaction with TLR-9 following internalization by the target cell population resulting in plasmacytoid dendritic (pDC) cell and B cell activation. CPG ODNs can thus activate both the innate and the adaptive immune response. Activation of B cells by CpG ODNs results in increased IgM production in addition to several cytokines, including IL-6. These activated B cells can then differentiate into plasma cells and memory B cells, providing a longer-term humoral response to infection.

The Th1 T cell response is important in the body's response to intracellular pathogens (such as viruses). When TLR-9 in pDCs are stimulated by the CpG ODN, the cells upregulate surface markers and secrete cytokines which help support cell differentiation and survival of the antigen presenting cells. In addition, these stimulated pDCs also produce Type I IFNs, which is important for limiting viral expansion. It has also been shown that CpG adjuvants result in increased survival of CD8+ T cells and differentiation into antigen-specific memory CD8+ T cell subsets. This impact on the T cell response results in increased cell-killing ability of T cell populations and an increased ability to respond to repeat pathogen long-term.

CpG 1018 Shows Better Adjuvant Activity Vs Alum With Better Safety Profile

Dynavax has demonstrated that its CpG 1018 adjuvant can generate a higher and more immediate protective antibody response when compared to alum. In addition, the adjuvant has been shown to have an acceptable safety profile. Alum adjuvants, while

capable of inducing a vaccine response, can cause irritation of both the skin and mucous membranes. In fact, studies have shown that vaccination using an alum adjuvant has resulted in increased respiratory disease burden including eosinophilia and lung histopathology, potentially due to certain CD4+ T cell and inflammatory DC subsets. Our consultants have highlighted the risk associated with alum adjuvants in reference to the ongoing COVID-19 pandemic, especially as the disease can cause severe respiratory distress. Physicians expect that vaccine candidates that use alternative, Th1-directed adjuvants would likely have a higher chance of success.

Dynavax's Partnered Programs Advancing; COVID-19 Candidates Have Entered The Clinic With The First Data Anticipated in H2:20

Dynavax has entered several research and clinical collaborations in which it will supply CpG 1018 to the partners for use in vaccine candidates. Six of the collaborations have been announced publicly. Two of these programs, both potential COVID vaccines, have entered clinical development. The company is working with CEPI to identify programs globally working on a COVID-19 vaccine that could benefit from CpG 1018 adjuvant. Dynavax announced its first COVID-19 focused collaboration with the University of Queensland in early March which was a CEPI initiative.

A Phase 1 trial evaluating a combination of CpG 1018 with Clover Biopharmaceuticals' COVID-19 S-Trimer vaccine candidate is ongoing. Initial safety and immunogenicity data from the study are expected in September 2020.

A Phase 1 clinical trial is also ongoing investigating CpG 1018 in combination with Medicago's corona virus-like particle (CoVLP). Initial data are anticipated in October 2020.

A Phase 1 study investigating CpG 1018 in combination with Medigen's subunit vaccine candidate is expected to begin in September.

Dynavax is also collaborating on potential COVID-19 vaccines with Sinovac, and Valneva.

There are several reasons to think that CpG 1018 could improve the profile of and be incorporated into a number of novel vaccines. There are substantial pre-clinical and clinical data around the CpG 1018 adjuvant through its use in Heplisav. These data demonstrate the potency of CpG 1018 at inducing immune responses, and partially de-risk its use in novel vaccines. For COVID-19 vaccines specifically, our consultant thinks that adjuvants, which produce predominantly a Th1 response like CpG 1018, will be safer in the context of coronavirus than those that produce a Th2 response. Additionally, Dynavax has developed much expertise in CpG 1018's use. We expect collaborators to benefit from the data and product knowledge, which could accelerate development timelines. Our model contains no revenue from SARS-CoV-2 vaccines, so the success of any would represent upside.

A Phase 1 Trial Evaluating A Combination Of CpG 1018 With Clover Biopharmaceuticals' COVID-19 S-Trimer Vaccine Candidate Ongoing, Data Anticipated In September

In June, Dynavax announced that the first participants had been dosed in a Phase 1 study of Clover Biopharmaceuticals' vaccine candidate, which is being combined with DVAX's CpG 1018 adjuvant. SCB-2019 is a COVID-19 S-Trimer vaccine that utilizes Clover's Trimer-Tag technology. The study is a randomized trial investigating multiple doses levels of SCB-2019 administered via two intramuscular injections. The study is expected to enroll n=90 healthy volunteers aged 18-54 years and n=60 healthy volunteers aged 55-75 years. Patients will be randomized to receive either SCB-2019

alone, SCB-2019 with the CpG 1018 adjuvant+alum, and SCB-2019 with another adjuvant.

Pre-clinically, the vaccine candidate has demonstrated the ability to generate neutralizing antibodies in multiple animal species. Initial safety and immunogenicity data from the Phase 1 trial are expected in September 2020.

Medicago/Dynavax's Phase 1 To Produce Data In October

A Phase 1 clinical trial is also ongoing investigating CpG 1018 in combination with Medicago's corona virus-like particle (CoVLP). The trial will investigate three doses of antigen in combination with CpG 1018 and in parallel with another adjuvant. The vaccines will be administered as a one- and two-dose vaccination schedule, given 21 days apart. CoVLP will be produced using Medicago's plant-based system which uses plants as mini factories to create proteins. The companies anticipate being able to deliver up to 100MM vaccine doses by YE:21. An anticipated manufacturing expansion by Medicago is expected to complete by YE:2023, which would allow for the production of up to 1B doses annually.

Initial data are anticipated in October 2020. Should the Phase 1 be successful, we expect a full pivotal trial to follow.

Medigen's Candidate Is Next In Line To Initiate Clinical Studies In Combination With CpG1018

In July, Dynavax announced that it had entered into a collaboration with Medigen to develop a COVID-19 vaccine candidate combining the CpG 1018 adjuvant with Medigen's subunit vaccine. Medigen's vaccine candidate is a stable prefusion form of the SARS-CoV2 recombinant spike protein. The companies indicated that pre-clinically the combination drove "strong virus neutralizing antibody responses and cellular immunity". A Phase 1 study is expected to begin in September. We are encouraged that the combination of CpG 1018 and Medigen's recombinant spike protein has already produced good pre-clinical data and that a Phase 1 trial is set to initiate in the near term.

Dynavax's CpG 1018 May Improve Upon Sinovac's Alum-Based Candidate

Sinovac entered a Phase 1 study in April and following a safety observation, entered Phase 2 studies in May with a COVID-19 vaccine candidate that uses alum rather than the CpG 1018 adjuvant. Sinovac has expressed high confidence that the approach will provide protection against viral disease. Pre-clinically, the initial Sinovac vaccine candidate was able to generate SARS-CoV-2-specfic neutralizing antibodies in mice, rats, and NHPs. The company indicates that the antibodies were neutralizing against 10 SARS-CoV-2 strains which could suggest broad coverage against the virus. In challenge studies conducted in NHPs, a course of three immunizations at two dose levels provided full or partial protection against SARS-CoV-2 infection. The vaccine did not provide an antibody-based enhancement in viral infectivity. Based on our KOL commentary and the science underlying the CpG vs. alum adjuvants, we expect that the efficacy and safety profile Sinovac's vaccine may be improved by using Dynavax's CpG 1018 instead of alum.

Viral-Vector Based Vaccines Are Validated And Hot In Pursuit With Big Pharma Sponsors

Viral-vector based vaccines are a validated technology in vaccine development. The vectors come in two forms: replicating and non-replicating. The adenoviral vector vaccines in development by AstraZeneca/Oxford, JNJ and CanSino represent non-replicating vectors. Merck is developing two replicating viral vectors—one uses the measles virus and the other uses recombinant vesicular stomatitis virus (rVSV) as a vector.

Both the replicating and non-replicating forms of viral-vector based vaccines deliver the genetic material needed to create proteins containing the antigenic part of the target virus. This approach has advantages as including:

1. high efficiency gene transfer,
2. high fidelity gene transfer, and
3. generation of a strong immune response.

The efficiency of viral-vector based vaccines relates to the delivery of many genome copies per target cell, translating into very high expression. Additionally, relatively large genetic sequences can be encoded (25-30kb) due to the stability of the vector genomes. This modality typically does not require use of an adjuvant and promotes a robust cytotoxic T cell response to eliminate virus-infected cells.

Viral-vector based vaccines carry the same theoretical danger of genomic integration as DNA vaccines, though this is a very low risk. The other risk to this vaccine modality is the potential for anti-vector immunity. This has been an issue for CanSino, for example, with a large percentage of subjects having pre-existing antibodies to the adenovirus used in its vaccine. AstraZeneca/Oxford, in contrast, use an adenovirus only known to chimpanzees which removes the risk of pre-existing immunity in their human studies but does not preclude the risk of developing immunity which could hinder multiple dosing.

Johnson & Johnson (JNJ) Has Deep Expertise In Vaccine Development And Production

Viral Vector Vaccines in Development

Modality	Vaccine Name	Developer(s)	Immunologic Target	Current Phase	Potential News	Estimated Timing	Manufacturing Expectations
Adenoviral	**AZD1222**	AstraZeneca/Oxford	Full S protein	Ph2/3	Phase 3 Data Regulatory Approval	October-20 Q4:20	400MM doses in Sept (at-risk), >1B doses in 2021
	Ad5-nCoV	CanSino	Full S protein	Ph3	Initial Phase 3 Data	December-20	100-200M doses per year in 2021
	Ad26.COV2-S	Janssen Pharma	Full S protein	Ph1/2	Phase 1 Data Start Phase 3 Trial	September-20 September-20	500M doses in 2020, 1B doses in 2021
Replicating Viral Vector	**V591 (Measles vector)**	Merck	Undisclosed DNA cargo	Preclinical	Start Phase 1 Trial	Q3:20	No specific guidance
	V590 (rVSV vector)	Merck	Full S protein	Preclinical	Start Phase 1 Trial	H2:20	No specific guidance

Source: Cowen and Company

JNJ Jumps Quickly Using Its Validated AdVac And PER.C6 Vaccine Platforms

JNJ has already made significant progress in the development of a COVID-19 vaccine, having selected its lead candidate in late March. This accelerated pace of development has been driven by the company's innovative and established AdVac and PER.C6 vaccine technology platforms, which have been used in the development and manufacturing of an Ebola vaccine and to build vaccine candidates for Zika, RSV and HIV.

JNJ's COVID-19 Vaccine Efforts Will Leverage Its Past Vaccine Successes

JNJ's Ebola vaccine regimen also uses the AdVac and PER.C6 technologies being utilized for the SARS-CoV-2 vaccine research program. The regimen is made up of two doses utilizing different vaccines, including JNJ's AdVac technology (Ad26.ZEBOV) and Bavarian Nordic's MVA-BN technology (MVA-BN-Filo). The regimen is well tolerated and induces durable and robust immune responses to the Ebola virus (Zaire strain). The Zaire strain was the cause of the recent infections in the Democratic Republic of Congo (DRC), which is the second-largest Ebola outbreak in history. JNJ had scaled up its manufacturing for its Ebola vaccine regimens utilizing its PER.C6 cell line.

JNJ's Ebola vaccine was deployed in the DRC starting in November 2019 (up to 500K regimens) and also in Rwanda (up to 200K regimens). A stockpile of up to 1.5M investigational Ebola vaccine regimens potentially for use in public health emergencies has been established. To date, approximately 50K people have been vaccinated by JNJ's Ebola vaccine.

We think JNJ's success with its Ebola vaccine validates its development process, which in turn bodes well for its prospects with a COVID-19 vaccine. The Ebola vaccine received a positive CHMP opinion from the European Commission in early June and, if approved, will be the second of only two vaccines available to combat the threat of Ebola.

AdVac Employs Adenovirus Coding For The Spike Protein

JNJ's AdVac viral vector technology is grounded on the genetic modification of a specific undisclosed type of adenovirus. Adenoviruses cause the common cold and thus represent a well-known and efficient vector. To make its vaccine candidate, the company places a piece of DNA – specifically, one that codes for the coronavirus "spike" protein that latches on to human cells – inside a dead adenovirus. This modification disables viral replication in humans and prevents the vector's ability to cause disease. Once the vaccine is injected into muscle tissue, the vector enters a cell and releases its DNA payload into the nucleus. This causes the host cell to express the transgenic antigens in the cytoplasm, which are presented to T-cells to elicit immune responses. When the patient is exposed to the SARS-CoV-2 virus, the patient's immune system will respond faster and more effectively to fight off an infection and prevent severe disease.

PER.C6 Cell Line To Rapidly Scale Production

To produce high concentrations of AdVac vector, JNJ utilizes its proprietary PER.C6 complementing cell line. The PER.C6 cell line has special characteristics that allow cells to multiply while floating suspended at high cell densities. AdVac can replicate in higher numbers and concentrations using PER.C6, which allows JNJ to rapidly scale production.

Ad26 Vector Platform Support Standard Distribution Channels

JNJ's platform has already accrued a convincing safety profile, as the Ad26 vector platform has been used in vaccinating more than 50K people to date. Also working to the company's benefit is the favorable thermostability profile of the platform (more than two years at 2-8 degrees Celsius), which makes it compatible with standard vaccine distribution channels and obviates the need for new infrastructure.

Extensive Testing with Research Partners Enabled JNJ to Select Its Lead COVID-19 Vaccine Candidate

JNJ's efforts to develop a COVID-19 vaccine began back in January 2020, when the earliest sequences of the COVID-19 virus became available for researching. JNJ began

extensive testing on several vaccine candidates in collaboration with researchers from Beth Israel Deaconess Medical Center, part of Harvard Medical School. The group of vaccines developed by JNJ and its research partners then transitioned to pre-clinical testing in an effort to identify the candidates that trigger the most promising immune response. Through this testing, JNJ has been able to select the lead vaccine that is now moving toward the initial phases of manufacturing.

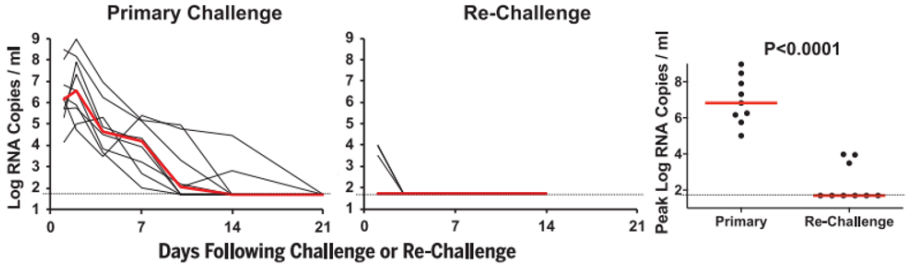
In addition to its lead candidate, JNJ has identified two backup candidates. All three of these candidates have entered the pre-master seed production phase, and a final selection is slated for later this month.

JNJ Has Published Two Pre-Clinical Studies of Its COVID-19 Vaccine Work

Two animal studies, published in *Science* in May, clarified the role of antibodies against COVID-19, thereby helping JNJ to validate its process for selecting a vaccine candidate. Both studies, led by Dr. Dan Barouch and others including JNJ, used prototype vaccine constructs. The studies were designed to answer: (1) whether antibodies developed during infection guard against future infection, (2) if the level of neutralizing antibodies directly correlates with the level of protection offered and (3) whether protective antibodies can be elicited by a vaccine.

In the first study by Chandrashekar et al., adult rhesus macaques were infected with SARS-CoV-2. The animals showed signs of active viral replication and cleared the virus over time. When re-exposed to a second dose of SARS-CoV-2, the macaques were protected against reinfection, which correlated with the presence of SAR-CoV-2 neutralizing antibodies.

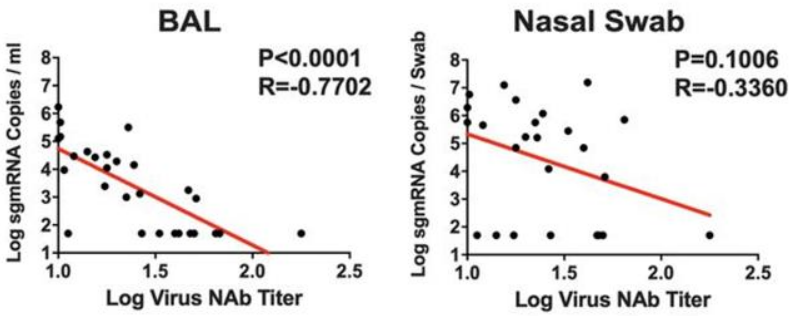
Viral Loads in Bronchoalveolar Lavage (BAL) Minimal After Rechallenge In Rhesus Macaques



Source: Chandrashekar et al., *Science* 2020

In the second study by Yu et al., investigators immunized adult rhesus macaques with a series of prototype DNA vaccines. The animals developed a significant level of protection against SARS-CoV-2 replication in the lung upon challenge with the virus. The investigators also observed that the different prototypes generated different degrees of antibody response and that higher levels of antibodies correlated with higher levels of protection.

Live Neutralizing Antibody Titer Levels Correlated With Protection From Infection Upon Challenge



Source: Yu et al., *Science* 2020

Of course, neither study is predictive of the data that JNJ's vaccine candidates in development will eventually generate. Still, these findings established a non-human primate challenge model that the company can leverage to help assess a human vaccine's potency.

Phase 1/2a Will Commence In July – Could Lead To EUA Or Phase 3 Studies

JNJ aims to initiate a first-in-human Phase 1/2a clinical study in the second half of July (accelerated from September 2020) in the U.S. and Belgium. The trial will evaluate the safety, response to vaccination (reactogenicity), and immune response (immunogenicity) of the investigational SARS-CoV-2 vaccine, Ad26.COV2-S, recombinant in 1,045 healthy adults age 18-55 and adults age 65+. Although JNJ now has three vaccine candidates, the team will initiate the Phase 1 program with the lead candidate while the two backup contenders will stay on the sideline. Additionally, JNJ is in discussions with the National Institutes of Allergy and Infectious Diseases with the goal of initiating its Phase 3 trial ahead of its original schedule, pending the outcome of the Phase 1 study and regulators' approval. We estimate that the company will be in a position to deliver clinical safety and efficacy data by the end of this year. With such a timeline, the vaccine can potentially be available through an emergency use authorization by early 2021.

We do not yet know many details regarding JNJ's plan for the vaccine once it is launched. Given how early we are in responding to the pandemic, the company cannot yet finalize variables such as pricing, though it has said that it intends to make the vaccine available at a not-for-profit price during the emergency use phase. We also do not yet know how the vaccine doses will be rationed globally. JNJ will likely make the first doses available to those at the greatest risk – for example, frontline workers – but will need more time to develop a full rollout plan. Right now, its primary goal is to develop a safe and effective vaccine.

New Manufacturing Partnerships Should Enable JNJ to Hit Its Supply Targets

JNJ's goal is to enable the global supply of more than 1B doses of a safe and effective COVID-19 vaccine. In March, it announced that it would expand its worldwide manufacturing capacity to facilitate the rapid production of a vaccine. These expansion measures include establishing new U.S. vaccine manufacturing capabilities as well as scaling up its existing manufacturing capacity in other countries. The company opted to begin production at risk, which is part of its commitment to launching an affordable vaccine on a not-for-profit basis.

Collaboration With Emergent BioSolutions Will Boost Capacity Starting in FY21

In April 2020, Emergent BioSolutions and JNJ announced that they entered into a CDMO agreement whereby EBS will provide contract development and manufacturing services to support JNJ's COVID-19 vaccine candidate. Under the terms of the agreement, JNJ is investing to expand drug substance capacity related to the vaccine candidate. Beginning this year, Emergent will provide drug substance manufacturing services with its molecule-to-market CDMO offering. Starting next year, Emergent will reserve operations capacity to support commercial manufacturing of JNJ's vaccine.

The vaccine program leverages JNJ's PER.C6 and AdVac platforms. PER.C6 is intended to provide high-yield production of vaccines and antibodies and was previously used to accelerate Ebola vaccine development during an active outbreak in West Africa, resulting in production of >2MM doses in <1 year. The platform has also been used in the company's Zika, RSV, and HIV vaccine candidates.

Incremental to the April agreement, JNJ announced in early July a five-year agreement with Emergent. Emergent will provide large scale drug substance manufacturing for JNJ's lead COVID-19 vaccine candidate starting in 2021, and for subsequent years starting in 2023, will provide a flexible capacity deployment model for additional drug substance batches annually. The first 2 years of the agreement are valued at $480MM. This contract reserves 1 of 4 independent suites at EBS' Bayview facility for JNJ's program. Discussions with EBS indicate that the vast of majority of the $480MM would still be received even if JNJ's vaccine does not receive regulatory approval as the revenue is tied to reserving the facility. Commitments for 2023 and beyond will be negotiated at a later time and to support additional manufacturing as needed. Discussions with EBS indicate that an 18-month lead time for negotiation would be typical in this case, so we would anticipate additional updates in 2021 regarding outyear activities.

Agreement with Catalent Provides For Substantial Capacity

JNJ also has an agreement with Catalent to manufacture JNJ's lead vaccine candidate. The deal involves a joint investment and technology transfer, and Catalent said it will hire about 300 more workers at its Bloomington, Indiana, site starting in July. By January 2021, Catalent expects to be able to produce the vaccine 24 hours a day, seven days a week.

JNJ Hopes To Reach 1B Dose Goals

JNJ's existing vaccine facility in Leiden, Netherlands, has the capacity to produce approximately 300M doses. We await details on the incremental capacity provided by the company's internal scale-up initiatives and its two partnerships. We may see additional deals in the coming weeks that further JNJ's efforts to reach its 1B dose supply goal.

$1B+ BARDA Agreement Supports Its Efforts

The company also expanded its partnership with the Biomedical Advanced Research & Development Authority (BARDA). The partnership has co-funded $1B-plus for vaccine R&D and clinical testing.

AstraZeneca/Oxford University/Vaccitech ChAdOx1 nCov-19 (AZD1222) Shows Promising Phase 1 Data

Viral Vector Vaccines in Development

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	Ad26.COV2-S	Janssen Pharma	Full S protein	Ph1/2	Phase 1 Data Start Phase 3 Trial	September-20 September-20	500M doses in 2020, 1B doses in 2021
Replicating Viral Vector	V591 (Measles vector)	Merck	Undisclosed DNA cargo	Preclinical	Start Phase 1 Trial	Q3:20	No specific guidance
	V590 (rVSV vector)	Merck	Full S protein	Preclinical	Start Phase 1 Trial	H2:20	No specific guidance

Source: Cowen and Company

AZD1222 Is A Chimp Adenovirus Vaccine To Full Spike Protein

AZD1222 is a replication-deficient chimpanzee adenovirus-vectored vaccine containing a full-length SARS-CoV-2 spike protein transgene. The chimpanzee adenovirus is being studied as a vaccine vector for other pathogens, including the coronavirus that causes MERS, but there are no approved vaccines based on this technology. The only clinical data available for the vector (developed by Vaccitech) were generated with an unrelated antigen payload in prostate cancer patients. Detailed safety outcomes have not yet been reported for this study, but no serious AEs were attributable to the drug. Although more empirical data are needed, theoretical issues with this approach include pre-existing or developed anti-adenovirus immunity which could create safety risks and potentially blunt immune response to the antigen payload.

AZD1222 Showed Th1 Protective Immunity And Reduced Subgenomic RNA (sgRNA) in Non-Human Primates

Preclinical data for AZD1222 have so far demonstrated Th1-biased protective immune responses in both mice and non-human primates (NHP), a finding consistent with prior results in MERS models. AZD1222 was shown to induce a Th1-biased immune response in mice, and when administered (2.5×10^{10} viral particles, IM) to non-human primates (NHP) resulted in generation of virus and spike protein-specific neutralizing antibodies and T-cell responses by day 14 post-vaccination.

These animals were subsequently challenged with SARS-CoV-2 via upper and lower respiratory tract inoculation. On day 5 post-inoculation, SARS-CoV-2 subgenomic RNA (sgRNA; indicative of viral replication) was detected in bronchoalveolar fluid (BAL) of 0/6 vaccinated vs. 3/3 unvaccinated NHP but there was no difference in sgRNA in nose swabs.

After necropsy, sgRNA was detected in lung tissue at day 7 post-inoculation in 1/6 vaccinated vs. 2/3 unvaccinated NHP. These data suggest that the vaccine did not prevent infection outright, but rather slowed viral replication and spread of the infection. Consistent with this finding, there was a shortened course of respiratory symptoms (dyspnea/tachypnea) in vaccinated vs. unvaccinated NHP, and pulmonary pathology, including signs of viral pneumonia, were found in 0/6 vaccinated vs. 2/3 unvaccinated NHP.

Phase 1/2 Completed Enrollment In May

A Phase 1/2 trial of AZD1222 completed enrollment in May (NCT04324606 ; n=1,090 healthy volunteers age 18-55) assessing the ability of AZD1222 (5×10^{10} vp, IM)

administered either as a single dose or with a booster shot to prevent SARS-CoV-2 infection by month 6 (primary endpoint) compared against the approved MenACWY vaccine as an active control. Study arms including paracetamol are also included to determine if the fever reducer blunts efficacy of the vaccine.

Initial Data Of Oxford/AZN's ChAdOx1 Vaccine Show Promising Antibody And T Cell Response

In July, Oxford/AZN reported interim results from the ongoing Phase 1/2 COV001 of AZD1222. Detailed results were also published in the Lancet, which showed that this vaccine was tolerated and generated robust immune responses against the SARS-CoV-2 virus.

Notably, COV001 is a blinded, RCT Phase 1/2 trial (n = 1,077) in healthy adults aged 18-55 years that assessed a single dose of AZD1222 (0·5 mL) against a comparator meningococcal conjugate vaccine, MenACWY. Ten participants also received two doses of AZD1222 one month apart (not randomized).

The data confirmed that a single dose of AZD1222 resulted in a rapid increase in antibodies in 95% of participants one month after injection. An encouraging T-cell response was seen in all subjects, peaking by day 14 and maintained two months after injection.

AZD1222 Showed Only Modest Neutralizing Antibody Titers With Single Dose Regimen But Improved With A Booster Dose

On the efficacy side, 100% of subjects (n=35) achieved neutralizing antibody (nAb) titers with a median IC50 of 201 measured by the Public Health England microneutralization assay PHE MNA). No convalescent serum reference was reported. By comparison, the group that received a booster dose had a PHE MNA IC50 of 372 at 2 weeks post the 2nd dose.

Based on the pseudotyped virus neutralization (PseudoNA) assay (n=29), the single dose of AZD1222 achieved an IC50 of 88 on day 28 which was far below the ~400 level seen in convalescent serum used as a comparison. A booster dose achieved PseudoNA nAb titers of 451 at day 42 or 2 weeks post the 2nd dose (n=9).

Encouraging T Cell Responses Were Seen Though Only Mildly Enhanced By Booster Dose

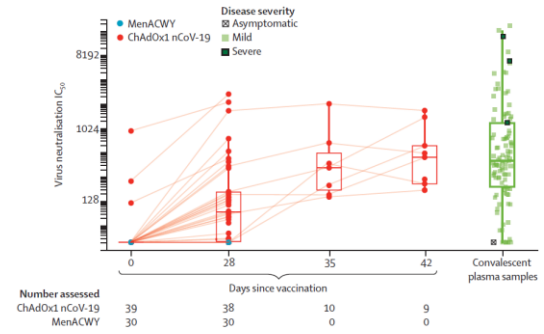
More so, AZD1222 resulted in marked increases in SARS-CoV-2 spike-specific effector T-cell responses (n=10) as early as day 7 (IFNγ ELISpot response, 183 SFC/million PBMCs), peaking at day 14 (856) and maintained up to day 56 (424).

Notably, only a mild boost in cellular responses was observed in the group that received a booster dose (614 at 28 days post the 2nd dose compared to 554 in the single dose group on day 28).

Vaccine Appears Safe And Booster Dose Was Safe Despite Being A Chimp Adenovirus

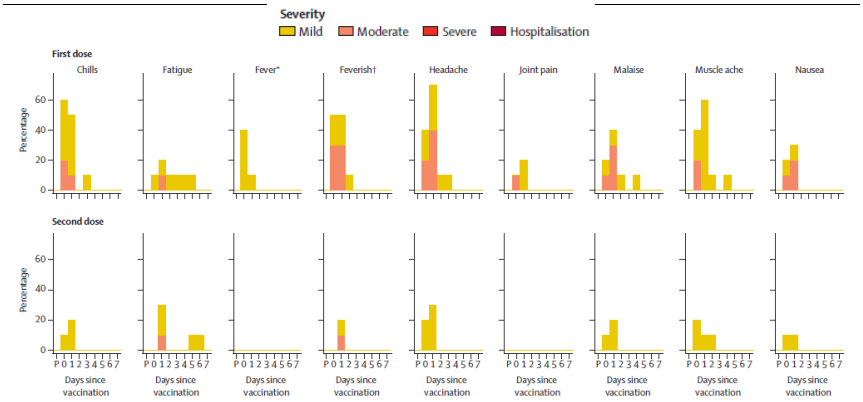
On the safety side, the local and systemic AEs due to AZD1222 were transient and comparable to previous trials and other adenoviral vector vaccines. The AEs included temporary injection site pain and tenderness, mild-to-moderate headache, fatigue, chills, feverishness, malaise and muscle ache, with no serious AEs reported. Of note, the AEs occurred less frequently after a second dose.

NAb Titers Were Encouraging With A Single Dose, But More Robust After A Booster Dose (Days 35 & 42)



Source: *Lancet*, AstraZeneca

Systemic AEs In First 7 Days After Priming And Booster Doses



Source: *Lancet*, AstraZeneca

AZD1222's Antibody Data Not As Strong as mRNA Vaccines But T Cell Responses Likely In-Line With BNT162b1 And Stronger Than mRNA-1273

We view the nAb titers of AZD1222 as somewhat disappointing, especially given the single dose group failing to reach the level of convalescent serum as measured by the PseudoNA assay (88 vs ~400). This compares poorly to Moderna's mRNA-1273 (232 at 28 days post the 2nd 100 µg dose vs 109 in the convalescent serum group) and Pfizer/BioNTech's BNT162b1 (437 at two weeks post the 2nd 30 µg dose vs 94 in the convalescent serum group). The subjects that received two doses of AZD1222 had a more robust nAb response than the single dose group, though the levels were mainly in the same range as convalescent serum rather than in excess by the margin of the mRNA vaccines.

AZD1222's SARS-CoV-2 spike-specific effector T-cell response seems to be at least equal to that of BNT162b1 (though difficult to compare across studies) and likely superior to mRNA-1273. Importantly, there are accumulating data to suggest T-cell responses play an important role in fighting COVID-19 as asymptomatic patients developed a robust memory T-cell response in the absence of a measurable humoral response.

Multiple Late Stage Trials Underway – Pivotal Data Expected By YE:20

A late-stage Phase 2/3 trial (n=10,260 children, adults, elderly) is currently underway in the UK, Brazil and South Africa to determine the vaccine's effectiveness and safety in different age ranges and at various doses. The study commenced based on encouraging early signals from an IDMC look at the Phase 1 data. Enrollment and completion of the Phase 3 portion of the study is somewhat dependent on the course of pandemic and the breadth of community transmission. Recruitment may need to be shifted to different locations as certain areas see fewer cases.

At the end of August, AstraZeneca launched a 30,000-patient trial in the US funded by BARDA. According to ClinicalTrials.gov, the estimated primary completion date of this double-blind study is Dec. 2, 2020. The trial will evaluate the efficacy and safety of the vaccine in all participants, and local and systemic reactions and immune responses in all age groups.

Importantly, the company also reiterated its commitment to "stringent efficacy and safety standards" and its goal to move "quickly but without cutting corners".

There have been an increasing number of questions/concerns around the safety of vaccines given the intensified race of vaccine development. Regulators also said that speed will not compromise the safety of vaccines, as the accelerated development would stem from conducting in parallel trials, which were usually done sequentially in the past.

We are encouraged by AstraZeneca's commitment to high standard of safety and efficacy as it is essential for the vaccine manufacturers and regulators to ensure their efforts to fight COVID-19 aren't hampered by public distrust.

AstraZeneca Hopes To Have 400MM Doses In Sept '20 and Additional 1B in FY21

The company has begun manufacturing at-risk and is estimating availability of 400MM doses in September with an additional 1B doses in 2021. Prospects for rapid scaling benefit from:

1. HEK293 host cell production in standard bioreactors,
2. the potential for single dose administration, and
3. ability to use cold-chain (2-8°C) rather than cryogenic (-20°C) distribution.

At the end of July, AZN struck a deal with EBS to expand manufacturing capacity. Under the agreement, EBS will provide contract development and manufacturing (CDMO) services for AZD1222. In return, EBS will receive ~$174M through 2021. This follows an $87M production contract in June between the two companies.

AstraZeneca Pledges To Price Vaccine At Cost To Developing Nations

In June, AstraZeneca struck two deals to provide 1.3B doses of its vaccine to low- and middle-income countries at cost. These agreements followed deals with the U.S. and U.K. governments to supply 300M and 100M doses, respectively. The U.S. agreement priced the vaccine at $4 per dose.

AstraZeneca has also entered into a 300M dose supply pact with Europe's Inclusive Vaccines Alliance (IVA), spearheaded by Germany, France, Italy and the Netherlands, with the option for an additional 100M doses. AstraZeneca will receive €750M ($843M) in the deal, which translates to €2.50 ($2.81) per dose.

CanSino Biologic's Ad5 Vaccine (Ad5-nCoV) Encodes Full Length S Protein

Viral Vector Vaccines in Development

Modality	Vaccine Name	Developer(s)	Immunologic Target	Current Phase	Potential News	Estimated Timing	Manufacturing Expectations
Adenoviral	**AZD1222**	AstraZeneca/Oxford	Full S protein	Ph2/3	Phase 3 Data Regulatory Approval	October-20 Q4:20	400MM doses in Sept (at-risk), >1B doses in 2021
	Ad5-nCoV	CanSino	Full S protein	Ph3	Initial Phase 3 Data	December-20	100-200M doses per year in 2021
	Ad26.COV2-S	Janssen Pharma	Full S protein	Ph1/2	Phase 1 Data Start Phase 3 Trial	September-20 September-20	500M doses in 2020, 1B doses in 2021
Replicating Viral Vector	**V591 (Measles vector)**	Merck	Undisclosed DNA cargo	Preclinical	Start Phase 1 Trial	Q3:20	No specific guidance
	V590 (rVSV vector)	Merck	Full S protein	Preclinical	Start Phase 1 Trial	H2:20	No specific guidance

Source: Cowen and Company

CanSino's recombinant adenovirus type-5 (Ad5) vectored vaccine (Ad5-nCoV) encodes the full-length S protein. In preclinical challenge studies, 7 of 8 ferrets were protected 21 days post-vaccine (no detectable virus copies via nasal dripping) compared to 1 of 8 in the control group. The vaccine was made in China and rapidly entered a sizable Phase 1 study.

Phase 1 Data Was Published In Lancet – Showed Good Dose Response

Phase 1 data was published in The Lancet in May 2020. The trial was conducted in Wuhan, China in collaboration with the National Key R&D Program of China and showed the vaccine was tolerable and immunogenic in healthy adults.

Compared to pre-existing adenovirus type-5 neutralizing antibody titers collected at baseline, 18 (50%) participants in the low dose group, 18 (50%) in the middle dose group, and 27 (75%) in the high dose group had at least a 4-fold increase in neutralizing antibody titers by day 28. Rapid binding antibody responses to the receptor binding domain (RBD) reached a 4-fold increase from baseline in 94–100% of participants by day 28.

There was a moderate positive correlation of ~0.75 between (1) ELISA antibodies to RBD and neutralizing antibody titers, and (2) ELISA antibodies to spike glycoprotein and neutralizing antibody titers.

The highest dose tested was the most immunogenic, but also highly reactogenic with some subjects developing severe fever, fatigue, dyspnea and muscle pain. Only the low and middle dose were further assessed in the Phase 2 trial.

Phase 2 Data Showed Underwhelming Immune Responses In An Older Population

Similar to the Phase 1 data released in May for CanSino's Ad5-vectored COVID-19 vaccine, the nAb response was underwhelming with GMTs of 19.5 and 18.3 in subjects receiving 1×10^{11} and 5×10^{10} viral particles, respectively. Further, only 59% of subjects in the higher dose group and 47% of subjects in the lower dose group achieved an increase in nAb titer of 4x their pre-vaccination level by 28 days post-vaccination.

Perhaps most interesting, this study is the first to report on antibody responses in subjects ≥55 years of age. Broken down by age group, the geometric mean nAb titer in the high dose group to live SARS-CoV-2 was 24.6 in the 18 to 44 age group, 16.6 in the 44 to 54 age group, and 9.6 in the ≥55 age group. The muted response with increased age is not a surprise, though the degree of difference seen with younger cohorts is noteworthy and will be a key datapoint to watch for as other vaccine candidates release data in the future.

Pre-Existing Immunity to Ad5 Poses A Problem

One potential concern for CanSino's Ad5 vector is that a large segment of the population has been exposed to Ad5 in the past, which raises concern about pre-existing immunity. In the Lancet publication, it was noted that the subjects with high baseline levels of neutralizing antibodies to the adenovirus used in the vector were less likely to develop high levels of neutralizing antibodies to SARS-CoV-2. Thus, this vaccine may have a limited effect in a portion of the population and those people would likely be unable to receive additional doses.

Of note, this issue of pre-existing immunity to the vector is not relevant for AZN/Oxford's vaccine which uses a chimpanzee adenovirus and thus carries no risk of pre-existing immunity in humans.

CanSino Moves Into Phase 3 Development

CanSino announced initiation of a Phase 3 trial in early September 2020. The study will include sites in Russia, Saudi Arabia, Brazil and Chile.

While CanSino's vaccine could be a local option for the China market, we believe the data is not competitive relative to AZN/Oxford or mRNA vaccines.

Manufacturing Scaling Up to Support >100MM Doses in FY21

In terms of manufacturing, the company has reported that their current production capacity can produce 70-80MM doses, and they aim to produce >100MM doses in 2021. Chinese regulators have already approved a vaccine using CanSino's Ad5 technology (for Ebola), which should help expedite the regulatory process in China.

Merck Is Developing 2 Different Replicating Viral Vector Vaccines

Viral Vector Vaccines in Development

Modality	Vaccine Name	Developer(s)	Immunologic Target	Current Phase	Potential News	Estimated Timing	Manufacturing Expectations
Adenoviral	AZD1222	AstraZeneca/Oxford	Full S protein	Ph2/3	Phase 3 Data Regulatory Approval	October-20 Q4:20	400MM doses in Sept (at-risk), >1B doses in 2021
	Ad5-nCoV	CanSino	Full S protein	Ph3	Initial Phase 3 Data	December-20	100-200M doses per year in 2021
	Ad26.COV2-S	Janssen Pharma	Full S protein	Ph1/2	Phase 1 Data Start Phase 3 Trial	September-20 September-20	500M doses in 2020, 1B doses in 2021
Replicating Viral Vector	V591 (Measles vector)	Merck	Undisclosed DNA cargo	Preclinical	Start Phase 1 Trial	Q3:20	No specific guidance
	V590 (rVSV vector)	Merck	Full S protein	Preclinical	Start Phase 1 Trial	H2:20	No specific guidance

Source: Cowen and Company

Adenovirus-based vaccines are not able to replicate due to genetic manipulation (one of its genes is replaced), thereby protecting against undesired viral replication and making these vaccines safe in the immunocompromised population.

Merck believes that a live replicating viral-vector will be more effective with a single dose, even though development may take longer. The company points to the problematic nature of expecting compliance with booster shots as an important motivation for a single shot regimen.

By making copies of themselves, live replicating viruses should be more effective at potentially lower doses compared to other modalities. They also have the advantage of being more likely to stimulate both B and T cell responses.

Recombinant Measles-Vectored SARS-CoV-2 Vaccine

Based on technology developed by Themis (acquired by Merck), this vaccine will leverage a replication-competent live-attenuated Measles vaccine modified to harbor recombinant DNA cargo. The cargo in this case is likely to comprise some or all of the SARS-CoV-2 spike protein sequence, but details have not yet been released. This vector has not yet been approved, but the vector backbone is a widely used Measles vaccine (Schwarz strain) that improves prospects for both acceptable safety and efficacy. Retained replication competence allows for propagation of the payload antigen over time and could promote more robust immune responses. A chikungunya vaccine based on this technology (MV-CHIK) has been evaluated in a Phase 2b study. The vaccine (5 x 10^5 TCID50) induced neutralizing antibodies after one administration but was more effective after a second immunization. Pre-existing measles immunity did not appear to affect potency. Safety was comparable to a control traditional MMR vaccine.

There are no data available for the specific SARS-CoV-2 vaccine in development, but Merck plans to initiate clinical trials in 2020. Specific timelines have not been disclosed.

Recombinant Vesicular Stomatitis Virus (rVSV)-Vectored SARS-CoV-2 Vaccine

rVSVΔG-SARS-CoV-2 is a live-attenuated recombinant vesicular stomatitis virus (rVSV)-vectored SARS-CoV-2 vaccine based on the same rVSV platform recently approved for Ebola immunization (Ervebo). In rVSVΔG-SARS-CoV-2, the VSV gene coding for the VSV surface protein has been replaced with a gene coding for the surface spike protein of SARS-CoV-2. To the extent that insight can be gleaned from Ervebo, it was shown to be 100% efficacious in preventing Ebola virus disease in 2,108 healthy adults with known primary or secondary contacts to Ebola virus-infected persons. Virus neutralizing antibody responses were seen in separate studies. Per the vaccine's label, the most common injection-site AEs were injection-site pain (70%), swelling (17%), and redness (12%). The most common systemic AEs were headache (37%), feverishness (34%), muscle pain (33%), fatigue (19%), joint pain (18%), nausea (8%), arthritis (5%), rash (4%) and abnormal sweating (3%). Ervebo only requires one dose (72MM pfu, IM), and an oral formulation is in development. No data are available for rVSVΔG-SARS-CoV-2, but if it shares Ervebo's characteristics, then prospects are good for efficacy and safety.

rVSVΔG-SARS-CoV-2 is in preclinical development with first-in-human studies planned for late 2020.

Manufacturing capabilities for the rVSV vector platform are already in place and can be expanded to produce millions of doses. Should the measles-based vaccine be successful, existing infrastructure could be retrofitted/repurposed as well as supplemented where needed. However, Merck has not provided specific guidance on production timing or capacity for either vaccine.

Protein-Based Vaccines Are Validated But Require An Adjuvant To Boost Immunity

Protein-based vaccines represent another validated method of vaccine development, with success in viruses such as shingles and hepatitis B.

One of the important advantages of protein-based vaccines is their ability to preferentially display the critical antigens on a protein that may not naturally be immunogenic or easily accessible. Through advances in structural biology, detailed antigen characterization has contributed to the design and optimization of protein-based vaccines in three ways:

1. potential weakness in an antigen can be resolved by designing a novel form (successful with RSV in raising higher nAb titers),
2. conformational heterogeneity in an antigen can be simplified to only the preferred confirmation most likely to elicit an immune response, and
3. structural information can be used to generate novel immunogenic protein surfaces that contain multiple pathogenic variants onto a single vaccine antigen.

The downsides to protein-based vaccines include the lack of amplification (only one protein antigen molecule is introduced per molecule of vaccine delivered) and the requirement for adjuvant to elicit a robust immune response.

As a result, each of the advanced protein vaccines involves a collaboration with a major adjuvant developer, including Emergent Bio, Dynavax and GSK.

Sanofi/GSK Behind But Have Major Manufacturing Firepower, To Start Phase 1/2 Trial in September

Protein-Based Vaccines in Development

Modality	Vaccine Name	Developer(s)	Immunologic Target	Current Phase	Potential News	Estimated Timing	Manufacturing Expectations
Protein Subunit	**NVX-CoV2373**	Novavax/Emergent Bio	Full S protein	Ph1/2	Start Phase 3 Trial Initial Phase 3 Data	October-20 December-20	100M doses in 2020, >1B doses in 2021
	SCB-2019	Clover/GSK/Dynavax	Full S protein	Ph1	Phase 1 Data	September-20	Hundreds of millions of doses in 2021
	Unnamed	Sanofi/GSK	Protein Subunit	Ph1/2	Phase 1/2 Data Start Phase 3 Trial Regulatory Approval	December-20 December-20 H1:21	100M doses in 2020, >1B doses by mid-2021
	MVC-COV1901	Medigen/Dynavax	S-2P protein	Preclinical	Start Phase 1 Trial	September-20	Dynavax able to supply 600M to 1.2B doses of adjuvant per year

Source: Cowen and Company

Recombinant SARS-CoV-2 Spike Protein

This vaccine candidate is based on recombinant SARS-CoV-2 spike protein, produced in a baculovirus expression system. The manufacturing platform is the same as that used for production of the marketed influenza vaccine Flublok. Several years ago, SNY partner Protein Sciences leveraged this platform to mount a recombinant vaccine program against SARS but since that pandemic was short-lived, it was not progressed. That vaccine candidate was based on the extracellular portion of the spike protein. It produced neutralizing antibodies in mice. In rabbits, 3 injections resulted in neutralizing antibody production beginning on day 14 and persisting to day 42. Addition of the AlOH adjuvant potentiated this response.

Recombinant Protein COVID-19 Vaccine Development Is Slower, But The Platform Is Battle Tested

Sanofi is one of the major vaccine makers but might be one of the last among the leaders to post initial COVID-19 vaccine data. The Phase 1/2 start for its recombinant SARS-CoV2 vaccine is expected in Q3:20 with preliminary immunogenicity/safety data in December, potential emergency use authorization in January 2021 concurrent with Phase 3 initiation, and possible approval by June 2021. At-risk production of the drug substance is already underway. Sanofi plans to produce 100 million doses by January 2021, and 1 billion doses by end of 2021. These milestones are a few months behind those set by Pfizer/BioNTech, AstraZeneca, and Moderna. Unlike these companies, however, Sanofi stressed that its recombinant+adjuvant approach is based on commercial-stage development and manufacturing techniques (the same as those used for FluBlok) and a marketed adjuvant (GlaxoSmithKline's AS03). The decision to pursue this approach played to the company's strengths while deliberately trading R&D pace for probability of success. Recombinant vaccines take longer to produce than mRNA-based vaccines primarily due to the need to express and purify the recombinant protein at scale.

Sanofi deliberately traded R&D pace for probability of success

Sanofi Plans To Combine Its Vaccine With GSK's AS03 Adjuvant

For SARS-CoV-2, SNY will collaborate with GSK to combine its viral antigen with the AS03 adjuvant to complete the vaccine.

GlaxoSmithKline's AS03 is an Adjuvant System composed of α-tocopherol, polysorbate 80, and squalene in phosphate-buffered saline as the aqueous carrier. AS03 immunostimulant adjuvant properties derive primarily from the oil-in-water emulsion phase as well as from α-tocopherol. AS03 activates the innate immune response at the injection site which goes on to enhance adaptive immune responses to the vaccine antigen. The AS03 adjuvant was used in the H1N1 pandemic flu vaccine Pandemrix, and is also licensed in the US for use in a pandemic H5N1 (avian flu) vaccine. AS03 promotes a stronger and broader immune response which enables antigen dose reduction, facilitating vaccine production volume. However, there are not yet any data on AS03 combined with a SARS-CoV-2 vaccine/antigen.

GSK is providing AS03 in 7 different collaborations, 5 of which have been made public (Sanofi, Clover Biopharmaceuticals, ZFSW, Innovax, Vir, and The University of Queensland).

Phase 1/2 Study Started Early September, Aim To Move Into Phase 3 by YE:20

Sanofi and GSK initiated a Phase 1/2 clinical trial of its adjuvanted COVID-19 vaccine in early September. The trial will include 440 healthy adults across 11 investigational sites in the US. The companies anticipate first results by December 2020.

A Phase 3 trial is planned to begin in December 2020 on the back of the Phase 1/2 data readout. The companies hope to request regulatory approval in H1:21.

Sanofi Has Capacity For 100MM By YE '20 and >1B Doses By Q2:21

Sanofi has existing capacity to manufacture 100-600MM doses but has set a goal to produce >1B doses by Q2:21. GSK intends to produce a billion doses of AS03 adjuvant in 2021 to apply across its collaborations. Of these, hundreds of millions would be dedicated to the Sanofi vaccine, if successful.

In terms of potential initial pricing for the vaccine, the Sanofi France CEO Olivier Bogillot stated that the price will likely be below €10.

Novavax/Emergent BioSolutions Demonstrate Strong Neutralizing Antibody Response In Early Data

Protein-Based Vaccines in Development

Modality	Vaccine Name	Developer(s)	Immunologic Target	Current Phase	Potential News	Estimated Timing	Manufacturing Expectations
Protein Subunit	**NVX-CoV2373**	Novavax/Emergent Bio	Full S protein	Ph1/2	Start Phase 3 Trial Initial Phase 3 Data	October-20 December-20	100M doses in 2020, >1B doses in 2021
	SCB-2019	Clover/GSK/Dynavax	Full S protein	Ph1	Phase 1 Data	September-20	Hundreds of millions of doses in 2021
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	MVC-COV1901	Medigen/Dynavax	S-2P protein	Preclinical	Start Phase 1 Trial	September-20	Dynavax able to supply 600M to 1.2B doses of adjuvant per year

Source: Cowen and Company

Emergent BioSolutions has entered into multiple agreements with potential vaccine developers and HHS in order to support clinical drug supply and commercial production at several of its facilities.

Novavax and Emergent Bio Collaborate On A Vaccine

In March 2020, EBS announced that it has entered into a collaboration with Novavax to develop and produce a vaccine candidate against SARS-CoV-2, specifically targeting the S protein. The vaccine also utilizes Novavax's Matrix-M adjuvant platform which is a purified saponin-based mixture with synthetic phospholipids to form stable particles. The adjuvant simulates antigen-presenting cell entry to the injection site and antigen presentation at local lymph nodes to enhance the immune response to the vaccine. Novavax has noted the adjuvant has been associated with transient injection site reactions, but not systemic toxicity.

EBS is acting as the downstream manufacturing partner for the program while development is owned and driven by Novavax at this time. Specifically, EBS indicated that the drug substance will be produced at the company's Baltimore/Bayview location, designated a CIADM facility by HHS, and the drug product will be produced at the Baltimore/Camden facility. The company noted that further involvement or expansion of the partnership can be negotiated at a later time. We believe that EBS's existing relationships with governments arising from its stockpiled products would be a positive for the partners if the vaccine is approved.

NVX-CoV2373 Generates Robust Peak nAb Titers In Phase 1 Study

In early August, Novavax announced the Phase 1 portion of their ongoing Phase 1/2 clinical trial for COVID-19 vaccine candidate, NVX-CoV2373. The study included 131 healthy adults ages 18-59 years and tested a prime-boost dosing regimen at two dose levels (5 µg and 25 µg) with and without Matrix-M adjuvant. The adjuvanted regimens exhibited superior results.

Both dose levels given with Matrix-M adjuvant were generally well-tolerated with no Grade ≥3 events after either the prime or boost inoculations. The 5 µg and 25 µg adjuvanted doses generated a peak nAb geometric mean titer (GMT) of 3,906 and 3,305 one week after the booster dose, respectively. This compared favorably to convalescent plasma from patients with clinically significant COVID-19 disease which had a GMT of 984.

When comparing these nAb titers to other vaccines, the absolute values are much higher than any other studies, but this was true in the reference group as well. Thus, using the 3-4x convalescent serum is the most useful parameter and this places NVX-CoV2373 in the same arena as the vaccines from Moderna and Pfizer/BioNTech.

NVX-CoV2373 also induced antigen-specific CD4+ T cells with a largely T helper 1 (Th1) phenotype. The study did not assess CD8+ T cell response.

Phase 3 Trial Likely To Begin in October

We expect a Phase 3 trial to start in October 2020, with initial data potentially as early as Q1:21. Though Novavax is not as far along in development with their vaccine candidate, NVX-CoV2373 has the potential to be a top player in 2021.

Novavax/Emergent Bio Expect >1B Doses To Be Available in 2021

In terms of manufacturing capacity, the companies expect to produce 100M doses in 2020 and more than 1B doses in 2021.

In July 2020, Novavax struck a deal with the U.S. government (through Operation Warp Speed) in the amount of $1.6B for the delivery of 100M doses of NVX-CoV2373 as early as late 2020. The price of $16/dose is in-line with competing agreements with the U.S. government.

U.S. Funding For Vaccine Development Has Reached Over $10B, Paying Btw $4-$20/Dose

	US Government Vaccine Funding				
Company	Supply Agreement ($MM)	Doses (MM)	$/Dose	Development Funding ($MM)	Total ($MM)
Sanofi/GSK	$2,042	100	$20.42	$30	$2,072
Pfizer/BioNTech	$1,950	100	$19.50	$0	$1,950
Novavax	$1,600	100	$16.00	$0	$1,600
Moderna	$1,525	100	$15.25	$955	$2,480
JNJ	$1,000	100	$10.00	$456	$1,456
AstraZeneca	$1,200	300	$4.00	$0	$1,200
Merck	$0	-	-	$38	$38
Total	**$9,317**	**800**		**$1,479**	**$10,796**

Source: Cowen and Company

EBS And Vaxart Also Announce A Manufacturing Agreement

Separately in March 2020, EBS and Vaxart announced a CDMO agreement whereby EBS will produce clinical material to support Vaxart's clinical development of its oral coronavirus vaccine candidate. The agreement will leverage some of the same EBS facilities that are involved with the Novavax collaboration with drug substance to be manufactured at the Bayview facility in Baltimore and development activities to be completed out of the Gaithersburg location. A Phase 1 trial is projected to start in H2:20. Vaxart's vaccine leverages the company's VAAST (Vector-Adjuvant-Antigen Standardized Technology) platform which enables intestinal delivery of the vaccine.

EBS Expands Partnership With HHS For COVID-19 Vaccines - $543M Agreement

In June 2020, EBS announced a significant expansion of its 2012 Public-Private Partnership with HHS to secure additional manufacturing capacity for government-

backed COVID-19 vaccine candidates. The full task order is valued at $628MM of which $542.7MM is tied to manufacturing of COVID-19 vaccines. An addition $85.5MM is provided to enable and expansion of EBS' viral and non-viral CDMO drug product fill/finish capacity. The assets associated with the expansion would remain under EBS' control and be available for use in other programs once COVID-19 efforts have been completed. The expansion is provided under the Federal Gov's 'Warp Speed' (OWS) effort to support development, manufacturing, and distribution of COVID-19 vaccines in the US. Discussions with management indicate that the OWS task order essentially 'buys out' uncommitted capacity for drug substance production through YE:21 while some fill/finish capacity remains in the company's network. The Federal government would decide how to allocate production capacity under OWS among several vaccine programs under the umbrella. Discussions with management following the recent HHS task order indicate that the $542MM in projected CDMO revenue through 2021 would serve as a floor to secure EBS' manufacturing capacity for vaccine candidates. Incremental revenue would be available depending on exactly how that capacity was actually used and the specific technology involved.

AZN Agreement Broadens EBS' Reach Among COVID-19 Programs

In June 2020, EBS announced a collaboration agreement with AstraZeneca to support the company's SARS-CoV-2 vaccine candidate under the US Gov's OWS initiative to support vaccine development. AstraZeneca's AZD1222 is a viral vector-based vaccine (attenuated adenovirus unable to replicate in humans) encoding the spike protein. Early development was completed by Oxford University and clinical development began in April 2020. AstraZeneca has communicated that it has sourced total global capacity for >2B doses in 2020 and 2021. AstraZeneca has previously agreed to supply 400MM doses to the US and UK. The program has received >$1B is support from BARDA.

The agreement between EBS and AstraZeneca is valued at $87MM through 2020. The agreement shares common elements with previous CDMO contracts the company has signed with SARS-CoV-2 vaccine developers. Under the agreement EBS will provide development, tech transfer, analytics, drug substance process and performance qualification. Large-scale manufacturing capacity will also be reserved through 2020. Development steps will be completed out of the Gaithersburg site and drug manufacturing will be performed at the CIADM-designated Bayview facility. Bayview is capable of producing 10s to 100s of millions of doses per year depending on the technology being used.

Clover/GSK COVID-19 S-Trimer Targets The Spike Protein

Protein-Based Vaccines in Development

Modality	Vaccine Name	Developer(s)	Immunologic Target	Current Phase	Potential News	Estimated Timing	Manufacturing Expectations
Protein Subunit	**NVX-CoV2373**	Novavax/Emergent Bio	Full S protein	Ph1/2	Start Phase 3 Trial Initial Phase 3 Data	October-20 December-20	100M doses in 2020, >1B doses in 2021
	SCB-2019	Clover/GSK/Dynavax	Full S protein	Ph1	Phase 1 Data	September-20	Hundreds of millions of doses in 2021
	Unnamed	Sanofi/GSK	Protein Subunit	Ph1/2	Phase 1/2 Data Start Phase 3 Trial Regulatory Approval	December-20 December-20 H1:21	100M doses in 2020, >1B doses by mid-2021
	MVC-COV1901	Medigen/Dynavax	S-2P protein	Preclinical	Start Phase 1 Trial	September-20	Dynavax able to supply 600M to 1.2B doses of adjuvant per year

Source: Cowen and Company

Clover Biopharmaceuticals' vaccine candidate, COVID-19 S-Trimer, is based on recombinant SARS-CoV-2 spike protein, which has been developed in an expression system intended to preserve the native trimeric structure of the fully assembled

protein. This approach is part of a broader pipeline of RNA virus vaccines in which envelope proteins are expressed and trimerized via proprietary Trimer-Tag technology to mimic their native conformation (e.g. gp120/HIV-1, HA/Influenza, Fusion F glycoprotein/RSV). Preserving the native structure of the antigen may be important for generating immunity with conserved cross-reactivity to wild-type virus upon infection.

In support of this approach, Clover conducted a study in which the S-Trimer antigen was found to bind to antibodies in the convalescent sera of 11/11 previously infected COVID-19 patients in China. S-Trimer is being developed in combination with GSK's AS03 adjuvant, as well as Dynavax's CpG 1018.

Phase 1 Commenced in June – Capacity For 100MM Doses Annually

Clover initiated a Phase 1 trial for its protein-based vaccine, SCB-2019, in June. We anticipate interim data to be shared in September.

If successful, Clover has indicated that it has in-house manufacturing capacity to produce over 100MM doses of the vaccine antigen annually.

Antibody Therapeutics Will Play A Critical Role In Helping Patients Who Will Not Benefit From Vaccines

Key remaining unknowns are: whether these vaccines will confer duration immunity, whether approval will be based on hard clinical endpoints from Phase 3 studies, and whether interim data from biomarkers will be sufficient to support Emergency Use Authorization (EUA).

COVID-19 vaccines are expected to elicit durable protection, which is critical to breaking the curve and restarting economies globally. Vaccine development is now at a historic pace support by government funding in the US and to a lesser extent in Europe. More so, recent FDA guidance in May should help expedite development of both vaccines and therapeutics.

Ability Of COVID-19 Vaccines To Elicit High Response And Durable Immunity Is Still Uncertain

No vaccine has ever been approved for use against previous forms of human coronavirus. Whether COVID-19 vaccines will have varying response and durability in different patient subgroups is still unknown. Inherently, new COVID-19 vaccines face technological uncertainties because many promising programs are based on new, unproven technologies (such as mRNA therapies).

Recall, recently released data for AstraZeneca/Oxford University's AZD1222 showed macaques were protected from COVID-19, but still had high levels of viral load in their upper airways (i.e., the vaccine was unable to obliterate the viral colonization of the nasal passages that have less immune surveillance).

Additionally, initial data from Moderna's mRNA-1273 suggests that titers of neutralizing antibodies decline after several weeks, suggesting that antibody immunity alone might not be sufficient and that T cell responses must be robust to confer durable protection.

As data are very early, the level of efficacy and durability from vaccines are too hard to predict. More so, it is expected that the elderly and patients who are immunocompromised are less likely to benefit from a vaccine as they are less likely to mount a robust immune response.

There Are Concerns About Risks Of Antibody-Dependent Enhancement (ADE) Associated With Vaccines

Given the urgent need, we think it is possible that the FDA might be flexible in using biomarker or initial data to support Emergency Use Authorization (EUA) so the first vaccine can be released early to help people at high risk. Recall, the Ebola vaccine was released for emergency use in 2014 while it was being studied for efficacy and eventually got approved in 2019.

In May, the FDA allowed Moderna to advance its vaccine candidate into a Phase 2 efficacy study without having full Phase 1 safety data and Moderna then commenced a Phase 3 study in the summer.

Pfizer/BioNTech are also moving quickly ahead while neutralizing antibodies from Regeneron, Lilly, and AstraZeneca have also moved toward pivotal studies before having final results from Phase 1 or 2 studies.

However, there has been a theoretical concern regarding suboptimal vaccine responses inducing non-neutralizing antibodies, which can result in antibody-dependent enhancement (ADE) of proinflammatory effects. ADE occurs when non-neutralizing antibodies enable the virus to use the antibody's Fc domain to bind to the Fc receptors of immune cells or epithelial cells. This leads to uptake of the virus and subsequent dysregulated cytokine release or Th2 immune responses (cellular in nature that can lead to tissue injury).

Our consultants believe that ADE must be carefully considered with SARS-CoV-2 vaccines based on preclinical data from SARS-CoV and MERS-CoV, as well as data from feline coronavirus. In their view, the best mitigating factor is a robust neutralizing antibody response.

Of note, ADE might be less of a problem for antibody therapies as the Fc domain of antibody candidates could be muted or modified, such as introducing a LALA mutation, to minimize the FcγR activation and Fc-mediated toxicity. Yet even this point is controversial as Regeneron has not induced any mutations to the Fc region of their SARS-CoV2 antibody cocktail since they believe that the risk of ADE is low based on the high potency of their antibodies and encouraging preclinical animal data.

There Are Uncertainties Regarding Vaccine Manufacturing Capacity And Cold Storage Supply Requirements For mRNA Vaccines

Manufacturing capacity is yet another uncertainty regarding vaccine development. As it is unlikely for the world to reach herd immunity in the next 1-2 years at the current infection rates, we estimate that hundreds of millions or even billions of doses could be needed. Encouragingly (as covered earlier in the report), there will be several billions worth of vaccine capacity being projected from Moderna, Pfizer/BioNTech, AstraZeneca and J&J, who are likely the leaders partly supported by Operation Warp Speed. But the gating factor is being able to execute on their capacity projections and requirement for regulatory approvals.

The scalability of vaccines varies depending on their particular technologies. However, whether the developer of an effective vaccine can scale up the manufacturing capacity fast enough to meet the growing demand remains uncertain.

More so, certain vaccines (such as mRNA therapeutics) will require a tightly controlled cold storage supply chain which is cumbersome and not readily available for broad distribution volumes.

Before a viable vaccine is developed, we anticipate that there will be a tangible demand for a solution that can protect people from the COVID-19 infection prophylactically or as a therapeutic especially because the likelihood of a second wave hitting in the fall is high.

Convalescent Plasma Therapy Holds Some Promise By Inducing Passive Immunity But Data Has Been Equivocal

Most people who recover from COVID-19 develop antibodies to the SARS-CoV-2 virus. Convalescent plasma therapy involves taking antibody-rich serum from the blood of recovered patients and transferring it to newly infected patients to boost their immune response. The approach has been used historically to combat viral and bacterial outbreaks since before the Spanish flu.

Since January 2020, Chinese researchers have been using it to treat COVID-19 patients. In March, the FDA gave emergency clearance both to start convalescent plasma trials and to treat COVID-19 patients under emergency use. It is estimated that over 40,000 patients in the US have received this therapy through a joint program between HHS and the Mayo Clinic.

FDA Grants Emergency Use Authorization (EUA) Despite Major Reservation With Little Convincing Data

The FDA has been preparing to issue an emergency authorization for convalescent plasma based on historical use of plasma therapy in other diseases and in animal research of plasma studies. This includes the Mayo Clinic's program of more than 66,000 infused COVID-19 patients.

However, several health officials, including Dr. Francis Collins, NIH director, Dr. Anthony Fauci, clinical director of the NIAID, and Dr. Clifford Lane, NIAID deputy director for clinical research and special projects, believe the emerging convalescent plasma data has not been strong enough for emergency approval. Despite these concerns, likely fueled by political pressure from President Trump, FDA provided EUA for this approach in late August 2020.

We note that there is still no data from a large randomized trial to determine whether this approach works and, if it does, on which patients.

Importantly, plasma transfusions have been safe and well tolerated in most cases. While the most common side effect is a mild allergic reaction, some rare serious side effects include heart or lungs sequalae and infections.

Convalescent Plasma Was Used For Prior Pandemics

Convalescent plasma therapies have been used successfully as post-exposure prophylaxis and/or treatment of H1N1, Ebola, SARS, and MERS. In 2009, a prospective study showed that H1N1 patients treated with convalescent plasma had a significant reduction in the relative risk of mortality (odds ratio: 0·20, p=0·01). In 2014, the use of convalescent plasma therapy was recommended by WHO as an empirical treatment during Ebola outbreaks. A convalescent plasma treatment protocol for MERS was also established in 2015.

Benefit Of Convalescent Plasma Therapy Was Inconclusive Based On Early Data From Small COVID-19 Studies

Preclinical studies also showed that plasma from recovered COVID-19 patients has anti–SARS-CoV-19 antibodies that can be used to neutralize the virus. Early data from small studies in China highlighted potential clinical benefits, such as reduction in viral loads, shorter hospital stay, and improvement of survival in severe/critical COVID-19 patients.

But a recent review article by Valk et al. published in the *Cochrane Database of Systematic Reviews* was unable to determine whether convalescent plasma is effective in hospitalized patients due to data inconsistency. The conclusion was derived based on data from 8 clinical studies (7 case-series and 1 prospective, single-arm study) with 32 patients.

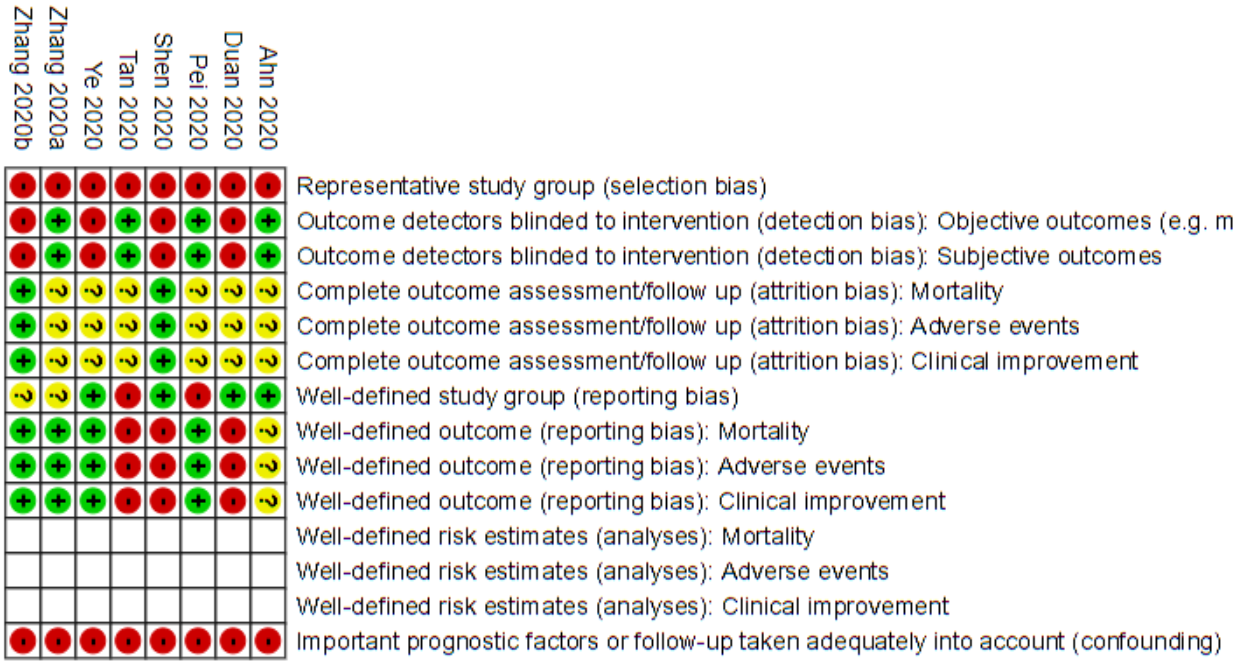
On the efficacy side, all participants in these studies were alive at the end of the reporting period, and overall there were 15 confirmed discharges of participants by the end of the studies (while 6 other patients are still hospitalized and the status of 11 patients is unclear). The follow- up period ranged from 3 days to 37 days post-transfusion.

Six (n=28 in total) out of the 8 studies reviewed by Valk et al. reported the level of respiratory support required and all 8 studies reported improvement in clinical symptoms in at least some participants. In particular, six of these studies reported time to discharge from hospital of 4-35 days after convalescent plasma therapy.

On the safety side, all 8 studies did not report the grade of adverse events after convalescent plasma therapy. But one separate case study reported that a participant had moderate fever (38.9 °C) and another study (n=3) reported a case of severe anaphylactic shock. Four studies did not report any moderate or severe AEs (n=19).

Another review study by Rajendran et al. published in *J. Med. Virol.* analyzed five of these same studies. The authors of both review articles reached similar conclusions that the reported outcomes could be related to the underlying natural history of the disease or other concomitant treatment, rather than convalescent plasma as those studies were not randomized control studies. The authors also found that the overall risk of bias of these studies was high due to many factors, such as study design, small sample size, poor reporting, and variability of disease severities.

Data From Early Non-Randomized Studies Raised Uncertainties Regarding The Efficacy And Safety Of Convalescent Plasma



Source: Valk et al., *Cochrane Database of Systematic Reviews,* 2020

A Large Retrospective Study Showed Promising Safety In Severe/Critical COVID-19

A recent study by Joyner et. al. published on *medRxiv* (not peer reviewed) analyzed safety data in the first 5,000 severe or life-threatening COVID-19 patients who were treated with 1-2 units of convalescent plasma. The authors reported an incidence of <1% for severe adverse events and a 7-day mortality rate of 14.9%, which is consistent with the natural history of severe infection. Of the SAEs, 15 deaths were reported (0.3% of all transfusions) with 4 of them considered as treatment related. The other 21 non-death SAEs included 7 reports of transfusion-associated circulatory overload (TACO), 7 reports of transfusion-related acute lung injury (TRALI), and 3 reports of severe allergic transfusion reaction.

In our view, the safety data in such a large sample size is encouraging as there have been theoretical concerns about antibody-dependent enhancement (ADE). This theoretical concern is supported by reports of ADE in macaques given a specific antibody prior to inducing a SARS-CoV-1 infection and ADE effects with other coronaviruses.

However, some researchers think it is possible that ADE could lead to more severe disease only in a subset of patients who are genetically susceptible.

More Recent Retrospective Data Also Showed Signs Of Efficacy

More recently, another study by Joyner et. al. published on *medRxiv* (not peer reviewed) analyzed data in 35,322 COVID-19 patients who were treated with convalescent plasma. This cohort included a high proportion of critical COVID-19 patients, with 52.3%

in the intensive care unit (ICU) and 27.5% receiving mechanical ventilation at the time of plasma transfusion.

The 7-day mortality rate was 9% in patients transfused within 3 days of COVID-19 diagnosis but 12% in patients transfused ≥4 days after diagnosis ($p < 0.01$). Similar findings were reported for 30-day mortality (22% vs. 27%, $p < 0.0001$). Notably, some correlation was observed between mortality and IgG antibody levels in the transfused plasma. For patients who received high IgG plasma (>18.45 S/Co), medium IgG plasma (4.62 to 18.45 S/Co) and low IgG plasma (<4.62 S/Co), 7-day mortality rates were 9%, 12%, and 14%, respectively (p=0.048). A similar dose-response with IgG was also observed in 30-day mortality (p=0.021).

Overall, the pooled relative risk of mortality among patients transfused with high antibody level plasma units was 0.65 for 7 days and 0.77 for 30 days compared to low antibody level plasma units.

In our view, the reduced mortality due to earlier time to transfusion and higher antibody levels shows promising signs of efficacy for convalescent plasma. However, we think this retrospective data is not robust enough. We await data from well-designed randomized clinical trials to future evaluate the efficacy of convalescent plasma therapy.

First RCT Study Stopped Early Due To Slow Enrollment, But Showed Optimistic Signals In Severe COVID-19 But Not Critically Ill Patients

Data from the first randomized control trial of convalescent plasma vs standard treatment alone (n = 103) was published by Li et al. in *JAMA*. This Chinese study was stopped early (target n = 200) due to low enrollment as the outbreak in China was being contained. The primary outcome of time to clinical improvement within 28 days is defined as patients being discharged alive or having a reduction of 2 points on a 6-point disease severity scale.

The data showed that convalescent plasma therapy has potential benefits in severe patients but not in the critically ill patients. In the severe patients (n = 45), 91% of patients receiving convalescent plasma showed clinical improvement vs 68% for standard treatment (HR = 2.15, p=0.03).

Convalescent plasma therapy did not show clinical improvement in the 58 critically ill patient (21% for convalescent plasma vs 24% for standard treatment (HR, 0.88, P = .83). This is consistent with our expectation that antibody therapies may generally work better in an earlier stage of COVID-19.

In the overall patient population, convalescent plasma achieved a shorter time (-2.2 days, 95% CI: -5.28 to 0.99 days) to clinical improvement, and higher rate of clinical improvement (52% vs 43% for standard treatment alone, HR = 1.40, p=0.26) at 28 days. Death rates were not significantly different between the convalescent plasma group (16%) and the control group (24%) (OR = 0.59, p=0.30).

Convalescent Plasma Is Well Tolerated Generally

On the safety side, there were 2 cases of reported transfusion-associated adverse events following convalescent plasma transfusion. One severe patient developed chills and rashes within 2 hours of transfusion but recovered fully after corticosteroid treatment. The other critical ill patient developed shortness of breath, cyanosis, and severe dyspnea within 6 hours of transfusion but gradually improved after corticosteroid treatment.

We Await Data From Large Randomized Studies To Generate More Evidence Of Benefit For Convalescent Plasma Therapy

We think the available efficacy data and low rate of adverse events of convalescent plasma therapy in severe COVID-19 are encouraging.

However, additional data from randomized controlled trials are needed for further evaluating the profile of convalescent plasma therapy. This is because the data is equivocal on comparisons between the treatment and control groups in the *JAMA* paper because the Chinese study was underpowered due to early study termination.

Recall, FDA guidelines recommend serum neutralization titers of ≥1:160 for convalescent plasma therapy and consider a titer of 1:80 as acceptable if an alternative matched unit is not available.

The fact that the antibody titers used in the Chinese study were much lower than the levels recommended by the FDA guidelines further complicates the interpretation of the results. Recall, the Chinese study published in JAMA tested convalescent plasma with S-RBD–specific IgG titer of 1:640 (a titer of 1:1280 for S-RBD–specific IgG is approximately equivalent to a serum neutralization titer of 1:80).

Some researchers considered convalescent plasma from donors who have recovered and who are at week 12 after onset with a neutralization titer level of ≥ 1:160 as being more effective.

Many Studies Are Ongoing Testing Convalescent Plasma

Currently, there are over 20 ongoing randomized controlled trials that are testing convalescent plasma therapy in COVID-19 patients. For example, Takeda is looking to develop a plasma-derived therapy, TAK-888, also derived from the blood of coronavirus patients who have recovered from the respiratory disease. We await additional data from large RCTs to better define the role of convalescent plasma therapy in treating COVID-19 patients and alleviate the theoretical concerns about ADE associated with suboptimal antibody responses.

Role Of Convalescent Plasma Therapy Is Likely Limited Due To Many Challenges

Thus far, over 14M patients have recovered from COVID-19. Many blood centers across the world have robust infrastructure for collecting and storing convalescent plasma.

However, the requirements to meet standards for detailed testing records and high levels of SARS-CoV-2 neutralizing antibody titers might limit the supply of donor serum. High neutralizing antibody titers are needed to achieve optimal therapeutic potency and reduce the theoretical risk of ADE.

Convalescent plasma therapy also faces regulatory, logistical, and production challenges that could limit capability and fall short of meeting the growing demand. In particular, the lack of standardized neutralizing antibody assays is a challenge.

Hence, we anticipate that convalescent plasma therapy will likely play a limited role adjunctive to antiviral therapies (such as Gilead's Veklury, aka remdesivir) in patients with less severe disease.

Neutralizing Antibodies Titer Is A Good Correlate Of Protection, But Assays For Neutralizing Antibody Titer Are Not Widely Available

Blocking the virus's interaction with host cell via spike protein is the primary way of antibody neutralizing activity during viral infection. Neutralizing antibody titer has been considered as a correlate of protection based on experience with other coronaviruses. Recall, neutralizing antibody titer (NAT_{50} or plaque reduction neutralization

titer/$PRNT_{50}$) is defined as the reciprocal of the highest test serum dilution for which the virus infectivity is reduced by 50% when compared with the control.

However, the challenge is that assays for measuring viral neutralizing antibody titers are not widely available. This is partly because these assays are labor intensive and require a biosafety level 3 laboratory if live virus is used.

Therefore, an easier and more practical way is desired as a surrogate of neutralizing antibody titer in many situations.

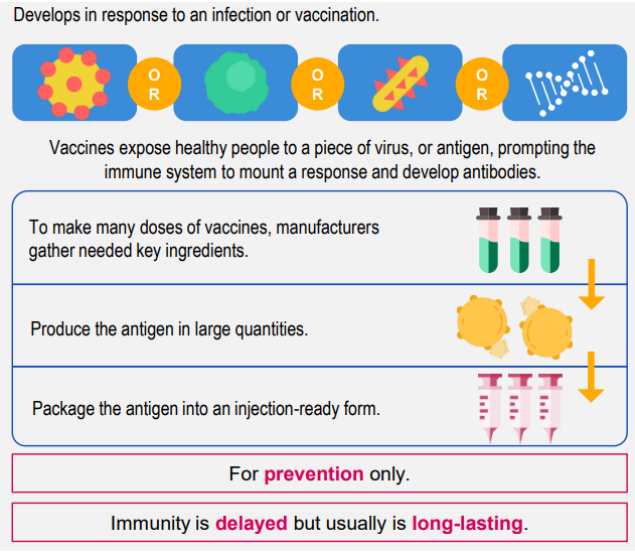
Neutralizing Antibody Therapy Is Promising And Will Be Used Adjunctive To Vaccines

Different from vaccines that induce active immunity by exposing healthy people to a piece of virus, or antigen, recombinant antibody therapies produce passive immunity. The benefit is that neutralizing antibodies can confer immediate protection and be used as:

1. prophylaxis (i.e., prevention) especially in high risk populations (such as healthcare workers, elderly, nursing home residents, immunocompromised),
2. therapy when given early after exposure,
3. adjunctive to vaccines in high risk patients, or
4. therapy in patients who are infected despite receiving a vaccine.

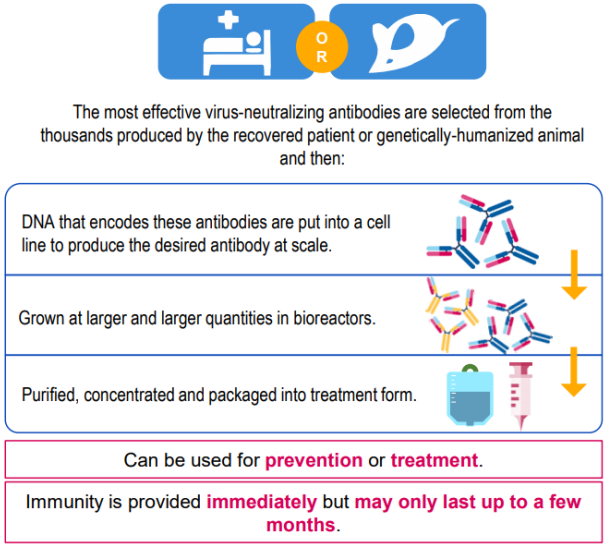
As monoclonal antibodies have a relatively long half-life (~3 weeks for IgG_1, a single dose of antibody therapy might last up to 2-3 months.

Vaccines Produce Active Immunity



Source: Regeneron

Antibody Therapies Produce Passive Immunity



Source: Regeneron

Antibody Therapies Will Still Be Used Adjunctively For Prophylaxis After Vaccines Become Widely Available

Neutralizing antibody therapies could find utility in people who may not respond well to vaccines, especially the elderly and immuno-compromised patients. This is because vaccination requires having a strong immune system that would mount a response to the vaccine challenge.

Additionally, it might take time for a vaccine to take effect and perhaps even require a 2nd booster shot to induce long-lasting immunity. Unlike vaccines, antibody therapies are

not expected to induce durable protection against COVID-19 but can take effect immediately.

Therefore, we anticipate that antibody therapies will play an adjunctive role to vaccines in people who do not respond well to vaccines or who are not able to wait until the effect of their vaccines kick-in.

We also see a lucrative opportunity for antibody therapies in the high-risk groups as prophylaxis ahead or immediate after exposure to SARS-CoV-2.

Antibody Therapy Can Be Used In Treating Patients With Early Stage Disease

In the treatment setting, neutralizing antibodies might also have a role in patients early in their infection. In other infectious diseases, antibody therapies have been used to boost the immune system rapidly for a short period to fight off an early stage infection.

We note that one of the key questions is the bioavailability of passively infused antibodies in tissues affected by the disease. For example, we know that these antibodies should provide ample protection in lung tissue that is well supplied by blood vessels but will offer much lower protection to the nasal passages.

At the same time, we do not expect antibody therapies to provide significant benefits in patients with late stage COVID-19 where high levels of inflammation cause coagulopathy, myocarditis, pneumonitis and cytokine storms that are too far advanced and have less to the do with the underlying viral infection.

In essence, neutralizing antibodies should be effective in preventing the virus from attaching to the ACE2 receptor and infecting the cell. Once the underlying immune response to the virus takes hold after the virus colonizes the lung parenchyma, this approach will be considerably less effective.

Our Consultants Anticipate Neutralizing Antibodies To Be More Beneficial For Early Protection Than Antiviral Treatment

Our consultants are optimistic that these therapeutics will have utility in treating the early stage of infection. They note that the strength of antibody-based therapeutics is their ability to neutralize live viruses, but he does not think that they have a strong ability to kill the “factories” that produce new viruses (while direct anti-virals can). In their view, these antibodies will be more beneficial in protecting patients from acute respiratory distress syndrome, and perhaps less effective in preventing coagulopathy.

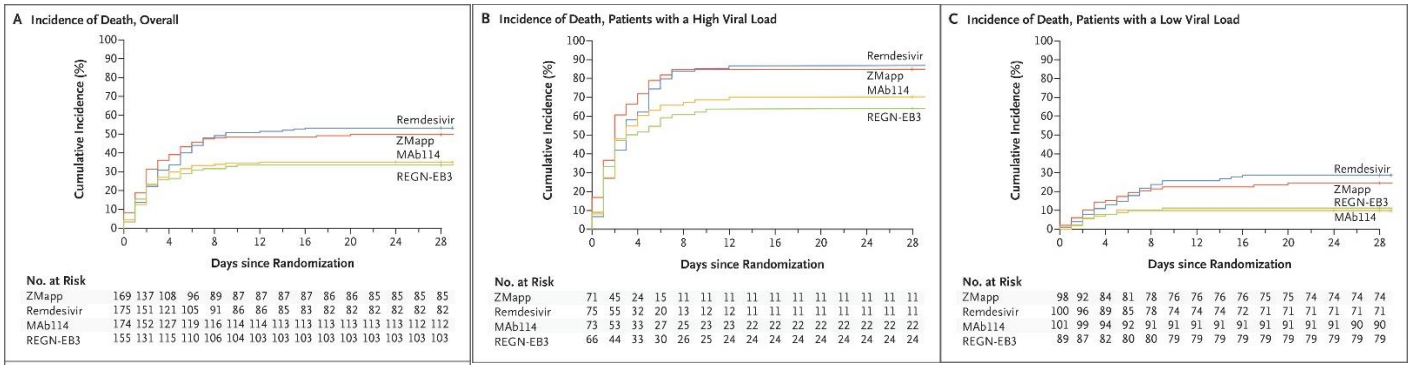
Antibody Modalities Hold Promise Given Historical Successes In Ebola And MERS

Antibody modalities have been used to develop therapies to treat other diseases, such as Ebola and Middle East Respiratory Syndrome (MERS). Recall, during the 2018 outbreak of Ebola, Regeneron successfully developed a monoclonal antibody triplet therapy, REGN-EB3, using its VelocImmune platform. Notably, REGN-EB3 uses the same rapid response technology platform as REGN-COV2, Regeneron's investigational COVID-19 antibody cocktail.

In August 2019, the Phase 3 PALM study of REGN-EB3 stopped early upon showing superiority to ZMapp in preventing death. The rolling submission of REGN-EB3 is ongoing (PDUFA: 10/25/2020). In July 2020, BARDA and Regeneron entered into an agreement to procure REGN-EB3 as part of the HHS' goal of building national preparedness for public health emergencies.

MERS is a respiratory illness caused by a coronavirus called Middle East Respiratory Syndrome Coronavirus (MERS-CoV). Two antibodies, REGN3048 and REGN3051, from Regeneron's VelociSuite platform have already been studied in a Phase 1 trial for MERS. Both these antibodies bind to the spike protein of the MERS coronavirus. In a mouse model of MERS, the cocktail resulted in a high-level neutralization of the MERS coronavirus in circulating blood and reduced viral loads in the lungs. The Phase 1 study for MERS was completed in 2019 (n=48, data from this study has not been published yet).

The *VelocImmune*-based Technologies Were Validated By The Rapid Development Of REGN-EB3 And Successful Treatment For Ebola



Source: Regeneron, *NEJM*

Spike Protein Is A Promising Target For Antibodies Against Coronavirus Based On Historical Data

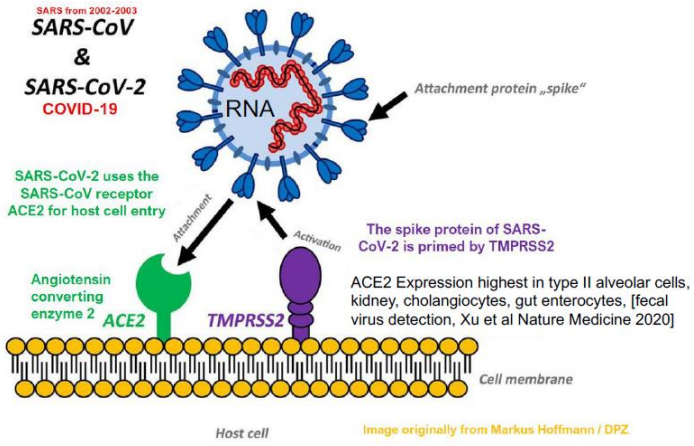
Neutralizing antibodies target the spike protein on the viral surface to block its interaction with the angiotensin-converting enzyme 2 (ACE2) receptor on host cells.

The spike protein is the most abundant protein on the virus, and it is a validated target for developing antibodies against coronavirus. Both the SARS-CoV (virus that causes SARS) and SARS-CoV-2 (virus that causes COVID-19) spike proteins are similar and have similar receptor binding domains (RBD) for the ACE2 protein. However, the affinity for the ACE2 receptor is 10X higher for SARS-CoV-2 than SARS-CoV, resulting in more invasion of epithelial cells and higher infectivity.

Historical data of SARS-CoV showed that neutralizing antibodies and/or T-cell immune responses were raised which mainly targeted the S protein. It suggests that S protein-induced specific immune responses play important roles in immunity against the virus.

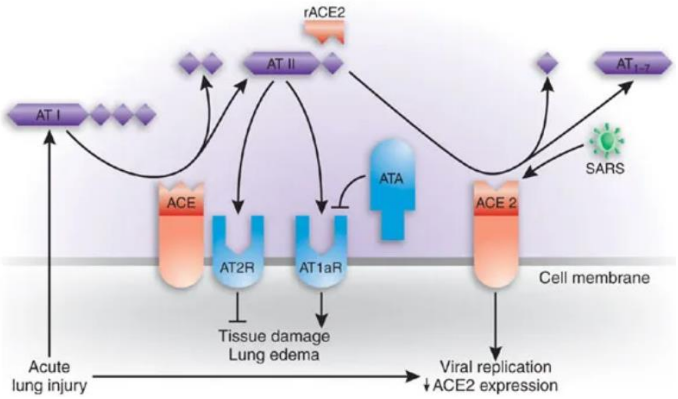
Our consultants have noted that the spike protein is a good target for antibody intervention as recent animal data from preclinical studies shows encouraging outcomes.

SARS-CoV-2 Spike Protein Binds To ACE2 Receptors To Initiate Cell Infection



Source: Cleveland Clinic Deck

Viral Binding Results In Lung Damage



Source: Cleveland Clinic Deck

Risk Of ADE Can Be Mitigated By Antibody Therapies Through Fc Domain Modifications

Our consultants note that antibody-dependent enhancement (ADE) is less of a problem for antibody therapies as the Fc portion of the antibody can be muted to avoid ADE (by not binding immune cells).

Importantly, our consultants believe that a robust neutralizing antibody response is the best way to mitigate the risk. At this point, the biology of the virus is not sufficiently known to assess how to best modulate the immune response to dampen toxicity or activate beneficial downstream pathways that regulate cellular response (i.e., upregulate Th1 pathways without trigger Th2 response).

Different approaches have been explored, including mutating the Fc domain and modifying the Fc domain, as antibodies lacking a functional Fc domain should have a reduced risk of ADE, but at the cost of a potentially shortening their half-life.

However, this point is controversial as Regeneron opted to not mutated the Fc domain as their preclinical data suggests that highly potent neutralizing antibodies have low risks of ADE.

SARS-CoV-2 Undergoes Slow Genetic Drift Thereby Unlikely To Outpace Antibody Development

Based on analyses of SARS-C0V-2, from the Bedford lab at Nextstrain, there are an average of ~25 mutations per year, which we note is roughly in line with other coronavirus strains.

A recent study out of Wuhan, China that examined samples from 11 patients claims to have detected 33 strains of SARS-CoV-2 (including 19 novel strains), which showed varying viral loads when tested in vitro. Importantly, the study has not yet been peer-reviewed, but also suggests that select viral mutations may confer additional pathogenicity.

But the mutation rate of SARS-CoV-2 appears considerably slower than the flu and is not expected to drastically shift within each season. More so, research has shown that the native S protein is metastable with an energy barrier preventing it from undergoing a major conformational change. While the protein does mutate, it is stable enough to be targeted with an antibody. Therefore, we think the mutations are unlikely to outpace antibody therapy development.

D614G Variant Of SARS-CoV-2 Is Potentially Associated With Greater Infectivity And Higher Viral Loads, But Is Also Unlikely To Affect Antibody Therapy Development

A recent study by Korber et al. published in *Cell* in early July showed that a SARS-CoV-2 variant carrying the spike protein amino acid change D614G has replaced D614 as the most prevalent form in the global pandemic. The researchers revealed a recurrent pattern of G614 increase at multiple geographic levels: national, regional and municipal by dynamically tracking the variant frequencies.

Importantly, the highly statistically significant consistency of this pattern suggests that the G614 variant may have a fitness advantage. The article found that the G614 variant grows to higher titer as pseudotyped virions and is associated with lower RT-PCR cycle thresholds, suggesting higher viral loads in patients without increasing disease severity.

Of note, factors other than the higher infectiousness of the G614 variant, such as epidemiological factors, could also account for its rapid spread and persistence. But we think these new findings are important for advancing our understanding of the infectivity of this virus and support continuing surveillance of spike mutations to inform antibody therapy and vaccine development.

Importantly, D614G is not located in the RBD of the spike protein. Rather, it is in the interface between the individual spike protomers that stabilize its trimeric form on the virion surface. Therefore, it is thought that D614G is unlikely to drastically affect the immunogenicity of RBD epitopes, which are important for antibody neutralization.

Notably, a few studies by Korber et al. and others reported that the antibodies generated from natural infection with viruses containing either D614 or G614 could cross-neutralize, suggesting that it is not critical for antibody-mediated virus neutralization.

More so, the specific effect of D614G on the entry and fusion of the spike function is unknown. Therefore, the impact of this mutation on therapeutic entry inhibitors is still unknown. So far, no evidence has been found that D614G would interfere with drugs designed to disrupt spike binding with ACE2 or modulate downstream processes such as endosomal acidification.

Antibody Cocktails Are More Promising As They Are Designed To Reduce The Risks Of ADE And Viral Escape

Antibody cocktails combine individual neutralizing antibodies that simultaneously bind to non-competitive locations on the viral spike protein. Recall, antibody cocktails of two or three neutralizing antibodies have been successfully developed to treat MERS and Ebola.

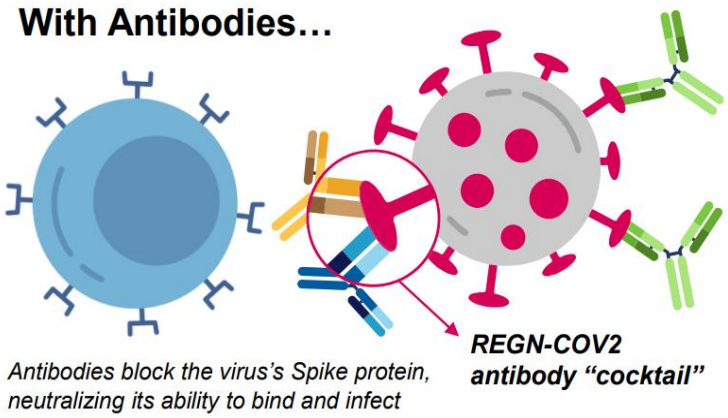
An antibody cocktail is expected to produce a more potent and durable neutralization response than individual antibodies as viral escape would presumably require simultaneous viral mutations at two distinct genetic sites. This is an unlikely event.

A few recent preclinical studies showed that the combination of individual neutralizing antibodies targeting non-competitive locations on the viral spike protein induced more potent neutralization responses than individual antibodies or combinations of antibodies

that require binding to the same epitope. Recall, potent antibody response is believed to be crucial for reducing the risk of antibody-dependent enhancement (ADE).

Importantly, preclinical data also demonstrated that antibody cocktails may prevent rapid mutational escape seen with individual antibodies. Encouragingly, our consultants are supportive of the antibody cocktail approach, which can potentially improve the potency and reduce the risk of ADE or viral escape.

Antibody Cocktail Binds To Multiple Sites Of S Protein To Improve Potency And Prevent Viral Escape



Source: Regeneron

Most Antibody Therapies Target The RBD Of S Protein While Antibodies Targeting The N-Terminal Domain (NTD) Offer A Promising Alternative For Cocktail

During infection, the S protein is cleaved into the N-terminal S1 subunit and C-terminal S2 subunit by host proteases and undergo conformational changes to enable membrane fusion with the host cell. The S1 subunit consists of the receptor binding domain (RBD) and the N-terminal domain (NTD).

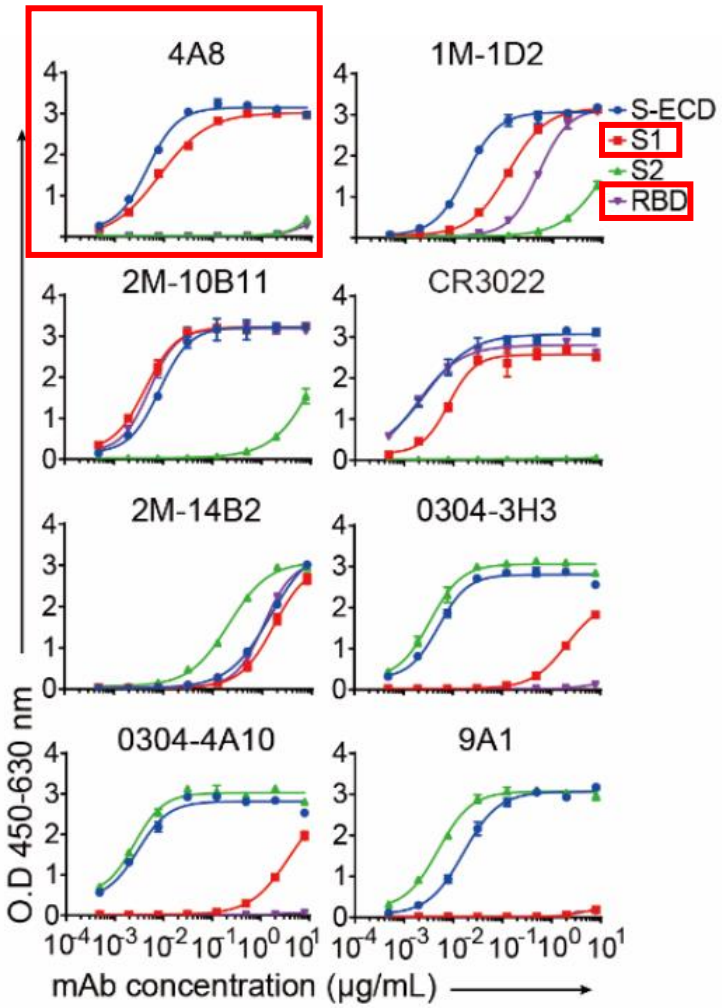
As the SARS-CoV-2 spike protein binds to the ACE2 receptor through the receptor-binding domain (RBD), it is not surprising that most neutralizing antibodies bind to the RBD of the S protein to prevent the virus from binding to ACE2.

A recent study by Chi et al. published in Science also showed that an antibody, 4A8, that binds to the NTD of the S protein also exhibited high neutralization potency against both authentic and pseudotyped SARS-CoV-2 in vitro. The study showed that 4A8 neutralized authentic SARS-CoV-2 with a median EC50 of 610 ng/ml in Vero-E6 cells. Importantly, this study showed that binding affinities against RBD do not correlate fully with neutralizing abilities.

In turn, the S1-targeting mAb 4A8 does not block the interaction between ACE2 and the S protein. Instead, it recognizes a vulnerable epitope of the NTD of the S protein and neutralizes the virus entry likely by restraining the conformational changes of the S protein. In that way, this might be a different mechanism from receptor binding inhibition.

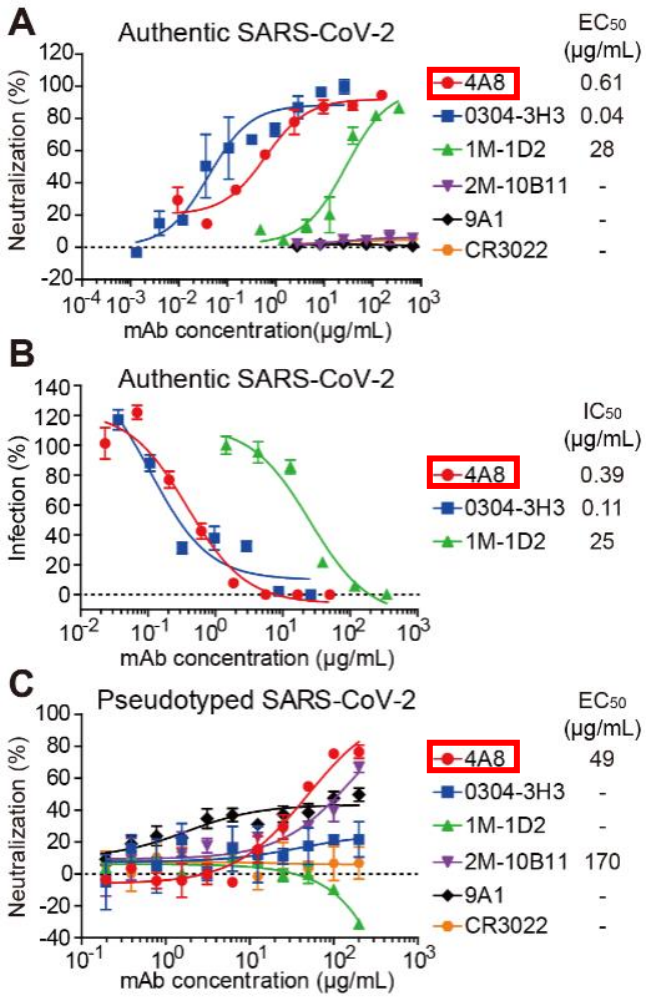
Therefore, combining NTD-targeting antibodies with RBD-targeting antibodies offers an alternative cocktail strategy to avoid viral escape.

4A8 Binds To S1 But Does Not Bind To RBD Of The S Protein



Source: Chi et al., *Science* 2020

4A8 Exhibited High Neutralization Potency Against Both Authentic And Pseudotyped SARS-CoV-2



Source: Chi et al., *Science* 2020

Multiple Players Are In The Pursuit – Lots Of Data To Read Out In The Next Few Months

Several companies, such as Eli Lilly/Abcellera/Junshi, Regeneron, Vir/GSK, AstraZeneca, Celltrion, Amgen, BeiGene/Singlomics, and AbbVie, are currently in the race for developing neutralizing antibodies against SARS-CoV-2 for prophylactic and therapeutic uses. Eli Lilly/Abcellera/Junshi and Regeneron have advanced their programs into human trials in early June. Both have quickly advanced into Phase 3 studies. Celltrion started its Phase 1 in mid-July. AstraZeneca commenced its Phase 1 testing in late August. Vir/GSK also started a Phase 2/3 study in late August.

Preliminary safety data from Lilly/Junshi's Phase 1 trial of JS016 is encouraging. Interim neutralizing antibody and biomarker data from Regeneron's program are expected in late September. Vir/GSK expect to release initial results from VIR-7831's Phase 2/3 by YE:20. We await more clinical data that is expected to read out from multiple trials in the next few months to further evaluate the profile of antibody therapies.

Multiple Antibody Therapy Programs Will Have Data By Early Fall – We Think The Cocktail Strategy Is More Promising

Company	Approach	Candidate	Target	Regimen	IC_{50}	Fc Domain Modification	Platform/ Source	Clinical Status	Catalyst/Milestone
Eli Lilly/ AbCellera/ Junshi	Single antibody and antibody cocktail	LY-CoV555 (Human IgG1)	Spike protein	IV	NA	LALA mutation being investigated	DARPA Pandemic Prevention Platform	Ph1 in hospitalized pts started on 6/1 BLAZE-1 Ph2 in mild to moderate pts started on 6/17 BLAZE-2 Ph3 prevention trial started on 8/3	To report efficacy data from BLAZE-1 in Q4:20 To start a Ph3 treatment trial in the coming weeks
		JS016	RBD	IV	36 ng/ml	LALA mutation to minimize FcγR activation and Fc -mediated toxicity	Convalescent COVID-19 patients	Ph1 in healthy subjects started on 6/8 and reported positive topline safety data with no DLE as of 7/12	To start a Ph1b trial in non-severe COVID-19 patients and Ph2/3 trials in severe and critical patients soon
		A third candidate	SARS-CoV-2 (not spike protein	NA	NA	NA	NA	NA	Might be combined with LY-CoV555 and/or JS016
Regeneron	Two-antibody cocktail	REGN-COV2 (REGN10987 + REGN10933)	Spike protein	IV for treatment, SC for prevention	37-42 pM	No modification	Convalescent COVID-19 patients or genetically-humanized mice (VelociMab)	The first 2 adaptive Ph1/2/3 treatment studies in hospitalized and non-hospitalized patients started on 6/11 and moved to the Ph2/3 on 7/6 Ph3 prevention study started on 6/30	To report initial data from the treatment trials in September
Celltrion	Single antibody and two-antibody cocktail	CT-P59	SARS-CoV-2	NA	NA	NA	Convalescent COVID-19 patients	Ph1 in healthy volunteers started in UK in mid July; Global Phase 1 in mild COVID-19 patients started in August	To complete Ph1 in healthy volunteers by Q3:20; To to start further global Phase 2 and 3 prevent and treatment trials soon and have pivotal data by YE:20
Vir/GSK	Single antibody	VIR-7831/ VIR-7832 (Human IgG1)	SARS-CoV-2	NA	79 ng/ml for S309	One mutation to extends the half-life and potentially a second mutation to enhance binding to activating receptors	Modified from S309, human IgG1 isolated from a convalescent SARS patient	Ph2/3 of VIR-7831 started in late August	To report initial data from Ph2/3 of VIR-7831 by YE:20 and complete data in Q1:21 To start a Ph2 of VIR-78312 in H2:20. Both will be tested as prophylaxis and treatment To provide potentially early access to the antibody treatment as soon as H1:21.
Amgen/ Adaptive	NA	NA	NA	NA	NA	NA	Convalescent COVID-19 patients	NA	NA
AstraZeneca/ Vanderbilt Univ.	Two-antibody cocktail	AZD7442 (AZD8895 +AZD1061)	SARS-CoV-2	IV and IM	15-4,000 ng/mL	YTE mutation for half-life extension	Convalescent COVID-19 patients or genetically-humanized mice via YTE technology platform	Ph1 started in late August	Likely to have initial data in Q4:20
BeiGene/ Singlomics	Single antibody and a potential two-antibody cocktail	DXP-593 and DXP-604	SARS-CoV-2	NA	1.2 ng/ml and 15 ng/mL	NA	Convalescent COVID-19 patients	NA	To start a placebo-controlled Ph1 trial in September; To start a global Phase 1/2 trial in mild-to-moderate COVID-19 by early October
AbbVie/ Harbour/ Utrecht U/ Erasmus Med Center	Single antibody	47D11	SARS-CoV-2		61 ng/ml	NA	From genetically-humanized mice (Harbour's H2L2 Harbour mice)	Not started yet	NA

Source: Cowen and Company, company reports

Lilly/AbCellera And Lilly/Junshi Entered The Clinic First With Two Separate Antibody Candidates – Initial Phase 1 Safety Results Encouraging And More Data Expected In The Fall

Lilly/AbCellera have commenced Phase 3 testing with LY-CoV555 after partnering to develop a therapeutic by characterizing neutralizing antibodies obtained from one of the first U.S. patients who recovered from COVID-19.

Separately, JS016 is being co-developed by Junshi and Lilly, with Junshi leading development in Greater China and Lilly having exclusive rights in the rest of the world.

Eli Lilly/AbCellera/Junshi Commenced The First Phase 1 Studies

Company	Approach	Candidate	Target	Regimen	IC_{50}	Fc Domain Modification	Platform/ Source	Clinical Status	Catalyst/Milestone	Manufacturing Capacity By 2020	Manufacturing Capacity By 2021
Eli Lilly/ AbCellera/ Junshi	Single antibody and antibody cocktail	LY-CoV555 (Human IgG1)	Spike protein	IV	NA	LALA mutation being investigated	DARPA Pandemic Prevention Platform	Ph1 in hospitalized pts started on 6/1 BLAZE-1 Ph2 in mild to moderate pts started on 6/17 BLAZE-2 Ph3 prevention trial started on 8/3	To report efficacy data from BLAZE-1 in Q4:20 To start a Ph3 treatment trial in the coming weeks	Several hundred thousand doses by YE:20	Not disclosed
		JS016	RBD	IV	36 ng/ml	LALA mutation to minimize FcγR activation and Fc -mediated toxicity	Convalescent COVID-19 patients	Ph1 in healthy subjects started on 6/8 and reported positive topline safety data with no DLE as of 7/12	To start a Ph1b trial in non-severe COVID-19 patients and Ph2/3 trials in severe and critical patients soon		
		A third candidate	SARS-CoV-2 (not spike protein	NA	NA	NA	NA	NA	Might be combined with LY-CoV555 and/or JS016		

Source: Cowen and company, company reports

LY-CoV555 Entered Phase 1 In June

Their first candidate, LY-CoV555, targets the SARS-CoV-2 spike protein. On June 1st, Eli Lilly and AbCellera started the world's first Phase 1 randomized, placebo-controlled human trial in hospitalized patients.

BLAZE-1 Phase 2 Treatment Study Started In Mid-June – Efficacy Data Expected In Q4:20

In mid-June, Lilly initiated the Phase 2 BLAZE-1 study (n=400) of LY-CoV555 (IV injection) to assess efficacy in recently diagnosed mild-to-moderate COVID-19 patients based on data from the Phase 1 trial (not released).

Lilly plans to release preliminary efficacy data from BLAZE-1 in Q4:20 and start a registrational study of LY-CoV555 in recently diagnosed COVID-19 patients in both the ambulatory and hospitalized settings in the coming weeks.

Lilly Initiated BLAZE-2 Phase 3 Prevention Study In August

In early August, Lilly announced the initiation of the BLAZE-2 Phase 3 prevention trial of LY-CoV555 (IV injection) in residents and staff at long-term care facilities in the US (nursing homes and assisted living facilities). This trial is being run jointly with the

National Institute of Allergy and Infectious Diseases (NIAID) with a target enrollment of up to 2,400 at long-term care facilities.

The study will evaluate the efficacy and safety of LY-CoV555 for the prevention of SARS-CoV-2 infection and COVID-19, testing whether a single dose of LY-CoV555 reduces the rate of SARS-CoV-2 infection through 4 weeks, as well as complications of COVID-19 through 8 weeks.

We note that there is an urgent need for therapies to prevent COVID-19 in the vulnerable population at long-term care facilities. According to recent data from the CDC, community transmission of COVID-19 has been associated with rapid spread and high morbidity and mortality among older adults in long-term skilled nursing facilities.

Lilly's 2nd Antibody (JS016/LY-CoV016) Partnered With Junshi Started A Chinese And U.S. Phase 1 Studies

Lilly's second antibody therapy candidate, JS016 (aka CB6, LY-CoV016), also targets the SARS-CoV-2 spike protein. On June 7th, Eli Lilly's partner, Junshi Biosciences, started a Chinese Phase 1 randomized, double blind, placebo-controlled, study in healthy volunteers in China. The drug also entered the clinic in the US in Q2.

The Chinese trial is testing the safety and tolerability of single dose JS016 IV injection in 40 healthy subjects. This trial completed its enrollment and dosing in all 40 subjects in 4 dosing groups on July 12th. Encouragingly, no dose-limiting event (DLE) has been observed.

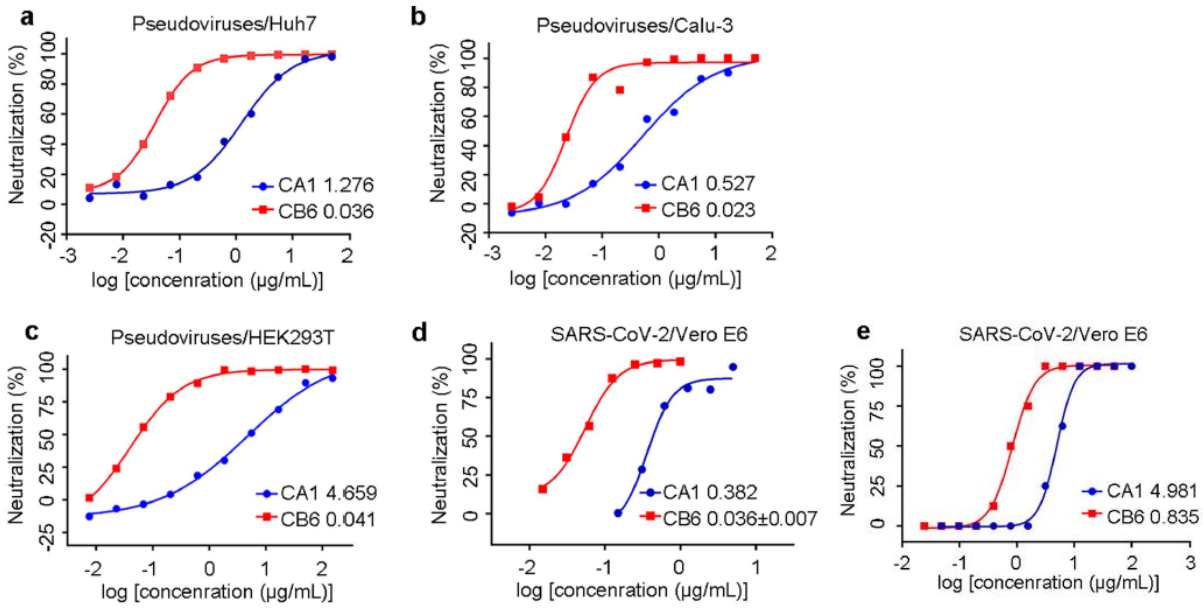
Both LY-CoV555 And JS016 Target The RBD – Fc Portion Was Modified To Reduce Risk Of Acute Lung Injury

JS016 (CB6) recognizes epitopes in SARS-CoV-2 RBD that overlap with angiotensin converting enzyme 2 (ACE2)-binding sites, thereby directly blocking virus/receptor interactions. The Fc domain of JS016 was modified with LALA mutation to minimize FcγR activation and reduce the risk of Fc-mediated toxicity. The same, LALA mutation, is also being investigated for LY-CoV555.

Data In Rhesus Macaques Shows Solid Potency And Reduces Viral Loads

A recent study by Shi et al. published in *Nature* showed that JS016 was effective against COVID-19 in rhesus macaques in both prophylactic and therapeutic settings. Data showed that CB6 potently neutralized SARS-CoV-2 with an IC50 of 36 ± 7 ng/ml in three tested cell lines (Huh7, Calu-3 and HEK293T cells). Importantly, CB6 reduced virus levels by ~3 logs in rhesus monkeys when given one day after infection. When given one day before viral challenge, CB6 was able to keep viral load at ≤ 103 RNA copies/ml, showing strong protection as prophylaxis.

CB6 Can Effectively Neutralize SARS-CoV-2 Pseudovirus Or Live SARS-CoV-2 Virus *In Vitro*



Source: Shi et al., *Nature* 2020

Companies Are Planning To Initiate Phase 2 and Phase 3 Studies In Several Subgroups

JS016 is the first COVID-19 antibody to enter the clinic in China and the second globally behind LY-CoV555. Lilly will initiate a Phase 2 proof of concept study to assess efficacy for both LY-CoV555 and JS016 in vulnerable populations if the Phase 1 trials demonstrate an adequate safety profile.

Lilly/Junshi plan to initiate a Phase 1b trial of JS016 in non-severe COVID-19 patients and Phase 2/3 trials in severe and critical patients soon. The companies also plan to study preventative potential of JS016 in the high-risk population, such as health-care workers and the elderly.

Lilly's third antibody therapy candidate acts on a different part of the virus and will most likely be tested in combination with one or both other candidates.

Of note, Lilly also plans to test the combination of JS016 with LY-CoV555 in case such a combination is needed to combat viral resistance.

Large Scale Manufacturing Started In June For LY-CoV555 – Several Hundreds Of Thousand Doses Possible By YE:20

Lilly also announced on June 1st that it started large scale manufacturing with the goal of having several hundred thousand doses available by the end of the year. Lilly is working to rapidly scale up production through internal manufacturing and partnerships.

Regeneron Has An Advanced Antibody Program – Initial Data From Treatment Studies Expected In Late September

Regeneron's Antibody Cocktail Is In Pivotal Studies For Both Treatment And Prevention

Company	Approach	Candidate	Target	Regimen	IC_{50}	Fc Domain Modification	Platform/ Source	Clinical Status	Catalyst/Milestone	Manufacturing Capacity By 2020	Manufacturing Capacity By 2021
Regeneron	Two-antibody cocktail	REGN-COV2 (REGN10987 + REGN10933)	Spike protein	IV for treatment, SC for prevention	37-42 pM	No modification	Convalescent COVID-19 patients or genetically-humanized mice (VelociMab)	The first 2 adaptive Ph1/2/3 treatment studies in hospitalized and non-hospitalized patients started on 6/11 and moved to the Ph2/3 on 7/6 Ph3 prevention study started on 6/30	To report initial data from the treatment trials in September	70k-300k potential treatment doses or 420k- 1,300k prevention doses as early as end of summer	1M doses per month by FY21

Source: Cowen and company, company reports

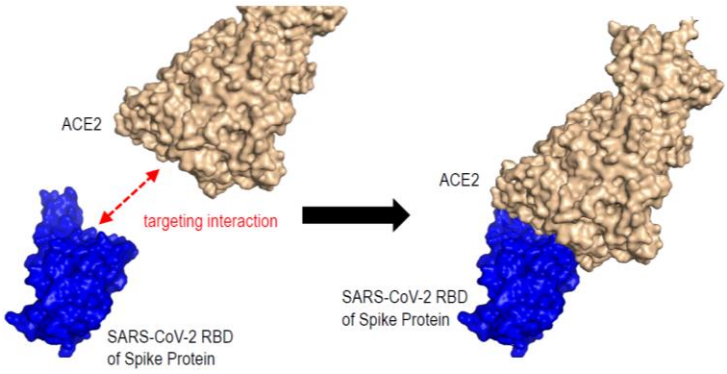
Regeneron's antibody therapy program entered the clinic shortly behind Lilly's program. But Regeneron's program is more advanced now as its cocktail of two-antibodies, REGN-COV2, is in Phase 2 development as a therapeutic and in Phase 3 for prophylaxis.

Regeneron uses humanized VelocImmune mice and blood samples from recovered COVID-19 patients to identify antibodies targeting multiple different regions of the critical receptor-binding domain (RBD) of the SARS-CoV-2 spike protein.

REGN-COV2 Is Composed Of Two Antibodies That Bind Two Distinct Epitopes On The RBD

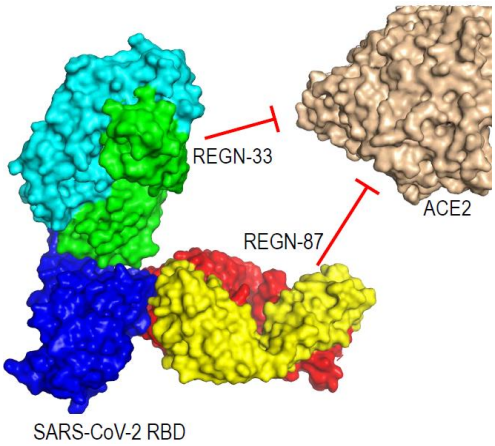
Regeneron is evaluating REGN-COV2, its combination of two antibodies REGN10933 and REGN10987, that bind to 2 distinct epitopes on the RBD of SARS-CoV-2 spike protein with high potency.

SARS-CoV-2 Spike Protein Binds To ACE2 Receptors To Initiate Cell Infection



Source: Regeneron

Antibody Cocktail Potently Blocks Infection And Avoids Mutant Escape



Source: Regeneron

REGN-COV2 Is Being Developed For Four Different Populations

Regeneron is developing this regimen as prophylaxis or therapeutic for four separate study populations:

1. hospitalized COVID-19 patients,
2. non-hospitalized symptomatic COVID-19 patients,
3. uninfected people in groups that are at high-risk of exposure, and
4. uninfected people with close exposure to COVID-19.

Regeneron has already started the first two adaptive Phase 1/2/3 studies in hospitalized and non-hospitalized patients with COVID-19.

Regeneron Commenced Enrollment In The Phase 2/3 Treatment Studies In Hospitalized And Non-Hospitalized Patients Based On IDMC Review Of The Phase 1 Data – Initial Virology And Biomarker Data Expected In Late September

On June 11, Regeneron dosed the first patients in the hospitalized study (n=1860, the primary completion in March 2021). On June 16th, Regeneron dosed the first patients in the non-hospitalized study (n=1054) with the primary completion anticipated in November 2020. The Phase 1 will assess safety of both the low and high doses of REGN10987 + REGN10933 (IV single dose).

The Phase 2 will assess clinical endpoints. Data from the Phase 1 and Phase 2 parts are expected to inform the Phase 3 endpoints and sample size.

On July 6, Regeneron announced that REGN-COV2 has moved into the Phase 2/3 portion of two adaptive Phase 1/2/3 trials, following a positive review from the Independent Data Monitoring Committee (IDMC) of REGN-COV2 Phase 1 safety results in an initial cohort of 30 hospitalized and non-hospitalized patients with COVID-19.

Of note, the two Phase 2/3 treatment trials in hospitalized and non-hospitalized patients with positive COVID-19 diagnosis are planned to be conducted at ~150 sites in the US, Brazil, Mexico and Chile. The trials will evaluate virologic and clinical endpoints, with preliminary data expected later this summer.

Regeneron plans to report initial virology and biomarker results from the treatment trials in late September 2020.

Enrollment Of The Phase 3 Prevention Study Commenced

On June 30, Regeneron also announced the initiation of the world's first Phase 3 prevention study (n=2000) to evaluate the efficacy and safety of REGN-COV2 (REGN10933+REGN10987) SQ injections compared to placebo in preventing asymptomatic or symptomatic infection (confirmed by RT-qPCR). This Phase 3 trial is being conducted at ~100 sites to evaluate the cocktail's ability to prevent infection among uninfected people who have had close exposure to a COVID-19 patient, and is being run jointly with the National Institute of Allergy and Infectious Diseases (NIAID), part of the National Institutes of Health (NIH).

In particular, the study is randomizing asymptomatic healthy adults with sustained exposure (at least 48 hours) to an infected individual 96 hours of collection of the positive SARS-COV-2 diagnostic test.

Regeneron Has Multiple Phase 2/3 Trials Ongoing For Treatment And Prophylaxis With Data Expected By Late September

Drug	Trial Name	Arms	n	Primary Endpoint	Start Date	Est. Primary Completion	Status
REGN-COV2	Phase 1/2/3 for COVID-19 Treatment of Hospitalized Patients	REGN10933+REGN10987 IV vs pbo	2,970	Ph1: Safety, Ph2/3: Time-weighted average change in viral shedding, % w/ ≥1-point improvement on a 7-Point Ordinal Scale in clinical status	6/11/2020	Jan. 2021	Ph2 Recruiting
REGN-COV2	Phase 1/2/3 for COVID-19 Treatment of Non-hospitalized Patients	REGN10933+REGN10987 IV vs pbo	2,104	Ph1: Safety, Ph2: Time-weighted average change in viral shedding, Ph3: % of ≥1 COVID-19 visit	6/16/2020	Dec. 2020	Ph2 Recruiting
REGN-COV2	Phase 3 for COVID-19 Prevention	REGN10933+REGN10987 SC vs pbo	2,000	% of positive COVID-19 infection based on RT-qPCR, Safety	7/13/2020	Jun. 2021	Recruiting

Source: Regeneron, *clinicaltrials.gov,* Cowen and Company

Regeneron Did Not Modify The Fc Domain As Preclinical Data Did Not Show Risk Of ADE Because Of The Potency Of The Antibodies

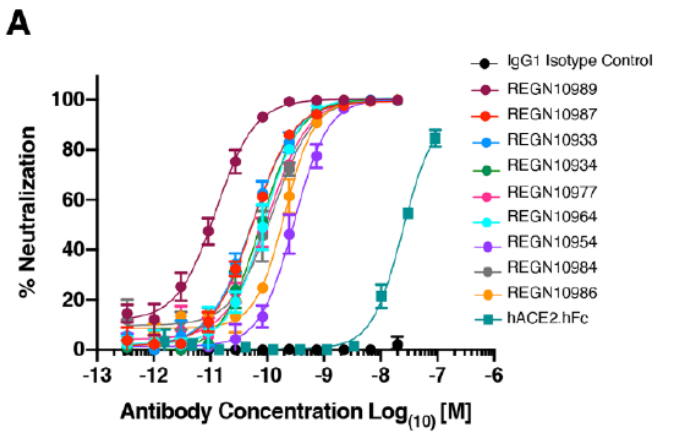
Interestingly, Regeneron reported that the Fc domain of the antibody candidates was not modified as the company has not seen an elevated risk for ADE and is not concerned about the Fc-mediated toxicity.

Study In *Science* Highlights Importance Of A Dual Antibody Cocktail Approach

A recent study by Baum et al. published in *Science* showed that Regeneron has identified several antibody candidates and combinations that showed solid potency in several assays including the pVSV-SARS-CoV-2-S(mNeon) neutralization in the human lung epithelial Calu3 cell line, neutralization of replicating VSV-SARS-CoV-2-S in Vero cells, and neutralization of SARS-CoV-2 in VeroE6 cells.

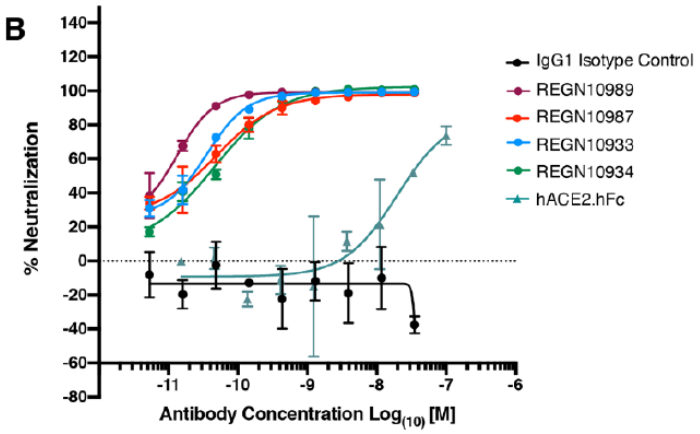
Notably, data showed that both antibodies were highly potent: REGN10987 (IC_{50} = 4.21 × 10^{-11} M) and REGN10933 (IC_{50} = 3.74 × 10^{-11} M).

Antibody Candidates Showed Promising Neutralization Potency In Vero Cell Line



Source: *Science*, Regeneron

Antibody Candidates Showed Promising Neutralization Potency In Calu3 Cell Line



Source: *Science*, Regeneron

Antibody Cocktail Overcomes Potential For Resistance Mutations

A separate study by Hansen et al. recently published in *Science* reported that the combination of REGN10987+REGN10933 was more potent relative to other cocktails since these two antibodies bind to 2 distinct epitopes on the RBD of SARS-CoV-2 spike protein. For combination of antibodies that require binding to the same epitope, such as REGN10989+REGN10934, a single amino acid substitution was enough to ablate neutralization of the cocktail.

The data also showed that the antibody cocktail (REGN10989+REGN10934) blunted the emergence of VSV-SARS-CoV-2-S viral mutants. This is because escape would presumably require the simultaneous viral mutation at two distinct genetic sites, which is unlikely to occur.

Regeneron's Antibody Cocktail Program Is Differentiated And Supported By Robust Preclinical Data

We think this cocktail approach should differentiate Regeneron vs many competitors as viral escape/resistance has been seen with highly potent antibodies in animal models. In comparison, most of other competing programs are only developing a single antibody therapy at the present time.

Of note, Regeneron's program is the most advanced antibody program. Although Lilly and Celltrion also announced plans to potentially test an antibody cocktail, AstraZeneca is the only other company that entered the clinic for its antibody cocktail candidate at the present time. AstraZeneca's program is at least 2-3 months behind Regeneron as AstraZeneca initiated a Phase 1 trial of AZD7442 (AZD8895 + AZD1061) in preventing and treating COVID-19 in mid-August.

Results Of The Escape Study Showed REGN-COV2 Did Not Result In Outgrowth Of Escape Mutants

Passage	Antibody concentration μg/ml						
P1	50	10	2	0.4	0.08	0.016	No Ab
REGN10989	15%	30%	30%	30%	30%	≥ 90%	≥ 90%
REGN10987	0%	15%	50%	≥ 90%	≥ 90%	≥ 90%	≥ 90%
REGN10933	0%	0%	5%	20%	≥ 90%	≥ 90%	≥ 90%
REGN10934	2-5%	2-5%	30%	50%	≥ 90%	≥ 90%	≥ 90%
REGN10989 + REGN10987	0%	0%	0%	0%	20%	≥ 90%	≥ 90%
REGN10989 + REGN10934	2-5%	2-5%	20%	20%	50%	≥ 90%	≥ 90%
REGN10987 + REGN10933	0%	0%	0%	0%	60%	≥ 90%	≥ 90%
IgG Isotype Control	≥ 90%	≥ 90%	≥ 90%	≥ 90%	≥ 90%	≥ 90%	≥ 90%
P2	50	10	2	0.4	0.08	0.016	No Ab
REGN10989	≥ 90%	≥ 90%	≥ 90%	≥ 90%	≥ 90%	≥ 90%	≥ 90%
REGN10987	5%	40%	≥ 90%	≥ 90%	≥ 90%	≥ 90%	≥ 90%
REGN10933	70%	80%	≥ 90%	≥ 90%	≥ 90%	≥ 90%	≥ 90%
REGN10934	80%	≥ 90%	≥ 90%	≥ 90%	≥ 90%	≥ 90%	≥ 90%
REGN10989 + REGN10987	0%	0%	0%	0%	0%	0%	50%
REGN10989 + REGN10934	≥ 90%	≥ 90%	≥ 90%	≥ 90%	≥ 90%	≥ 90%	≥ 90%
REGN10987 + REGN10933	0%	0%	0%	0%	0%	60%	≥ 90%
IgG Isotype Control	≥ 90%	≥ 90%	≥ 90%	≥ 90%	≥ 90%	≥ 90%	≥ 90%

Source: *Science*, Regeneron, Cowen and Company

Regeneron's Subcutaneous Regimen In The Prevention Setting Is Also Favorable

Regeneron is the only company with a SQ formulation at the present time

Notably, Regeneron is testing a subcutaneous formulation (SQ) of its REGN-COV2 cocktail in the prevention setting. It is the only SQ regimen among all antibody therapy programs at the present time.

Preclinical Data Shows Robust Data Both As Prophylaxis and Therapeutic In Rhesus Macaques And Hamsters

Importantly, Regeneron reported preclinical data of REGN-COV2 in early August, showing the cocktail is effective as prophylaxis and as treatment in rhesus macaques and hamster models. Detailed data was published on *bioRxiv* (not peer reviewed).

Notably, the ability of REGN-COV2 prophylaxis (50mg/kg, 25mg/kg of each antibody dosed 3 days prior to virus challenge) to protect against SARS-COV-2 viral replication (as measured by sgRNA) in this study matches or exceeds the efficacy seen in vaccine studies that evaluated the same animal models including Moderna's mRNA-1273, Sinovac's PiCoVacc, JNJ's adenovirus serotype 26 (Ad26), Inovio's INO-4800, and AstraZeneca/Oxford's ChAdOx1. In addition, treatment with REGN-COV2 at 1-day post-infection (25mg/kg or 150mg/kg) demonstrated accelerated reduction of upper airway virus load in rhesus macaques whereas Gilead's Veklury (remdesivir) showed no difference in nasal viral RNA levels (viral load was only reduced in lower airways).

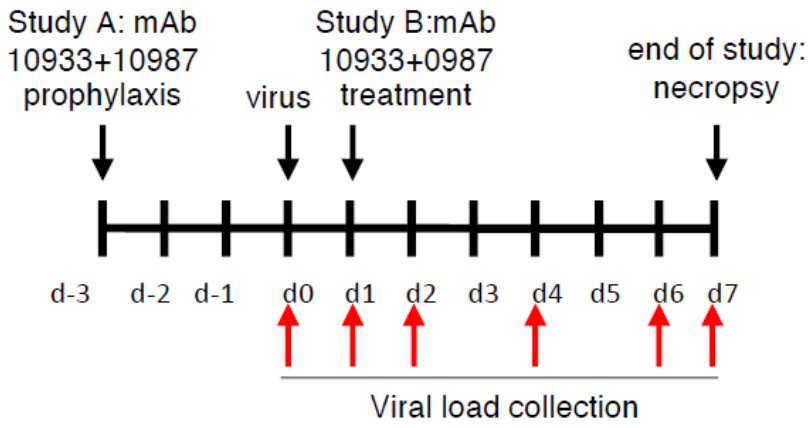
REGN-COV2 Effective In Both Mild And Severe Models Corresponding To Pre- And Post-Exposure Settings

Regeneron's antibody cocktail appears effective in both mild and severe models if given prophylactically or early post-exposure. The ability to show pathological lung benefits, reduction in viral loads in both nasopharyngeal and oral samples, and benefit on weight loss provide differentiation for REGN-COV2 and could lead to reduced spread in humans. The overall profile is promising in both mild and severe phenotypes (likely better in milder patients based on the data).

Importantly, the data showed a clean safety profile, without any signs of increased viral load and/or worsening of pathology in presence of antibodies at either high or low doses in the rhesus macaque model.

We note that the study was limited to REGN-COV2 dosed 3 days prior to virus challenge and 1-day post virus challenge with a short follow-up time (7 days post virus challenge). We think the study applies more to the pre- and post-exposure settings. .

Preclinical Study Only Looked At A Limited Time Period Pre- And Post- Virus Challenge



Source: Baum et al., *bioRxiv* 2020, Regeneron

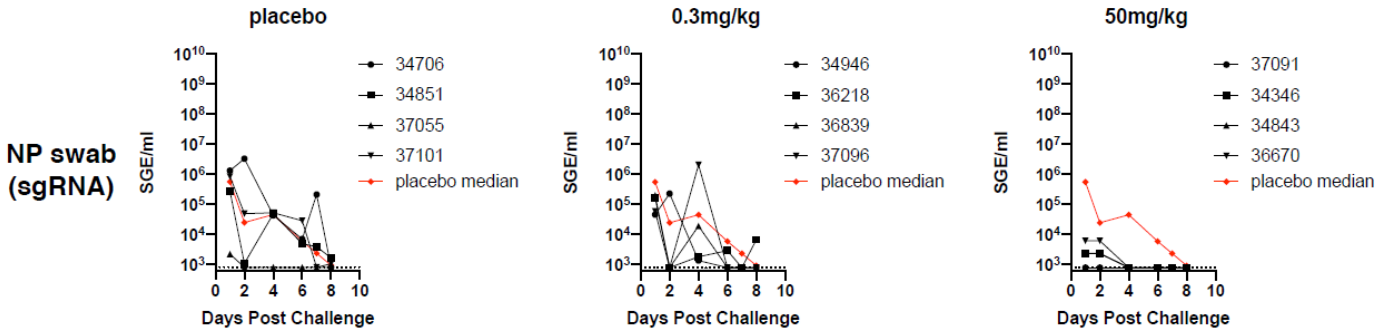
As background, rhesus macaques generally have a mild clinical course when infected with SARS-CoV-2 and may mimic mild human disease. On the other hand, golden hamsters suffer more severe disease, including rapid weight loss and significant lung pathology, and may more closely mimic severe disease in humans.

In the first prophylaxis cohort of the rhesus macaque model, REGN-COV2 was intravenously dosed at 50mg/kg (25mg/kg of each antibody) followed in 3 days by challenge with $1x10^5$ PFU of virus (intranasal + intratracheal routes). In the second prophylaxis cohort, animals were tested at different doses and a larger viral load; animals received a 0.3mg/kg dose or a 50mg/kg cocktail dose followed in 3 days by challenge with $1.05x10^6$ PFU of virus (a 10-fold higher viral challenge than in the first cohort).

In both cohorts, the 50mg/kg antibody cocktail dose protected against viral replication as can be seen in the subgenomic RNA (sgRNA) levels measured by nasopharyngeal swabs and bronchoalveolar lavage. The prophylactic effect was greatly diminished with

the 0.3mg/kg dose. Of note, sgRNA represents newly replicating virus, whereas genomic RNA (gRNA) may reflect remaining viral inoculum.

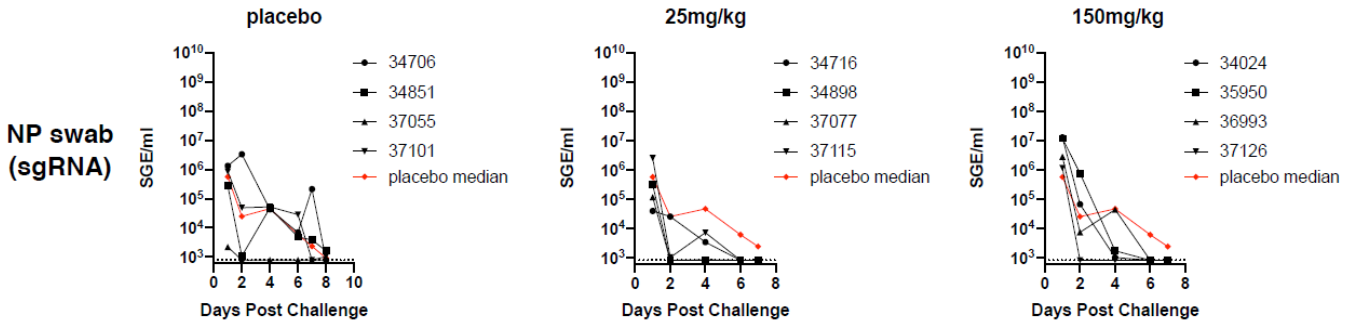
50mg/kg Prophylactic Dose of REGN-COV2 Protected Rhesus Macaques Against Infection with High Dose Viral Challenge



Source: Baum et al., *bioRxiv* 2020, Regeneron

To test REGN-COV2 as a treatment, 25mg/kg or 150mg/kg of the antibody cocktail was given to rhesus macaques one day post-infection with $1x10^6$ PFU of SARS-COV-2. The study demonstrated accelerated viral clearance at both doses compared to placebo as measured by both nasopharyngeal and oral swabs.

Both Treatment Doses of REGN-COV2 Given 1 Day Post-Infection Accelerated Viral Clearance In The Upper Airway

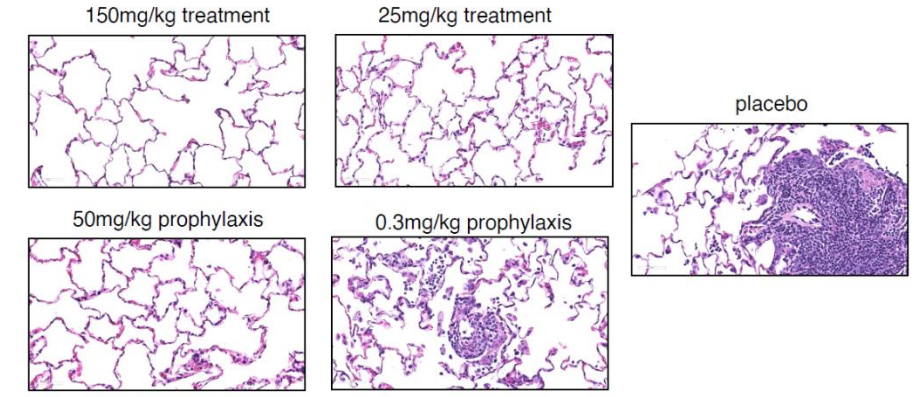


Source: Baum et al., *bioRxiv* 2020, Regeneron

REGN-COV2 Showed Improvement In Lung Pathology On Top Of Reduction In Viral RNA

Pathological analysis of lung tissue in infected animals also demonstrated that prophylactic and therapeutic use of REGN-COV2 greatly reduced virus induced pathology in rhesus macaques.

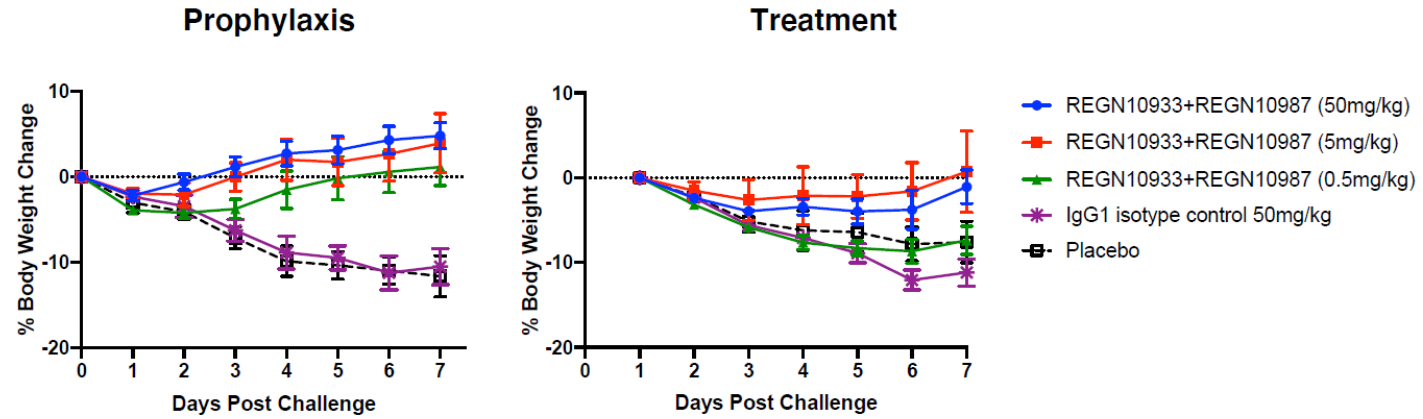
REGN-COV2 Reduced Virus Induced Lung Pathology In Rhesus Macaques



Source: Baum et al., *bioRxiv* 2020, Regeneron

In the hamster model, prophylactic REGN-COV2 given 2 days prior to viral challenge protected against weight loss and led to decreased pulmonary viral load at all doses tested (0.5, 5, and 50mg/kg). There was also a therapeutic benefit in hamsters treated with 5mg/kg and 50mg/kg one day post-infection.

Hamster Model (Mimics More Severe Disease) Demonstrates REGN-COV2 Protects Against Weight Loss As Both Prophylaxis and Treatment



Source: Baum et al., *bioRxiv* 2020, Regeneron

Several Key Questions Remain Despite Promising Preclinical Data

While the data is promising, these preclinical studies did not answer a few important questions, such as

1. How long a pre-exposure prophylaxis can provide protection against infection? Can it last for much longer than 3 days?
2. How early does a prophylactic dose must be given after a known exposure? Does it have to be the next day?
3. What is the long-term safety profile of antibody therapy?

Regeneron Is Ramping Up Its Manufacturing Capacity With $450M Funding From BARDA – Key Unknown Is Dosing

The other key questions are about manufacturing capacity and price. Presumably the therapeutic use can carry a higher price than use as prophylaxis. But then, prophylaxis dosing might be monthly with a lower than the single IV dose given for treatment. At this point, Regeneron has not disclosed much about the dosing in the Phase 3 in both prophylactic and therapeutic settings.

Regeneron began rapidly scaling up its manufacturing capacity at risk during the spring of 2020. In April, Regeneron moved its leading neutralizing antibodies into pre-clinical and clinical-scale cell production lines. In order to enable the US manufacturing site to produce large-scale quantities, Regeneron is working with the FDA to accelerate licensing of additional commercial products manufactured at its Ireland facility and free up capacity at the upstate NY facility to produce the cocktail.

REGN-COV2's preclinical development and preclinical/clinical manufacturing has been funded in part with federal funds from the Biomedical Advanced Research and Development Authority (BARDA). On July 7th, Regeneron announced that, as part of Operation Warp Speed, the company has signed a $450M agreement with the Biomedical Advanced Research and Development Authority (BARDA) and the Department of Defense Joint Program Executive Office for Chemical, Biological, Radiological and Nuclear Defense to manufacture and supply REGN-COV2.

The BARDA agreement supports manufacturing scale up so that the product could be made available immediately in the US if clinical trials are successful and the FDA grants Emergency Use Authorization (EUA) or product approval.

Regeneron Expects To Have Capacity To Deliver 1M+ Doses Per Month In FY21

Under the BARDA agreement, Regeneron expects to manufacture a fixed number of bulk lots beginning in the summer of 2020 and commence fill/finish and storage activities in Q3:20.

The ongoing REGN-COV2 clinical programs are evaluating multiple dosages and will help establish the exact number of potential treatment doses (estimated range of 70k to 300k) or prevention doses (estimated range of 420k to 1,300k).

We anticipate that Regeneron will have manufacturing capacity to deliver 1M+ doses per month in FY21.

Roche/Regeneron Entered Into A Global Collaboration To Increase Supply By 3.5x

In mid-August, Roche/Regeneron announced that the companies have entered into a global agreement to develop, manufacture, and commercialize REGN-COV2 for COVID-19 prevention and treatment. The term of this agreement will expire 7 years after the first commercial sale in EU unless the parties mutually agree to extend the term.

Under this agreement, Roche and Regeneron are obligated to dedicate and utilize the equivalent of at least 100K liters and at least 40K liters of annualized bioreactor capacity on a full-time campaign basis for the antibody production, respectively. This collaboration will allow the companies to deliver at least 3.5X as many doses of REGN-COV2 worldwide.

Notably, the companies will split the costs of clinical development. The global gross profits will be shared with Regeneron receiving approximately 50% - 60%, depending on the antibody products delivered by each party.

If the development of REGN-COV2 is successful, Regeneron will be responsible for the distribution in the US and Roche will handle the distribution for the rest of the world.

We think that this deal is encouraging as it is expected to dramatically expand the supply of REGN-COV2 to meet the potential demand. Of note, we estimate tens of millions of antibody doses may be needed globally in FY21.

Vir/GSK Directly Started A Phase 2/3 In August With VIR-7831 With Initial Data Expected By YE:20 – VIR-7832 Phase 2 To Follow

Vir is a biotechnology company focused on discovering and developing novel therapies to treat and prevent serious infectious diseases. Vir has assembled four innovative technology platforms that have the potential to cure or prevent infections from previously untreatable pathogens. Based on its focus and technologies, Vir is well-positioned to be a leader in the discovery and development of therapeutics for COVID-19. Vir has identified VIR-7831 and VIR-7832, antibody candidates that have a high affinity for the SARS-CoV-2 spike protein and started the Phase 2/3 trials of VIR-7831 in late August.

Vir/GSK Commenced The Phase 2/3 Study Of VIR-7831 In August – Initial Data Expected By YE:20 – Phase 2 Of VIR-7832 To Start In H2:20

Company	Approach	Candidate	Target	Regimen	IC_{50}	Fc Domain Modification	Platform/ Source	Clinical Status	Catalyst/Milestone	Manufacturing Capacity By 2020	Manufacturing Capacity By 2021
Vir/GSK	Single antibody	VIR-7831/ VIR-7832 (Human IgG1)	SARS-CoV-2	NA	79 ng/ml for S309	One mutation to extends the half-life and potentially a second mutation to enhance binding to activating receptors	Modified from S309, human IgG1 isolated from a convalescent SARS patient	Ph2/3 of VIR-7831 started in late August	To report initial data from Ph2/3 of VIR-7831 by YE:20 and complete data in Q1:21 To start a Ph2 of VIR-78312 in H2:20. Both will be tested as prophylaxis and treatment To provide potentially early access to the antibody treatment as soon as H1:21.	Hundreds of thousands of doses by YE:20	Tens of millions of doses by FY21

Source: Cowen and company, company reports

Antibodies From Survivors Can Help Drive Immunity And Therapeutic Activity

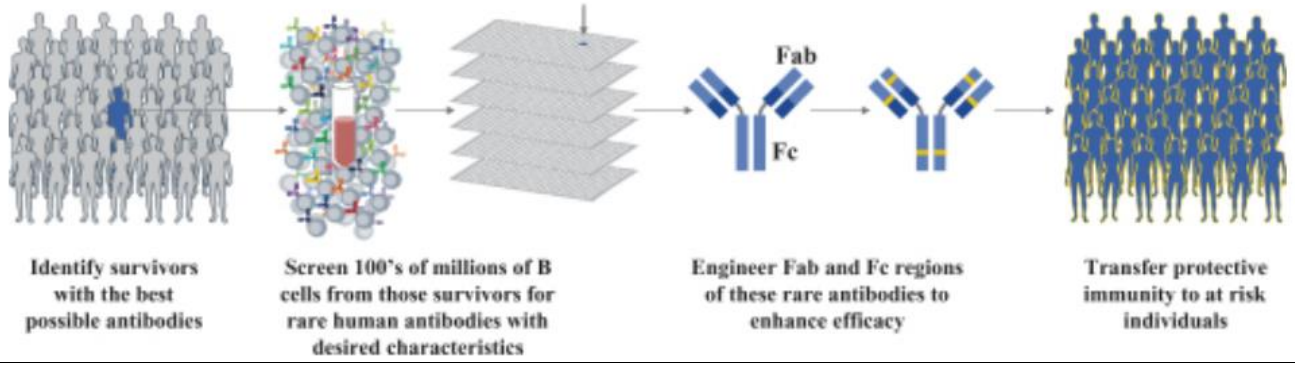
Vir is taking a unique approach to the generation of monoclonal antibodies (mAbs), which should produce candidates that have several advantages over antibodies that are generated naturally by the body. Vir first investigates a population of individuals who have been exposed to a certain infection and identifies those survivors who mount a particularly robust and effective antibody response. B cells (100's of millions) from these individuals are isolated and undergo high throughput screening in order to identify antibodies that have the characteristics necessary to be developed into effective medicines (e.g. those targeting multiple different pathogens, or those that bind to antigens highly conserved between infected individuals).

Once the desired antibodies are identified, the genes are cloned and the company optimizes both the antigen binding portion of the antibody (Fab domain) and the cellular

binding domain which attaches to proteins or receptors on effector cells (Fc domain). Engineering of the Fab domain to allow for the recognition of several epitopes could provide the mAb superior efficacy and coverage compared to the naturally occurring antibody. Through specific engineering of the Fc domain, the body's response to the mAb can be adjusted. As the Fc domain on the mAb can interact with various effector cells through their Fc receptors (FcRs), an engineered antibody can tune both the time of the immune response and help to govern downstream effector function.

Vir is striving to generate antibodies that cover a broad range of epitopes of an invading pathogen (or even multiple pathogens), with an extended half-life when compared to naturally occurring antibodies, and increased affinity binding, which could potentially reduce resistance mechanisms. In addition, as these antibodies are derived from humans and would be delivered directly to the recipient, the potential for self-reactivity will likely be reduced and the therapy should not rely on the recipient's own immune system in order to mount an effective response to the invading pathogen.

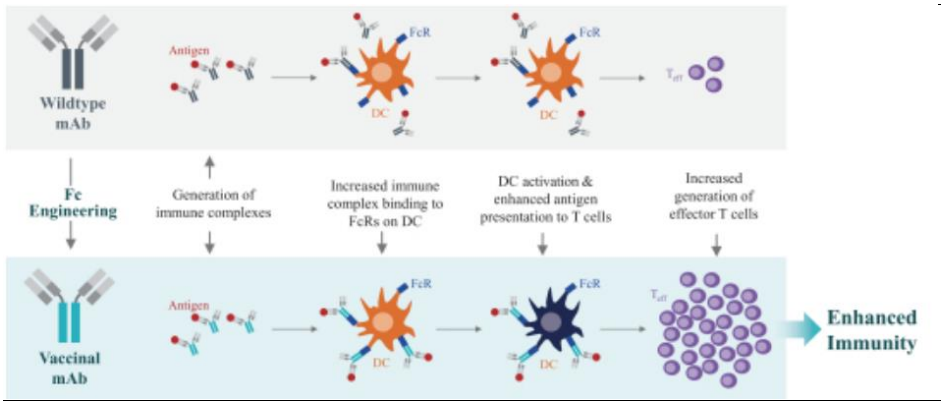
Vir's Approach To Optimal Antibody Production



Source: Vir Biotechnology

Vir is also hoping to use Fc engineering to convert the recovered "wild-type" antibodies into those that convey a vaccinal response for patients. The engineered Fc regions are designed to interact with dendritic cells (DCs), which can stimulate a T cell response to the targeted antigen. The generation of T cell effector and memory subtypes can then hopefully provide long-term protection and immunity to the invading pathogen.

Engineered Antibody Fc Regions Can Drive Increased DC Binding And Downstream T Cell Function, Providing A Vaccinal Immune Response



Source: Vir Biotechnology

GSK And Vir Form Partnership To Advance Efforts Against COVID-19

In April 2020, VIR and GSK (Scala) announced that the companies entered a collaboration to advance vaccine and therapeutic approaches against COVID-19 and other coronavirus infections. The partnership will also utilize genome-wide screening methods developed by both companies to identify products based on host targets.

The antibody program will utilize Vir's antibody discovery platform to identify anti-viral antibodies and accelerate the development of those already identified by the company for SARS-CoV-2. The companies also will work to combine GSK's vaccine development expertise with Vir's ability to identify broadly conserved viral epitopes to develop treatments covering a range of viral families. In the host-target program, GSK's CRISPR screening capabilities will be used to identify novel anti-coronavirus compounds that target cellular host genes, while Vir's CRISPR screening platform will be used to identify targets whose inhibition can prevent viral infection.

Under the terms of the collaboration GSK made an equity investment of $250MM ($37.73/share). Vir will bear 72.5% of the development costs for the antibody program, and 27.5% of the costs for the vaccine program. Vir and GSK will share equally the costs for the functional genomics program. The parties will share all profits and losses arising from the collaborative products in the same ratios in which they bore the development costs.

Vir Identified Potent Coronavirus Antibody In Serum From Patient Infected With SARS-CoV

In findings published in *Nature*, Vir discovered multiple antibodies, which target the SARS-CoV-2 spike protein in memory B cells obtained from a patient who was infected with SARS-CoV in 2003. The company analyzed blood which was obtained from the patient in a blood draw in 2004 and found 19 human neutralizing antibodies against SARS-CoV isolates. A subsequent blood draw in 2013 added 6 additional antibody candidates. One of these antibodies, S309, was found to bind to the immobilized SARS-CoV-2 S domain with sub-picomolar avidity. The antibody potently neutralized SARS-CoV-2, as well as SARS-CoV and SARS-CoV-2 pseudoviruses in pre-clinical assays. Vir has determined that S309 recognizes a glycan-containing epitope which is conserved between sarbecoviruses.

In addition to traditional antibody neutralization, Fc-dependent cellular mechanisms including NK cell-mediated antibody dependent cell toxicity (ADCC) and macrophage/DC-mediated antibody-dependent cellular phagocytosis (ADCP) can help to control viral infections. S309 was the only antibody identified that was able to demonstrate both ADCC and ADCP.

While other antibodies identified in Vir's pre-clinical work did not alone neutralize virus activity better than S309, differential binding characteristics suggest increased potency with combination approaches. In fact, Vir demonstrated that S309 in addition to two other antibodies, S304 and S315 provided increased neutralization potency. Thus, potential antibody cocktail approaches may be considered to provide optimal activity against coronaviruses.

VIR-7831 Is Designed To Achieve Enhanced Lung Bioavailability And Extended Half-life While VIR-7832 Is Engineered To Have Extended Half-Life And Vaccine-like Function

Vir's lead antibody candidates VIR-7831 and VIR-7832 are based on the S309 antibody. VIR-7831 was been engineered to have an extended half-life, and VIR-7832 has been engineered to both have an extended half-life, and to potentially function as a T-cell vaccine. Vir expects that because the candidates target a highly conserved epitope between SARS-CoV-2 and SARS-CoV-1 that it may be more difficult for escape mutants to develop.

VIR-7831 has been designed to achieve high lung tissue concentrations, and the planned trials focus on early treatment, hospitalized treatment, and prophylaxis. Importantly, the antibody has been engineered to have an extended half-life with the potential to provide protection for up to six months.

Vir/GSK Initiated A Phase 2/3 Study Of VIR-7831 For The Early Antibody Treatment In Patient At High Risk Of Hospitalization In Late August – Initial Data Expected By YE:20

In late August, Vir and GSK announced the dosing of the first patient in the Phase 2/3 COMET-ICE study of their antibody candidate, VIR-7831, for the early treatment of patients with mild or moderate COVID-19.

This global study plans to enroll ~1,300 patients with early symptomatic infection to assess the safety and efficacy of a single dose of VIR-7831 (IV infusion) for preventing hospitalization due to COVID-19. The trial has two parts: the "Lead-In" phase and the "Expansion" phase. The "Lead-In" aims to recruit 20 participants and will randomized them to a single 500 mg IV infusion of VIR-7831 or placebo over a 2-week period to assess safety and tolerability. The second part of the trial is the "Expansion" phase, which will recruit 1,300 participants. It will randomize patients to a single 500 mg IV infusion of VIR-7831 or placebo and assess the proportion of patients who worsen, as defined by the need for hospitalization or death, within 29 days of randomization.

The companies plan to report initial data by YE:20 with final results expected in Q1:21.

The COMET clinical program also includes trials of VIR-7831 for treatment in severely ill hospitalized patients and for the prophylaxis of symptomatic infection. Management has suggested that the prophylaxis trials will be conducted in high-risk settings (such as nursing homes) which may potentially limit the size of the clinical studies necessary to demonstrate benefit.

Phase 2 Trial Of VIR-7832 Is Expected To Start Later This Year

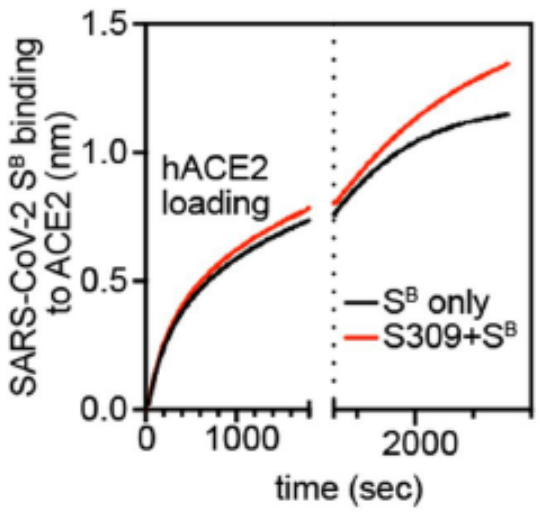
The companies also expect to start a Phase 2 trial of VIR-7832 later this year. VIR-7832 shares the same characteristics as VIR-7831 but may also function as a therapeutic and/or prophylactic T cell vaccine.

VIR-7831 And VIR-7832 Showed Robust Neutralization - Will Be Developed As Prophylaxis And Treatment

VIR-7831 and VIR-7832 are based on S309, an antibody isolated from a 2003 recovered SARS patient. The candidates have shown encouraging preclinical activity in neutralizing the virus in cellular assays. Both antibodies will be investigated as prophylaxis and treatment; VIR-7832 can also function as a T cell vaccine.

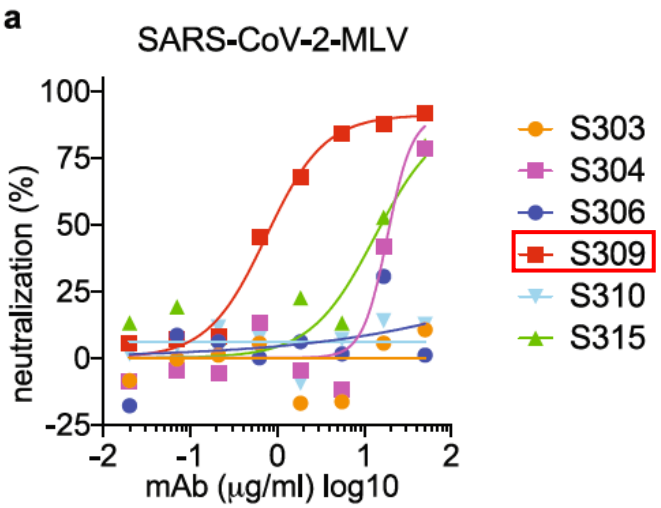
A recent study by Pinto et al. published in *Nature* showed encouraging preclinical data of S309 in neutralizing the SARS-CoV-2 virus in cellular assays. Notably, data showed that S309 potently neutralized SARS-CoV-2 with an IC50 of 79 ng/ml (Vero E6 cells).

Competition Of S309 With ACE2 To Bind To SARS-CoV-2 RBD



Source: *Nature*, Vir Biotechnology

S309 Showed Encouraging Neutralization Potency In SARS-CoV-2-MLV Assay



Source: *Nature*, Vir Biotechnology, Cowen and Company

Vir believes that S309 likely covers the entire family of related coronaviruses and would be challenging for the virus to develop resistance as it evolves. Prophylaxis trials will be conducted in high-risk settings (such as nursing homes) which may potentially limit the size of the clinical studies necessary to demonstrate benefit.

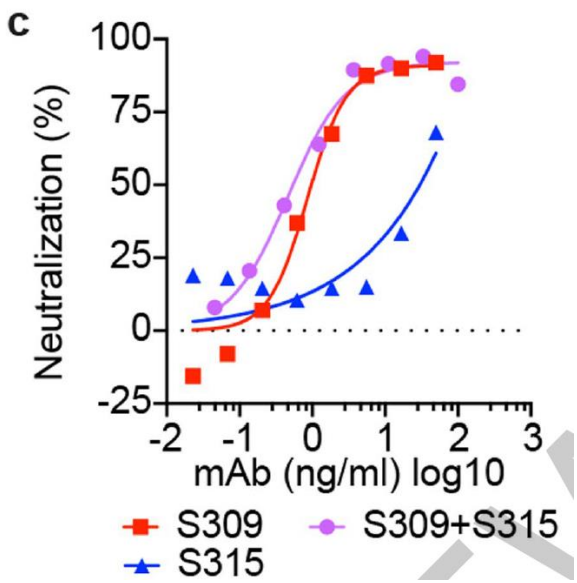
Vir is also collaborating with the NIAID to characterize and identify antibodies targeting SARS-CoV-2 and potentially other coronaviruses.

Vir's Data Also Shows That Antibody Cocktails Result In Higher Neutralization And Blunt Emergence Of Viral Resistance

Notably, confirming Regeneron's data, the *Nature* article also reports that antibody cocktails boost the neutralization capacity over a single antibody and blunt the emergence of mutant strains. The analysis showed that the combination of either S304

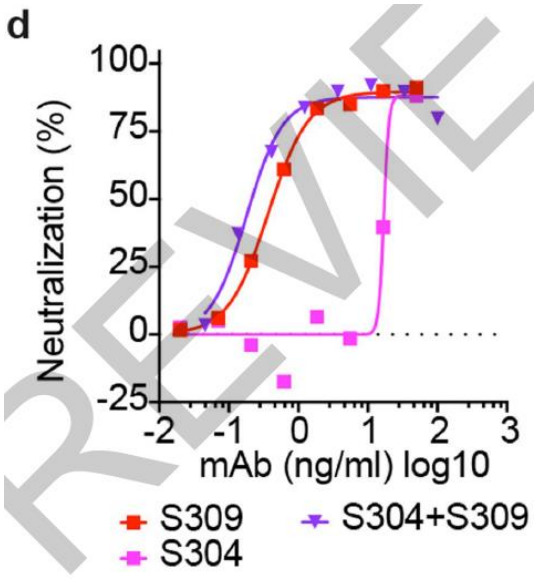
or S315 (both antibodies that bind to the SARS-CoV-2 spike protein) with S309 resulted in an enhanced potency of neutralization, compared to single antibodies.

Combination Of S309 And S315 Showed Enhanced Neutralization Potency



Source: *Nature*, Vir Biotechnology

Combination Of S309 And S304 Showed Enhanced Neutralization Potency



Source: *Nature*, Vir Biotechnology

Manufacturing Capacity: Hundreds Of Thousands Of Doses By YE:20 And Tens Of Millions By 2021

Manufacturing capacity has been the gating factors to initiating clinical trials.

Vir has executed an agreement with Biogen for process development and commercial manufacturing services. The companies will develop highly productive clonal cell lines and the manufacturing processes necessary for the clinical and commercial batches of Vir's coronavirus antibody candidates. Biogen will conduct cGMP clinical manufacturing in the US and also provide technical support to transfer the process to Samsung Biologics and other biomanufacturing facilities for large-scale supply globally. Vir also established a development and manufacturing collaboration with WuXi Biologics in February 2020.

Vir expects early access to the antibody treatment to be as soon as H1:21. The company expects to have hundreds of thousands of doses by YE and tens of millions of doses by 2021. Vir also has entered into agreements with multiple partners for the development and manufacturing of clinical and commercial antibodies including WuXi Biologics, Biogen, and Samsung Biologics.

Additional Collaborations Also Focus On Vir's Antibody Platform

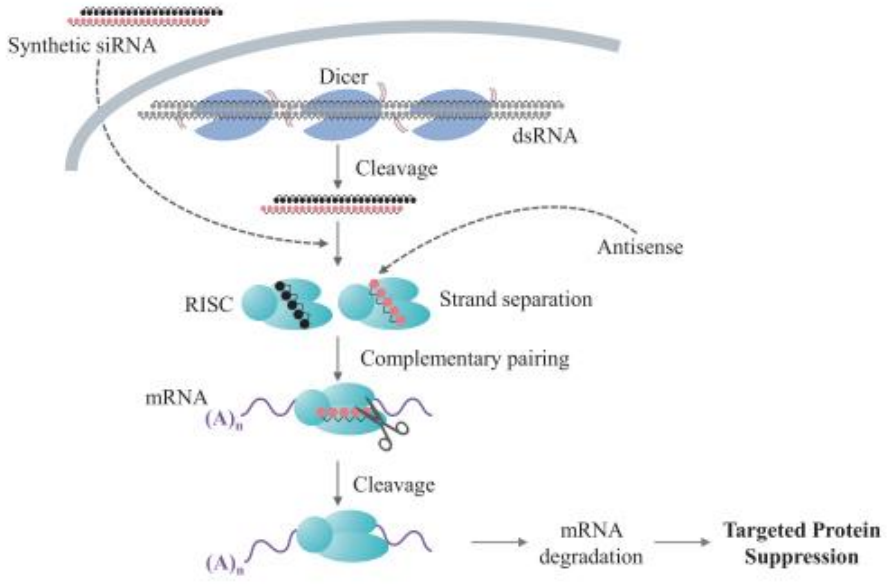
Vir is collaborating with the NIAID to characterize and identify antibodies targeting SARS-CoV-2 and potentially other coronaviruses. Promising antibodies will then be investigated alone or in combination through *in vivo* animal studies. A collaboration with Generation Bio will explore potential non-viral gene therapy approaches to extend the potential utility of Vir's SARS-CoV-2 monoclonal antibodies.

Separately Vir And Alnylam Collaborate On COVID-19 siRNA Therapeutics – 1st IND Expected BY YE '20

Vir's second strategy to advance products for the treatment and prevention of COVID-19 focuses on siRNA technology to regulate gene expression and downstream protein suppression.

For review, siRNAs, or short interfering RNAs, are double-stranded RNA molecules that often originate from long, exogenous (e.g. environmental or experimental) double-stranded RNAs. When introduced into the cytoplasm, these RNAs are cleaved by Dicer into siRNAs. siRNA "guide" strands usually have perfect complementarity to target messenger RNAs and induce their cleavage/degradation. In some cases, siRNAs are also endogenously encoded within the genome via convergent transcripts, transposons, pseudogene/gene duplexes, centromeres, and repetitive elements. Importantly, endogenous and viral siRNAs almost always silence the same loci from which they originate, unlike microRNAs which commonly target genes from other genomic loci. This makes siRNAs particularly well-suited for host genome defense: double-stranded viral RNAs can be cleaved by Dicer, and the resulting siRNAs are then incorporated into RISC and used to silence viral RNA with complementary sequences. In a similar manner, transposons and other selfish genetic elements can be silenced. It is also worth noting that siRNAs are often synthesized and used as experimental tools to knock down gene expression.

Overview Of SiRNA Mechanism



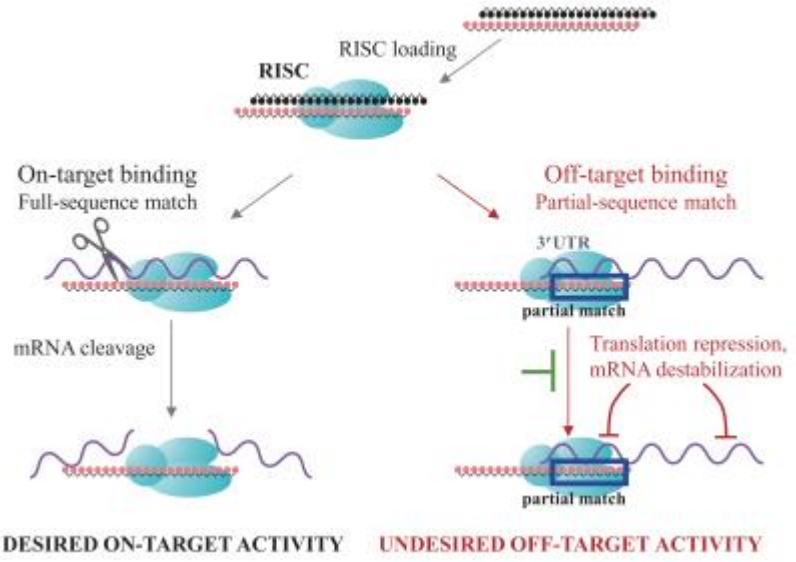
Source: Vir Biotechnology

An enhanced stabilization chemistry platform was developed by Alnylam, which utilizes a GalNAc sugar modification procedure and helps to maintain synthetic siRNAs. Unmodified siRNAs can be unstable in blood, and Alnylam initially demonstrated that this modification allows for subcutaneous administration and efficient delivery to hepatocytes (as the GalNAc receptor is highly expressed on hepatocytes). The company further demonstrated that GalNAc-siRNAs can also be administered to the lung through

inhaled administration. This is the approach that the companies will be using for the COVID-19 targeted products.

With siRNA technology, there is the possibility of generating off-target effects through partial sequence matching of the siRNA 5' end another mRNA which is not the intended binding partner. MicroRNAs are short, noncoding RNA molecules that are endogenously encoded within the genome. As microRNAs bind with imperfect complementarity to the mRNA and variably induce target cleavage, the off-target effects are thought to be at least partially due to microRNA activity. Thus, it is necessary to maintain the siRNA activity, while decreasing the potential for microRNA activity in order to get the appropriate and intended RNAi activity. To get around this, Alnylam has developed a technology to introduce glycol nucleic acid (GNA) into the siRNA sequence which generates the microRNA activity. This modification allows for potentially increased doses of siRNA or longer duration of therapy while still maintaining an acceptable tolerability profile.

Targeted And Off-Target Function Of SiRNA Technology



Source: Vir Biotechnology

IND Submission For VIR-2703 Expected Around YE:20

The expansion of Vir and Alnylam's existing collaboration was announced in March, 2020. Alnylam has designed and synthesized >350 siRNAs covering all SARS-CoV and SARS-CoV-2 genomes. The company will screen the candidates for potency *in vitro* and will also investigate potential *in vitro* and *in vivo* anti-viral activity. Vir is in charge of development and commercialization of development candidates, while Alnylam has the option to share in the profits and losses associated with the program equally at clinical proof-of-concept. If Alnylam does not select to do so, the company can instead earn milestones and royalties related to developed products.

The first candidate to come from the collaboration is VIR-2703 targeting a highly conserved nucleic acid sequence in the SARS-CoV-2 and SARS-CoV-1 genome. The

candidate has demonstrated the ability to reduce SARS-CoV-2 viral replication through its mechanism of viral genome degradation, which blocks viral protein synthesis and production of the infectious virus. Specifically, the therapy has demonstrated an EC50 of <100pm and an EC95 of <1nm in a live virus model.

An IND submission for VIR-2703 is expected by YE:20 and the companies anticipate that it will be used as either a therapeutic or a vaccine to be delivered via inhalation using a fine mesh nebulizer. Initial trials are expected to be in infected patients early in the treatment course with downstream efforts targeting prophylactic use in uninfected volunteers, who have an increased risk for infection.

Vir and Alnylam have also indicated that they will aim to develop siRNA therapies against host proteins ACE2 and TMPRSS2, which function to mediate viral entry into cells.

AstraZeneca Initiated Antibody Cocktail Phase 1 Trial In Late August – We Anticipate Initial Data In Q4:20

AstraZeneca Started The Phase 1 Study In August With Data Likely In Q4:20

Company	Approach	Candidate	Target	Regimen	IC_{50}	Fc Domain Modification	Platform/ Source	Clinical Status	Catalyst/Milestone	Manufacturing Capacity By 2020	Manufacturing Capacity By 2021
AstraZeneca/ Vanderbilt Univ.	Two-antibody cocktail	AZD7442 (AZD8895 +AZD1061)	SARS-CoV-2	IV and IM	15-4,000 ng/mL	YTE mutation for half-life extension	Convalescent COVID-19 patients or genetically-humanized mice via YTE technology platform	Ph1 started in mid August	Likely to have initial data in Q4:20	NA	1M doses to start as early as H1:21

Source: Cowen and company, company reports

AstraZeneca performed a preclinical evaluation of 1,500 neutralizing antibody candidates and licensed six candidates from Vanderbilt University Medical Centers' vaccine center isolated from the blood of patients recovered from COVID-19.

IDBiologics, a Nashville-based biotechnology firm, has licensed a separate set of the antibodies from Vanderbilt University and is also planning to start clinical trials this summer.

***Nature* Article Highlights Reduction In Viral Load And Lung Inflammation**

In mid-July, the study by Zost et al. was published in *Nature*, describing how two of the antibodies discovered by researchers at Vanderbilt University, COV2-2196 and COV2-2130, bind to distinct sites on the S protein. The data showed that these antibodies, either alone or in combination, reduce the viral burden in a mice model and protect the subjects from weight loss and lung inflammation. The antibodies had a wide range of potency (IC50 values from 15 to over 4,000 ng/mL) in a panel of 40 anti-S human mAbs as measured by a quantitative focus reduction neutralization test (FRNT, as discussed in the earlier section).

AstraZeneca plans to advance a pair of these six neutralizing antibodies into clinical development as a combination therapy.

AZD7442 (Antibody Cocktail) Can Have An Extended Half Life With Dosing Every 150 Days

In late July 2020, AstraZeneca announced that the company has identified AZD7442, the combination of two monoclonal antibodies (mAbs), AZD8895 and AZD1061, licensed from Vanderbilt University. The antibody candidates were developed through AstraZeneca's proprietary YTE technology with extended half-life and a predicted dosing of around every 150 days, making the AZD7442 ideal for both prophylaxis and treatment regimens.

AZD7442 Is Optimized To Have Improved Safety

AstraZeneca noted that the antibody candidates were optimized for reduced Fc receptor binding.

Recall, there has been a theoretical concern regarding suboptimal immune responses inducing non-neutralizing antibodies, which can result in antibody-dependent enhancement (ADE) of proinflammatory effects. ADE occurs when non-neutralizing antibodies enable the virus to use the antibody's Fc domain to bind to the Fc receptors of immune cells or epithelial cells, leading to uptake of the virus and subsequent dysregulated cytokine release.

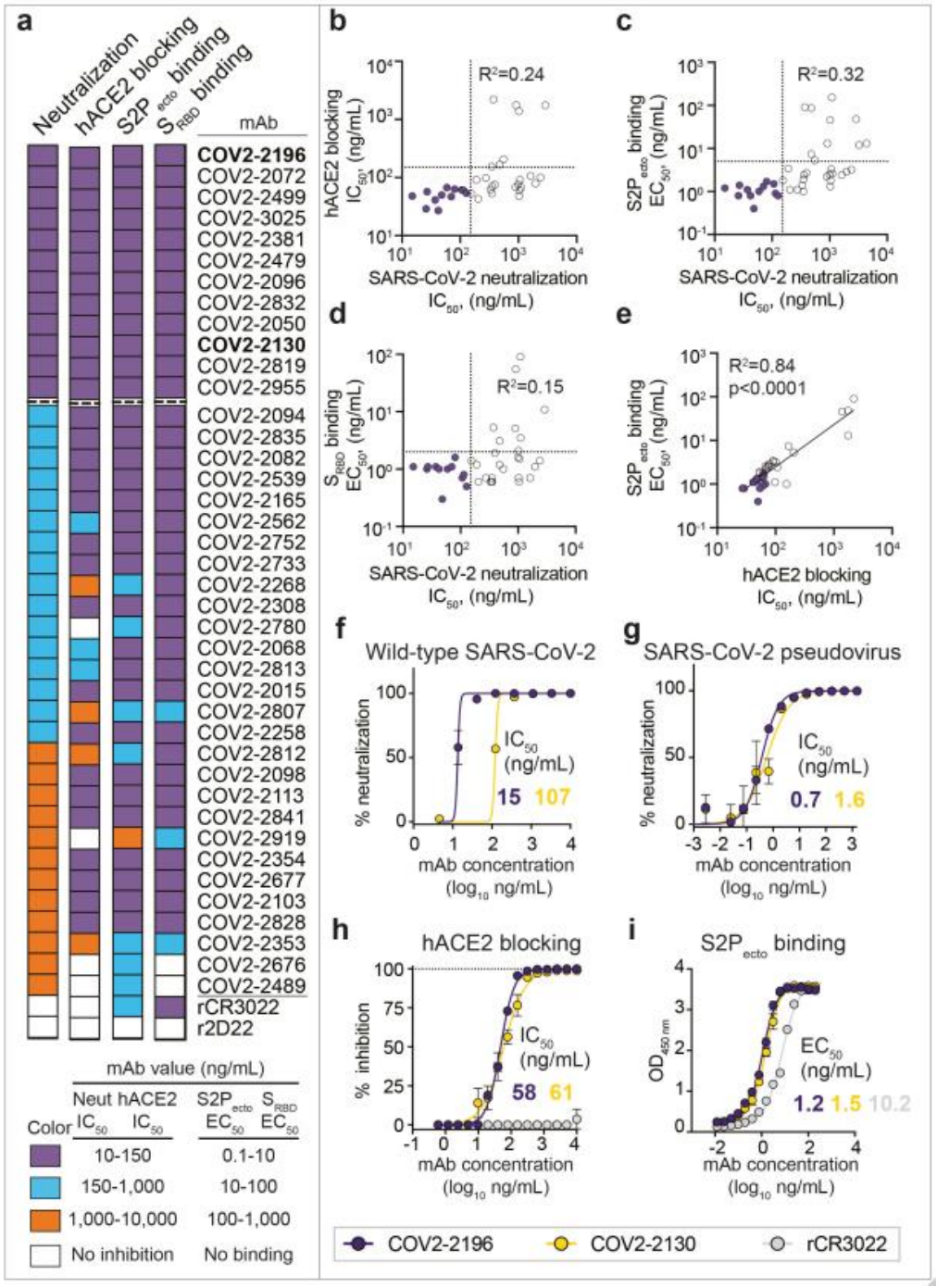
Phase 1 Study Underway Testing IV And IM AZD7442 (AZD8895 + AZD1061) As Prophylaxis And Treatment – DARPA Provides Funding

A placebo-controlled Phase 1 prevention and treatment trial (n = 48) was initiated in late August to evaluate the efficacy and safety of AZD7442 (AZD8895 + AZD1061) IV injection in healthy participants in the UK aged 18 to 55 years (n=48). Participants will receive AZD7442 doses across four fixed-dose cohorts via IV infusions and direct gluteal intramuscular (IM) injections. Participants randomized to AZD7442 will be administered dose 1, each in Cohort 1a (IM) and Cohort 1b (IV). Participants in Cohort 2 and 3 will receive AZD7442 (IV) doses 2 and 3, respectively. We estimate that initial data will be available in Q4:20.

Notably, the two antibodies target different parts on the SARS-CoV-2 spike protein RBD to increase potency and mitigate the risk of resistance. AstraZeneca has entered a funding agreement with DARPA to support the antibody production and Phase 1 testing.

If successful in early phase trials, AstraZeneca plans to test the therapy as a COVID-19 prophylactic and/or as add-on to SARS-CoV-2 vaccination in high-risk groups. If the antibodies reach the market, AstraZeneca has suggested that it would price them conservatively.

Antibodies Discovered By Vanderbilt Univ. Showed Promising Neutralization Potency



Source: *Nature*, AstraZeneca

Amgen Is Partnered With Adaptive Bio To Discover Neutralizing Antibody Candidates – Combination With Others A Likely Path

Amgen has tremendous manufacturing capacity and has used its DeCode Genetics subsidiary to mine data about viral strains and mutations in Iceland. However, the company is behind in pursuit of an antibody therapy. In collaboration with Adaptive Biotechnologies, Amgen hopes to discover fully human neutralizing antibodies from the blood of patients who are actively fighting or have recently recovered from COVID-19.

Amgen has not guided on timing or manufacturing capacity as it will depend on many characteristics of the therapy. But the company noted that they can scale relatively quickly given its highly developed antibody engineering and drug development technology. This is also aided from their sequencing of patient samples in Iceland via DeCode Genetics, which is generating a catalog of viral mutations.

Given that the partners are behind, Amgen has noted that its likely strategy will be to develop a novel neutralizing antibody that can be used in combination with other potent antibodies which are already ahead in development.

Approaches Used By Regeneron/Vir/Amgen Are Largely Similar, But Regeneron's Cocktail Strategy Should Provide Some Differentiation

Company	Regeneron	Vir	Amgen
Approach	Two-antibody cocktail	Single antibody	Not disclosed
Background	• Two-antibody cocktail based on library of antibodies, including from patients who recovered from COVID-19 and genetically-humanized mice • Antibodies will be chosen based on potency and binding ability to the SARS-CoV-2 spike protein	• Prioritizing a single antibody against an epitope that is conserved between SARS-CoV-1 and SARS-CoV-2 • Received a $250MM investment by GlaxoSmithKline	• Developing in collaboration with Adaptive Biotechnologies • Hope to discover neutralizing antibodies from recovered COVID-19 patients • Amgen's deCODE Genetics subsidiary has been sequencing samples of SARs-CoV-2 RNA taken cases in Iceland which can help provide insight
Intended Use	• Prophylaxis and Treatment	• Prophylaxis and Treatment	• Prophylaxis and Treatment
Study Timeline	• Company began clinical testing in mid June	• Company started a Ph2/3 study in August	• Company has not guided on timing
Manufacturing Process	• Regeneron's VelociMab® technology allows rapid generation of manufacturing-ready cell lines as lead antibodies are selected	• Limiting to one antibody will aid manufacturing capacity	• Will take advantage of Amgen's highly developed antibody engineering and drug development technology
Manufacturing Capacity	• Hundreds of thousands of doses by YE • Tens of millions of doses in 2021 • In partnership with BARDA to further increase production capacity	• Hundreds of thousands of doses by YE • Tens of millions of doses in 2021	• Company has not guided on manufacturing capacity
Commercial Opportunity (If clinical trials successful)	• Prior to vaccine: Potentially could be given to all front-line workers and vulnerable populations prophylactically (less likely to be given to low-risk population due to cost) • Would also be used in hospitalized and non-hospitalized patients with positive diagnoiss	• Same as for Regeneron	• Same as for Regeneron
Impact of Vaccine on Opportunity	• Likely adjunctive use before the effect of vaccines kicks in • Limited opportunity post widespread introduction of an effective vaccine (limited to early stage patients that did not get vaccine or did not respond well to vaccine)	• Same as for Regeneron	• Same as for Regeneron

Source: Cowen and company, company reports

Celltrion Plans To Complete Phase 1 In Q3:20 With Pivotal Data Expected By YE:20

Celltrion's Phase 1 Study Is Underway With Pivotal Data Expected By YE:20

Company	Approach	Candidate	Target	Regimen	IC_{50}	Fc Domain Modification	Platform/ Source	Clinical Status	Catalyst/Milestone	Manufacturing Capacity By 2020	Manufacturing Capacity By 2021
Celltrion	Single antibody and two-antibody cocktail	CT-P59	SARS-CoV-2	NA	NA	NA	Convalescent COVID-19 patients	Ph1 in healthy volunteers started in UK in mid July; Global Phase 1 in mild COVID-19 patients started in August	To complete Ph1 in healthy volunteers by Q3:20; To start further global Phase 2 and 3 prevention and treatment trials soon and have pivotal data by YE:20	NA	Mass-production to cover up to 5M patients a year by H1:21

Source: Cowen and company, company reports

Celltrion's Antibody Shows 100x Reduction of Viral Loads

Celltrion started a Phase 1 trial of its lead antibody treatment for COVID-19 in July. Celltrion is looking at whether combining different antibodies into a single treatment yields better results, like Regeneron's cocktail. Celltrion is also hoping to develop a "super antibody" capable of neutralizing SARS-CoV-2 and related strains by extending the efficacy of the treatment beyond COVID-19.

In April, Celltrion announced that the company identified the antibody candidates with promise for neutralizing SARS-CoV-2. These antibodies are based on the blood of recovered patients in Korea. Celltrion reported that its antibody candidate demonstrated a 100-fold reduction in viral load of SARS-CoV-2 as well as improvement in lung lesions.

Phase 1 In Healthy Volunteered Underway– Data In Q3:20 – Has Activity Against D614G Variant

In mid-July, Celltrion started the Phase 1 study of its antibody therapy candidate, CT-P59, in healthy volunteers (n=32) in the UK following the approval of the clinical trial authorization (CTA) application from the UK Medicines and Healthcare products Regulatory Agency (MHRA). Celltrion has also completed an infusion and initial safety assessment for the Phase 1 study in healthy volunteers in Korea and the study is set for completion by Q3:20.

In late August 2020, the Korean Ministry of Food and Drug Safety (MFDS) approved Celltrion's IND application to initiate a Phase 1 trial of CT-P59 in patients.

Celltrion also initiated an in-human global Phase 1 clinical trial of CT-P59 in mild COVID-19 patients.

Importantly, Celltrion reported that CT-P59 has been proven to be effective in neutralizing different kinds of coronavirus related strains including the D614G variant.

Additional Studies To Commence Soon – Initial Pivotal Data By YE:20

Celltrion plans to start further global Phase 2 and 3 trials in mild COVID-19 soon. Additionally, Celltrion plans to combine the Phase 2 and 3 trials in patients with moderate-to-severe COVID-19 with the prevention clinical trials.

The company anticipates preliminary data from these pivotal treatment and prevention studies by YE:20.

BeiGene Is Partnered With Singlomics Bio To Develop Neutralizing Antibodies – Phase 1 And Phase 1/2 Trials Expected To Start By Early October

BeiGene Will Focus On The Ex-China Opportunity With Trials To Start In September/Early October

Company	Approach	Candidate	Target	Regimen	IC_{50}	Fc Domain Modification	Platform/ Source	Clinical Status	Catalyst/Milestone	Manufacturing Capacity By 2020	Manufacturing Capacity By 2021
BeiGene/ Singlomics	Single antibody and a potential two-antibody cocktail	DXP-593 and DXP-604	SARS-CoV-2	NA	1.2 ng/ml and 15 ng/mL	NA	Convalescent COVID-19 patients	NA	To start a placebo-controlled Ph1 trial in September; To start a global Phase 1/2 trial in mild-to-moderate COVID-19 by early October	NA	NA

Source: Cowen and company, company reports

In late August, BeiGene and Singlomics Biopharmaceuticals announced that the companies have executed an exclusive license agreement for BeiGene to develop, manufacture and commercialize globally outside of greater China Singlomics' investigational anti-COVID-19 antibodies, including DXP-593 and DXP-604.

The antibodies were identified by Singlomics using high-throughput single-cell sequencing of convalescent blood samples from over 60 recovered COVID-19 patients. The antibody candidates have been shown to be highly potent in pre-clinical studies in neutralizing SARS-CoV-2.

Notably, DXP-593 has exhibited strong neutralization potency in preclinical testing, with an IC_{50} of 1.2 ng/mL and 15 ng/mL against pseudotyped and authentic SARS-CoV-2, respectively. It displayed strong therapeutic and prophylactic efficacy in SARS-CoV-2-infected rodent models. DXP-604 binds to a different epitope from DXP-593, also with demonstrated high potency. Therefore, DXP-593 and DXP-604 can potentially be used as a cocktail treatment option to avoid resistance due to viral mutation.

The companies plan to start a randomized, double-blind, and placebo-controlled Phase 1 trial with up to 30 healthy subjects in Australia in September 2020. The global Phase 1/2 trial in mild-to-moderate COVID-19 is also expected to start by early October.

Under the agreement, Singlomics has granted BeiGene exclusive rights to DXP-593 and DXP-604, as well as a series of neutralizing antibodies in ex-China. BeiGene plans to develop one or more of these antibodies globally outside of greater China.

Singlomics will receive an upfront payment and be eligible to receive payments upon the achievement of regulatory and commercial milestones. Singlomics will also be eligible to receive tiered royalties, up to double-digits, on future product sales.

AbbVie Joins Race By Forming Partnerships With Three Organizations

AbbVie Identified The Antibody Candidate, But The Clinical Study Timing Is Still Uncertain

Company	Approach	Candidate	Target	Regimen	IC_{50}	Fc Domain Modification	Platform/ Source	Clinical Status	Catalyst/Milestone	Manufacturing Capacity By 2020	Manufacturing Capacity By 2021
AbbVie/ Harbour/ Utrecht U/ Erasmus Med Center	Single antibody	47D11	SARS-CoV-2		61 ng/ml	NA	From genetically-humanized mice (Harbour's H2L2 Harbour mice)	Not started yet	NA	NA	NA

Source: Cowen and company, company reports

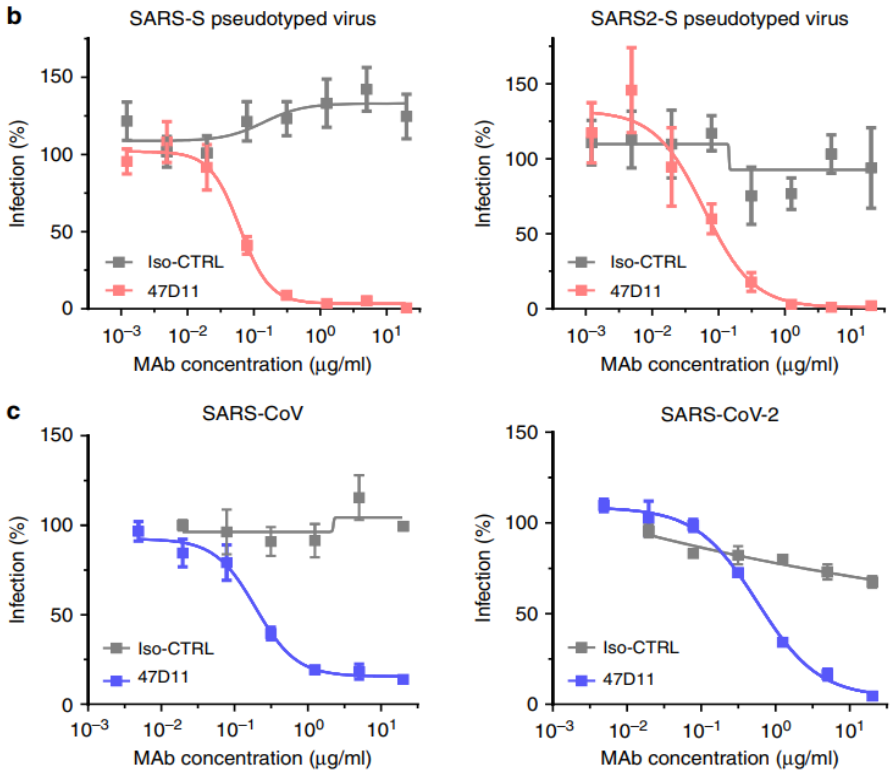
AbbVie joined the pursuit in June by collaborating with the Netherlands' Utrecht University, Erasmus Medical Center, and Chinese-Dutch biotech Harbour Biomed.

AbbVie will support early preclinical work and prepare for later preclinical and clinical development. AbbVie will have the option to exclusively license the antibody for clinical development and commercialization across the world, but the financial terms of this collaboration were not disclosed.

47D11 Has Potent Activity Against Both SAR-CoV-2 In Preclinical Models

AbbVie's partners discovered a neutralizing antibody, 47D11, which exhibited cross-neutralizing activity for SARS-S and SARS2-S infections in preclinical studies. A recent study by Wang et al. published in *Nature Communications* reported that 47D11 potently neutralized SARS-CoV-2 with an IC50 of 61 ng/ml (Vero E6 cells).

47D11 Showed Infection Neutralization On Pseudotyped Virus And VeroE6 Cells



Source: *Nature Communication,* AbbVie

Adagio Plans To Enter The Clinic In Q1:21 With Candidates Potentially Potent Enough For Twice A Year Dosing

In July, Adagio, an Adimab spinout, closed a $50M series A to advance its antibodies as therapeutics and prophylactics for SARS-CoV-2 and for any future outbreaks due to resistant coronaviruses. The funding is expected to support the candidates through IND studies and into early clinical development.

These antibodies were isolated by Adimab from a survivor and bind to a highly conserved epitope on the spike protein of multiple coronaviruses — SARS-CoV-2, SARS-CoV-1, and two circulating bat coronaviruses.

The company is developing antibody products that could be administered twice annually with 90% efficacy against COVID-19. If successful, we think it will be very competitive and potentially become an alternative to a vaccine, given that the durability of vaccine is uncertain and may not be highly effective or may have limited durability.

The company hopes to advance these antibodies into a human trial in Q1:21, looking to quickly advance into a pivotal. The management noted that a pre-IND meeting is slated for September, with the IND due in December 2020.

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ADDENDUM

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POINTS OF CONTACT

Analyst Profiles

Yaron Werber, M.D.
New York
646 562 1415
yaron.werber@cowen.com

Yaron Werber is a senior biotech analyst. He rejoined Cowen in 2018 having previously worked at Citigroup and Ovid Therapeutics.

Leo Ai, Ph.D.
New York
646 562 1419
leo.ai@cowen.com

Leo Ai is an associate covering biotechnology. He joined Cowen in 2018 having previously worked at Edwards Lifesciences and Leerink.

Steve Scala, R.Ph., CFA
Boston
617 946 3923
steve.scala@cowen.com

Steve Scala is a senior analyst covering global big cap pharmaceutical companies for over 20 years, his entire career with Cowen.

Phil Nadeau, Ph.D.
New York
646 562 1336
phil.nadeau@cowen.com

Phil Nadeau is a senior analyst covering biotech. He joined Cowen in 2000 and holds an SB/M.Eng from MIT, and a Ph.D. from Harvard.

Joshua Jennings, M.D.
New York
646 562 1333
josh.jennings@cowen.com

Josh Jennings is a senior analyst covering medical devices. At Cowen since 2011, Josh has been covering the sector since 2007.

Boris Peaker, Ph.D., CFA
New York
646 562 1377
boris.peaker@cowen.com

Boris Peaker is a senior analyst covering biotechnology. He re-joined Cowen in 2014, having previously worked at Oppenheimer & Co.

Reaching Cowen

Main U.S. Locations

New York
599 Lexington Avenue
New York, NY 10022
646 562 1010
800 221 5616

Boston
Two International Place
Boston, MA 02110
617 946 3700
800 343 7068

Cleveland
20006 Detroit Road
Suite 100
Rocky River, OH 44116
440 331 3531

San Francisco
One Maritime Plaza, 9th Floor
San Francisco, CA 94111
415 646 7200
800 858 9316

Atlanta
3424 Peachtree Road NE
Suite 2200
Atlanta, GA 30326
866 544 7009

Chicago
181 West Madison Street
Suite 3135
Chicago, IL 60602
312 577 2240

Stamford
262 Harbor Drive
Stamford, CT 06902
646 616 3000

Washington, D.C.
2900 K Street, NW
Suite 520
Washington, DC 20007
202 868 5300

International Location

Cowen International Limited

London
1 Snowden Street - 11th Floor
London EC2A 2DQ
United Kingdom
44 20 7071 7500

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