TRINITY

Beyond Vaccines

How Monoclonal Antibodies Can Help in the Fight Against the COVID-19 Pandemic

Executive Summary

The COVID-19 pandemic has potentially been the most significant event of the century thus far, affecting the lives of most of the world's population, either directly or indirectly. The pandemic has pushed science beyond its previous limits and shifted clinical development paradigms within the pharmaceutical world, ultimately driving the development of a new vaccine in under one year. However fast, this breakthrough alone does not mark the end of the pandemic. Other tools to combat COVID-19 must be developed and deployed as soon as possible in order to enable the world to move past the pandemic despite the threat of further outbreaks and viral mutations.

In this article, we aim to explain how monoclonal antibodies can help in the fight against the COVID-19 pandemic. While there are still unknowns about these drugs – such as their real-life efficacy and long-term effects, amongst others – antibodies nonetheless have the potential to effectively target several stages of the disease with evident benefits at a patient level (by alleviating symptoms and preventing progression to severe disease) and at a systemic level (by reducing the strain on the overburdened health systems worldwide). The next months will be crucial to understand how antibodies will be accepted by the market and to assess how they will be used, however, recent government agreements show that countries best act soon to ensure supply, as access may be mainly dictated by country-level agreements.

1 COVID-19 and vaccines: opportunities and challenges to stop the pandemic

The SARS-CoV-2 pandemic is undeniably the health event with the highest, broadest impact in recent history since three worldwide outbreaks of influenza in the 20th century (Kilbourne, 2006). The communicability of COVID-19 and lack of effective treatments led to more than 80 million COVID-19 cases worldwide in 2020, including 1.8 million deaths (European Centre for Disease Prevention and Control, 2020).

Immunization against SARS-CoV-2 is key to ending the pandemic and effectively reducing its associated health, economic and social burden. In order to attain herd immunity and prevent the spread of the virus, it has been estimated that 60-70% of the population should be immune (Aschwanden, 2020). Fortunately, the first vaccines for the virus were authorized for emergency use by the FDA and EMA in December (Ledford, 2020; European Medicines Agency, 2020) and their distribution and administration is ongoing (Tidey, 2020).

Nevertheless, vaccination faces some limitations that make effective therapies for COVID-19 necessary, at least in the short- and medium-term. Achieving herd immunity via vaccination is a complex process and how fast it happens depends on how effective vaccines are, the level of vaccine supply, the speed of the vaccination process and the level of acceptance by the population.

The vaccines that have been authorized in the US and EU have proved ~60-95% efficacy preventing symptomatic infections (Pfizer, 2020; Moderna, 2020; Administration, 2021; Agency, 2021) – one of them demonstrated efficacy only against moderate to severe symptomatic infections; although preventing symptomatology is certainly positive to decrease severity and potential sequels of the disease as well as healthcare system saturation and costs, it is unclear whether the vaccines have any effect on preventing infection and transmission of the virus. If the vaccinated population does not get immune to the virus, vaccination will play no role in achieving herd immunity faster, although it would still be key to reduce the health burden while population naturally build immunity upon exposure to the virus.

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Additionally, virus variants are a key aspect to consider. Just when the scientific community believed it was closer to finding a way out of this health crisis, the SARS-CoV-2 virus started to develop mutations with the potential of higher transmissibility or mortality (Forster, 2021). The first variant was identified in the United Kingdom in Autumn 2020, and two others have emerged in South Africa and Brazil since then – all of which have already been identified in several other countries across the world (CDC, 2021) (World Health Organization, 2021). Infection with different virus mutations has been shown to trigger different immune responses, sometimes generating antibodies that respond to several variations, others generating a narrower response. Response to vaccines is expected to be similar as they are based on the viruses themselves. As a result, the new variants are being studied for virologic, epidemiologic and clinical characteristics, which will help experts understand the implications they can have for vaccinations in the goal of achieving herd immunity. While some vaccine refinement is already in place, scientists believe that redesigning vaccines is not the only way to manage new variants, and they are currently studying other ways to ensure a broad protection can be achieved (Callaway, 2021). Overall, it is still not clear if the existing vaccines will be sufficient and what type of immunity can be expected for those who have already been vaccinated. This further highlights the evident weaknesses of vaccines and the need for different tools against this pandemic.

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To ensure vaccines are administered, US, EU and other governmental authorities agreed closed deals with the vaccine manufacturers to acquire doses upon approval (Sagonowsky, Liu, Blankenship, Hale, & Kansteiner, 2021; Pfizer, 2021; Moderna, 2021; Johnson & Johnson, 2021; European Commission, 2021; AstraZeneca, 2021). The number of doses from approved vaccines that have been acquired would allow vaccination of the whole population of the US and EU (U.S. Department of Health & Human Services, 2021; Kansteiner, 2020; European Commission, 2021). Nevertheless, immunization of 60-70% of the population is needed to achieve herd immunity, and it could take more than one year taking into account the population that already received one and two doses and current vaccination rates across different countries in the world (Table 1) (Our World in Data, 2021).

Table 1: Time to Achieve Herd Immunity Based on Current Vaccination Rates

Country	Current vaccination rate (vaccines*Day^{-1}*100 inhabitants^{-1})	Population (M)	% population fully vaccinated (2 doses)	% population partially vaccinated (1 dose)	% population to be vaccinated to achieve herd immunity*	Time to achieve herd immunity (months)
Israel	0.85	9	51.7%	7.7%	8.3 - 18.3%	0.3 - 1.1
US	0.75	331	12.4%	10.4%	47.6 - 57.6%	3.8 - 4.7
UK	0.68	68	2.8%	35.1%	57.2 - 67.2%	3.9 - 4.9
Italy	0.26	60	3.8%	4.6%	56.2 - 66.2%	13.8 - 16.4
Germany	0.27	84	3.7%	4.6%	56.3 - 66.3%	13.3 - 15.8
France	0.31	65	3.5%	5.1%	56.5 - 66.5%	11.6 - 13.7
Spain	0.2	47	4.0%	4.7%	56.0 – 66.0%	17.9 - 21.2

**Herd immunity threshold = 60-70% of population (Aschwanden, 2020; Our World in Data, 2021; United Nations, 2019; U.S. Food and Drug Administration, 2020)*

Finally, COVID-19 vaccine hesitancy across US and EU5 ranges between 25-41% (Lazarus, et al., 2020), meaning that a substantial share of the population would not immediately accept the vaccine or would completely refuse vaccination despite availability of vaccination services, which could hamper achieving herd immunity.

Furthermore, some population segments should not get the vaccine: people who have a known history of a severe allergic reaction to any component of the vaccine, people who had a severe allergic reaction after getting the first dose of a COVID-19 vaccine and children under age 16-18 (Centers for Disease Control and Prevention, 2021) – vaccine testing on younger children has recently started (U.S. National Library of Medicine, 2020; U.S. National Library of Medicine, 2021). Pregnant and breastfeeding women and people who have a suppressed immune system due to a condition or disease or because they are undergoing a treatment for a disease like cancer may decide to not get vaccinated, although there is still no specific data about this population (Centers for Disease Control and Prevention, 2021; U.S. Food and Drug Administration, 2020).

Taking all this into account and provided vaccines do offer immunity against SARS-CoV-2 infection, herd immunity may not happen until Q3 2021 in the US. Most countries will require more time to achieve herd immunity due to lower vaccination rates and/or lower access to vaccines. Until herd immunity is achieved in a majority of countries, there will be a period in which SARS-CoV-2 will still spread and cause infections that will require effective treatments to reduce the risk of long-term adverse effects and, ultimately, mortality.

2 Treatments for COVID-19: role of monoclonal antibodies

Since the onset of the pandemic in late 2019, researchers and physicians have learnt a great deal about the virus, the disease and best practices in prevention, diagnosis, and patient management. Nevertheless, only the antiviral remdesivir (Veklury) has been approved for the treatment of COVID-19 to date (U.S. Food and Drug Administration, 2021; Marshal, 2020; European Medicines Agency, 2021) and treatment relies on general supportive care, respiratory support and nutritional support (Majumder & Minko, 2021). In addition to this, different therapeutic approaches are necessary to prevent host-cell infection, suppress different phases of the virus replication cycle inside the cells and reduce negative effects associated with inflammation. Therapeutic options other than remdesivir include other repurposed drugs such as baricinitib (authorized for emergency use in combination with remdesivir), dexamethasone, lopinavir/ritonavir and chloroquine and hydroxychloroquine (FDA revoked the authorization for emergency use due to severe cardiac effects) (Marshal, 2020; Majumder & Minko, 2021; Agencia Española de Medicamentos y Productos Sanitarios, 2020). While promising preliminary results were observed, further clinical investigation is needed to assess both the efficacy and safety of these drugs.

Besides pharmacotherapy, immunotherapy has arisen as a safer, potentially efficacious treatment option to treat critically ill COVID-19 patients or prevent disease progression to more severe stages. Immunotherapy has been used for more than 30 years with the first monoclonal antibody approved in 1986 for the prevention of transplant rejection (Cancer Research Institute, 2021; Barnes, 2018). Immunotherapy has been applied to the treatment of cancer, transplant rejection, and autoimmune diseases (e.g. multiple sclerosis, Crohn's disease, psoriasis) showing high efficacy and safety due to the high specificity of the antibodies used (Lu, et al., 2020).

Immunotherapy for the treatment of COVID-19 aims to neutralize the virus with antibodies targeting virus epitopes that are key for infection and virulence (Levi-Schaffer & de Marco, 2021). These antibodies are administered intravenously and either come from the convalescent plasma of people who have recovered from COVID-19 (Shaz, et al., 2020; Mayo Clinic, 2020) or are developed and synthetically manufactured (Levi-Schaffer & de Marco, 2021). While immunotherapy with convalescent plasma showed efficacy and safety to treat clinical presentations of Ebola, Influenza A-H1N1 and emerging SARS-CoV-1 and MERS (Canedo-Marroquin, et al., 2020), the amount and power of neutralizing antibodies in plasma differs a lot among donors and outcomes are highly variable.

On the other hand, synthetic monoclonal antibodies are often a better option for clinical use as they offer high specificity and binding affinity through accurate lab design and lower risk of side-effects while ensuring an optimal concentration and standardization across batches (Levi-Schaffer & de Marco, 2021).

Three monoclonal antibody treatments have obtained Emergency Use Authorization (EUA) by the FDA and more than 80 are in different stages of the development pipeline (U.S. Food and Drug Administration, 2021; Milken Institute, 2021).

3 ***Monoclonal antibody treatments have obtained Emergency Use Authorization***

>80 ***Monoclonal antibody treatments are in different stages of the development pipeline***

Authorized monoclonal antibodies are indicated in mild to moderate COVID-19 disease in adults and pediatric patients older than 12 years with positive SARS-CoV-2 viral testing who are at high risk for progressing to severe COVID-19 and/or hospitalization. While the treatments did not show a faster reduction of viral load compared to placebo, they did result in lower hospitalization rates after 28 days after treatment and a lower median time to symptom improvement. Effects were more pronounced in the high-risk group compared to placebo. Additionally, no differences in safety were shown between treatment and placebo groups (U.S. Food and Drug Administration, 2021). Ongoing trials will provide more information on long-term effects and safety and might allow to broaden the indication if benefits in different settings are demonstrated (U.S. National Library of Medicine, 2021; U.S. National Library of Medicine, 2020).

In order to ensure that effective monoclonal antibodies are developed and available for eligible COVID-19 patients, governments are engaging with pharmaceutical companies to support research, purchase doses and facilitate distribution and administration of the treatments. The US government closed deals with major manufacturers of authorized monoclonal antibodies to secure more than three million doses of monoclonal antibodies (each patient will require the administration of two doses) (Lilly, 2021; Regeneron, 2020) and started their distribution and administration at the end of November as part of the governmental project 'Operation Warp Speed' (Court & Griffin, 2020; Weixel, 2020; U.S. Department of Health & Human Services, 2021).

In contrast, the EU has funded extensive research projects to develop new monoclonal antibodies against SARS-CoV-2 across Europe (European Commission, 2020), with Germany and France being the only EU countries to reach an agreement with antibody manufacturers, securing 200,000 and 100,000 doses respectively (Deutsche Welle, 2021; Deutsche Welle, 2021; France Bleu, 2021).

Despite enough financial support to develop and manufacture monoclonal antibody treatments, pharmaceutical companies might lack enough manufacturing capabilities to supply enough doses to satisfy demand. Major antibody developers have partnered with other biotech companies to join manufacturing efforts and substantially increase global manufacturing capabilities (Regeneron, 2020; Lonza, 2020; Blankenship, 2020; Sagonowsky, 2020).

The Trinity Perspective

While antibodies may present an interesting strategy in the mitigation of the pandemic, a question still arises: are they really necessary? Antibodies do present a few drawbacks. Firstly, they are expensive – specifically for COVID-19 and in the US, antibodies have an average price of $1,375. Such a value may limit breadth of prescription, with doctors and governments requiring clear demonstration of positive effect before these are utilized more broadly. For these reasons, antibodies will probably be limited to a small percentage of the population in the short-term – i.e., COVID-19 positive patients with mild to moderate disease and at high risk of progressing to severe disease.

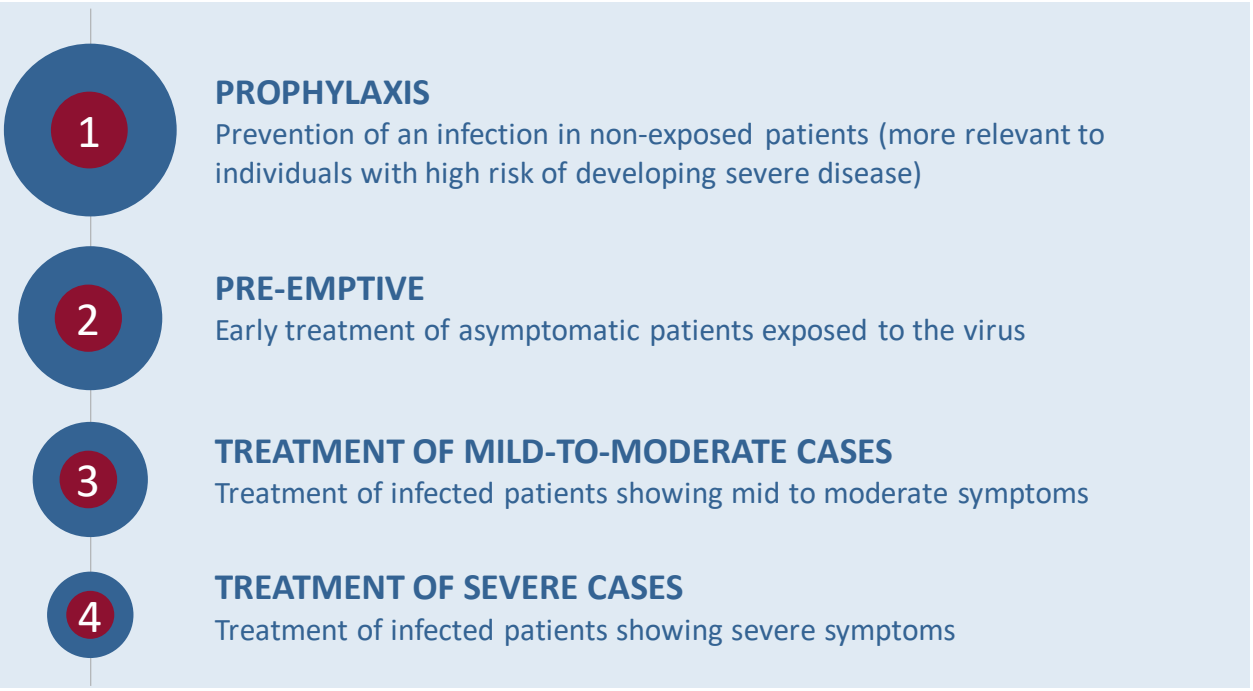
The lack of robust and detailed evidence is clearly another weakness of antibodies. Although they have shown positive effects and met their clinical endpoints in the existing trials, the most advanced antibodies are still in phase 2/3 trials (for the antibodies which received FDA's EUA). Before antibodies are broadly utilized, data from trials must be analyzed.

Another potential limitation of monoclonal antibodies relates to their utilization in the clinic – even if antibodies prove to be effective, it is unclear whether they can or will be prescribed in the appropriate timeframe. For example, a patient who would be eligible for antibody medication has a high likelihood of only visiting the hospital when the disease has already progressed to a severe state, when antibodies may no longer be efficacious. It is key that broad distribution is ensured and that clear treatment guidelines ensure doctors will cooperate and have patients medicated in the appropriate timeframe.

Lastly, there are questions to whether manufacturers will be capable of meeting the global demand, despite them scaling up their plans. And, even if they are so, there are moral concerns to whether it is reasonable for producers to prioritize COVID-19 over all other diseases, as scaling up may mean stopping other drugs' production.

Despite all these potential limitations, antibodies can still be a powerful weapon in the fight against COVID-19 – if truly successful, they can bring great value for patients and to the whole health system. At a patient level, antibodies can alleviate symptoms and decrease the severity of the disease, and consequently reduce the long-term effects of severe disease (effects which are still not fully known, as there are no long-term studies of recovered COVID-19 patients) and potentially a reduction in the mortality rate.

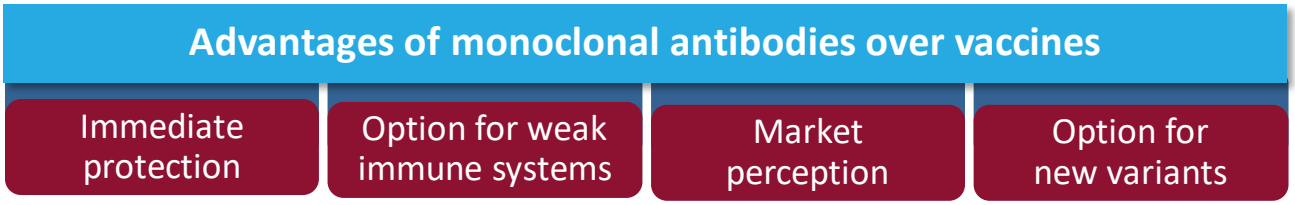
Figure 1: Four potential approaches for the administration of monoclonal antibodies in the disease by SARS-CoV-2



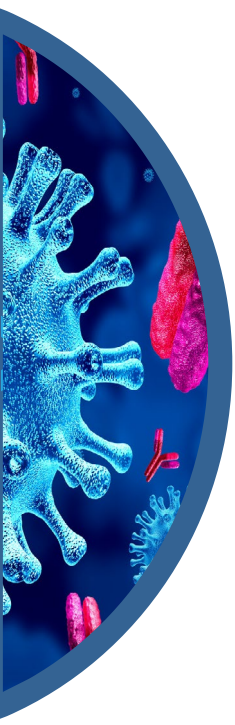
Furthermore, while there is still need for studies to assess this, there is a potential for antibodies to be used in four distinct approaches, targeting different stages of the disease (Figure 1). The first indication, prophylaxis, has the potential to greatly impact the progression of the pandemic. Further down the line, antibodies have the potential to be used as a preemptive therapy – that is, after a patient has been exposed to the virus but before symptoms appear. Under this indication, antibodies could result in different outcomes, from preventing individuals from developing the disease altogether, to a mild reduction in the symptoms they experience.

A third indication is the one currently approved for Regeneron and Lilly (U.S. Food and Drug Administration, 2020), that is – for the treatment of mild to moderate disease. The fourth and last approach would be for the treatment of severe disease. Treatment rates will vary according to the label approved within each country, which will be in line with the respective approach to the pandemic (i.e., some countries may opt for generalized prophylaxis, while another may focus on patients at high risk of progressing to severe disease). Within all indications, the total eligible population just amongst the US and EU5 could amount to over 70 million people. If all (or even just some of) these people were medicated before significant disease progression, the strain on healthcare systems could be greatly relieved – namely by freeing up crowded emergency rooms, reducing the burden on exhausted healthcare professionals, lightening the presently high economic costs, amongst others.

One potentially critical indication for monoclonal antibodies could be prophylaxis, immunizing the population even before exposure to the virus. Antibodies can obtain a similar protection to vaccines, through a very different mechanism of action – while a vaccine stimulates the patient's immune system to produce antibodies against the virus, antibodies are the defense against the virus (COVID-19 Prevention Network, 2021). This provides monoclonal antibodies with clear advantages when compared to vaccines.



Firstly, they can offer immediate protection, by targeting viruses as soon as they are inoculated, whereas vaccines require the patient's immune system to respond and hence take longer and generally more doses until a minimum protection is achieved. Furthermore, monoclonal antibodies may be an option for individuals with weak immune systems, who cannot receive a vaccine due to the associated risk of developing the infection. Antibodies also have advantages in terms of how they are seen by the market – monoclonal antibodies are a fairly known and trusted drug class, with few side effects based on a great deal of past experience. This becomes particularly relevant when the competing drug class is mRNA vaccines, a novel mechanism which the scientific community needs more experience with. Monoclonal antibodies can still play an important role while we wait for more data on vaccines to reduce the hesitancy towards novel vaccinations. Even though they can probably only guarantee an immune response for a short period, thus requiring injections repeated over time, monoclonal antibodies can be a tool in a gradual reopening of the economy. Additionally, monoclonal antibodies can help with the response to new variants while the scientific community waits for more effective and broad reaching vaccines, as some have demonstrated the potential to be equally affective against variants.



Conclusion

The US distribution of monoclonal antibodies for COVID-19 has started but their uptake has been slow, while several other companies are developing new antibodies. Vaccines are still the main focus, however, it is increasingly clear that vaccines alone are not enough. All in all, there is a place for antibodies in the fight against COVID-19.

While antibodies have their limitations, they do have the potential to play an important role in the treatment of individual patients and in the health system as a whole. If their role is proven in time, there will be a high demand for these drugs. There is a clear opportunity for pharma companies to develop new antibodies – and for other players in the market to join this collaborative effort, such as biotech companies and Contract Manufacturing Organizations which can help produce antibodies via partnerships.

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