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Original Research Article

Models to inform neutralizing antibody therapy strategies during pandemics: the case of SARS-CoV-2

Donovan Guttieres[1], Anthony J. Sinskey[1,2,*] and Stacy L. Springs[1,*]

[1]Center for Biomedical Innovation, Massachusetts Institute of Technology, Cambridge, MA 02139, USA, and
[2]Department of Biology, Massachusetts Institute of Technology, Cambridge, MA 02139, USA

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Abstract

Background: Neutralizing antibodies (nAbs) against SARS-CoV-2 (severe acute respiratory syndrome coronavirus 2) can play an important role in reducing impacts of the COVID-19 pandemic, complementing ongoing public health efforts such as diagnostics and vaccination. Rapidly designing, manufacturing and distributing nAbs requires significant planning across the product value chain and an understanding of the opportunities, challenges and risks throughout.
Methods: A systems framework comprised of four critical components is presented to aid in developing effective end-to-end nAbs strategies in the context of a pandemic: (1) product design and optimization, (2) epidemiology, (3) demand and (4) supply. Quantitative models are used to estimate product demand using available epidemiological data, simulate biomanufacturing operations from typical bioprocess parameters and calculate antibody production costs to meet clinical needs under various realistic scenarios.
Results: In a US-based case study during the 9-month period from March 15 to December 15, 2020, the projected number of SARS-CoV-2 infections was 15.73 million. The estimated product volume needed to meet therapeutic demand for the maximum number of clinically eligible patients ranged between 6.3 and 31.5 tons for 0.5 and 2.5 g dose sizes, respectively. The relative production scale and cost needed to meet demand are calculated for different centralized and distributed manufacturing scenarios.
Conclusions: Meeting demand for anti-SARS-CoV-2 nAbs requires significant manufacturing capacity and planning for appropriate administration in clinical settings. MIT Center for Biomedical Innovation's data-driven tools presented can help inform time-critical decisions by providing insight into important operational and policy considerations for making nAbs broadly accessible, while considering time and resource constraints.

Statement of Significance: Based on MIT Center for Biomedical Innovation's BioACCESS models presented in this paper, equitable access to neutralizing antibodies against SARS-CoV-2 requires products that have high potency, productive manufacturing platforms and effective distribution that is integrated with ongoing vaccination campaigns.

KEYWORDS: neutralizing antibodies; pandemic response; epidemiology; biomanufacturing; product design

INTRODUCTION

SARS-CoV-2 (severe acute respiratory syndrome coronavirus 2) continues to spread across the globe, leading to over 114 million infections and 2.5 million deaths as of 1 March 2021 [1]. The public health response to the COVID-19 pandemic continues to be insufficient, leading to increasing social and economic costs since the World Health Organization (WHO) declared a 'Public Health Emergency of International Concern' on 30 January 2020. Beyond preventive measures such as facial coverings and physical distancing, large investments have gone into the discovery, development and eventual distribution of

*To whom correspondence should be addressed. Stacy L. Springs. Tel: +1-617-253-3084; Email: ssprings@mit.edu.

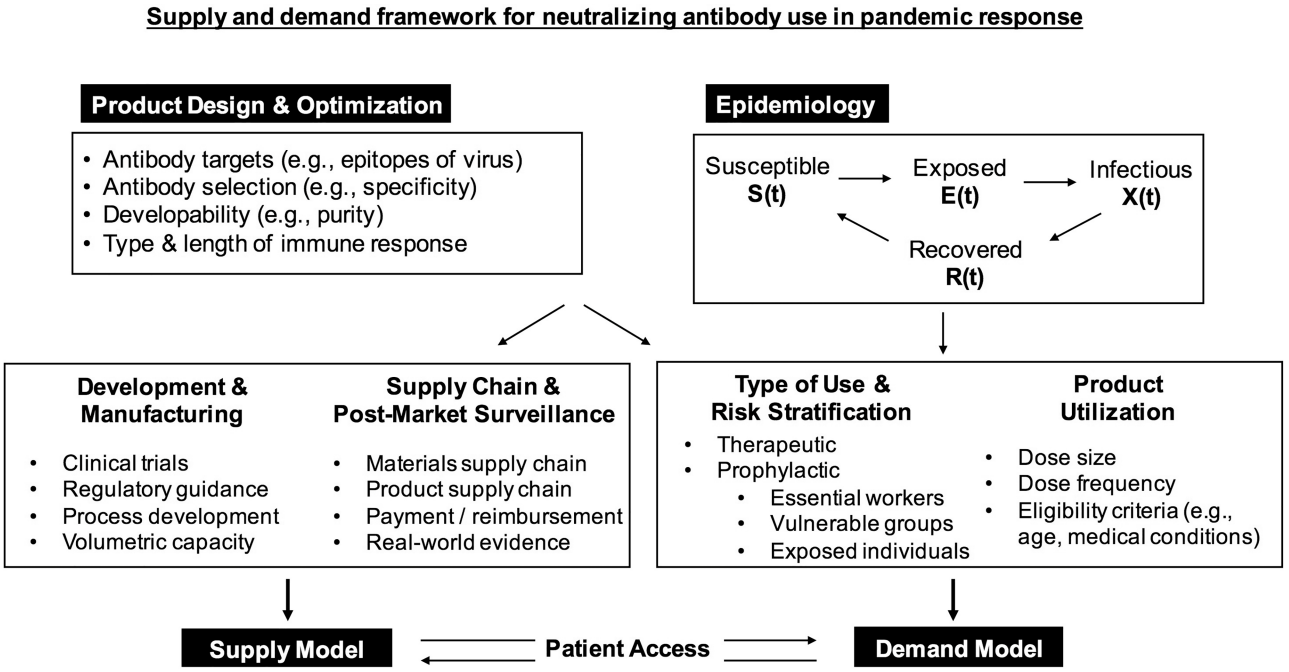


Figure 1. Framework for designing an effective end-to-end antibody strategy to meet clinical needs during COVID-19 and other future pandemics. Specifically, the framework presents four interconnected factors that impact patient access: (1) product design & optimization, (2) epidemiology, (3) demand and (4) supply.

vaccines, with the aim of reaching population-wide immunity. Even with some vaccines becoming available since Q4 of 2020, for example through Emergency Use Authorization (EUA) by the US Food and Drug Administration (FDA), neutralizing antibodies (nAbs) can serve as an additional tool to reduce disease burden and healthcare costs. nAbs can be useful as a prophylactic to block viral infection and/or a therapy for those currently infected, especially in specific subpopulations (e.g. immunocompromised patients, immunosenescent elderly patients, those with allergies to ingredients found in vaccines) and to achieve certain objectives (e.g. rapid cluster control) since they provide immediate protection against viral infection [2, 3].

The potential for nAbs to play an important role in pandemic response against SARS-CoV-2 builds on a long history of serving as effective targeted therapies against a wide range of clinical indications in both the chronic (e.g. cancers) and infectious (e.g. respiratory syncytial virus, rabies) disease space [4, 5]. To assess if nAbs will be an effective component of the COVID-19 pandemic response strategy and to promote widespread access, there is need to better define opportunities, challenges and risks across the product value chain. A systems approach is useful to understand the interconnected factors that influence the design, development, manufacture and supply of nAbs against SARS-CoV-2. The framework presented in Figure 1 highlights four critical factors to consider when developing an effective end-to-end nAb strategy: (1) product design and optimization, (2) epidemiology, (3) demand and (4) supply. This paper explores each factor in detail and provides examples of data-driven models aimed at informing time-critical decisions.

PRODUCT DESIGN AND OPTIMIZATION

As a prophylactic, nAbs help avoid infection by effectively blocking interaction, binding and eventual entry of viruses into host cells, especially for exposed individuals who are not immune. As a therapeutic, nAbs need to be administered during the incubation period following viral exposure. The use of convalescent human sera for treatment against the 1918 H1N1 influenza and 2009 H1N1 influenza, as well as during the current COVID-19 pandemic, demonstrates the potential role nAbs could play in accelerating recovery following infection [6, 7]. Rather than using sera with a mixture of antibodies with different affinities to epitopes on the virus of interest, techniques such as sorting of individual B cells have been established to isolate monospecific and homogeneous antibodies that target the desired antigen [8].

Designing effective nAbs requires an understanding of their relative potency and targets. In the case of SARS-CoV-2, structural proteins—spike glycoprotein (S), membrane glycoprotein (M), envelope protein (E) and nucleocapsid protein (N)—serve as potential targets for antibody-mediated neutralization. Data from dose response curves generated using pseudovirus neutralizing assays can be used to calculate the instantaneous inhibitory potential, a measure that combines the binding affinity and neutralizing capacity of different nAbs [9]. Further structural, biophysical and bioinformatics analyses of nAbs can help design antibody cocktails and provide correlates of protection for therapeutic use [10]. These factors play an important role in determining the dose size needed to neutralize the virus and thus product volume required to meet clinical needs. Most nAbs targeting SARS-CoV-2 have been shown to recognize the receptor-binding domain

(RBD) of the S1 unit of the S protein, as it serves as the gateway for SARS-CoV-2 into cells [11]. Since nAbs targeting different epitopes (e.g. N-terminal domain of the S protein) on SARS-CoV-2 also exist, a combination of several potent antibodies could lead to stronger immune protection, as previously shown in the case of Ebola and SARS [12, 13].

Several techniques have been established for isolating and selecting potent antibodies to ensure an optimal safety and efficacy profile. One approach has been to use SARS-CoV-1 hybridomas to develop SARS-CoV-2 cross-nAbs, especially since the S proteins of the two viruses are 77.5% identical in their primary amino acid sequence and have a high degree of structural homology [14]. Alternatively, RBD-specific memory B cells from sera of recovered COVID-19 patients can serve as a useful source of high-affinity nAbs [15]. In this case, nAbs are isolated from convalescent plasma of recovered patients, selected, engineered for improved potency and amplified via cloning [16]. A third source of nAbs are from individuals who have acquired immunity after a strong immune response to antigens presented in vaccines [17]. A fourth technique to isolate nAbs is to generate potent antibodies from transgenic animals, for example genetically humanized mice that can be induced to produce optimized fully human antibodies [18]. Finally, an *in vitro* approach to isolating nAbs selected against a specific target is by site-directed screening of a phage display library constructed based on patient samples collected in the acute phase of the disease [19]. More work is needed to better understand mechanisms underpinning neutralization of the virus in order to isolate and optimize nAbs with maximal affinity to the desired epitopes on SARS-CoV-2.

There are numerous nAb products in the development pipeline, either for prophylactic and/or therapeutic use against SARS-CoV-2. Most target the SARS-CoV-2 S protein and have a conventional full-length IgG-based monoclonal antibody (mAb) format [20]. Novel single-domain antibodies or nanobodies are also being explored, especially given their potential to bind to novel epitopes inaccessible by conventional antibodies and to serve as building blocks for the design of multivalent and multispecific molecules [21]. Novel anti-SARS-CoV-2 antibodies currently in clinical trials are predominantly being developed in the USA and China. As of November 2020, both Eli Lilly and Regeneron have received EUA from the US FDA for their respective mAb products, with each committing to an initial limited supply of 300 000 doses by Q1 of 2021 [22]. Several other late-stage clinical trials, for example a program jointly led by GlaxoSmithKline and Vir Biotechnology, may lead to the availability of more and diverse anti-SARS-CoV-2 nAbs in the future.

When designing nAbs and during postmarket surveillance, thorough consideration is needed to guard against factors that can inhibit their therapeutic efficacy. Antibody-dependent enhancement (ADE) occurs when antibodies bind but fail to neutralize the virus in such a way that enhances viral entry into cells, facilitates viral replication and worsens the infection [23]. This phenomenon has been observed with other viruses (dengue, Zika, Ebola, SARS-CoV-1) and often tied to waning immunity as antibodies are cleared from the body, with effective neutralization at high antibody concentrations but ADE of infection at subneutralizing concentrations [24, 25]. While studies have shown that some anti-SARSCoV-2 IgG mAbs can lead to ADE of viral entry *in vitro*, it is not yet known how that manifests *in vivo* and whether the invading virus undergoes active replication or leads to enhanced viral shedding [26]. Several strategies can help reduce the risk of ADE, for example, probabilistic mapping of ADE-associated epitopes using high-throughput peptide-based scanning in order to design higher affinity nAbs that can reach neutralization at lower concentrations [27, 28]. Engineering the Fc or constant region of antibodies, which differ from the variable Fab region that binds to the specific target of interest, could allow for a longer half-life and to tune interaction with Fc receptors in ways that prevent viral uptake in immune cells [29, 30].

Another challenge arises when mutations on the virus confer resistance to convalescent plasma or RBD-specific nAbs. This leads to the need for antibody combinations that target nonoverlapping neutralizing epitopes in order to maintain therapeutic effectiveness [31]. A library of viral mutants was used to demonstrate escape from both the Eli Lilly and Regeneron products with EUA as a result of unique mutations in the RBD's receptor binding motif, in particular the E406W mutation [32]. Analysis of all human-derived SARS-CoV-2 sequences available as of 11 January 2021 indicates that escape mutations may already exist among circulating strains of the virus, for example K417N present in the B.1.351 lineage first identified in South Africa and N501Y present in the B.1.1.7 lineage originally identified in the UK. While not unique to SARS-CoV-2, titers of antibodies against the RBD of the S protein significantly decay with time following infection, though the number of memory B cells is more constant [33, 34]. In order to effectively defend against the virus upon re-exposure, it would be important for the immune system's humoral response to evolve in ways that lead to the production of antibodies with increased neutralizing breadth and potency [35]. While more data are needed to understand the extent to which escape variants risk jeopardizing SARS-CoV-2 countermeasures, there is need to design nAbs robust against attenuation of antibody neutralization.

EPIDEMIOLOGY

Understanding changes in the number of infections, hospitalizations and deaths associated with SARS-CoV-2 is important to better define the pandemic's impact. Investments in diagnostic testing, contact tracing and data collection have allowed for better monitoring of viral transmission. The use of real-time and location-specific data helps inform the types of interventions needed to curb the pandemic, such as strategic planning and allocation of limited resources (e.g. provisioning beds for COVID-19 patients within a hospital). Data collected on infected patients also provide insight into divergent disease pathways (e.g. asymptomatic versus symptomatic), the length of contagiousness, the time to recovery, initial and follow-on symptoms due to the infection and risk factors for severe illness.

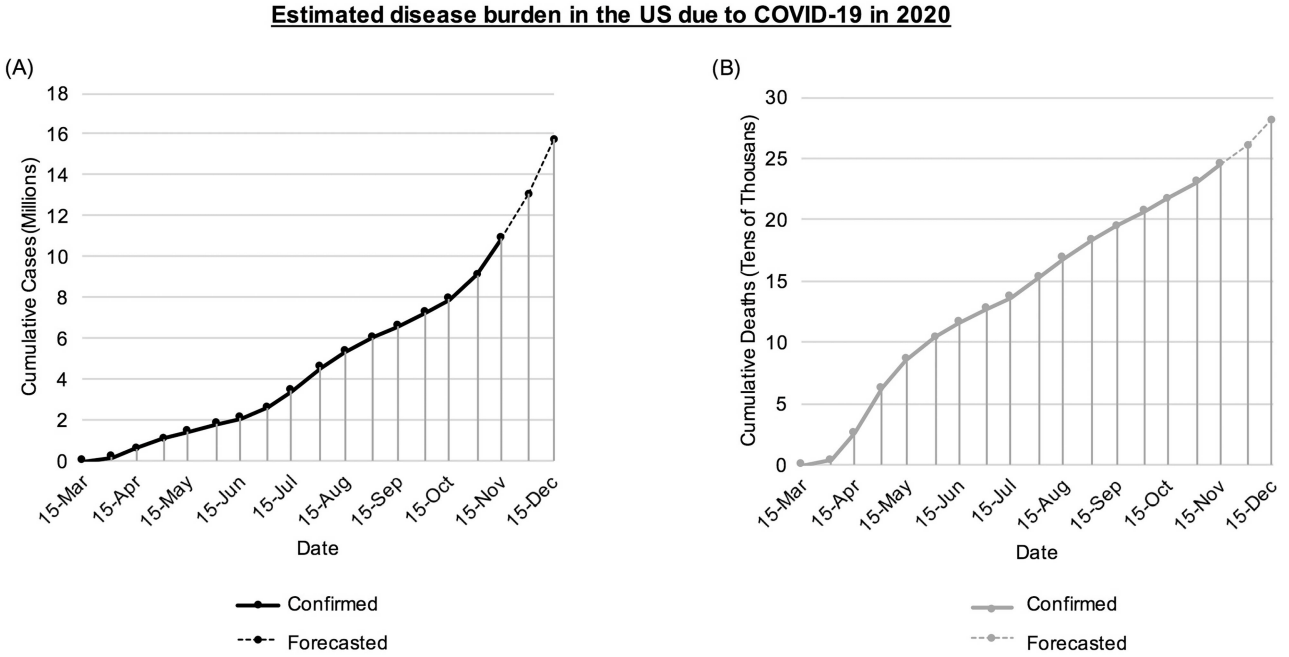


Figure 2. Burden of disease due to the COVID-19 pandemic in the USA. Cumulative number of confirmed cases (A) and deaths (B) from 15 March 2020 to 15 November 2020 and projections until 15 December 2020. Data source for confirmed, historical data are from Our World In Data, a project of the Global Change Data Lab. Data source for the projections is from the Ensemble model created by the COVID-19 Forecast Hub.

Additionally, models have been developed to predict future impact of the pandemic and potential strain SARS-CoV-2 infections may have on health care systems. Many of these models employ the classical SEIR framework to explain time-dependent transmission dynamics of the virus as a sequence of transitions among a finite number of health states: S (susceptible), E (exposed), I (infectious) and R (recovered) [36]. The utility of such predictive models depends on the quality and timeliness of data available, especially as uncertainty in data reporting appears across the entire process (e.g. false negative or positive results of laboratory tests, deviations in ways confirmed and probable cases are defined across different jurisdictions). Models also differ in assumptions made, for example how levels of social distancing will change in the future or adjusting for the delay between the onset of symptoms and reporting. Nevertheless, data-driven models are important to forecast the scale of pandemics and anticipated changes in infections to better inform decisions.

To develop an effective nAbs strategy against an infectious virus, forecasting product demand is an important step to determine the manufacturing capacity required to supply therapies to all those who need them. A key challenge is that estimates for the effective reproduction number (R_t), a measure used to determine viral spread, can vary based on the mathematical method used to calculate it, geographic region considered, period of time covered by available dat and public health measures implemented (e.g. facial coverings). Another challenge is that in a pandemic response, nAbs would likely be used in combination with other prophylactic (e.g. vaccines) and therapeutic (e.g. antiviral drugs) agents, whereas some noncritical patients recover without the need for any intervention. Therefore, the product demand calculated is a measure based on the total clinically eligible patients if they were all to seek care. This measure provides an upper bound for the total product volume needed to satisfy public health needs during a pandemic, based on both product properties and disease epidemiology. In this paper, the USA will be taken as a case study for assessing historical trends and projecting the future number of infections due to COVID-19. Specifically, a 9-month period from 15 March to 15 December 2020 is used as initial time bounds for the model presented. The calculations performed and subsequent analysis can be updated as more data become available with time and generalized to all countries for a global estimate of the product demand.

Figure 2 presents the cumulative number of confirmed cases and deaths between 15 March 2020 and 15 November 2020, with projections until December 15, 2020. Data on the historical, daily cumulative burden of disease are based on both confirmed and suspected infections. This estimate is likely lower than the true total because not everyone is tested to confirm suspected infections. Projections for the future number of cases are generated by combining estimates from multiple models into a single 'ensemble' forecast that increases the robustness of the prediction [37]. While each individual model has an underlying level of uncertainty and different assumptions, the 'ensemble' model provides the median prediction across all eligible models for a given location to provide a probabilistic distribution of the forecast. For the 4-week ahead forecast between 15 November and 15 December 2020, the 'ensemble' model is generated by integrating predictions submitted by 42 independent research groups. Based on the analysis presented, the total number of SARS-CoV-2 infections in the USA between 15 March 2020 and 15 December 2020 is projected to be 15.73 million.

DEMAND CONSIDERATIONS AND MODELS

Estimates for the amount of nAbs required to meet demand can be made using the epidemiologic trends provided above. This is crucial in order to appropriately and proactively plan manufacturing operations, as well as downstream supply, distribution and delivery of finished products. For biopharmaceutical companies, the projected demand is an indication for the potential revenue flow and biomanufacturing capacity (including human, capital and material resources) needed to supply safe, efficacious drugs to patients in a sustained manner. For healthcare providers, it helps inform purchase orders, conduct inventory management and allocate products, especially if in limited supply.

While the maximum number of clinically eligible patients could refer to the susceptible (S), exposed (E) and infectious (I) populations of the SEIR model, thus excluding those with natural immunity after recovery and acquired immunity from vaccines, this is likely beyond the biopharmaceutical industry's available production capacity. In some cases, more accurate estimates of a product's demand can be made by identifying patient subgroups based on genotypic or other features. For example, advances in the mechanistic understanding of how antibody cocktails prevent viral escape could allow for the design of specific antibody combinations effective against unique viral mutants [38]. Since periods of scarcity are inevitable when responding to a global pandemic, leading to willingness-to-pay as the determinant factor of who gets a product, accounting for people with low purchasing power in demand forecasts is crucial to reduce inequalities in access [39]. Another challenge comes from the dynamic nature of infectious pandemics and time-dependent changes in viral transmission, thus highlighting the need for continuous learning of demand models by incorporating real-time data.

In this exercise, several factors are considered and assumptions made to generate a forecast for the total nAb volume, for a given product i, required to meet demand if it were the only product on the market. The demand model can be generalized by the following equations:

$$V_{total,i} = V_{prophylactic,i} + V_{therapeutic,i} \tag{1.1}$$

$$V_{prophylactic,i} = \left(N_{essential\ workers} + \left(R_t * N_{confirmed\ cases}\right)\right) * D_{p,i} \tag{1.2}$$

$$V_{therapeutic,i} = (1 - P_h) * \left(N_{confirmed\ cases} * D_{t,i}\right) \tag{1.3}$$

In these equations, V is the product volume calculated in grams, N is a subgroup of the population, R_t is a multiplier for the number of unique individuals that catch the virus from each infected person. For each product i, D_p and D_t are the dose sizes needed to induce immunity for prophylactic and therapeutic use, respectively. The total number of confirmed cases is the sum of people that are hospitalized and those with noncritical infections, whereas P_h is the percentage of patients not eligible to receive therapeutic nAbs. In this model, the maximum number of eligible patients is determined based on a patient's disease severity and potential need for hospitalization. An important variable is the dose size required for each person, since it can vary greatly across each product (i) in development. Regeneron's clinical trial for its casirivimab and imdevimab cocktail tested both a 2.4 and 8.0 g dose size, each of which led to a reduction in viral load and medically attended visits relative to the placebo group [40]. The dose range tested for Eli Lilly's bamlanivimab was 0.7 to 7.0 g, with the EUA granted for the lowest dose size to allow access to more patients since the results were comparable across all treatment groups [41].

While nAbs are typically dosed based on a patient's weight, clinical trials are being conducted by testing the impact of standard, one-time intravenous injections. A challenge is determining the ideal dose size relative to viral load, as well as characterizing the neutralizing capability of different nAbs since they do not all have the same binding targets or affinities, especially in light of circulating viral mutants. There are little data on the relative dose size for prophylactic use compared with that for use in hospitalized or noncritical patients; therefore, it is assumed that $D_{p,i} = 0.75\ D_{t,i}$. Furthermore, antibody titers in asymptomatic and mild COVID-19 patients were attenuated several months from the onset of symptoms, indicating the potential short-term protection conferred by nAbs and risk of reinfection [42]. The timing of nAbs administration for therapeutic use is also important to effectively block viruses from invading healthy cells. Anti-SARS-CoV-2 nAbs should be administered as early as possible to keep viral load as low as possible, at least within 10 days of symptom onset based on FDA guidelines [43].

To illustrate application of the demand model, Figure 3 shows the hypothetical prophylactic and therapeutic demand of nAbs, assuming a dose range between 0.5 and 2.5 g, in the USA during a 9-month period between 15 March and 15 December 2020. This takes into account the historical number of infections reported (15 March to 15 November 2020) as well as projections (15 November to 15 December 2020). Prophylactic and therapeutic demands are considered separately given their distinct subpopulations. One dose is assumed for each administration and the potential for reinfection is not accounted for in this model.

For prophylactic demand, the estimated number of essential health workers with direct patient contact is 13.8 million [44]. R_t is a useful estimate for the average number of people that will catch the virus from a single infected person while keeping into account the percentage of the population that has acquired immunity over time. However, there is a high level of heterogeneity in reported values and it can miss out on 'superspreaders', with as few as 10–20% of infected people accounting for close to 80% of new COVID-19 cases [45]. Estimates for the daily R_t, calculated using an SEIR simulator together with machine learning algorithms to minimize errors, ranged between 0.83 and 2.81 in the USA for the months included in the case study [46]. The large difference in the prophylactic demand calculated using the lower and upper bounds of the R_t demonstrates high sensitivity to the rate of viral spread and importance of public health measures aimed at limiting community transmission.

Therapeutic demand is calculated based on an estimated 15.73 million SARS-CoV-2 infections. The EUA given to

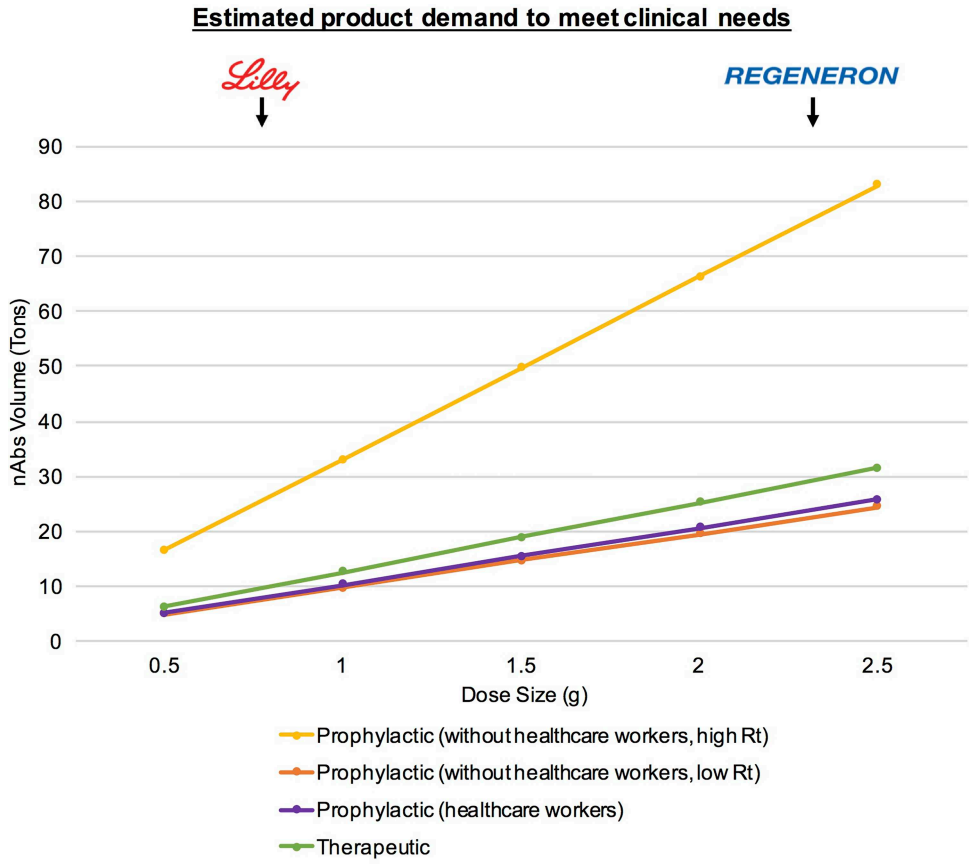


Figure 3. Projected demand for nAbs as prophylactic and therapeutic agents against SARS-CoV-2, between 15 March and 15 December 2020 in the USA, as a function of dose size. Shown are products with EUA from the US Federal Drug Administration, as of 23 November 2020.

Eli Lilly and Regeneron specify that investigational use of nAbs are limited to nonhospitalized adult and pediatric patients with mild to moderate infection, not those in critical care or hospitalized. The proportion (P_h) of infected individuals whose pathogenesis worsens so much that they need to be hospitalized, thus no longer eligible for post-exposure therapy, increases with age and assumed to be 20% in this model [47]. As a result, the total number of patients eligible to receive therapeutic nAbs in the case study presented is assumed to be 12.58 million. Specific treatment guidelines and contraindications may further limit the number of eligible patients. For example, preference has been given to high-risk groups, including those ≥65 years, with immunosuppressive disease, or other comorbidities (e.g. chronic kidney disease, diabetes).

The product volume required to meet prophylactic use is significantly larger than that for therapeutic use. Given initial periods of scarcity, this presents decision makers with important tradeoffs to consider. Limited doses are likely to be prioritized for therapeutic use, especially if vaccines are the primary prophylactic agents and available at greater volumes. Another factor that might limit the use of nAbs is their high cost relative to vaccines, as well as need for specialized staff, equipment and facilities during administration. The estimated product volume needed to meet therapeutic demand ranges between 6.3 and 31.5 tons for 0.5 and 2.5 g dose sizes, respectively. The production of mAbs is likely to put significant strain on the global biomanufacturing capacity, especially since the industry also needs to continue making and supplying non-COVID-19-related antibodies for a range of different indications. According to the Top1000bio database provided by BioPlan Associates, the total worldwide bioprocessing capacity is approximately 16.5 million liters, with close to two-thirds using Chinese hamster ovary (CHO) host cells for mAb production [48]. Based on these estimates, the total mAb CHO-cell-based production capacity is approximately 41.8 tons. While it is not clear how much of that capacity is unused, finding space in existing facilities or shifting production of non-COVID-19 pandemic nAbs to contract manufacturing organizations is important given the long lead-time (several years in the case of traditional stainless steel facilities and up to 18 months for modular single-use facilities) required to establish new production capacity.

SUPPLY CONSIDERATIONS AND MODELS

nAbs have a large molecular weight (approximately 150 kDA) require a host organism for their production (e.g, mammalian cells) and have high target affinity to extracellular targets [49]. Despite being more complex than small molecule drugs, the production of nAbs has benefited from rapid technological progress and standardization

that provides a common process platform for these types of products [50]. Different process parameters can be modified to yield a range of production volumes within a given time schedule. Based on expert input and literature review, the following baseline parameters were used to model process operations in a traditional stainless steel facility: production titer of 5 g/l, 80% yield for drug substance, 95% yield for drug product, run time of 15 days, turnaround time of 3 days between runs and a batch success rate of 90% [51–53]. While these parameters and associated manufacturing costs vary across products and processes, they are based on best practices in the industry. Bioreactor volume used in simulations range between 10 and 25 kl, depending on the facility size. These user-defined parameters determine the production capacity for the manufacturing facility being modeled. The model output is a standard product volume that can be manufactured by a bioreactor per run and over a given time duration, though some bioreactor runs may yield batches that are unfit for use after quality testing.

In the simulations presented, the focus is on therapeutic rather than prophylactic use of nAbs, assuming that limited supply will be preferentially given to actively infected rather than at-risk patients. More specifically, it evaluates production operations across three different types of scenarios: a small-size facility (50 kl), medium-size facility (100 kl) and large-size facility (250 kl). The following equations outline how to determine the number of batches and production time needed to meet demand for a given product (i):

$$N_{runs} = \left[\left(\frac{V_{therapeutic,i}}{t_p * V_{facility} * y_{ds} * y_{dp}}\right)/S\right] * N_{br} \qquad (2.1)$$

$$T_{production} = \left[N_{runs} * \left(t_{run} + t_{change}\right)\right]/N_{br} \qquad (2.2)$$

In these equations, N_{runs} is the total number of bioreactor runs needed to meet a desired product volume, $V_{therapeutic,i}$ is the estimated product demand, t_p is the production titer, $V_{facility}$ is the total volumetric capacity for the facility being modeled, y_{ds} and y_{dp} are the production yields for drug substance and drug product, respectively, N_{br} is the number of bioreactors in the facility being modeled and S is the batch success rate. It assumes that all bioreactors within a facility are of the same volume and run in parallel: small-size facility (five bioreactors, 10 kl reach), medium-size facility (five bioreactors, 20 kl reach) and large-size facility (10 bioreactors, 25 kl reach). To calculate production time ($T_{production}$) to meet demand, N_{runs} is equivalent to the number of runs calculated, t_{run} is the run time for each bioreactor and t_{change} is the turnaround time between each bioreactor run. Since facilities do not run year-round (e.g. due to scheduled maintenance), the model assumes an idle time of 30 days per year. In a scenario where production is distributed across multiple facilities, the total number of runs needed to meet demand can be determined by accounting for the relative number and volume of bioreactors in each facility.

Once the biomanufacturing process has been defined, the cost of production can be determined. A cost model is used to identify key financial and other factors within a product's value chain that are often the main drivers for company decisions and can impact affordability of the product. The conventional unit used for the cost-of-goods (COGs) is dollars per gram ($/g). The components of the cost model are found in Table 1, with further details of calculations available in Supplementary Material A1. Through literature review, major cost contributors to drug substance and drug product manufacturing at commercial scale were identified [54–56]. These include: labor, utilities, materials (including consumables), capital investment, fill & finish and tax & insurance. While this list is not exhaustive, it highlights factors most likely to change as a result of innovations in biomanufacturing and those that impact overall COGs. The model does not account for the costs related to the sale of products (e.g. supply chain, inventory, marketing, tax on revenue). Many cost centers (e.g. labor) are a function of a facility's utilization rate, for which the number of shifts, bioreactors and runs are used as proxies.

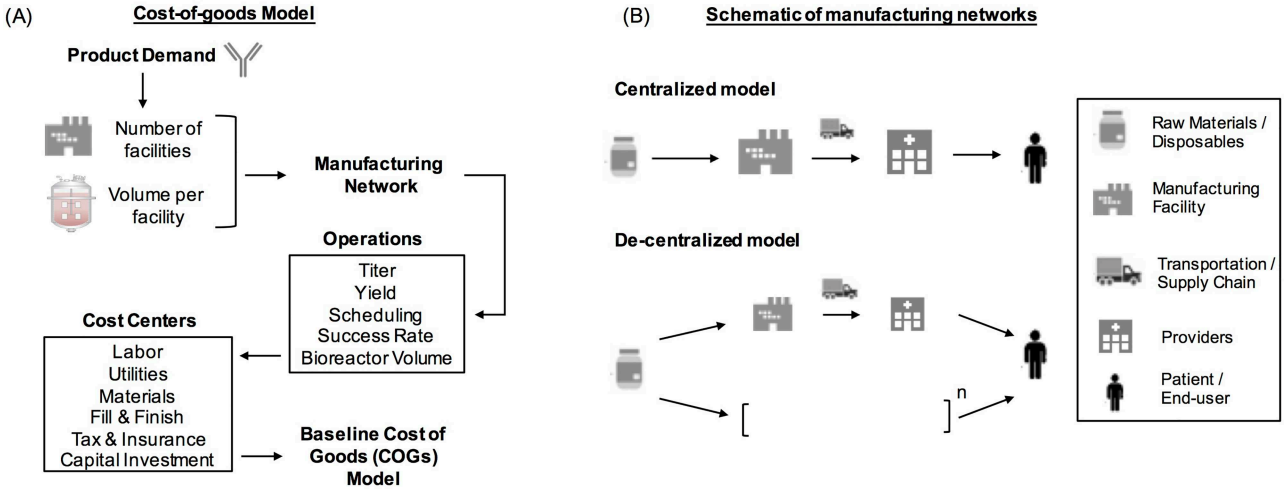
Verification and validation of the supply model is important to ensure applicability and robustness in accurately conveying current biomanufacturing processes. This was primarily done by setting bounds on the input variables based on appropriate and widely accepted values. Additionally, interaction among input variables and outputs of the model were compared with other existing, licensed software packages such as SimBioPharma and SuperProDesigner. Finally, third-party reviewers were engaged to check for any errors and confirming that the model was built to fulfill the function it was designed for.

The methodology used for calculating the COGs can be found in Figure 4A, integrating product demand, manufacturing operations and different cost centers. The baseline model for nAbs production assumes that both drug substance and finished product manufacturing take place in the same facility, whereas inventory cost is minimized since products are continuously shipped to healthcare providers, with demand greater than supply for the timeframe considered. In a single-facility manufacturing network (i.e. centralized model) all products are made at a single site and supplied globally. In a multifacility manufacturing network, production is distributed across the number of sites within the network. The relative product volume manufactured at each site can either be (1) split evenly at each site, (2) proportional to the estimated demand in the regions in which the sites are located geographically, or (3) any other combination of production levels that the user chooses. Figure 4B provides a graphical representation of centralized versus distributed manufacturing networks. While both Regeneron and Eli Lilly are US-based companies, they have established manufacturing partnerships with Roche and Fujifilm Diosynth, respectively, for production and distribution of nAbs overseas. Having more facilities within a network allows for more rapid scaling of manufacturing capacity, while also segmenting production lines for different markets.

Depending on the manufacturing network employed, the production time needed to meet the large therapeutic product demand for nAbs in the USA can be prohibitive. Based on simulations, the Eli Lilly (0.7 g) and Regeneron (2.4 g) products approved under EUA could meet the 9-month projected therapeutic demand in the US in approximately

Table 1. Factors influencing the cost of manufacturing mAbs and variables used to calculate them. Further details of calculations are available in Supplementary Material A1. Drug demand is used to determine the product volume needed to satisfy the market, whereas specific production parameters (e.g. number of bioreactors, runs, etc.) impact overall process cost

Input variable	Units	Dependent upon
Drug demand	g	Population size, dose size, eligibility (Fig. 3)
Production volume	L/Bioreactor/Run	Bioreactor volume, product titer, yield, utilization rate
Labor	$/Facility/Year	Total FTE, salary, utilization rate
Utilities	$/Facility/Year	Utilization rate
Materials	$/Facility/Run	Raw material cost, consumables costs, utilization rate
Capital investment	$/Year	Facility size, depreciation rate, project duration
Fill & finish	$/Facility/Dose	Vial and process cost, product volume
Tax & insurance	$/Year	Capital investment



(C) **Number of facilities needed to meet demand in 6 months**

Dose Size (g)	Product volume (tons)	Number of Facilities		
		Small (50 kL)	Medium (100 kL)	Large (250 kL)
0.5	6.3	5	3	1
1.5	18.9	13	7	3
2.5	31.5	21	11	5

(D) **Baseline COGs ($/g) for manufacturing scenarios**

Dose Size (g)	Product volume (tons)	COGs ($/g)		
		Small (50 kL)	Medium (100 kL)	Large (250 kL)
0.5	6.3	94	87	68
1.5	18.9	70	58	54
2.5	31.5	65	53	52

Figure 4. (A) Framework for calculating the COGs of antibody production. (B) Graphical representation of centralized vs distributed manufacturing networks. (C) Number of facilities within a manufacturing network needed to reach therapeutic demand for nAbs under user-defined time constraints (scenario shown: 6 months). (D) COGs ($/g) for the production of nAbs under different manufacturing scenarios.

0.5 and 1.8 years, respectively, assuming normal operations in a single large-size facility. For a single medium-size facility, the production time goes up to 1.3 and 4.4 years, respectively. As a virus propagates, rapid response during a pandemic is essential to reduce the burden of disease. If production takes too long, patients will not be able to access potentially life-saving therapies. One way to reduce production time is by increasing the number of facilities making the nAbs of interest. Figure 4C shows the calculated number of facilities needed to reach therapeutic demand for nAbs under user-defined time constraints, for example within 6 months. Using typical process parameters, a bioreactor goes through nine complete runs within a 6-month time period. Given uncertainty around nAbs currently in development, the dose range considered is between 0.5 and 2.5 g. Given a nAb therapy with a dose size of 2.5 g, the total therapeutic demand calculated (31.5 tons) could be met within 6 months under either of the three scenarios of distributed manufacturing networks: (i) 21 small-sized 50 kl facilities, (ii) 11 medium-sized 100 kl facilities or iii) five large-sized 250 kl facilities. The number of facilities needed is rounded up to ensure that the minimum demand is met. These estimates provide a sense for the manufacturing capacity required to rapidly respond to clinical needs as a result of emerging pandemics. These scenarios serve as a basis for calculating the COGs, found in Figure 4D. The COGs are a function of the biomanufacturing network employed to produce the nAbs, including the number and

size of bioreactors in each respective facility. Using the same example of a nAb therapy with a dose size of 2.5 g, the COGs to meet therapeutic demand is $63/g, $51/g and $49/g under each of the three manufacturing networks models. Economies of scale are seen by decreasing COGs when the facility size or product volume increases while keeping the other constant, as expenses are amortized over more units of production.

Comparing decentralized and distributed manufacturing systems can provide insight into the impact operational decisions have on the ability to meet public health needs, as well as the associated costs and logistical challenges. By increasing the complexity of manufacturing networks, specifically the number and relative location of facilities, tradeoffs are introduced. Redundancy in manufacturing operations can help reduce risks associated with supply chain dependence, especially if manufacturing challenges halt or delay production at one or more sites [57]. Additionally, having multiple production sites may help expedite regulatory review of dossiers across jurisdictions that have different requirements and allow for more flexible commercial contracts [58]. Our modeling results show that when keeping the production volume constant, COGs are comparable when production is split across one or two facilities, whereas the potential benefits of noncentralized production need to be weighed against the relatively higher costs when more facilities are added to the network. Other challenges related to distributed manufacturing include ensuring a reliable raw material supply chain from qualified vendors to all production sites. The risk of raw material shortages is increasing given the number of anti-SARS-CoV-2 nAbs at or approaching late-stage development, while there may be competition with overlapping materials in the production of vaccines and non-COVID-19-related therapeutics. Additionally, many factors can make geographies unsuitable for the production of complex biologic therapeutics: poor infrastructure (e.g. transportation networks, constant power supply), reliance on imports to source raw materials and equipment, lack of trained technical personnel, inadequate investments, issues with smuggling of substandard medicines from neighboring countries as well as unfavorable environmental or political conditions [59]. The production of mAbs continues to be a highly regulated and intensive process, with challenges such optimizing cellular productivity, ensuring a consistent glycosylation profile, effective purification during downstream processing and analytical technologies for rapid quality control and release [60].

DISCUSSION

The models presented seek to provide a better understanding of the relative production scale and cost associated with using nAbs to meet public health needs during a pandemic. The demand and supply projections could be further improved by more granular, location-specific data on viral spread and manufacturing cost as well as the likelihood and impact of various catastrophic events that could significantly impact production and supply operations. This would allow for more detailed simulations of manufacturing scenarios, including under various types of exogenous risks. For example, the increasingly complex raw material and product supply chains may be susceptible to geopolitical instability, accidental or deliberate contamination, competition for supplies used across multiple industries, trade disputes (e.g. Italy blocking Oxford-AstraZeneca COVID-19 vaccines from being shipped to Australia) and currency exchange rate volatility in ways that negatively influence business continuity and patient access [61].

Beyond production, unique considerations need to be accounted for throughout the supply chain, including product storage, inventory management, fair allocation and delivery. nAbs are time- and resource-intensive products to administer, as they require IV infusions that usually take place in outpatient facilities with appropriate healthcare staffing, training and equipment [62]. Administration in a clinical setting, while important to treat potential adverse reactions during the infusion, requires overcoming logistical hurdles to minimize viral transmission and may be in competition with other clinical needs if hospitals are overwhelmed by the surge of patients with severe SARS-CoV-2 infections. Alternative sites of administration are being explored, but need to be validated to ensure appropriate staffing, equipment and services, while minimizing additional costs to patients [63, 64]. Successfully administering nAbs also means overcoming various logistical hurdles, such as access to infusion sites, which are not accessible in all geographies and may compete with other routine procedures such as cancer care. More data are needed on the number of anti-SARS-CoV-2 antibodies that have been supplied relative to those administered in clinic in order to understand where bottlenecks exist. Although data from the US Department of Health and Human Services show that 664 691 of the 798 591 allotted doses of Eli Lilly's therapy were delivered to hospitals as of 2 March 2021, hospitals have reported that many fewer doses have been administered to patients [65, 66].

Doses of nAbs purchased by the US government will be available at no costs to patients, however, healthcare facilities could charge for administering the therapies. In the biologics space, in particular mAbs, prices have been an impediment to global and equitable access to life-saving therapies. Although 85% of the global population and a growing underserved market exists outside North America and Europe, these two regions account for 80% of mAbs sold globally at a median price of $15 k–200 k per year in the USA for a given treatment [67]. In low-and-medium-income countries (LMICs), mAbs are rarely available despite a growing number of such products appearing on the WHO Model List of Essential Medicines over the past few years and are often not reimbursed by public health systems when available. Innovative business and financial models have been suggested with the aim of making antibodies therapies more affordable. This includes financing through partnerships with traditional donors and newer funding mechanisms, as seen in the case of the COVAX Advance Market Commitment for anti-SARS-CoV-2 vaccines, as well as product development partnerships, and social impact bonds, among others [68, 69].

As the COVID-19 pandemic continues to grow, with more cases and deaths each day, a comprehensive response

that includes both vaccines and therapies is important to reduce the global burden of disease. The models presented and analysis provided point to the resource- and-time-intensive process of ramping up nAb production to large scales. For nAbs to be an important component of the pandemic response and complement efforts of ongoing vaccination campaigns, deliberate investments and partnerships are needed. With limited supply in the near-to-medium term future and hospitals already overwhelmed by the effects of the pandemic, ethical questions around the distribution and rationing of limited doses become increasingly pertinent. Effectively identifying at-risk individuals infected with SARS-CoV-2 who can avoid hospitalization as a result of taking nAbs would be beneficial both for their individual well-being and alleviating pressure on health systems.

For pandemic preparedness and response, a challenge will continue to be the need for substantial levels of resources to scale production capacity to meet high levels of demand under constrained timelines. However, although biopharmaceutical manufacturing continues to be a technically challenging and tightly regulated process, it only makes up part of the overall product value chain necessary to introduce a new therapy as part of a pandemic response. Other considerations include product development, clinical trials, supply chain logistics, procurement, inventory management and last-mile delivery. There is a need to better understand total system costs and effectiveness to identify areas of improvement. For example, the fast-changing nature of the COVID-19 pandemic is at odds with the long lead-time required by the biopharmaceutical industry to establish the required manufacturing capacity. Increasingly, manufacturing facilities can be designed with flexibility built into them, thus allowing for expansion to meet different production needs over time (e.g. under normal scenarios and in pandemic response). Integrated solutions that engage all stakeholders are needed to make access to nAb therapies a reality. Furthermore, there is need for enhanced coordination across all policy spheres (e.g. international, regional, national, local) to implement a comprehensive nAbs strategy that can effectively meet public health needs. This will be especially important to overcome challenges, for example viral mutations that escape antibodies that risk hindering the effectiveness of all current and prospective therapies. In this context, the FDA has released guidance to encourage sponsors of individual nAbs to collaborate in designing antibody cocktails that can be responsive to emerging needs [70]. In doing so, integrating antibody strategies with other public health measures during a pandemic response, such as vaccine distribution, is valuable to use material, financial and human resources in the most effective way.

nAbs are expected to continue to grow in importance, especially as markets expand in LMICs and products are molecularly engineered to be more potent in ways that reduce the dose size and total product volume required to meet demand. Various innovations, across technology, policy and operations need to be considered and rapidly tested to design end-to-end nAbs strategies that serve public health needs. The magnitude of the COVID-19 pandemic and risk of future outbreaks of known and unknown pathogens highlight the importance of developing fit-for-purpose nAbs strategies, especially when under uncertainty and in a resource-scarce environment.

AUTHOR CONTRIBUTIONS

D.G., A.J.S. and S.L.S. contributed equally to the preparation of the manuscript. All authors have read and agreed to the published version of the manuscript.

DATA AVAILABILITY STATEMENT

The data presented in this study are available on request from the corresponding author.

SUPPLEMENTARY DATA

Supplementary data are available at *ABT* online

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