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REVIEW

Emerging antibody-based products for infectious diseases: Planning for metric ton manufacturing

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ABSTRACT

This review focuses on the emerging monoclonal antibody market for infectious diseases and the metric ton scale manufacturing requirements to meet global demand. Increasing access to existing antibody-based products coupled with the unmet need in infectious disease will likely exceed the current existing global manufacturing capacity. Further, the large numbers of individuals infected during epidemics such as the ongoing COVID-19 pandemic emphasizes the need to plan for metric ton manufacturing of monoclonal antibodies by expanding infrastructure and exploring alternative production systems.

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Introduction

Monoclonal antibodies (mAbs) have shown impressive therapeutic benefit for a range of diseases including cancer, autoimmune disease and infectious disease. As such, they are the fastest growing sector in the biopharmaceutical market, with over $100B in sales each year and a projection to double that within the next several years.[1] Today, the market for mAbs is overwhelming high-income countries.[2] Almost no mAb products are registered in low-income countries, and the few registered in middle-income countries are often unavailable within their public health systems. This accessibility gap will only widen as mAbs continue to become an increasingly large proportion of pharmaceutical company pipelines.

A global call to action recently issued by IAVI and the Wellcome Trust seeks to expand access to these potentially life-saving monoclonal antibody (mAb) products[2] and to prioritize their more equitable distribution. Perhaps the most critical factor controlling wide accessibility is the cost of goods (COGS) associated with mAb manufacturing. A consensus target for the COGS for mAbs to enable global access to these products is ~ $10/g,[3] far from the current COGS ranging from $95-200/g.[2]

The metric ton manufacturing scale required to meet anticipated demand may be as great a challenge as cost reduction, but when achieved, would be expected to further lower costs. The total mass of mAbs manufactured worldwide is estimated at 30 metric tons annually[2,4] and as evidenced by the limited global access to mAb-based antivirals during the ongoing COVID-19 pandemic, will not be sufficient for rapidly addressing broad scale public health infectious disease threats.

The majority of the more than 500 mAbs now in clinical testing[5] are for oncology and autoimmune indications. However, with the recent clinical success and regulatory approvals of mAbs for Ebola virus disease and COVID-19, neglected infectious diseases are anticipated to represent a significant percentage of the future therapeutic antibody market. Currently, there are over 75 clinical trials of mAbs against ~20 infectious pathogens and mAbs for ~70 pathogens in preclinical development.[2] These include mAbs against SARS-CoV-2, HIV, influenza, respiratory syncytial virus (RSV), filoviruses, viral enteric pathogens and gram negative bacterial enteric pathogens, including *E.coli, Klebsiella, Shigella* and *Salmonella*.[2]

This review focuses on an overview of existing anti-infective mAb products, the emerging antibody market for infectious diseases, and the metric ton scale manufacturing requirements necessary to meet the future demand of this growing class of products. Although different antibody formats are being explored clinically (antibody-drug conjugates, antibody-protein fusions, antibody fragments, single-chain antibodies, camelid IgG), this review is limited to fully assembled, monoclonal antibodies (IgG, IgA, and IgM, including multispecific formats) that have high avidity due to multivalency and also have functional Fc regions that can be engineered for extended half-life and/or varying levels of effector functions.[6]

Licensed antibody-based products for infectious diseases

Of the 100+ mAbs licensed for use (https://www.antibodysociety.org/resources/approved-antibodies/), only nine have infectious disease indications: palivizumab for respiratory syncytial virus (RSV), raxibacumab and obiltoxaximab for anthrax, bezlotoxumab for *C. difficile*, ibalizumab for HIV, Rabishield and Rabimabs for rabies, and inmazeb and ebanga for Ebola virus. A brief overview of these products, none of which currently require metric ton manufacturing, is provided here.

Palivizumab for respiratory syncytial virus immunoprophylaxis

RSV is a ubiquitous pneumovirus, infecting nearly all children by 2 years of age.[7] In the U.S., RSV is the leading cause of lower

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respiratory tract disease in young children and has been associated with asthma and wheezing throughout childhood.[8] Among children less than 5 years of age, RSV is estimated to account for 132,000 to 172,000 hospitalizations in the U.S. annually.[9] Globally, RSV is responsible for 3.2 million hospital admissions and 48,000–75,000 deaths each year for children younger than 5 years of age,[10] and it is estimated to cause 6.7% of all deaths for children between 1 month and 1 year of age.[11] In the U.S., RSV has a disease burden similar to that of non-pandemic influenza A for elderly (>65 years of age) and high-risk adults (congestive heart failure or chronic pulmonary disease).[12] It is estimated that in this population RSV is responsible for 125,000 hospitalizations and 10,000 deaths per year.[13]

Palivizumab, a humanized murine IgG1 antibody, is indicated for immunoprophylaxis in neonates; however, its high cost and frequent administration requirements (monthly dosing throughout the RSV season) have restricted its use to high-risk infants. It has been estimated that 16–18 preterm infants need to be treated with palivizumab to prevent a single RSV-related hospitalization.[14] In order to provide prophylactic protection during the 4 to 5-month annual peak in RSV circulation, neonates are treated monthly with 15 mg/kg intramuscular administrations, necessitating ~200 mg of drug for a 3 kg neonate. As this single course can cost in excess of $5,000 per infant, the resulting cost-effectiveness analysis is debated. Moreover, due to this high cost, palivizumab is inaccessible to children in developing nations and is unavailable in 4 of the 5 most populous countries – more than half the world's population does not have access to this life-saving drug. Opportunities for expanding the accessibility of RSV immunoprophylaxis are discussed below in the next section (Emerging Antibody Products for Infectious Diseases).

Raxibacumab and obiltoxaximab for prophylaxis and treatment of inhalational anthrax

Bacillus anthracis, the causative agent of anthrax, is classified as a Category A bioterror agent. Multiple countries developed anthrax as a weapon during the 20th century and fears remain that a nation state or terrorist organization could deploy weaponized anthrax. Raxibacumab, a human IgG_1 against protective antigen (PA), one of the toxins secreted by the bacteria, received FDA approval in 2012. Obiltoxaximab is a humanized anti-PA mAb that was licensed in 2016 by the FDA. Both products are indicated for patients with inhalational anthrax and administered in combination with antibiotics. These products are also recommended for prophylaxis of inhalational anthrax if alternative options are not available. Dosing is 40 mg/kg dose intravenously for raxibacumab and 16 mg/kg for obiltoxaximab.[15]

While the U.S. stockpile requirements for these products are not publicly available, a conservative estimate given a number of factors is approximately 1 million doses. Assuming 60 kg as the average weight of a potential patient, 0.96–2.4 metric tons of mAb are needed to supply 1 million doses. Factoring in the additional consideration of expiration dates associated with any drug and using a 5-year shelf-life as an example here, this translates to manufacturing of 0.19–0.48 metric tons per year.

Bezlotoxumab for preventing recurrence of C. difficile infection

Clostridium difficile infection (CDI) is the main cause of infectious diarrhea in patients following hospitalization and antibiotic treatment.[16] In developed countries, *C. difficile* has become the most common cause of nosocomial diarrhea.[16,17] Treatment usually involves initial antibiotic therapy with either vancomycin, metronidazole, or fidaxomicin. However, up to 35% of the patients have recurrent infections,[18] which are more difficult to treat and associated with increased hospitalization time. Further, subsequent infections can have more severe outcomes and higher costs than the first infection, in addition to a 50–60% chance of a continuing recurrent infection.[19] In 2018, there were 36 million hospital admissions in the US for CDI.

Bezlotoxumab is a fully human IgG1 mAb that binds and neutralizes *C. difficile* toxin B. In two global Phase 3 trials, the observed safety and efficacy of 10 mg/kg intravenous treatment with bezlotoxumab was supportive of licensure; however, the incidence of recurrence remained stubbornly at ~20% in the treatment groups, indicating that additional intervention may be required to eliminate recurrences altogether.

There is no evidence of access to bezlotoxumab in low- and middle-income countries.[2] With the underwhelming clinical adoption of bezlotoxumab, and more efficacious treatments on the horizon,[20] current manufacturing capacity is likely sufficient to meet demand for this drug.

Ibalizumab for multi-drug resistant HIV infection

The use of mAbs for HIV therapy offers unique mechanisms of action and the potential for an improved safety profile compared to standard antiretrovirals. Further, mAb therapy may be especially appropriate for multi-drug resistant (MDR) HIV infection.[21] Ibalizumab is a licensed humanized IgG4 mAb product that acts as a CD4-directed post-attachment inhibitor and is currently approved for patients with MDR HIV infection. Patients receive a 2 g loading dose followed by 800 mg maintenance doses every 2 weeks, or approximately 20 g on an annual basis. With the disadvantages of intravenous administration, biweekly dosing, and high cost, the use of Ibalizumab is limited to heavily treated adults with multidrug-resistant infection failing their current antiretroviral therapy regimen.[22] Pharmacoeconomic analysis suggests a 90% reduction in price would be necessary to make this a cost-effective therapy.[23] Current manufacturing capacity is sufficient to meet current demand for this drug.

Rabishield and Rabimabs for rabies post-exposure prophylaxis

Rabies virus is prevalent in 150 countries around the globe. The virus is transmitted through the bite of a rabid animal and infects the central nervous system of the host, causing encephalopathy and, if untreated before symptoms appear, ultimately results in death. It is estimated that 30 million people undergo rabies post-exposure prophylaxis each year[24] with polyclonal antibody preparations in combination with post-exposure vaccination. Treatment prior to the appearance of

symptoms is highly efficacious, yet WHO reports that rabies infections claim the lives of more than 55,000 people each year. India suffers the biggest impact with approximately 35% of the world's rabies deaths. The majority of deaths occur in rural and resource poor areas where physical and/or economic access to treatment is limited. In the U.S., domestic animals like dogs and cats, and wildlife like bats, raccoons, and skunks are the major carriers of rabies. The Centers for Disease Control and Prevention indicates that 30,000 to 60,000 persons in the U.S. are treated for rabies exposure each year. Although human or equine polyclonal immunoglobulins are the most commonly used products for exposures, supplies are limited and the quality variable. India has recently begun use of two human monoclonal products for rabies exposure, Rabishield, a single human IgG1 mAb product, and RabiMabs, a murine dual mAb (IgG1 and IgG2b) product.[24] These products are dosed intramuscularly at fractions of a mg/kg. With 30 million people receiving post-exposure prophylaxis annually, to completely replace animal-derived polyclonal products with mAb products would require on the order of 50 kg of mAb per year.

Inmazeb and ebanga for Ebola virus immunotherapy

Ebolavirus, one of several filoviruses that infects humans, causes hemorrhagic fever disease with a high mortality rate (40–90%).[25] Sporadic outbreaks in Africa historically have ranged from 1 to 28,000+ patients, with the 2013–2016 West African outbreak being the largest.[26] Recently, two human IgG1 intravenous mAb products, inmazeb (3 mAb cocktail) and ebanga (single mAb), were demonstrated in a clinical trial conducted during an outbreak in the Democratic Republic of the Congo[27] to be superior to ZMapp, a three mAb cocktail used as a benchmark based on its previously characterized activity in a truncated trial in West Africa.[28] Both products were approved by the FDA in late 2020. With inmazeb dosed at 150 mg/kg and Ebanga at 50 mg/kg, fulfilling the U.S. Strategic National Stockpile (SNS) goal of 750,000 courses of treatment, economics aside, would require approximately 3–9 metric tons of mAb. With a 5-year shelf-life as an example, this translates to manufacturing of 0.6–1.8 metric tons per year.

Emerging antibody-based products for infectious diseases

With the recent clinical successes of mAbs for highly virulent and lethal infections,[27,29] anti-infectious disease mAbs as a product class are expected to grow dramatically. In this section, we focus on several disease targets for which mAb therapeutics or prophylactics are expected to significantly and positively impact public health, with the caveat that widespread deployment will require significant reductions in manufacturing cost and an expansion of existing manufacturing capacity to be feasible from a pharmaco-economic standpoint. Assuming global access to these emerging antibody-based products, metric ton needs are estimated in Table 1. The metric ton requirements for emerging antibody-based products are substantially greater than licensed products for infectious diseases because of larger unmet needs. Establishing unmet need and estimating market share is complex, so the metric ton

Table 1. Potential indications, antibody doses and estimates of metric ton (MT) requirements (per 1 M Users).

Target*	Indication	Unmet Need	Assumptions**	Product Requirements/ 1 M Users/Yr (MT)
Respiratory Syncytial Virus	Prophylaxis (healthy infants)	140 M births/yr	50 mg dose	0.05
	Prophylaxis (adults)	600 M > 65 years old globally	10 mg/kg dose	0.6
HIV	Therapy	1.9 M with MDR HIV 38 M with HIV	Weekly 0.35 g dose	18.2
	Prophylaxis (parenteral)	High-risk individuals; difficult to estimate	2 mAb cocktail at 1 mg/kg each and 3 doses/year	0.36
SARS-CoV-2	Therapy	> 80 M infected; >1.8 M deaths	2 Abs; 10 mg/kg	1.2
	Prophylaxis		2 Abs; 1 mg/kg	0.12
Malaria	Prophylaxis	1.1 B at high risk***	5 mg/kg; 3 times per year	0.9
Influenza	Prophylaxis	High-risk individuals; difficult to estimate	1–10 mg/kg	0.06–0.6
	Therapy	~10 M hospitalizations/yr	1–8 g/dose	1–8
Mucosal MPT (HIV, Sperm, HSV)	Prophylaxis	~140 M (for contraception)****	4 Abs (2 HIV Abs, 1 HSV antibody, 1 contraceptive antibody); 50 doses/year X 40 mg total per dose	2.0

MDR = multi-drug resistant; MPT = multipurpose prevention technology.
*emphasis on mAb product concepts that have been through a Phase 1 clinical trial.
**based on a global average weight of 60 kg.
*** https://www.who.int/data/gho/data/themes/malaria.
**** Because people are good at estimating their risk for unintended pregnancy but underestimate risk for STI acquisition, contraceptive activity is likely to be a major driver for use of a multipurpose prevention technology (MPT).

requirements are presented as per one million users/year. The estimates for emerging products are based on clinical trial doses, but generally assume the lowest dose evaluated. A mass of 60 kg per individual is used for calculations, as it is the mean global weight for a potential user. Overall, conservative assumptions are used so that the requirements are likely underestimates.

Respiratory syncytial virus

Healthy infants

Currently, there is no approved RSV prophylaxis for healthy infants (140 million births per year globally), a significant unmet need. Palivizumab's requirement for monthly intramuscular administration, the emergence of escape mutants, and its high-cost limit its clinical usefulness for prophylaxis in high-risk infants.[30] Most of the approximately 100,000 young children in the United States who are hospitalized annually for RSV infection have no recognized risk factors and do not qualify for monthly palivizumab prophylaxis. This partially explains why palivizumab has had a minimal effect on the overall burden of RSV infection. An alternative approach would be the administration of a long-lasting mAb to all infants born shortly before or during the RSV season.[30] If a single intramuscular dose at birth could provide several months of protection, the burden of infection would be shifted to older children who are at lower risk for hospitalization. Several mAbs are in clinical development with enhanced neutralizing activity compared with palivizumab and containing point mutations in the Fc region to promote extended half-life. These potential products would support a vaccine-like strategy to protect infants from RSV with doses administered once per RSV season (which typically spans 5 months of the fall and winter). A 50 mg single intramuscular dose of one of these mAbs, MEDI-8897, has been evaluated in a Phase 2 trial in healthy preterm infants entering their first RSV season.[31] The incidence of medically attended, RSV-associated lower respiratory tract infection was 70% lower than with placebo (2.6% vs. 9.5%) through 150 days after administration, and the incidence of hospitalization for RSV was 78% lower (0.8% vs. 4.1%).[31] These data provide excellent proof of concept for a healthy infant approach and the product is now being evaluated in phase 3 clinical trials. Assuming a 50 mg dose, 0.05 metric tons would be required annually for protecting 1 M newborns (Table 1). Ignoring accessibility issues, with 140 million births per year, and limiting use to the half of newborns born prior to onset or during the RSV season, 3.5 metric tons would be required to protect all at-risk newborns.

Senior citizens

RSV infection is now recognized as a significant health burden in elderly adults. For example, 5–10% of elderly patients in long-term care facilities develop RSV infections per year with rates of pneumonia and death of 10–20% and 2–5%, respectively.[32] The total number of annual RSV infections is 3% to 7% of healthy elderly patients, or 1.4 to 3.3 M RSV infections among the elderly (using 2015 population). There are 1.4 million adults living in nursing care facilities in the U.S. Use in these populations could range from treatment of diagnosed infections, to immunoprophylaxis in nursing care facilities when an RSV index case is identified, to universal dosing of the elderly once per RSV season. For context, the indication currently being explored for anti-SARS-CoV-2 mAb LY-CoV555 in a Phase 3 study is prophylaxis in long-term care facilities (ClinicalTrials.gov Identifier: NCT04497987). For a 10 mg/kg dose, 0.6 metric tons would be required for 1 million users (Table 1).

HIV

HIV therapy

mAb products in clinical development may offer safety and efficacy benefits that dramatically expand the patient populations from the current limited population for which ibalizumab is indicated. For example, leronlimab (previously known as PRO 140) is a humanized IgG4 against CCR5, an HIV co-receptor, that has reemerged as a potential novel agent for HIV treatment. Leronlimab is only under consideration for patients with CCR5 tropic virus; however, the majority of patients harbor this HIV tropism. In a Phase 2b trial, weekly leronlimab administered subcutaneously to patients who discontinued antiretroviral therapy (ART) was found to maintain viral suppression in 56% of the patients for 12 weeks.[33] In a subsequent Phase 3 trial, the results of which have yet to be published, the sponsor reported that 81% of the subjects who completed the trial (leronlimab + ART) achieved viral suppression without any increased safety risk observed (https://www.cytodyn.com/pipeline/hiv). The primary mechanism of resistance is the emergence of CXCR4 or mixed tropism; however, this observation has reportedly been rare to date, with some patients having over 4 years of ongoing use of leronlimab. Leronlimab is administered as a weekly 0.35 g subcutaneous injection (18.2 g/patient/year = 18.2 metric tons/million users). A Phase 3 study evaluating leronlimab as a monotherapy is planned. Potential use of this drug could range from the approximately 5% of all HIV patients having MDR infections to first-line monotherapy. With approximately 38 million people living with HIV (https://www.unaids.org/en/resources/fact-sheet), treating the entire global MDR population would require manufacturing of 34.6 metric tons of mAb annually and treating all HIV infected individuals would require 690 metric tons per year.

HIV prevention (systemic delivery)

With serum half-life of 2–4 months observed clinically with Fc-modified mAbs,[34–37] the use of systemically delivered mAbs for the prevention of HIV acquisition in high-risk individuals has become technically feasible. Parenteral antibody dosages required for protection against SHIV mucosal challenge in non-human primates,[38] and the serum concentrations of broadly neutralizing Abs (bnAbs) needed to provide complete protection against viral challenge in the SHIV model have been reviewed.[39] Comparison of *in vitro* neutralization with *in vivo* protection across different SHIV studies has indicated that a serum concentration roughly 200-fold above the neutralization IC_{50} measured *in vitro* is generally needed to ensure 100% protection against viral challenge in passive transfer non-human primate (NHP) studies. Two

large Phase 2B clinical trials (ClinicalTrials.gov Identifier: NCT02568215; NCT02716675), referred to as the antibody-mediated prevention (AMP) study (www.ampstudy.org), evaluated the efficacy of the first generation broadly neutralizing antibody (bnAb) VRC01 in reducing acquisition of HIV-1 infection in high-risk populations. The mAb was infused intravenously at doses of either 10 or 30 mg/kg bimonthly for a total of eight infusions, and participants are tested for HIV infection through 80 weeks after initiation of mAb treatment. Since VRC01 infusions were found to protect against HIV acquisition of strains most susceptible to VRC01,[40] this validates the concept and will facilitate the study of second-generation bnAbs that have longer half-lives requiring less frequent dosing, the ability to neutralize a broader array of HIV strains, and/or increased potency leading to lower dosing and allowing for more user-friendly dosing in the form of subcutaneous delivery; second-generation HIV bnAbs require 5–10x lower doses (~1 mg/kg) for protection in passive immunization studies than first-generation bNAbs.[39]

Combinations of HIV bnAbs targeting different epitopes might have even more potent, potentially synergistic effects;[41] NIAID and IAVI have partnered to develop antibody-based products for HIV prevention and treatment (https://www.niaid.nih.gov/news-events/antibodies-hiv-prevention). The collaboration (including the Serum Institute of India) will develop combinations of HIV bnAbs that can be produced at low cost to prevent and possibly treat HIV. The consortium will identify the best bnAb combinations to develop a product designed to be efficacious against the widest variety of circulating HIV strains. New potent and broad-acting antibody combinations could be administered by subcutaneous injection rather than intravenous infusion.

Estimated 1.7 million individuals worldwide acquired HIV in 2019; the size of the at-risk population is challenging to define. Assuming a 2 mAb cocktail at 1 mg/kg each and 3 doses/year, the manufacturing need is 0.36 metric tons per year per 1 million users (Table 1).

HIV prevention (mucosal delivery)

With sexual transmission being the primary route of HIV acquisition, there is interest in developing products for topical use. Indeed, there is an entire field devoted to the development of multipurpose prevention technologies (MPT) for the prevention of sexual transmission of HIV and other sexually transmitted infections. Several studies have demonstrated that topical administration of anti-HIV mAbs can protect macaques from SHIV mucosal (vaginal) challenge.[38] A mAb-based prototype of an MPT, containing the HIV bnAb VRC01 and a mAb specific for the herpes simplex virus (HSV) was formulated as a vaginal film (10 mg of each mAb), and evaluated in a phase 1 clinical trial.[42] The film product was found to be safe and well accepted. Cervico-vaginal lavage samples collected 24 hours after film insertion significantly neutralized both HIV-1 and HSV-2 *ex vivo*.

To enhance efficacy, a next-generation MPT may contain additional mAbs, such as more potent bNAbs and mAbs that block cell-associated HIV transmission. To increase product desirability, mAbs that agglutinate and trap sperm in mucus may be included to provide contraceptive protection. A prototype MPT vaginal ring for sustained release of mAbs has been developed and tested in macaques.[43] Sustained release of mAbs from a vaginal ring could improve user compliance and decrease antibody doses.

Assuming a 40 mg dose (10 mgs each of two HIV Abs, one HSV antibody and one human contraceptive antibody; 50 doses per person per year; one million users/year), ~2.0 metric ton is required for a mucosal MPT product that is regularly used by one million couples. In addition to manufacturing scale requirements, cost is a clear constraint for such a product. We estimate that COGs for a dose would need to be no more than $0.25,[44] translating to $6.25 per gram, a goal not yet achieved by existing manufacturing platforms.

COVID-19

The SARS-CoV-2 pandemic is a striking and timely example of both the potential mAbs offer for infectious diseases as well as the current limitations that exist with manufacturing capacity. MAbs have the potential to be used for both prevention and treatment of COVID-19 infection.[45] Even though effective vaccines are now available, the weeks of time required to generate an effective immune response emphasizes the benefits of passive immunity in a variety of circumstances including health-care settings and facilities where outbreaks have been common and devastating. MAbs with Fc mutations to extend serum half-life could be administered to nursing home residents during an outbreak and might also serve to limit the progression of disease during undetected early infection. In addition, older individuals and those with underlying comorbid conditions might not mount a robust protective response after vaccination and may need mAb prophylaxis.

Multiple clinical trials are underway evaluating the efficacy of mAbs for prophylaxis, post-exposure prophylaxis and therapy. Based on preliminary clinical trial results, bamlanivimab[46] and the cocktail consisting of casirivimab and imdevimab[29] are currently available under Emergency Use Authorization in the U.S. for pediatric and adult patients with mild-to-moderate COVID-19. These two products are authorized for patients with positive results of direct SARS-CoV-2 viral testing who are 12 years of age and older, and who are at risk for progressing to severe COVID-19 and/or hospitalization. Bamlanivimab was not found to be effective in hospitalized patients.[47] Casirivimab and imdevimab are actively being evaluated in hospitalized patients; the trial has been modified to focus on patients receiving low flow-oxygen and excluding the most critical patients requiring high-flow oxygen or mechanical ventilation at baseline, following a recommendation by the Independent Data Monitoring Committee.[48]

Globally >150 M have been infected with COVID-19, and >3 M have died. With the existence of circulating strains with mutations that increase transmissibility,[49] for capacity calculations, we assume a two mAb cocktail with a single 10 mg/kg/mAb dose, or a 1.2 g total dose (via infusion); this drug would require 1.2 metric tons per million users. Alternative delivery formulations such as subcutaneous or intramuscular injection may be required to increase uptake of these drugs, especially in non-hospitalized patients – health-care systems are not well equipped to provide

infusions to non-hospitalized patients on a large scale.[50] Indeed, a Phase 3 trial with subcutaneously delivered casirivimab and imdevimab is currently underway looking at prophylaxis in people who are household contacts to an RT-PCR positive individual (ClinicalTrials.gov Identifier: NCT04452318). Alternatively, should it prove effective in clinical trials, mucosal delivery via inhalation (*e.g.* nebulizer) could be a drug delivery option (assuming 10–50 mg X 5 doses, 2 Abs) with lower manufacturing scale requirements of 0.2 to 1.0 metric tons per 1 M users.

It had been estimated[51] that over the next year in the U.S. alone, hospitalized patients would require 0.71 million doses of neutralizing mAbs, non-hospitalized symptomatic patients 12.8 million doses, and people with close exposure to confirmed cases would need about 55 million doses. The proposed 70 million systemic doses[51] would require a staggering >80 metric tons of manufacturing for the U.S. alone, more than doubling the current global mAb manufacturing capacity.

Influenza

Influenza spreads globally in yearly outbreaks, resulting in ~10 million hospitalizations and >145,000 deaths during a typical non-pandemic year.[52] A global influenza pandemic remains one of the biggest infectious disease public health concerns. Similar to the HIV and COVID-19 long-acting mAbs being developed for prophylaxis in high-risk individuals, mAbs may be appropriate for prevention of influenza in cases where an effective influenza vaccine is not accessible in a pandemic scenario, when an influenza vaccine cannot be provided to the individual (*i.e.* in children under 6 months), or when a vaccine will not offer protection in time to prevent infection (*i.e.* after exposure to an infected individual).[24,53,54] In these cases, the relative costs and benefits of mAb use for prevention will need to be compared to other interventions that can potentially be used in this situation. With highly potent mAbs and a long serum half-life, 2 mg/kg is a reasonable estimate for a two mAb dose, suggesting 0.24 metric tons/million users would be required for a single-use product.

Influenza mAbs in clinical development are primarily focused on therapy of active infection.[55] Given the annual variation in circulating strains, the majority of mAbs being developed target the highly conserved stem region of the HA molecule.[55] Similar to what has been observed clinically with mAbs for COVID-19, efficacy of anti-influenza mAbs is likely going to depend on intervening early enough in the course of disease. Clinical trials of antibody-based therapies for influenza tend to use 1–8 g doses per patient, suggesting a need for 1–8 metric tons/million users.

Malaria

Globally, the WHO estimates that 1.1 billion people are at high risk (>1 in 1000 chance in a year) of acquiring malaria.[56] There were over 200 million cases of malaria in 2018 and over 400,000 malaria deaths. There are approximately 8.5 million cases of recurrent malaria every year and it is the most common form of the disease outside of sub-Saharan Africa; the dormancy of the parasite means it can avoid eradication by most antimalarial agents used against blood-stage parasites. The greatest unmet need is among children and pregnant women. Indeed, in 2018, children younger than 5 years of age accounted for 67% of malaria deaths worldwide.[56] Children born to infected women are at higher risk of low birthweight and become susceptible when acquired immunity from the mother wanes. Half of pregnant women with severe malaria will die from the infection, often from anemia; this group has been left behind in traditional drug development.

Based on promising preclinical data from two mouse models of *P. falciparum* infection,[57] mAb CIS43LS is being developed as a long-acting immunoprophylactic. A Phase 1 clinical trial testing safety and efficacy have begun enrolling healthy adult volunteers at the National Institutes of Health Clinical Center in Bethesda, Maryland. One group of volunteers will receive a single dose of CIS43LS at 5 mg/kg subcutaneously. Patients in other groups will receive a single dose of the mAb intravenously at one of a series of escalating dosages (5, 20, or 40 mg/kg of body weight). Study volunteers will then take part in a controlled human malaria exposure, which will occur between 10 days and 10 weeks after CIS43LS administration. Volunteers will be exposed via mosquito bites to a curable strain of malaria parasite (*P. falciparum* 3D7). Assuming 5 mg/kg doses administered three times per year, 0.9 metric tons of drug would be required for 1 M people.

Antibody-based therapy for existing malarial infections is expected to be considerably more challenging than prophylaxis due largely to the complicated lifecycle of the parasite.

Metric ton manufacturing

Global demand for mAb products continues to increase. Current manufacturing capacity from mammalian-cell culture is estimated at 30 metric tons of drug substance annually.[4] Greater than 75% of manufacturing capacity in the U.S. and Europe is dedicated to existing commercial products.[51] Manufacturing capacity is expected to increase by 11% per year over the next 5 years.[4] An ongoing need for COVID-19 mAb products or the successful clinical development of a mAb product for an indication with a massive unmet need like Alzheimer's disease[58] could result in an even more accelerated expansion in capacity. Because of the capital costs as well as ongoing operational costs for GMP manufacturing facilities, manufacturing capacity currently tracks demand closely. This is especially problematic when unanticipated events, like the COVID-19 pandemic occur, potentially leaving a shortfall in capacity for other urgently needed drugs.

Non-mammalian cell culture production platforms include yeast, fungus, and transgenic plants and have the potential to expand manufacturing capacity (Table 2). While increased titers have a large influence on required manufacturing capacity, increased potency of mAbs and increased half-life could result in reduced and less frequent dosing, further easing the burden on manufacturing infrastructure and reducing cost per dose. Combinations of improvements in these three variables can have a major impact on manufacturing requirements as represented in this formula:

Table 2. GMP manufacturing scale of mAbs: potential annual drug substance production per single manufacturing unit.

	Mammalian		Plant (transient)	Yeast/fungus
Productivity	1–10 g/L		0.1–1 g/kg of biomass	1–5 g/L
Scale of unit	2,000 L single use	20,000 L fixed	3,500 kg biomass/week	Up to 300,000 L
Yield*	2–20 kg	20–200 kg	0.35–3.5 kg	300–1500 kg
Production cycle	14 d	14 d	14 d	12 d
Assumed annual manufacturing cycles	18	14	20	20
Potential annual production	0.036–0.36 MT	0.28–2.8 MT	0.006–0.06 MT	6–30 MT

*for simplicity we assume 100% process yield in all production systems.

$$\text{Metric tons required cost per dose } \alpha \frac{1}{(\text{productiontiter})(\text{mAbpotency})(\text{serumhalf}-\text{life})}$$

So a modest 1.5-fold increase in production titer, 3-fold increase in serum half-life, and a 5-fold increase in mAb potency could reduce the metric tons required and cost per dose [1/(1.5)(3)(5) = 1/22.5] by up to 22.5-fold.

Mammalian cell culture

Currently, most commercial mAbs are produced in mammalian cells (*e.g.* CHO, NS0) engineered to secrete large quantities of antibodies (typically in the 1–10 gram/liter range). Stainless-steel bioreactors have historically been used for large-scale production, though single-use bioreactors have become more common in recent years due to the reduced turnaround time between manufacturing runs (clean-up operations are quicker) and reduced costs with respect to upfront investment as well as ongoing operational/maintenance expenses. Manufacturers specializing in one product generally tend to use stainless-steel bioreactors, while single-use bioreactors are often used by contract manufacturers who produce a variety of different products. Setting up new manufacturing capacity has a significant lead time; modular platforms are being completed within 18 months while traditional fixed facilities can require several years.

Multiple single-use bioreactors can be used to produce mAbs at scale and require significantly lower capital investment to construct. This technology has enabled the development of global mAb production facilities via distributed manufacturing. Integrated continuous biomanufacturing processes are also faster and cheaper and may offer more consistent processing and greater product quality. Economic analyses of continuous biomanufacturing coupled with continuous chromatographic processes (referred to as integrated continuous processing) can reduce costs by 55% compared to conventional batch processing, when both capital and operating expenses are considered.[59,60] Indeed, a recent analysis suggests that commercial scale continuous process production could achieve COGs of $25/g.[60]

Historically, 12–18 months has been the rule of thumb for estimating the time from the availability of mAb genes to release of GMP material; however, new strategies using transient expression for supply of Phase 1 drug while establishing a GMP stable clone for later stages of development may become more common and is the strategy that enabled multiple mAb drugs to rapidly enter clinical trials for COVID-19.

Transient expression of antibodies in Nicotiana

Over the last 15 years, transient expression systems in *Nicotiana* tobacco plants have been developed that produce full length, assembled mAb.[61,62] This process can be accomplished in less than a week from the time of plant transfection to harvest of raw material expressing high levels of antibodies, and gene to GMP manufacturing can be accomplished in under 3 months. Via the use of transgenic plants with modified N-glycosylation pathways, mAbs can be expressed with mammalian glycans.[63–66] The approach can accommodate gram-to-kilogram level production with existing infrastructure and is well suited for orphan or pediatric indications that require modest manufacturing scale. The current observed expression levels of antibodies at large scale (~100 mg/kg of plant mass) and the limited number of facilities that can manufacture mAbs in plants under GMP suggest that metric ton manufacturing is challenging until improvements in yield can be achieved and additional infrastructure developed. This platform has produced GMP material for a number of clinical trials, including a personalized antibody for non-Hodgkin's lymphoma;[67] ZMapp, a three antibody cocktail for treatment of Ebola virus;[27,28] MB66, a two antibody vaginal film for the prevention of sexual transmission of HIV and HSV;[42] and ZB06, a contraceptive antibody incorporated into vaginal film being evaluated in a surrogate efficacy trial (clinicaltrials.gov identifier: NCT04731818). A techno-economic model has been described for the transient *Nicotiana* platform.[68]

Production of mAbs in yeast

A number of characteristics, such as the stability of the production system, the relative ease of cultivation and rapid doubling time, and advances in production host engineering, make yeasts such as *Saccharomyces cerevisiae* and *Pichia pastoris* attractive hosts for the production of mAbs.[69] A variety of transferase, transporter, and glycosidase genes have been used for glycoengineering of *P. pastoris*. These modifications have made it possible to use glycoengineered *P. pastoris* strains for the production of full-length mAbs with human-compatible glycans.[70,71] Production levels for a monoclonal antibody in a glycoengineered strain of methylotrophic yeast *P. pastoris* have been reported at 1.6 g/L when produced at 1.2 KL scale.[72]

Production of mAbs in filamentous fungi

Species such as *Trichoderma reesei* and *Myceliophthora thermophila* C1 are exceptionally good secretors of proteins outside the growing hyphae. This property has been optimized to the

extent that current industrial production strains are capable of secreting 100 g/L of homologous proteins into a defined cultivation medium under optimized fermentation conditions. As these levels are generally better than other organisms, the secretory capabilities of filamentous fungi make them candidates as production hosts for recombinant proteins on an industrial scale. However, this industrialization goal[73] has yet to be achieved for mAbs. Engineering of *Myceliophthora thermophila* C1 has focused on reduction of proteases to increase yield of intact antibody and glycoengineering for secretion of mAbs with mammalian glycoforms. Expression levels reaching 24.5 g/L and rates up to 3.5 g/L/day have been reported.[74] Existing infrastructure, including 300,000 L bioreactors currently used for manufacturing enzymes and food could potentially – depending on regulatory considerations and need – be multipurpose, including for the manufacture of mAbs. Use of existing fermentation facilities such as these may significantly reduce capital costs,[2] and markedly shorten the time spent meeting metric ton requirements of newly emerging infectious diseases.

Metric ton manufacturing: challenges and opportunities

There is a large mAb pipeline for priority pathogens in the categories of fungi,[75] bacteria[76] and emerging viral infectious diseases with epidemic potential identified by WHO, BARDA and CEPI. Manufacturing antibodies against a significant number of pathogens, coupled with large unmet needs, is likely to challenge the existing manufacturing infrastructure. From a market-based view, as COGs continue to decrease over time, additional indications for mAbs are expected to become economically viable. As they do, manufacturing capacity will grow to address the demand. However, from a public health perspective, expanding capacity and reducing COGs are investments that may be necessary in advance of the market demand in order to improve global access for existing and emerging antibody-based products. The ongoing COVID-19 pandemic is a current example where additional manufacturing capacity for mAbs would help with global access to mAb-based prevention and therapy. In the U.S., the Department of Health and Human Services has invested in access to manufacturing through the Centers for Innovation in Advanced Development and Manufacturing (CIADM) program to address the needs of the Strategic National Stockpile, and the Department of Defense through its Medical Countermeasures Advanced Development and Manufacturing facility for providing vaccines and therapeutics for the military. As just one example, inmazeb, one of two approved filovirus products, is a cocktail of 3 mAbs administered at a total dose of 150 mg/kg, or approximately 10 g per dose. The goal for the SNS is to maintain 750,000 doses of filovirus treatments which would equate to 7.5 metric tons of inmazeb. Manufacturing and budgetary constraints prevent this target from being realized until significant improvements are made in manufacturing capacity and COGs.

With sufficient improvements in potency, capacity and COGs (which by definition includes improvements in purification, with continuous processing an example), whole new categories of mAb products may become economically viable. Most pathogens are mucosally transmitted (200 sq. ft. of mucosal surfaces in an adult compared to 6 sq. ft. of skin surface area), so antibodies at the site of infection may be more effective, and can rely on unique mechanisms of action, such as mucus trapping[77–80] and can be engineered to not bind pro-inflammatory Fcgamma receptors to minimize safety concerns. There are currently no approved products based on direct delivery of antibodies to mucosa. However, there are several mucosal products in clinical development. Prevention of vaginal transmission of HIV and HSV coupled with a contraceptive antibody has been discussed above.[42,44]

There are more than 10 mAbs in preclinical or early stage clinical development for enteric diseases[2] that may be amenable to oral delivery. In the respiratory tract, the limited bioavailability of systemically delivered IgG in tissues affected by the disease, especially the lungs, may be limiting the efficacy of mAbs for diseases such as RSV, influenza and SARS-CoV-2. This shortcoming of parenteral delivery can potentially be addressed by evaluating the efficacy of inhaled antibodies; clinical trials with inhaled SARS-CoV-2 mAbs are nearing initiation (https://www.aridispharma.com/ar-711-covid-19-mab/ and personal communication with Dr. Sam Lai, Inhalon). If scale and cost improvements are dramatic enough, one could even imagine mAbs incorporated in products for daily mucosal use, such as toothpaste: mAbs against *S. mutans*[81] and *P. gingivalis*[82] have been shown clinically to prevent oral recolonization by these bacteria that cause dental caries and gingivitis, respectively.

Although the focus of this review has been on manufacturing of recombinant mAbs, alternative genetic-based technologies, which have their own unique manufacturing challenges,[83] may help in meeting global health goals for some infectious disease indications.[84] Both mRNA and DNA constructs offer an alternative to manufacturing platforms that express antibodies recombinantly and require protein purification, as they use host cells to express mAbs *in vivo*. mRNA has been delivered mucosally in animal models[85,86] and both mRNA[87] and DNA (Clinicaltrials.gov: NCT03831503) have been delivered systemically for expression of mAbs in clinical trials. Although only low circulating levels of mAb (Cmax ~10 μg/mL) have been reported to date, these technologies are in their clinical infancy and expression levels are likely to improve as the technology is further developed.

Finally, in the 35 years since the first mAb was licensed by the FDA (OKT3 in 1986), the use of mAbs for a wide range of indications has grown exponentially in high-income countries, concurrent with dramatic improvements in manufacturing technology, cost and scale. Hopefully, these types of advancements will continue for both established and up-and-coming technologies to the point where mAbs can also play a role in the health of populations in middle- and low-income countries for infectious diseases and beyond.

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