The emerging role of monoclonal antibodies in epidemic/pandemic preparedness and response

The ongoing COVID-19 pandemic highlights the urgent need to prepare for and respond to emerging infectious diseases and the essential role that vaccines and monoclonal antibodies (mAbs) play in this process.

Vaccines and mAbs are complementary approaches – vaccines ideally provide long-term protection to uninfected individuals, whereas mAbs have the potential to treat infected patients or prevent infection in all individuals including immunocompromised people, the elderly and young children. Although there are many mAbs in preclinical development for pandemic and epidemic disease threats, few are in clinical development (Figure 1, next page), though that is likely to change quickly as the world grapples with the COVID-19 pandemic.

The pathogens highlighted below are pressing public health threats for which there are not broadly effective treatments, vaccines or both, and for which mAbs may play an important role.

COVID-19

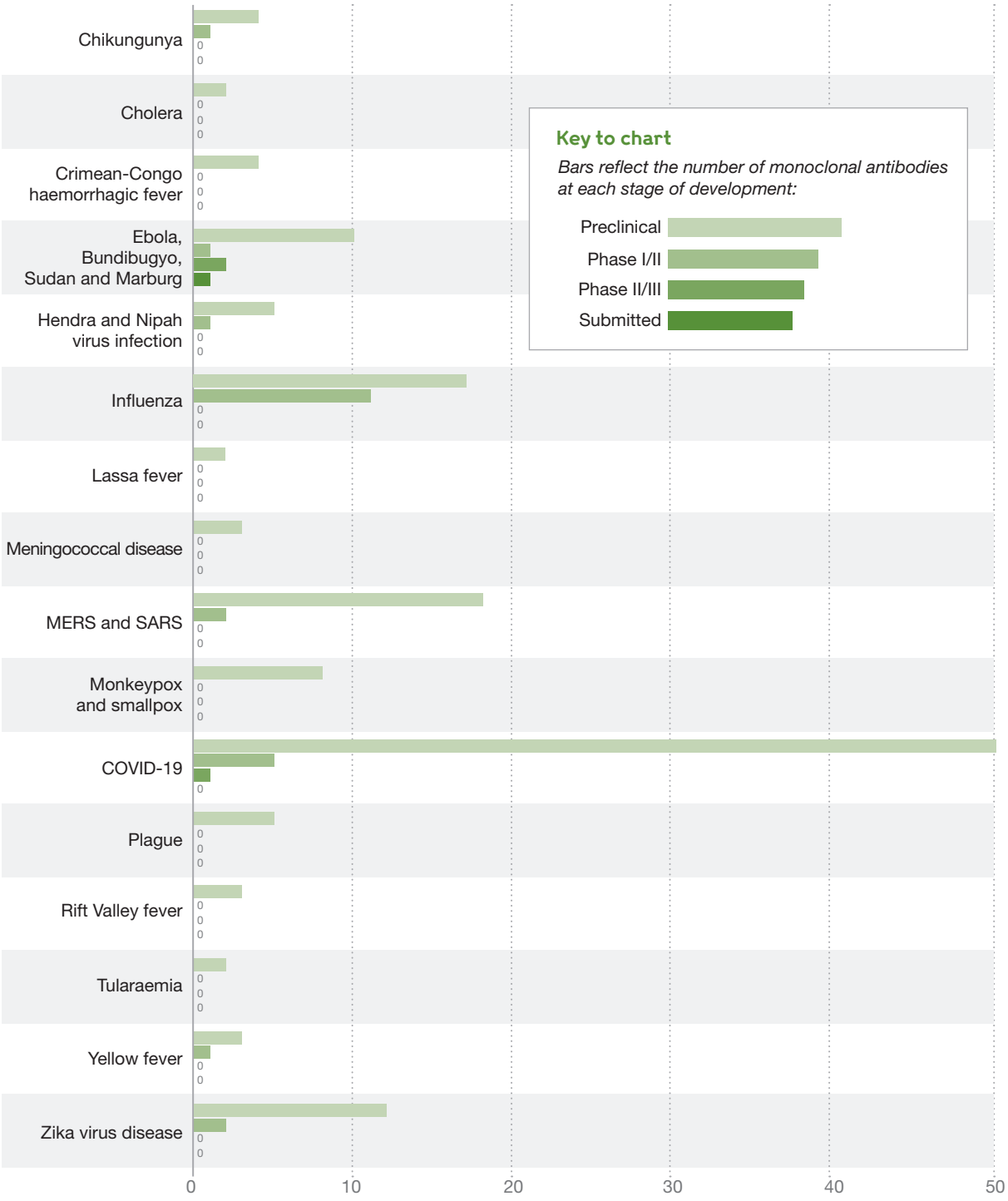
The recently identified Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2), the virus that causes COVID-19, first emerged in China in late 2019. It quickly spread and was declared a pandemic by the World Health Organization (WHO) in March 2020[1]. The scope and scale of the COVID-19 pandemic has elicited an extraordinary response – pharmaceutical companies, government agencies, academic institutions and non-profit organisations across the globe are focused on combatting this new virus, which is significantly more contagious and fatal than influenza. Researchers are rapidly developing vaccine candidates, evaluating existing drugs and developing new therapies, including mAbs.

Several mAbs that are either licensed or in development for unrelated diseases that do not directly target SARS-CoV-2 are being tested clinically to see if they can alleviate complications of COVID-19, including the overactive immune response or cytokine storms that occur in a subset of patients. Researchers are also identifying neutralizing antibodes (nAbs) that specifically target SARS-CoV-2 proteins and are able to block virus infection in tissue culture studies and in preclinical animal models. By the spring of 2020, more than 50 groups had established SARS-CoV-2 mAb programmes employing an array of discovery techniques including phage display libraries, hybridoma approaches with humanised mice, computational design and direct isolation from survivors of SARS-CoV-2, SARS-CoV-1 and other coronaviruses[2]. SARS-CoV-2 neutralizing monoclonal antibodies have entered clinical trials with unprecedented speed to explore their efficacy in treating and preventing COVID-19.

The global spread of SARS-CoV-2 has also triggered unprecedented global collaboration to accelerate research and development. Some examples of the partnerships related to mAbs are:

- The Accelerating COVID-19 Therapeutic Interventions and Vaccines (ACTIV): a public-private partnership to coordinate and accelerate the development of countermeasures including mAbs[3].
- The Coronavirus Immunotherapy Consortium (CoVIC): a global partnership to accelerate discovery, optimisation and delivery of antibody-based therapeutics that is supported by the COVID-19 Therapeutics Accelerator of the Bill & Melinda Gates Foundation, Wellcome Trust and the MasterCard Impact Fund[4].

Figure 1: Pandemic and epidemic diseases mAbs



Note: Repurposed mAbs for SARS-CoV-2 symptomatic treatment not shown

- Vir Biotechnology is partnering with GSK and Samsung Bio to develop COVID-19 mAbs. Vir also has an agreement with WuXi Biologics and a letter of intent from Biogen Inc. to manufacture mAbs at scale. Vir is also working with the National Institute of Allergy and Infectious Diseases's Vaccine Research Center at the US National Institutes of Health (NIH) to further characterise and optimise these mAbs, including incorporating Xencor's technology for extending mAb half-life[5].

- As part of the US Defense Advanced Research Projects Agency's Pandemic Preparedness Platform programme, AstraZeneca is partnering

with The Chinese Academy of Sciences and Vanderbilt University Medical Center[6] to identify and develop SARS-CoV-2 mAbs.

- Eli Lilly is working with AbCellera and Junshi Biosciences to develop mAbs to treat COVID-19[7].

Many companies, including AstraZeneca, Celltrion, Regeneron, Eli Lilly and Vir, are accelerating their development plans and several SARS-CoV-2 mAbs are already in human clinical trials[5–9].

As part of multiple public and private initiatives, several countries, global health organisations and pharmaceutical companies have pledged to accelerate the development, production and equitable access to new COVID-19 diagnostics, therapeutics and vaccines[10]. Johnson & Johnson and Sanofi have each publicly stated their COVID-19 vaccine would be developed "without a profit motive" if they are successful in their development efforts[11,12]. But there aren't yet any public plans to address the need for large-scale manufacturing capacity of SARS-CoV-2 mAbs or to provide global and affordable access to them if they are found to be safe and efficacious.

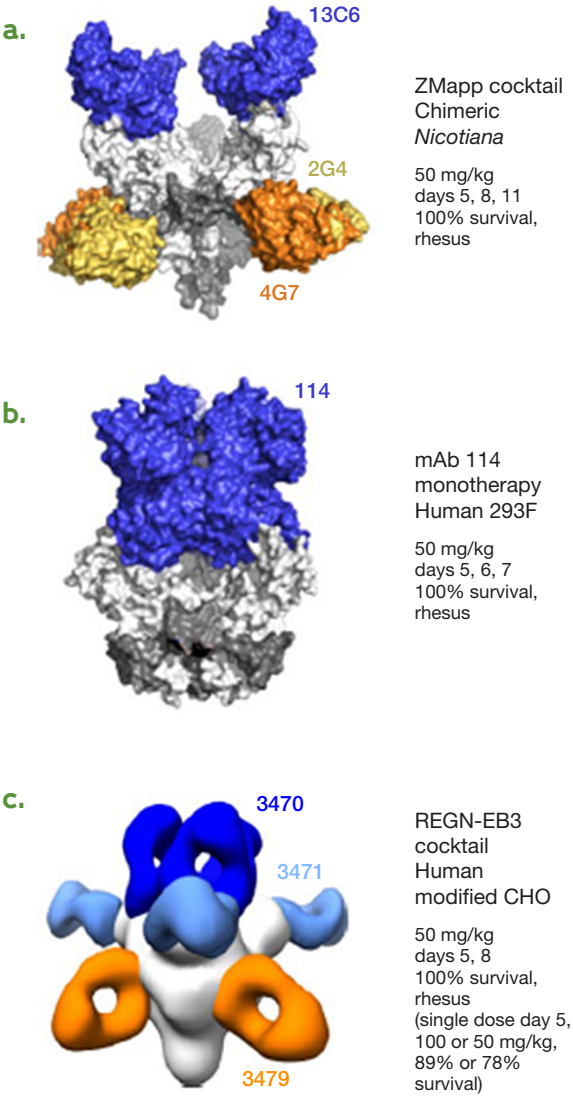
Ebola

Another infectious disease for which mAbs are being tested therapeutically is Ebola. In 2014, the largest Ebola viral hemorrhagic fever outbreak in history began and eventually resulted in more than 11,000 deaths[13]. A series of outbreaks have also recently occurred in the Democratic Republic of the Congo (DRC), resulting in more than 2,100 deaths so far, with fatality rates of approximately 67 per cent. The recent European Medicines Agency approval of the first Ebola vaccine (ERVEBO®) should help curtail new infections[14], but there are still no approved therapies for this highly fatal virus[15].

In 2015, a cocktail of three antibodies known as ZMapp, produced in tobacco plants by MAPP Biopharmaceutical (MAPPBio) was tested in a randomised controlled trial with patients from West Africa diagnosed with Ebola virus disease (EVD). The effect of ZMapp appeared to be beneficial on mortality compared to standard of care; however, the result did not meet the prespecified statistical threshold for efficacy[16].

More promising clinical data was released recently for two Ebola mAb products: Regeneron's REGN-EB3 combination mAb product and mAb114 developed by the NIH/Ridgeback Biotherapeutics. Clinical studies comparing the effects of all three mAb products (Figure 2), which have their unique epitope binding signature on the Ebola virus surface glycoprotein, indicate that ZMapp increases survival rates in Ebola-infected patients from 33 per cent to 50 per cent. Data for mAb114 and REGN-EB3 indicate an enhanced improvement in survival rates from 33 per cent to 65 per cent[17]. Both mAb114 and REGN-EB3 are being made available as part of an expanded access programme in the DRC. In April 2020, the U.S. Food and Drug Administration granted REGN-EB3 a six-month priority review[18].

Figure 2: Ebola monoclonal antibody products (single/combination) bind to the glycoprotein



Source: Saphire EO (2018) Nat Immunol.

Dosage of all three mAb products in late-stage development is in the range of 50-150 mg/kg[17] – more than ten-fold higher than the average dose (1-5 mg/kg) of most marketed antibodies. This high dose could present significant challenges in terms of cost and supply. To address this, next generation Ebola antibodies with improved potency are in development. These next generation single and combination mAbs products to treat and prevent multiple Ebola viruses (Zaire, Sudan and Bundibugyo) are also being designed to be cross-reactive to other filoviruses including Marburg[19–21].

Nipah

Nipah virus (NiV) is one of the pathogens in the WHO R&D Blueprint list of epidemic threats requiring urgent action[22]. First identified during an outbreak in Malaysia in 1998, Nipah infections can cause severe encephalitis and respiratory illness and are a result of both animal-to-human and human-to-human transmission. Since then, several outbreaks, mostly in Asia, have occurred with fatality rates between 50 per cent to 100 per cent.

Nipah and Hendra viruses (HeV) are related zoonotic paramyxoviruses, belonging to the Henipavirus (HNV) genus. There are no vaccines or therapies available for either NiV or HeV. The anti-HNV antibody m102.4, that is cross reactive against NiV[23–25], completed a phase I study and has been used on a compassionate basis to treat individuals with significant HeV or NiV exposure risk in Australia and Asia. In 2018, in response to a Nipah outbreak in Kerala, India, the Indian Council of Medical Research (ICMR) partnered with regulatory authorities in Australia, the US and India to fast-track the procurement of this experimental mAb from Australian health authorities; however, the mAb arrived too late and 21 of 23 infected patients died[26].

More recently, another anti-HNV m102.4 neutralising mAb, h5B3.1 was identified, which targets a distinct epitope compared to the m102.4 mAb. This mAb has the potential to be used for pre-exposure prophylaxis and treatment[25,27]. A combination of the two mAbs that bind distinct epitopes, either as bispecific constructs or combination products, may limit the emergence of escape mutants; however, as yet, there are no publicly stated clinical studies reported for this antibody.

Influenza

Influenza causes a significant number of deaths and widespread illness each year around the globe. The WHO estimates that seasonal influenza may result in 290,000-650,000 deaths each year due to respiratory diseases alone.

Influenza viruses type A and B are the most significant public health threats due to their potential to rapidly mutate and trigger a pandemic. Depending on the origin host, influenza A viruses can be classified as human, avian, swine or other types of animal influenza viruses. Ongoing circulation of some avian influenza viruses in poultry, such as A(H5) and A(H7) viruses, cause severe disease in humans and their potential to mutate could increase transmissibility among humans[28]. Influenza B viruses circulate among humans and cause seasonal epidemics[28].

The antigenic diversity and mutation rates of influenza viruses make it more challenging to develop vaccines and treatments. The high antigenic diversity of the influenza virus requires that vaccines are produced and formulated annually for seasonal influenza strains. The efficacy of seasonal flu vaccines ranges from 10 per cent to 60 per cent, with lower efficacy in the elderly and immunocompromised individuals[29]. Small molecule anti-viral treatments for influenza can lead to viral resistance and there are no treatments for hospitalised patients with severe influenza. However, single or combination antibody products that bind to conserved epitopes on surface proteins from multiple influenza strains have the potential to reduce viral escape and resistance.

Several broadly neutralising antibodies (bnAbs) that target the hemagglutinin (HA) conserved stalk region of the influenza virus have been evaluated in early to mid-stage clinical studies[30,31] as potential therapies. Visterra's VIS410, which is currently in phase II clinical trials, is active *in vitro* against all circulating human and avian strains of influenza A with pandemic potential[30]. Vir's candidate VIR-2482 for all influenza A strains is in phase I studies. This antibody candidate is engineered to have an extended half-life that would cover the entire flu season.

Clinical studies of systemically delivered HA-specific bnAbs indicate that they are safe and can modestly reduce symptoms in uncomplicated influenza. However, their potential to treat severe influenza or to prevent influenza is questionable given their limited distribution in the lungs and their inability to protect against all circulating influenza A and B viruses.

Recent technological advancements have led to the development of bnAbs that target influenza A and B viruses with improvements in strain coverage and delivery to relevant tissues. These include bispecific mAbs, multidomain camelid mAbs expressed at

the nasopharyngeal mucosa through intranasal administration of a recombinant adeno-associated virus (AAV) vector and mRNA/DNA encoded mAbs, all of which are in preclinical development.

As is the case with other hypervariable viruses such as HIV, the next generation of broader and more potent antibodies for influenza offer great promise in both treating and preventing this virus.

Lessons learned

Monoclonal antibodies may play a vital role in both preparing for and responding to emerging infectious diseases, but they will need to be potent, rapidly produced, procured and supplied, and affordable if they are to reach their full potential in controlling future epidemics/pandemics. A sustained commitment from the global health community will be required to make mAb access a reality. The next generation of more potent and broadly cross-reactive antibodies could lower production costs and supply and have broader utility to treat and prevent infections from multiple viruses belonging to the same family and from multiple strains of hypervariable viruses.

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