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Monoclonal antibodies (mAbs) targeting the spike protein of SARS-CoV-2 have been widely used in the ongoing COVID-19 pandemic. In this paper, we review the properties of mAbs and their effect as therapeutics in the pandemic, including structural classification, outcomes in clinical trials that led to the authorisation of mAbs, and baseline and treatment-emergent immune escape. We show how the omicron (B.1.1.529) variant of concern has reset treatment strategies so far, discuss future developments that could lead to improved outcomes, and report the intrinsic limitations of using mAbs as therapeutic agents.

Introduction
The first monoclonal antibody (mAb) for clinical use (muromonab-CD3) was approved by the US Food and Drug Administration (FDA) in 1986.1 Since then, about ten new mAbs have been approved each year (mostly IgG1), with an estimated global yearly sale of US$75 billion in 2021.2 Most of these mAbs have been licensed for non-infectious disease indications. However, successful efforts have been made in the COVID-19 pandemic to research and develop mAbs against SARS-CoV-2. At the beginning of the COVID-19 pandemic, IgG mAbs against the spike protein of SARS-CoV-2, either as single agents or mAb cocktails (ie, a combination of two or more mAbs), were announced and advertised by many authorities as the most effective antibody therapeutic solution for COVID-19.3 As of March 4, 2022, the Coronavirus Antibody Database (CoV-AbDab) contains 5210 antibodies and nanobodies against SARS-CoV, MERS-CoV, and SARS-CoV-2.

Many randomised clinical trials of mAb therapy and prophylaxis have been launched, initially for patients being treated in hospital and then for outpatients, all showing overall moderate efficacy and good safety (tables 1, 2). Many classifications of anti-spike mAbs according to the targeted epitopes have been suggested (table 3). In this paper, we review the information available for mAbs against SARS-CoV-2 (panel 1) to identify the strengths and weaknesses of this therapeutic strategy, which are apparent from 2 years of clinical experience.

Efficacy in randomised clinical trials
Efficacy of mAbs was measured as reduction of infection rates when mAbs were used in pre-exposure or post-exposure prophylaxis, reduction in hospital admissions when mAbs were administered as treatment for outpatients, or reduction in disease progression or mortality when mAbs were used as treatment for inpatients. Similar to therapies based on neutralising antibodies, such as the cheaper COVID-19 convalescent plasma, therapeutic efficacy was exclusively shown in seronegative and early inpatients. Reductions of the plasma, therapeutic efficacy was exclusively shown in seronegative and early inpatients. Reductions of the measured variables ranged between 30% and 40%, which was enough to meet statistical significance, but the effect was not sufficiently large for these mAbs to be considered an effective therapy, since a substantial proportion of patients treated with mAbs did not appear to benefit.

Better results were observed for prophylactic indications and in outpatients, especially when patients at high risk of disease progression were recruited to increase the cost-effectiveness of the procedure.

Specifically, a randomised clinical trial that led to the authorisation of bamlanivimab (Eli Lilly, Indianapolis, IN, USA) showed that the efficacy of bamlanivimab administered alone was not significant: the proportion of patients who recovered in, or were discharged from, hospital ranged from 82% to 88% for the bamlanivimab group versus 79% to 90% for the placebo group.3 REGN-COV2 (a cocktail of two mAbs, casirivimab and imdevimab; Regeneron and Roche, New York, NY, USA) use led to an 84–92% relative risk reduction in developing symptomatic COVID-19 infections, and a significant reduction in mortality in patients treated in hospital at day 28 from baseline.4 Sotrovimab (GSK, Brentford, UK) use led to a relative risk reduction of 85% in progression of the infection leading to admission to hospital or death.

| FDA | EMA |
|-----------------------------------------------|-----------------------------------------------|
| **Bamlanivimab** | EUA Nov 9, 2020, for early therapy in outpatients at high risk of disease progression; revoked on April 15, 2021 | Not authorised |
| **Bamlanivimab and etesevimab** | EUA Feb 9, 2021, for early therapy in outpatients at high risk of disease progression; restricted on Jan 24, 2022 | Marketing authorisation granted on March 11, 2021, for early therapy in outpatients at risk of disease progression; withdrawn by Eli Lilly on Oct 29, 2021 |
| **Casirivimab and imdevimab** | EUA Nov 21, 2021, for early therapy in outpatients at high risk of disease progression; restricted on Jan 24, 2022 | Marketing authorisation granted on Nov 12, 2021, for early therapy in outpatients at risk of disease progression and post-exposure prophylaxis |
| **Tixagevimab and cilgavimab** | EUA Dec 8, 2021, for pre-exposure prophylaxis in rolling review | In rolling review |
| **Sotrovimab** | EUA May 26, 2021, for early therapy in outpatients at high risk of disease progression; withdrawn on April 5, 2022 | Marketing authorisation granted on Dec 17, 2021, for early therapy in outpatients at risk of disease progression |
| **Regdanvimab** | Not approved yet | Marketing authorisation granted on Nov 12, 2021, for early therapy in outpatients at risk of disease progression |
| **Bebtelovimab** | EUA Feb 11, 2022, for early therapy in outpatients at high risk of disease progression | Not authorised |
| **Damuviravimab and romlusevimab** | Not authorised | Not authorised |

Table 1: Authorisation status for selected monoclonal antibodies by the FDA and EMA

Efficacy in randomised clinical trials
| Location, Study Group | Date of recruitment | Treatment group (n) | Control group (n) | Main efficacy outcomes |
|-----------------------|---------------------|---------------------|-------------------|------------------------|
| **Bamlanivimab**       |                     |                     |                   |                        |
| Gottlieb et al (2021)  | USA and Puerto Rico | June 17–Aug 21, 2020| Three groups with different doses: 700 mg (n=101), 2800 mg (n=107), and 7000 mg (n=101) | Placebo (n=156) | (1) The change from baseline to day 29 in viral load AUC was significant for the 2800 mg dose group (difference –9.50 [95% CI –16.32 to –2.68]; p=0.006) compared with the placebo group; (2) the change in symptom improvement from baseline to day 11 was significant for the 700 mg dose group (difference 16.0% [95% CI 3.6–28.4]; p=0.02) and the 7000 mg dose group (15.0% [2.6–27.4]; p=0.02) compared with the placebo group; (3) the change from baseline to day 29 in the proportion of patients with COVID-19-related hospitalisation or emergency department admission was not significant for any treatment group compared with the placebo group; and (4) no deaths during the study |
| ACTIV-3/TVCOV555 Study Group et al (2021)  | USA, Argentina, Denmark, Georgia, Greece, India, Mexico, Mozambique, Nigeria, Poland, Singapore, Spain, Switzerland, Ukraine, and UK | Aug 5–Oct 13, 2020 | n=163 | Placebo (n=151) | (1) 82% of the patients in the treatment group had a sustained recovery vs 79% in the placebo group; (2) 88% of the patients in the treatment group had a hospital discharge vs 90% in the placebo group; and (3) nine patients in the treatment group died vs five in the placebo group; of these 14 deaths, 12 were attributed to worsening of COVID-19 and two to cardiopulmonary arrest |
| **Bamlanivimab and etesevimab** | USA and Puerto Rico | Aug 22–Sept 3, 2020 | n=112 | Placebo (n=156) | (1) The change from baseline to day 11 in viral load AUC was significant for the treatment group (difference –0.57 [95% CI –1.00 to –0.14]; p=0.01) compared with the placebo group; (2) the change from baseline to day 29 in viral load AUC was significant for the treatment group (difference –17.91 [95% CI –25.25 to –10.58]; p<0.001) compared with the placebo group; (3) the change in symptom improvement from baseline to day 11 was not significant compared with the placebo group; (4) the proportion of patients with COVID-19-related hospitalisation or emergency department admission at day 29 was 0.9% in the treatment group vs 5.8% in the placebo group, with the difference between groups being significant (difference –4.9% [95% CI –8.9 to –0.8]; p=0.049); and (5) no deaths during the study |
| **Casirivimab and imdevimab** | USA and Mauritius | June 16–Aug 13, 2020 | Three groups with different doses: 1200 mg (n=736), 2400 mg (n=1355), and 8000 mg (n=625) | Placebo (n=1341) | (1) In the full analysis set, 3% of patients in the treatment groups reported at least one medically attended visit, compared with 6% in the placebo group; (2) in the serum antibody-negative subgroup, 15% of patients had a medically attended visit, compared with 6% in the placebo group; and (3) mean difference in viral load from baseline to day 7 was –0.71 log₁₀ copies per mL (95% CI –0.90 to –0.53) for the 1200 mg dose group and –0.86 log₁₀ copies per mL (–1.00 to –0.72) for the 2400 mg dose group compared with the placebo group |
| Isa et al (2021)  | USA | Not reported | n=729 | Placebo (n=240) | (1) 92.4% reduction in relative risk of developing symptomatic COVID-19 and 100% risk reduction for SARS-CoV-2 seroconversion (anti-nucleocapsid IgG) in the treatment group compared with the placebo group; (2) no patient in the treatment subgroup of seronegative patients at baseline (n=617) was seropositive at the end of the study vs 20 patients in the placebo seronegative subgroup (n=208); and (3) no deaths during the study |
| O’Brien et al (2021)  | USA, Moldova, and Romania | Not reported | n=753 | Placebo (n=752) | (1) 84% reduction in relative risk of developing symptomatic COVID-19 in the treatment group compared with the placebo group; (2) in the overall population, the mAb cocktail prevented symptomatic and asymptomatic infections; and (3) the median time to resolution of symptoms and the duration of a high viral load was 2 weeks shorter in the treatment group than in the placebo group |
| RECOVERY Collaborative Group (2022)  | UK | Sept 19, 2020–May 22, 2021 | n=4839 | Best standard of care (n=4946) | (1) Significant reduction in mortality at day 28 (relative risk 0.80 [95% CI 0.70 to 0.91]) for COVID-19 hospitalised patients (seronegative for SARS-CoV-2 on admission to hospital) treated with the mAb cocktail; and (2) in the subgroup of patients who were seronegative for SARS-CoV-2 and not on ventilation at baseline, patients in the treatment group had a less frequent progression to use of ventilation than patients in the control group, although this finding was not observed in the overall population |
Regdanvimab (Celltrion, Incheon, South Korea) use reduced the risk of admission to hospital or death by 72% in patients at high risk of progression to severe COVID-19, and only few patients with symptomatic infection required admission to hospital or oxygen therapy, or died.13 Bebtelovimab (Eli Lilly, Indianapolis, IN, USA) was approved in patients with mild-to-moderate COVID-19 at high and low risk of disease progression, either administered alone or together with bamlanivimab and etesevimab (Eli Lilly, Indianapolis, IN, USA). In the overall population treated with bebtelovimab alone or the mAb cocktail, a small proportion of patients (1.7–4.0%) required admission to hospital or died.13 AZD7442 (a cocktail of tixagevimab and cilgavimab; AstraZeneca, UK) was approved in patients with mild-to-moderate COVID-19 at high and low risk of disease progression, either administered alone or with different doses in study 1.1: 10 mg/kg (n=6); three groups with different doses in study 1.2: 80 mg/kg (n=6); three groups with different doses in study 1.2: 80 mg/kg (n=6); and etesevimab (Eli Lilly, Indianapolis, IN, USA) in the post-hoc subgroup analysis, risk of developing symptomatic COVID-19 was reduced by 73% (95% CI 27–96) in the treatment subgroup of patients who were PCR-negative at time of dosing compared with the placebo group; and in the pre-planned subgroup analysis, risk of developing symptomatic COVID-19 was reduced by 73% (95% CI 27–96) in the treatment subgroup of patients who were PCR-negative at time of dosing compared with the placebo group; and in the post-hoc subgroup analysis, risk of developing symptomatic COVID-19 was reduced by 92% (32–99) in the treatment subgroup of patients who were PCR-negative at baseline with follow-up for >7 days after dosing compared with the placebo group.

| Location                  | Date of recruitment | Treatment group (n) | Control group (n) | Main efficacy outcomes                                                                 |
|---------------------------|---------------------|---------------------|-------------------|----------------------------------------------------------------------------------------|
| **Tixagevimab and cilgavimab** |                     |                     |                   | In the primary efficacy analysis, patients treated with the mAb cocktail had a 76.7% reduction (95% CI 60–90; p<0.001) in relative risk of developing symptomatic COVID-19 compared with the placebo group; the risk reduction was 82.8% at 6 months (65.8–91.4; p value not available) |
| Levin et al (2022)14      | USA, Belgium, France, Spain, and UK | Nov 21, 2020–March 22, 2021 n=3460 Placebo (n=3737) (1) No significant reduction in the risk of developing symptomatic COVID-19 in the overall population; (2) in the pre-planned subgroup analysis, risk of developing symptomatic COVID-19 was reduced by 73% (95% CI 27–96) in the treatment subgroup of patients who were PCR-negative at time of dosing compared with the placebo group; and (3) in the post-hoc subgroup analysis, risk of developing symptomatic COVID-19 was reduced by 92% (32–99) in the treatment subgroup of patients who were PCR-negative at baseline with follow-up for >7 days after dosing compared with the placebo group |
| AstraZeneca (2021)15      | USA and UK          | Not reported n=749 Placebo (n=372) (1) Risk of progression to severe COVID-19 or death was 4.4% in the treatment group (outpatients within 8 days from symptom onset) at day 29 compared with 8.9% in the placebo group (ie, 50% relative risk reduction); and (2) risk of progression to severe COVID-19 or death was 3.5% in the treatment subgroup of patients who received treatment within 5 days from symptom onset compared with 10.7% in the placebo group |
| AstraZeneca (2021)15      | USA, Argentina, Brazil, Czech Republic, Germany, Hungary, Italy, Japan, Mexico, Peru, Poland, Russia, Ukraine, Spain, and UK | Not reported n=407 Placebo (n=415) (1) The mean reduction in viral titres in nasopharyngeal swabs from baseline to day 14 was greater for patients in the treatment group compared with patients in the placebo group; and (2) all patients (except one in the placebo group) recovered from COVID-19 at day 14 with a shorter mean time to recovery (3.39 days for patients in the treatment groups vs 5.25 days in the placebo group) |
| **Sotrovimab**            |                     |                     |                   | (1) 1% of patients in the treatment group, compared with 7% in the placebo group, had disease progression leading to admission to hospital for any cause, or death (relative risk reduction 85% [97.24–100.06]; p=0.002); and (2) one patient in the placebo group died |
| Gupta et al (2021)13      | USA, Austria, Brazil, Canada, Peru, Spain, and UK | Jan 19–Feb 17, 2021 n=291 Placebo (n=292) (1) 1% of patients in the treatment group, compared with 7% in the placebo group, had disease progression leading to admission to hospital for any cause, or death (relative risk reduction 85% [97.24–100.06]; p=0.002); and (2) one patient in the placebo group died |
| **Regdanvimab**           |                     |                     |                   | (1) Median time from receiving a positive RT-qPCR test result to a negative one was 12.7 days for patients in the 40 mg/kg dose group and 11.89 days in the 80 mg/kg dose group, compared with 12.94 days in the placebo group (2) 4.0% of patients in the 40 mg/kg dose group and 4.9% in the 80 mg/kg dose group required admission to hospital or oxygen therapy from baseline to day 28, compared with 8.7% in the placebo group; and (3) no deaths during the study |
| Kim et al (2021)14        | South Korea         | Dec 16, 2020–March 1, 2021 | Phase 1; four groups with different doses in study 1: 10 mg/kg (n=6); 20 mg/kg (n=6), and 80 mg/kg (n=6); three groups with different doses in study 1: 20 mg/kg (n=5), 40 mg/kg (n=5), and 80 mg/kg (n=5) | (1) The mean reduction in viral titres in nasopharyngeal swabs from baseline to day 14 was greater for patients in the treatment groups compared with patients in the placebo group; and (2) all patients (except one in the placebo group) recovered from COVID-19 at day 14 with a shorter mean time to recovery (3.39 days for patients in the treatment groups vs 5.25 days in the placebo group) |
| Eom et al (2021)15        | South Korea         | Oct 7–Dec 18, 2020 | Phase 2; two groups with different doses: 40 mg/kg (n=105) and 80 mg/kg (n=111) | (1) The mean reduction in viral titres in nasopharyngeal swabs from baseline to day 14 was greater for patients in the treatment groups compared with patients in the placebo group; and (2) all patients (except one in the placebo group) recovered from COVID-19 at day 14 with a shorter mean time to recovery (3.39 days for patients in the treatment groups vs 5.25 days in the placebo group) |
| Celltrion Healthcare      | South Korea         | Not reported Phase 3 (n=undisclosed) Placebo (n=undisclosed) | (1) 10% of patients at risk for severe COVID-19 at day 28 patients in the treatment group had a 72% reduction in risk of hospitalisation or death compared with the placebo group (3.1% vs 11.1%; p<0.001); and (2) no deaths during the study |

(Continued from previous page)
Efficacy of anti-spike mAbs approved so far for clinical use in randomised clinical trials

AUC=area under the receiver operating characteristic curve. mAb=monoclonal antibody. TICO=Therapeutics for Inpatients with COVID-19.

| Location | Date of recruitment | Treatment group (n) | Control group (n) | Main efficacy outcomes |
|----------|---------------------|---------------------|-------------------|------------------------|
| **Bebtelovimab** | | | | |
| Dougan et al (2022)17 | USA, Argentina, and Puerto Rico | Not reported | Placebo (n=128) | (1) Low-risk patients (based on the Centers for Disease Control and Prevention guidance): 14% of patients receiving treatment with bebtelovimab and 13% of patients receiving treatment with the combination of mAbs had a persistently high viral load at day 7; and (2) median time to symptom resolution ranged from 6 to 7 days for patients in the treatment group vs 8 days in the placebo group. |
| Dougan et al (2022)17 | As above | Bebtelovimab (n=100); bebtelovimab plus bamlanivimab and etesevimab (n=50) | As above | High-risk patients (based on the Centers for Disease Control and Prevention guidance): 3% of patients receiving treatment with bebtelovimab were hospitalised or died because of COVID-19, compared with 4% of patients receiving treatment with the combination of mAbs. |
| | | Bebtelovimab plus bamlanivimab and etesevimab (n=176) | As above | (1) High-risk patients (based on the Centers for Disease Control and Prevention guidance): COVID-19 related hospitalisations were reported for 17% of patients, and (2) no deaths during the study. |

| **Damubarvimb and romlusevimab** | | | | |
| ACTIV-3/TICO Study Group (2022)13 | USA, Argentina, Denmark, Georgia, Greece, India, Mexico, Mozambique, Nigeria, Poland, Singapore, Spain, Switzerland, Ukraine, and UK | Dec 16, 2020–March 1, 2021 n=176 | Placebo (n=178) | (1) 45% of patients in the treatment group and 51% in the placebo group had an improvement in the seven-category pulmonary ordinal scale from baseline to day 5; and (2) the adjusted odds ratio (active treatment vs placebo) for patients being in a more favourable category on the pulmonary scale on day 5 was 0.88 (95% CI 0.67-1.14). |

AUC=area under the receiver operating characteristic curve. mAb=monoclonal antibody. TICO=Therapeutics for Inpatients with COVID-19.

Table 2: Efficacy of anti-spike mAbs approved so far for clinical use in randomised clinical trials

Cambridge, UK) is the only combination approved by the FDA for pre-exposure prophylaxis: among patients who had a negative SARS-CoV-2 PCR test at baseline, tixagevimab and cilgavimab reduced the risk of developing symptomatic COVID-19 by 73–92%, and the risk of disease progression or death ranged from 3·5% to 4·4%.11

Unfortunately, no randomised clinical trial was done by a pharmaceutical company after vaccine coverage was high, and thus mAbs continued to be administered to individuals with vaccine-induced seropositivity, without any conclusive evidence supporting their efficacy in these settings. Such lack of reappraisal by public investigators is a serious concern for reliability of current evidence on mAbs. However, mAb efficacy in individuals with vaccine-induced seropositivity is likely to be much lower than in individuals who are not vaccinated: novel randomised clinical trials are hence needed to support the assessment of cost versus efficacy of the intervention in this group of individuals, who represent most people nowadays.

Notably, when poor results were observed for patients who were treated in hospital, pharmaceutical research moved to establishing efficacy of, and using, mAbs in outpatients, for whom mAbs were more likely to be effective on the basis of previous experience with antiviral mAbs. These mAb trials had an advantage compared with randomised clinical trials of COVID-19 convalescent plasma because they were sponsored by pharmaceutical companies: trials of COVID-19 convalescent plasma, in which efficacy was likely to be low and there were not as many outpatients, were instead supported by physicians and the medical community to assist patients with advanced disease.57

The rapid development of the pandemic highlighted some predictable limitations in the development of mAb therapies: of a very broad pipeline,58 only a few candidates were initially approved by regulatory authorities in sufficient time to be used. The initial success of some mAbs, such as casirivimab and imdevimab, discouraged small companies from pursuing other research and development efforts, because of the assumption that the mAbs that had reached the market first would have been adequate and sufficient therapeutics. With the emergence of the delta (B.1.617.2) and omicron (B.1.1.529) variants of SARS-CoV-2, the mAbs that were used early in the pandemic against the wild-type and alpha (B.1.1.7) variants lost their neutralising activity. Therefore, when other mAbs were needed, manufacturing bottlenecks largely hindered large-scale deployment.59 However, even if additional mAbs had been widely available, their cost would have probably remained prohibitive even for high-income countries. Notably, when mAbs were ultimately made available, many did not show to be effective against SARS-CoV-2 within a short time after their introduction, because the virus rapidly escaped their narrow specificity with the generation of mAb-resistant variants.60
Safety in randomised clinical trials

The safety of mAbs was measured as the number of adverse events and serious adverse events occurring after their administration. Generally, adverse events were non-severe (eg, diarrhoea and nausea) and self-limiting. The most common adverse events were injection-site reactions, headache, chills, and bronchospasm.1,4-8,10-12,19 Serious adverse events occurred very rarely,4,6,8-10,12,19 and those affecting the respiratory tract (eg, shortness of breath) were probably related to the progression of COVID-19. Death occurred only in few patients, especially those clinically at high risk of disease progression or treated in hospital. More than 95% of patients completed the infusion of mAbs. The incidence of antidrug antibodies was assessed only in the regdanvimab trial,19 in which they were not detected. Nevertheless, repeated exposure to mAbs, such as in pre-exposure prophylaxis, comes with concerns, such as a growing incidence of treatment-emergent resistance.

Resistance to mAbs

As for any other therapeutic, resistance to mAbs binding the spike protein can be either initial (ie, pre-existing before treatment) or treatment-emergent (ie, positive selection of immune-escape variants after treatment). Both types of resistance can be predicted in vitro, using gene sequencing efforts for initial resistance, or viral serial passage in the presence of the mAb for treatment-emergent resistance. However, the implications of these types of resistance are different. Initial resistance discourages regulatory bodies from introducing a mAb into therapeutic guidelines, when the prevalence of the mutations that confer initial resistance to the mAb in the circulating strains is high. By contrast, a high incidence of treatment-emergent resistance could trigger a mandate follow-up order to promptly detect immune escape and treatment failure. With regard to viral fitness, although widespread circulation of a resistant strain invariably indicates enhanced fitness, typically only a few mutations associated with treatment-emergent resistance are sufficiently fit to spread within communities. This reduced viral fitness is clearly shown by the relative scarcity of SARS-CoV-2 lineages with E406 mutations that are resistant to REGN-COV2 in the Global Initiative on Sharing All Influenza Data (GISAID). In addition to REGN-COV2, the spike E406W mutation abrogates neutralisation mediated by cilgavimab. E406W results in REGN-COV2, the spike E406W mutation abrogates neutralisation mediated by cilgavimab. E406W results in

The in-vitro studies that have investigated spike mutations in variants of interest and variants of concern conferring resistance to mAbs are summarised in

| Protein Data Bank identification code | Finkelnstein et al (2021) classification | Barnes et al (2020) classification | Yuan et al (2021) classification |
|--------------------------------------|------------------------------------------|----------------------------------|---------------------------------|
| 4A8                                  | 7e2l                                    | NTD binding                      | 7e2l                            |
| CC12:3                               | 6xc4                                    | RBM class I                      | Class 1                         |
| C105                                 | 6xcm                                    | RBM class I                      | Class 1                         |
| P2G3                                 | 7qtg (held for release)                 |                                  |                                 |
| S53-49                               | 7wog (held for release)                 |                                  |                                 |
| B18                                  | 7bs5                                    | RBM class I                      | Class 1                         |
| C102                                 | 7k8m                                    | RBM class I                      | Class 1                         |
| COVA2-39                             | 7tmp                                    | RBM class I                      | Class 2                         |
| CC12:1                               | 6xc2                                    | RBM class I                      |                                 |
| Casirivimab                          | 6xdg                                    | RBM class I                      |                                 |
| CV30                                 | 6xe1                                    | RBM class I                      |                                 |
| CV07-250                             | 6xkq                                    | RBM class I                      |                                 |
| BD-604                               | 7ch4                                    | RBM class I                      |                                 |
| BD-629                               | 7sh5                                    | RBM class I                      |                                 |
| BD-236                               | 7chb                                    | RBM class I                      |                                 |
| COVA2-04                             | 7jmo                                    | RBM class I                      |                                 |
| Etesevimab                           | 7c01                                    | RBM class I                      |                                 |
| S2H14                                | 7jk3                                    | RBM class I                      |                                 |
| S2E12                                | 7k4n                                    | RBM class I                      |                                 |
| Abevanimab                           | 7cdd                                    | RBM class I*                     |                                 |
| COR-101 or STE90-C11                 | 7b30                                    | RBM class I*                     |                                 |
| 87G7                                 | 7k40                                    | RBM class I*                     |                                 |
| CV07-287                             | 7s5p, 7s5q, or 7s5r                     | RBM class I*                     |                                 |
| PSC3                                 | 7p40 or 7phg                            | RBM class I*                     |                                 |
| S2K146                               | 7tas or 7tat                            | RBM class I*                     |                                 |
| CV07-270                             | 6xkp                                    | RBM class II                     |                                 |
| P2B-2F6                              | 7bwj                                    | RBM class II                     | Class 2                         |
| C002                                 | 7k8s                                    | RBM class II                     | Class 2                         |
| C104                                 | 7k8u                                    | RBM class II                     | Class 2                         |
| C119                                 | 7k8w                                    | RBM class II                     | Class 2                         |
| C121                                 | 7k8x                                    | RBM class II                     | Class 2                         |
| H11-D4                               | 6ys5                                    | RBM class II                     |                                 |
| H11-H4                               | 6xhd                                    | RBM class II                     |                                 |
| Sb23                                 | 7a29                                    | RBM class II                     |                                 |
| BD-368-2                             | 7che or 7chc                            | RBM class II                     |                                 |
| S2H13                                | 7jw2                                    | RBM class II                     |                                 |
| Ty1                                  | 6xmn                                    | RBM class II                     |                                 |
| SA6                                  | 7m71                                    | RBM class II*                    |                                 |
| Cilgavimab                           | 7de                                    | RBM class II*                    |                                 |
| P13                                  | 7cwo                                    | RBM class II*                    |                                 |
| Ab2-4                                | 6xey                                    | RBM class III                    | Class 2                         |
| BD-23                                | 7byr                                    | RBM class III                    | Class 2                         |
| C144                                 | 7k90                                    | RBM class III                    | Class 2                         |
| Nb20                                 | 7wjb                                    | RBM class III                    |                                 |
| S2M11                                | 7k43                                    | RBM class III                    |                                 |
| Nb6                                  | 7kkk                                    | RBM class III                    |                                 |
| Bamlanivimab                         | 7kmg                                    | RBM class III*                   |                                 |

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For more on GISAID see https://www.gisaid.org/epiflu-mutations-app/

Table 3: Competition clusters for anti-SARS-CoV-2 spike monoclonal antibodies according to different classification schemes

| Protein Data Bank identification code | Finkelshtein et al (2021) classification | Barnes et al (2020) classification | Yuan et al (2021) classification |
|--------------------------------------|------------------------------------------|-----------------------------------|---------------------------------|
| (Continued from previous page)       |                                          |                                   |                                 |

Table 3: Competition clusters for anti-SARS-CoV-2 spike monoclonal antibodies according to different classification schemes

For more on GISAID see https://www.gisaid.org/epiflu-applications/covsurver-mutations-app/

panel 2. Caution should be used when drawing conclusions on these complex variants: for example, the delta variant of concern consists of more than 200 sublineages, many of which harbour spike mutations that could affect mAb sensitivity of individual sublineages. The reduction of mAb neutralising activity by different circulating variants of interest and variants of concern of SARS-CoV-2 is shown in table 4.

We previously reviewed immune escape to therapeutics based on neutralising antibodies, including mAbs, and we provide an update of our previous research as of Feb 15, 2022, in the appendix (pp 1–6).

The omicron hurricane

In November, 2021, omicron emerged, a new variant of concern that led to an unexpected change in the pandemic, due to its high reproduction number and ability to cause breakthrough infections in vaccinated individuals. Because of omicron’s high number of spike mutations and deletions compared with previous variants of concern, most clinically approved mAbs suddenly lost their efficacy against SARS-CoV-2 (appendix pp 1–6). The FDA was among the first regulatory authority to issue updated guidance documents on mAbs; on Jan 24, 2022, the FDA revised the authorisations for two mAb treatments—REGN-COV2, and a cocktail of bamlanivimab and etesevimab—to limit their use to patients who are likely to have been infected with, or exposed to, a variant that is susceptible to these treatments. Attributing infection to a specific variant requires sequencing efforts, which are expensive and poorly scalable, and the long turnaround time is not compatible with early administration of mAbs to seronegative patients. When omicron emerged, only sotrovimab retained in-vitro efficacy; however, because sotrovimab is a single mAb rather than a cocktail, it is susceptible to the emergence of immune-escape variants, such as the E340K mutation, which has been reported in up to 10% of recipients of sotrovimab. After new omicron sublineages emerged, resistance of the BA.2 sublineage, which is nowadays dominant, was reported, the FDA first restricted the use of sotrovimab on Feb 25, 2022, and withdrew authorisation on April 5, 2022. Despite losses in neutralisation in vitro, sotrovimab (the parent mAb of sotrovimab) or AZD7442 treatments reduced BA.1, BA.1.1, and BA.2 lung infection in susceptible mice that expressed human ACE2 (K18-hACE2); however, animal models are clearly not enough.

To improve preparedness, the FDA approved bebtelovimab for outpatients on Feb 11, 2022, on the basis of only a phase 2 clinical trial; however, similar to sotrovimab, because bebtelovimab is a single mAb, it is susceptible to the emergence of immune-escape variants. Consequently, in the trial, bebtelovimab was co-administered with etesevimab plus bamlanivimab, representing the first cocktail of three mAbs against SARS-CoV-2.

We previously reviewed the limitations of the bamlanivimab plus etesevimab, and the casirivimab plus imdevimab cocktails, and especially their loss of neutralising activity against the omicron variant of
concern, which is currently the dominant variant worldwide. Fortunately, all the currently available small molecule antivirals—remdesivir, molnupiravir, and nirmatrelvir—have remained effective in vitro against omicron. However, these antivirals are expensive, moderately effective in vivo, and sometimes come with safety concerns, such as the mutagenicity of molnupiravir to host RNA. Because of the scarcity of antiviral agents, both the FDA and the International Swaps and Derivatives Association also reassessed COVID-19 convalescent plasma for outpatients at risk of progression, because its polyclonal nature makes it less susceptible to immune escape by variants.

**Perspectives**

Despite the widespread use of mAbs in medicine, relatively few have been developed against viral diseases: among them, palivizumab (AstraZeneca, Cambridge, UK) has been approved for pre-exposure prophylaxis of respiratory syncytial virus in infants at high risk, RAB-1 (Serum Institute of India, Pune, India) for post-exposure prophylaxis of rabies, and the REGN-EB3 cocktail (Regeneron, New York, NY, USA), which is a combination of atoltivimab, maftivimab, and odesivimab, for the treatment of Ebola virus disease. In contrast to the respiratory viruses that cause systemic infections, such as measles, rubella, varicella, and smallpox (which was declared eradicated by WHO in 1980), the endemic coronaviruses, influenza viruses, respiratory syncytial viruses, parainfluenza viruses, and SARS-CoV-2 primarily infect epithelial cells on mucosal surfaces and generate a reduced systemic immune response, at least initially and in patients who have mild disease. Furthermore, because replication of these viruses occurs in the nostrils, systemic humoral immunity is low such that antibodies specific for viral antigens are not able to always prevent infection. These antibodies thus elicit incomplete and transient protective immunity leading to reinfections. Additionally, systemically administered vaccines elicit systemic responses that are effective at moderating the severity of disease but do not prevent infection.

The coronaviruses pose major challenges because they combine high infectivity and genomic variability that translates into frequent protein changes, resulting in high antigenic variation. Consequently, coronaviruses are hard to eradicate; yet, pandemic preparedness plans include the development of universal vaccines and mAbs targeting shared epitopes among coronaviruses. Furthermore, modern recombinant mAb technology introduces several modifications to the primary sequence to improve or ablate effector functions and increase circulation half-life.

**Extending mAb half-life**

The fragment crystallisable (Fc) region of immunoglobulin is responsible for its isotype and serum half-life, and for engaging the cellular Fc receptors to promote phagocytosis, complement activation, and antibody-dependent cell cytotoxicity. Hence, the Fc region has received considerable attention in efforts to alter the properties of mAbs to improve pharmacokinetic and effector functions of immunoglobulins. Fc-modified mAbs with the amino acid substitution M252Y/S254T/T256E (YTE; a modification associated with a serum half-life two to four times longer than the unmodified mAbs) were developed for the prophylaxis of respiratory syncytial viruses in infants (eg, nirsevimab [AstraZeneca, Cambridge, UK and Sanofi, Paris, France]). Additionally, the same technology was used in the development of AZD7442, the anti-SARS-CoV-2 mAb cocktail containing tixagevimab and cilgavimab approved for pre-exposure prophylaxis. mAb half-life can also be expanded with the LS mutation (Met428Leu/Asn434Ser), which does not affect antibody-dependent cell

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### Panel 1: List of main anti-spike mAbs and mAb cocktails authorised or in advanced development stages

| Company | Description |
|---------|-------------|
| Adagio Therapeutics | Adintrevimab (ADG20) |
| AstraZeneca | AZD7442 long-acting antibody (combination of tixagevimab [AZD8895 or COV2-2196] and cilgavimab [AZD1061 or COV2-2130]) |
| Beigene | BGB-DXP604 |
| BGB-DXP593 |
| BMS | C135 (C135-LS if with LS mutation) |
| | C144 (C144-LS if with LS mutation) |
| Brii Biosciences | Amubavimab (BRII-196) |
| | Romlusevimab (BRII-198) |
| Celltrion | Regdanvimab (CT-P59) |
| Eli Lilly (AbCellera and Junshi [ie, original manufacturers before commercial agreements]) | Etesevimab (LyCoV016, CB6, J5016, or LY3832479) |
| | Bamlanivimab (LY-CoV555 or LY3819253) |
| | Bebtelovimab (LY-CoV1404 or LY3853113) |
| Regeneron and Roche | REGN-COV2 (combination of imdevimab [REGN10987] and casirivimab [REGN10933]) |
| GSK (Vir Biotechnology) | Sotrovimab (VIR-7831 or GSK-4182136; derived from S309) |
| VIR-7832 or GSK-4182137 (derived from S309) |

mAb=monoclonal antibody.
cytotoxicity function. This modification was used in the anti-spike mAbs sotrovimab and adintrevimab (Adagio Therapeutics, Waltham, MA, USA), and the CI35-LS and CI44-LS cocktail (BMS, New York, NY, USA).

Ablation of effector functions
The immunoglobulin Fc region can also be modified to reduce effector functions. Such modifications are desirable in clinical situations in which stimulation of other components of the immune system, such as complement activation or engaging Fc receptors, can trigger side-effects. To reduce the risk of both antibody-dependent enhancement and antibody-dependent cell cytotoxicity, IgG1 Fc regions can be modified to eliminate binding to the Fcγ receptors FcγRI, FcγRIIa, and FcγRIIb.

Expanding antigen specificity
Broadly neutralising antibodies targeting cross-reactive epitopes found in all or most variants are sought after when designing therapies for antigenically variable viruses, such as HIV-1 and SARS-CoV-2. Within the genus Betacoronavirus, broadly neutralising antibodies have neutralising activity across all sarbecoviruses (appendix p 7). Pan-sarbecovirus antibodies are elicited by BNT162b2 vaccination in SARS-CoV survivors. Candidate pan-sarbecovirus mAbs targeting the spike protein have been variously referred to as cluster VII, class IV, or receptor binding domain (RBD) core cluster II (table 3, figure): examples of these mAbs include S2X25940 and DH1047. Other pan-sarbecovirus mAbs belong to the class I cluster 1 receptor-binding motif (RBM; eg, S2K146) or class 3 (eg, sotrovimab), or bind to the class I cluster I receptor-binding motif (RBM; eg, S2K146) or class 3 (eg, sotrovimab), or bind to the base of the stem-helix at the HR2 boundary in the S2 subunit (eg, CV3-25,144 1249A8,44 and the CC series 145).

Panel 2: Spike mutations associated with resistance in vitro to clinically approved monoclonal antibodies

| Bamlanivimab
| L452R (>100-fold reduction); E484D/K/Q (>100-fold reduction); G485P; F490S/L (100-fold reduction); Q493R/K (100-fold reduction); and S494P/R (100-fold reduction) |
| Bebtelovimab
| K444Q (>83-fold reduction) and V445A (>83-fold reduction) |
| Casirivimab
| E406W/D (50–93-fold reduction); K417E/N/R/T (25–100-fold reduction); V455T (>100-fold reduction); L455F (80-fold reduction); A475R (44-fold reduction); E484K (20–55-fold reduction); F486x; F486K/L/R/S/Y (100-fold reduction); N487R (>100-fold reduction); and Q493E/K (25–100-fold reduction) |
| Cilgavimab
| E484K (3–2-fold reduction) |
| Etesevimab
| K417N/T (100-fold reduction); D420N (100-fold reduction); F456R/A/K (100-fold reduction); N460K/S/T/Y (50–100-fold reduction); L452R (>100-fold reduction); E484D/K/Q (>100-fold reduction); I472D; A475R/V (20–100-fold reduction); E484K; F486K/L/R/S/Y (100-fold reduction); and N487R (100-fold reduction); G485P; and Q493R/K (100-fold reduction) |
| Imdevimab
| E406W (>100-fold reduction); N439K (25–100-fold reduction); N440K (28–96-fold reduction); K444L/M/N/Q/T (100-fold reduction); V445A (>100-fold reduction); G446V (100-fold reduction); N450D (9–32-fold reduction); Q498H (17-fold reduction); P499S (>100-fold reduction); and E484K (16-fold reduction) |
| Regdanvimab
| L452R (35-fold reduction); E484K (8-7-fold reduction); and N501Y (5-5-fold reduction) |
| Sotrovimab
| P337R/L/H/T (180–276-fold reduction) and E340K/A/G (27–300-fold reduction) |
| Tixagevimab
| E484K (4–11-fold reduction) and S982A (3-2-fold reduction) |

Data are sourced via the Stanford University Coronavirus Antiviral and Resistance Database (accessed online on March 4, 2021, at https://covdb.stanford.edu/search-drdb).
### Variants of concern

| Variants of concern | Alpha (B.1.1.7) | Beta (B.1.351) | Gamma (P.1) | Delta (B.1.617.2) | Omicron (B.1.529) | Eta (B.1.526) | Zeta (P.1) | Epsilon (B.1.427) | Theta (P.3) | Kappa (B.1.617.1) | Mu (B.1.621) | Lambda (C.37) |
|---------------------|-----------------|----------------|-------------|-------------------|-------------------|--------------|-------------|------------------|-------------|----------------|-------------|--------------|
| Etesevimab          | >5 FR           | No reduction   | >5 FR       | NA                | >5 FR            | NA           | NA          | 3–5 FR          | NA          | No reduction   | NA          | NA           |
| Bamlanivimab       | >5 FR           | No reduction   | >5 FR       | >5 FR            | >5 FR            | NA           | NA          | >5 FR          | NA          | No reduction   | NA          | NA           |
| Bebtelovimab       | No reduction    | No reduction   | No reduction | NA                | No reduction      | NA           | NA          | No reduction    | NA          | No reduction   | NA          | NA           |
| Imdevimab           | No reduction    | No reduction   | No reduction | No reduction     | >5 FR            | NA           | NA          | No reduction    | NA          | No reduction   | NA          | NA           |
| Casirivimab        | >5 FR           | >5 FR          | >5 FR       | >5 FR            | >5 FR            | NA           | NA          | >5 FR          | NA          | No reduction   | NA          | No reduction |
| Regdanvimab       | 3–5 FR          | NA             | >5 FR       | >5 FR            | >5 FR            | NA           | NA          | >5 FR          | NA          | No reduction   | NA          | No reduction |
| Tixagevimab        | >5 FR           | >5 FR          | No reduction | NA                | No reduction      | NA           | NA          | >5 FR          | NA          | No reduction   | NA          | No reduction |
| Cilgavimab         | No reduction    | No reduction   | No reduction | No reduction     | >5 FR            | NA           | NA          | No reduction    | NA          | No reduction   | NA          | No reduction |

### Variants of interest

| Variants of interest | Zeta (P.2) | Epsilon (B.1.427) | Theta (P.3) | Eta (B.1.526) | Iota (B.1.526 with E484K or S477N) | Kappa (B.1.617.1) | Mu (B.1.621) | Lambda (C.37) |
|---------------------|--------|------------------|-------------|--------------|-----------------------------------|-------------------|-------------|--------------|
| Etesevimab          | No reduction   | No reduction   | No reduction | No reduction | No reduction                      | NA                | NA          | NA           |
| Bamlanivimab       | No reduction   | No reduction   | No reduction | No reduction | No reduction                      | NA                | NA          | NA           |
| Bebtelovimab       | No reduction   | No reduction   | No reduction | No reduction | No reduction                      | NA                | NA          | NA           |
| Imdevimab           | No reduction   | No reduction   | No reduction | No reduction | No reduction                      | NA                | NA          | NA           |
| Casirivimab        | >5 FR          | >5 FR          | >5 FR       | >5 FR         | >5 FR                            | NA                | NA          | NA           |
| Regdanvimab       | 3–5 FR         | NA             | >5 FR       | >5 FR         | >5 FR                            | NA                | NA          | NA           |
| Tixagevimab        | >5 FR          | >5 FR          | No reduction | NA             | No reduction                      | NA                | NA          | NA           |
| Cilgavimab         | No reduction    | No reduction   | No reduction | No reduction  | >5 FR                            | NA                | NA          | NA           |

| C135 and C135-LS   | No reduction    | No reduction    | No reduction | No reduction | No reduction                      | NA                | NA          | NA           |
| C144 and C144-LS   | NA              | NA              | NA           | NA           | NA                                | NA                | NA          | NA           |
| Sotrovimab and VIR-7832 | No reduction | No reduction | No reduction | No reduction | 1–3 FR against BA.1, BA.1.1, and BA.2.75     | NA                | NA          | NA           |
| BGB-DX0604        | NA              | NA              | NA           | NA           | 1–3 FR                            | NA                | NA          | NA           |
| BGB-DX0593        | NA              | NA              | NA           | NA           | 1–3 FR                            | NA                | NA          | NA           |
| Arnabivimab       | NA              | NA              | NA           | NA           | >5 FR                             | NA                | NA          | NA           |
| Romlusevimab       | NA              | NA              | NA           | NA           | 3–5 FR against BA.1 and BA.1.1 and BA.2     | NA                | NA          | NA           |
| Adintrevimab      | No reduction    | No reduction    | No reduction | No reduction | >5 FR                             | NA                | NA          | NA           |

FR in geometric mean titre of neutralising antibodies for mAbs compared with the wild-type D614G SARS-CoV-2 strain (eg, Wuhan-Hu-1, USA-WA1/2020, B.1, or other reference strains). FR=fold reduction. mAbs=monoclonal antibodies. NA=data not available.

Table 4: In-vitro efficacy of mAbs against SARS-CoV-2 variants of concern and variants of interest
The experience with SARS-CoV-2 has shown that use of single mAbs is susceptible to losing their neutralising activity as new variants emerge, because of viral evolution or antibody selection of immune-escape mutants. Because of the large development costs associated with any antibody therapy, losing an existing therapy as a consequence of viral changes is a substantial loss with regard to clinical therapeutic options and monetary investment. Consequently, there is great interest in identifying epitopes that cannot be altered easily or generating mAb cocktails that reduce the likelihood of viral immune escape, by targeting the virus at more than one epitope (overlapping or not). In essence, combining mAbs creates a polyclonal product. Cocktails have been used against SARS-CoV-2 (table 1), Ebola virus, and rabies (CL184—a cocktail of two mAbs, CR57 and CR4098; Johnson & Johnson, New Brunswick, NJ, USA). Apart from protecting the product against viral evolution, cocktails also have the potential for triggering additive or synergistic effects through the action of two or more mAbs; however, cocktails with two or more mAbs are associated with substantially increased costs. Another alternative would be to create bispecific antibodies (e.g., 14-H-06147), by combining two fragment antigen-binding regions that bind to different epitopes. Bispecific antibodies might be a cost-effective alternative to mAb cocktails and are a promising strategy to improve antibody potency and breadth.

Routes of administration
Immunoglobulins are large protein molecules, and only systemic routes have been investigated so far in clinical use. The initial approach of mAb therapy for COVID-19 used intravenous infusion, which was suitable for treating patients in hospital. After data suggested that mAb use in patients who were SARS-CoV-2 seropositive and being treated in hospital had no or marginal benefit, most subsequent clinical developments focused on individuals who were SARS-CoV-2 seronegative, involving primarily outpatients. The need to provide mAbs systematically to outpatients generally proved difficult since their administration required the existence of infusion facilities suitable for treating patients who were infectious. This issue led to alternative dosing routes of mAbs, such as subcutaneous (REGN-COV2) or intramuscular (AZD7442, sotrovimab, and adintrevimab) administration, which have been eventually authorised by different regulatory authorities since February, 2021.

The need for systemic administration is a problem for a therapy targeting a virus that replicates in the nasal epithelium, because only a proportion of serum IgG penetrates mucosal surfaces. Pharmacokinetic modelling suggests that, because of poor affinity to the polymeric Ig receptor, only one of 1000 IgG molecules infused intravenously reaches the respiratory mucosa. Consequently, the most effective route of mAb delivery against a respiratory pathogen would be one that delivered
Conclusions

The rapid deployment of multiple mAb therapies during the pandemic has been a remarkable human accomplishment. mAb therapies have undoubtedly saved thousands of lives by preventing progression of early disease to life-threatening conditions that would have otherwise required treatment in hospital. However, the experience of the past 2 years has also shown limitations of this approach, which could have been foreseen from what was known about antibody action and the antigenic variability of SARS-CoV-2. Although a few regulatory authorities promptly issued recommendations to avoid the inappropriate use of mAbs against resistant variants of concern as soon as they became locally dominant

**Figure: Three-dimensional representation of spike epitopes targeted by mAbs approved to date according to different classifications**

For each spike glycoprotein epitope classification scheme, structural coordinates of anti-spike mAbs in complex with spike were collected and binned into classes described in each reference. Corresponding RBD monomers are overlaid in complex with a single spike monomer (PDB 7CL2), with NTD and RBD domains. NTD binding, RBD core clusters I and II, and RBM classes I–III are displayed as mesh space-filling representation. (B) Structures of anti-spike mAbs classes adapted from Barnes and colleagues41 are overlaid in complex with a single RBD domain (PDB 7XBM). Antibody binding classes 1–4 are displayed as mesh space-filling. (C) Structures of anti-spike mAbs classes adapted from Yuan and colleagues42 are overlaid in complex with a single RBD domain (PDB 6XEF). Antibody binding classes RBS-A, RBS-B, RBS-C, CR3022, and S309 are displayed in spheres representation. (D) Classes RBS-A, RBS-B, and RBS-C adapted from Yuan and colleagues42 are displayed in complex with the full spike trimer in the RBD open conformation (top, PDB 6VYY) and RBD closed conformation (bottom, PDB 6VXO) to show the accessibility of each epitope with respect to spike protein conformation. (E) Summary of anti-spike mAbs classes, as described by Finkelstein and colleagues,9 Barnes and colleagues,41 and Yuan and colleagues.42 Each classification was binned into six unifying categories for the purposes of this Review, on the basis of the descriptions and structural alignment of members of each class with available mAb–spike complex coordinates. **E**

| Our proposed binning | Colour scheme in figure | Finkelstein et al (2021) classification | Barnes et al (2020) classification | Yuan et al (2021) classification |
|----------------------|------------------------|--------------------------------------|---------------------------------|---------------------------------|
| 1                    | NTD binding (strain-specific; antibody binding either prevents critical spike conformational changes or interferes with ACE2-binding site) | Not classified | Not classified | |
| 2                    | RBM class I (epitope directly overlaps with ACE2-binding site; RBM required to be in the up conformation. All members are strain-specific, and many have IGVF3-53 or IGVH3-66 heavy chain gene usage with a variety of light chains) | Class 1 (antibodies block ACE2; accessibility of RBM epitope only in up conformation) | Class 2 (antibodies block ACE2; accessibility of RBM epitope in up or down conformations) | Class 2 (antibodies target the back side of RBS on opposite site of RBS ridge, different angle of approach compared with RBS-A or RBS-B antibodies) |
| 3                    | RBM class II (strain-specific; epitope directly overlaps with ACE2-binding site, but less so than RBM class I members; therefore, they can bind RBM that is in up or down conformation) | Class 1 (antibodies block ACE2; accessibility of RBM epitope only in up conformation) | Class 2 (antibodies block ACE2; accessibility of RBM epitope in up or down conformations) |
| 4                    | RBM class III (strain-specific; similar properties to RBM class II, except these antibodies make contact with nearby RBMUs in addition to the ones they are bound to. This additional contact limits conformational motions and some antibodies even lock the trimer in a closed state) | Class 1 (antibodies block ACE2; accessibility of RBM epitope only in up conformation) | Class 2 |
| 5                    | RBM core cluster I (antibodies prevent ACE2 from binding by either clashing with ACE2 or locking the spike homotrimer in a closed conformation. S309 can cross-neutralise SARS-CoV and SARS-CoV-2) | Class 3 (epitopes do not overlap with ACE2-binding site; accessibility of RBM epitope only in up conformation) | Class 3 (epitopes do not overlap with ACE2-binding site; accessibility of RBM epitope only in down conformation) | |
| 6                    | RBM core cluster II (antibodies bind a cryptic epitope that is accessible only when the RBM is in the up conformation and, in some cases, open as well. These members are capable of disrupting the spike homotrimer and prompting S1 shedding. CR3022, F1E6A, S304, H014, and VH4-72 can cross-neutralise SARS-CoV and SARS-CoV-2) | Class 4 (epitopes do not overlap with ACE2-binding site; accessibility of RBM epitope only in up conformation) | Class 4 (epitopes do not overlap with ACE2-binding site; accessibility of RBM epitope only in down conformation) | Class 4 (epitopes do not overlap with ACE2-binding site; accessibility of RBM epitope only in up or down conformation) |

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the mAb directly to the mucosa, such as intranasal or intratracheal administration. In parallel with mucosal vaccines,111 passive immunotherapies are also being developed by taking advantage of mucosal immunity. Previous research suggested that fully human mAbs aggregated and lost activity after jet and ultrasonic nebulisation,112–116 but did not when delivered with vibrating mesh nebulisers.117–120 In particular, IN-006 is a muco-trapping formulation of regdanvimab that, when delivered via vibrating mesh nebuliser instead of being dosed intravenously, has resulted in 100 times higher mAb concentration levels in the lungs of rats than in serum.121 Several investigators have proposed edible122 or intranasal113 egg-derived IgY for passive immunotherapy, and expression of viral antigens in the leaves of edible plants (eg, lettuce) is also being investigated to induce immunity.123 Similarly, an inhalable, bispecific, single-domain antibody has been shown to neutralise omicron in a mouse model.124

For each spike glycoprotein epitope classification scheme, structural coordinates of anti-spike mAbs in complex with spike were collected and binned into classes described in each reference. Corresponding RBD monomers are overlaid in complex with a single spike monomer (PDB 7CL2), with NTD and RBD domains. NTD binding, RBD core clusters I and II, and RBM classes I–III are displayed as mesh space-filling representation. (B) Structures of anti-spike mAbs classes adapted from Barnes and colleagues41 are overlaid in complex with a single RBD domain (PDB 7XBM). Antibody binding classes 1–4 are displayed as mesh space-filling. (C) Structures of anti-spike mAbs classes adapted from Yuan and colleagues42 are overlaid in complex with a single RBD domain (PDB 6XEF). Antibody binding classes RBS-A, RBS-B, RBS-C, CR3022, and S309 are displayed in spheres representation. (D) Classes RBS-A, RBS-B, and RBS-C adapted from Yuan and colleagues42 are displayed in complex with the full spike trimer in the RBD open conformation (top, PDB 6VYY) and RBD closed conformation (bottom, PDB 6VXO) to show the accessibility of each epitope with respect to spike protein conformation. (E) Summary of anti-spike mAbs classes, as described by Finkelstein and colleagues,9 Barnes and colleagues,41 and Yuan and colleagues.42 Each classification was binned into six unifying categories for the purposes of this Review, on the basis of the descriptions and structural alignment of members of each class with available mAb–spike complex coordinates. mAb=monoclonal antibody. NTD=N-terminal domain. RBM=receptor-binding domain. RBM= receptor-binding motif. RBM=receptor-binding site.
(NCT04501978), the use of ineffective and costly treatments has often continued for months, thus wasting economical resources and increasing the incidence of unnecessary side-effects. Such unjustified use of therapeutics is unacceptable in modern, evidence-based medicine, and can have serious consequences during a pandemic.

The clinical efficacy of mAbs has remained limited to patients with early and mild disease stages, as would be expected for a therapy that works primarily as an antiviral agent. Their high cost means that they are unlikely to become prominent treatment options in low-income and middle-income countries that cannot afford them. Scaling up of manufacturing is also a bottleneck for high-income economies, which often have had difficulties at procurement. Several lessons were learnt from the pandemic, such as the need for combining different (ideally non-overlapping) mAbs to minimise immune escape. Recombinant technology has been deployed to increase half-life and minimise off-target toxicity.

Overall, mAbs remain an important achievement of modern science, but their feasibility and economical sustainability against pathogens are likely to be maximal in small outbreaks and localised epidemics, rather than under pandemic settings. During a pandemic, an enormous number of affordable doses would be needed to have a positive impact on a global scale. In such instance, alternatives that are more robust and scalable than mAbs are preferred, such as convalescent plasma, or oral or intravenous small-chemical antivirals; however, small-chemical antivirals are expensive and often associated with pharmacokinetic contraindications.

Contributors
DF wrote the first draft of the manuscript and designed the figure in the appendix. DF, EC, and GV designed the tables. SM designed the figure. MT and AC revised the manuscript.

Declaration of interests
AC is the Chair of the US National COVID-19 Convalescent Plasma Project and reports being part of the scientific advisory board of SAB Therapeutics; a company developing cow polyclonal antibodies. All other authors declare no competing interests.

References
1 Barnes K, Milestone L. The first monoclonal antibody therapy. Nature Protocols, December, 2018. https://media.nature.com/original/magazine-assets/d42859-018-00024-6/d42859-018-00024-6.pdf (accessed June 1, 2022).
2 El Abd Y, Tahli R, Smolic R, Smolic M. Mini-review: the market growth of diagnostic and therapeutic monoclonal antibodies—SARS-CoV-2 as an example. Hum Antibodies 2022; 30: 15–24.
3 Tuccori M, Ferraro S, Convertino I, et al. Anti-SARS-CoV-2 neutralizing monoclonal antibodies: clinical pipeline. Mabs 2020; 12: 1854149.
4 Gottlieb RL, Nirsala A, Chen P, et al. Effect of hamlanivimab as monotherapy or in combination with etesevimab on viral load in patients with mild to moderate COVID-19: a randomized clinical trial. JAMA 2021; 325: 612–44.
5 ACTIV-3/TICO ET-CoV555 Study Group, Lundgren JD, Grund B, et al. A neutralizing monoclonal antibody for hospitalized patients with COVID-19. N Engl J Med 2021; 384: 905–14.
6 Weinreich DM, Sivapalasingam S, Norton T, et al. REGEN-COV antibody combination and outcomes in outpatients with COVID-19. N Engl J Med 2021; 385: e81.
7 Isa F, Forleo-Neto E, Meyer J, et al. Repeat subcutaneous administration of REGEN-COV in adults is well-tolerated and prevents the occurrence of COVID-19. medRxiv 2021; published online Nov 16. https://doi.org/10.1101/2021.11.20.21268389 (preprint).
8 O’Brien MP, Forleo-Neto E, Musser BJ, et al. Subcutaneous REGEN-COV antibody combination to prevent COVID-19. N Engl J Med 2021; 385: 1184–95.
9 RECOVERY Collaborative Group. Casirivimab and imdevimab in patients admitted to hospital with COVID-19 (RECOVERY): a randomised, controlled, open-label, platform trial. Lancet 2022; 399: 665–76.
10 Levin MJ, Ustianowski A, De Wit S, et al. Intramuscular AZD7442 (tigavimab–cilgavimab) for prevention of COVID-19. N Engl J Med 2022; 386: 2188–200.
11 AstraZeneca. Update on AZD7442 STORM CHASER trial in post-exposure prevention of symptomatic COVID-19. June 15, 2021. https://www.astrazeneca.com/media-centre/press-releases/2021/update-on-azd7442-storm-chaser-trial.html (accessed Feb 22, 2022).
12 AstraZeneca. AZD7442 reduced risk of developing severe COVID-19 or death in TACKLE Phase III outpatient treatment trial. Oct 11, 2021. https://www.astrazeneca.com/content/astrazeneca/media-centre/press-releases/2021/azd7442-phsii-trial-positive-in-covid-outpatient.html (accessed Feb 22, 2022).
13 Gupta A, Gonzalez-Rojas Y, Juarez E, et al. Early treatment for COVID-19 with SARS-CoV-2 neutralizing antibody sotrovimab. N Engl J Med 2021; 385: 1941–50.
14 Kim JY, Jung YR, Hong JH, et al. Safety, virologic efficacy, and pharmacokinetics of CT-P59, a neutralizing monoclonal antibody against SARS-CoV-2 spike receptor-binding protein: two randomized, placebo-controlled, phase I studies in healthy individuals and patients with mild SARS-CoV-2 infection. Clin Ther 2021; 43: 1706–27.
15 Eom JS, Ison M, Streinu-Cercel A, et al. Efficacy and safety of CT-P59 plus standard of care: a phase 2/3 randomized, double-blind, placebo-controlled trial in outpatients with mild-to-moderate SARS-CoV-2 infection. Res Std 2021; published online March 15. https://www.researchsqure.com/article/rs-29638v1 (preprint).
16 Celltrion Healthcare. Celltrion announces positive top-line results from global phase III trial of regdanvimab (CT-P59), an anti-COVID-19 monoclonal antibody treatment. June 14, 2021. https://www.celltrionhealthcare.com/en-us/board/newsdetail?modify_key=498&pagenumber=2&keyword=&keyword_type= (accessed June 1, 2022).
17 Dougan M, Azizad M, Chen P, et al. Bebtelovimab, alone or together with bamlanivimab and etesevimab, as a broadly neutralizing monoclonal antibody treatment for mild to moderate, ambulatory COVID-19. medRxiv 2022; published online March 12. https://www.medrxiv.org/content/10.1101/2021.11.10.21265889 (preprint).
18 Centers for Disease Control and Prevention. COVID-19 information for specific groups of people. March 22, 2022. https://www.cdc.gov/coronavirus/2019-ncov/need-extra-precautions/index.html?CDC_AA_refVal=https%3A%2F%2Fwww.cdc.gov%2FCoronavirus%25 (accessed June 1, 2022).
19 ACTIV-3/Therapeutics for Inpatients with COVID-19 (TICO) Study Group. Efficacy and safety of two neutralising monoclonal antibody therapeutics, tixagevimab–cilgavimab, in adults hospitalised with COVID-19 (TICO): a randomised controlled trial. Lancet Infect Dis 2022; 22: 622–35.
Cross-neutralizing antibodies bind a broadsarbecovirus receptor binding domain by neutralizing properties. bioRxiv 2022; published online March 18. https://doi.org/10.1101/2022.03.18.484873 (preprint).

Zhan W, Tian X, Zhang X, et al. A potent SARS-CoV-2 antibody neutralizes omicron variant by disassembling the spike trimer. bioRxiv 2022; published online March 22. https://doi.org/10.1101/2022.03.21.485243 (preprint).

Piccoli L, Park YJ, Tortorici MA, et al. Mapping neutralizing and immunodominant sites on the SARS-CoV-2 spike receptor-binding domain by structure-guided high-resolution serology. Cell 2020; 183: 1024–42.

Tortorici MA, Beltranmello L, Lempp FA, et al. Ultrapotent human antibodies protect against SARS-CoV-2 challenge via multiple mechanisms. Science 2020; 370: 950–57.

Bertoglio F, Fühner V, Ruscig M, et al. A SARS-CoV-2 neutralizing antibody selected from COVID-19 patients binds to the ACE2-RBD interface and is tolerant to most known RBD mutations. Cell 2021; 184: 109331.

Du W, Hurdiss DL, Drabek D, et al. An ACE2-blocking antibody confers broad neutralization and protection against omicron and other SARS-CoV-2 variants. Sci Immunol 2022; published online April 26. https://doi.org/10.1126/sciimmunol.abf9312.

Yao H, Sun Y, Deng J, Kernaiz H-C, et al. SARS-CoV-2 beta variant infection elicits potent lineage-specific and cross-reactive antibodies. Science 2022; 375: 782–87.

Ferwicz C, Turelli P, Perez L, et al. A highly potent antibody effective against SARS-CoV-2 variants of concern. Cell Rep 2021; 36: 109331.

Park YJ, De Marco A, Starr TN, et al. Antibody-mediated broad sarbecovirus neutralization through ACE2 molecular mimicry. Science 2022; 375: 449–54.

Yao H, Sun Y, Deng J, Kernaiz H-C, et al. SARS-CoV-2 beta variant infection elicits potent lineage-specific and cross-reactive antibodies. Science 2022; 375: 782–87.

Ferwicz C, Turelli P, Perez L, et al. A highly potent antibody effective against SARS-CoV-2 variants of concern. Cell Rep 2021; 37: 109814.

Park YJ, De Marco A, Starr TN, et al. Antibody-mediated broad sarbecovirus neutralization through ACE2 molecular mimicry. Science 2022; 375: 449–54.

Yao H, Sun Y, Deng J, Kernaiz H-C, et al. SARS-CoV-2 beta variant infection elicits potent lineage-specific and cross-reactive antibodies. Science 2022; 375: 782–87.

Ferwicz C, Turelli P, Perez L, et al. A highly potent antibody effective against SARS-CoV-2 variants of concern. Cell Rep 2021; 37: 109814.

Park YJ, De Marco A, Starr TN, et al. Antibody-mediated broad sarbecovirus neutralization through ACE2 molecular mimicry. Science 2022; 375: 449–54.

Yao H, Sun Y, Deng J, Kernaiz H-C, et al. SARS-CoV-2 beta variant infection elicits potent lineage-specific and cross-reactive antibodies. Science 2022; 375: 782–87.

Ferwicz C, Turelli P, Perez L, et al. A highly potent antibody effective against SARS-CoV-2 variants of concern. Cell Rep 2021; 37: 109814.
SARS-CoV-2 omicron variant to neutralization by vaccine-elicited antibodies and circulating variants. Nature 2021; 592: 616–22.

Chen RE, Zhang X, Case JB, et al. Resistance of SARS-CoV-2 variants to neutralization by monoclonal and serum-derived polyclonal antibodies. Nat Med 2021; 27: 717–26.

Dong J, Zou SJ, Greaney AJ, et al. Genetic and structural basis for SARS-CoV-2 variant neutralization by a two-antibody cocktail. Nat Microbiol 2021; 6: 1233–44.

Ryu D-K, Woo H-M, Kang B, et al. The in vitro and in vivo potency of CT-P59 against delta and its associated variants of SARS-CoV-2. bioRxiv 2021; published online July 23. https://doi.org/10.1101/2021.07.23.434497 (preprint).

Focosi D, Maggi F, McConnell S, Casadevall A. Spike mutations in SARS-CoV-2 BA.2 sublineages of the delta variant of concern: implications for the future of the pandemic. Future Microbiol 2022; 17: 219–21.

Wang R, Zhang Q, Ge J, et al. Spike mutations in SARS-CoV-2 BA.2 variants confer resistance to antibody neutralization. bioRxiv 2021; published online March 9. https://doi.org/10.1101/2021.03.09.434467 (preprint).

Wang P, Casner RG, Nair MS, et al. Increased resistance of SARS-CoV-2 variant P.1 to antibody neutralization. Cell Host Microbe 2021; 29: 747–51.

Iketani S, Liu L, Guo Y, et al. Antibody evasion properties of SARS-CoV-2 omicron sublineages. Nature 2022; 604: 553–56.

Zhao H, Tada T, Dcosta BM, Landau NR. Neutralization of SARS-CoV-2 omicron BA.2 by therapeutic monoclonal antibodies. bioRxiv 2021; published online Feb 24. https://doi.org/10.1101/2021.02.15.480166v2 (preprint).

Cao Y, Wang J, Juan F, et al. Omicron escapes the majority of existing SARS-CoV-2 neutralizing antibodies. Nature 2021; 602: 657–63.

Gruell H, Vanshylla K, Tober-Lau P, et al. mRNA booster immunization elicits potent neutralizing serum activity against the SARS-CoV-2 omicron variant. Nat Med 2022; 28: 477–80.

Hoffmann M, Krüger N, Schulz S, et al. The omicron variant is highly resistant against antibody-mediated neutralization: implications for control of the COVID-19 pandemic. Cell 2022; 185: 447–56.

Planas D, Landers N, Maes P, et al. Considerable escape of SARS-CoV-2 omicron to antibody neutralization. Nature 2022; 602: 671–75.

Liu L, Iketani S, Guo Y, et al. Striking antibody evasion manifested by the omicron variant of SARS-CoV-2. Nature 2022; 602: 676–81.

vanBlaarbon LA, Errico JM, Halfmann P, et al. An infectious SARS-CoV-2 B.1.1.529 omicron virus escapes neutralization by therapeutic monoclonal antibodies. Nat Med 2022; 28: 490–95.

Shewad DJ, Kim C, Ehling RA, et al. Variable loss of antibody potency against SARS-CoV-2 B.1.1.529 (omicron). bioRxiv 2021; published online Dec 20. https://doi.org/10.1101/2021.12.19.473534 (preprint).

Tada T, Zhou H, Dcosta BM, et al. Increased resistance of SARS-CoV-2 omicron variant to neutralization by vaccine-elicited and therapeutic antibodies. eBioMedicine 2022; 78: 103944.

Tourret F, Baronti C, Bousidi H, de Lamballerie X. In vitro evaluation of therapeutic antibodies against a SARS-CoV-2 omicron B.1.1.529 isolate. Sci Rep 2022; 12: 4683.

Boschi C, Colson P, Bancod A, Moal V, La Scala B. Omicron variant escapes therapeutic mAbs contrary to eight prior main VOC. bioRxiv 2022; published online Jan 3. https://doi.org/10.1101/2022.01.03.2126769 (preprint).

Takahata E, Kinoshita N, Yamayoshi S, et al. Efficacy of antiviral agents against the SARS-CoV-2 omicron subvariant BA.2. bioRxiv 2022; published online June 1. https://doi.org/10.1101/2022.06.01.481178 (preprint).

Yamasoba D, Konugi Y, Kimura I, et al. Neutralisation sensitivity of SARS-CoV-2 omicron subvariants to therapeutic monoclonal antibodies. Lancet Infect Dis 2022; 22: 942–43.

McCallum M, Bassi J, De Marco A, et al. SARS-CoV-2 Immune evasion by the B.1.427/B.1.429 variant of concern. Science 2021; 373: 648–54.

Annavajhala MK, Mohri H, Wang P, et al. Emergence and expansion of SARS-CoV-2 B.1.526 after identification in New York. Nature 2021; 597: 701–08.

Hoffmann M, Arora P, Groß R, et al. SARS-CoV-2 variants B.1.351 and P.1 escape from neutralizing antibodies. Cell 2021; 184: 2388–93.

Liu H, Wei P, Zhang Q, et al. 501YV2 and 501YV3 variants of SARS-CoV-2 lose binding to bamlanivimab in vitro. MAb 2021; 13: 1939285.

Widera M, Wilhelm A, Hoehl S, et al. Bamlanivimab does not neutralize two SARS-CoV-2 variants carrying E484K in vitro. medRxiv 2021; published online Feb 26. https://doi.org/10.1101/2021.02.24.21252372 (preprint).

Hoffmann M, Hofmann-Winkler H, Krüger N, et al. SARS-CoV-2 variant B.1.617 is resistant to bamlanivimab and evades antibodies induced by infection and vaccination. Cell Rep 2021; 36: 109415.

Zhang L, Huynh T, Luan B. In silico assessment of antibody drug resistance to bamlanivimab of SARS-CoV-2 variant B.1.617. bioRxiv 2021; published online May 14. https://doi.org/10.1101/2021.05.12.443826 (preprint).

Tada T, Zhou H, Dcosta BM, Samanovic M, Milligan MJ, Landau NR. Partial resistance of SARS-CoV-2 delta variants to vaccine-elicited antibodies and convalescent sera. iScience 2021; 24: 103341.

Planas D, Veyer D, Baidalnik A, et al. Reduced sensitivity of SARS-CoV-2 variant delta to antibody neutralization. Nature 2021; 596: 276–80.

Arora P, Kempf A, Nehlmes I, et al. Increased lung cell entry of B.1.6172 and evasion of antibodies induced by infection and BNT162b2 vaccination. bioRxiv 2021; published online June 23. https://doi.org/10.1101/2021.06.23.449568 (preprint).

Liu H, Wei P, Zhang Q, et al. The lambda variant of SARS-CoV-2 has a better chance than the delta variant to escape vaccines. bioRxiv 2021; published online Aug 26. https://doi.org/10.1101/2021.08.25.457692 (preprint).

Aggarwal A, Ospina Stella A, Walker G, et al. SARS-CoV-2 omicron: evasion of potent humoral responses and resistance to clinical immunotherapeutics relative to viral variants of concern. medRxiv 2021; published online Dec 15. https://doi.org/10.1101/2021.12.14.21267772 (preprint).

Zhou H, Dcosta BM, Samanovic MJ, Milligan MJ, Landau NR. Tada T. B.1.526 SARS-CoV-2 variants identified in New York City are neutralized by vaccine-elicited and therapeutic monoclonal antibodies. mBio 2021; 12: e0138621.

Fenwick C, Turelli P, Pellaton C, et al. A high-throughput cell- and virus-free assay shows reduced neutralization of SARS-CoV-2 variants by COVID-19 convalescent plasma. Sci Transl Med 2021; 13: eabi8452.

Tada T, Zhou H, Samanovic M, et al. Neutralization of SARS-CoV-2 variants by mRNA and adenoviral vector vaccine-elicited antibodies. Front Immunol 2022; 13: 1797589.

Ohashi H, Hishiki T, Akazawa D, et al. Different efficacies of neutralizing antibodies and antiviral drugs on SARS-CoV-2 omicron subvariants, BA.1 and BA.2. bioRxiv 2021; published online Feb 28. https://doi.org/10.1101/2021.02.27.824167 (preprint).

Wilmel A, Widera M, Grikoschev K, et al. Reduced neutralization of SARS-CoV-2 omicron variant by vaccine sera and monoclonal antibodies. medRxiv 2021; published online Dec 8. https://doi.org/10.1101/2021.12.07.21267632 (preprint).

Ikeura N, Hoshino A, Higuchi Y, Taminiishi S, Inaba T, Matoba S. SARS-CoV-2 omicron variant neutralization by vaccinated and convalescent sera and therapeutic monoclonal antibodies. medRxiv 2021; published online Dec 14. https://doi.org/10.1101/2021.12.31.21267761 (preprint).
019 Wilhelm A, Toptan T, Pallas C, et al. Antibody-mediated neutralization of authentic SARS-CoV-2 B.1.617 variants harboring L452R and T478K/E48Q. Viruses 2021; 13: 1691.

020 Tada T, Zhou H, Docta BM, Samanovic M, Mulligan MJ. Landau NR. SARS-CoV-2 lambda variant remains susceptible to neutralization by mRNA vaccine-elicited antibodies and convalescent serum. bioRxiv 2021; published online July 3. https://doi.org/10.1101/2021.07.02.459559 (preprint).

021 Ryu D-K, Song R, Kim M, et al. Therapeutic effect of CT-P59 against SARS-CoV-2 South African variant. Biochem Biophys Res Commun 2021; 566: 135–40.

022 Ryu D-K, Kang B, Woo S-j, et al. Therapeutic efficacy of CT-P59 against P.1 variant of SARS-CoV-2. bioRxiv 2021; published online July 9. https://doi.org/10.1101/2021.07.08.451696 (preprint).

023 Liu Y, Arase N, Kishikawa J-i, et al. The SARS-CoV-2 delta variant is poised to acquire complete resistance to wild-type spike vaccines. bioRxiv 2021; published online Aug 23. https://doi.org/10.1101/2021.08.22.457114 (preprint).

024 Benotmane I, Velay A, Taunat O, et al. Pre-exposure prophylaxis with Euvshield elicits limited neutralizing activity against the omicron variant in kidney transplant patients. medRxiv 2021; published online March 23. https://doi.org/10.1101/2022.03.21.2227669 (preprint).

025 US Food and Drug Administration. Coronavirus (COVID-19) update: FDA limits use of certain monoclonal antibodies to treat COVID-19 due to the omicron variant. Jan 24, 2022. https://www.fda.gov/news-events/press-announcements/coronavirus-covid-19-update-fda-limits-use-certain-monoclonal-antibodies-treat-covid-19-due-omicron (accessed Feb 3, 2022).

026 Therapeutic Goods Administration, Australian product information: XEVUDY (sotrovimab) concentrated injection solution for infusion. Dec 28, 2021. https://www.tga.gov.au/sites/default/files/xevudy-pi.pdf (accessed Mar 21, 2022).

027 Rockett RJ, Basile K, Maddocks S, et al. Resistance mutations in SARS-CoV-2 delta variant after sotrovimab use. N Engl J Med 2022; 386: 1077–79.

028 Reuters. GSK-Vir therapy has neutralising activity against omicron sub-variant, data shows. Feb 10, 2022. https://www.reuters.com/business/healthcare-pharmaceuticals/gsk-vir-therapy-works-against-omicron-sub-variant-data-suggests-2022-02-10/ (accessed Feb 15, 2022).

029 Case JB, Mackin S, Errico J, et al. Resilience of S309 and AZD7442 monoclonal antibody treatments against infection by SARS-CoV-2 omicron lineage strains. bioRxiv 2022; published online March 18. https://doi.org/10.1101/2022.03.17.847878 (preprint).

030 US Food and Drug Administration. Coronavirus (COVID-19) update: FDA authorizes new monoclonal antibody for treatment of COVID-19 that retains activity against omicron variant. Feb 11, 2022. https://www.fda.gov/news-events/press-announcements/coronavirus-covid-19-update-fda-authorizes-new-monoclonal-antibody-treatment-covid-19-retains (accessed Feb 17, 2022).

031 Tiacci M, Convertino I, Ferraro S, et al. Preclinical discovery and development of bamlanivimab for the treatment of novel coronavirus infection (COVID-19): reasons for preclinical discovery and development of bamlanivimab for the treatment of novel coronavirus infection (COVID-19). bioRxiv 2021; published online March 7. https://doi.org/10.1101/2022.03.04.479488 (preprint).

032 Case JB, Mackin S, Errico J, et al. Resilience of S309 and AZD7442 monoclonal antibody treatments against infection by SARS-CoV-2 omicron lineage strains. bioRxiv 2022; published online March 18. https://doi.org/10.1101/2022.03.17.847878 (preprint).

033 Ku Z, Xie X, Lin J, et al. Engineering SARS-CoV-2 cocktail antibodies to broadly neutralize emerging SARS-CoV-2 variants. bioRxiv 2021; published online Dec 28, 2021. https://www.fda.gov/media/141477/download (accessed June 11, 2022).
149 Peebles RS Jr, Liu MC, Lichtenstein LM, Hamilton RG. IgA, IgG and IgM quantification in bronchoalveolar lavage fluids from allergic rhinitics, allergic asthmatics, and normal subjects by monoclonal antibody-based immunoenzymetric assays. *J Immunol Methods* 1995; 179: 77–86.

150 Wu H, Pfarr DS, Johnson S, et al. Development of motavizumab, an ultra-potent antibody for the prevention of respiratory syncytial virus infection in the upper and lower respiratory tract. *J Mol Biol* 2007; 368: 652–65.

151 Focosi D, Maggi F, Casadevall A. Mucosal vaccines, sterilizing immunity, and the future of SARS-CoV-2 virulence. *Viruses* 2022; 14: 187.

152 Mayor A, Thibert B, Hulille S, Respaud R, Audat H, Heuzé-Vourc’h N. Inhaled antibodies: formulations require specific development to overcome instability due to nebulization. *Drug Deliv Transl Res* 2021; 11: 1625–33.

153 Bodier-Montagutelli E, Respaud R, Perret G, et al. Protein stability during nebulization: mind the collection step! *Eur J Pharm Biopharm* 2020; 152: 23–34.

154 Lewis RA, Fleming JS. Fractional deposition from a jet nebulizer: how it differs from a metered dose inhaler. *Br J Din Ches* 1985; 79: 361–67.

155 Niven RW, Ip AY, Mittelman S, Prestrelski SJ, Arakawa T. Some factors associated with the ultrasonic nebulization of proteins. *Pharm Res* 1995; 12: 53–59.

156 Fahy JV, Cockcroft DW, Boulet LP, et al. Effect of aerosolized anti-IgE (E25) on airway responses to inhaled allergen in asthmatic subjects. *Am J Respir Crit Care Med* 1999; 160: 1023–27.

157 Bodier-Montagutelli E, Mayor A, Vecellio L, Respaud R, Heuzé-Vourc’h N. Designing inhaled protein therapeutics for topical lung delivery: what are the next steps? *Expert Opin Drug Deliv* 2013; 15: 729–36.

158 Respaud R, Vecellio L, Diet P, Heuzé-Vourc’h N. Nebulization as a delivery method for mAbs in respiratory diseases. *Expert Opin Drug Deliv* 2015; 12: 1027–39.

159 Fröhlich E, Salar-Behzadi S. Oral inhalation for delivery of proteins and peptides to the lungs. *Eur J Pharm Biopharm* 2021; 163: 198–211.

160 Pritchard JN, Hatley RH, Denyer J, von Hellen D. Mesh nebulizers have become the first choice for new nebulized pharmaceutical drug developments. *Ther Deliv* 2018; 9: 121–36.

161 McSweeney MD, Stewart I, Richardson Z, et al. Stable nebulization and muco-trapping properties of regdanvimab/IN-006 supports its development as a potent, dose-saving inhaled therapy for COVID-19. *bioRxiv* 2022; published online March 1. https://doi.org/10.1101/2022.02.27.2482162 (preprint).

162 Kadiyala G, Iyer S, Meher K, Vangala S, Chandran S, Saxena U. Preparation of ingestible antibodies to neutralize the binding of SARS-CoV-2 RBD (receptor binding domain) to human ACE2 receptor. *bioRxiv* 2021; published online Oct 20. https://doi.org/10.1101/2021.10.19.464951 (preprint).

163 Frumkin LR, Lucas M, Scribner CL, et al. Egg-derived anti-SARS-CoV-2 immunoglobulin Y (IgY) with broad variant activity as intranasal prophylaxis against COVID-19: preclinical studies and randomized controlled phase 1 clinical trial. *medRxiv* 2022; published online Jan 10. https://doi.org/10.1101/2022.01.07.22268914 (preprint).

164 Power M, Azad T, Bell JC, MacLean AM. Plant-based expression of SARS-CoV-2 antigens for use in an oral vaccine. *bioRxiv* 2021; published online Dec 9. https://doi.org/10.1101/2021.12.07.471131 (preprint).

165 Li C, Zhan W, Yang Z, et al. Broad neutralization of SARS-CoV-2 variants by an inhalable bispecific single-domain antibody. *Cell* 2022; 185: 1389–401.

166 Aleccia J. Some states still pushing ineffective covid antibody treatments. Medscape. Jan 21, 2022. https://www.medscape.com/viewarticle/967020 (accessed April 26, 2022).

167 Gottlieb RL, Vaca CE, Paredes R, et al. Early remdesivir to prevent progression to severe COVID-19 in outpatients. *N Engl J Med* 2022; 386: 305–15.