This is an Open Access document downloaded from ORCA, Cardiff University's institutional repository: https://orca.cardiff.ac.uk/id/eprint/143440/

This is the author's version of a work that was submitted to / accepted for publication.

Citation for final published version:

Scourfield, D. Oliver, Reed, Sophie G., Quastel, Max, Alderson, Jennifer, Bart, Valentina M. T., Teijeira Crespo, Alicia, Jones, Ruth, Pring, Ellie, Richter, Felix Clemens, Ahern, David J., Almuttaqi, Hannah, Alonzi, Dominic S., Alrubayyl, Aljawharah, Alsaleh, Ghada, Bart, Valentina M. T., Batchelor, Vicky, Bayliss, Rebecca, Berthold, Dorothee L., Bezbradica, Jelena S, Bharuchq, Tehmina, Borrmann, Helene, Borsa, Mariana, Borst, Rowie, Brun, Juliane, Burnell, Stephanie E. A., Capitani, Lorenzo, Cavounidis, Athena, Chapman, Lucy, Chauveau, Anne, Cifuentes, Liliana, Codd, Amy Susan, Compeor, Ewoud Bernardus, Coveney, Clarissa, Cross, Amy, Danielli, Sara, Davies, Luke C, Dendrou, Calliope A., Dimonte, Sandra, Peter Durairaj, Ruban Rex, Dustin, Lynn B., Dyer, Arthur, Fielding, Ceri, Fischer, Fabian, Gallimore, Awen, Galloway, Sarah, Gammage, Anis, Gea-Mallorquí, Ester, Godkin, Andrew, Hanna, Stephanie Jean, Heuberger, Cornelia, Hulin-Curtis, Sarah, Issa, Fadi, Jones, Emma, Jones, Ruth, Ladell, Kristin, Lauder, Sarah N., Liddiard, Kate, Ligoxygakis, Petros, Lu, Fangfang, MacLachlan, Bruce, Maleki-Toyserkani, Shayda, Mann, Elizabeth H., Marzeda, Anna M., James Matthews, Reginald, Mazet, Julie M., Millicic, Anita, Mitchell, Emma, Moon, Owen, Nguyen, Van Dien, O'Hanlon, Miriam, Eléonore Pavillet, Clara, Peppa, Dimitra, Pires, Ana, Pring, Eleanor, Quastel, Max, Reed, Sophie, Rehwinkel, Jan, Richmond, Niamh, Richter, Felix Clemens, Robinson, Alice J. B., Rodrigues, Patricia R. S., Sabberwal, Pragati, Sami, Arvind, Peres, Raphael Sanches, Sattentau, Quentin, Schonfeldova, Barbora, Scourfield, David Oliver, Selvakumar, Tharini A., Shepherd, Freya R., Shorten, Cariad, Simon, Anna Katharina, Smith, Adrian L., Crespo, Alicia Teijeira, Tellier, Michael, Thornton, Emily, Uhl, Lion F. K., van Grinsven, Erinke, Wann, Angus K. T., Williams, Richard, Wilson, Joseph D., Zhou, Dingxi, Zhu, Zihan and Burnell, Stephanie E. A. 2021. The role and uses of antibodies in COVID-19 infections: a living review. Oxford Open Immunology 2 (1) , iqab003. 10.1093/oxfimm/iqab003

Publishers page: http://dx.doi.org/10.1093/oxfimm/iqab003

Please note:
Changes made as a result of publishing processes such as copy-editing, formatting and page numbers may not be reflected in this version. For the definitive version of this publication, please refer to the published source. You are advised to consult the publisher's version if you wish to cite this paper.

This version is being made available in accordance with publisher policies. See http://orca.cf.ac.uk/policies.html for usage policies. Copyright and moral rights for publications made available in ORCA are retained by the copyright holders.
The role and uses of antibodies in COVID-19 infections: a living review

D. Oliver Scourfield1,*,‡, Sophie G. Reed1, Max Quastel2, Jennifer Alderson3, Valentina M. T. Bart1, Alicia Teijeira Crespo4, Ruth Jones5, Ellie Pring1, Felix Clemens Richter 3, The Oxford-Cardiff COVID-19 Literature Consortium and Stephanie E. A. Burnell 1,*,‡

1Division of Infection and Immunity, School of Medicine, Cardiff University, Cardiff, CF14 4XN, UK, 2Nuffield Department of Medicine, University of Oxford, Oxford, OX3 7FZ, UK, 3Kennedy Institute of Rheumatology, NDORMS, University of Oxford, Oxford, OX3 FTY, UK, 4Division of Cancer and Genetics, School of Medicine, Cardiff University, Cardiff, CF14 4XN UK, 5Dementia Research Institute, Cardiff University, Cardiff, CF24 4HQ, UK

*Correspondence address. Stephanie E. A. Burnell, Division of Infection and Immunity, School of Medicine, Cardiff University, Heath Park, Cardiff, CF14 4XN, UK. Tel: 02920687060, E-mail: BurnellS@Cardiff.ac.uk and ScourfieldDO@Cardiff.ac.uk

‡These authors contributed equally to this work.

Extensive author list of The Oxford-Cardiff COVID-19 Literature Consortium is given in Appendix 1.

ABSTRACT

Coronavirus disease 2019 has generated a rapidly evolving field of research, with the global scientific community striving for solutions to the current pandemic. Characterizing humoral responses towards SARS-CoV-2, as well as closely related strains, will help determine whether antibodies are central to infection control, and aid the design of therapeutics and vaccine candidates. This review outlines the major aspects of SARS-CoV-2-specific antibody research to date, with a focus on the various prophylactic and therapeutic uses of antibodies to alleviate disease in addition to the potential of cross-reactive therapies and the implications of long-term immunity.

Key words: antibodies; COVID-19; SARS-CoV-2; convalescent plasma, nanobodies; vaccines; long-term immunity.

INTRODUCTION

Humoral immunity is a vital aspect of the immune system highly implicated in infection control. Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is a highly infectious virus that is responsible for the current worldwide coronavirus disease 2019 (COVID-19) pandemic. Understanding the immune response to this virus is paramount to limit disease burden in the population, and to discover new therapeutic options. One such response is that of antibodies; the immunoglobulins secreted by B-cells following antigen recognition. Antibodies have a multitude of effector functions and can coordinate the
Box 1: What is the consensus on antibodies in SARS-CoV-2 infection?

When infected with COVID-19, patients produce antibodies to fight off the infection. These antibodies are known as immunoglobulins; IgM, IgA and IgG, and are key players in the response to COVID-19. Each has a unique role and therefore takes different lengths of time to be detected in the blood, to reach the maximum quantity and diminish from the system. As this is still a new disease, further work is needed to determine how long these antibody responses last in the body. Most COVID-19 patients that do not display any symptoms have low levels of IgM, while levels of IgA and IgG antibodies are higher in more severe, symptomatic patients. However, more in-depth study is needed to see if these antibody responses are important in controlling infection and how they co-ordinate with other immune responses to COVID-19. Patients with strong immune responses to COVID-19 have high levels of neutralizing antibodies, which successfully control the infection. Once recovered, plasma can be taken from these patients and be administered to those who are currently severely infected. This is known as CP treatment. Other treatment options, which include mAbs and nanobodies, are more focused therapies, having developed from the most potent antibodies. Approval of two potent mAb therapies signifies the importance of antibodies in overcoming infection. However, these are most effective at preventing severe disease, so research to identify treatments to benefit those severely infected is still needed. However, these are most effective at preventing progression to severe disease, so research to identify treatments to benefit those severely infected is still needed. Work is also being carried out to investigate previous coronavirus infections to see what we can learn from them. It is possible that antibodies made against these other strains may help protect people during this pandemic. It is currently unknown whether people who have recovered from COVID-19 are protected against a future SARS-CoV-2 infection as reinfection has been reported in several people worldwide. This has implications for vaccine design as regular boosters may be required if the immune response declines. Key components to creating a long-lasting immunity to the virus will become clearer once further research has been conducted.

Box 2: Why do antibodies in SARS-CoV-2 infection matter?

COVID-19 has rapidly changed the World, from countless deaths and long-term health problems in survivors, to creating a social and economic burden. Research on COVID-19 is being produced quickly, so it is crucial that we view this critically to distinguish robust data. From this baseline, we are then able to produce successful therapies as soon as possible to help fight this pandemic. Looking at previous coronavirus strains is necessary to gain useful insights into this new and novel virus. There are similarities between SARS-CoV-2 and former strains we have faced, which give us invaluable knowledge in treating patients and limiting global disease burden. What we learn from COVID-19 may also be applied to future epidemic or pandemic strains. Using antibodies taken from patients that have recovered from COVID-19 infection and giving them to those that are struggling to fight off the infection has the potential to save lives and bridge the gap while doctors and scientists are learning more about how to fight the virus and produce other treatments and vaccines.

**ANTIBODY RESPONSES TO SARS-COV-2 IN DIFFERENT PATIENT POPULATIONS**

Immunoglobulins IgM, IgA and IgG are key components of the antibody response towards SARS-CoV-2 and differ in titre and duration of response, as with other viral infections (Figure 1) [4]. Table 1 summarizes the SARS-CoV-2 antibody literature to date. This includes seroconversion; how long it takes antibodies to be detected in the serum following infection, response kinetics; how long it takes antibodies to achieve their peak titre, and the prediction of response duration.

IgG levels were shown to peak earlier in asymptomatic and mild cases compared to severe cases (~20 vs. ~35 days post symptom onset (d.p.s.o)) and most asymptomatic patients, many of whom were children, had low or undetectable IgM levels, leading to speculation that high and persistent IgM may result in more severe symptoms [19, 21, 25–27]. Interestingly, many publications have shown significant correlations of
higher antibody titres in both older patients and those with more severe disease [7, 13, 17, 19, 28–30]. Relative levels of IgA and IgG have been reported to be significantly higher in severe patients in addition to a significant correlation between IgA levels and APACHE-II score in critically ill patients [16, 23]. A study investigating the specificity and functionality of antibody responses in children found that SARS-CoV-2 positive children had low levels of IgM, IgA and IgG when compared to severe COVID-19 adults and demonstrated that children predominantly generated an anti-S IgG response compared to the broader antibody response generated by adults [31]. It has been suggested that the reduced symptoms demonstrated by children could be due to the reduced expression of the viral receptor in children or that children generate a more robust innate immune response [32, 33].

In addition to age, biological sex is also a potential factor in COVID-19 disease severity. Several countries have reported higher hospital admissions and mortality rates in males, with a case fatality rate 1.7 times higher for men than for women [34]. The production of IgG appears to be higher in females in the early stages of infection, possibly preventing the progression to advanced disease and decreasing the mortality rate [35, 36]. Patients that succumb to SARS-CoV-2 infection were unable to generate a functional IgG response, coordinate Fc receptor-binding and produce innate immune effector binding [37]. Further to this, patients with severe COVID-19, particularly males, have been shown to generate IgG1 antibodies with significantly reduced Fc fucosylation, in addition to increased IgG3 antibodies when compared to patients with mild symptoms and children, indicating that severe COVID-19 resulted from the production of pro-inflammatory IgG antibodies [38].

Coordinated responses between B cells, CD4+ and CD8+ T cells are necessary to control and clear infection, without a functional B–cell response, virus-specific memory T cells cannot provide complete protection [39]. Neutralizing antibody (nAb) responses and B cell memory decline over time and depend on CD4+ T cell help, leaving the role of long-term protection to the memory T cells [40, 41]. This, therefore, indicates that the immune system as a whole must be analysed, in addition to the individual components, to understand why some people are asymptomatic while others succumb to the disease.

Table 1: Summary of analysis of IgM, IgA and IgG responses to SARS-CoV-2 infection

|                  | IgM                        | IgA                        | IgG                        |
|------------------|----------------------------|----------------------------|----------------------------|
| Per cent seroconversion | >73 [5–9]                 | >72 [5, 6, 10]             | 84–100 [5–12]              |
| Seroconversion (d.p.s.o) | 10–14 [8, 13–16]         | 13 [16]                    | 12–14 [8, 13–16]           |
| Peak titre (d.p.s.o)    | 15–30 [3–5, 7, 9, 14, 17–19] | 16–30 [3, 5, 20–23]       | 16–50 [3–7, 9, 17, 19, 20, 22–24] |
| Median seronegative prediction | 49.6 days [6]           | 51.0 days [6]              |                            |

Following infection by SARS-CoV-2, IgM, IgA and IgG are rapidly seroconverted within the first 2 weeks; IgM and IgA appear to reach their peak titre at similar d.p.s.o, whereas IgG often peaks at a later time point.

THE USE OF ANTIBODIES AS THERAPY FOR COVID-19

There are various strategies to treat SARS-CoV-2 infection with antibodies, as summarized in Figure 2. Plasma extracted from recovered COVID-19 patients is known as convalescent plasma (CP). CP contains antibodies of various diversity (polyclonal) and affinities to SARS-CoV-2 and was greatly employed during the early phases of the pandemic. More recently, monoclonal antibodies (mAbs) and nanobodies/sybodies have been developed. By isolating memory B cells from recovered patients and immunized animals or screening of antibody mRNA using phage display, highly selective candidates with high-neutralization capacity have been identified. Neutralizing responses to SARS-CoV-2 target the receptor-binding domain (RBD) of the spike (S) glycoprotein, which is required to interact with the target receptor angiotensin-converting enzyme 2 (ACE2) on host cells [42–48]. Steric hindrance of the RBD–ACE2 interaction by antibodies will block viral entry and prevent infection. It should be noted that other neutralizing epitopes, distant from the RBD, exist but are less studied [43–50].

CONVALESCENT PLASMA

CP has been used to successfully reduce mortality in a variety of viral epidemics, including influenza, SARS and Middle East Respiratory Syndrome (MERS) [51, 52]. During the current COVID-19 pandemic, several studies have investigated CP trans-fusions with high nAb titres as a treatment option (see Figure 2A). Plasma is harvested from donors with total anti-spike IgG titres of >1:320 using plasmapheresis, this can then be transfused into an ABO-compatible patient [53]. Table 2 summarizes studies investigating the use of CP in COVID-19 patients.

An early meta-analysis of CP treatment for COVID-19 found evidence of reduced mortality as well as increased viral clearance, and clinical improvements [60]. Additionally, a more recent meta-analysis of larger, better quality studies confirmed these findings [61]. However, both the PLACID and PlasmAr randomized trials found no differences in disease progression or mortality in COVID-19 patients receiving CP or best standard of care/placebo [58, 59]. Larger, blinded, randomized control trials are still ongoing to confirm the efficacy of CP treatment, the RECOVERY trial in Oxford is one such Phase 3 trial of CP (NCT04381936).

In SARS patients, early CP treatment within 14 days of infection significantly improved outcomes [62]. This has also been suggested for COVID-19, but more studies are required to fully evaluate this [55]. Recovered patients with high nAb titres have relatively stable levels but these do decrease over time. Gontu et al. observed that the optimal time window for recovered patients to donate plasma is within 60 d.p.s.o [9].

Finally, CP treatment could be particularly beneficial for individuals who are immunocompromised [63, 64]. The nAbs in CP are likely targeted to a range of SARS-CoV-2 S protein epitopes, which is advantageous compared to single or even ‘cocktail’ mAb treatment where there is greater likelihood of escape mutations [65].

Monoclonal antibodies

Many studies have tested the neutralizing capacity of mAbs against SARS-CoV-2 in vitro (Figure 2B) and assessed their...
functionality in vivo. Neutralizing mAbs have shown a reduction in viral load and protection from challenge in animal models [42, 44–50, 66, 67]. This ability to inhibit infection highlights mAbs as potential therapeutic candidates for COVID-19.

Multiple candidates are in advanced clinical trials (Table 3). Recently, two mAb therapies (bamlanivimab, formerly LY-CoV555, and REGN-COV2) have received emergency use authorization by the Food and Drug Administration (FDA) to prevent mild-to-moderately-infected patients from progressing to severe disease. While bamlanivimab is a single mAb isolated from the B cells of a convalescent patient [68], REGN-COV2 is a cocktail of two mAbs (casirivimab and imdevimab) identified using both recovered patients and humanized mice [70]. Casirivimab and imdevimab recognize non-overlapping epitopes on the RBD which may overcome resistance posed by ‘viral escape’ mutations, such as D614G, a missense mutation in the spike protein that results in a more transmissible form of SARS-CoV-2 [72]. This approach of ‘antibody cocktails’ is also being explored by AstraZeneca, with their candidate AZD7442, comprising two mAbs, recently entering Phase 3 trials [42].

Cross-reactive nAb therapies

Multiple SARS-CoV and MERS-CoV mAbs were identified following the SARS and MERS epidemics in 2003 and 2012, respectively [73]. However, therapeutic developments were limited due to the short duration of these outbreaks. Both SARS-CoV and SARS-CoV-2 utilize ACE2 as their cell-entry receptor and the S-glycoprotein of SARS-CoV-2 is over 70% identical to that of SARS-CoV [74–79]. Conversely, MERS-CoV binds to the CD26 receptor and is less homologous to SARS-CoV-2 [79, 80]. Antibody cross-reactivity could potentially allow repurposing of these SARS-CoV mAbs to combat COVID-19.

RBD-directed mAbs, which interfere with ACE2 binding, thereby neutralizing SARS-CoV (e.g. 80R, CR3014), were unable to bind to SARS-CoV-2-RBD [81, 82]. Conversely, multiple SARS-CoV-targeted mAbs, which do not compete with ACE2, have shown potent cross-neutralizing capacity including 47D11 and CR3022 [82–84]. The ability of CR3022 to neutralize SARS-CoV-2 has been disputed by Yuan et al., however, who used a pseudovirus neutralization assay to assess this rather than one with live virus as with Huo et al. [84, 85]. A further explanation for the differences seen is that antibodies that show cross-reactivity recognize epitopes that are highly conserved between the strains. For example, the epitope of CR3022 is 86% conserved between SARS-CoV and SARS-CoV-2, and the more recently identified S309 (see Table 3) binds an epitope that is 77% conserved [47, 85]. Additional work has shown that further increasing the conservation of CR3022’s epitope vastly increases the antibody’s affinity to SARS-CoV-2 RBD, suggesting that antibody cross-reactivity is highly dependent on epitope recognition [86].

Nanobodies

Efforts have also been directed towards the development of nanobodies to treat COVID-19 (Figure 2C). Sequences of these
| Author and study type | Dose | No. of patients | Patient severity | Administration | Patient outcomes |
|-----------------------|------|----------------|-----------------|----------------|-----------------|
| Li et al. [54]        | >1:640 S-RBD-specific IgG | 103 | Control group: 29 life-threatening, 22 severe CP group: 29 life-threatening, 23 severe | 4–13 ml/kg of recipient body weight | Mortality: 15.7% CP group vs. 24% control $P = 0.30$ Clinical improvement: Severe patients 91.3% CP group vs. 68.2% control $P = 0.03$ Critically ill patients 20.7% CP group vs. 24.1% control $P = 0.83$ |
| Duan et al. [55]      | >1:640 nAb | 10 | 10 severe | 1 dose of 200 ml | All recovered |
| Shen et al. [56]      | >1:80 nAb | 5 | 5 critically ill | 2 transfusions of 200 ml | No severe adverse effects observed Of the five patients, three discharged and two were in stable condition |
| Liu et al. [53]       | >1:320 S-specific IgG | 39 | CP group: 39 severe to life-threatening Matched controls: 152 severe to life-threatening | Two transfusions of 250 ml | 12.8% mortality for CP group 24.4% mortality for matched controls ($P = 0.039$) CP improved survival in non-intubated patients ($P = 0.015$) but not for intubated patients ($P = 0.752$) |
| Donato et al. [57]    | >1:500 nAb | 47 | 32 non-mechanically ventilated, 22% immunocompromised and 19% had active cancer 15 mechanically ventilated | 400–500 ml | Non-mechanically ventilated: 15.6% intubation rate compared to institutional data (not reported; $P = 0.038$) 87.5% survival rate compared to 66% from institutional data ($P = 0.012$) Mechanically ventilated: 46.7% 30-day mortality rate compared to institutional data 68.5% ($P = 0.093$) |
| Agarwal et al. [58]   | >1:20 nAb | 464 | Moderate illness | Two transfusions of 200 ml | Progression to severe disease or mortality: 19% CP group vs. 18% control |
| Simonovich et al. [59]| >1:800 S-specific IgG | 333 | Patients with severe COVID-19 pneumonia | 5–10 ml/kg of recipient body weight | Mortality: 10.96% CP group vs. 11.43% control |
| Company | mAb name | Comments | Stage of development | Study group |
|---------|----------|----------|----------------------|-------------|
| Eli Lilly and Company  <br> (Developed with AbCellera) | Bamlanivimab<sup>a</sup>  <br> (LY-CoV555/LY3819253) | Human IgG1 isolated from convalesced patient using high-throughput microfluidic screening<sup>[68]</sup> | Phase 3—NCT04497987  <br> ‘BLAZE-2’  <br> Phase 3—NCT04501978  <br> ‘ACTIV-3’  <br> Phase 2/3—NCT04518410  <br> ‘ACTIV-2’ | Nursing Home residents and staff  <br> Inpatients  <br> Outpatients |
| Regeneron Pharmaceuticals  <br> REGN-COV2<sup>a</sup> (Casirivimab + Imdevimab) | LY-CoV555 (LY3819253) + LY-CoV016 (LY3832479) | Identified from humanized mice and convalescent samples. This dual-antibody cocktail targets non-overlapping epitopes<sup>[70]</sup> | Phase 3—NCT04452318  <br> ‘RECOVERY’  <br> Phase 2/3—NCT04381936  <br> ‘RECOVERY’  <br> Phase 1/2—NCT04425629  <br> Phase 1/2—NCT04426695  <br> Phase 1—NCT04519437 | Healthy adults who are household contacts with a positive case  <br> COVID-19 Patients  <br> Ambulatory COVID-19 patients  <br> Hospitalized patients  <br> Volunteers—Healthy, Chronic stable illness |
| Vir Biotechnology/GlaxoSmithKline | Sotrovimab (VIR-7831/GSK4182136) | Fully human based on S309 IgG which was isolated from the memory B-cells of an individual recovered from SARS-CoV (cross-reactive)[47] | Phase 3—NCT045060  <br> ‘COMET-ICE’ | Patients who are at high risk of hospitalization |
| AstraZeneca | AZD7442 (Tixagevimab + Cilgavimab) | Antibodies with non-overlapping epitopes identified from a convalescent patient[42]. The antibodies have been optimized to extend half-life so they should be prevalent for 6–12 months—‘Long-Acting Antibody Combination’ | Phase 3—NCT04625972  <br> ‘STORM CHASER’  <br> Phase 3—NCT04625725  <br> ‘PROVENT’ | Adults with potential recent (within 8 days) exposure to a confirmed positive case  <br> Adults who have no history of SARS-CoV-2 but have been exposed |
| Celltrion | Regdanvimab (CT-P59) | Targets the RBD of the spike protein | Phase 2/3—NCT04602000 | Diagnosed outpatients with mild conditions |

Included are the most advanced candidates, determined as those that have entered Phase 2/3 clinical stage.  
<sup>a</sup> Those which have received emergency use authorization by the FDA. Table created with aid from Yang et al. [71].
single-domain antibodies (VHH) capable of blocking the RBD/ACE2 interaction and neutralize SARS-CoV-2 have been identified using synthetic libraries (synthetic nanobodies, sbodies) and camels (nanobodies), which produce heavy-chain-only antibodies [13, 87–95]. Nanobodies have multiple benefits over conventional antibodies such as their biophysical and biochemical characteristics, and ease of manufacture and varied administrative potential (e.g. via inhalation) [91, 96].

Recent literature has shown a variety of ways in which antibodies can be used as treatment for COVID-19. While CP may work as a polyclonal approach, mAbs and nanobodies recognizing the RBD epitope of the virus are more promising since they are potent, high titre, relatively safe and can be readily manufactured in bulk. Because of this, multiple candidates are reaching clinical trials within a short timescale. Candidates recognizing epitopes that are highly conserved between coronaviruses have scope as potential pan-coronavirus therapies and may protect individuals from future epidemic/pandemic strains.

**ANTIBODY RESPONSES TO SARS-COV-2 VACCINES AND LONG-TERM IMMUNITY**

Prophylactic vaccines are in development to protect against COVID-19, with the aim of inducing nAb and T cell responses to combat infection. In vivo antiviral efficacy has been demonstrated in animal models, including preventing infection when challenged, and is being tested in clinical trials [97–117].

The majority of vaccines include the whole SARS-CoV-2 spike protein, and may also include the nucleocapsid protein (NP), while others only employ the RBD [97–109, 112–117]. The NP antigen does not generate antibodies that are neutralizing against SARS-CoV-2, whereas RBD and spike protein antigens elicit nAb responses [102]. The RBD and S1 domain of the spike protein unsurprisingly produce the greatest nAb responses, as these domains are responsible for ACE2 binding and gaining entry to host cells [118, 119]. Smith et al. and Yarmarkovich et al. took a computational approach to predict epitopes that produce humoral and cell-mediated responses, which may be broadly protective across various coronaviruses [120, 121]. Unfortunately, some non-neutralizing antibodies may have the potential to bridge viral entry into host immune cells via Fc receptors, known as antibody-dependent enhancement (ADE). This leads to increased infectivity, higher viral loads, more severe disease and has been observed in previous SARS/MERS vaccines [122]. Thus far, no study has yet shown evidence of vaccine-induced ADE for SARS-CoV-2.

The duration of long-term immunity to SARS-CoV-2 following infection or vaccination, as well as the level of nAb required for immunity, is currently unknown. Using a mathematical model of antibody kinetics determined by follow-up of coronavirus convalescent patients, one study has predicted that antibody responses will decline according to a biphasic pattern—a rapid decline initially, followed by a slower rate of decay [123]. This study indicated that, due to the substantial initial reduction of antibodies, up to 50% of patients could test seronegative after just 1 year [123]. Although these results cannot be verified until those patients are followed for several years following infection, other studies have estimated the time of seroreversion of SARS-CoV-2 antibodies based on the time taken for patients to become seronegative; 46.9 days for IgM and 51 days for IgA, as of yet, there is no consensus on IgG (Table 1) [6]. The nAb titres initially increase and remain stable for 3–4 months [5, 124–127]. Individuals with high peak nAb titres were observed to maintain these, but levels decreased to those of less severe groups at >90 d.p.s.0 [5, 127].

The duration of the immune response resulting from seasonal coronavirus infection varies, but the results obtained from these can help predict the duration of antibody responses until longer-term studies with large cohorts of patients can be carried out for SARS-CoV-2. Previous work carried out on SARS-CoV has indicated convalescent patients remained IgG positive for 2–4 years and antibody responses declined after 2–3 years, with severely affected individuals more likely to maintain detectable responses [128–134]. However, antibody responses for six out of nine volunteers inoculated with seasonal coronavirus strain 229E were no longer sufficient to prevent reinfection 1 year later [135]. Furthermore, a 35-year-long study found that most seasonal coronavirus reinfections occurred every 3 years, depending on re-exposure and lingering immunity [136]. Adapted seasonal coronavirus modelling estimates that SARS-CoV-2 immunity may last approximately 45 weeks, but an antibody response may not confer complete protection from reinfection [133, 137].

Reinfection has been reported in a number of cases, summarized in Table 4. The majority of the infected individuals had an initial mild or asymptomatic infection, and these may not elicit a sufficiently robust antibody response to be sustained and protective since patients whose nAb responses were measured had low to undetectable responses [138–145]. These

**Table 4: A summary of SARS-CoV-2 reinfection cases confirmed by whole-genome sequencing**

| Location | Patient: age (years) and sex (M/F) | Severity of first infection | Severity of second infection | Days between first and second infection | Reference |
|----------|-----------------------------------|----------------------------|-----------------------------|----------------------------------------|-----------|
| Hong Kong | 34 (M)                             | Mild                       | Asymptomatic                | 142                                    | [138]     |
| USA      | 25 (M)                             | Mild                       | Severe                      | 48                                     | [139]     |
|          | 42 (M)                             | Mild                       | Moderate                    | 51                                     | [140]     |
|          | 60–69*                             | Severe                     | Mild                        | 118                                    | [141]     |
| Ecuador  | 46 (M)                             | Mild                       | Moderate                    | 47                                     | [142]     |
| India    | 25 (M)                             | Asymptomatic               | Asymptomatic                | 100                                    | [143]     |
|          | 28 (F)                             | Asymptomatic               | Asymptomatic                | 101                                    | [144]     |
|          | 27 (M)                             | Mild                       | Moderate                    | 66                                     | [144]     |
|          | 31 (M)                             | Asymptomatic               | Mild                        | 65                                     |           |
|          | 27 (M)                             | Asymptomatic               | Mild                        | 19                                     |           |
|          | 24 (F)                             | Mild                       | Moderate                    | 55                                     |           |

*Patient details only gave age range of 60–69 years.

*Asymptomatic but had a higher viral load upon reinfection.*
reinfection cases highlight that since most cases of COVID-19 will be mild, reinfection is possible especially following a reduction in nAbs and the possibility of spike protein mutations that reduce nAb-binding affinity [65]. Two patients were reinfected with a D614G variant, and one patient was reinfected with an N440K variant, which is a known nAb escape mutation [65, 140, 141, 143]. A recent study has demonstrated that although antibody titres decrease substantially over time, neutralization activity is retained for up to 6 months [146]. Longer studies involving more individuals are required to evaluate when people might become vulnerable to reinfection. This work supports a vaccine-based approach to controlling SARS-CoV-2 transmission but if serology of vaccinated individuals follows a similar pattern to those who have recovered, then regular boosters may be required.

Conclusion
Antibodies are an important aspect of the immune response to COVID-19. While there remains a lot to learn, it is encouraging to see that in a matter of months, many promising antibody-based prophylactics and therapies are making their way into the clinic. Considering the number of reported cases of SARS-CoV-2 reinfection, the uncertainty surrounding long-term immunity will hopefully be more conclusively addressed in the months to come. To date, the current estimate of antibody longevity is 46.9 days for IgA and 51 days for IgM, with no consensus on IgG. Reinfections have occurred between 19 and 142 days, with the majority greater than 50 days, after recovery from the first infection, resulting in both mild and severe illness. These numbers could change greatly in the coming months and may not be representative of the population. It is important to stress that antibodies are not the sole immune defence against COVID-19, and many vaccines aim to elicit general adaptive immune responses. Evaluating the collective immune response to SARS-CoV-2 will advance our understanding of the mechanism of disease and its control.

ACKNOWLEDGEMENTS
We would like to thank Professor Awen Gallimore, Professor Paul Morgan, Dr Wioleta Zelek, Dr Jakub Kopycinski, Dr Gemma Hancock and Professor Quentin Sattentau for their help, suggestions and expertise when writing this manuscript. We would also like to thank the Oxford-Cardiff COVID19 Literature Consortium for initiating these COVID-19 discussions and providing the opportunity to write this review.

AUTHORS’ CONTRIBUTIONS
S.E.A.B. and D.O.S. are responsible for conceptualization. S.E.A.B. and F.C.R. are responsible for supervision. S.E.A.B., D.O.S., S.G.R., V.M.T.B., A.T.C., R.J., E.P. and The Oxford-Cardiff COVID-19 Literature Consortium contributed to writing—original draft. S.E.A.B., D.O.S., S.G.R., M.Q. and J.A. contributed to writing—review and editing.

CONFLICTS OF INTEREST STATEMENT
The authors declare no conflicts of interest

DATA AVAILABILITY STATEMENT
All data are contained within the manuscript. This review was facilitated by frequent releases of the Oxford-Cardiff COVID19 Literature Consortium journal club—a database of reviewed articles and journals will be made available on request.

APPENDIX 1
David J. Ahern1, Hannah Almuttaqi1, Dominic S. Alonzi2, Aljawharah Alrubayyi3, Ghada Alsaei4, Valentina M. T. Bart5, Vicky Batchelor1, Rebecca Bayliss1, Dorothée L. Berthold1, Jelena S. Bezbradic1, Tehmina Bhuruch1, Helene Borrmann7, Mariana Borza6, Rowie Borst8, Juliane Brun9, Stephanie E. A. Burnell9, Lorenzo Capitani4, Athena Cavoudis4, Lucy Chapman1, Anne Chauveau1, Liliana Cifuentes1, Amy Susan Codd4, Ewoud Bernardus Compeer1, Clarissa Coveney1, Amy Cross1, Sara Danieli1, Luke C. Davies2, Calliope A. Dendrou3, Sandra Dimonte4, Ruban Rex Peter Dunrajaj5, Lynn B. Dustin6, Arthur Dyer2, Ceri Fielding1, Fabian Fischer1, Awen Gallimore4, Sarah Galloway4, Anis Gammage1, Ester Gia-Mallorqui1, Andrew Godkin1, Stephanie Jean Hanna4, Cornelia Heuberger2, Sarah Hulin-Curtis4, Fadi Issa9, Emma Jones9, Ruth Jones9, Kristin Ladell4, Sarah N. Lauder9, Kate Liddiard4, Petros Ligoyyakis1, Fangfang Lu12, Bruce MacLachlan4, Shyad Maleki-Toyerkerani4, Elizabeth H. Mann1, Anna M. Marzeda2, Reginald James Matthews13, Julie M. Mazer1, Anita Milicic14, Emma Mitchell4, Owen Moon5, Van Dien Nguyen9, Miriam O’Hanlon1, Clara Éloénon Pavillier15, Dimitra Peppe3, Ana Pires4, Eleanor Pring4, Max Quaste16, Sophie Reid4, Jan Rehwinkel17, Niamh Richardson2, Felix Clemens Richter1, Alice J. Robinson1, Patricia R. S. Rodrigues4, Pragati Sabberwal4, Arvind Sami18, Raphael Sanches Peres1, Quentin Sattentau12, Barbora Schonfeldova1, David Oliver Scourfield4, Tharini A. Selvakumar16, Freya R. Shepherd4, Cariad Shorten15, Anna Katharina Simon1, Adrian L. Smith19, Alicia Teijeira Crespo9, Michael Tellier12, Emily Thornton17, Lion F. K. Uhl11, Enrike van Grinsven5, Angus K. T. Wann1, Richard Williams1, Joseph D. Wilson15, Dingxi Zou1 and Zihan Zhu12

AFFILIATIONS OF CONSORTIUM MEMBERS
1Kennedy Institute of Rheumatology, Nuffield Department of Orthopaedics, Rheumatology and Musculoskeletal Sciences, University of Oxford, Oxford, UK; 2Oxford Glycobiology Institute, Department of Biochemistry, University of Oxford, Oxford, UK; 3Nuffield Department of Clinical Medicine, Nuffield Department of Medicine, University of Oxford, Oxford, UK; 4Division of Infection and Immunity, School of Medicine, Cardiff University, Cardiff, UK; 5Division of Cancer and Genetics, School of Medicine, Cardiff University, Cardiff, UK; 6Translational Gastroenterology Unit, Nuffield Department of Medicine, University of Oxford, Oxford, UK; 7Wellcome Centre for Human Genetics, Nuffield Department of Medicine, University of Oxford, Oxford, UK; 8Sir William Dunn School of Pathology, Medical Science Division, University of Oxford, Oxford, UK; 9Centre for Medical Education, School of Medicine, Cardiff University, Cardiff, UK; 10The Jenner Institute, Nuffield Department of Medicine, University of Oxford, Oxford, UK;
References

1. Hsu DC. Janeway’s immunobiology. Shock 2008;29:770.
2. Yao X-Y, Liu W, Li Z-Y et al. Neutralizing and binding antibody kinetics of COVID-19 patients during hospital and convalescent phases. medRxiv 2020; doi: 10.1101/2020.07.18.20155374.
3. Xiao AT, Gao C, Zhang S. Profile of specific antibodies to SARS-CoV-2: the first report. J Infect 2020;81(1):147–178. doi: 10.1016/j.jinf.2020.03.015.
4. Jacofsky D, Jacofsky EM, Jacofsky M. Understanding antibody binding domain of the viral spike protein is an immunodominant and highly specific target of antibodies in SARS-CoV-2 and its clinical implication. Nat Med 2020;16(2):1598–1607. doi: 10.1038/s41564-020-00813-8.
5. Iyer AS, Jones FK, Nodoushania A et al. Dynamics and significance of the antibody response to SARS-CoV-2 infection. medRxiv 2020; doi: 10.1101/2020.07.18.20155374.
6. Hu Q, Cui X, Liu X et al. The production of antibodies for SARS-CoV-2 and its clinical implication. medRxiv 2020; doi: 10.1101/2020.04.20.20065953.
7. Lou B, Li T-D, Zheng S-F et al. Serology characteristics of SARS-CoV-2 infection after exposure and post-symptom onset. Eur Respir J 2020;56(2):2000763. doi: 10.1183/13993003.00763-2020.
8. Gontu A, Srinivasan S, Salazar E et al. Longitudinal observation and decline of neutralizing antibody responses in the three months following SARS-CoV-2 infection in humans. Nat Microbiol 2020;5(12):1598–1607. doi: 10.1038/s41564-020-00813-8.
9. Jhi A, Graham C, Merrick B et al. Antibody dynamics to SARS-CoV-2 in asymptomatic COVID-19 infections. medRxiv 2020; doi: 10.1101/2020.08.21.20116909.
10. Rijkers G, Mufk J, Wintersb M et al. Differences in antibody kinetics and functionality between severe and mild severe acute respiratory syndrome coronavirus 2 infections. J Infect Dis 2020;222(8):1265–1269. doi: 10.1093/infdis/jiaa463.
11. Phipps WS, SoRelle JA, Li Q-Z et al. SARS-CoV-2 antibody responses do not predict COVID-19 disease severity. Am J Clin Pathol 2020;154(4):459–465. doi: 10.1093/ajcp/aqaa123.
12. Premkumar L, Segovia-Chumbez B, Jadi R et al. The receptor-binding domain of the viral spike protein is an immunodominant and highly specific target of antibodies in SARS-CoV-2 patients. Sci Immunol 2020;5(48):eabc8413. doi: 10.1126/sciimmunol.abc8413.
13. Zhao J, Yuan Q, Wang H et al. Antibody responses to SARS-CoV-2 in patients of novel coronavirus disease 2019. Clin Infect Dis 2020;71(16):2027–2034. doi: 10.1093/cid/ciaa344.
14. Long Q-X, Liu B-Z, Deng H-J et al. Antibody responses to SARS-CoV-2 in patients with COVID-19. Nat Med 2020;26(6):845–848. doi: 10.1038/s41591-020-0897-1.
15. Lynch KL, Whitman JD, Lacanienta NP et al. Magnitude and kinetics of anti-SARS-CoV-2 antibody responses and their relationship to disease severity. Clin Infect Dis 2020: ciaa979. doi: 10.1093/cid/ciaa979.
16. Yu H-q, Sun B-q, Fang Z-f et al. Distinct features of SARS-CoV-2-specific IgA response in COVID-19 patients. Eur Respir J 2020: 56(2); 2001526. doi: 10.1183/13993003.01526-2020.
17. Tan W, Lu Y, Zhang J et al. Viral kinetics and antibody responses in patients with COVID-19. medRxiv 2020; doi: 10.1101/2020.03.24.2004382.
18. Nakano Y, Kurano M, Morita Y, Shimura T, Yokoyama R, Qian C, et al. Time course of the sensitivity and specificity of anti-SARS-CoV-2 IgM and IgG antibodies for symptomatic COVID-19 in Japan. Sci Rep. 2021;11(1):2776. doi: 10.1038/s41598-021-82428-5.
19. Li K, Huang B, Wu M et al. Dynamic changes in anti-SARS-CoV-2 antibodies during SARS-CoV-2 infection and recovery from COVID-19. Nat Commun 2020;11(1):6044. doi: 10.1038/s41467-020-19943-y.
20. Isbo B, Abe KT, Zuo M et al. Persistence of serum and saliva antibody responses to SARS-CoV-2 spike antigens in COVID-19 patients. Sci Immunol 2020;5:eab5511. doi: 10.1126/sciimmunol.eab5511.
21. Cervia C, Nilsson J, Zuruchen Y et al. Systemic and mucosal antibody responses specific to SARS-CoV-2 during mild versus severe COVID-19. J Allergy Clin Immunol 2020; 147(2): 545–557.e9. doi: 10.1016/j.jaci.2020.10.040.
22. Sterlin D, Mathian A, Miyara M et al. IgA dominates the early neutralizing antibody response to SARS-CoV-2. Sci Transl Med 2021; 13(577):eabd2223. doi: 10.1126/scitranslmed.abd2223.
23. Ma H, Zeng W, He H et al. Serum IgA, IgM, and IgG responses in COVID-19. Cell Mol Immunol 2020; 17(7): 773–775. doi: 10.1038/s41423-020-0474-x.
24. Gozalbo-Rovira R, Gimenez E, Latorre V et al. SARS-CoV-2 antibodies, serum inflammatory biomarkers and clinical severity of hospitalized COVID-19 patients. J Clin Virol 2020; 131: 104611. doi: 10.1016/j.jcv.2020.104611.
25. Zhang Z, Xiao T, Wang Y et al. Early viral clearance and antibody kinetics of COVID-19 among asymptomatic carriers. medRxiv 2020; doi: 10.1101/2020.04.28.20083139.
26. Hansen CB, Jarlheit I, Pérez-Alós L et al. SARS-CoV-2 antibody responses are correlated to disease severity in COVID-19 convalescent individuals. J Immunol 2020; 206(1): 109–117. doi: 10.4049/jimmunol.2000898.
27. Lei Q, Li Y, Hou H-y et al. Antibody dynamics to SARS-CoV-2 in asymptomatic COVID-19 infections. Allergy. 2020; doi: 10.1111/all.14622.
28. Fang X, Guo X, Xin Q et al. Neutralizing antibodies responses to SARS-CoV-2 in COVID-19 inpatients and convalescent patients. Clin Infect Dis 2020; doi: 10.1093/cid/ciaa721.
29. Wu F, Wang A, Liu M et al. Neutralizing antibody responses to SARS-CoV-2 in a COVID-19 recovered patient cohort and their implications. medRxiv 2020; doi: 10.1101/2020.03.30.20047365.
30. Hasan Ali Q, Bonze D, Risch L et al. Severe COVID-19 is associated with elevated serum IgA and antiphospholipid IgA-antibodies. Clin Infect Dis 2020; doi: 10.1093/cid/ciaa1496.
31. Weisberg SP, Connors TJ, Zhu Y et al. Distinct antibody responses to SARS-CoV-2 in children and adults across the COVID-19 clinical spectrum. Nat Immunol 2020; 22(1), 25–31 (2021). doi: 10.1038/s41590-020-00826-9.
32. Bunyavanich S, Do A, Vicencio A. Nasal gene expression of angiotensin-converting enzyme 2 in children and adults. JAMA 2020;323(23):2427–2429. doi: 10.1001/jama.2020.8707.
33. Pierce CA, Preston-Hurlbut P, Dai Y et al. Immune responses to SARS-CoV-2 infection in hospitalized pediatric and adult patients. Sci Transl Med 2020;12(564):eabd5487. doi: 10.1126/scitranslmed.abd5487.
34. Scully EP, Haverfield J, Ursin R et al. Considering how biological sex impacts immune responses and COVID-19 outcomes. Nat Rev Immunol 2020;20(7):442–447. doi: 10.1038/s41577-020-0348-8.
35. Zeng F, Dai C, Cai P et al. A comparison study of SARS-CoV-2 IgG antibody between male and female COVID-19 patients: a possible reason underlying different outcome between sex. J Med Virol 2020;92(10):2050–2054. doi: 10.1002/jmv.25989.

36. Salazar E, Christensen PA, Graviss EA et al. Significantly decreased mortality in a large cohort of coronavirus disease 2019 (COVID-19) patients transfused early with convalescent plasma containing high-titer anti-severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) spike protein IgG. Am J Pathol 2020;191(1):2039–2047. doi: 10.1016/j.ajpath.2020.10.008.

37. Zohar T, Loos C, Fischinger S et al. Compromised humoral functional evolution tracks with SARS-CoV-2 mortality. Cell 2020;183(6):1508–1519.e12. doi: 10.1016/j.cell.2020.10.052.

38. Chakraborty S, Gonzalez J, Edwards K et al. Proinflammatory IgG Fc structures in patients with severe COVID-19. Nat Immunol 2020;21(1):67–73. doi: 10.1038/s41590-020-00828-7.

39. Xu R-H, Fang M, Klein-Szanto A et al. Antigen-specific adaptive immunity to SARS-CoV-2 in acute COVID-19 and associations with age and disease severity. Cell 2020;183(4):996–1012.e19. doi: 10.1016/j.cell.2020.09.038.

40. Channappanavar R, Zhao J, Perlman S. T cell-mediated immune response to respiratory coronaviruses. ImmunoL Res 2014;59(1-3):118–128. doi: 10.1007/s12016-014-8534-z.

41. Zost Sj, Gilchuk P, Chen Re et al. Rapid isolation and profiling of a diverse panel of human monoclonal antibodies targeting the SARS-CoV-2 spike protein. Nat Med 2020;26(9):1422–1427. doi: 10.1038/s41591-020-0998-x.

42. Ju B, Zhang Q, Ge J et al. Human neutralizing antibodies elicited by SARS-CoV-2 infection. Nature 2020;584(7819):115–119. doi: 10.1038/s41586-020-2380-z.

43. Wu Y, Wang F, Shen C et al. A noncompeting pair of human neutralizing antibodies block COVID-19 virus binding to its receptor ACE2. Science (N Y) 2020;368(6496):1274–1278. doi: 10.1126/science.abc2241.

44. Cao Y, Su B, Guo X et al. Potent neutralizing antibodies against SARS-CoV-2 identified by high-throughput single-cell sequencing of convalescent patients’ B cells. Cell 2020;182(1):73–84.e16. doi: 10.1016/j.cell.2020.05.025.

45. Shi R, Shan C, Duan X et al. A human neutralizing antibody targets the receptor binding site of SARS-CoV-2. Nature 2020;584(7819):120–124. doi: 10.1038/s41586-020-2381-y.

46. Pinto D, Park Y-J, Beltramello M et al. Cross-neutralization of SARS-CoV-2 by a human monoclonal SARS-CoV antibody. Nature 2020;583(7815):290–295. doi: 10.1038/s41586-020-2394-y.

47. Lv Z, Deng YQ, Ye Q et al. Structural basis for neutralization of SARS-CoV-2 and SARS-CoV by a potent therapeutic antibody. Science (N Y) 2020;369(5510):1505–1509. doi: 10.1126/science.abc5881.

48. Chi X, Yan R, Zhang J et al. A neutralizing human antibody binds to the N-terminal domain of the Spike protein of SARS-CoV-2. Science (N Y) 2020;369(5604):650–655. doi: 10.1126/science.abc6952.

49. Poh CM, Carissimo G, Wang B et al. Two linear epitopes on the SARS-CoV-2 spike protein that elicit neutralizing antibodies in COVID-19 patients. Nat Commun 2020;11(1):2806. doi: 10.1038/s41467-020-16638-2.

50. Al-Tawfiqu JA, Arabi Y. Convalescent plasma therapy for coronavirus infection: experience from MERS and application in COVID-19. Hum Vaccines Immunother 2020;16(12):2973–2979. doi: 10.1080/21645515.2020.1793712.

51. Mair-Jenkins J, Saavedra-Campos M, Baillie JK et al. The effectiveness of convalescent plasma and hyperimmune immunoglobulin for the treatment of severe acute respiratory infections of viral etiology: a systematic review and exploratory meta-analysis. J Infect Dis 2015;211(1):80–90. doi: 10.1093/infdis/jiu396.

52. Liu STH, Lin H-M, Baine I et al. Convalescent plasma treatment of severe COVID-19: a propensity score–matched control study. Nat Med 2020;26(11):1708–1713. doi: 10.1038/s41591-020-1088-9.

53. Li L, Zhang W, Hu Y et al. Effect of convalescent plasma therapy on time to clinical improvement in patients with severe and life-threatening COVID-19: a randomized clinical trial. JAMA 2020;324(5):460–470. doi: 10.1001/jama.2020.10044.

54. Duan K, Liu B, Li C et al. Effectiveness of convalescent plasma therapy in severe COVID-19 patients. Proc Natl Acad Sci USA 2020;117(7):9490–9496. doi: 10.1073/pnas.2004168117.

55. Shen C, Wang Z, Zhao F et al. Treatment of 5 critically ill patients with COVID-19 with convalescent plasma. JAMA 2020;323(16):1582–1589. doi: 10.1001/jama.2020.4783.

56. Donato M, Park S, Baker M et al. Clinical and laboratory evaluation of patients with SARS-CoV-2 pneumonia treated with high-titer convalescent plasma: a prospective study. medRxiv 2020. doi: 10.1101/2020.07.20.20156398.

57. Agarwal A, Mukherjee A, Kumar G Convalescent plasma in the management of moderate covid-19 in adults in India: open label phase II multicentre randomised controlled trial (PLACID Trial). BMJ 2020;371:m3939. doi: 10.1136/bmj.m3939.

58. Simonovich VA, Burgos Pratx LD, Schibona P et al. A randomized trial of convalescent plasma in Covid-19 severe pneumonia. N Engl J Med 2020. doi: 10.1056/NEJMoa2031304.

59. Sarkar S, Soni KD, Khanna P. Convalescent plasma is a clutch at straws in COVID-19 management! A systematic review and meta-analysis. J Med Virol 2021; 93(2):1111–1118. doi: 10.1002/jmv.26408.

60. Joyner MJ, Klassen SA, Senefeld J et al. Evidence favouring the efficacy of convalescent plasma for COVID-19 therapy. medRxiv 2020. doi: 10.1101/2020.07.29.20162917.

61. Cheng Y, Wong R, Soo Yoy et al. Use of convalescent plasma therapy in SARS patients in Hong Kong. Eur J Clin Microbiol Infect Dis 2005;24(1):43–47. doi: 10.1007/s10096-004-1229-1.

62. Clark E, Guilpain P, Filip IL et al. Convalescent plasma for persisting COVID-19 following therapeutic lymphocyte depletion: a report of rapid recovery. Br J Haematol 2020;196(3):e154–e156. doi: 10.1111/bjh.16981.

63. Wright Z, Bersabe A, Eden Ret al. Successful use of COVID-19 convalescent plasma in a patient recently treated for follicular lymphoma. Clin Lymphoma Myeloma Leuk 2021;21(1):66–68. doi: 10.1016/j.clml.2020.06.012.

64. Weisblum Y, Schmidt F, Zhang F et al. Escape from neutralizing antibodies by SARS-CoV-2 spike protein variants. Elife 2020;9:e61312. doi: 10.7554/elife.61312.

65. Baum A, Ajithdoss D, Copin R et al. REGN-COV2 antibodies prevent and treat SARS-CoV-2 infection in rhesus macaques and hamsters. Science (N Y) 2020;370(6520):1110–1115. doi: 10.1126/science.abe2402.

66. Rogers TF, Zhao F, Huang D et al. Isolation of potent SARS-CoV-2 neutralizing antibodies and protection from disease in a small animal model. Science (N Y) 2020;369(6506):956–963. doi: 10.1126/science.abd7520.

67. Jones BE, Brown-Augsburger PL, Corbett KS et al. LY-CoV555, a rapidly isolated potent neutralizing antibody, provides protection in a non-human primate model of SARS-CoV-2 infection. bioRxiv 2020; doi: 10.1101/2020.09.30.318972.
A highly conserved cryptic epitope in the receptor binding domains of SARS-CoV-2 and a clinically proven protease inhibitor. PLOS Pathogens 2020;16(12):e1009089. doi: 10.1371/journal.ppat.1009089.

Custódio TF, Das H, Sheward DJ et al. Selection, biophysical and structural analysis of synthetic nanobodies that effectively neutralize SARS-CoV-2. Nat Commun 2020;11(1):5588. doi: 10.1038/s41467-020-19204-y.

Schoof M, Faust B, Saunders RA et al. An ultrapotent synthetic nanobody neutralizes SARS-CoV-2 by stabilizing inactive Spike. Science (N Y) 2020; 370(6523):1473-1479. doi: 10.1126/science.abd3255.

Walter JD, Hutter CAJ, Zimmermann I et al. Sybodies targeting the SARS-CoV-2 receptor-binding domain. bioRxiv 2020; doi: 10.1101/2020.04.16.045419.

Wrapp D, De Vlieger D, Corbett KS et al. Structural basis for potent neutralization of betacoronaviruses by single-domain camelid Antibodies. Cell 2020;181(5):1004-1015.e15. doi: 10.1016/j.cell.2020.04.031.

Gai J, Ma L, Li G et al. A potent neutralizing nanobody against SARS-CoV-2 with inhaled delivery potential. bioRxiv 2020; doi: 10.1101/2020.08.09.242667.

Hanke L, Vidakovic Perez I, Sheward DJ et al. An alpaca nanobody neutralizes SARS-CoV-2 by blocking receptor interaction. Nat Commun 2020;11(1):4420. doi: 10.1038/s41467-020-18174-5.

Huo J, Le Bas A, Ruza RR et al. Neutralizing nanobodies bind SARS-CoV-2 spike RBD and block interaction with ACE2. Nat Struct Mol Biol 2020;27(9):846-854. doi: 10.1038/s41594-020-0469-6.

Bao L, Deng W, Gao H et al. Lack of reinfection in rhesus macaques infected with SARS-CoV-2. bioRxiv 2020; doi: 10.1101/2020.03.13.990226.

Hamers-Casterman C, Atarhouch T, Muyldermans S et al. Naturally occurring antibodies devoid of light chains. Nature 1993;363(6428):446-448. doi: 10.1038/363446a0.

Kolkmann JA, Law DA. Nanobodies – from llamas to therapeutic proteins. Drug Discov Today Technol 2010;7(2):e139-146. doi: 10.1016/j.ddte.2010.03.002.

McKay PF, Hu K, Blakney AK et al. Self-amplifying RNA SARS-CoV-2 lipid nanoparticle vaccine candidate induces high neutralizing antibody titers in mice. Nat Commun 2020;11(1):3523. doi: 10.1038/s41467-020-17409-9.

Erasmus JH, Khandhar AP, O’Connor MA et al. An Alphavirus-derived replicon RNA vaccine induces SARS-CoV-2 neutralizing antibody and T cell responses in mice and nonhuman primates. Sci Transl Med 2020;12(555):eaab9396. doi: 10.1126/scitranslmed.abc9396.

Smith TRF, Patel A, Ramos S et al. Immunogenicity of a DNA vaccine candidate for COVID-19. Nat Commun 2020;11(1):2601. doi: 10.1038/s41467-020-16505-0.

Rice A, Verma M, Shin A et al. A next generation bivalent human AdS COVID-19 vaccine delivering both spike and nucleocapsid antigens elicits Th1 dominant CD4+, CD8+ T-cell and neutralizing antibody responses. bioRxiv 2020; doi: 10.1101/2020.07.29.227595.

Routhu NK, Gangadhara S, Cheedarla N et al. Modified vaccinia ankara based SARS-CoV-2 vaccine expressing full-length spike induces strong neutralizing antibody response. bioRxiv 2020; doi: 10.1101/2020.06.27.175166.

Chiuppesi F, Salazar MdA, Contreras H et al. Development of a multi-antigenic SARS-CoV-2 vaccine candidate using a synthetic poxvirus platform. Nat Commun 2020;11(1):6121. doi: 10.1038/s41467-020-19819-1.

Mandolesi M, Sheward DJ, Hanke L et al. SARS-CoV-2 protein subunit vaccination elicits potent neutralizing antibody responses. bioRxiv 2020; doi: 10.1101/2020.07.31.228486.
104. Zang J, Gu C, Zhou B et al. Immunization with the receptor-binding domain of SARS-CoV-2 elicits antibodies cross-neutralizing SARS-CoV-2 and SARS-CoV without antibody-dependent enhancement. Cell Discov 2020:6:61. doi: 10.1038/s41421-020-00199-1.

105. Dai L, Zheng T, Xu K et al. A universal design of betacoronavirus vaccines against COVID-19, MERS, and SARS. Cell 2020; 182(3):722-733.e11. doi: 10.1016/j.cell.2020.06.035.

106. Quinlan BD, Mou H, Zhang L et al. The SARS-CoV-2 receptor-binding domain elicits a potent neutralizing response without antibody-dependent enhancement. bioRxiv 2020; doi: 10.1101/2020.04.10.036418.

107. Yu J, Tostanoski LH, Peter L et al. DNA vaccine protection against SARS-CoV-2 in rhesus macaques. Science (N Y) 2020; 369(6505):806–811. doi: 10.1126/science.abc6284.

108. van Doremalen N, Lambe T, Spencer A et al. ChAdOx1 nCoV-19 vaccine prevents SARS-CoV-2 pneumonia in rhesus macaques. Nature 2020; 586(7830):578-582. doi: 10.1038/s41586-020-2608-y.

109. Tian J-H, Patel N, Haupt R et al. SARS-CoV-2 spike glycoprotein vaccine candidate NVX-CoV2373 elicits immunogenicity in baboons and protection in mice. bioRxiv 2020; doi: 10.1101/2020.06.29.178509.

110. Wang H, Zhang Y, Huang B et al. Development of an inactivated vaccine candidate, BBIBP-CoV, with potent Protection against SARS-CoV-2. Cell 2020; 182(3):713–721.e9. doi: 10.1016/j.cell.2020.06.008.

111. Gao Q, Bao L, Mao H et al. Development of an inactivated vaccine candidate for SARS-CoV-2. Science (N Y) 2020; 369(6499):77–81. doi: 10.1126/science.abc1932.

112. Jackson LA, Anderson EJ, Rouphael NG et al. An mRNA vaccine against SARS-CoV-2 - preliminary report. N Engl J Med 2020; 383(20):1920-1931. doi: 10.1056/NEJMoa2022483.

113. Mulligan MJ, Lyke KE, Kitchin N et al. Phase 1/2 study of COVID-19 RNA vaccine BNT162b1 in adults. Nature 2020; 586(7830):589-593. doi: 10.1038/s41586-020-2639-4.

114. Sabin U, Muik A, Derhovanessian E et al. Concurrent human antibody and TH1 type T-cell responses elicited by a COVID-19 RNA vaccine. medRxiv 2020; doi: 10.1101/2020.07.17.20140533.

115. Folgatti PM, Ewer KJ, Aley PK et al. Safety and immunogenicity of the ChAdOx1 nCoV-19 vaccine against SARS-CoV-2: a preliminary report of a phase 1/2, single-blind, randomised controlled trial. Lancet 2020; 396(10249):467–478. doi: 10.1016/S0140-6736(20)31604-4.

116. Zhu F-C, Guan X-H, Li Y-H et al. Immunogenicity and safety of a recombinant adenoivirus type-5-vected COVID-19 vaccine in healthy adults aged 18 years or older: a randomised, double-blind, placebo-controlled, phase 2 trial. Lancet 2020; 396(10249):479–488. doi: 10.1016/S0140-6736(20)31208-3.

117. Zhu F-C, Li Y-H, Guan X-H et al. Safety, tolerability, and immunogenicity of a recombinant adenoivirus type-5 vectored COVID-19 vaccine: a dose-escalation, open-label, non-randomised, first-in-human trial. Lancet 2020; 395(10240):1845–1854. doi: 10.1016/S0140-6736(20)31208-3.

118. Ravichandran S, Coyle EM, Klenow L et al. Antibody signature induced by SARS-CoV-2 spike protein immunogens in rabbits. Sci Transl Med 2020; 12(550):eaab3539. doi: 10.1126/scitranslmed.abc3539.

119. Bertoglio F, Meier D, Langreder N et al. SARS-CoV-2 neutralizing human recombinant antibodies selected from pre-pandemic healthy donors binding at RBD-ACE2 interface. bioRxiv 2020; doi: 10.1101/2020.06.05.135921.

120. Smith CC, Entwistle S, Willius C et al. Landscape and selection of vaccine epitopes in SARS-CoV-2. bioRxiv 2020; doi: 10.1101/2020.06.04.135004.
postpandemic period. Science (N Y) 2020;368(6493):860–868. doi: 10.1126/science.abb5793.
138. To KK, Hung IF, Ip JD et al. COVID-19 re-infection by a phylogenetically distinct SARS-coronavirus-2 strain confirmed by whole genome sequencing. Clin Infect Dis 2020; doi: 10.1093/cid/ciaa1275.
139. Tillett RL, Sevinsky JR, Hartley FD et al. Genomic evidence for reinfection with SARS-CoV-2: a case study. Lancet Infect Dis. 2020; 21(1):52-58. doi: 10.1016/S1473-3099(20)30764-7.
140. Larson D, Brodniak SL, Voegtly LJ et al. A case of early re-infection with SARS-CoV-2. Clin Infect Dis 2020; doi: 10.1093/cid/ciaa1436.
141. Goldman JD, Wang K, Rolfgen K et al. Reinfection with SARS-CoV-2 and failure of humoral immunity: a case report. medRxiv 2020; doi: 10.1101/2020.09.22.20192443.
142. Prado-Vivar B, Becerra-Wong M, Guadalupe JJ et al. COVID-19 re-infection by a phylogenetically distinct SARS-CoV-2 variant, first confirmed event in South America. First Confirmed Event in South America, 3 September 2020, Preprint SSRN 2020; doi: 10.2139/ssrn.3686174.
143. Gupta V, Bhoyar RC, Jain A et al. Asymptomatic reinfection in two healthcare workers from India with genetically distinct SARS-CoV-2. Clin Infect Dis 2020; doi: 10.1093/cid/ciaa1451.
144. Shastri J, Parikh S, Agarwal S et al. Whole genome sequencing confirmed SARS-CoV-2 reinfections among healthcare workers in India with increased severity in the second episode. Preprint SSRN 2020; doi: 10.2139/ssrn.3688220.
145. To KK-W, Hung IF-N, Chan K-H et al. Serum antibody profile of a patient with COVID-19 reinfection. Clin Infect Dis 2020; doi: 10.1093/cid/ciaa1368.
146. Figueiredo-Campos P, Blankenhans B, Mota C et al. Seroprevalence of anti-SARS-CoV-2 antibodies in COVID-19 patients and healthy volunteers up to 6 months post disease onset. Eur J Immunol 2020;50(12):2025–2040. doi: 10.1002/eji.202048970.