

Immunological mechanisms of vaccine-induced protection against COVID-19 in humans

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Abstract | Most COVID-19 vaccines are designed to elicit immune responses, ideally neutralizing antibodies (NAbs), against the SARS-CoV-2 spike protein. Several vaccines, including mRNA, adenoviral-vectored, protein subunit and whole-cell inactivated virus vaccines, have now reported efficacy in phase III trials and have received emergency approval in many countries. The two mRNA vaccines approved to date show efficacy even after only one dose, when non-NAbs and moderate T helper 1 cell responses are detectable, but almost no NAbs. After a single dose, the adenovirus vaccines elicit polyfunctional antibodies that are capable of mediating virus neutralization and of driving other antibody-dependent effector functions, as well as potent T cell responses. These data suggest that protection may require low levels of NAbs and might involve other immune effector mechanisms including non-NAbs, T cells and innate immune mechanisms. Identifying the mechanisms of protection as well as correlates of protection is crucially important to inform further vaccine development and guide the use of licensed COVID-19 vaccines worldwide.

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), the causative agent of coronavirus disease 2019 (COVID-19), caused more than 3 million deaths worldwide in the 16 months since it was identified in December 2019 (REFS^{1–3}). It was evident early on that the pandemic could only be controlled with effective vaccines. This resulted in rapid vaccine development, with limited insight into what would constitute protective immunity. Currently licensed vaccines for COVID-19 are based on experience with SARS-CoV and Middle East respiratory syndrome coronavirus (MERS-CoV); but although multiple SARS-CoV and MERS-CoV vaccine candidates were developed, none had advanced beyond phase I clinical trials⁴. There are currently >270 candidate COVID-19 vaccines in development, including >90 in clinical trials^{5–7}. These include nucleic acid vaccines (RNA and DNA)^{8–11}, human and simian replication-deficient and replication-competent adenoviral-vectored vaccines^{12,13}, whole-cell inactivated virus^{14,15},

subunit protein vaccines¹⁶ and virus-like particles⁶. As of April 2021, 28 of these vaccines have entered phase III clinical trials, and 5 (TABLE 1) have reported efficacy in the peer-reviewed literature and/or through detailed publicly available reports submitted to regulatory authorities, resulting in emergency authorizations for their use in a large number of countries. These include the mRNA vaccines BNT162b2 (Pfizer/BioNTech) and mRNA-1273 (Moderna), and the three adenoviral-vectored vaccines ChAdOx1 nCoV-19 (University of Oxford/AstraZeneca), Gam-COVID-Vac (Gamaleya Research Institute) and Ad26.COV2.S (Janssen). One protein subunit vaccine (NVX-CoV2372; Novavax) and one whole-cell inactivated viral vaccine (BBV152; Bharat Biotech) have reported positive efficacy results via official company press releases (TABLE 1), and BBV152 has received emergency authorization in several countries. A further four vaccines have suggested positive efficacy via media reports — the adenoviral-vectored vaccine Ad5-nCoV (CanSino Biologics)

and the whole-cell inactivated vaccines CoronaVac (Sinovac Biotech), BBIBP-CorV (Sinopharm) and WIBP-CorV (Sinopharm) (TABLE 1) — and these plus another three with no publicly available efficacy data — EpiVacCorona peptide vaccine (VECTOR Center of Virology, Russia), CoviVac inactivated vaccine (Chumakov Centre, Russia) and ZF2001 recombinant vaccine (Anhui Zhifei Longcom/Chinese Academy of Sciences) — have received emergency authorizations in some countries¹⁷. This represents a remarkable feat for biomedical science, but there are many outstanding issues. For example, most approved vaccines are believed to require two doses for optimal protection, as do the majority of the other vaccines that are still in clinical development, which translates into logistical challenges and a slower roll-out. In addition, logistical hurdles posed by the requirement for cold chains, and in particular the ultra-cold chains required for mRNA-based vaccines, impede the roll-out of the currently licensed vaccines in low and middle-income countries. Furthermore, the ongoing evolution of this virus generates mutations that can reduce vaccine-induced immunity¹⁸. Although there is no evidence to date of an ongoing ‘antigenic drift’, such as that observed with influenza virus, mutations affecting transmission and disease severity can occur¹⁹, and vaccine-induced immune selection pressure at a population level may accelerate the development of escape mutants as has been suggested for other pathogens^{20,21}. Vaccines for COVID-19 must therefore continue to be optimized as a matter of urgency.

Here, we provide a brief overview of the immune response to SARS-CoV-2, followed by a discussion of the mechanisms of immune protection of the five vaccines for which detailed results from phase III trials are publicly available. We then discuss how insights into vaccine-induced immune protection and the identification of correlates of protection may be used to guide vaccine development and speed up the licensing of the next generation of vaccines.

Immune responses to SARS-CoV-2

Recovery following infection with SARS-CoV-2 in humans appears to involve both humoral and cell-mediated immunity^{22–24}. In patients hospitalized

Table 1 | Human studies of COVID-19 vaccines with reported efficacy

Vaccine (developer) (dosing regimen)	Formulation	Efficacy against symptomatic infection (phase III trials)	Effectiveness (post implementation)	Antibody responses in humans	T cell responses in humans
mRNA					
BNT162b2 mRNA (BioNTech/Pfizer) (30 µg mRNA, 2 doses, 21 days apart) ⁸¹	mRNA-lipid nanoparticle encoding full-length S protein, modified by two proline mutations to lock protein in the pre-fusion conformation ^{110–112}	95% after 2 doses; 52% after 1 dose ⁸¹ , although review of the data suggests efficacy of 93% 14 days after 1 dose ¹¹³ , 91% at 6 months post second dose ¹¹⁴	Symptomatic infection: 94–96% (2 doses) and 46–80% (1 dose) Any infection: 86–92% (2 doses) and 46–72% (1 dose) Hospitalization: 87% (2 doses) and 71–85% (1 dose) Asymptomatic infection: 79% (1 dose) and 90% (2 doses) ^{93–95,115–123}	S1-binding antibody present after first dose, responses increased following the second dose ¹²⁴ ; significant NAb was only present after second dose ¹²⁴	Increases in antigen-specific IFN γ ⁺ CD4 ⁺ and CD8 ⁺ T cells after second dose ¹²⁵ ; predominance of IFN γ and IL-2 secretion, compared with IL-4, suggesting T _H 1 cell polarization
mRNA-1273 (Moderna) (100 µg mRNA, 2 doses, 28 days apart)	mRNA-lipid nanoparticle encoding full-length S protein, modified by two proline mutations to lock protein in the pre-fusion conformation ¹²⁶	95% after 2 doses; 92% after 1 dose ⁸²	Symptomatic infection: 90% (2 doses) and 80% (1 dose) ¹²³	S-binding antibody detected 14 days after first dose, levels increased slightly by 28 days, with marked increase after second dose ¹²⁶ ; minimal NAb present after first dose, peak at 14 days after second dose ¹²⁷	Significant increases in CD4 ⁺ T cells secreting T _H 1 type cytokines (TNF > IL-2 > IFN γ) after second dose, small increases in TNF-secreting and IL-2-secreting cells after first dose ¹²⁶ ; minimal change in T _H 2 cell responses; low levels of CD8 ⁺ responses ¹²⁶
Viral vector					
ChAdOx1 nCoV-19 (University of Oxford/Astra-Zeneca) (2.5–5 × 10 ¹⁰ viral particles, 2 doses, ≥28 days apart) ⁸⁷	Recombinant, replication-deficient simian adenovirus vector expressing the full-length S protein with a tPA leader sequence ¹²⁸	62–67% after 2 doses ⁸⁷ , 76% after 1 dose ⁸⁸ ; 90% in participants who received a low dose followed by a high dose; interval between doses varied with a median of 36–69 days; 81% with ≥12-week interval, 55% with <6-week interval ⁸⁸	Hospitalization: 80–94% after 1 dose ^{95,115}	S-binding antibody present 14 days after first dose, levels increased by 28 days ¹²⁸ ; marked increase after second dose, peak at 14 days after second dose; predominantly IgG3 and IgG1 (REF. ¹²⁹); significant NAb detected after first dose, increased by 14 days after second dose; IgG avidity increased 28–56 days after single dose ¹²⁹ ; peak IgM and IgA responses at day 14 or 28	Peak T cell responses 14 days after first dose, but slightly higher responses measured 28 days after second dose ¹²⁸ ; increase in TNF and IFN γ production by CD4 ⁺ T cells at day 14
Gam-COVID-Vac (Gamaleya Research Institute) (10 ¹¹ viral particles, 2 doses, 21 days apart) ⁹⁰	Recombinant, replication-deficient human adenovirus 26 (dose 1) and human adenovirus 5 (dose 2) expressing full-length S protein ¹³⁰	91% after 2 doses; 74% after 1 dose (moderate to severe infection) ⁹⁰	–	S-binding antibody detected in 85–89% and NAb in 61% of individuals 14 days after first dose ¹³⁰ ; S antibody levels (binding and neutralizing) boosted by second dose, with binding antibody in 98% and neutralizing antibody in 95% of individuals 14 days after second dose ⁹⁰	CD4 ⁺ and CD8 ⁺ T cell responses observed by 14 days after first dose (based on proliferation assays and antigen-specific IFN γ secretion) ¹³⁰ ; all individuals had S-specific IFN γ responses 7 days after second dose based on in vitro stimulation of PBMCs
Ad26.COV2.S (Janssen) (5 × 10 ¹⁰ viral particles, 1 dose) ^{89,131}	Recombinant, replication-deficient human adenovirus 26 expressing full-length S protein with two amino acid changes in S1/S2 junction that delete furin cleavage site and two proline substitutions in hinge region that lock protein in the pre-fusion conformation ¹³²	67% after 1 dose ⁸⁹	–	S-binding and neutralizing antibody present by 28 days after vaccination in 99% of individuals and antibody levels sustained until at least 84 days post vaccination ^{89,131}	CD4 ⁺ and CD8 ⁺ T cell responses present at 14 and 28 days post vaccination, based on presence of CD4 ⁺ and CD8 ⁺ T cells secreting IFN γ and/or IL-2 and not IL-4 or IL-3, suggesting T _H 1 cell polarization of the CD4 ⁺ T cell response ^{89,131}

Table 1 (cont.) | Human studies of COVID-19 vaccines with reported efficacy

Vaccine (developer) (dosing regimen)	Formulation	Efficacy against symptomatic infection (phase III trials)	Effectiveness (post implementation)	Antibody responses in humans	T cell responses in humans
Viral vector (cont.)					
Ad5-nCoV (CanSino Biologics) (5 × 10 ¹⁰ viral particles, 1 dose) ⁹¹	Recombinant, replication-deficient human adenovirus 5 expressing full-length S protein with a tPA leader sequence ¹²	66% after 1 dose, decreasing to 50% by 5–6 months post immunization ^{133,134}	–	14 days after vaccination, 44% of individuals had RBD-binding antibodies; 28 days after vaccination, 97% had anti-RBD binding antibodies and 47–50% had NABs; individuals with pre-existing anti-Ad5 antibody titre >1:200 had reduced levels of both binding antibodies and NABs ^{12,91}	28 days after vaccination, 78–88% of participants had T cell responses, based on IFN γ ELISpot, although peak T cell responses were observed at day 14 after vaccination ^{12,91}
Protein subunit					
NVX-CoV2373 (Novavax) (5 μ g protein, 2 doses, 21 days apart) ¹³⁵	Recombinant nanoparticle of full-length S protein with mutations at the S1/S2 cleavage sites to confer protease resistance and two proline substitutions to stabilize protein in a pre-fusion conformation, with saponin-based adjuvant (Matrix-M1) ¹³⁶	90% by 7 days after second dose ¹³⁷	–	S-binding antibody detected 21 days after first dose, with a marked increase after the second dose; some NAB present after the first dose, with a significant increase by 7 days after second dose ¹³⁶	CD4 ⁺ T cell responses present by 7 days after second dose, based on IFN γ , IL-2 and TNF production in response to S protein stimulation, with a strong bias towards a T _H 1 cell phenotype; minimal T _H 2 cell responses (as measured by IL-5 and IL-13) ¹³⁶
Whole-cell inactivated virus					
CoronaVac (Sinovac Biotech) (3 μ g protein, 2 doses, 14–28 days apart) ^{138,139}	SARS-CoV-2 grown in Vero cells, inactivated with β -propiolactone and adsorbed onto aluminium hydroxide ¹³⁸	50–84% after 2 doses ^{140,141}	–	By day 28 day after second dose, RBD-specific binding antibody detected in 88–97% of participants with a 14-day dosing interval and 99–100% with a 28-day interval; NAb present in 94–100% of individuals 28 days after second dose ^{138,139}	–
BBIBP-CorV (Sinopharm) (4 μ g protein, 2 doses, 21 days apart) ¹⁴²	SARS-CoV-2 grown in Vero cells, inactivated with β -propiolactone and adsorbed onto aluminium hydroxide ¹⁴²	86% after 2 doses ¹⁴³	–	By day 14 after second dose, 46–87% of individuals had binding antibodies; this increased to 92–100% by day 28; all recipients had NABs by 21 days after second dose ¹⁴²	–
WIBP-CorV (Sinopharm) (5 μ g protein, 2 doses, 21 days apart) ¹⁴⁴	SARS-CoV-2 grown in Vero cells, inactivated with β -propiolactone and adsorbed onto aluminium hydroxide ¹⁴⁴	73% after 2 doses ¹⁴⁵	–	By day 14 after second dose, 100% of participants had binding antibodies against whole inactivated SARS-CoV-2 and 98% had neutralizing antibodies ¹⁴⁴	–
BBV152 (Bharat Biotech) (6 μ g protein, 2 doses, 28 days apart) ¹⁴⁶	SARS-CoV-2 grown in Vero cells, inactivated with β -propiolactone and adsorbed onto aluminium hydroxide and an imidazoquinoline molecule (TLR7/TLR8 agonist) ¹⁴⁶	78% after 2 doses ¹⁴⁷	–	After first dose, 65% of participants had anti-S binding antibodies, increasing to 98% by day 14 after second dose; 48% had NABs after first dose, increasing to 97% by day 14 after second dose; GMTs for binding and NABs markedly increased by second dose ^{100,146}	Strong bias towards a T _H 1 cell phenotype (IFN γ and TNF), with minimal T _H 2 cell responses (as measured by IL-5 and IL-13) after in vitro stimulation. Increase in CD4 ⁺ CD45RO ⁺ memory T cells by day 76 after second dose ^{100,146}

ELISpot, enzyme-linked immunosorbent spot; GMT, geometric mean titre; IFN γ , interferon- γ ; IL-2, interleukin-2; NAb, neutralizing antibody; PBMC, peripheral blood mononuclear cell; RBD, receptor-binding domain; S, spike; T_H1 cell, T helper 1 cell; TLR, Toll-like receptor; TNF, tumour necrosis factor; tPA, tissue plasminogen activator.

Box 1 | The SARS-CoV-2 spike protein as vaccine target

Most candidate COVID-19 vaccines are designed to elicit immune responses, ideally mediated by neutralizing antibodies (NAb)s, against the trimeric SARS-CoV-2 spike (S) protein. The S protein is a class I fusion protein that facilitates binding of the virus to the angiotensin-converting enzyme 2 (ACE2) receptor on the host cell surface, which triggers fusion between the virus and cell membrane^{110,148,149}. Prior to contact with the host cell, the S protein is in a metastable pre-fusion conformation and the trimer undergoes substantial rearrangement at the time of virus–cell fusion^{150,151}. Some COVID-19 vaccines include mutations that stabilize the S protein in this pre-fusion form, on the basis that this is the expected conformation prior to epithelial cell attachment, and thus immune responses directed against the pre-fusion S protein are more likely to be protective and reduce transmission. However, vaccines without this stabilization (for example, ChAdOx1 nCoV-19) have proven efficacy and so the importance of this for COVID-19 vaccines is uncertain. The S protein consists of an amino-terminal S1 subunit and a carboxy-terminal S2 subunit. Within the S1 subunit lies the receptor-binding domain (RBD), which binds the ACE2 receptor, and this domain can undergo conformational rearrangement that transiently hides or exposes the determinants of receptor binding. Eliciting an immune response that targets the RBD has been a major focus of vaccine development on the assumption that antibodies that bind this critical domain can prevent viral entry into host cells, thereby allowing for sterilizing immunity (that is, the complete prevention of infection)^{152–154}, which would support herd immunity if vaccine coverage is sufficiently high¹⁵⁵. Other S protein epitopes can also be valuable vaccine targets. A polyclonal antibody against multiple epitopes of the S protein beyond the RBD might, for example, inhibit viral attachment^{156–160}, provide additional neutralizing activity¹⁶¹ and/or prevent post-attachment fusion¹⁶². A vaccine targeting multiple epitopes would also mitigate the possibility of immune escape by mutation¹⁵⁶. There is currently no defined correlate of protection against COVID-19 or SARS-CoV-2 infection, and as such the immunological thresholds required for vaccine efficacy have not yet been defined¹⁶³.

with COVID-19, the early presence of broadly functional antibodies directed at the SARS-CoV-2 spike (S) protein (see also BOX 1) correlated with survival²⁵, and S-protein-targeted neutralizing antibodies (NAb)s are present in the majority of individuals following infection. The magnitude of these NAb responses appear to correlate with viral load, with higher responses reported in patients with more severe disease, and in older adults compared with younger adults^{26–29}. In early studies of SARS-CoV-2 vaccine candidates in a rhesus macaque model, the amount of NAb)s directed at the S protein, which mediates cellular binding, emerged as the strongest correlate of protection^{10,30}. This led to a general acceptance that it was imperative for vaccines to elicit NAb responses. Non-NAb)s can also have an important role in protection, however, via Fc-mediated effector functions including antibody-dependent phagocytosis, antibody-dependent cellular cytotoxicity and antibody-dependent natural killer cell activation^{10,25,31}. On the other hand, antibodies promoting inflammatory responses may contribute to a cytokine storm resulting in severe disease^{32,33}. The complexity of antibody-dependent effector functions and their relationships with the structure of the Fc component of IgG, including subclass and glycosylation, can be assessed by system serology approaches, allowing multivariate analyses of correlates of immunity and disease³⁴.

Although mucosal immunity is likely key to the prevention of SARS-CoV-2 infection, relatively little is known regarding mucosal antibody responses in COVID-19. Historical studies of controlled human infection with endemic coronaviruses indicated that levels of nasal IgA correlate with protection against these infections^{35,36}. SARS-CoV-2-specific IgA is detected in nasal washes and in saliva of patients who are in convalescence and could contribute to a reduced interpersonal spread through neutralization and Fc-dependent effector functions³⁷.

SARS-CoV-2 is able to spread from cell to cell without exposure to the extracellular environment³⁸, and it is therefore possible that antibodies that only target intact extracellular viral particles have a limited role in reducing viral spread within the host. As expected for a viral infection, T cells are also important mediators in the host response to SARS-CoV-2 infection, by killing infected cells, supporting B cell function and antibody responses, and, possibly, reducing the risk of vaccine-induced enhanced disease^{39,40} (see BOX 2). Both reduced and increased CD8⁺ and CD4⁺ T cell responses have been observed following infection⁴¹. Milder disease and recovery have been associated with a more robust clonal expansion of CD8⁺ T cells in both the lungs and blood^{42,43}, although whether this is the cause of milder disease or an effect of recovery is unclear. Virus-specific CD8⁺ and CD4⁺ T cells, including CD8⁺ memory T cells, are

present in patients who have recovered from COVID-19 (REFS^{44,45}), but their importance in protection against future infection and/or severe disease remain uncertain^{44,46–48}.

Interferon- γ (IFN γ)-producing T helper 1 cells (T_H1 cells) are produced during acute infection, and it has been suggested that this T_H1 cell-biased phenotype is associated with less severe disease^{24,49} — an important consideration given that current COVID-19 vaccines have been designed to induce responses skewed towards the T_H1 cell phenotype (TABLE 1). There are indications that individuals with higher levels of IFN γ -secreting T cells (measured by enzyme-linked immunosorbent spot) against the S protein, nuclear proteins and membrane proteins of SARS-CoV-2 may have better protection from disease⁵⁰. Moreover, individuals with mild disease favour more efficient T follicular helper cell responses in the germinal centre, which supports an increase in plasmablast numbers and enhances antibody production⁵¹.

Studies showed that adoptive transfer of antigen-specific T cells protected immunodeficient mice from infection after challenge with the SARS-CoV-2-related coronaviruses SARS-CoV and MERS-CoV⁵². The passive transfer of NAb)s was also found to be protective in non-human primate models, whereas removal of CD8⁺ T cells in the same models impaired protection, suggesting a role for both components⁵³. Evidence from human and animal studies has suggested that in addition — or, possibly, instead of high titres of NAb)s — a robust cytotoxic CD8⁺ T cell response and a T_H1 cell-biased CD4⁺ T cell effector response would result in protective immunity against COVID-19 (REF⁵⁴).

Like other pathogenic respiratory RNA viruses (including other coronaviruses, respiratory syncytial virus and enteroviruses)⁵⁵, SARS-CoV-2 can evade innate immune responses via multiple mechanisms^{55,56}, indicating that innate immunity is likely crucial for host protection^{54,57}. A predominant strategy appears to be the inhibition of the type I interferon response^{58–60} at multiple points, including impaired recognition of viral RNA^{61,62}, decreased nuclear translocation of pro-inflammatory transcription factors (such as IRF3, IRF7 and STAT1)^{61,63} and suppression of STAT1 and STAT2 phosphorylation^{64,65}. Furthermore, humans deficient in producing or responding to type I interferon have an increased risk of severe COVID-19 (REFS^{66–68}). Although it is likely that there are many innate immune

components that are relevant to protection from COVID-19, type I and type III interferons appear centrally important^{69,70}. The timing of induction of type I interferon (or type III interferon in mucosal tissue) is crucial as the presence of type I interferon early in infection appears to be protective, whereas its relevance for viral control at later time points may be reduced or may even contribute to immunopathology^{57,71,72}.

Insights into vaccine-induced immunity

In order to understand how vaccine-induced immune responses relate to protection against disease for COVID-19, it is important to consider the available immunologic data within the context of vaccine efficacy from similar populations (Supplementary Figure 1) — this Progress article therefore focuses on the five vaccines for which both detailed efficacy and immunological data are available.

For completeness, data from other vaccines with reported efficacy are included in the tables and figures. Few immunological data have so far been published from the phase III trials in which vaccine efficacy was determined, and the assessment of human immunologic responses to vaccination are therefore largely reliant on analyses from the earlier phase I/II clinical trials. Some of these studies used multiple different formulations and/or different antigens to the final formulations included in phase III trials, so the descriptions below are focused on the formulations that were used in subsequent clinical trials and for which efficacy has been established (TABLE 1). Although numerous studies have reported vaccine effectiveness and immunologic evaluations from initial mass vaccination campaigns, prioritization of older individuals and groups with high-risk medical conditions means that most of these data do not improve our ability to link the immunological data with clinical outcomes. Although antigen-specific antibodies (including NABs) and T cell responses have been determined for all of the vaccines discussed here (TABLE 1), the specific assays have varied and, thus, are not directly comparable. However, most of the studies used previously established assays to analyse samples from patients who are in convalescence after SARS-CoV-2 infection. Although the source of the convalescent samples differed between studies (for example, asymptomatic versus mild versus severe disease), these data provide the basis on which comparisons between studies can be made (FIG. 1; see Supplementary Table 1).

mRNA vaccines. Both BNT162b2 and mRNA-1273 have demonstrated very high efficacy in clinical trials, including >90% protection from symptomatic disease after only a single dose, when levels of NABs are <5% of the post-second dose peak (TABLE 1; see Supplementary Figure 1). mRNA-1273 was shown to elicit T_H1 cell responses after the first dose, with 0.05% of circulating CD4⁺ T cells secreting tumour necrosis factor (TNF) and/or interleukin-2 (IL-2) following *in vitro* stimulation with S protein peptides⁷³ (TABLE 1; see Supplementary Table 1); and both vaccines, after just a single dose, induced levels of anti-S and/or anti-receptor-binding domain (anti-RBD) binding antibodies that were equivalent to or higher than those observed in patients who are in convalescence (FIG. 1; see Supplementary Table 1). By contrast, relatively low levels of CD8⁺ T cell responses are elicited after one or two doses (TABLE 1; see Supplementary Table 1). These data would suggest that protection after one dose of these vaccines either requires extremely low levels of NABs, is the result of non-NABs leading to other effector mechanisms and/or is mediated by a relatively low frequency of antigen-specific T cells. Alternatively, it is possible that there are non-adaptive (that is, innate) immune mechanisms that are responsible for this early protection after vaccination, for example via type I or type III interferons^{57,71,72}, with the possibility of a ‘trained immunity’-type effect that has been described for the Bacillus Calmette–Guérin (BCG) vaccine in the COVID-19 context⁷⁴. Both BNT162b2 and mRNA-1273, as well as the adenoviral-vectored vaccine

ChAdOx1 nCoV-19, have been shown to induce type I interferon, thus potentially inducing pathogen-agnostic protection^{75–77}. Unfortunately, given the urgency of the situation, the trials of the currently licensed COVID-19 vaccines did not include a vector control (such as scrambled mRNA or simian adenovirus without the S protein), and therefore the role of pathogen-agnostic immunity in humans cannot be assessed with the currently available data; however, antigen non-specific stimulation of type I interferon pathways has been demonstrated with other formulations of mRNA in animal models^{78,79}. If such a mechanism was occurring, there would be a possibility of protection against pathogens other than SARS-CoV-2, and it is vital that any data collected on other infections in the trials are analysed to evaluate this possibility. It must also be considered that mechanisms of protection may differ after two doses versus one dose, where NABs may mediate the predominant protective mechanism following subsequent doses of vaccine. Data from medium-term follow-up of individuals after infection suggest that T cell responses wane more rapidly than antibody responses⁸⁰. Therefore, if there are different mechanisms of protection involved after one versus two doses, a complete understanding of this will enable decisions on intervals between doses to be made on a scientific basis — current guidelines already vary between countries, with intervals of 21–28 days used in the vaccine trials^{81,82}, a recommendation of 6 weeks from the WHO (World Health Organization)⁸³ and up to 12 or 16 weeks in the UK and

Box 2 | Antibody-dependent enhancement and vaccine-induced enhanced disease

One of the concerns that was raised early in the pandemic was that any vaccines used in humans could lead to enhanced disease in individuals who were infected following vaccination¹⁶⁴. Postulated mechanisms for this were antibody-dependent enhancement (ADE), where SARS-CoV-2 is enabled to enter cells not expressing the angiotensin-converting enzyme 2 (ACE2) receptor via Fc-mediated attachment in the presence of binding, non-neutralizing antibody (non-NAB); or vaccine-associated enhanced respiratory disease (VAERD) via immune complex deposition or ‘aberrant’ T cell responses in the lungs of individuals who are vaccinated¹⁶⁴. In animal models of infections with other coronaviruses and for previous whole-cell inactivated vaccines developed for respiratory syncytial virus and measles virus, VAERD has usually been associated with the development of T helper 2 cell (T_H2 cell)-biased CD4⁺ T cell responses, with significantly increased levels of interleukin-4 (IL-4), IL-5 and/or IL-13 (REFS^{12,126,165–174}). By contrast, VAERD has not usually occurred if a T_H1 cell-biased CD4⁺ T cell response is elicited, reflected by increased levels of interferon- γ (IFN γ), IL-2 and tumour necrosis factor (TNF)^{44–46,49}. COVID-19 vaccines developed to date have therefore attempted to elicit either a T_H1 cell-biased response or a balanced T_H1 cell/T_H2 cell response. Current evidence indicates that SARS-CoV-2 does not productively infect macrophages, making enhancement of infection unlikely, and ADE and VAERD have so far not been demonstrated for SARS-CoV-2 (REFS^{175,176}). However, the potential role of IgG with reduced Fc fucosylation and enhanced binding to Fc γ RIII in the development of severe COVID-19 suggests that the quality of antibodies induced by vaccination may also be important in minimizing the risk of ADE^{32,33}. There is also a possibility that the risk of ADE may be higher in the presence of low to moderate amounts of antibody, which will occur as antibody levels wane post immunization¹⁷⁷, although recurrent SARS-CoV-2 infections have not been consistently associated with severe disease.

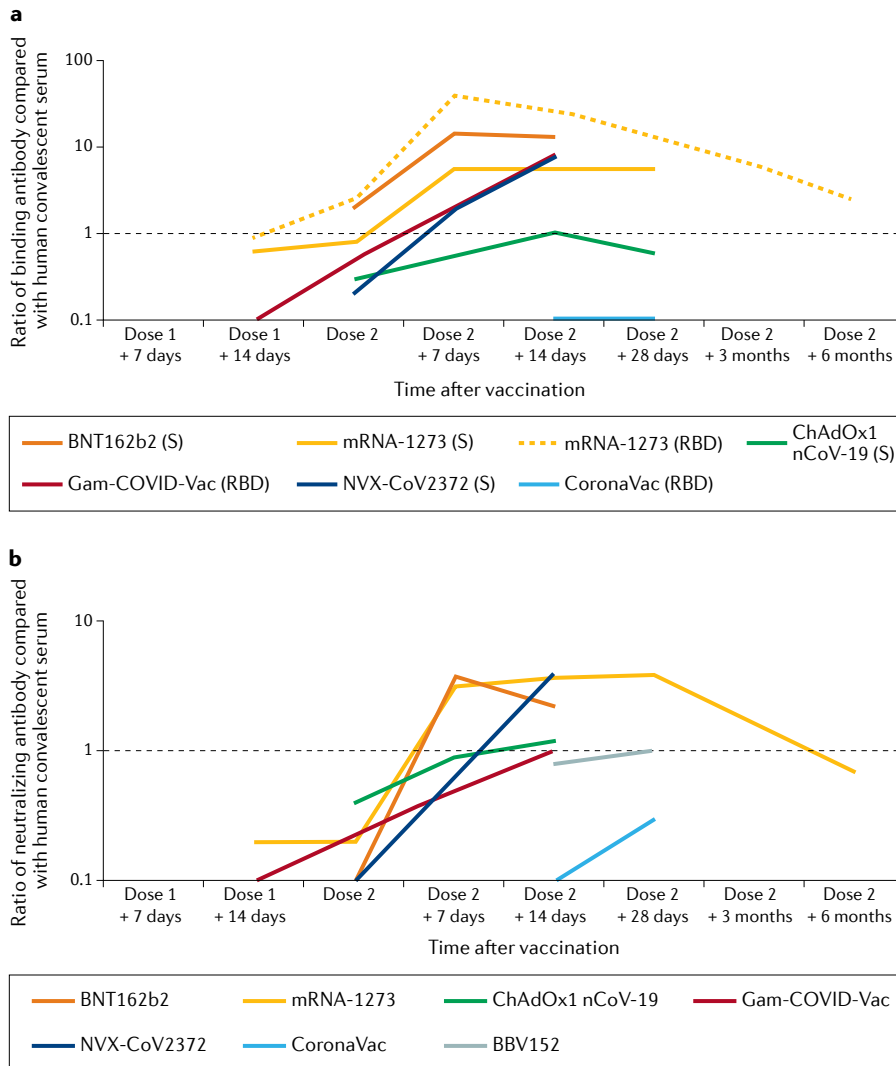


Fig. 1 | Comparison of antibody responses induced by different COVID-19 vaccines. a | Vaccine immunogenicity based on antibody against the spike (S) protein of SARS-CoV-2 and/or against the receptor-binding domain (RBD) of the S protein relative to levels seen in convalescent serum. **b** | Vaccine immunogenicity based on neutralizing antibodies (NAbs) against SARS-CoV-2, again relative to levels seen in convalescent plasma. Relative antibody levels induced are indicated for seven COVID-19 vaccines where these data are available. To enable direct comparison, only vaccines tested in two-dose schedules are included. For antibody data, all comparisons are based on relative amount of antibody compared with human convalescent serum used in the same study (see data in Supplementary Table 1). Although the source of these samples differed between studies, these data enable reasonable direct comparisons between different vaccines, accounting for different assays used in different trials. In parts **a,b**, a ratio of one (black horizontal dashed line) indicates equivalence in amount of antibody between individuals who are vaccinated and average value for the relevant human convalescent serum — note logarithmic vertical axes. Where a range of data were reported for a specific parameter at a given time point (for example, between different age groups), the maximum reported value was used.

Canada, respectively^{84,85}. This will also be critical in determining the timing of any future booster doses that may be needed, to ensure that these can be given before protection has waned. The role of B cell memory is also critical — a study comparing individuals who are SARS-CoV-2 naïve and individuals who have recovered from SARS-CoV-2 identified that either prior

infection or vaccination with BNT162b2 was able to efficiently prime memory B cell responses, such that the second exposure (first vaccine dose after previous infection or second vaccine dose in individuals who are SARS-CoV-2 naïve) resulted in boosting of memory B cell responses⁸⁶. This may enable sparing of vaccine doses by recommending only one dose in individuals who had been

previously infected, although the critical interval between infection and efficient boosting requires further investigation. Finally, an additional potential advantage of mRNA vaccines compared with repeated homologous administration of viral-vectored vaccines is that anti-vector immunity will not be a potential issue that may result in attenuation of responses to booster doses.

Adenoviral-vectored vaccines. It is apparent from the data available that there are both similarities and differences between the mRNA vaccines and the adenoviral-vectored vaccines. For protection against symptomatic COVID-19 infection, the mRNA vaccines have an efficacy of ~95% in clinical trials after two doses^{81,82}, whereas data from the viral-vectored vaccines are mixed. There was ~70% efficacy for ChAdOx-1 nCoV-19 (after one or two doses)^{87,88} and Ad26.COV2.S (after one dose)⁸⁹ (TABLE 1). Additional benefit of a second dose is evident for Gam-COVID-Vac, when efficacy is ~90%^{87–90} (TABLE 1; see Supplementary Figure 1). This may be, in part, due to the fact that Gam-COVID-Vac uses different adenovirus vectors for each dose (adenovirus 26 for dose one and adenovirus 5 for dose two), thus circumventing the potential problem of anti-vector immunity that could inhibit anti-S responses, as has been identified for Ad5-nCoV (REFS^{12,91}) (TABLE 1) and non-COVID-19 adenovirus-based vaccines⁹². It should be noted that high effectiveness (>80%) against severe disease and hospitalization has been reported for both BNT162b2 (REFS^{93,94}) and ChAdOx1 nCoV-19 (REF⁹⁵). Both mRNA and adenoviral-vectored vaccines, after two doses, elicit levels of NAbs that are equivalent to or higher than those seen in patients who are in convalescence (FIG. 1), although the level of NAbs induced seems to be relatively higher with the mRNA vaccines. One dose of ChAdOx1 nCoV-19 was shown to elicit polyfunctional antibodies, which are capable of mediating neutralization and multiple other antibody-dependent effector mechanisms — all of which may contribute to protection against disease. ChAdOx1 nCoV-19-induced antibodies were shown to facilitate monocyte-mediated and neutrophil-mediated phagocytosis. Both functions were already induced following only one dose, although they were substantially increased by the second⁹⁶. The first dose of ChAdOx1 nCoV-19 also induces antibodies capable of antibody-dependent complement deposition; again, this functionality was increased following a second dose⁹⁶. In addition, this vaccine

induced potent T cell responses that peaked at 14 days after a single dose, based on production of TNF and IFN γ from CD4⁺ T cells upon antigen stimulation *in vitro* (TABLE 1; see Supplementary Figure 1). The similar efficacy after one and two doses of this vaccine, despite decreased T cell responses and increased antibody responses after the second dose, suggests that different protective mechanisms may therefore be prominent after one compared with two doses. Increased immunogenicity and efficacy was observed with increasing interval between doses for the ChAdOx1 nCoV-19 vaccine⁸⁸, and this strategy may therefore result in better protection after two doses and could be considered for other vaccines. In the long term, a strategy involving homologous prime–boost with identical viral-vectored vaccines may be limited by anti-vector immunity^{12,91,92}. Heterologous prime–boost strategies, such as that employed with Gam-COVID-Vac or based on using combinations of different vaccines, may be able to overcome this issue.

Future of COVID-19 vaccine development

Although the speed of vaccine development for COVID-19 already represents a remarkable landmark, the conceptual breakthroughs now appearing on the horizon — for example, data showing that protective mechanisms beyond NAb are likely to be important — will produce further monumental achievements. In order to identify correlates and mechanisms of protection without a massive financial outlay and substantial delay, we need to fully utilize the existing data via a data-driven approach to carefully assess which immunological pathways are associated with protection against COVID-19. Specifically, the trials leading to licensure of the current vaccines have already collected biological samples, analysis of which will usher in a revolution in our understanding of host responses. An initial analysis from trials of seven current vaccines has suggested that anti-S antibody is a reasonable correlate of protection — a robust correlation was reported between NAb titre and vaccine efficacy (rank correlation $r_s = 0.79$) and between anti-S binding antibody titre and efficacy ($r_s = 0.93$) after a complete vaccine series (one or two doses, depending on the vaccine)⁹⁷. However, this analysis did not fully consider efficacy and immune responses after one dose for the two-dose vaccines, or T cell responses. In addition, these analyses were based on short-term efficacy over 2–3 months and correlation with longer-term outcomes will

also be necessary. To accurately identify a correlate and/or mechanism of protection against COVID-19, trial samples will need to be analysed in an unbiased manner (that is, not just focused on NAb or antibodies, or even just adaptive immunity)⁹⁸. These correlates would then need to be validated in prospective cohort studies in different populations and controlled human infection models. In light of emerging viral variants with multiple mutations in the S protein — some of which are able to evade both natural and vaccine-induced immunity¹⁸ — it is paramount to target both humoral and T cell immunity, and potentially innate immune mechanisms. Reduced protection against any symptomatic COVID-19 disease caused by the B.1.351 variant of concern (now known as the Beta variant) has been reported from clinical trials¹⁸, but emerging data suggest that there remains high protection against the important end points of severe disease and hospitalization⁹⁹. This indicates the importance of immune mechanisms other than NAb, including T cell immunity. It may also be important to include SARS-CoV-2 antigens other than S, which are genetically much more stable, in the design of next-generation vaccines. For example, anti-nucleocapsid as well as anti-S binding antibodies are elicited by the whole-cell inactivated vaccine BBV152 (REF.¹⁰⁰), and comparison of outcomes post vaccination stratified by both anti-S and anti-nucleocapsid responses will aid our understanding of the role of non-S responses in protection. This includes assessing areas of mammalian physiology far beyond classical immunology that have long been known to be central in host defence during viral infections, such as metabolism, via interrogation of proteomic and metabolomics changes that occur after vaccination and how they relate to vaccine efficacy^{101,102}. Both the samples as well as the analytical pipelines to achieve this mammoth task are in place. Long-term follow-up of individuals who are vaccinated is needed to identify precisely how memory B and T cell responses correspond to the risk of infection and/or severe disease following vaccination. In addition, controlled human infection models may enable a more rapid evaluation of multiple vaccines and/or combinations of vaccines¹⁰³. Moreover, such models will allow us to evaluate the role of reinfection in individuals who have previously been infected and/or are vaccinated — given the relative scarcity of natural reinfection, these studies will enable the interrogation of early immune responses and identify the relevant mucosal and systemic mechanisms

that protect against reinfection. It will be important that discovery is not confined by what we expect, but allows the emerging data rather than dogma to guide formulating the hypothesis on how these vaccines protect.

Identifying correlates of protection will not only enable a pathway to licensure of additional vaccines based on immunogenicity, thus requiring smaller numbers of participants compared with efficacy trials, but would also allow one to rapidly investigate the effects of modified vaccination regimens (lower dose, single dose, dose spacing and heterologous vaccine) and predict protection in specific populations (such as pregnant women and patients who are immunocompromised) — all of which could result in more rapid global deployment of these precious resources. Therefore, there is significant urgency that these analyses will be undertaken by the custodians of the relevant data and samples. This has been highlighted globally, with the WHO identifying an urgent need to ‘accelerate research to establish correlates of protection from COVID-19 vaccines against infection and disease, including for variants of concern’¹⁰⁴. It is important that such correlates enable both the licensure of vaccines using already approved platforms for vaccines targeting these variants and also the licensure of vaccines based on additional platforms that are still in development.

Concluding remarks. As effective vaccines for COVID-19 are deployed in some high-income countries, it will still be many months, possibly even years, before sufficient numbers of doses of these vaccines are available to supply the global population. In the meantime, vaccine trials must continue^{105,106}. As effective vaccines are gradually rolled out, conducting large phase III efficacy trials will become increasingly difficult — for many reasons, including the ethical issues of a placebo-controlled trial in the context of an effective vaccine being available and also the likelihood of decreasing disease incidence in countries where vaccines are being used — which are usually the same countries that would be able to support large clinical trials^{105,106}. It may therefore become even more important to establish an immunologic correlate of protection against COVID-19, which could be used as the basis for vaccine licensure in the future. The data from these early trials highlight the challenges associated with this — multiple immunologic parameters

will likely need to be measured, and if there are multiple pathways of protection against disease, it is possible that correlates will be different at different time points after vaccination and/or with different vaccines. Comprehensive and careful analyses of all immunologic data, comparing initial post-vaccine responses in individuals who are infected after vaccination with those who are not, will ultimately provide an answer. Such analyses are expected in the first half of 2021, but the high vaccine efficacy means the number of individuals who are infected after vaccination is relatively low, limiting the statistical power of these analyses until sufficient cases occur. Uncertainties also remain around the importance of protecting not only against symptomatic disease but also against asymptomatic infection, and understanding this will be critically important when considering vaccines that may block transmission. Some early post-implementation analyses have suggested that the mRNA vaccines also reduce the incidence of asymptomatic infection and the nasopharyngeal viral load in individuals who become infected despite the vaccination^{93,107}, but it is yet unclear how this translates to risk of transmission. Inhibition of disease transmission would allow for the protection of individuals who are not vaccinated, and additional analyses that specifically evaluate herd immunity in the context of vaccination campaigns are required to confirm this. In addition to the polyfunctionality of vaccine-induced antibodies and T cells, it is important that vaccines induce polyclonal responses against a range of epitopes on the S protein, in order to avoid viral escape mutations. Thus, high-quality post-implementation surveillance of vaccine effectiveness and a careful study of vaccine failures will be a vital part of ongoing monitoring once vaccines are introduced. This will require viral genetic and immunologic analysis of infecting strains in cases of vaccine failure, including sieve analyses whereby pathogen isolates are compared genetically (for example, using whole-genome or targeted sequencing) between subjects who are infected after vaccination and those who are infected and not vaccinated¹⁰⁸. Finally, most individuals have pre-existing immune responses to other endemic human coronaviruses¹⁰⁹. The impact of these baseline responses on vaccination needs to be fully assessed and understood, especially if COVID-19 vaccines become part of future routine immunization schedules worldwide. Understanding how

responses to the initial series (one or two doses) of a COVID-19 vaccine further shape this immune response will be critical, including use of heterologous vaccines for second and/or third doses. Unprecedented insight has been extracted in only 16 months of this pandemic. But work must continue at the same pace in order to control the current COVID-19 pandemic and to be adequately prepared for the next pandemic.

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<https://doi.org/10.1038/s41577-021-00578-z>

Published online 1 July 2021

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Acknowledgements

M.S. is supported via salary awards from the BC Children's Hospital Foundation, the Canadian Child Health Clinician Scientist Program and the Michael Smith Foundation for Health Research. T.R.K. is supported through the Telethon Kids Institute and Perth Children's Hospital Foundation. A.M. is Research Director of the Fund for Scientific Research (F.R.S.-FNRS), Belgium.

Author contributions

All authors researched data for the article and contributed substantially to discussion of the content. M.S. wrote the first draft of article. All authors reviewed and edited the manuscript before submission.

Competing interests

M.S. has been an investigator on projects funded by GlaxoSmithKline, Merck, Pfizer, Sanofi-Pasteur, Seqirus, Symvivo and VBI Vaccines. A.M. has been an investigator on projects funded by GlaxoSmithKline and Sanofi-Pasteur, and is a member of the Clinical Advisory Board of Curevac. T.R.K. is an investigator in the Human Vaccines Project. All funds have been paid to their respective institutes to support research, and the authors have not received any personal payments.

Peer review information

Nature Reviews Immunology thanks R. Kennedy, Z. Xing and the other, anonymous, reviewer(s) for their contribution to the peer review of this work.

Publisher's note

Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.

Supplementary information

The online version contains supplementary material available at <https://doi.org/10.1038/s41577-021-00578-z>.

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