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REVIEW

Durability of Vaccine-Induced and Natural Immunity Against COVID-19: A Narrative Review

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ABSTRACT

Vaccines developed against SARS-CoV-2 have proven to be highly effective in preventing symptomatic infection. Similarly, prior infection with SARS-CoV-2 has been shown to provide substantial protection against reinfection. However, it has become apparent that the protection provided to an individual after either vaccination or infection wanes over time. Waning protection is driven by both waning immunity over time since vaccination or initial infection, and the evolution of new variants of SARS-CoV-2. Both antibody and T/B-cells levels have been investigated as potential correlates of protection post-vaccination or post-infection. The activity of antibodies and T/B-cells provide some potential insight into the underlying causes of waning protection. This review seeks to summarise what is currently known about the waning of protection provided by both vaccination and/or prior infection, as well as the current information on the respective antibody and T/B-cell responses.

Keywords: SARS-CoV-2; Waning immunity; Breakthrough infection; Reinfection; Antibody levels; Cellular immunity

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Key Summary Points

The protection provided against SARS-CoV-2 wanes over time post-vaccination or post-initial infection.

Protection against severe disease is more durable and takes longer to wane.

Waning protection is driven by both waning immunity over time following vaccination or initial infection and the evolution of new variants of SARS-CoV-2.

The evidence supports the hypothesis that protection is initially provided by neutralising antibodies with the more durable T-cell and B-cell responses, providing a large amount of the protection from severe infection.

Future studies should investigate the impact of patient-specific variables, such as age, ethnicity, comorbidities, and concomitant medications, on the effectiveness of the vaccines, as well as prior infection.

An established process is needed to evaluate the durability and protection provided by new vaccines designed with new variants so that they may be evaluated and rolled out in time for peaks in SARS-CoV-2-related burden.

INTRODUCTION

Randomised placebo-controlled trials showed that the initial efficacy of vaccines in preventing symptomatic SARS-CoV-2 infection ranges from 66 to 95% [1–9]. However, this high efficacy wanes over time, resulting in substantive reductions in vaccine protection [10, 11]. Similarly, while prior infection with SARS-CoV-2 can provide a high level of protection (87%) from re-infection [12], this protection declines over time. Despite waning protection against mild to moderate SARS-CoV-2 infection, protection against severe infection appears to be more durable, for underlying reasons which are not yet fully understood [10].

Waning protection is driven by both waning immunity over time following vaccination or initial infection and the evolution of new variants of SARS-CoV-2. Immunity is not a singular state: a wide range of immune states now exist globally, including those who are infection and vaccination-naïve, those who are fully vaccinated with or without booster shots, those recovered from one or more prior infections, and those who have both been vaccinated and recovered from prior infection. This is quite different from the context in which COVID-19 vaccines were first introduced.

Waning immunity is compounded by the evolution of new SARS-CoV-2 variants with greater immune escape. The first available vaccines for SARS-CoV-2 were developed against the original D614 variant, but multiple new variants of concern (VOC) have since arisen and spread globally [13]. The Omicron variant emerged at the end of November 2021, and the current global epidemiology of SARS-CoV-2 is characterised by the continued rapid global spread of Omicron sub-lineages. Updated SARS-CoV-2 vaccines, which incorporate the spike protein of the variants Omicron BA.1, BA.4, and BA.5 and the SARS-CoV-2 original strain, have received regulatory approval [14, 15]. The World Health Organization (WHO) has to date named five of the genetically mutated SARS-CoV-2 viruses as VOC, the Alpha, Beta, Gamma, Delta and Omicron variants [13]. At the time of publication, Omicron and its various sub-lineages were the only currently recognised VOC to be circulating [13]. Each VOC is designated based on mutations compared to the ancestral strain, with varying levels of immune escape against both previous infection and vaccination.

The aim of this review was to assimilate the current knowledge on the waning of protection by both vaccination and/or prior infection, as well as antibody and T/B-cell responses. A comprehensive understanding of these characteristics is required to support future vaccine products and programme development. This

article is based on previously conducted studies and does not contain any new studies with human participants or animals performed by any of the authors. Ethics approval was not required for this narrative review.

WANING VACCINE EFFICACY AND EFFECTIVENESS

Both the effectiveness and the efficacy of vaccines developed against SARS-CoV-2 have been extensively studied. Efficacy refers to the performance of the vaccines under ideal and controlled circumstances, for example clinical trials, compared with effectiveness, which measures vaccine performance under real-world conditions, such as observational trials. It is now well-established that the vaccine effectiveness of a primary series of SARS-CoV-2 vaccination wanes over time, resulting in an increased risk of breakthrough infection. The waning of vaccine efficacy and effectiveness have been assessed in mRNA vaccines (BNT162b2 [16–30] and mRNA-1273 [20, 25, 30, 31]), adenoviral vector vaccines (ChAdOx1-S [16, 20, 28, 32] and Ad26.COV2.S [20, 25, 27, 30]), and an inactivated virus vaccine (CoronaVac) [22]. Additionally, studies have reported combined results [33, 34].

Overall, every vaccine platform studied has shown reduced vaccine effectiveness against symptomatic infection over time [18, 27, 28]. Two systematic reviews and meta-analyses have summarised the rate at which protection against infection (both asymptomatic and symptomatic) waned in SARS-CoV-2 vaccines, regardless of vaccine platform (Table 1). Feikin et al.[10] found a 23% decrease in protection over 6 months post-vaccination, while Ssentongo et al.[11] found a decline in protection from 83 to 21% over 5 months. It was noted that the latter analysis relied on only two studies for the latest timepoint [11].

Despite substantial waning protection against symptomatic SARS-CoV-2 infection, most vaccines are still highly efficacious in preventing severe disease, hospitalisation, and death over time [16, 19, 20, 22, 30, 32, 33]. In the meta-analysis on severe infection by Feikin et al. [10], vaccine effectiveness declined by only 9.0% over the first 6 months post-full vaccination (Table 1) [10]. When limited to severe disease, Ssentongo et al. [11] found no evidence of decline at 5 months post-vaccination (Table 1).

Both meta-analyses represent studies in which multiple variants were circulating whilst the studies were performed, and that were conducted after the emergence of the Delta variant but before Omicron [10, 11].

In some studies, high-risk groups, including older people and persons with immunosuppression [16, 25, 35], have been observed to have faster rates of waning protection [16]. However, reports on this observation have not been consistent in their findings. For example, there have been some studies which have not found an impact of age on waning vaccine effectiveness [18, 29], and no statistically significant effect of age on the rate at which immunity waned was found in the meta-analysis by Feikin et al. [10].

The emergence and broad circulation of a potentially new VOC presents an additional variable which should be accounted for when discussing the durability of protection provided by vaccines, particularly in the case of the Omicron variant, where the virus-neutralizing activity of vaccine-induced antibodies is substantially lower compared to the earlier VOCs [18, 36]. Effectiveness as low as, − 2.7% (95% CI − 4.2 to − 1.2), 8.8% (95% CI 7.0–10.5) and 14.9% (95% CI 3.9–24.7) against Omicron at 25 + weeks post-full vaccination has been reported for the ChAdOx1, BNT162b2, and mRNA-1273 vaccines, respectively [37]. There is, however, still evidence that, despite a reduction in effectiveness against any Omicron infections, vaccination continues to provide substantial protection against severe infections. A test-negative case–control study has shown that the effectiveness against symptomatic Omicron infections of 3 doses of mRNA vaccine is 54% (95% CI 50.4, 57.3). Despite the reduced level of protection against symptomatic infection, the effectiveness against severe, critical, or fatal Omicron infections has remained remarkably high at 92.5% (95% CI 84.4, 96.3) [38].

Table 1 Summarised results of meta-analyses of waning vaccine efficacy/effectiveness over time

Author year	Vaccines evaluated	Severity of infection	Result
Feikin (2022) [10]	BNT162b2 ($n = 4$); mRNA-1273 ($n = 3$); Ad26.COV2.S ($n = 2$); ChAdOx1-S ($n = 1$)	Any infection[a]	Decrease % in VE (95% CE) from 1 to 6 months
			All ages: 23.3% (12.1–38.1) $p = 0.0003$
	BNT162b2 ($n = 4$); mRNA-1273 ($n = 2$)		Decrease % in VE (95% CE) from 1 to 6 months
			$\geq$ 50 years: 18.1% (7.5–35.1) $p = 0.003$
	BNT162b2 ($n = 3$); mRNA-1273 ($n = 2$); Ad26.COV2.S ($n = 2$); ChAdOx1-S ($n = 1$)	Symptomatic disease[a]	Decrease % in VE (95% CE) from 1 to 6 months
			All ages: 27.8% (13.0–51.5) $p = 0.0005$
	BNT162b2 ($n = 1$); mRNA-1273 ($n = 1$); Ad26.COV2.S ($n = 1$)		Decrease % in VE (95% CE) from 1–6 months
			$\geq$ 50 years: 36.1% (16.3–70.5) $p = 0.008$
	BNT162b2 ($n = 7$); mRNA-1273 ($n = 4$); Ad26.COV2.S ($n = 3$)	Severe disease[a]	Decrease % in VE (95% CE) from 1 to 6 months
			All ages: 9.9% (4.8–17.1) $p = 0.0001$
	BNT162b2 ($n = 5$); mRNA-1273 ($n = 3$); Ad26.COV2.S ($n = 1$)		Decrease % in VE (95% CE) from 1 to 6 months
			$\geq$ 50 years: 7.7% (2.7–15.8) $p = 0.0032$
Ssentongo (2022) [11]	BNT162b2 ($n = 9$); mRNA-1273 ($n = 6$); Ad26.COV2.S ($n = 2$)	Any infection[a]	VE% (95% CE) at 1 month post-vaccination
			All ages: 82.5% (74.8–90.2)
	BNT162b2 ($n = 3$); mRNA-1273 ($n = 1$)		VE% (95% CE) at 4 months post-vaccination
			All ages: 71.4% (52.3–90.39)
	BNT162b2 ($n = 2$)		VE% (95% CE) at 5 months post-vaccination
			All ages: 21.8% (− 24.2 to 67.8)

Table 1 continued

Author year	Vaccines evaluated	Severity of infection	Result
	BNT162b2 ($n = 8$); mRNA-1273 ($n = 4$)	Symptomatic infection[a]	VE% (95% CE) at 1 month post-vaccination
			All ages: 93.7% (93.3–94.2)
	BNT162b2 ($n = 2$)		VE% (95% CE) at 4 months post-vaccination
			All ages: 63.6% (24.2–103.0)
	BNT162b2 ($n = 7$); mRNA-1273 ($n = 2$); Ad26.COV2.S ($n2$)	Severe disease[a]	VE% (95% CE) at 1 month post-vaccination
			All ages: 85.0% (71.6–98.3)
	BNT162b2 ($n = 3$); mRNA-1273 ($n = 1$); Ad26.COV2.S ($n = 1$)		VE% (95% CE) at 4 months post-vaccination
			All ages: 78.4% (63.4–93.5)
	BNT162b2 ($n = 2$)		VE% (95% CE) at 5 months post-vaccination
			All ages: 89.5 (89.5–89.5)

mRNA messenger ribonucleic acid, *VE* vaccine efficacy/effectiveness

[a]The results represent studies in which there were a mixture of variants represented, all studies were performed before the emergence of the omicron variant

WANING IN POST-INFECTION PROTECTION

Multiple systematic and pragmatic literature reviews have investigated the effectiveness of natural post-infection protection [12, 39–43]. Published meta-analyses show consistently high levels of protection (81.0–87.0%) provided by prior infection, even over 7 months post-initial infection (Table 2) [12, 41, 43]. One meta-analysis assessed the estimated protection provided by prior infection from either any reinfection or symptomatic reinfection and found similar levels of protection ($\sim$ 87.0%) [12]. None of the three meta-analyses reported an analysis by variant, which would be challenging to study, since variants of both the initial infection and the reinfection must be considered [12, 41, 43].

Five studies investigating the risk of reinfection over time found no statistically significant waning in protection from reinfection (Table 3), [28, 44–47] with the protection from reinfection at the final study follow-up estimated to range from 69.0 to 93.0%. The protection against reinfection at > 1 year was estimated to be 69.0% in the study with the longest follow-up [28]. The estimated protection against milder versus more severe infections was only compared in two studies, which produced contradictory results [45, 47].

Nordstrom et al. (2022) found the estimated protection against hospitalisation (which the study stated was not affected by limitations associated with selection bias) was lower than protection against any infection at both 3–-6 months and ≥ 9 months, although a larger study should be performed to achieve a more accurate result, as hospitalisation events in this study were rare [45]. Sheehan et al. (2021) found

that the estimated protection against symptomatic infection (71%) was higher than protection against any infection (60%) at 90–150 days post-infection, although statistical significance was not assessed [47]. This was not seen at either the 151–210- or ≥ 210-day timepoints, where estimated protection was ~ 90% against both types of infection [47].

Only one study, Hall et al. (2022), took place during a time period in which the Delta VOC predominated [28]. The original infections included in the study occurred prior to the emergence and spread of Delta, which could explain the substantial, but not statistically significant, reduction in protection (Table 3) [28]. The other studies all took place prior to the widespread prevalence and predominance of VOC [44–47].

The relative protection provided by natural immunity compared to vaccination has been assessed in a systematic review and meta-analysis [42], which categorised studies into randomised controlled trials (RCTs) (3 studies) [48–50] and observational studies (4 studies) [51–54]. In the RCTs, no statistically significant difference [overall RR of 0.59 (95% CI 0.04–8.28, P = 0.69)] between vaccination and natural immunity was found, while in the observational studies, natural immunity provided better protection [3.71 (95% CI 1.75–7.86; $P = 0.0006$)] against any infection [42].

Some preliminary clinical trial evidence casts doubt on the ability of prior infection with an earlier variant of SARS-CoV-2 to provide protection against a different, newer VOC [55]. A trial assessing the efficacy of NVX-CoV2373 against the B.1.351 variant found that prior infection with a pre-B.1.351 virus did not appear to reduce the risk of Covid-19 due to subsequent infection with B.1.351 variants among placebo recipients during the initial 2 months of follow-up [55]. Data from a test-negative, case–control study from Qatar found that the effectiveness of previous infection in preventing reinfection ranged from 90.2% (95% CI 60.2–97.6) against the alpha variant, 85.7% (95% CI 75.8–91.7) against the beta variant and 92.0% (95% CI 87.9–94.7) against the delta variant, while against the Omicron variants, protection was reduced to 56.0% (95% CI 50.6–60.9). Prior infection did provide robust protection against hospitalisation or death regardless of variant, including 87.8% protection against hospitalisation due to the Omicron variant [56]. A separate analysis found that prior infection and a median interval of 324 days prior to reinfection, provided 50.8% (45.4–55.7) protection against symptomatic infections and 71.6% (15.7–90.4) protection against severe, critical, or fatal infections with the Omicron variant [38].

BOOSTED AND HYBRID IMMUNITY

Several studies have demonstrated that a single booster dose restores protection to the levels seen soon after either full vaccination or recovery from SARS-CoV-2 infection, including against the Omicron variant [18, 29, 57, 58]. However, protection against symptomatic infection provided by current mRNA boosters, compared to no booster dose, was higher against Delta (93.5–97.0%) than Omicron (62.4–67.3%) [18, 37].

Heterologous booster doses, in which the booster vaccine is different to the original vaccine series, may in some cases provide superior protection to homologous boosters [37]. Vaccination with a primary two-dose series of ChAdOx1, followed by a booster dose of ChAdOx1, provided protection against Omicron of only 46.7% (95% CI 34.3–56.7) at 5–9 weeks post-booster vaccination versus 52.9% (95% CI 52.1–53.7) and 60.9% (95% CI 59.7–62.1) at the same timepoint post-booster with BNT162b2 and mRNA-1273, respectively [37]. No benefit of a heterologous booster was observed when the two mRNA vaccines were given sequentially [37].

The advantages of a fourth booster dose of BNT162b2 against Omicron were investigated in a recent observational study in Israel [59]. While a two-fold increase in protection against confirmed SARS-CoV-2 infection was seen at 4 weeks post-booster vaccination, the effect had waned by 8 weeks. However, against severe cases of SARS-CoV-2, the fourth dose provided a four-fold increase in effectiveness at 6 weeks with no results provided for 8 weeks [59].

Table 2 Summary of meta-analyses of protection from reinfection provided by prior infection

Author year	Studies in meta-analysis	Time to reinfection	Severity of reinfection	Estimated protection (%, 95% CI)
Mao (2022) [12]	10	≥ 90 days (≥ 45 days with likely exposure)	Any reinfection[a]	87.0% (83.2–90.0%)
	4		Symptomatic reinfection[a]	87.2% (83.1–90.3%)
Chivese (2022) [43]	5	≥ 7 months	Any reinfection[a]	81.0% (68.0–89%)
Petras (2021) [41]	15	Mean days: 234 (180–360)	Any reinfection[a]	87.0% (82.0–91.0%)

[a]No analysis by variant of concern was possible, most studies represent an initial infection by the wild-type SARS-CoV-2

Table 3 Estimated protection from reinfection over time from published studies

Author, year	Measure of initial infection	Severity of reinfection	Estimated protection by time (%, 95% CI)
Hansen (2021) [44]	Any PCR positive	Any PCR positive[a]	3–6 months: 79.3 (74.4–83.3)
			≥ 7 months: 77.7 (70.9–82.9)
Nordstrom (2022) [45]	Any documented infection	Any document infection[b]	3–6 months: 96.0 (95.0–96.0)
			≥ 9 months: 93.0 (92.0–94.0)
		Hospitalisation[b]	3–6 months: 89 (86.0–91.0)
			≥ 9 months: 78 (66.0–85.0)
Spicer (2022) [46]	Any PCR positive	Any PCR positive[a]	91–120 days: 70.1 (65.6–74.0)
			241–270 days: 79.8 (65.0–88.4)
Sheehan (2021) [47]	Any PCR positive	Any PCR positive[a]	90–150 days: 60.0
			≥ 210 days: 93.9
	Any PCR positive	Symptomatic PCR positive[a]	90–150 days: 71.0
			≥ 210 days: 91.5
Hall (2022) [28]	Any PCR positive	Any PCR positive[c]	≤ 1 year: 86.0 (0.81 to 0.89)
			> 1 year: 69.0 (0.38 to 0.84)

[a]Study performed prior to widespread VOC
[b]Study performed during three waves of SARS-CoV-2: prior to widespread sequencing, prior to alpha variant becoming dominant, and after the alpha variant became dominant
[c]The initial infections occurred prior to widespread VOC, while the follow-up occurred during a period when the delta variant was predominant

Table 4 Summary of data synthesis from Chivese et al. (2022)

Author, year	Timepoint	T-cell subset	Prevalence of detectable T-cells
Chivese et al. (2022) [43]	≤ 1 month	CD4	100% (95% CI 83.9, 100.0)
	1–2 months		93.3% (95% CI 70.2, 98.8)
	4.5 months		78.8% (95% CI 65.1, 88.0)
	6–8 months		91.7% (95% CI 78.2, 97.1)
	≤ 1 month	CD8	70.0% (95% CI 48.1, 85.5)
	1–2 months		86.7% (95% CI 62.1, 96.3)
	4.5 months		57.4% (95% CI 43.3, 70.5)
	6–8 months		50.0% (95% CI 34.5, 65.5)

Hybrid immunity, in which people are either vaccinated after a prior SARS-CoV-2 infection or have a breakthrough infection after vaccination, is an increasingly common immune status [28]. The combination effect seems to provide greater protection than natural immunity on its own (> 90.0%), with no waning ≥ 1 year after infection or > 6 months after vaccination [28].

Relative protection provided by hybrid immunity versus natural immunity was investigated in a meta-analysis. In the three RCTs, no statistically significant difference between hybrid immunity and natural immunity was found, whereas in the four observational studies, hybrid immunity provided statistically significantly better protection against infection (risk ratio 1.94 95% CI (1.17–3.21), $P = 0.01$] [42].

Two additional observational studies supported the conclusion that hybrid immunity gives greater protection than natural immunity. One study found that one-dose hybrid immunity with either ChAdOx1, BNT162b2, or mRNA-1273, was associated with a 58.0% lower risk of SARS-CoV-2 reinfection than natural immunity for up to 2 months, with evidence of attenuation thereafter up to the 9-month follow-up. Two-dose hybrid immunity improved this further to a 66.0% lower risk of SARS-CoV-2 reinfection than natural immunity, with no statistically significant attenuation up to 9 months [45]. In the second study, the patients who had recovered from SARS-CoV-2 and received one or two doses of the BNT162b2 vaccine had a significantly lower risk of recurrent infection. Vaccine effectiveness in this previously infected population was estimated to be 82% (95% CI 80–84) in patients between 16 and 64 years old and 60% (95% CI 36–76) among those who were over 65 years old [60].

ANTIBODY DYNAMICS OVER TIME

Levels of neutralising antibodies have been shown to correlate with protection from symptomatic infection [61, 62]. Understanding the antibody dynamics after initial SARS-CoV-2 infection and vaccination is crucial for estimating the potential levels of protection provided.

Post-Initial Infection

In a systematic review and meta-analysis of adaptive immunity and reinfection after recovery from SARS-CoV-2 over the first 6–8 months post-infection by Chivese et al., 90.0% of individuals had evidence of SARS-CoV-2 specific immunological memory [43].

Anti-receptor binding domain (RBD) immunoglobulins (Ig) IgM and IgA are the main contributors to neutralization in the early phase of SARS-CoV-2 infection, while anti-RBD IgG represents most of the neutralising activity in

the late phase of infection and during convalescence [63–65].

Levels of neutralising antibodies decline over the first 4 months post-initial SARS-CoV-2 infection, especially for IgA and IgM, with less evidence of a substantial decline over the same time period for IgG [66]. Despite these initial declines in some antibodies, the neutralising antibody response after natural infection persists for up to 18 months, even following mild infection [63, 67].

However, the initial levels and durability of the neutralising antibody response depended upon the severity of the initial SARS-CoV-2 infection. Mild SARS-CoV-2 infections gave heterogeneous neutralising antibody titres and patients with asymptomatic SARS-CoV-2 had low titres or no measurable response at all [63, 68].

Antibodies elicited by initial SARS-CoV-2 variants show reduced activity against the RBD proteins of new variants of concern, which correlates with the reduction in protection provided by prior infection with an initial variant [67, 69]. One small study found that sera and plasma collected within 2 months of convalescence from mild or severe SARS-CoV-2 inhibited entry driven by the Omicron viral spike protein 80-fold less efficiently as compared with the B.1 spike (which is identical to the S protein of the Wuhan-Hu-1 isolate, except for the presence of mutation D614G), and 44-fold less efficiently compared with the Delta spike [69].

Post-Vaccination

Antibody dynamics post-vaccination depend on the vaccine used. The mRNA vaccines, BNT162b2 and mRNA-1273, produce a high peak neutralising antibody response which then rapidly declines within 6–8 months post-vaccination [70–73], while the adenoviral vector vaccines have a lower initial antibody response [74]. The inactivated virus vaccine, CoronaVac, also produces a lower initial antibody response than mRNA vaccines, and this level falls below the positive cut-off by 4 months post-vaccination [75, 76].

Multiple factors, including age and underlying conditions, can affect post-vaccination antibody levels and their longer-term dynamics [35]. The impact of age on post-vaccination levels have been seen to vary by vaccine with age over 50 years, being associated with lower IgG levels in people receiving BNT162b2 but not in those receiving mRNA-1273 [77]. The impact of various immunocompromised individuals and associated factors have been investigated in a prospective study. Seropositivity in participants with various immunocompromising conditions was statistically significantly lower than in healthcare workers [78]. Factors associated with poor seropositivity included age, greater immunosuppression, time since vaccination, anti-CD20 monoclonal antibody levels, and type of vaccination, with mRNA-1273 being superior to BNT162b2 or adenovirus vector vaccines [78].

Antibodies generated by the currently available vaccines, designed against the original D614 SARS-CoV-2 strain, produce antibodies with a substantially reduced recognition of, and activity against, new variants of concern, particularly Omicron [69, 79]. Sera and plasma collected mostly within 1 month post-vaccination with BNT162b2 has been seen to inhibit entry by the Omicron spike protein, with 34-fold lower efficiency than the B.1. spike, and with 12-fold lower efficiency than the Delta spike [69]. Furthermore, sera and plasma collected 1 month after heterologous vaccination with a first dose of ChAdOx1 and a second dose of BNT162b2 was 14-fold less efficient when compared with the B.1. spike, but only threefold less efficient relative to the Delta spike [69].

Booster doses of homologous and heterologous vaccines seem to be effective in recovering the neutralising antibody response in both fully vaccinated people and those with prior SARS-CoV-2 infections against variants of SARS-CoV-2, including the Omicron variant [58, 69, 80–86]. A recent meta-analysis concluded that heterologous immunisation was more effective than homologous immunisation in increasing antibody levels [87].

T-CELL AND MEMORY B-CELL RESPONSE OVER TIME

Although the contribution of T-cells and memory B-cells to protection against SARS-CoV-2 is still to be fully established, there is good evidence to support important roles of CD4 and CD8 virus-specific T-cells, as well as memory B-cells, in their response to SARS-CoV-2 infection [43, 88–94]. It must be noted that there is currently a lack of data on the tissue-associated (lung, lymph node, mucosa) T- and B-cell memory in response to SARS-CoV-2.

Post-Initial Infection

A cellular response has been shown to occur without an antibody response, although the overall relationship between the two response types is not fully understood. The concept of "cellular sensitization without seroconversion" refers to people who have developed a virus-specific cellular response, while not exhibiting the presence of neutralizing antibodies post-infection with SARS-CoV-2 [93, 95–98]. However, a study in healthcare workers found that only 1.5% (16/1076) of seronegative individuals responded to a SARS-CoV-2-specific peptide pool, which argues against widespread generation of T-cell immunity in the absence of seroconversion [99].

A recent systematic literature review and meta-analysis has combined available studies reporting the prevalence of T-cells and memory B-cells after SARS-CoV-2 infection [43]. Synthesis of the four reported studies, with a total of 118 participants [100–103], showed the prevalence of CD4 + T-cells reduced slightly after 6–8 months to 91.7%, while the prevalence of CD8 + T cells fell significantly to 50% (Table 4) [43]. Two additional studies reported a prevalence of SARS-CoV-2-specific memory B-cells of 92.9% (95% CI 68.5–98.7) for anti-spike-RBD class-switched memory B-cells at 2–3 months post-recovery and 80.6% (95% CI 65.0–90.2) having RBD-specific memory B-cells at 4–-5 months [43].

Durability up to 1 year post-infection has been demonstrated in some patients by the maintained prevalence and induction of virus-specific CD4 + and CD8 + T-cells, and memory B-cells [104–106].

The severity of the original SARS-CoV-2 infection can affect the cellular response; T-cell responses are significantly higher at 1-year post-in patients with severe infection compared to patients with milder infections [99, 104]. However, one study showed that, even when the magnitudes of both humoral and cellular immune responses were dependent on disease severity, asymptomatic to mild infection was still associated with a substantially reduced risk of reinfection ≥ 9 months [99].

Post-Vaccination

All available SARS-CoV-2 vaccines produce T-cell and B-cell responses, with differing responses depending on the vaccine used [107]. Both mRNA vaccines elicit a robust T-cell and B-cell response, although studies comparing the two show that the mRNA-1273 vaccine appears to produce a stronger T-cell and B-cell response than the BNT162b2 vaccine [108–111].

One study which directly compared mRNA vaccines and the adenoviral vector vaccine Ad26.COV2.S showed a similar magnitude of response [112]. However, other studies have indicated that the T-cell and B-cell responses of mRNA vaccines, especially mRNA-1273, are superior to adenoviral vector vaccines. One study analysed the T-cell responses in the mRNA vaccines, BNT162b2 and mRNA-1273, versus the adenoviral vector vaccine, Ad26.COV2.S. Superior bulk T-cell response and anti-spike cytotoxic T-cell response in recipients of mRNA-1273 or BNT162b2 was observed compared to recipients given Ad26.COV2.S [113]. Another study evaluated BNT162b2, mRNA-1273, Ad26.COV2.S, and NVX-CoV2373 vaccination-induced immune responses longitudinally for 6 months [114]. The magnitude of the CD4 + T cell responses was greatest with mRNA-1273, BNT162b2 and NVX-CoV2373 vaccination, which were equivalent, whereas Ad26.COV2.S-vaccinated subjects had the smallest response. Additionally, both mRNA and Ad26.COV2.S vaccines induced comparable

acute and memory CD8 + T cell frequencies, with NVX-CoV2373 having the lowest response, which was in line with previous findings for a protein-based vaccine [114]. Finally, a study on the SARS-CoV-2–specific T-cell response elicited by the ChAdOx1 and BNT162b2 vaccines over a 3-month period indicated that the BNT162b2 vaccine caused the more durable response of the two comparators [115].

The inactivated vaccine, CoronaVac, has been shown to cause a response in CD4 + and CD8 + T-cells, and in memory B-cells, in a study of up to 8–10 weeks [76], but the studies identified in this review comparing inactivated vaccines to other vaccine platforms do not provide details regarding the relative levels of T-cells and B-cells [75, 116].

As discussed, the antibody response to all available vaccines shows signs of waning with time since vaccination. However, there is evidence that T-cell and B-cell immunity produced by vaccination is more durable than the antibody response in studies of up to 8 months [71, 114, 117–120].

Additionally, while the antibodies produced by current SARS-CoV-2 vaccines have been shown to have a greatly reduced neutralising effect against new variants, most significantly Omicron, this has not been the case for T-cell responses [121–126]. Effective T-cell responses have been shown against both the Delta and Omicron variants, which could partially explain why current vaccines still provide significant protection against severe infection, hospitalisation, and death, despite an observed fall in protection against infection [127, 128]. Retention of the T-cell response can likely be ascribed to the ability of vaccine-induced T-cells to recognise spike proteins regardless of variant, as evidenced in both mRNA [122, 129, 130] and adenovirus-based vaccine responses [131].

As well as T-cells, memory B-cells elicited by the currently available vaccines are able to recognise variants of concern up to, and including, Delta [124, 132]. Unfortunately, this ability has been reduced in the case of Omicron, with, in one study, recognition of the RBD being reduced to 42.0% compared to other variants [124].

Some evidence suggests that T-cell and B-cell responses may be impacted by the timing of vaccination. For instance, a longer dosing interval of the BNT162b2 vaccine can give rise to more typical helper T-cells and long-term memory T-cells, indicating greater promotion of immune memory and generation of antibodies [117, 133]. In a separate study, extending the dosing interval of the BNT162b2 vaccine also led to an increase in peak B-cells and a skew in the T-cells produced towards S-specified CD4 + T cells [134].

CORRELATES OF PROTECTION

There is an urgent need to establish correlates of protection against SARS-CoV-2 infection, as proxy measurements for vaccine effectiveness and duration of immunity against emerging variants, and to help in the development of new vaccines [135]. Neutralising antibodies have been considered the prime candidate as a correlate of protection against clinical infection [61, 62], but, with novel variants emerging, the extent to which these antibody levels still correlate to a good level of protection is diminished in those who have received vaccines based on wild-type SARS-CoV-2 [69, 79].

Emerging evidence shows that different components of the immune system are involved in protection against asymptomatic or mild SARS-CoV-2 infection compared with severe SARS-CoV-2 infection [107]. For example, studies note that protection is seen against severe disease in vaccinated people with a robust T-cell response despite reduced neutralising antibody levels. This may lead to a need to stratify correlates of protection by disease severity [135].

Many potential correlates of protection have yet to be assessed and further study will be required [136].

CONCLUSIONS

The protection provided against SARS-CoV-2 infection wanes with time from vaccination or prior infection. The protection provided by

vaccination against symptomatic SARS-CoV-2 infection wanes over time, diminishing by a quarter to a third in 6 months. The protection from symptomatic reinfection provided by previous infection wanes at a slower rate, with only slight declines seen at 12 months. With both vaccination and prior infection, protection against symptomatic disease wanes more rapidly than protection against severe, critical, or fatal disease. Booster vaccinations have been shown to recover protection levels of primary vaccination series, and hybrid immunity may provide more robust protection than either vaccination or primary infection; however, in both cases, the protection provided still wanes over time.

The emergence of new VOC has reduced the levels of protection provided by vaccination and prior infection with an earlier variant. However, while protection against symptomatic infection/reinfection is greatly reduced, especially with the Omicron variant, protection against severe, critical, or fatal infection/reinfection remains robust.

The antibody and T/B-cell dynamics post-vaccination or reinfection provides some potential insights into understanding why protection from severe, critical, and fatal infection/reinfection are more robust against waning with time and new VOC. Antibody dynamics post-vaccination are dependent upon multiple factors, including the vaccine used, the number of doses, the presence of hybrid immunity, age and whether the individual is immunocompromised. However, in all cases, circulating antibody levels provided by vaccination are greatly reduced by 6–8 months post-vaccination. This aligns with the time period over which protection against symptomatic infection declines. Post-infection antibody dynamics show a slower decline than post-vaccination titres, which matches the longer-lasting protection seen. However, the initial antibody levels provided by an infection are heavily dependent upon the severity of the initial infection, implying that asymptomatic or mild infections may not provide robust protection. Antibodies elicited by currently available vaccines and prior infections with older variants are not as effective at neutralising new VOC, especially Omicron.

The T/B-cell response to both vaccination and prior infection are more long lasting than the antibody response. Additionally, T/B-cells elicited from current vaccinations and prior infections with older variants show a reduced but still robust ability to recognise new VOC, including Omicron.

The current evidence supports the hypothesis that the initial protection provided by SARS-CoV-2 vaccination or prior infection is initially provided by neutralising antibodies, with the more durable T-cell and B-cell responses providing a large amount of the protection from severe infection. Additionally, antibodies from both vaccines or prior infections seem to lose neutralising activity against new variants more rapidly. T-cells and B-cells provide more robust protection against severe, critical, and fatal infection/reinfection.

While a large amount of research has been performed on the topic of waning protection provided by vaccination and prior infection, many topics still require investigation. These include the impact of patient-specific variables, such as age, ethnicity, comorbidities, and concomitant medications, on the effectiveness of the vaccines, as well as prior infection. Other topics for further investigation should also include the definition of a standardised antibody test and the timepoint of testing. Such studies should be the focus of future investigations. An established process is needed to evaluate the durability and protection provided by new vaccines designed with new variants (e.g. Beta or Omicron) so that they may be evaluated and rolled out in time for peaks in SARS-CoV-2-related disease burden. To date, vaccine roll-out has been conducted in more of an ad hoc manner: it is recognised that high antibody levels are required to prevent breakthrough infection, especially when a new variant of concern arises, so that booster vaccinations are administered as antibody titres wane. Peak antibody levels are typically reached after three vaccine doses, then further doses boost levels back to this peak following waning. There is substantial debate on whether maintaining a saw-tooth level of antibody titres through

repeated vaccinations, as is being done in Israel, is a sustainable public health strategy in the long term. Further research is required to develop vaccines that produce a more durable response or an immune response that is not variant-dependent.

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DATA AVAILABILITY

This manuscript has no associated data or the data will not be deposited. [Authors' comment: There are no associated data available.].

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