City University of New York (CUNY)

CUNY Academic Works

Publications and Research

Queens College

2021

Are COVID-19 Vaccine Boosters Needed? The Science behind Boosters

Rachel M. Burckhardt
American Academy of Microbiology

John J. Dennehy
CUNY Queens College

Leo L. M. Poon
University of Hong Kong

Linda J. Saif
The Ohio State University

Lynn W. Enquist
Princeton University

[How does access to this work benefit you? Let us know!](#)

More information about this work at: https://academicworks.cuny.edu/qc_pubs/507

Discover additional works at: <https://academicworks.cuny.edu>

This work is made publicly available by the City University of New York (CUNY).
Contact: AcademicWorks@cuny.edu

1 **Are COVID-19 Vaccine Boosters Needed? The Science behind Boosters**

2

3 Rachel M. Burckhardt^a, John J. Dennehy^b, Leo L. M. Poon^c, Linda J. Saif^d, and Lynn W. Enquist^{e*}

4

5 ^aAmerican Academy of Microbiology, Washington, DC, USA

6 ^bBiology Department, Queens College and The Graduate Center of The City University of New York, New
7 York, USA

8 ^cSchool of Public Health & HKU-Pasteur Research Pole, LKS Faculty of Medicine, The University of Hong
9 Kong, Hong Kong, China

10 ^dCenter for Food Animal Health, Department of Animal Sciences, College of Food, Agricultural and
11 Environmental Sciences, OARDC, Veterinary Preventive Medicine Department, College of Veterinary
12 Medicine, The Ohio State University, Wooster, Ohio, USA

13 ^eDepartment of Molecular Biology, Princeton University, Princeton, New Jersey, USA

14

15 *corresponding author: lenquist@princeton.edu

16

17 Running Title: Science of COVID-19 Boosters

18

19 **Authors' ORCID numbers**

20 RMB: 0000-0001-6290-2534

21 JJD: 0000-0002-9678-4529

22 LLMP: 0000-0002-9101-7953

23 LJS: 0000-0002-3224-9009

24 LWE: 0000-0001-9968-8586

25

26

27 *The views expressed in this Commentary do not necessarily reflect the views of the journal or of*
28 *ASM.*

29

30

31 **Abstract**

32 Waning vaccine-induced immunity coupled with the emergence of SARS-CoV-2 variants has led to
33 increases in breakthrough infections, prompting consideration for vaccine booster doses. Boosters have
34 been reported to be safe and increase SARS-CoV-2-specific neutralizing antibody levels, but how these
35 doses impact the trajectory of the global pandemic and herd immunity is unknown. Information on
36 immunology, epidemiology and equitable vaccine distribution should be considered when deciding the
37 timing and eligibility for COVID-19 vaccine boosters.

38

39

40 The global impact of the COVID-19 pandemic has been unprecedented, but so too has the speed of
41 development and efficacy of vaccines for COVID-19. Less than a year from first identifying SARS-CoV-2 as
42 the causative agent of COVID-19, multiple safe and highly effective vaccines were authorized for use
43 around the world. But the longevity of vaccine-induced immunity is unknown, sparking debate on the
44 need for “booster” vaccine doses in the hopes these will increase protection from SARS-CoV-2 infection
45 and disease. Fears of waning immunity and the emergence of variants of concern (VOC) have fueled this
46 debate. But deciding who should receive boosters and when are not easy questions to answer,
47 especially given global vaccine distribution inequity. To make a decision, scientists must take into
48 consideration known data on vaccines and immune memory, public health, epidemiology and ethics for
49 diverse age ranges and socioeconomic groups.

50

51 **SARS-CoV-2 Vaccines Induce Robust and Protective Immune Responses, Even Against Viral Variants**

52 A plethora of vaccines to SARS-CoV-2 were developed in an unprecedented rapid time frame. They
53 included conventional inactivated (Sinovac, SinoPharm), adenovirus (Ad) vectored (Gamelaya, J&J
54 Janssen, AstraZeneca) and mRNA vaccines (Pfizer, Moderna). In the randomized clinical trials, their

Burckhardt, et al.

Science of COVID-19 boosters

55 efficacy against severe disease ranged from 59 to >95%, but was lower against mild or asymptomatic
56 disease (~47 to 94%) (1, 2). The mRNA vaccines showed consistently higher efficacy rates, but they
57 elicited lower neutralizing antibodies (NAbs) titers in those >70 years at 6 months post vaccination (30%
58 no NAbs) (2, 3). In a Pfizer mRNA vaccine 6-month cohort in Israel, lower IgG Ab levels, especially in
59 those >60 years, were correlated with subsequent infection (4).

60 Both the Ad vector and mRNA vaccines were engineered to express the pre-fusion spike protein
61 (S) to induce NAbs. Both vaccine types stimulated effective innate immune responses (adjuvant effects)
62 leading to enhanced adaptive immune responses. mRNA and Ad vector vaccines induced serum IgG S
63 and receptor-binding domain (RBD) binding Ab and NAbs. These Ab responses generally were highly
64 correlated and the Abs persisted for at least 6 months (2, 3, 5). Primarily S-specific Th1 and T follicular
65 helper (Tfh) CD4+ T cells, with lower CD8+ T cell responses and persisting memory T and B cells were
66 also documented in mRNA vaccinees (6). Emerging data from non-human primates (NHP) and vaccinees
67 suggest that as for most other licensed vaccines, NAbs may be a potential correlate of protection (7-9).

68 Serum Abs are produced by short-lived plasmablasts leading to the early peak of Ab responses
69 that are then maintained by long-lived plasma cells (10-12). Multiple studies have documented 5 to 10-
70 fold decreased serum IgG Abs within 5 to 6 months after mRNA vaccination (10, 12), but serum IgG and
71 NAb were detectable for 10 months in mild COVID-19 cases (13). Data from long-term follow-up studies
72 of vaccinated individuals are yet to be released, but B and T cell responses can still be detected in
73 vaccinees for at least 6 months after the second dose (5, 14). Additionally, a recent study demonstrated
74 that the durability of vaccine-induced B or T cell responses in recovered COVID-19 individuals was
75 similar to those of uninfected vaccinated individuals (14). Moreover, after mRNA vaccination or natural
76 infection, the memory B cells induced continued to evolve in germinal centers with increasing levels of
77 somatic hypermutation and Abs of increased affinity. These memory B cells persist longer term and are
78 essential for recall secondary Ab responses to protect against reinfection (5, 10-12, 14-16). Notably,

Burckhardt, et al.

Science of COVID-19 boosters

memory B cell expressed Abs had greater potency and breadth after natural infection compared with mRNA vaccination (10, 15, 16). This may explain in part why natural infection conferred a higher level of protection against S variants in some studies (10, 17). In contrast, an epidemiologic analysis of U.S. patients hospitalized with COVID-19-like illness and whose previous infection or mRNA vaccination accrued 90-179 days earlier found convalescent but unvaccinated patients were 5.49-fold more likely to have laboratory confirmed COVID-19 than mRNA vaccine recipients with no prior documented infection (19.75-fold higher if >65 years) (18). However, differences from the Israeli retrospective cohort study included: protection against infection (any SARS-CoV-2 positive test) vs protection against hospitalization, and a longer interval of 6-month vs 90-179 days prior to mRNA vaccination or infection, respectively.

Emergence of SARS-CoV-2 variants of concern with multiple substitutions in key Ab epitopes of the S glycoprotein may compromise immunity by partial escape from NAbs. Multiple studies suggest equivalent NAbs against the Alpha (B.1.1.7) variant, but several-fold reduced NAbs to the Gamma (P.1) and Delta (B.1.617.2) variants vs. original strains in sera of vaccinated or recovered individuals. In most studies, NAb titers were lowest against the Beta (B.1.351) variant, but all variants were neutralized to a variable extent attributable to the polyclonal Ab responses induced (3, 12, 19). In contrast, T cell responses induced by mRNA vaccines or natural infection were not substantially affected by the variant substitutions (20). CD4+ T cells from recovered individuals mounted a broader antigen-specific response across the structural and accessory gene products, whereas the CD8+ T cells are predominantly nucleocapsid-specific while spike-specific responses are substantially lower in frequency (20). Potentially these CD8+T cells against the nucleocapsid (N) may also contribute to immunity after natural infection, since these N-specific responses, which are not induced by mRNA or Ad vector vaccines, may be more highly conserved against VOCs (20).

102 The half-life of SARS-CoV-2 NABs in recovered COVID-19 individuals is a few months, depending
103 on disease severity (12, 13, 19). Although these antibody responses wane rapidly, SARS-CoV-2-specific B
104 and T cell memory responses can still be detected at least 1 year after the infection (12, 16, 21). Similar
105 waning of antibody response can also be found in non-infected vaccinees. Of interest, modeling of
106 genetic traits between SARS-CoV-2 and the 5 other human coronaviruses to estimate Ab decline and the
107 probability of reinfection revealed short-lived immunity of 3 months to 5 years (median 16 months)
108 after peak Ab titer (22). Waning of Ab-mediated protection and the emergence of variants is consistent
109 with occurrence of reinfections after 8 months in convalescent individuals infected with the Gamma
110 variant (23) and vaccine breakthrough infections by variants (4, 24). However, despite lower NAB titers
111 against variants, mRNA and other vaccines protected against most hospitalizations and deaths, including
112 those resulting from infection with the Delta variant (5, 25). Whether the variants contribute to reduced
113 symptomatic protection in vaccinees ("breakthrough infections") and convalescents is an important
114 unanswered question.

115 Those individuals with lower initial SARS-CoV-2 Ab responses (elderly, immunocompromised)
116 and whose Ab responses have waned after 6 months may be at increased infection risk. The elderly,
117 who are the most susceptible to COVID-19 disease and deaths, have more restricted Ab and naïve T cell
118 repertoires that likely constrain their immune responses (12). The increased transmissibility of the Delta
119 variant along with the lower initial magnitude and waning Ab responses appear to have contributed to
120 vaccine breakthrough infections, especially for severe cases in elderly and those with co-morbidities (4,
121 24), or immunocompromised individuals (26). These data prompted recommendations for booster
122 vaccine doses for these vulnerable groups.

123 Importantly, infected vaccinees still shed and transmitted the virus, more so for the Delta than
124 the Alpha variant (27), although of shorter duration and with lower amounts of infectious virus (28-30).
125 Thus, virus transmission was reduced, but not eliminated by the current vaccines. An explanation is that

126 the current parenteral vaccines induce mainly serum IgG Abs, highly effective against prevention of
127 systemic or lower respiratory tract (LRT) infections (reduce severe disease and hospitalizations), but less
128 effective at blocking virus infection of the oral cavity and upper RT (URT) to prevent virus shedding and
129 transmission. Studies of mRNA vaccine in challenged NHP confirmed that lower serum S Ab levels
130 were required to reduce virus replication in the LRT versus the URT (7). Likewise mRNA vaccinees had
131 fewer S-specific T cells expressing longevity (CD127) or nasopharynx homing markers compared with
132 convalescents (31). These findings coupled with the time needed for antigen re-stimulation of vaccine-
133 induced memory T and B cells to evoke secondary immune responses (12), may enable the highly
134 transmissible variants to infect the URT and transit to the LRT in vulnerable patients or those with
135 waning serum Abs, increasing disease risk. Future vaccines that induce broadly reactive mucosal IgA and
136 serum IgG NAb and augment T cell repertoires may provide enhanced protection against both disease
137 and transmission after exposure to variants (32).

138

139 **Known Impact of SARS-CoV-2 Vaccine Booster Doses**

140 Several publications have described the impact of SARS-CoV-2 vaccine booster on human immune
141 responses (33-37). However, many primarily targeted specific groups (e.g., elderly or
142 immunocompromised individuals) and analyzed different vaccine types. Some of these studies included
143 only a small number of participants. With the exception of antibody neutralization, our understanding of
144 immune correlates of SARS-CoV-2 protection is limited (7-9, 38). In addition, the minimal NAb level
145 required for preventing infection or severe clinical outcomes and the importance of vaccine-induced
146 memory B and T cells against SARS-CoV-2 are yet to be fully determined. Thus, the findings of these
147 studies should be interpreted with caution and not extrapolated to the entire human population.

148 Different types of COVID-19 vaccines including mRNA, viral vector, inactivated and protein-
149 based vaccines are used as boosters (33, 36, 38-41). In general, a booster dose can substantially increase

Burckhardt, et al.

Science of COVID-19 boosters

150 NAb levels or its surrogate markers (e.g., anti-spike IgG) against SARS-CoV-2. A booster dose also helps
151 stimulate SARS-CoV-2 Abs in those who did not respond to a standard vaccine, such as
152 immunocompromised individuals (29, 35, 42). The level of Abs with cross-reactivity against different
153 SARS-CoV-2 VOCs is also enhanced by a booster (33, 36). This finding suggests that a high level of SARS-
154 CoV-2-specific Abs maintained by repeated immunizations is sufficient to control COVID-19 caused by
155 existing antigenic variants. Recent real-world data from Israel show that a third dose of an mRNA
156 vaccine substantially reduced the risk of infection or severe illness caused by the Delta variant (33).
157 Similarly, a recent large-scale study from Chile also showed that 2 doses of an inactivated vaccine
158 followed by a third dose of an inactivated, mRNA or adenovirus-based vaccine enhanced the vaccine-
159 induced protection against SARS-CoV-2 (Chile Ministry of Health, unpublished data). In a preliminary
160 study of 458 mix and match mRNA and Ad vector vaccine booster recipients, substantial increased NAb
161 responses occurred in all recipients post-homologous or heterologous booster vaccination, including
162 against Delta and Beta variants, even in the absence of pre-boost NAb titers (39). Likewise, NHPs
163 boosted 6 months after the primary mRNA 1273 vaccination with either homologous mRNA 1273 or
164 heterologous Beta variant (mRNA 1273Beta) developed broader NAb titers to the Beta and Delta
165 variants and protection to Beta variant challenge (43).

166 Although the protective role of vaccine-induced T cell responses against COVID-19 is not clear,
167 these responses are induced by different types of SARS-CoV-2 vaccines (5, 6, 14, 44). Cross-reactive T
168 cell responses against different VOCs can be stimulated by vaccination (14), indicating that conserved
169 epitopes are shared by SARS-CoV-2 antigenic variants. Such T cell responses can be further boosted by a
170 third dose (36). A study on transplant patients showed that T cell responses can be detected in the
171 majority of patients after a booster (37). Assuming these vaccine-induced T cell responses have a
172 protective role against COVID-19, a third dose of vaccine might increase the chance of inducing an
173 addition level of protection to immunocompromised patients or poor vaccine responders. Together,

174 these data demonstrate that there are some short-term benefits of using a booster dose to enhance
175 vaccine-protective effects in adults, especially for vulnerable populations.

176 Several studies have demonstrated that SARS-CoV-2 vaccine boosters are safe for adults (36, 45,
177 46). In these studies, adverse reactions induced by a booster of mRNA or Ad vectored vaccine usually
178 are mild and are comparable to those caused by the second dose of an mRNA vaccine. Thus far, there is
179 no evidence that a COVID-19 vaccine booster shot can induce any unexpected adverse reactions or
180 additional risk of having severe adverse reactions. Although there is no short-term safety concern for a
181 booster dose, the long-term immune consequences of repeated immunizations are not known. Studies
182 have shown that repeated administration of influenza vaccine boosters within a short time (e.g., 2
183 doses/year) may result in blunting of vaccine-induced antibody responses (47). As SARS-CoV-2 continues
184 to evolve in humans, we do not know whether repeated immunization of the same antigens would
185 induce undesirable immune imprinting effects, thereby skewing the breadth of our immune response in
186 our future encounters of other novel SARS-CoV-2 antigenic variants. Some preliminary studies on
187 vaccine-induced immune responses in recovered COVID-19 individuals argue against this possibility (14,
188 15); however, further characterization of Ab and T and B cell immune memory responses and their
189 longevity in individuals who have received multiple doses of COVID-19 vaccines are still needed.

190

191 **Herd Immunity is Achieved Via Global Vaccination**

192 Vaccines not only protect individuals from infectious disease, but also protect those who are unable to
193 be vaccinated and those for whom vaccinations are less effective. That is, vaccines protect the
194 community as well as the individual (48). This protection is called “herd immunity.” As the proportion of
195 immune individuals in a population rises, the proportion of susceptible individuals declines, and
196 consequently, the probability of an infected individual encountering a susceptible individual also
197 declines. Theoretically, there is a threshold beyond which the proportion of immune individuals is so

198 large that infected individuals are likely to recover before spreading infections to susceptible individuals.
199 Once the herd immunity threshold is exceeded, the rate at which new infections are initiated will be
200 insufficient to sustain the epidemic and eventually the epidemic will subside.

201 It is important to note, however, that the herd immunity threshold is not a fixed parameter. The
202 herd immunity threshold will vary, even in the midst of an epidemic, according to the characteristics of
203 the virus and the population in which it is spreading. Relevant virus properties may include infectivity,
204 transmissibility and durability outside a host. Important population parameters may include contact
205 rates between individuals, behavioral interventions such as masking, availability of treatments and
206 population clustering. All of these characteristics can be subsumed under a single parameter termed R_0
207 or R naught, which is defined as the expected number of new infections generated by an infected
208 individual in a population of susceptible individuals (49). If $R_0 > 1$, then an epidemic will persist; and
209 conversely if $R_0 < 1$, then an epidemic will wane. The herd immunity threshold relates to R_0 in that it
210 must be equal or greater than $1 - 1/R_0$ in order to arrest an epidemic (49). For example, if a virus's $R_0 = 4$,
211 then the herd immunity threshold = 0.75, meaning that 75% of the population must be rendered
212 immune to infection in order to stop this virus's continuing transmission.

213 So when will we achieve herd immunity to SARS-CoV-2? How will vaccine boosters affect this
214 timeline? To answer these questions, it is helpful to consider how R_0 is embedded in an approach to
215 epidemiological theory called compartmental models. In their simplest form, compartmental models
216 assign individuals in a population to one of three categories: susceptible, infectious and removed.
217 Infectious individuals are generated when susceptible individuals are infected by a pathogen, which
218 occurs at a transmission rate, β . Individuals are removed from the infectious compartment at a rate γ
219 when they recover from infection, succumb to infection or are quarantined. Vaccinated individuals
220 transition directly from the susceptible compartment to the removed compartment, and are included in
221 the removal rate, γ . In deceptively simple terms, $R_0 \approx \beta/\gamma$ (49).

222 It must be recognized that θ and γ vary over time and place. θ may increase with virus evolution,
223 as is seen with the highly transmissible SARS-Cov-2 Delta variant (50), or due to host behavioral changes
224 such as reduced mask usage and social distancing. Removal rate γ may increase with improved
225 treatments and expanded vaccine access. Furthermore, except in cases of death, residence in the
226 removed compartment is not permanent. Vaccines are not 100% effective and breakthrough infections
227 occur (51). Reinfections of individuals who have recovered from COVID-19 are also possible (52).
228 Immunity, whether vaccine-induced or natural, wanes. SARS-CoV-2 vaccine booster shots will reduce
229 reversions to virus susceptibility (33).

230 As of the time of writing, there have been 250 million confirmed COVID-19 cases globally
231 (<https://covid19.who.int/>), but this number is almost certainly an underestimate. Roughly extrapolating
232 from US data suggesting that 60% of infections have gone unreported (53), actual global cases may
233 number ~615 million. In addition, an estimated 4.02 billion people have received at least one dose of a
234 SARS-CoV-2 vaccine ([https://www.nytimes.com/interactive/2021/world/covid-vaccinations-](https://www.nytimes.com/interactive/2021/world/covid-vaccinations-tracker.html)
235 [tracker.html](https://www.nytimes.com/interactive/2021/world/covid-vaccinations-tracker.html)). Thus, the removed category may contain as many as 4.5 billion individuals, or ~57% of the
236 world population. Despite the difficulties estimating R_0 , as alluded to above, it would appear that herd
237 immunity threshold is approaching, but some wonder whether herd immunity to SARS-CoV-2 will ever
238 be achieved (54). The UK may be an important indicator. Although 68% of the population is fully
239 vaccinated and at least 13.5% have recovered from infection, the UK reported an average of 41,326
240 cases per day in the last week of October, 2021, a number that has remained relatively stable since July
241 2021 (<https://covid19.who.int/>).

242 The UK situation reflects an important axiom regarding herd immunity: we won't get there
243 unless we *all* get there. No country can hope to escape the pandemic by itself. Concerningly, vaccine
244 distribution has been uneven. Much of the Global South remains unvaccinated. Even in countries where
245 availability is high, vaccine hesitancy limits full uptake. Slow or incomplete vaccine uptake prolongs the

246 epidemic and exacerbates other issues, namely waning immunity and pandemic-fatigue. Remaining
247 vigilant and engaging in protective behaviors is draining and lapses become increasingly likely.
248 Collectively these factors permit continuing virus evolution and the accession of mutations enhancing
249 virus transmission and evasion of antibody mediated neutralization. New variants may emerge that
250 negate our progress unless we ensure protection for the entire global community.

251 In record time, a multitude of safe and effective COVID-19 vaccines have been developed. Yet,
252 as with most vaccines, immunity wanes, and this coupled with the emergence of SARS-CoV-2 variants
253 has led to increases in breakthrough infections. Booster doses have been shown to be safe and increase
254 SARS-CoV-2-specific neutralizing antibody levels that are cross-reactive to current VOCs. This is
255 especially important for protecting elderly and immunocompromised individuals who are at highest risk
256 for severe COVID-19.

257 However, current vaccines provide highly effective and sustained protection against COVID-19-
258 related hospitalizations and deaths across age groups, indicating that a booster dose may not be needed
259 for all fully vaccinated individuals. Additionally, reaching herd immunity requires equitable vaccine
260 distribution and access worldwide. Resources spent on administering booster doses may prolong
261 unequal global vaccine distribution as well as increase vaccine hesitancy. Public health officials and
262 policy makers should take these factors into consideration when deciding what groups should receive
263 boosters and when.

264

265 **References**

- 266 1. Krause PR, Fleming TR, Peto R, Longini IM, Figueroa JP, Sterne JAC, Cravioto A, Rees H, Higgins
 267 JPT, Boutron I, Pan H, Gruber MF, Arora N, Kazi F, Gaspar R, Swaminathan S, Ryan MJ, Henao-
 268 Restrepo AM. 2021. Considerations in boosting COVID-19 vaccine immune responses. *Lancet*
 269 398:1377-1380.
- 270 2. Muller L, Andree M, Moskorz W, Drexler I, Walotka L, Grothmann R, Ptok J, Hillebrandt J, Ritchie
 271 A, Rabl D, Ostermann PN, Robitzsch R, Hauka S, Walker A, Menne C, Grutza R, Timm J, Adams O,
 272 Schaal H. 2021. Age-dependent immune response to the Biontech/Pfizer BNT162b2 COVID-19
 273 vaccination. *Clin Infect Dis* doi:10.1093/cid/ciab381.
- 274 3. Doria-Rose N, Suthar MS, Makowski M, O'Connell S, McDermott AB, Flach B, Ledgerwood JE,
 275 Mascola JR, Graham BS, Lin BC, O'Dell S, Schmidt SD, Widge AT, Edara VV, Anderson EJ, Lai L,
 276 Floyd K, Roupheal NG, Zarnitsyna V, Roberts PC, Makhene M, Buchanan W, Luke CJ, Beigel JH,
 277 Jackson LA, Neuzil KM, Bennett H, Leav B, Albert J, Kunwar P, m RNASG. 2021. Antibody
 278 Persistence through 6 Months after the Second Dose of mRNA-1273 Vaccine for Covid-19. *N*
 279 *Engl J Med* 384:2259-2261.
- 280 4. Kertes J, Gez SB, Saciuk Y, Supino-Rosin L, Stein NS, Mizrahi-Reuveni M, Zohar AE. 2021.
 281 Effectiveness of the mRNA BNT162b2 vaccine six months after vaccination: findings from a large
 282 Israeli HMO. *medRxiv* doi:<https://doi.org/10.1101/2021.09.01.21262957>.
- 283 5. Pegu A, O'Connell SE, Schmidt SD, O'Dell S, Talana CA, Lai L, Albert J, Anderson E, Bennett H,
 284 Corbett KS, Flach B, Jackson L, Leav B, Ledgerwood JE, Luke CJ, Makowski M, Nason MC, Roberts
 285 PC, Roederer M, Rebolledo PA, Rostad CA, Roupheal NG, Shi W, Wang L, Widge AT, Yang ES,
 286 Beigel JH, Graham BS, Mascola JR, Suthar MS, McDermott AB, Doria-Rose NA, Arega J, Beigel JH,
 287 Buchanan W, Elsafty M, Hoang B, Lampley R, Kolhekar A, Koo H, Luke C, Makhene M, Nayak S,
 288 Pikaart-Tautges R, Roberts PC, Russell J, Sindall E, Albert J, Kunwar P, Makowski M, et al. 2021.
 289 Durability of mRNA-1273 vaccine-induced antibodies against SARS-CoV-2 variants. *Science*
 290 373:1372-1377.
- 291 6. Sahin U, Muik A, Derhovanessian E, Vogler I, Kranz LM, Vormehr M, Baum A, Pascal K, Quandt J,
 292 Maurus D, Brachtendorf S, Lorks V, Sikorski J, Hilker R, Becker D, Eller AK, Grutzner J, Boesler C,
 293 Rosenbaum C, Kuhnle MC, Luxemburger U, Kemmer-Bruck A, Langer D, Bexon M, Bolte S, Kariko
 294 K, Palanche T, Fischer B, Schultz A, Shi PY, Fontes-Garfias C, Perez JL, Swanson KA, Loschko J,
 295 Scully IL, Cutler M, Kalina W, Kyrtatsous CA, Cooper D, Dormitzer PR, Jansen KU, Tureci O. 2020.
 296 COVID-19 vaccine BNT162b1 elicits human antibody and TH1 T cell responses. *Nature* 586:594-
 297 599.
- 298 7. Corbett KS, Flynn B, Foulds KE, Francica JR, Boyoglu-Barnum S, Werner AP, Flach B, O'Connell S,
 299 Bock KW, Minai M, Nagata BM, Andersen H, Martinez DR, Noe AT, Douek N, Donaldson MM, Nji
 300 NN, Alvarado GS, Edwards DK, Flebbe DR, Lamb E, Doria-Rose NA, Lin BC, Louder MK, O'Dell S,
 301 Schmidt SD, Phung E, Chang LA, Yap C, Todd JM, Pessaint L, Van Ry A, Browne S, Greenhouse J,
 302 Putman-Taylor T, Strasbaugh A, Campbell TA, Cook A, Dodson A, Steingrebe K, Shi W, Zhang Y,
 303 Abiona OM, Wang L, Pegu A, Yang ES, Leung K, Zhou T, Teng IT, Widge A, et al. 2020. Evaluation
 304 of the mRNA-1273 Vaccine against SARS-CoV-2 in Nonhuman Primates. *N Engl J Med* 383:1544-
 305 1555.
- 306 8. Earle KA, Ambrosino DM, Fiore-Gartland A, Goldblatt D, Gilbert PB, Siber GR, Dull P, Plotkin SA.
 307 2021. Evidence for antibody as a protective correlate for COVID-19 vaccines. *Vaccine* 39:4423-
 308 4428.
- 309 9. Khoury DS, Cromer D, Reynaldi A, Schlub TE, Wheatley AK, Juno JA, Subbarao K, Kent SJ, Triccas
 310 JA, Davenport MP. 2021. Neutralizing antibody levels are highly predictive of immune protection
 311 from symptomatic SARS-CoV-2 infection. *Nat Med* 27:1205-1211.

- 312 10. Cho A, Muecksch F, Schaefer-Babajew D, Wang Z, Finkin S, Gaebler C, Ramos V, Cipolla M,
313 Mendoza P, Agudelo M, Bednarski E, DaSilva J, Shimeliovich I, Dizon J, Daga M, Millard K, Turroja
314 M, Schmidt F, Zhang F, Tanfous TB, Jankovic M, Oliveria TY, Gazumyan A, Caskey M, Bieniasz PD,
315 Hatzioannou T, Nussenzweig MC. 2021. Anti-SARS-CoV-2 receptor binding domain antibody
316 evolution after mRNA vaccination. *Nature* doi:10.1038/s41586-021-04060-7.
- 317 11. Dan JM, Mateus J, Kato Y, Hastie KM, Yu ED, Faliti CE, Grifoni A, Ramirez SI, Haupt S, Frazier A,
318 Nakao C, Rayaprolu V, Rawlings SA, Peters B, Krammer F, Simon V, Sapphire EO, Smith DM,
319 Weiskopf D, Sette A, Crotty S. 2021. Immunological memory to SARS-CoV-2 assessed for up to 8
320 months after infection. *Science* 371.
- 321 12. Sette A, Crotty S. 2021. Adaptive immunity to SARS-CoV-2 and COVID-19. *Cell* 184:861-880.
- 322 13. Vanshylla K, Di Cristanziano V, Kleipass F, Dewald F, Schommers P, Giesemann L, Gruell H,
323 Schlott M, Ercanoglu MS, Stumpf R, Mayer P, Zehner M, Heger E, Johannis W, Horn C, Suarez I,
324 Jung N, Salomon S, Eberhardt KA, Gathof B, Fatkenheuer G, Pfeifer N, Eggeling R, Augustin M,
325 Lehmann C, Klein F. 2021. Kinetics and correlates of the neutralizing antibody response to SARS-
326 CoV-2 infection in humans. *Cell Host Microbe* 29:917-929 e4.
- 327 14. Goel RR, Painter MM, Apostolidis SA, Mathew D, Meng W, Rosenfeld AM, Lundgreen KA,
328 Reynaldi A, Houry DS, Pattekar A, Gouma S, Kuri-Cervantes L, Hicks P, Dysinger S, Hicks A,
329 Sharma H, Herring S, Korte S, Baxter AE, Oldridge DA, Giles JR, Weirick ME, McAllister CM,
330 Awofolaju M, Tanenbaum N, Drapeau EM, Dougherty J, Long S, D'Andrea K, Hamilton JT,
331 McLaughlin M, Williams JC, Adamski S, Kuthuru O, Frank I, Betts MR, Vella LA, Grifoni A,
332 Weiskopf D, Sette A, Hensley SE, Davenport MP, Bates P, Luning Prak ET, Greenplate AR, Wherry
333 EJ, Adamski S, Alam Z, Addison MM, Byrne KT, et al. 2021. mRNA vaccines induce durable
334 immune memory to SARS-CoV-2 and variants of concern. *Science*
335 doi:10.1126/science.abm0829:eabm0829.
- 336 15. Goel RR, Apostolidis SA, Painter MM, Mathew D, Pattekar A, Kuthuru O, Gouma S, Hicks P, Meng
337 W, Rosenfeld AM, Dysinger S, Lundgreen KA, Kuri-Cervantes L, Adamski S, Hicks A, Korte S,
338 Oldridge DA, Baxter AE, Giles JR, Weirick ME, McAllister CM, Dougherty J, Long S, D'Andrea K,
339 Hamilton JT, Betts MR, Luning Prak ET, Bates P, Hensley SE, Greenplate AR, Wherry EJ. 2021.
340 Distinct antibody and memory B cell responses in SARS-CoV-2 naive and recovered individuals
341 following mRNA vaccination. *Sci Immunol* 6.
- 342 16. Wang Z, Muecksch F, Schaefer-Babajew D, Finkin S, Viant C, Gaebler C, Hoffmann HH, Barnes
343 CO, Cipolla M, Ramos V, Oliveira TY, Cho A, Schmidt F, Da Silva J, Bednarski E, Aguado L, Yee J,
344 Daga M, Turroja M, Millard KG, Jankovic M, Gazumyan A, Zhao Z, Rice CM, Bieniasz PD, Caskey
345 M, Hatzioannou T, Nussenzweig MC. 2021. Naturally enhanced neutralizing breadth against
346 SARS-CoV-2 one year after infection. *Nature* 595:426-431.
- 347 17. Gazit S, Shlezinger R, Perez G, Lotan R, Peretz A, Ben-Tov A, Cohen D, Muhsen K, Chodick G,
348 Patalon T. 2021. Comparing SARS-CoV-2 natural immunity to vaccine-induced immunity:
349 reinfections versus breakthrough infections. *medRxiv*
350 doi:<https://doi.org/10.1101/2021.08.24.21262415>.
- 351 18. Bozio CH, Grannis SJ, Naleway AL, Ong TC, Butterfield KA, DeSilva MB, Natarajan K, Yang DH, Rao
352 S, Klein NP, Irving SA, Dixon BE, Dascomb K, Liao IC, Reynolds S, McEvoy C, Han J, Reese SE, Lewis
353 N, Fadel WF, Grisel N, Murthy K, Ferdinands J, Kharbanda AB, Mitchell PK, Goddard K, Embi PJ,
354 Arndorfer J, Raiyani C, Patel P, Rowley EA, Fireman B, Valvi NR, Griggs EP, Levy ME, Zerbo O,
355 Porter RM, Birch RJ, Blanton L, Ball SW, Steffens A, Olson N, Williams J, Dickerson M, Mc Morrow
356 M, Schrag SJ, Verani JR, Fry AM, Azziz-Baumgartner E, Barron M, et al. 2021. Laboratory-
357 Confirmed COVID-19 Among Adults Hospitalized with COVID-19-Like Illness with Infection-
358 Induced or mRNA Vaccine-Induced SARS-CoV-2 Immunity - Nine States, January-September
359 2021. *MMWR Morb Mortal Wkly Rep* 70:1539-1544.

- 360 19. Lau EHY, Tsang OTY, Hui DSC, Kwan MYW, Chan W-h, Chiu SS, Ko RLW, Chan KH, Cheng SMS,
361 Perera RAPM, Cowling BJ, Poon LLM, Peiris M. 2021. Neutralizing antibody titres in SARS-CoV-2
362 infections. *Nature Communications* 12:63.
- 363 20. Tarke A, Sidney J, Methot N, Yu ED, Zhang Y, Dan JM, Goodwin B, Rubiro P, Sutherland A, Wang
364 E, Frazier A, Ramirez SI, Rawlings SA, Smith DM, da Silva Antunes R, Peters B, Scheuermann RH,
365 Weiskopf D, Crotty S, Grifoni A, Sette A. 2021. Impact of SARS-CoV-2 variants on the total CD4(+) and CD8(+) T cell reactivity in infected or vaccinated individuals. *Cell Rep Med* 2:100355.
- 366 21. Cohen KW, Linderman SL, Moodie Z, Czartoski J, Lai L, Mantus G, Norwood C, Nyhoff LE, Edara
367 VV, Floyd K, De Rosa SC, Ahmed H, Whaley R, Patel SN, Prigmore B, Lemos MP, Davis CW, Furth
368 S, O'Keefe JB, Gharpure MP, Gunisetty S, Stephens K, Antia R, Zarnitsyna VI, Stephens DS,
369 Edupuganti S, Roupael N, Anderson EJ, Mehta AK, Wrammert J, Suthar MS, Ahmed R, McElrath
370 MJ. 2021. Longitudinal analysis shows durable and broad immune memory after SARS-CoV-2
371 infection with persisting antibody responses and memory B and T cells. *Cell Rep Med* 2:100354.
- 372 22. Townsend JP, Hassler HB, Wang Z, Miura S, Singh J, Kumar S, Ruddie NH, Galvani AP, Dornburg
373 A. 2021. The durability of immunity against reinfection by SARS-CoV-2: a comparative
374 evolutionary study. *Lancet Microbe* doi:10.1016/s2666-5247(21)00219-6.
- 375 23. Romano CM, Felix AC, Paula AV, Jesus JG, Andrade PS, Candido D, Oliveira FM, Ribeiro AC, Silva
376 FCD, Inemami M, Costa AA, Leal COD, Figueiredo WM, Pannuti CS, Souza WM, Faria NR, Sabino
377 EC. 2021. SARS-CoV-2 reinfection caused by the P.1 lineage in Araraquara city, Sao Paulo State,
378 Brazil. *Rev Inst Med Trop Sao Paulo* 63:e36.
- 379 24. Kuzmina A, Khalaila Y, Voloshin O, Keren-Naus A, Boehm-Cohen L, Raviv Y, Shemer-Avni Y,
380 Rosenberg E, Taube R. 2021. SARS-CoV-2 spike variants exhibit differential infectivity and
381 neutralization resistance to convalescent or post-vaccination sera. *Cell Host Microbe* 29:522-528
382 e2.
- 383 25. Abu-Raddad LJ, Chemaitelly H, Butt AA, National Study Group for C-V. 2021. Effectiveness of the
384 BNT162b2 Covid-19 Vaccine against the B.1.1.7 and B.1.351 Variants. *N Engl J Med* 385:187-189.
- 385 26. Kamar N, Abravanel F, Marion O, Couat C, Izopet J, Del Bello A. 2021. Three Doses of an mRNA
386 Covid-19 Vaccine in Solid-Organ Transplant Recipients. *N Engl J Med* 385:661-662.
- 387 27. Eyre DW, Taylor D, Purver M, Chapman D, Fowler T, Pouwels KB, Walker AS, Peto TEA. 2021. The
388 impact of SARS-CoV-2 vaccination on Alpha & Delta variant transmission. *medRxiv*
389 doi:<https://doi.org/10.1101/2021.09.28.21264260>.
- 390 28. Chia PY, Ong SWX, Chiew CJ, Ang LW, Chavatte JM, Mak TM, Cui L, Kalimuddin S, Chia WN, Tan
391 CW, Chai LYA, Tan SY, Zheng S, Lin RTP, Wang L, Leo YS, Lee VJ, Lye DC, Young BE. 2021.
392 Virological and serological kinetics of SARS-CoV-2 Delta variant vaccine-breakthrough infections:
393 a multi-center cohort study. *medRxiv* doi:<https://doi.org/10.1101/2021.07.28.21261295>.
- 394 29. Shamier MC, Tostmann A, Bogers S, de Wilde J, Ijpelaar J, van der Kleij WA, de Jager H,
395 Haagmans BL, Molenkamp R, Munnink BBO, van Rossum C, Rahamat-Langendoen J, van der
396 Geest N, Bleeker-Rovers CP, Wertheim H, Koopmans MPG, GeurtsvanKessel CH. 2021.
397 Virological characteristics of SARS-CoV-2 vaccine breakthrough infections in health care workers.
398 *medRxiv* doi:<https://doi.org/10.1101/2021.08.20.21262158>.
- 399 30. Singanayagam A, Hakki S, Dunning J, Madon KJ, Crone MA, Koycheva A, Derqui-Fernandez N,
400 Barnett JL, Whitfield MG, Varro R, Charlett A, Kundu R, Fenn J, Cutajar J, Quinn V, Conibear E,
401 Barclay W, Freemont PS, Taylor GP, Ahmad S, Zambon M, Ferguson NM, Lalvani A, Badhan A,
402 Dustan S, Tejpal C, Ketkar AV, Narean JS, Hammett S, McDermott E, Pillay T, Houston H, Luca C,
403 Samuel J, Bremang S, Evetts S, Poh J, Anderson C, Jackson D, Miah S, Ellis J, Lackenby A.
404 Community transmission and viral load kinetics of the SARS-CoV-2 delta (B.1.617.2) variant in
405 vaccinated and unvaccinated individuals in the UK: a prospective, longitudinal, cohort study. *The*
406 *Lancet Infectious Diseases* doi:10.1016/S1473-3099(21)00648-4.
- 407

- 408 31. Neidleman J, Luo X, McGregor M, Xie G, Murray V, Greene WC, Lee SA, Roan NR. 2021. mRNA
409 vaccine-induced T cells respond identically to SARS-CoV-2 variants of concern but differ in
410 longevity and homing properties depending on prior infection status. *Elife* 10.
- 411 32. Saif LJ. 2020. Vaccines for COVID-19: perspectives, prospects, and challenges based on candidate
412 SARS, MERS, and animal coronavirus vaccines. *Eur Med J* doi:10.33590/emj/200324.
- 413 33. Bar-On YM, Goldberg Y, Mandel M, Bodenheimer O, Freedman L, Kalkstein N, Mizrahi B, Alroy-
414 Preis S, Ash N, Milo R, Huppert A. 2021. Protection of BNT162b2 Vaccine Booster against Covid-
415 19 in Israel. *N Engl J Med* 385:1393-1400.
- 416 34. Bensouna I, Caudwell V, Kubab S, Acquaviva S, Pardon A, Vittoz N, Bozman DF, Hanafi L, Faucon
417 AL, Housset P. 2021. SARS-CoV-2 Antibody Response After a Third Dose of the BNT162b2
418 Vaccine in Patients Receiving Maintenance Hemodialysis or Peritoneal Dialysis. *Am J Kidney Dis*
419 doi:10.1053/j.ajkd.2021.08.005.
- 420 35. Bertrand D, Hamzaoui M, Lemée V, Lamulle J, Laurent C, Etienne I, Lemoine M, Lebourg L, Hanoy
421 M, Le Roy F, Nezam D, Farce F, Plantier JC, Boyer O, Guerrot D, Candon S. 2021. Antibody and T-
422 cell response to a third dose of SARS-CoV-2 mRNA BNT162b2 vaccine in kidney transplant
423 recipients. *Kidney Int* doi:10.1016/j.kint.2021.09.014.
- 424 36. Flaxman A, Marchevsky NG, Jenkin D, Aboagye J, Aley PK, Angus B, Belij-Rammerstorfer S, Bibi S,
425 Bittaye M, Cappuccini F, Cicconi P, Clutterbuck EA, Davies S, Dejnirattisai W, Dold C, Ewer KJ,
426 Folegatti PM, Fowler J, Hill AVS, Kerridge S, Minassian AM, Mongkolsapaya J, Mujadidi YF,
427 Pledsted E, Ramasamy MN, Robinson H, Sanders H, Sheehan E, Smith H, Snape MD, Song R,
428 Woods D, Srean G, Gilbert SC, Voysey M, Pollard AJ, Lambe T. 2021. Reactogenicity and
429 immunogenicity after a late second dose or a third dose of ChAdOx1 nCoV-19 in the UK: a
430 substudy of two randomised controlled trials (COV001 and COV002). *Lancet* 398:981-990.
- 431 37. Peled Y, Ram E, Lavee J, Segev A, Matezki S, Wieder-Finesod A, Halperin R, Mandelboim M,
432 Indenbaum V, Levy I, Sternik L, Raanani E, Afek A, Kreiss Y, Lustig Y, Rahav G. 2021. Third dose of
433 the BNT162b2 vaccine in heart transplant recipients: Immunogenicity and clinical experience. *J*
434 *Heart Lung Transplant* doi:10.1016/j.healun.2021.08.010.
- 435 38. Sadarangani M, Marchant A, Kollmann TR. 2021. Immunological mechanisms of vaccine-induced
436 protection against COVID-19 in humans. *Nature Reviews Immunology* 21:475-484.
- 437 39. Atmar RL, Lyke KE, Deming ME, Jackson LA, Branche AR, El Sahly HM, Rostad CA, Martin JM,
438 Johnston C, Rupp RE, Mulligan MJ, Brady RC, Frenck RW, Bäcker M, Kottkamp AC, Babu TM,
439 Rajakumar K, Edupuganti S, Dobryzynski D, Posavad CM, Archer JI, Crandon S, Nayak SU, Szydlo
440 D, Zemanek J, Islas CPD, Brown ER, Suthar MS, McElrath MJ, McDermott AB, O'Connell SE,
441 Montefiori DC, Eaton A, Neuzil KM, Stephens DS, Roberts PC, Beigel JH. 2021. Heterologous
442 SARS-CoV-2 Booster Vaccinations - Preliminary Report. *medRxiv*
443 doi:10.1101/2021.10.10.21264827.
- 444 40. Yang S, Li Y, Dai L, Wang J, He P, Li C, Fang X, Wang C, Zhao X, Huang E, Wu C, Zhong Z, Wang F,
445 Duan X, Tian S, Wu L, Liu Y, Luo Y, Chen Z, Li F, Li J, Yu X, Ren H, Liu L, Meng S, Yan J, Hu Z, Gao L,
446 Gao GF. 2021. Safety and immunogenicity of a recombinant tandem-repeat dimeric RBD-based
447 protein subunit vaccine (ZF2001) against COVID-19 in adults: two randomised, double-blind,
448 placebo-controlled, phase 1 and 2 trials. *Lancet Infect Dis* 21:1107-1119.
- 449 41. Yue L, Xie T, Yang T, Zhou J, Chen H, Zhu H, Li H, Xiang H, Wang J, Yang H, Zhao H, Wei X, Zhang
450 Y, Xie Z. 2021. A third booster dose may be necessary to mitigate neutralizing antibody fading
451 after inoculation with two doses of an inactivated SARS-CoV-2 vaccine. *J Med Virol*
452 doi:10.1002/jmv.27334.
- 453 42. Benotmane I, Gautier G, Perrin P, Olagne J, Cognard N, Fafi-Kremer S, Caillard S. 2021. Antibody
454 Response After a Third Dose of the mRNA-1273 SARS-CoV-2 Vaccine in Kidney Transplant
455 Recipients With Minimal Serologic Response to 2 Doses. *Jama* 326:1063-5.

- 456 43. Corbett KS, Gagne M, Wagner DA, S OC, Narpala SR, Flebbe DR, Andrew SF, Davis RL, Flynn B,
457 Johnston TS, Stringham CD, Lai L, Valentin D, Van Ry A, Flinchbaugh Z, Werner AP, Moliva JI,
458 Sriparna M, O'Dell S, Schmidt SD, Tucker C, Choi A, Koch M, Bock KW, Minai M, Nagata BM,
459 Alvarado GS, Henry AR, Laboune F, Schramm CA, Zhang Y, Yang ES, Wang L, Choe M, Boyoglu-
460 Barnum S, Wei S, Lamb E, Nurmukhambetova ST, Provost SJ, Donaldson MM, Marquez J, Todd
461 JM, Cook A, Dodson A, Pekosz A, Boritz E, Ploquin A, Doria-Rose N, Pessaint L, Andersen H, et al.
462 2021. Protection against SARS-CoV-2 beta variant in mRNA-1273 vaccine-boosted nonhuman
463 primates. *Science* doi:10.1126/science.abl8912:eabl8912.
- 464 44. Deng Y, Li Y, Yang R, Tan W. 2021. SARS-CoV-2-specific T cell immunity to structural proteins in
465 inactivated COVID-19 vaccine recipients. *Cell Mol Immunol* 18:2040-2041.
- 466 45. Hause AM, Baggs J, Gee J, Marquez P, Myers TR, Shimabukuro TT, Shay DK. 2021. Safety
467 Monitoring of an Additional Dose of COVID-19 Vaccine - United States, August 12-September 19,
468 2021. *MMWR Morb Mortal Wkly Rep* 70:1379-1384.
- 469 46. Shapiro Ben David S, Shamir-Stein N, Baruch Gez S, Lerner U, Rahamim-Cohen D, Ekka Zohar A.
470 2021. Reactogenicity of a third BNT162b2 mRNA COVID-19 vaccine among
471 immunocompromised individuals and seniors - A nationwide survey. *Clin Immunol* 232:108860.
- 472 47. Tam YH, Valkenburg SA, Perera R, Wong JHF, Fang VJ, Ng TWY, Kwong ASK, Tsui WWS, Ip DKM,
473 Poon LLM, Chau CKV, Barr IG, Peiris JSM, Cowling BJ. 2018. Immune Responses to Twice-Annual
474 Influenza Vaccination in Older Adults in Hong Kong. *Clin Infect Dis* 66:904-912.
- 475 48. Anderson RM, May RM. 1985. Vaccination and herd immunity to infectious diseases. *Nature*
476 318:323-329.
- 477 49. Hethcote HW. 2000. The Mathematics of Infectious Diseases. *SIAM Review* 42:599-653.
- 478 50. Dagpunar J. 2021. Interim estimates of increased transmissibility, growth rate, and reproduction
479 number of the Covid-19 B.1.617.2 variant of concern in the United Kingdom. *medRxiv*
480 doi:10.1101/2021.06.03.21258293:2021.06.03.21258293.
- 481 51. Hacisuleyman E, Hale C, Saito Y, Blachere NE, Bergh M, Conlon EG, Schaefer-Babajew DJ, DaSilva
482 J, Muecksch F, Gaebler C, Lifton R, Nussenzweig MC, Hatzioannou T, Bieniasz PD, Darnell RB.
483 2021. Vaccine Breakthrough Infections with SARS-CoV-2 Variants. *New England Journal of*
484 *Medicine* 384:2212-2218.
- 485 52. Babiker A, Marvil CE, Waggoner JJ, Collins MH, Piantadosi A. 2021. The Importance and
486 Challenges of Identifying SARS-CoV-2 Reinfections. *J Clin Microbiol* 59.
- 487 53. Irons NJ, Raftery AE. 2021. Estimating SARS-CoV-2 infections from deaths, confirmed cases,
488 tests, and random surveys. *Proc Natl Acad Sci U S A* 118.
- 489 54. Ashwanden C. 2021. Five reasons why COVID herd immunity is probably impossible. *Nature*
490 591:520-522.

491