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Krause, P. R., Fleming, T. R., Peto, R., Longini, I. M., Figueroa, J. P., Sterne, J. A. C., Cravioto, A., Rees, H., Higgins, J. P. T., Boutron, I., Pan, H., Gruber, M. F., Arora, N., Kazi, F., Gaspar, R., Swaminathan, S., Ryan, M. J., & Henao-Restrepo, A.-M. (2021). Considerations in boosting COVID-19 vaccine immune responses. *Lancet*, *398*(10308), 1377-1380. https://doi.org/10.1016/S0140-6736(21)02046-8

Peer reviewed version

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10.1016/S0140-6736(21)02046-8

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Considerations in boosting COVID vaccine immune responses

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Summary: While most data are preliminary and difficult to interpret due to potential confounding in the observational studies used to obtain them, these reports indicate that COVID vaccines continue to be efficacious over time against severe disease, including that caused by the delta variant. Careful and public scrutiny of evolving data will be needed to assure that decisions about boosting are informed by science instead of politics. Even if boosting were ultimately shown to have marginal benefit, existing doses of vaccine could save many more lives if made available to people who have not yet been immunized than if used for uncertain benefit as boosters.

As a new wave of COVID cases caused by the highly transmissible delta variant is exacerbating the worldwide public health crisis, this new wave has led to consideration of the potential need for and optimal timing of booster doses for previously vaccinated recipients [1]. While the idea of further reducing the number of COVID cases by enhancing immunity in those previously vaccinated is appealing, any decision to do so should be evidence-based in the context of benefits and risks for individuals and society.

Boosting might ultimately be needed in the general population because of waning immunity to the primary vaccination (defined as the original one- or two-dose series of each vaccine) or because variants have evolved to the point where immune responses to the original vaccine antigens no longer adequately protect against circulating viruses. Boosting may also be justified for certain individuals in whom the primary vaccination series likely did not induce adequate protection, as may occur in the immunocompromised [2] or in recipients of vaccines with low efficacy. One concern is that people who do not respond well to the primary vaccination series may also not respond well to a booster. It is not known whether these individuals would receive more benefit from an additional dose of the same vaccine vs. an additional dose of a different vaccine that may boost and complement the primary immune response.

There may, however, be risks if boosters are widely introduced too soon, or too frequently, especially with vaccines that can have immune-mediated vaccine side-effects (such as myocarditis, which is more common after the second dose of some mRNA vaccines [3], or Guillain-Barre syndrome (GBS), which has been associated with adenovirus-vectored COVID vaccines) [5]. If unnecessary boosting causes significant adverse reactions, this could have implications for vaccine acceptance that goes beyond COVID vaccines. Thus, boosting should be done only if there is clear evidence that it is appropriate.

Current data do not support a need for boosting in the general population. For example immune parameters after vaccination with an adenovirus vectored vaccine are durable over 8 months [6]. Even where humoral immunity appears to wane, reductions in neutralizing antibody titer do not necessarily predict vaccine efficacy over time, and reductions in vaccine efficacy against mild disease do not necessarily predict reductions in typically much higher efficacy against severe disease (see Figures 1 and 2). This could well be because protection against severe disease is partly mediated by memory responses and cell-mediated immunity, which are longer-lived [7] and not assessed by antibody tests. Increasing success in delivering vaccines will inevitably lead to increasing numbers of breakthrough cases, especially if vaccination leads to behavioral changes in vaccinees, even without any changes in vaccine efficacy.

The ability of current vaccines (which present the antigens of earlier phases of the pandemic rather than variant-specific antigens) to boost immune responses against circulating variants[8 9], indicates that these variants have not yet evolved to the point where they are likely to escape the memory immune responses induced by those vaccines. Figure 1 summarizes recently reported vaccine efficacy against variants. Many of these studies have not yet undergone peer review, so some may not be reliable, but together they provide a partial but useful snapshot of the changing situation. It appears that while the efficacy of most vaccines against symptomatic disease caused by the delta variant is somewhat less than that against earlier variants, the reports to date are consistent with reasonably high vaccine efficacy against severe infections or hospitalization with the delta variant.

There are significant challenges in estimating vaccine efficacy based on observational studies conducted in the context of rapid vaccine rollout. Estimates may be confounded by both by patient characteristics at the start of the rollout and by time-varying factors that are incompletely recorded in electronic health records. For example, unvaccinated control groups may include some vaccinated individuals as well as people who are already protected due to previous infection or may include people whose vaccination was deferred due to symptoms consistent with COVID-19. The likelihood that there are systemic differences between vaccinated and unvaccinated people increases as more people get vaccinated. Apparent reduced efficacy among people immunized at the beginning of the pandemic could arise because individuals at higher risk were prioritized for early immunization. More of the severe infections in vaccinees may be in immunocompromised individuals, who are plausibly more likely to be offered and seek vaccination even though efficacy is lower[2]. The probability that individuals with asymptomatic or mild infection seek testing is likely also influenced by whether they are vaccinated. Vaccine coverage influences the risk that vaccinees that will be exposed to virus by the unvaccinated, further confounding evaluation of efficacy. In addition, outcomes may be affected over time by varying stress on health care facilities. Observational studies that examine efficacy against severe disease are less likely to be affected by diagnosis-dependent biases over time and should therefore provide more reliable indicators of changes in vaccine-induced protection. Thus, evidence of waning protection against severe disease will provide the clearest indication that a booster is needed.

To date, no studies have provided credible evidence of declining protection against severe disease, which is also the primary goal of vaccination. Figure 2 shows studies that have reported vaccine efficacy over time. Of note, even where there appear to be declines over time in vaccine efficacy against symptomatic disease, efficacy against severe disease is not appreciably reduced. In a single study in Minnesota[10], point estimates of efficacy of mRNA vaccines against hospitalization appeared lower in July 2021 than in January-July, but these estimates had wide confidence intervals and may have been affected by some of the issues described above. Of interest, reported effectiveness against severe disease in Israel was lower among people who received vaccines in January vs. those who received vaccines in February or March, but effectiveness in those vaccinated in April was similar to those vaccinated in January [11], exemplifying the difficulty of interpreting time-variable data with so many potential confounders.

Even vaccines that are highly effective against severe disease do not prevent asymptomatic disease or transmission from infected people. Nevertheless, even in populations with high vaccination rates, it is still the unvaccinated who are the major drivers of transmission and at the highest risk of serious disease[12].

If new variants that can escape the current vaccines are going to evolve, they are most likely to do so from strains that had already become widely prevalent. The effectiveness of boosting against the main variants now circulating and against even newer variants could well be greater and longer-lived if the booster vaccine antigen is chosen to match the main circulating strains [8]. Thus, if boosters are ultimately to be widely used, it would be preferable to have had them developed to match the main currently circulating variants. There is an opportunity now to study variant-based boosters before there is widespread need for them. A similar strategy is used for influenza vaccines, where each annual vaccine is based on the most current data about circulating strains to increase the likelihood that the vaccine will remain effective even if there is further strain evolution.

The message that boosting may soon be needed, if not justified by robust data and analysis, could adversely affect confidence in vaccines and undermine messaging about the value of primary vaccination. Public health authorities will also need to consider carefully the consequences for primary vaccination campaigns of endorsing boosters only for selected vaccines. Booster programs that affect some but not all vaccinees may be difficult to implement—so it will be important to base recommendations on complete data about all vaccines available in a country, to consider the logistics of vaccination and to develop clear public health messaging before boosting is widely recommended.

If boosters (whether they express original or variant antigens) are ultimately to be used, it would be wise to deploy them in limited circumstances where the direct and indirect benefits of doing so are, on balance, clearly beneficial. Additional research could help in defining these circumstances. Furthermore, given the robust booster responses reported for some vaccines, adequate booster responses might be achievable at lower doses, potentially with reduced safety concerns. Given the data gaps, it would be unwise to deploy boosters widely without a plan to gather reliable data about how well they are working and how safe they are. Their effectiveness and safety could, in some populations, be assessed most reliably during deployment via extremely large- scale randomization[13] allocating the order of booster vaccinations over time to either individuals or to randomly chosen groups of people.

Thus, any decisions about the need for or timing of boosting should be based on careful analyses of adequately controlled clinical and/or epidemiological data indicating a meaningful reduction in vaccine efficacy against severe disease, together with evidence about whether a specific boosting regimen is likely to be safe and effective against currently circulating variants. As more data become available, they may first provide evidence that boosting is needed in certain subpopulations. However, these high-stakes decisions should be made based on peer-reviewed and publicly available data and only after robust international scientific discussion.

The vaccines that are currently available are safe, effective, and save lives. The limited supply of these vaccines will save the most lives if made available to people who are at appreciable risk of serious disease and have not yet received any vaccine. Even if marginal gains can ultimately be obtained from boosting, this will not outweigh the benefits of providing initial protection to the unvaccinated. If they are deployed where they would do the most good, vaccines could also hasten the end of the pandemic by inhibiting further evolution of variants. Indeed, the WHO has called for a moratorium on boosting until the benefits of primary vaccination have been made available to more people around the world[14]. This is a compelling moral issue, particularly because the currently available evidence does not currently justify widespread use of booster vaccines in people who have received an effective primary regimen.

Search strategy and selection criteria

We included all studies reported in English that reported (for Fig. 1) vaccine efficacy or effectiveness against the delta variant or for Fig. 2, vaccine efficacy or effectiveness in a time-dependent manner. We considered all studies indexed by the COVID-NMA initiative[15], those referenced by experts tasked with summarizing these data at a WHO meeting on August 13, 2021[16] and all studies referenced by the US Centers for Disease Control in presentations to the Advisory Committee on Immunization Practices on August 13, 2021[17]. No studies were excluded.

Funding sources:

JPTH is a National Institute for Health Research (NIHR) Senior Investigator (NF-SI-0617-10145), is supported by *NIHR Bristol Biomedical Research Centre at University Hospitals Bristol and Weston NHS Foundation Trust and the University of Bristol*, and is supported by the *NIHR Applied Research Collaboration West (ARC West) at University Hospitals Bristol and Weston NHS Foundation Trust*.

JACS is supported by the NIHR Bristol Biomedical Research Centre at University Hospitals Bristol and Weston NHS Foundation Trust and the University of Bristol, Health Data Research UK South West, the Longitudinal Health and Wellbeing COVID-19 National Core Study, and grant funding from UK Research and Innovation and the National Institute for Health Research.

IL is partially supported by National Institutes of Health (NIH)/National Institute of Allergy and Infectious Diseases (NIAID) grants ‘‘Design and Analysis of Vaccine Trials for Emerging Infectious Disease Threats’’ (R01 AI 139761) and “Mathematical and Statistical Methods for the Control of Global Infectious Disease Threats” (R56 AI1 48284)

TRF is supported by National Institutes of Health (NIH)/National Institute of Allergy and Infectious Diseases (NIAID) grant entitled, ‘‘Statistical Issues in AIDS Research’’ (R37 AI 29168)

Conflict of interest statement: The authors declare no conflicts of interest.

Contributions: All authors agree with the viewpoints expressed in the article, and contributed equally to conceptualisation, analysis, review and editing. The original draft was written by Dr. Krause. Data verification was performed by Drs. Kazi, Higgins, Boutron and Krause.

Vaccine	RCT or Observational Study (OS)	Study Location	Variant addressed	Effectiveness vs. severe disease or hospitalization	Effectiveness vs. symptomatic disease or infection (i)
BBV152	RCT Ph3	India [18]*	All Delta	93.4% (57-100)	77.8% (50-84) 65.2% (33-83)
BNT162b2	OS	UK [19]	Alpha delta		93.7% (92-95) 88% (85-90)
	OS	Qatar [20]	All Alpha Beta	97.4% (92.2-99.5)	 89.5% (86-92) (i) 75% (71-79) (i)
	OS	Qatar [21]	Delta	89.7% (61-98)	53.5% (44-61) (i)
	OS	Scotland [22]	Alpha Delta		92% (88-94) 83% (78-87)
	OS	Canada [23]	Alpha Beta/gamma Delta	95% (92-97) 95% (81-99) ^	89% (86-91) 84% (69-92) 87% (64-95)
	OS	Israel [24]	Mostly alpha	97.5% (97.1-97.8)	95.3% (94.9-95.7) (i)
	OS	Israel [11]	Mostly delta	91.4%	40.5%
	OS	UK[25]	Mostly alpha Mostly delta		78% (68-84) (i) 82% (79-85) (i)
mRNA-1273	OS	Canada [23]	Alpha Delta	94% (89-97) ^	92% (86-96)
	OS	Qatar [26]	All Alpha Beta	95.7% (73-100)	 100% (92-100) (i) 96.4% (92-99) (i)
	OS	Qatar [21]	Delta	100% (41-100)	84.8% (76-91) (i)
Ad26.COV2.S	RCT Ph3	Worldwide [27]	All Beta	83.5% (54-97) 81.7% (46-95)	66.5% (56-75) 64% (41-79)
	Press release	South Africa [28]	Beta Delta	67% 71%	
ChadOx1 nCoV-19	OS	UK [19]	Alpha Delta		74.5% (68-79) 67% (61-72)
	OS	Scotland [22]	Alpha Delta		81% (72-87) 61% (51-70)
	OS	Canada [23]	Alpha Beta/gamma Delta	85% (81-88)# 83% (66-92)# 88% (60-96%)#	64% (60-68)# 83% (66-92)# 67% (44-80)#
	OS	South Africa [29]	Beta		10.4% (-76- 55)
	OS	India [30]	Mostly delta	95% (44-100)	64% (38-78)
	OS	India [31]	Mostly delta	81.5% (10-99)	63.1% (52-72) (i)
	OS	UK[25]	Mostly alpha Mostly delta		79%(56-90) (i) 67% (62-=72) (i)
NVX-CoV2373	RCT Phase 2a/b	South Africa[32]	Beta		51% (-1 – 76)

	RCT	UK[33]	Alpha		86.3% (71-94)
Coronavac and China National Biotec	OS	China[34]	Delta	100%	59% (16-82)
Gam-COVID-Vac	OS	Russia[35]	Mostly delta	81% (68-88)	

#Single dose only;

^Insufficient data for two doses. Single dose efficacy comparable between delta and alpha

Table 1. Reported Efficacy in Studies addressing variants.

Vaccine developer	RCT or Observational Study (OS)	Location	Time period	Effectiveness against severe disease or hospitalization	Effectiveness against symptomatic or all disease
Pfizer BNT162b2	RCT	Multinational (mostly US) [36]	6 months	97% (80-100)	91% (89-93) #
	OS	Minnesota US [10]	Jan-July July (>70% delta)	85% (73-93) 75% (24-94)	76% (69-81) 42% (13-62)
	OS	Israel [11]	Vaccinated in: Jan Feb Mar Apr	 86%* 91% 94% 84%	 16%* 44%^ 69% 79%
	OS	UK[37]	Month 1 Month 5/6		88% 74%
Moderna mRNA-1273	OS	Minnesota US [10]	Jan-July July (>70% delta)	91.6% (81-97) 81% (33-96)	86% (81-91) 76% (58-97)
	RCT, Press release	US [38]	6 months		93%
ChAdOx nCOV-19	OS	UK[37]	Month 1 Month 4/5		77% 67%
Pfizer Moderna Janssen	OS	New York [39]	May July	93.8%-96.2%† 94.4%-95.3%	91.7%-92.7%† 78.2%-82.4%
Pfizer Moderna	OS	US [40]	2-12 wks‡ 13-24 wks	86% (82-88) 84% (77-90)	
Pfizer Moderna	OS	US nursing homes [41]	Pre-Delta (3/1-5/9/21) intermediate Post delta (6/21-8/1/21)		74.7%†† (70-79) 67.5% (60-74) 53.1% (49-57)

#~3% efficacy decline/month reported after 4 months

* Cases detected in late June-mid July (mostly delta).

^All confidence intervals overlap after January.

†Reported efficacy expressed as range of weekly figures from each month

‡Time since vaccination

††Each calculation used different facilities and included asymptomatic infections

Table 2. Reported efficacy in studies evaluating vaccine efficacy over time.

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