COVID-19

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Boosting with updated COVID-19 mRNA vaccines

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Emerging evidence shows that boosting with updated mRNA vaccines that target SARS-CoV-2 variants stimulates better neutralizing antibody responses than homologous boosters.

At the time of their authorizations, the COVID-19 mRNA vaccines showed efficacies of approximately 95% at preventing symptomatic SARS-CoV-2 infections[1,2] – putting them on a par with some of the most effective vaccines ever made. Protection against severe disease was exceptionally strong and even asymptomatic infections were markedly reduced by vaccination[3]. These efficacies have since declined, largely owing to viral evolution and escape from neutralizing antibodies[4], which are the best correlates of protection against COVID-19[5]. In theory, vaccines that are updated to match the circulating variants and administered as boosters might restore some of the primary protection that has been lost. However, there are many factors to consider in heterologous booster shots that could lead to over- or under-performance relative to primary responses, homologous boosters and expectations. In this issue of *Nature Medicine*, Chalkias et al.[6] demonstrate that bivalent boosters that contain spike protein sequences matched to the ancestral strain and to the Beta variant generate improved neutralizing antibody responses to the Beta variant than another dose of the monovalent ancestral spike vaccine. Although the Beta variant never swept to global predominance, its immune evasiveness justified clinical trials for vaccine updates, which in turn have provided a valuable data point in the campaign to keep up with the virus.

A common concern with heterologous boosters is that the generation of new antibody responses tailored to the variant antigen may be dampened by a phenomenon known as 'antigenic imprinting' or 'original antigenic sin' (OAS), a propensity of the immune system to respond to sequential exposures to variant viruses by rehashing responses made the first time the virus was encountered[7]. A consequence is that heterologous boosting may fail to induce new B cell responses to drifted epitopes, which – in cases where drift is driven by immune escape – are precisely the epitopes targeted by neutralizing antibodies[8]. Mouse studies have shown that the extent to which OAS will affect the effectiveness of a given heterologous booster is likely to be a function of the antigenic distance between the original and boosting variants[9], and as such must be determined empirically on a case-by-case basis. Given the strong similarity between the Beta and ancestral (Wuhan-Hu-1) strains of SARS-CoV-2 – 1,262 out of 1,273 amino acids in the spike protein sequence are the same – it was unclear whether or not specific responses to the variant could be induced at all.

Chalkias et al.[6] began by examining neutralizing antibody titers in individuals 7–10 months after completion of the primary two-shot series of the mRNA-1273 vaccine. Although levels of neutralizing antibodies against the ancestral strain were probably still high enough to provide protection[5], they were near the lower limit of detection against the Beta variant. After booster immunization with either the monovalent ancestral spike protein or the bivalent vaccine encoding both ancestral and Beta spike, neutralizing antibody titers to the Beta variant skyrocketed. Depending on the dose, the bivalent vaccine yielded only around 10–30% higher levels of Beta variant-neutralizing antibodies than the ancestral monovalent vaccine at 28 days after immunization. However, by 6 months, this difference became more evident, with neutralizing antibodies decaying less rapidly after the bivalent vaccine than after the monovalent ancestral booster (Fig. 1). There are some caveats to these conclusions, as the pre-booster baseline levels of spike-binding antibody were subtly but clearly different between the control and experimental groups. This in turn raises some questions as to whether the improvement in neutralizing antibodies is necessarily because of the bivalent nature of the vaccine as opposed to pre-booster immunological differences between the cohorts. However, as recent (not yet peer-reviewed) results on Omicron BA.1-updated

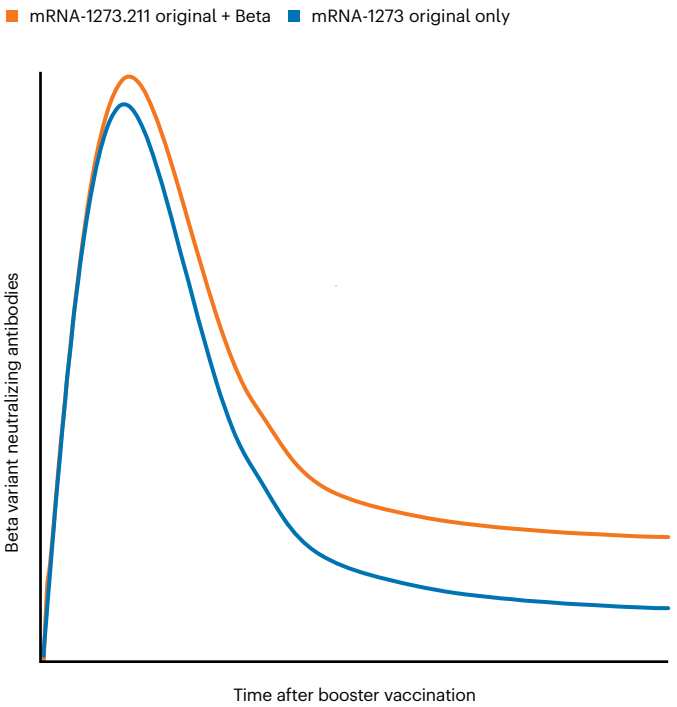

Fig. 1 | Beta variant-neutralizing antibodies are maintained better by bivalent boosters than homologous vaccination. Bivalent mRNA-1273.211 boosters, containing both ancestral and Beta variant-matched spike protein sequences, generate more Beta variant-neutralizing antibodies than homologous mRNA-1273 boosters. These differences become evident over time.

bivalent vaccines show larger improvements than with homologous boosters[10], the data collectively point to what we would hope: updating the vaccine is helpful.

Given that the Beta and ancestral spike proteins are antigenically close, it is not surprising that substantial cross-reactive neutralizing antibodies are elicited even by homologous boosting. Extensive affinity maturation driven by primary exposure to SARS-CoV-2 or its antigens has been shown to generate memory B cells that bind tightly enough to the spike protein to be resistant to small changes in epitopes[11]. These OAS-type responses can be so strong that it is difficult to measure new B cell responses induced specifically by the booster[9]. The findings by Chalkias et al.[6] that both homologous and bivalent boosting also induce neutralizing titers against the Delta and Omicron strains supports such a view.

Why is it that the differences between the bivalent and ancestral monovalent boosters only became obvious many months after the immunization? The simplest explanation is a technical one: the difference in the initial magnitude of neutralizing antibodies might simply be maintained over time and become clearer as the ancestral booster responses decline to low levels. But there may also be more complex biological explanations for this observation. For example, the kinetics of primary and secondary B cell responses are not the same[12]. It is possible that memory B cells that bind to conserved epitopes dominate the initial booster response, but are later joined by new Beta variant-specific naive B cell-derived clones that emerge progressively from germinal center responses induced by the boost after the four-week time point[9]. Clonal and kinetic analyses at both the cellular and serological level will be required to delve deeper into these issues.

Although the cellular mechanisms that underlie the improved responses to the bivalent boosters remain to be resolved, the data are encouraging in that the vaccine updates seem to improve — at least to some degree — neutralizing antibodies against SARS-CoV-2 variants. As would be predicted from the mouse studies mentioned above, the degree of the improvement relative to a homologous booster seems to be correlated with antigenic distance[9]. In support of this, the Omicron BA.1-updated vaccines show a more obvious benefit than the Beta variant bivalent booster[10]. In this sense, it seems that the virus and its evolution will tell us when we need to update the vaccines. A quantitative rubric that incorporates both antigenic distance and loss of neutralizing antibody titers as a rationale for vaccine updates would be valuable to help objectively guide these decisions.

The precise degree to which the enhanced antibody response elicited by updated bivalent vaccines will restore protection against infections and disease awaits real-world effectiveness studies. But given that previous studies have established neutralizing antibodies as a bona fide correlate of protection[5], it seems safe to predict that updated vaccines will perform better than another shot of the same old thing.

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Competing interests

D.B. is a co-founder of Clade Therapeutics. D.B. has intellectual property licensed by Gilead Sciences, Sana Biotechnology, and Clade Therapeutics. D.B. served on an advisory panel for GlaxoSmithKline on COVID-19 therapeutics.