The case against delaying SARS-CoV-2 mRNA vaccine boosting doses.

Paul Bieniasz[1,2]

[1]Laboratory of Retrovirology

The Rockefeller University

1230 York Avenue

New York

NY1065

[2]Howard Hughes Medical Institute

The Rockefeller University

1230 York Avenue

New York

NY1065

Dear Editor:

The extraordinarily rapid development of 2-dose, prime-boost SARS-CoV-2 mRNA vaccine regimens with excellent efficacy (~95%) is a key milestone in the COVID19 pandemic [1, 2]. These mRNA vaccines will provide an important tool to protect against severe disease and death, at least in developed nations.

In phase 3 clinical trials, prime and boost mRNA vaccine doses were given 21 or 28 days apart, with the vast majority of the monitoring period occurring after the boosting dose. Nevertheless, based on the observation of an efficacy signal following the priming dose and preceding the boosting dose[1, 2], it has been proposed (and adopted as policy in the UK) that the second, boosting dose should be withheld for several months. This would allow more individuals to receive a 'prime-only' vaccine regimen in the initial months of vaccine roll-out. Here, I present arguments against the adoption of such a strategy.

The first set of arguments center on the evidence of effectiveness, or lack thereof, for prime-only SARS-CoV-2 mRNA vaccination. The purported efficacy of prime-only regimens is based on a small number of infections that occurred over an extremely short time period, (~day 12 to ~day 21 or 28) between the prime and the boost[1, 2]. We simply do not know whether prime-only recipients will be protected beyond day 21 or 28 – this has not been tested in any clinical trial and assertions about effectiveness beyond day 21-28 are speculative. Even less certain is whether a prime-only regimen will allow onward transmission of SARS-CoV-2. An important benefit of the most effective vaccines, and a concept underlying 'herd' immunity, is that is that vaccines protect not only the recipient, but also to their subsequent contacts. At present, the degree to which 2-dose, prime-boosted mRNA vaccine recipients become asymptomatically infected and allow onward transmission is being assessed. We have essentially no information (certainly none beyond 21-28 days

after prime-only) about the ability of prime-only recipients to terminate or continue transmission chains. The more robust the immunity in a given vaccinated, SARS-CoV-2 exposed, individual, the less likely that individual would experience disease or pose a transmission hazard to contacts. Neutralizing antibodies are likely an important component protective immune response elicited by SARS-CoV-2 vaccines. With 2-dose prime-boost mRNA vaccination, high neutralizing antibody titers are elicited, up to 50-fold higher than with a prime-only regimen[3, 4]. It is almost inescapable that neutralizing titers will decline to sub-protective levels over a shorter interval in prime-only recipients. Will that decline occur before a months-delayed boost is administered? We simply don't know.

A second set of arguments is based on the potential for prime only vaccination to accelerate the erosion of vaccine potency. The slow rate at which SARS-CoV-2 populations have been seen to evolve is partly attributable to relatively high replication fidelity[5]. However, the immunological naivety of the human host population, and a consequent paucity of immune selective pressure is also a central factor[6]. A corollary of this scenario is that the vaccine trials completed to date have been conducted in a context where the natural SARS-CoV-2 challenge is genetically well matched to the vaccine – ideal conditions for observing the maximum possible vaccine efficacy.

A less well appreciated, but important consequence of uncontrolled SARS-CoV-2 spread in some countries, including the UK, is the generation of enormous viral populations. Although selective pressure on naturally circulating SARS-CoV-2 populations has not been obvious, there has clearly been significant accrual of genetic diversity (https://www.gisaid.org). From these large viral populations, SARS-CoV-2 variants associated with rapidly increasing case numbers have emerged in recent weeks[7-9]. These variants have convergent and, therefore, likely functionally important substitutions in the

receptor binding domain (RBD) of the spike glycoprotein. Certain substitutions (K417N/T, E484K and N501Y) confer high level resistance to commonly elicited RBD-specific neutralizing antibodies and, can confer a significant shift in sensitivity to polyclonal convalescent or vaccinee plasma[10, 11]. It is very likely that these variants represent the first steps of antigenic drift in SARS-CoV-2. The degree to which these emergent variants might erode vaccine efficacy is unknown, but given that they resist common antibodies, and emerged as immunity accumulated in host populations, a significant possibility exists that they will do so. In this regard, boosting a primed immune response not only increases the levels, but also the affinity of antibodies for their targets, through somatic mutation. Notably, acquisition of somatic mutations enables some antibodies to neutralize SARS-CoV-2 variants that would otherwise escape neutralization by their near-germline antibody ancestors[12].

A key substrate for the amplification and further acquisition of antibody resistance in viral populations are hosts in which sufficient immunological pressure is applied for resistance mutations to confer selective advantage, but in which insufficient immunity exists to prevent onward transmission of those variants[6]. The generation of partly immune individuals, using prime-only vaccination strategies in millions, risks generating such host populations. Doing so in the context of highly prevalent SARS-CoV-2 infection maximizes the opportunity for viral populations to encounter partly immune hosts and adapt to evade antibodies. While antigenic drift, driven by vaccine and/or natural host immunity will, in time, inevitably erode the potency of current SARS-CoV-2 vaccines, prime-only approaches applied at a population-wide level risks accelerating that process.

There are many unknows: What will the efficacy of a single mRNA dose be in prime-only vaccine recipients beyond 21-28 days, particularly if new, antibody resistant and

possible more transmissible SARS-CoV-2 variants dominate? Will the new antigenic drift variants be further enriched and how will they further evolve in host populations with prime-only vaccination and low antibody titers? Indeed, will single 'replacement' variants dominate global SARS-CoV-2 populations or will multiple variants emerge[6]? To what extent will prime-only versus prime-boost vaccination regimens reduce the number of susceptible hosts and break transmission chains? Should mitigation of the emergence of SARS-CoV-2 antibody resistance even be a consideration, when there are so many crucial unknowns? Ultimately, at the time of writing, we simply do not have sufficient information to know the optimal way to apply the available vaccine doses.

Although there is uncertainty, the key arguments against delaying the administration of mRNA vaccine boosting doses are ultimately more powerful: (1) there is no evidence for efficacy of a single dose mRNA vaccine beyond 21 or 28 days, and significant reason to think that efficacy observed at early time points will decline. (2) Prime-only vaccinated individuals may create a pool of millions of hosts with incomplete immunity that permit SARS-CoV-2 onward transmission, driving the selection of increasingly antibody resistant variants. Ultimately, I do not think that otherwise highly effective vaccines should be used in altered and untested regimes that may not be effective and risk accelerating their obsolescence.

The author has no potential conflicts

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