**Is a single COVID-19 vaccine dose enough in convalescents?**

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**ABSTRACT**

SARS-CoV-2 has infected more than 122 million persons worldwide. Most currently licensed COVID-19 vaccines require a two-dose course and many health systems are on a shortage of doses. The requirement for boosting the response after priming with the first dose is uncertain in convalescents already primed by the natural infection. Mounting evidences suggest that, after a single vaccine dose, convalescents develop antibody (total and neutralizing) levels similar to the ones measured in naïve vaccinees after the full two-dose course. While concerns remain on the equivalent duration of such response, optimizing vaccine delivery to convalescents seems effective and could accelerate achievement of herd immunity.

To date, more than 122 million persons across the world have been documented as infected with SARS-CoV-2. The ongoing vaccination campaigns are suffering a bottleneck because of shortage of doses, with most currently licensed vaccines (BNT162b2, mRNA-1273 and AZD1222/ChAdOx) requiring two separate doses (prime-boost) in order to provide protection from symptomatic COVID-19. Nevertheless, convalescents with previous confirmed SARS-CoV-2 exposure have been primed by the natural infection, and a single dose could be enough to boost immune memory.

In the mRNA-1273 vaccine phase 3 trial, 2.2% of vaccinees had evidence (serologic, virologic or both) of SARS-CoV-2 infection at baseline, but no subgroup analysis was reported.\(^1\) Recently, a growing amount of evidences from many different research groups joining thousands of vaccinees support that, with both marketed COVID-19 mRNA vaccines, the first dose leads to antibody levels comparable to the ones achieved after two doses in naïve vaccinees,\(^2\)\(^-\)\(^4\) with strong correlations between T helper and antibody immunity.\(^7\) Of interest, SARS-CoV-2-recovered individuals had a significant immune response after the first dose with no increase in circulating antibodies or antigen-specific memory B cells after the second dose.\(^10\) Actually, the immune response 7 d after the second dose of BNT162b2 in convalescents shows a decline in both antibody levels and ELISPOT-reactive T lymphocytes.\(^11\) Boosting post-COVID-19 antiphospholipid antibodies\(^12\) and/or development of anti-polyethylene glycol antibodies\(^13\),\(^14\) has been hypothesized to explain the decline.

The antibody response of convalescents depends on the IgG pre-vaccine titer\(^16\) and on the symptoms that they developed during the disorder, with anosmia/dysgeusia and gastrointestinal disorders being the most significantly positive correlates in the linear regression.\(^15\) Side effects also tended to associate with post-boost antibody levels, but not with post-boost memory B cells.\(^10\) Given the higher incidence of adverse reactions associated with the second vaccine dose in naïve recipients,\(^16\) such management could spare the concern of even higher incidences after second dose in convalescents.

While defining the serostatus in vaccine candidates globally could slow down vaccine deployment, it is much more logistically feasible for health-care workers, who have been universally included among the first categories to be vaccinated. From a pharmacoeconomics point of view, administering a single dose to convalescents is also economically sustainable (and likely convenient) in most countries. Additionally, a single injection of mRNA-1273 or BNT162b2 has been shown enough to induce novel antibody specificities that protect against the B.1.351 variant of concern.\(^17\) A similar phenomenon has been reported after two BNT162b2 doses against B.1.1.7.\(^18\)

A single dose of either mRNA vaccine has been shown to be approximately 80% effective at preventing hospitalization and a single dose of BNT162b2 is 85% effective at preventing death with COVID-19.\(^19\)

Most studies to date have focused on surrogate viral neutralization tests, which have often poor correlation with the titer of neutralizing antibodies (nAb). A few studies have nevertheless provided reassuring evidences: among 59 healthcare workers, at 0 and 14 d after a single dose of mRNA-1273 or BNT162b2, median reciprocal ID\(_{99}\) virus neutralization titers of each of the asymptomatic (80 and 40,960) and symptomatic (320 and 40,960) groups were higher than the Ab-negative group (<20 and 80).\(^20\)

A caveat has been raised by Demonbreun et al., who reported that persons seropositive for anti-Spike RBD IgG in the absence of acute viral diagnostic testing required two doses of mRNA-1273 or BNT162b2 to achieve equivalently high levels of IgG and neutralization activity. So, a positive swab seems required to identify convalescents who benefit from a single dose.\(^21\)

In the proposal of vaccinating confirmed, previously infected convalescents with a single dose gets implemented, we recommend neutralizing antibody screening in vaccinees...
older than 60,22 given recent reports that 30% of recipients in this group do not mount neutralizing antibodies after two doses BNT162b2 (vs. 2% below age 60) (98.8% vs. 84% 18 d after the first dose).10,23

In the current manufacturing bottleneck, most health systems are suffering shortages of vaccines, so that usage optimization of the existing stockpiles is being evaluated:24 the saved second vaccine doses could be readressed to fragile patients on the waiting list,25 contributing to reaching herd immunity faster. Further studies will be necessary to evaluate whether duration of immunity after a single dose in convalescents is equivalent to duration after the full course in naïve vaccinees.

Abbreviations
nAb neutralizing antibodies
RBD receptor-binding domain
RBM receptor-binding motif.

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D.F. conceived the design and wrote the first draft. F.M. and A.B. critically revised the final version.

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