HUMAN VACCINES & IMMUNOTHERAPEUTICS
2021, VOL. 17, NO. 9, 2959–2961
https://doi.org/10.1080/21645515.2021.1917238

Taylor & Francis
Taylor & Francis Group

COMMENTARY

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

Daniele Focosi[a], Andreina Baj[b], and Fabrizio Maggi[b]

[a]Department of Staff, Pisa University Hospital, Pisa, Italy; [b]Department of Medicine and Surgery, University of Insubria, Varese, Italy

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.

ARTICLE HISTORY
Received 24 March 2021
Accepted 9 April 2021

KEYWORDS
COVID-19; SARS-CoV-2; BNT162b2; mRNA-1273

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,[2–8] with strong correlations between T helper and antibody immunity.[9] 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[10] 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 health-care 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

CONTACT Daniele Focosi daniele.focosi@gmail.com Department of Staff, Pisa University Hospital, Via Paradisa 2, Pisa 56124, Italy

Key points: Dual-dose COVID19 vaccines are suffering manufacturing bottlenecks. After a single dose convalescents mount antibody levels equivalent to those seen in naïve subjects vaccinated with 2 doses. Adapting single doses to convalescents translates into saved doses.

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 readdressed 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.

Author contributions

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

Disclosure of potential conflicts of interest

No potential conflicts of interest were disclosed.

Funding

This manuscript received no funds.

ORCID

Andreina Baj http://orcid.org/0000-0003-0088-2712
Fabrizio Maggi http://orcid.org/0000-0001-7489-5271

References

1. Baden LR, El Sahly HM, Essink B, Kotloff K, Frey S, Novak R, Diemert D, Spector SA, Rouphael N, Creech CB, McGettigan J. Efficacy and safety of the mRNA-1273 SARS-CoV-2 vaccine. medrXiv [Preprint]. 2020;384:403–16.
2. Abu Jabal K, Ben-Amram H, Beiruti K, Batheesh Y, Sussan C, Zarka S, Edelstein M. Impact of age, gender, ethnicity and prior disease status on immunogenicity following administration of a single dose of the BNT162b2 mRNA Covid-19 vaccine: real-world evidence from Israeli healthcare workers, December-January 2020. medrXiv [Preprint]. 2021. doi:10.1101/2021.01.27.21250567.
3. Krammer F, Srivastava K, Simon V. Robust spike antibody responses and increased reactogenicity in seropositive individuals after a single dose of SARS-CoV-2 mRNA vaccine. medrXiv [Preprint]. 2021. doi:10.1101/2021.01.29.21250653.
4. Ebinger JE, Fert-Bober J, Printsev I, Wu M, Sun N, Figueiredo JC, Van Eyk J, Braun J, Cheng S, Sobhani K. Prior COVID-19 infection and antibody response to single versus double dose mRNA SARS-CoV-2 vaccination. medrXiv [Preprint]. 2021. doi:10.1101/2021.02.23.21252230.
5. Narasimhan M, Mahimainathan L, Araj E, Clark AE, Markantonis J, Green A, Xu J, SoRelle JA, Alexis C, Fankhauser K, Parikh H. Clinical evaluation of the Abbott Alinity SARS-CoV-2 spike-specific quantitative IgG and IgM assays in infected, recovered, and vaccinated groups. medrXiv [Preprint]. 2021. doi:10.1101/2021.02.17.21251940.
6. Velasco M, Galan MI, Casas ML, Perez-Fernandez E, Gonzalez-Pinyeiro B, Castilla V, Guijarro C. Impact of previous COVID-19 on immune response after a single dose of BNT162b2 SARS-CoV-2 vaccine. medrXiv [Preprint]. 2021. doi:10.1101/2021.03.08.21253065.
7. Callegaro A, Borleri D, Farina C, Napolitano G, Valenti D, Rizzi M, Maggiolo F. Antibody response to SARS-CoV-2 vaccination is extremely vivacious in subjects with previous SARS-CoV-2 infection. medrXiv [Preprint]. 2021. doi:10.1101/2021.03.09.21253203.
8. Kelsen SG, Braverman A, Patel P, Aksoy MO, Hayman J, Rajput C, Ruggieri MR, Gentile N. Heightened COVID-19 Vaccine Response Following SARS-CoV-2 Infection. medRxiv [Preprint]. 2021. doi:10.1101/2021.03.18.21253845.
9. Tauzin A, Nayrac M, Benlarbi M, Gong SY, Gasser R, Beaudoin-Bussieres G, Brassard N, Laumaea A, Vézina D, Prevost J, Anand SP. A single BNT162b2 mRNA dose elicits antibodies with Fc-mediated effector functions and boost pre-existing humoral and T cell responses. medrXiv [Preprint]. 2021. doi:10.1101/2021.03.18.435972.
10. Goel RR, Apostolidis SA, Painter MM, Mathew D, Pattekar A, Kuthuru O, Gouma S, Kuri-Cervantes L, Meng W, Adamski S, Baxter AE. Longitudinal analysis reveals distinct antibody and memory B cell responses in SARS-CoV2 naive and recovered individuals following mRNA vaccination. medrXiv [Preprint]. 2021. doi:10.1101/2021.03.03.21252872.
11. Samanovic-Golden MI, Cornelius AR, Wilson JP, Karmacharya T, Gray-Gaillard SL, Allen JR, Hyman SW, Moritz G, Ali M, Koralov SP, Mulligan MJ. Poor antigen-specific responses to the second BNT162b2 mRNA vaccine dose in SARS-CoV-2-experienced individuals. medrXiv [Preprint]. 2021. doi:10.1101/2021.02.07.21251311.
12. Zuo Y, Estes SK, Ali RA, Gandhi AA, Yalavarthi S, Shi H, Sule G, Gockman K, Madison JA, Zuo M, Woodard W. Prothrombotic antiphospholipid antibodies in COVID-19. medrXiv [Preprint]. 2020. doi:10.1101/2020.06.15.20131607.
13. Garay RP, El-Gewely R, Armstrong JK, Garratty G, Richette P. Antibodies against polyethylene glycol in healthy subjects and in patients treated with PEG-conjugated agents. Expert Opin Drug Deliv. 2012;9:1319–23. doi:10.1517/17425247.2012.720969.
14. Semple SC, Harasym TO, Clow KA, Ansell SM, Klimuk SK, Hope MJ. Immunogenicity and rapid blood clearance of liposomes containing polyethylene glycol-lipid conjugates and nucleic acid. J Pharmacol Exp Ther. 2005;312:1020–26. doi:10.1124/jpet.104.078113.
15. Levi R, Azzolini E, Pozzi C, Ubaldi L, Lagioia M, Mantovani A, Rescigno M. A cautionary note on recall vaccination in ex-COVID-19 subjects. medrXiv [Preprint]. 2021. doi:10.1101/2021.02.01.21250923.
16. Polack FP, Thomas SJ, Kitchin N, Absalon J, Gurtman A, Lockhart S, Perez JL, Pérez Marc G, Moreira ED, Zerbini C, Bailey R. Safety and efficacy of the BNT162b2 mRNA Covid-19 vaccine. N Engl J Med. 2020;383:2603–15. doi:10.1056/NEJMoa2034577.
17. Stamatatos L, Czartoski J, Wan Y-H, Homad L, Rubin V, Glantz H, Neradilek M, Seydoux E, Jennewein MF, MacCamy A, Feng J. Antibodies elicited by SARS-CoV-2 infection and boosted by vaccination neutralize an emerging variant and SARS-CoV-1. medrXiv [Preprint]. 2021. doi:10.1101/2021.02.05.21251182.
18. Trinite B, Pradenas E, Marfil S, Rovirosa C, Urrea V, Tarres-Freixas F, Ortiz R, Vergara-Alert J, Segales J, Guallar V, Lepore A. Previous SARS-CoV-2 infection increases B.1.1.7 cross-neutralization by vaccinated individuals. medrXiv [Preprint]. 2021. doi:10.1101/2021.03.05.433800.
19. Lopez Bernal J, Andrews N, Gower C, Stowe J, Robertson C, Tessier E, Simmons R, Cottrell S, Robertson R, O'Doherty M, Brown K. Early effectiveness of COVID-19 vaccination with BNT162b2 mRNA vaccine and ChAdOx1 adenovirus vector vaccine on symptomatic disease, hospitalisations and mortality in older adults in England. medrXiv [Preprint]. 2021. doi:10.1101/2021.03.01.21252652.
20. Saadat S, Tehrani ZR, Logue J, Newman M, Frieman MB, Harris AD, Sajadi MM. Binding and neutralization antibody titers after a single vaccine dose in health care workers previously

infected with SARS-CoV-2. JAMA. 2021;14:1467. doi:10.1001/jama.2021.3341.
21. Demonbreun AR, Sancilio A, Velez ME, Ryan DT, Saber R, Vaught LA, Reiser NL, Richard TD, Mustanski B, McNally EM, McDade TW. Comparison of IgG and neutralizing antibody responses after one or two doses of COVID-19 mRNA vaccine in previously infected and uninfected persons. medrXiv [Preprint]. 2021. doi:10.1101/2021.03.04.21252913.
22. Grupel D, Gazit S, Schreiber L, Nadler V, Wolf T, Lazar R, Supino-Rosin L, Perez G, Peretz A, Tov AB, Mizrahi-Reuveni M. et al. Kinetics of SARS-CoV-2 anti-s IgG after BNT162b2 vaccination. medrXiv [Preprint]. 2021; doi:10.1101/2021.03.03.21252844.
23. Müller L, Andree M, Moskorz W, Drexler I, Walotka L, Grothmann R, Ptok J, Hillebrandt J, Ritchie A, Rabl D, Ostermann PN. Age-dependent immune response to the Biontech/Pfizer BNT162b2 COVID-19 vaccination. medrXiv [Preprint]. 2021. doi:10.1101/2021.03.03.21251066.
24. Ayoub HH, Chemaitelly H, Makhoul M, Kanaani ZA, Kuwari EA, Butt AA, Coyle P, Jeremijenko A, Kaleeckal AH, Latif AN, Shaik RM Epidemiological impact of prioritizing SARS-CoV-2 vaccination by antibody status: mathematical modeling analyses. medrXiv [Preprint]. 2021. doi:10.1101/2021.01.10.21249382.
25. WHO. SAGE roadmap for prioritizing uses of COVID19 vaccines in the context of limited supply. Version 1.1., 2020.