**Title**

**Enhanced antibody responses to first vaccine dose in previously SARS-CoV-2 infected individuals may render the booster dose unnecessary**

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Rapid vaccine-induced population immunity is a key global strategy to control COVID-19. Vaccination programmes must maximise early impact, particularly with accelerated spread of new variants.1 Most vaccine platforms use a two-dose prime:boost approach to generate an immune response against the virus S1 spike protein, the titres of which correlate with functional virus neutralisation and increase with boosting.2,3 To enable larger numbers of people to receive the first dose, delayed administration of the second dose has been advocated and implemented by some.1 The impact of prior SARS-CoV-2 infection on the need for boosting is not known.

We reasoned that prior infection could be analogous to immune priming and as such, a first “prime” vaccine dose would effectively act as “boost”, so a second dose would not be needed. To test this, we undertook a nested case-control analysis of 51 participants of COVIDsortium,4,5 in an ongoing longitudinal observational study of healthcare workers who underwent weekly PCR and quantitative serology testing from the date of first UK lockdown for 16 weeks. 24/51 had prior laboratory-confirmed mild or asymptomatic SARS-CoV-2 infection (positive serology by anti-nucleocapsid and/or Roche anti-S (RBD) antibody), whereas 27 remained seronegative. A median of 12.5 time-points per participant permitted the identification of peak antibody levels in seropositives whilst avoiding false negatives.

All participants then received first dose Pfizer/BioNTech mRNA vaccine2,3 and were assayed at 22±2 days after the first vaccination dose. Among previously uninfected, seronegative individuals, anti-S levels after vaccination were comparable to peak anti-S levels following natural infection. Among those with prior SARS-CoV-2 infection, vaccination increased anti-S more than 140-fold from peak pre-vaccine levels (Figure). This increase appears to be at least an order of magnitude greater than reported after a conventional prime:boost vaccine strategy in the previously uninfected3

These data suggest that for individuals receiving vaccination (here Pfizer/BioNTech mRNA vaccine), a potential approach is to include serology testing at or before the time of first vaccination to prioritise use of booster doses. This could potentially accelerate vaccine roll-out. With increasing variants (UK, South Africa, Brazil), wider coverage without compromising vaccine induced immunity could help reduce variant emergence. Furthermore, reactogenicity after unnecessary boost risks an avoidable unwelcome increase in vaccine hesitancy.

Whether enhanced vaccine induced antibody levels among previously seropositive individuals will show differential longevity compared to boosted vaccines remains to be seen. In the meantime, our findings provide a rationale for serology-based vaccine dosing to maximise coverage and impact.



**Figure. Comparison of serological response (Roche anti-S1 RBD) to a single dose of the Pfizer/BioNTech vaccine in individuals with and without laboratory evidence of prior SARS-CoV-2 infection.**

51 participants (24 with prior laboratory confirmed SARS-CoV-2 infection) from a longitudinal, multi-timepoint COVID-19 healthcare worker study were sampled 22±2 days after a single dose of the Pfizer/BioNTech mRNA vaccine. Roche anti-S levels in those with no prior infection are similar to following mild SARS-CoV-2 infection. Anti-S levels among those with prior SARS-CoV-2 infection are more than 140-fold greater than at time of peak infection. \*P<0.0001 for both

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CHM - study design, data collection, funding, data analysis, interpretation, writing;

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