

Summary Document**Topic: Single Dose COVID Vaccination Irrespective of Baseline Serostatus****Version: 2.0; Dated 18 June 2021**

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Overview:

The high effectiveness of vaccines in preventing severe COVID-19 and hospitalisation after the first dose raises the prospect for single dose (SD) vaccine roll-out to increase the speed of vaccine coverage. This could result in a net effect of reduced morbidity and mortality, more rapid reduction of population viral load, and a reduced risk of new variants of concern (VOC).

Considering the rapidly increasing SARS-CoV-2-primed global population (either by vaccination or natural infection) and the high effectiveness of a SD in preventing severe, critical, and fatal COVID-19 in unprimed individuals, provision of a single vaccine dose regardless of baseline serostatus could represent the most effective vaccine allocation especially if followed by a strain-adapted next-generation COVID-19 vaccine booster six to 12 months later.

This summary document assesses the evidence regarding SD vaccine administration for vaccine platforms where the 50% vaccine efficacy threshold is achieved after a SD. This has been demonstrated for vaccines using mRNA (BNT162b2; mRNA-1273), adenovirus (ChAdOx-1; Ad26.COVS2), and the Novavax' nanoparticle (NVX-CoV2373) platform. We conclude that a first vaccine dose could act as a *de facto* booster in individuals with prior SARS-CoV-2 infection and question if SARS-CoV-2 infection could act as a *de facto* booster in individuals primed by a single vaccine dose, which would enable SD vaccine provision irrespective of serostatus (i.e., without baseline testing). This will inform the clinical development of SD 'next-generation' (e.g., adapted strain) COVID-19 vaccines. Whether a SD is the purview of vaccines with high SD efficacy/effectiveness remains to be defined.

Neutralising antibody responses are predictive of immune protection from COVID-19, although less so for severe disease manifestations. If breakthrough infection occurs in individuals primed by a single vaccine dose, cell-mediated immunity may prevent progression to severe disease and hospitalisation, even in case of mismatch between vaccine strain and infecting VOC. The long SARS-CoV-2 incubation period and slow progression to severe disease are expected to provide sufficient time for activation of memory B and T cells prior to progression to severe COVID-19. This also raises the prospect that breakthrough SARS-CoV-2 infection could act as a *de facto* booster when occurring after a SD of highly effective vaccine, in a similar manner by which a first vaccine dose in individuals with a history of COVID-19 boosts the immune response induced by natural infection. Trained innate immunity likely contributes to this level of protection and may explain the early onset of protection after SD vaccination.

Introduction - Single Dose Irrespective of Baseline Serostatus: Provision of a single dose (SD) of COVID-19 vaccine, irrespective of baseline serostatus, should be discussed given a SD can be highly effective in preventing hospitalisation due to COVID-19. From a public health perspective, the switch from a two- to one-dose strategy would instantly increase vaccine coverage, thus more rapidly decreasing the population viral load and substantially reducing the risk of escape variants of concern (VOC). In addition, modelling suggests that SD vaccination with a vaccine that has at least 50% SD efficacy averts more COVID-19 cases and prevents up to 48% more deaths compared to the standard two-dose regimen (1–4). The clinical development of next-generation COVID-19 vaccines should consider SD assessments across different settings and populations, perhaps excluding certain immunocompromised conditions (5–7).

The two critical clinical variables that drive SD efficacy are immune status (primed versus naive) and vaccine efficacy endpoint (i.e., severe versus mild COVID-19). Priming may occur by natural SARS-CoV-2 infection or vaccination. Resulting immune memory protects against reinfection and subsequent disease and is thus expected to increase SD vaccine efficacy. Despite the rapidly growing primed population, uncertainty over long-term SD effectiveness in unprimed individuals remains the primary concern with a blanket SD strategy without baseline serostatus testing.

SD efficacy may also be affected by antigenic change. In case of reduced vaccine efficacy against VOC, as shown for the beta and delta VOC, SD efficacy should be expected to be suboptimal, although protection against severe disease should be largely retained (8–12). Preliminary data suggest that alpha and gamma VOC are less impacted (13). Proof of principle for continued protection against severe disease despite a mismatch between vaccine and circulating viral strains, comes from an influenza efficacy trial where addition of an adjuvanted induced stronger cell-mediated immune (CMI) responses (14). Therefore, the crucial outcome measures for the assessment of SD effectiveness are severe or critical COVID-19, hospitalization, and death.

Single Dose in Individuals with Prior SARS-CoV-2 Infection: Neutralising antibody responses amongst other antibody functions, are important for the prevention of coronavirus infection (15) and are predictive of immune protection from COVID-19 (16,17). Following natural SARS-CoV-2 infection, especially after mild or subclinical disease, antibody responses can wane rapidly allowing for potential reinfection (18,19). A history of COVID-19 significantly reduces the risk of subsequent reinfection (20–22), at least for eight months with an increase in COVID-19 reported thereafter (23). This indicates that following natural infection, a booster dose is required to maintain protective antibody titres.

In early clinical development trials, SD post-vaccination antibody titres in seropositive individuals exceeded those following the second dose in seronegative participants (24,25). Similarly, in several small cohorts, mostly of health-care workers, SD in individuals with prior COVID typically elicited antibody titres that exceeded those of seronegative participants following the second dose (26–36). In a large diverse longitudinal cohort assessing SD up to 15 months post infection, neither the time interval between infection and vaccination, nor age or co-morbidities affected post vaccination antibody titres (37).

Thus, in individuals primed by natural SARS-CoV-2 infection, a SD of a COVID-19 vaccine is an efficacious immune booster that enhances binding and neutralising antibody responses elicited by prior infection (including against VOC) (32,33,38), mounts robust B and T cell responses, (31,32,38) and also prevents reinfection and transmission (39). The immune responses suggest that SD boosters following natural infection provide a level of protection comparable to that resulting from two vaccine doses in unprimed individuals.

Single Dose Boosters in Individuals with a Vaccination History: The clear boosting effect of SD in individuals with prior SARS-CoV-2 raises the possibility of a similar effect in vaccinated individuals. COVID vaccination will have been offered to the majority of adults in North America and Europe by the end of summer 2021. Despite immune persistence for six months following vaccination (40,41), administration of a single booster dose (with or without an adapted strain) nine to 12 months after the primary vaccination regimen should be anticipated. Boosters at six, 12, and 24 months are assessed in the Phase 1/2a Ad26.COV2 trial (42). Several manufacturers have started clinical assessment of SD boosters with prototype or adapted antigens (43–46). Immune data on late boosters from the heterologous prime boost ComCov trial (47) are imminent.

To date, the immune response to a SD in individuals primed by an earlier vaccine dose can only be inferred from studies comparing extended dosing intervals to the standard three- or four-week interval between two doses. Immune responses are significantly stronger when a second dose of ChAdOx-1 (AstraZeneca) or BNT162b2 (Pfizer) is administered 12 weeks after the first dose (2.5-fold and 3-fold higher, respectively) (48,49). It might be speculated that late boosters benefit from better memory B-cell maturation. Interestingly, the 2.5-fold difference in peak titres between dose intervals for ChAdOx-1 is in the same order of magnitude as the difference in peak titres between seropositive and seronegative volunteers in the Phase 1 trial (25). This would suggest that SD in those primed by vaccination may have a similar effect as SD in those primed by prior SARS-CoV-2 infection, at least in terms of peak antibody responses.

Single Dose Vaccine Efficacy in Unprimed Individuals: Randomised, placebo-controlled trials have reported peak vaccine efficacies of >90% in unprimed individuals for BNT162b2 and mRNA-2173 from 14 days after the first dose until the second dose, with protection commencing after 10 days (50–52). Similarly, vaccine efficacy two weeks after the first dose of the Novavax nanoparticle vaccine (NVX-CoV2373) was reported at 83% (53). The SD Ad26.COVID-19 (J&J) vaccine, has an efficacy 67% and 77%, against moderate-severe and severe-critical COVID-19, respectively (9). SD Ad26.COVID-19 efficacy is comparable to efficacy seen after two doses of ChAdOx-1, also an adenovirus-vectored vaccine (54). In the Phase 1/2 trial, antibody titres further increased and stabilised in the 71 days of follow up, suggesting durability of the immune response after a SD of Ad26.COVID-19 (55).

Early Onset of Protection after Single Dose: Early protection following the first dose of BNT162b2, mRNA-1273, and Ad26.COVID-19 vaccines, when neutralising antibody titres remain low to undetectable, could be a result of innate immune mechanisms. The concept of trained innate immunity (56) may help explain protection against symptomatic COVID-19 as early as 10 days after the first vaccine dose, which reflects the apparent onset of protection against SARS-CoV-2 infection within 2-3 days following vaccination when taking the mean and median pre-symptomatic incubation period of 5-6 and 6-7 days respectively into account.

Single Dose Vaccine Effectiveness in Unprimed Individuals: The feasibility of SD vaccination, irrespective of baseline serostatus, will depend on the proportion of the population that is primed in the medium to long term, and on SD vaccine effectiveness in preventing hospitalisation in unprimed individuals in the short term. Prevention of hospitalisation should be a principal effectiveness outcome for the foreseeable future, especially during waves caused by less well neutralised VOC associated with an increase in breakthrough infections.

A number of studies (in countries with vaccine roll-out programs) have assessed SD effectiveness where the vast majority of individuals were unprimed at the time of vaccination (20,57–64) (e.g., Israel, US, UK, Qatar). Most of these studies only provide short-term effectiveness estimates, but the UK policy to delay the second vaccine dose has enabled longer-term SD effectiveness assessments for the ChAdOx-1 and BNT162b2 vaccines. In an observational study of almost 20,000 COVID-related hospitalisations in older UK adults aged ≥ 70 years since the start of vaccine roll-out (i.e., from 9 December 2020 to 18 April 2021), SD effectiveness in preventing hospitalisation in those aged ≥ 80 years was 80% after one dose of either ChAdOx-1 and BNT162b2, increasing to 92% after two doses (65). In another UK test negative case control study among ≥ 70 year olds ($n \sim 156,000$), effectiveness was >60% and 80% against symptomatic COVID-19 and hospitalisation, respectively, following SD of a ChAdOx-1 or BNT162b2 vaccine (60). Interestingly, 60% SD effectiveness in preventing SARS-CoV-2 infection was reported in US care home residents with high nursing needs without past infection, similar to the 63% vaccine effectiveness among residents with past SARS-CoV-2 infection (63).

Protective Mechanisms & Protection Against Severe Disease and Hospitalisation: The clinical development of vaccines and definition of endpoints would benefit from a better understanding of protective mechanisms. The latter is informed by analyses of immune responses induced by SARS-CoV-2 infection or vaccination and coronavirus immunity following common cold coronaviruses, SARS-CoV-1, and MERS-CoV (66,67). Prevention of severe disease and hospital admissions arguably provides the most pressing public health benefit, despite the ultimate goal being prevention of transmission.

Antibody responses are important mediators of protection against coronaviruses. Beyond this, CMI are expected to play a key role. Whilst reinfection might be expected within a few months, evidence from SARS-

CoV-1 infection suggests that immunity can persist for much longer (67). The durable CMI observed in MERS and SARS is consistent with the view that antigen specific CD4 and CD8 T cell responses are likely involved in (long-term) prevention against severe disease outcomes. The relatively slow course of severe COVID-19 suggests that protective immunity involves mobilisation of circulating memory T and B cells, which then generate effector T cell responses and antibody responses (66). Dan et al. reported that T cell immunity declines with a half-life of three to five months and IgG (binding antibody) levels remain stable over six months despite declining neutralising antibodies following natural SARS-CoV-2 infection (18). Spike antigen-specific, long-lived quiescent bone-marrow plasma cells and resting memory B-cells indicate robust SARS-CoV-2 induced long-lived humoral responses that can be boosted by vaccination (68,69).

Reduced protection against infection with VOC or waning antibodies do not necessarily result in loss of protection against severe disease. Modelling by Khoury and colleagues suggests that a higher level of protection against severe infection is expected for any given level of vaccine efficacy against mild SARS-CoV-2 infection (16). The three to 14 day pre-symptomatic SARS-CoV-2 incubation period (70,71) and slow progression to severe COVID-19 allow, at least in theory, for the activation of pre-existing immune responses upon reinfection (seven and 10 days for humoral and cellular immune responses respectively) and boosting of primed memory B and T cells. A boosting effect of reinfection following natural infection has been reported in a cohort from Vo, Veneto (72). The cellular response should be able to moderate disease and provide high effectiveness for protection against severe disease. It is tempting to speculate that this post exposure immune protection would also benefit from innate immune activation.

Conclusion: In summary, SD vaccination irrespective of baseline serostatus can be justified where the 50% vaccine efficacy threshold is achieved following a SD, as has been demonstrated for vaccines using the mRNA (BNT162b2; mRNA-1273), adenovirus (ChAdOx-1; Ad26.CO2) and Novavax' nanoparticle (NVX-CoV2373) platform. In primed individuals, a SD achieves higher antibody titres and broader cellular immune responses than two doses in seronegative individuals and is likely to provide high protection against reinfection and symptomatic disease, including for VOC. In unprimed individuals, a SD is highly effective in preventing symptomatic COVID-19 and hospitalisation. Despite antibody titres providing a plausible correlate for prevention of infection, other mechanisms such as CMI and innate immunity may play a role in protection against severe disease.

The high effectiveness in preventing severe disease and hospitalisation in unprimed individuals after a single vaccine dose is sustained for 12 weeks as demonstrated from the roll-out of BNT162b2 and ChAdOx-1 vaccines in the UK. The activation of memory B and T cells, which is enabled during the long SARS-CoV-2 incubation period should typically occur before progression to severe COVID-19 and may, in combination with the trained innate immunity concept, provide protection against severe disease and hospitalisation. This raises the prospect that breakthrough SARS-CoV-2 infections following a SD of highly effective vaccine could act as a *de facto* booster dose even when these are caused by VOC. Thus, where prior SARS-CoV-2 infection may mimic prior vaccination, post SD SARS-CoV-2 infection may mimic a booster dose, if a SD prevents severe disease. With clear benefits for increased vaccine coverage, the implementation of a single, highly effective vaccine dose regardless of serostatus will be informed by lasting effectiveness of SD in preventing severe COVID-19 and hospitalisation and the possibility of a single booster dose with a VOC-adapted strain, six to 12 months following a single priming dose.

In summary, high SD effectiveness in preventing hospitalisation in unprimed individuals, and mortality-reducing optimum vaccine allocation supports the use of a single vaccine dose regardless of baseline serostatus, with the aim to provide a late booster dose, likely facilitating implementation of variant-based vaccine formulations.

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