Technical note on delayed shipments for the ChAdOx1-S [recombinant] vaccines: what are the implications for the administration of second doses?

Scientific brief

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Problem statement:

The global supply of ChAdOx1-[recombinant] vaccines is presently constrained, which impacts country access to ChAdOx1-S [recombinant] vaccine (AstraZeneca COVID-19 vaccine AZD1222, SII Covishield, SK Bioscience). This constraint is due to multiple factors including company related production delays, shipping delays and specific unforeseen country needs. Participating countries and economies of the COVAX Facility are particularly affected. The uncertainty of future supply has prompted countries to review policy and programmatic implications, as providing the second dose of the vaccine within the WHO recommended 8-12-week schedule may not be feasible in the near future. This document supplements information provided in a technical note entitled 'Considerations for optimizing deployment of ChAdOx1-S [recombinant] vaccines in a time-limited constrained supply situation'[1] and provides updated information relevant to the provision of a second dose in the current limited supply context. While definitive evidence is not currently available, the considerations below are based on expert review of the best available evidence and are designed to assist countries in making choices supported by previous WHO guidance.[1]

Background:

The WHO recommended schedule for ChAdOx1-S [recombinant] vaccines is two doses, given 8 to 12 weeks apart. Phase 3 clinical trial data show efficacy against symptomatic COVID-19 starts from 22 days after the first dose[2] and thereafter is about 76% (95%CI [confidence interval] 59–86%) between days 22 and 90, prior to the administration of a second dose. There is minimal waning of binding antibody levels by day 90 which is unlikely to be clinically significant. After administration of the second dose, both vaccine efficacy and antibody titres are higher in individuals who had a longer prime boost interval of 8-12 weeks versus < 6 weeks. In vaccinees with the longer prime-boost interval (8-12 weeks), efficacy at >14 days after the second dose was 81% (95%CI 60–91%).[3] These data are consistent with evidence that humoral and cellular immune responses are boosted more strongly with the longer interval between doses.[3,4]

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[1] Considerations for optimizing deployment of ChAdOx1-S [recombinant] vaccines in a time-limited constrained supply situation. https://www.who.int/publications/m/item/considerations-for-optimizing-deployment-of-astrazeneca-azd1222-and-sii-covishield-vaccines-in-a-time-limited-constrained-supply-situation

[2] Background document on the AZD1222 vaccine against COVID-19 developed by Oxford University and AstraZeneca. March 5, 2021 https://www.who.int/publications/i/item/background-document-on-the-azd1222-vaccine-against-covid-19-developed-by-oxford-university-and-astrazeneca

[3] Voysey et al. Single-dose administration and the influence of the timing of the booster dose on immunogenicity and efficacy of ChAdOx1 nCoV-19 (AZD1222) vaccine: a pooled analysis of four randomised trials. The Lancet. 2021; 397:881-91 https://doi.org/10.1016/S0140-6736(21)00432-3

[4] Interim recommendations for use of the ChAdOx1-S [recombinant] vaccine against COVID-19 (AstraZeneca COVID-19 vaccine AZD1222, SII Covishield, SK Bioscience). 21 April 2021 https://www.who.int/publications/i/item/WHO-2019-nCoV-vaccines-SAGE_recommendation-AZD1222-2021.1

Post-introduction vaccine effectiveness (VE) studies have corroborated clinical trial findings and have greater statistical power to evaluate severe disease outcomes. In the United Kingdom, in the first 6-12 weeks after the first dose, reductions of greater than 80% (95%CI 36–95%) in hospitalizations and deaths were seen.[5,6,7,8] These observational studies indicate that protection against severe disease from one dose is robust within these 12 weeks.

What is the duration and extent of protection against COVID-19 of first dose beyond 12 weeks?

There is little information on clinical protection with only one dose beyond 12 weeks. The phase 3 clinical trial included a relatively small number of individuals who received a second dose beyond 12 weeks. Effectiveness and observational studies of national vaccination programmes are limited to an inter-dose interval of not more than 12 weeks at this time. However, binding antibodies against the COVID-19 spike protein have only a slow decay over a period of 6 months.[3] An immunological correlate of protection is yet to be established, but antibodies persist over at least through 26 weeks after the first dose, albeit at a lower level compared with the peak antibody levels. Because ChAdOx1-S [recombinant] vaccines induce both a T cell and B cell response, it is likely that there is some degree of protection against clinical disease conferred by one dose beyond 12 weeks, in particular against severe disease, defined as requiring hospitalization or causing death. However, data to quantify this are not currently available. Both seroconversion rates and antibody titres are only slightly lower in older adults after administration of one dose, compared with younger adults.

In a situation of limited supply, what is the evidence to use a different vaccine product (if available) as the second dose, to replace the ChAdOx1-S [recombinant] vaccine?

As all currently authorized COVID-19 vaccines comprise the same target (spike protein), it would be expected that a heterologous (mix and match) COVID-19 vaccine as a second dose would boost the immune response. A number of countries (i.e. Germany, France, Sweden, Finland, Denmark and Norway) have introduced mix and match schedules as a result of introducing age restrictions for ChAdOx1-S [recombinant] vaccines. These age restrictions were introduced in some countries to minimize the very low risk of Thrombosis with Thrombocytopenia Syndrome (TTS) that has been observed[9]. Data on immunogenicity and clinical effectiveness of that strategy and those regimens are not yet known. Based on immunological principles, it would be expected that a boosting of the immune response would occur. Data on safety of mixed schedules are preliminary as described below.

Data from only two mix and match studies are currently available in preprint, and involve the ChAdOx1-S [recombinant] vaccine and the Pfizer vaccine. The UK study investigates using two doses of the same vaccine (either ChAdOx1-S [recombinant] vaccine or Pfizer BNT162b2 vaccine) versus a mix of these two vaccines; the study finds that there is an increase in reactogenicity after the second dose when these two vaccines are given in a mixed schedule. Symptoms experienced by trial participants who received a mixed schedule included increased rates of fever, fatigue, chills and headaches when compared to participants that received the same vaccine for both doses.[10] Immunogenicity results from

[5] Lopez Bernal et al. 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. 2021.(preprint) https://www.medrxiv.org/content/10.1101/2021.03.01.21252652v1

[6] Hyams et al. Assessing the Effectiveness of BNT162b2 and ChAdOx1nCoV-19 COVID-19 Vaccination in Prevention of Hospitalisations in Elderly and Frail Adults: A Single Centre Test Negative Case-Control Study. The Lancet. 2021. (preprint). https://papers.ssrn.com/sol3/papers.cfm?abstract_id=3796835

[7] Vasileiou et al. Interim findings from first-dose mass COVID-19 vaccination roll-out and COVID-19 hospital admissions in Scotland: a national prospective cohort study. The Lancet. 2021;397:1646-57.(preprint). https://www.thelancet.com/journals/lancet/article/PIIS0140-6736(21)00677-2/fulltext

[8] Vasileiou et al. Effectiveness of First Dose of COVID-19 Vaccines Against Hospital Admissions in Scotland: National Prospective Cohort Study of 5.4 Million People. The Lancet. 2021.(preprint). https://papers.ssrn.com/sol3/papers.cfm?abstract_id=3789264

[9] Global Advisory Committee on Vaccine Safety (GACVS) review of latest evidence of rare adverse blood coagulation events with AstraZeneca COVID-19 Vaccine (Vaxzevria and Covishield) https://www.who.int/news/item/16-04-2021-global-advisory-committee-on-vaccine-safety-(gacvs)-review-of-latest-evidence-of-rare-adverse-blood-coagulation-events-with-astrazeneca-covid-19-vaccine-(vaxzevria-and-covishield)

[10] Shaw et al. Heterologous prime-boost COVID-19 vaccination: initial reactogenicity data. The Lancet.2021. https://doi.org/10.1016/S0140-6736(21)01115-6

this study are not yet available. Evidence of protection from mix and match schedules that include the ChAdOx1-S [recombinant] vaccine on SARS-CoV-2 infection and COVID-19 disease are also not available.

Given the absence of data on immunogenicity and the increase in reactogenicity when switching the second dose from ChAdOx1-S [recombinant] vaccine to the Pfizer BNT162b2 vaccine, countries are advised to wait for favourable immunogenicity data from the interchangeability studies before deciding on such a mix and match schedule. Further studies with other vaccine combinations with ChAdOx1-S [recombinant] vaccine, in a mix and match schedule, have not yet been completed.

What would be the impact of delaying the second dose of ChAdOx1-S [recombinant] vaccine against variants of concern (VOC)?

There is emerging evidence on the protective efficacy of ChAdOx1-S [recombinant] vaccine against VOC. The Phase 3 clinical trials and observational studies show that in the context of B.1.1.7 transmission, efficacy and effectiveness was maintained or only slightly decreased.[11,12,13] Data against P.1 are not yet available. Data on effectiveness of ChAdOx1-S [recombinant] vaccine against P.1.617.2 shows that a single dose provides only limited protection against this VOC. Two doses provide better protection, only modestly lower than against the B.1.1.7 variant[14]. Limited data are available on efficacy against clinical disease for the B.1.351 variant. A single, small efficacy trial from South Africa showed no statistically significant efficacy against mild to moderate disease, but was not designed to address whether the vaccine would be protective against severe disease.[15] Very limited data are available on the protection against VOC's after administration of one dose only and are insufficient to draw conclusions.

Current evidence does suggest that higher antibody titres are associated with better protection against severe disease.[16] Additionally, there is evidence to suggest that higher antibody levels are needed to neutralize some VOCs.[17] Studies of antibodies following immunization with ChAdOx1-S [recombinant] vaccine against B.1.351, P.1 and B.1.617 show that neutralizing activity is lower than against the ancestral strain.[18,19,20] This information is relevant because single dose vaccination results in lower antibody titres. Whether this translates into lower effectiveness against VOCs is currently unknown. It is possible that effectiveness against mild-moderate disease diminishes, but is more preserved against severe disease, but data are not yet available to inform this question.

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[11] Emary K. et al. Efficacy of ChAdOx1 nCoV-19 (AZD1222) vaccine against SARS-CoV-2 variant of concern 202012/01 (B.1.1.7): an exploratory analysis of a randomised controlled trial. Lancet. 2021; 397: 1351–62. https://doi.org/10.1016/S0140-6736(21)00628-0

[12] Shah AS, Gribben C, Bishop J, Hanlon P, Caldwell D, Wood R, et al. Effect of vaccination on transmission of COVID-19: an observational study in healthcare workers and their households. medRxiv [Preprint]. 2021. [Online] www.medrxiv.org/content/10.1101/2021.03.11.21253275v1 . DOI: 10.1101/2021.03.11.21253275.

[13] Public Health England. COVID-19 vaccine surveillance report Week 20. https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/988172/Vaccine_surveillance_report_-_week_20.pdf

[14] Bernal Lopes J et al. Effectiveness of COVID-19 vaccines against the B.1.617.2 variant. 2021. (preprint) https://khub.net/documents/135939561/430986542/Effectiveness+of+COVID-19+vaccines+against+the+B.1.617.2+variant.pdf/204c11a4-e02e-11f2-db19-b3664107ac42

[15] Madhi et al. Efficacy of the ChAdOx1 nCoV-19 Covid-19 Vaccine against the B.1.351 Variant. The New England Journal of Medicine.2021. https://www.nejm.org/doi/full/10.1056/nejmoa2102214

[16] Garcia-Beltran et al. COVID-19-neutralizing antibodies predict disease severity and survival. Cell. 2021;184(2):479-488. https://www.cell.com/cell/fulltext/S0092-8674%2820%2931685-8

[17] Garcia-Beltran et al. Multiple SARS-CoV-2 variants escape neutralization by vaccine-induced humoral immunity. Cell. 2021; 184:2372-83. https://www.cell.com/cell/pdf/S0092-8674(21)00298-1.pdf

[18] Dejnirattisai et al. Antibody evasion by the P.1 strain of SARS-CoV-2. Cell. 2021;184:1-16. https://www.cell.com/cell/pdf/S0092-8674(21)00428-1.pdf

[19] Yadav et al. Neutralization potential of Covishield vaccinated individuals sera against B.1.617.1. bioRxiv (preprint). https://www.biorxiv.org/content/10.1101/2021.05.12.443645v1.full.pdf

[20] Zhou et al. Evidence of escape of SARS-CoV-2 variant B.1.351 from natural and vaccine-induced sera. Cell. 2021;184(9):P2348-2361 DOI: https://doi.org/10.1016/j.cell.2021.02.037

As supply of the ChAdOx1-S [recombinant] vaccine becomes available, what is the evidence to use this supply to provide the second dose, or use the supply to further increase population-level coverage with first dose?

The answer to this question depends on various factors: In addition to the vaccine performance issues described above, country specific considerations such as the severity of the COVID-19 epidemiological situation, access to health services, progress on vaccine coverage of the high-priority populations (older persons, health workers; see WHO Prioritization Roadmap[21]), the circulation of specific VOCs, programmatic and communication issues also need to be considered. More detail is provided in WHO's guidance document.[1]

Based on mathematical modelling[22,23], for a vaccine with characteristics similar to those documented to date for ChAdOx1-S [recombinant] vaccine and under the assumption of a relatively high protection from the first dose, greater public health impact is expected by using available vaccine supply as first doses to increase coverage of the high-priority groups. **In other words, countries can prevent more deaths and hospitalizations at a population level if more people in the higher priority groups (e.g., older adults and health workers) are vaccinated, even with just one dose, than they can achieve by using existing vaccine supply for second dose administration of these very same groups in smaller numbers. For settings with substantial circulation of VOCs which have been shown to have reduced single doses effectiveness, the importance of providing the most vulnerable groups with 2 doses must be considered.**

If circulating VOC result in a substantially lower one-dose efficacy relative to two doses, and/or if clinical protection wanes very quickly, then modelling evidence[16] supports prioritization of delivery of second doses to the high-priority groups instead of providing a single dose to all adults. This note may be updated in the future based on emerging evidence on vaccine effectiveness, duration of protection, and modelling in various country settings.

If the ChAdOx1-S [recombinant] vaccine is given more than 12 weeks after the first dose, does the vaccination series need to be restarted?

If the second dose is administered with substantial delay beyond the recommended 8-12 weeks interval, there is no need to restart a full course of vaccination. Unpublished data show a strong anamnestic response even after an interval between doses of 6 months, indicating that the first dose provides robust immunological priming.

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