Considerations for optimizing deployment of AstraZeneca/AZD1222 and SII/Covishield vaccines in a time-limited constrained supply situation

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KEY MESSAGES

- The generic group of ChAdOx1-S [recombinant] vaccines includes AstraZeneca/AZD1222 and SII/Covishield vaccines. For prolonged efficacy using ChAdOx1-S vaccines, **WHO recommends two standard doses (0.5ml) administered with an interval of 8 to 12 weeks between doses.**

- Clinical trials have demonstrated that after vaccination with a single 0.5ml dose, an efficacy as high at 76.0% (95% CI 59.3–85.9) could be expected against laboratory-confirmed Covid-19, as measured from 22 days after vaccination through 12 weeks.[1]

- **Evidence has demonstrated sustained vaccine efficacy after a single 0.5ml dose for a period of up to 12 weeks (3 months), yet antibody concentrations declined by 34% through 90 days**.[2] Limited data is available on the duration of efficacy or rapidly waning immunity past 12 weeks, and a second dose has been shown to maintain high efficacy.

- Unpublished mathematical modeling demonstrates that when supply is very limited during the initial introduction period, vaccinating more people in the highest priority population group with one dose as opposed to vaccinating half that number with two doses, would substantially increase the number of deaths prevented, if the 1-dose vaccine efficacy is at least 50% of the 2-dose efficacy.

- In view of the evidence suggesting the potential for disease rates to be reduced following administration of the first dose and data from mathematical modelling, **national immunization programmes faced with limited supply of AstraZeneca/AZD1222 or SII/Covishield vaccine might elect a strategy of vaccinating a maximum number of persons within a higher number of priority groups with a first dose and preferentially planning for the second dose to be provided at 12 weeks (3 months) later, or as soon as possible thereafter.**

- Given the equivalence of AstraZeneca/AZD1222 and SII/Covishield to ChAdOx1-S, the two products are interchangeable.

[1] Voysey et al. Lancet 2021; 397:881-91 https://doi.org/10.1016/S0140-6736(21)00432-3
[2] Voysey et al. Lancet 2021; 397:881-91 https://doi.org/10.1016/S0140-6736(21)00432-3

Purpose: This document provides an overview of the scientific basis and key programmatic considerations to guide national decision-making for countries on optimizing the deployment of AstraZeneca/AZD1222 and SII/Covishield vaccines under circumstances where vaccine supply is constrained, and future quantities and delivery dates cannot be reliably predicted. Further details on the available evidence and key studies are available at the SAGE website, while resources for implementation and training are available at the COVID-19 vaccine introduction toolkit webpage. [3,4]

Context: Currently, the global market supply of AstraZeneca/AZD1222 and SII/Covishield vaccines, both provided under the COVAX Facility, does not fully meet global demand.[5] While supply is expected to increase through the second half of 2021, the frequency of shipments to countries remains uncertain in the near to medium term and residual shelf life at the time of delivery may be as short as three months. Countries receiving fewer doses than required to fully vaccinate all highest priority groups will be challenged to strike the proper balance across key objectives:

- Maximizing immunity against COVID-19 in the highest priority groups according to the recommended schedule;
- Reaching as many people within as many priority groups as quickly as possible, with at least one dose; and
- Fully administering all doses available prior to their lot expiration date.

In the current supply situation that is dynamic and uncertain, it may not be possible to simultaneously pursue all three of the above objectives. Countries may need to consider modifying their planned vaccination strategies to achieve maximum protective impact, considering the quantity and shelf-life of vaccine received and the estimated time frame and quantities of future deliveries.

A. Evidence base

WHO SAGE interim recommendations on the AstraZeneca COVID-19 vaccines refer to a generic group of ChAdOx1-S [recombinant] vaccines against COVID-19. The ChAdOx1-S [recombinant] vaccine uses a DNA adenovirus vector to elicit antibodies to the SARS-CoV-2 spike protein. WHO recommendations apply to the AZD1222 product developed jointly by Oxford University (United Kingdom) and AstraZeneca, as well as to ChAdOx1-S [recombinant] vaccines produced by other manufacturers, namely AstraZeneca/AZD1222 (produced by AstraZeneca-SKBio in the Republic of Korea) and SII/Covishield (produced by the Serum Institute of India). Each of these products rely on the AstraZeneca core clinical data and demonstrated equivalence in their regulatory and WHO reviews. Conditional marketing authorization (CMA) by the European Medicines Agency (EMA) of the AstraZeneca/AZD1222 vaccine was received on 29 January 2021. WHO granted Emergency Use Listing (EUL) for both products on 15 February 2021.[6]

Current estimates on product efficacy are drawn from the pooled analysis of data from four randomized, controlled clinical trials conducted in the United Kingdom (two studies), Brazil, and South Africa, involving

[3] https://www.who.int/groups/strategic-advisory-group-of-experts-on-immunization/covid-19-materials
[4] https://www.who.int/tools/covid-19-vaccine-introduction-toolkit
[5] https://www.gavi.org/covax-vaccine-roll-out
[6] https://www.who.int/news/item/15-02-2021-who-lists-two-additional-covid-19-vaccines-for-emergency-use-and-covax-roll-out

approximately 24,000 adults aged 18 year and older. As the examined interval lengths between dose 1 and dose 2 varied across the different studies, inter-dose efficacy described below has been estimated. [7]

For the purpose of describing the scientific evidence supporting these products, the generic name of ChAdOx1-S will be used in the table below. It should be noted that given the equivalence of AstraZeneca/AZD1222 and SII/Covishield to ChAdOx1-S, the two products are interchangeable.[8]

Recommended schedule	WHO recommends that the **optimal regimen for prolonged efficacy using ChAdOx1-S vaccine consists of two standard doses (0.5ml) administered with an 8 to 12 week interval between doses.** As more data become available, this recommendation may be updated.
Vaccine efficacy with 2 doses	**ChAdOx1-S vaccines have an efficacy of 66.7% (95% CI 57.4-74.0) against symptomatic SARS-CoV-2 infection after administration of two doses.** Vaccine efficacy increased significantly when the interval between dose 1 and dose 2 was longer than 4 weeks. There is no data on vaccine efficacy when two doses are given with less than 4 weeks interval in between doses. Recent immunogenicity data also shows a binding antibody response more than two-fold higher after an interval of ≥12 weeks compared with an interval of <6 weeks.[9]
Vaccine efficacy with 1 dose	Efficacy after dose 1 has been shown to be high and persists through at least 12 weeks. Clinical trials have demonstrated that **after vaccination with a single 0.5ml dose, an efficacy as high at 76.0% (95% CI 59.3–85.9) could be expected against laboratory-confirmed Covid-19, as measured from 22 days after vaccination through 12 weeks.**[10] Limited data is available on the duration of efficacy or rapidly waning immunity past 12 weeks, and a second dose has been shown to maintain high efficacy. Observational studies on the effectiveness of COVID-19 vaccines after administration of the first dose have confirmed a very high vaccine effect against hospitalization (between 80-94%), including in older adults.[11,12,13]
Duration of immunity after 1 dose	**After vaccination with a single 0.5ml dose of vaccine, evidence has demonstrated sustained vaccine efficacy through the subsequent observation**

[7] https://www.who.int/publications/i/item/background-document-on-the-azd1222-vaccine-against-covid-19-developed-by-oxford-university-and-astrazeneca
[8] https://www.who.int/publications/i/item/WHO-2019-nCoV-vaccines-SAGE_recommendation-AZD1222-2021.1
[9] Voysey et al. Lancet 2021; 397:881-91 https://doi.org/10.1016/S0140-6736(21)00432-3
[10] Voysey et al. Lancet 2021; 397:881-91 https://doi.org/10.1016/S0140-6736(21)00432-3
[11] Lopez Bernal J, et al. MedRxiv preprint. https://doi.org/10.1101/2021.03.01.21252652
[12] Hyams C, et al. Lancet preprint. https://papers.ssrn.com/sol3/papers.cfm?abstract_id=3796835
[13] Vasileiou et al, Lancet preprint. https://papers.ssrn.com/sol3/papers.cfm?abstract_id=3789264

	period of up to 12 weeks (3 months), yet antibody concentrations declined by 34% through 90 days**.**[14] The duration of antibody presence and viral neutralization capacity has yet to be estimated beyond that time.

Mathematical modelling. Current unpublished mathematical modeling demonstrates that when supply is very limited during the initial introduction period, **vaccinating more people in the highest priority population group with one dose as opposed to vaccinating half that number with two doses would substantially increase the number of deaths prevented, as long as the 1-dose vaccine efficacy is at least 50% of the 2-dose efficacy.** As supply increases and the highest priority populations all receive one dose, a decision about using supply to vaccinate that group with a second dose or advance with first doses to the next risk group is needed. The decision depends on the relative risk of mortality between the priority risk groups, the relative vaccine efficacy of 1-dose and 2-doses, the durability of the 1-dose efficacy over time, and the supply pace.

As supply increases and the rollout moves to ever lower risk groups, the model indicates that the highest risk groups should be prioritized to complete their vaccination with a second dose in lieu of continuing to offer first doses to a lower priority group. The specific point at which this blended strategy should occur depends on supply volumes, pace, population sizes, relative disease risks, and vaccine efficacy characteristics.

Prioritizing first dose administration at the outset of the programme to highest priority groups is expected to provide greater benefit when supply is very limited; this holds true even when supply is insufficient to administer the second dose in a timely manner, as long as waning of first dose immunity is not very rapid.

B. Programmatic considerations

Given the short timelines from vaccine development to EUL, the available stability data for the AstraZeneca/AZD1222 and SII/Covishield vaccine only permit authorization with a shelf life of six months, as is the case for other COVID-19 vaccines. This is a much shorter shelf life than vaccines normally handled in the EPI programme, so any vaccination strategy with AstraZeneca/AZD1222 or SII/Covishield requires careful planning and accelerated implementation by countries to ensure that the vaccines can be administered prior to the lot expiration date.

Given the global production constraints and unpredictable nature of the frequency and quantity of future shipments, each country will need to properly evaluate what is operationally relevant in their national context. A range of programmatic factors are cited below for consideration; many of the factors are inter-linked and cannot be viewed independently. It is recommended that the NITAG plays a central role in the decision-making process, actively participating in the assessment of the risks and benefits of each alternative under consideration.

[14] Voysey et al. Lancet 2021; 397:881-91 https://doi.org/10.1016/S0140-6736(21)00432-3

Factor	Consideration
Size of priority groups to vaccinate (target population)	Relative to available or anticipated stock in country and anticipated shipments of additional doses, countries will need to calculate whether supply is sufficient to administer a 2-dose schedule for all desired priority groups, with an 8-12 week interval between dose 1 and dose 2. The identification of desired priority groups would be informed by national strategies and the ongoing COVID-19 transmission scenarios. If vaccine supply is insufficient to cover the target population with 2 doses, then countries should consider: **Option A:** Narrowing the number of target individuals by stratifying risk within the priority groups and providing all target individuals with 2 doses; or **Option B:** Stretching all available doses to vaccinate priority groups with at least one dose until supply is replenished. This option would provide an estimated efficacy of 76.0% against laboratory-confirmed Covid-19 after the first dose, with no waning immunity for a period of up to 12 weeks.
Vaccination delivery strategy	Different vaccination delivery strategies will impact the "speed" at which available doses can be administered. For example, a crowded urban center will face faster administration rates than a rural health facility. Countries should estimate the vaccine administration rate of their overall delivery strategy for the various target groups, taking into consideration the scheduled interval between dose 1 and dose 2, shelf life of the doses and logistical requirements (bearing in mind not to compromise equity). To ensure that the second dose can be provided within the 8-12 week interval, target populations will have to be reached very quickly with the first dose in order to allow for a second dose to be administered before the expiration date. If vaccine administration rate is expected to be slower, then administering one dose to a larger group of people may be necessary to maximize consumption of all vaccine before expiration. When scheduling vaccination for occupational groups, e.g., health workers, consideration should be given to the reactogenicity profile of the vaccine as observed in clinical trials, as vaccination may result in work absences for 24–48 hours post-vaccination.
Timing of future vaccine shipments	The timing of future vaccine shipments and quantity of doses may be uncertain and may result in a delivery schedule that does not allow full implementation of a country's initial vaccination plans. It should be noted that AstraZeneca/AZD1222 and SII/Covishield are interchangeable products, so shipments from different sources can be used in combination. There are strict conditions, however, under which COVAX financed vaccines must be tracked and traced for no-fault compensation purposes. [15]

[15] https://www.who.int/news/item/22-02-2021-no-fault-compensation-programme-for-covid-19-vaccines-is-a-world-first

	When vaccine resupply is uncertain, then countries must consider: **Option A:** Adjusting the size of the initial target population by stratifying risk within the priority groups to provide all highest risk, highest priority target individuals with two doses so the doses can be consumed prior to expiration date; or **Option B:** Stretching all available doses to vaccinate priority groups with at least one dose until supply is replenished, recognizing that an efficacy of 76.0% could be expected with no waning immunity for a period of up to 12 weeks. In this situation the country may consider maximizing the interval between doses to 12 weeks to provide more flexibility to accommodate the uncertain arrival of the replenishment. However, there could be the risk that additional shipments will not arrive within 12 weeks; the second dose should be provided as soon as possible thereafter.
Interval between dose 1 and dose 2	The recommended interval of 8-12 weeks between dose 1 and dose 2 allows some flexibility in delivering dose 2. Since vaccine efficacy increases with a longer duration between doses, it can be advantageous to extend the inter-dose interval up to 12 weeks. In a supply constrained scenario, erring on the side of accommodating longer time intervals between administration of doses is more prudent. Administration of the 2nd dose prior to 8 weeks is likely to result in lower long-term efficacy and is not advisable.
Recording	All doses administered should be recorded in accordance with national policy, and all vaccinees should be given a date to return for the second dose. If vaccine stocks are known to be limited and resupply uncertain, vaccinees should be advised to return in 12 weeks, and countries should establish a mechanism for contacting or communicating with first dose vaccine recipients if the second dose must be delayed beyond the 12 weeks. If there are unexpected delays, the second dose should be provided as soon as possible thereafter.
Public communication	Communication strategies should be adapted to clearly and simply explain the vaccine schedule to the public as necessary. This is especially critical if the country decides to initially adopt wide-spread vaccination with one dose. Effective communication explaining the rationale for the strategy as an interim measure, information on vaccine efficacy, and details regarding the potential timing for second dose administration are all important messages that need to be correctly understood by health workers and the public.

Conclusion

In view of the evidence suggesting the potential for disease rates to be reduced following administration of the first dose, **national immunization programmes faced with limited supply of AstraZeneca/AZD1222 or SII/Covishield vaccine might elect a strategy of vaccinating a maximum number of persons within a higher number of the priority groups with a first dose and preferentially planning for the second dose to be provided at 12 weeks (3 months) later, or as soon as possible thereafter.** Data supporting an extension beyond three months has yet to become available.

It should be noted that clinical trials did not assess the impact on antibody response if the interval between administration of dose 1 and dose 2 is extended beyond 12 weeks, nor what impact this would have in relation to protection against any circulating SARS-CoV-2 virus variants.

As further research on vaccine effectiveness is undertaken and risk monitoring associated with SARS-CoV-2 viral mutations allows for a better assessment of required responses, further information will be made available.