Evidence Summary on COVID-19 Vaccine (ChAdOx1-S [recombinant]) (*COVID-19 Vaccine AstraZeneca)* for the prevention of COVID-19

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Background

The COVID-19 pandemic, caused by severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2), has led to more than two million deaths worldwide, global economic and social disruption, and unprecedented challenges in the health system. As the world continues to face these challenges, several efforts, such as developing and implementing different health technologies that will ultimately lead us to our exit strategy from the crisis, were undertaken. Among these health technologies are vaccines against COVID-19 which are currently in different phases of trials around the world. Similar to other countries, the Philippine government has been exploring all means to access these vaccines and to prepare the country for its upcoming implementation within the coming months.

On January 28, 2021, the Philippine Food and Drug Administration (FDA) released the Emergency Use Authorization (EUA) for COVID-19 Vaccine (ChAdOx1-S[recombinant]) *(COVID-19 Vaccine AstraZeneca)* with Chimpanzee Adenovirus encoding the SARS-CoV-2 Spike glycoprotein (ChAdOx1-S) as its viral vector.

To date, at least eight countries have issued an EUA for this product in their respective jurisdictions and have started vaccine implementation. This vaccine is one of the few COVID-19 vaccines which has already published its Phase III trial interim results.

Basic information on *COVID-19 Vaccine AstraZeneca* is provided below:

Table 1.1 Characteristics of *COVID-19 Vaccine AstraZeneca*

Trade name	COVID-19 Vaccine AstraZeneca
Other name	COVID-19 Vaccine (ChAdOx1-S[recombinant]), AZD1222
Manufacturer/s	AstraZeneca AB (initiated by the University of Oxford with subsequent transfer of development activities to AstraZeneca AB)
Vaccine platform	Viral vector vaccine [Chimpanzee Adenovirus encoding the SARS-CoV-2 Spike glycoprotein (ChAdOx1-S)]
Dose strength and administration	Consists of 2 doses of 0.5 mL each; Dose 2 should be administered between 4 and 12 weeks after dose 1
Route of administration	Solution for injection, Intramuscular (IM)

Drug delivery system	Multidose vial of 2 different sizes: 10 dose vial (5 mL) in packs of 10 vials; 8 dose vial (4 mL) in packs of 10 vials
Storage condition	2-8°C; do not freeze; protect from light; shelf life = 6 months
Mechanism of action	Monovalent vaccine composed of a single recombinant, replication-deficient chimpanzee adenovirus (ChAdOx1) vector encoding the S glycoprotein of SARS-CoV-2. Following administration, the S glycoprotein of SARS-CoV-2 is expressed locally stimulating neutralising antibody and cellular immune responses. *(UK MHRA, 2020)*
PHL EUA status	Released as of 28 January 2021 *https://drive.google.com/file/d/1ceNnSHr63K_jIvuPmSJmY9xJT27NaFO9/view?usp=sharing*
PHL FDA EUA indication	For active immunization of individuals ≥18 years old for the prevention of coronavirus disease 2019
WHO EUL status	Not yet approved

Pursuant to the role of the Health Technology Assessment Council (HTAC) to develop coverage recommendations particularly in the selection and financing of COVID-19 vaccines using the Evaluation Framework set by the HTAC, this report presents all currently available evidence considered in the assessment of *COVID-19 Vaccine AstraZeneca*. This assessment follows the HTAC evaluation framework to assess COVID-19 vaccines using the following criteria: (1) responsiveness to magnitude and severity; (2) clinical efficacy and safety; (3) affordability and viability; (4) household financial impact; (5) social impact; and (6) responsiveness to equity.

Policy Question

The HTAC aims to answer the policy question:

Should **COVID-19 Vaccine (ChAdOx1-S [recombinant]) *(COVID-19 Vaccine AstraZeneca)*** be recommended for emergency use to reduce COVID-19 cases, severe infection, and deaths?

Recommendation

The HTAC **recommends the emergency use of *COVID-19 Vaccine AstraZeneca*** to reduce the burden of COVID-19 among eligible populations aged 18 years and older .

While there is insufficient direct evidence regarding efficacy and safety for ages 56 years and older based on the interim results of the Phase III trial on *COVID-19 Vaccine AstraZeneca* (Voysey et al, 2020) *[cut-off analysis: date: 04 November 2020]*, protection is expected given the immunogenicity profile seen in this age group and based on the experience of other countries with other vaccines, according to the European Medicines Agency (EMA). Using COVID-19 Vaccine AstraZeneca for the population aged 56 years and above is deemed acceptable. Further findings are expected from ongoing studies, which include a greater number of elderly participants.

The HTAC considered the following criteria in formulating its recommendation for the vaccine:

Criteria	HTAC Judgment
Can *COVID-19 Vaccine AstraZeneca* significantly reduce the magnitude and severity of COVID-19?	**Yes**. *COVID-19 Vaccine AstraZeneca*, with 62% efficacy has the potential to reduce the disease burden by averting a significant number of symptomatic infections and deaths assuming sufficient vaccine coverage.
Is *COVID-19 Vaccine AstraZeneca* efficacious and safe?	Based on the interim results of the Phase III trial on *COVID-19 Vaccine AstraZeneca* (Voysey et al, 2020) *[cut-off analysis: date: 04 November 2020]:* **Yes**, it is efficacious for preventing symptomatic COVID-19 based on moderate certainty of evidence. COVID-19 Vaccine AstraZeneca may also reduce hospitalization due to COVID-19 based on low certainty of evidence. However, we note that the vaccine efficacy precision is

	low for this outcome. Currently, the reported vaccine efficacy of *COVID-19 Vaccine AstraZeneca* on severe COVID-19 and asymptomatic COVID-19 is still inconclusive based on low certainty of evidence. The duration of protection cannot be assessed given the current data. **Yes**, it is safe in the known short-term safety outcomes, based on moderate certainty of evidence. Meanwhile, its long term safety outcomes are inconclusive based on low certainty of evidence. It should not be given to individuals below 18 years old and to those with a known history of severe allergic reaction to any component of the vaccine. While vaccination is not contraindicated in other special populations who were excluded in the analysis/trials (i.e., immunocompromised patients, pregnant and lactating women), close medical supervision will be required.
Is *COVID-19 Vaccine AstraZeneca* affordable and feasible to use in a national immunization program (viability)?	**Yes.** It is affordable. The share of the cost to implement vaccination using *COVID-19 Vaccine AstraZeneca* will constitute 21.45% of the total allocated budget for vaccination and will cover 40% of the 70 million target vaccinees for 2021. **Yes**, it is feasible as there are no significant barriers in vaccine implementation using *COVID-19 Vaccine AstraZeneca* in terms of storage, transport, and handling. However, there is still a need for training of vaccinators to ensure product integrity across the entire supply chain and close monitoring of adverse events.
Does *COVID-19 Vaccine AstraZeneca* reduce out-of-pocket (OOP) expenses of households due to COVID-19?	**Yes.** Based on interim *results from the clinical trial, COVID-19 Vaccine AstraZeneca showed vaccine efficacy to reduce risk for hospitalization due to COVID-19 by 87.6%, based on low certainty*

	of evidence. Thus, COVID-19 Vaccine AstraZeneca has the potential to reduce out-of-pocket expenses of Filipino households due to reduction of hospitalizations.
Does *COVID-19 Vaccine AstraZeneca* possess the characteristics desired by key stakeholders? (Social Impact)	**Yes.** Based on short term outcomes, *COVID-19 Vaccine AstraZeneca* possesses most of the characteristics desired by key stakeholders.
Does *COVID-19 Vaccine AstraZeneca* reduce or not further add to existing inequities in the health system?	**Yes.** Because of non-stringent logistic requirements, *COVID-19 Vaccine AstraZeneca* **does not aggravate** health inequities related to inoculation of recipients residing in isolated and disadvantaged locations. We also note that the trial population did not include important groups such as individuals aged 18 and below, immunocompromised individuals, pregnant and lactating women.

The HTA Council further emphasizes the need to enforce strict conditions for the emergency use of health products to safeguard against eventualities:

- Transparency and accountability in the processes of allowing emergency use of health products, especially for the public health response;
- Continuous collection of safety and effectiveness data in the context of clinical trials and actual use in the real world;
- Close monitoring of recipients and safeguards for expected and unexpected adverse events that may arise from the use of health products under an EUA;
- National coordination of the emergency use under the Philippine FDA and the DOH;
- Cascading of complete information to vaccinees on potential risks and benefits, and securing of informed consent with regard to receiving the intervention; and
- Just compensation mechanisms and provisions for medical management of adverse events for patients and vaccinees assured by the national government

Finally, the HTAC recommends the conduct of research to address the current gaps in evidence with regard to the use of the *COVID-19 Vaccine AstraZeneca*:

- Real-world effectiveness in the Philippine context particularly focused on the following:
    - Effectiveness in reducing COVID-19 cases, hospitalizations and deaths, and preventing outbreaks and transmission of disease across the population
    - Effectiveness in reducing asymptomatic infection
    - Duration of protection
    - Impact of the timing and number of doses received
    - Probable need for booster dosing
    - Differences in the effectiveness of the vaccine among special populations (i.e., elderly, individuals with comorbidities, pregnant and lactating women, immunocompromised patients)
    - Effectiveness of the vaccine against emerging SARS-CoV-2 viral strains
- Continuous safety surveillance and monitoring of all adverse events especially severe allergic reactions, Bell's palsy, serious adverse events and adverse events of special interest (AESI) following vaccination
    - Across the general population
    - In special populations: elderly, patients with comorbidities, pregnant and lactating women, immunocompromised individuals
- Randomized controlled trials should also be done among populations not currently included in clinical trials: children below 18 years of age
- Best practices, challenges, and barriers in implementation across different localities
- Monitoring of unexpected or additional costs associated with vaccine implementation.

Current Evidence on *COVID-19 Vaccine AstraZeneca*

The table below summarizes the appraisal of available evidence on *COVID-19 Vaccine AstraZeneca* against the HTAC evaluation framework.

In addition, the following appendices are provided for further details:

- Appendix 1. Evidence on evaluation criterion 2 - Clinical Efficacy and Safety
- Appendix 2. Evidence on evaluation criterion 3 - Affordability and Viability
- Appendix 3. References
- Appendix 4. Acknowledgment

Table 1.2 Key Findings in the Current Evidence Considered for the HTAC Evaluation of ***COVID-19 Vaccine AstraZeneca***

Evaluation Criteria	Question	Current Evidence	HTAC specification
1. Responsiveness to magnitude and severity	*Can the COVID-19 vaccine Astrazeneca significantly reduce the magnitude and severity of COVID-19?*	As of 31 January 2021, the total number of cases has exceeded more than 102 million cases and breached the 2 million mark in terms of the total number of deaths globally. In the Philippines, the cumulative number of laboratory-confirmed COVID-19 cases has already exceeded 525,000 cases with total deaths reported at 10,700 as of 31 January 2021. Based on the DOH-Epidemiology Bureau data, the young and productive age groups (20-49 years old) have the most exposure and highest prevalence of the disease. However, the most vulnerable are the senior citizens (>60 years) who have the highest case fatality rate (CFR) at 9.9% and comprise around 80% of COVID-19 deaths. In addition, individuals with existing comorbidities such as chronic kidney disease (CKD), chronic obstructive pulmonary disease (COPD), other pulmonary, cardiovascular and blood diseases are also vulnerable with CFR reported at around 25%. COVID-19 has led to significant disruptions not only in the delivery of other priority health services (e.g., immunization, maternal and child health, noncommunicable diseases) but also in the social	The vaccine can potentially reduce the COVID-19 disease burden (health, social and economic impact).

		and economic life of the nation by arresting the growth of the economy, displacing migrant and local workers, loss of jobs, and food insecurity (NEDA, 2020; PSA 2020; TESDA, 2020). Social safety nets for the poorest and other vulnerable sectors have not been enough to compensate for these losses (TESDA, 2020). The lockdowns and community quarantines have also been shown to have an impact on the mental health of Filipinos and have affected how common Filipino households adjust under the new normal, unable to visit and freely enjoy quality time with members of their families, as captured in some focus group discussions conducted by the HTAC and the HTA Unit. The potential impact of the COVID-19 Vaccine *AstraZeneca* vaccine in addressing the current burden of COVID-19 disease may be gleaned from the following: ● Modeling studies in the US concluded that a vaccine efficacy of 60% can avert 75% of symptomatic infections and deaths at approximately 60% coverage (Matrajt, 2020). These simulations assumed that children are less susceptible to infection than middle age adults, while older adults were more susceptible, and that both natural and vaccine-induced immunity last	

		at least one year. The study also assumed that 20% of the population have already been infected and are immune and all social distancing have been lifted, vaccinated individuals achieved full protection conferred by the vaccine and front-line healthcare workers and other essential personnel who should be prioritized, have already been vaccinated. ● A different simulation experiment suggested that to prevent an epidemic, the vaccine efficacy has to be at least 60% when vaccine coverage is 100% (reproduction number at 2.5 - 3.5). This vaccine efficacy threshold rises to 70% when coverage drops to 75% (Bartsch et al., 2020). Locally-contextualized modelling studies are needed for more accurate projections of the potential impact of vaccination along with other interventions, under different scenarios. These can better inform decision-making. **HTAC JUDGMENT**: *COVID-19 Vaccine AstraZeneca* has the potential to reduce the disease burden by averting a significant number of symptomatic infections and deaths assuming sufficient vaccine	

		coverage.	
2. Clinical efficacy and safety	*What is the efficacy of the COVID-19 Vaccine AstraZeneca in terms of reducing the incidence and/or severity of COVID-19 in the general and vulnerable populations?*	Currently, there is one published report (Voysey et al., 2020) [cut off date of analysis: 04 November 2020] which is a pooled interim analysis of efficacy and safety data of *COVID-19 Vaccine AstraZeneca* from four clinical trials (two Phase I/II trials and two Phase II/III trials). These trials included individuals 18 years of age or older who received 2 doses of *COVID-19 Vaccine AstraZeneca* or control (Meningococcal ACWY or placebo). One of the four sub-trials included two dosage groups: (1) a cohort who received low dose for their dose 1 and standard dose for their dose 2 prior (LD/SD) and (2) a subsequent cohort who received standard doses as their first and second dose (SD/SD) after the protocol was amended on 5 June 2020. Further, dosing intervals across the study population varied. Out of the four sub-trials, only two (one Phase II/III and one Phase III trial) were included in the efficacy analysis. Based on interim results of this trial: ● For critical efficacy outcomes: ○ Using *COVID-19 Vaccine AstraZeneca,* compared to Meningococcal ACWY or placebo, reduces the risk for: - Symptomatic COVID-19 more than 14 days after dose 2 (SD/SD) by 62.1% (95% CI: 41.0 to 75.7) [moderate	The vaccine achieves the following efficacy parameters: Preferred VE: ≥70% reduction in the risk of symptomatic infection with vaccination versus no vaccination **Minimum acceptable VE: 50% reduction** in the risk of symptomatic infection with vaccination versus no vaccination The following factors were taken into consideration upon setting the minimum acceptability of 50% efficacy: pandemic situation, no standard COVID-19 vaccine, limited production from each manufacturer, and the need for multiple sources of vaccines in the Philippines.

		certainty of evidence] - Hospitalization due to COVID-19 after at least one dose (LD/SD+SD/SD) by 87.59% (95% CI: 46.03 to 97.15); however, the precision is low [low certainty of evidence]. ○ *COVID-19 Vaccine AstraZeneca*, compared to MenACWY or placebo, shows inconclusive vaccine efficacy (VE) against the following critical efficacy outcomes: - Hospitalization due to COVID-19 more than 14 days after dose 2 (LD/SD+SD/SD) (VE cannot be estimated due to low number of events), [low certainty of evidence] - Severe COVID-19 after at least one dose (LD/SD+SD/SD) (VE cannot be estimated), and severe COVID-19 more than 14 days after dose 2 (LD/SD+SD/SD) (VE cannot be estimated) [low certainty of evidence] ● For <u>important efficacy outcomes:</u> ○ Using *COVID-19 Vaccine AstraZeneca*, compared to MenACWY or placebo, reduces the risk for: - Symptomatic COVID-19 more than 14 days after dose 2 (LD/SD+SD/SD) by 70.4% (95.8% CI: 54.8 to 80.6) [high certainty of evidence] - Symptomatic COVID-19 more than 14	Adapted from WHO, US FDA, other stringent regulatory authorities *Note: Pending legal provision allowing the use of evidence based on Phase III interim results*

		days after dose 2 with ≥ 6 weeks dosing interval (SD/SD) by 65.4% (95% CI: 41.1 to 79.6) [moderate certainty of evidence] - Symptomatic COVID-19 after at least 1 dose (SD/SD) by 64.1% (95% CI: 50.5 to 73.9) [high certainty of evidence] - Symptomatic COVID-19 more than 14 days after dose 2 in the population with comorbidities by 73.4% (95% CI: 48.5 to 86.3) [low certainty of evidence] ○ COVID-19 vaccine AstraZeneca, compared to MenACWY or placebo, shows inconclusive vaccine efficacy against the following important efficacy outcomes: - Symptomatic COVID-19 more than 14 days after dose 2 with less than 6 weeks dosing interval (SD/SD) [VE: 53.4% (95% CI: -2.5 to 78.8), moderate certainty of evidence]. - Asymptomatic COVID-19 after dose 2 (LD/SD+SD/SD) [VE: 27.3% (95% CI: -17.2 to 54.9), low certainty of evidence] Meanwhile, *COVID-19 Vaccine AstraZeneca* has no reported VE specific for Asians (4.4% of the study population) and older adults (≥56 years old, 12.2% of the efficacy population). The only data available for older adults came	

		from a product information document approved by the EU Committee for Medical Products for Human Use (CHMP) (pending endorsement by the European Commission) which has reported that among participants aged between 56 and 65 years old, there were 8 cases of COVID-19 reported in the intervention group (≥15 days post dose 2) compared with 9 cases for the control group. Meanwhile, there were 2 and 6 cases of COVID-19 reported in participants older than 65 years of age, for the intervention (≥15 days post dose 2) and control groups, respectively. In view of the limited efficacy and safety data specific for older adults, immunogenicity data for older adults were also reviewed as a surrogate outcome for protection against clinical disease: ● Based on preliminary reports from COV002 sub-trial (Ramasamy et al., 2020): - There is an increase in anti-spike IgG response in the vaccine arm as compared to the control across different age groups (18-55 years, 56-69 years, and ≥70 years).	

		- Similar levels of antibody titres were seen across the three age groups 28 days after receiving the second dose (SD/SD). ● Further, based on the pooled immunogenicity analysis of the four sub-trials (UK MHRA, 2020): - The Geometric Mean Titres (GMT) levels for pseudoneutralization antibodies were lower in older adults than in younger adults. However, an increase in GMT can still be observed when compared to the GMT of participants in the control group. Further, we note that the trial excluded populations with the following conditions: ● immunodeficiencies or on chronic immunosuppressant therapy; ● history of angioedema or anaphylaxis; ● severe and/or uncontrolled cardiovascular disease, respiratory disease, gastrointestinal disease, liver disease, renal disease, endocrine disorder and neurological illness (mild/moderate well controlled comorbidities are allowed); ● pregnancy, lactation or intention to become pregnant during the study (continuous effective contraception was required during the course of the study).	

		Lastly, there is a need for more evidence to establish the effect of dosing interval on VE in order to establish the appropriate/ recommended dosing interval. *Note: VE appears higher if the dosing interval is ≥ 6 weeks [VE: 65.4%(41.1 to 79.6)] versus if the dosing interval is < 6 weeks [VE: 53.4% (-2.5 to 78.8], although there is little data at this point to state this conclusively [moderate quality of evidence].* **HTAC Judgment**: While the best efficacy estimate using the standard dose of the *COVID-19 Vaccine AstraZeneca* is at 62.1% which satisfies the minimum acceptable efficacy, the HTAC notes the wide confidence interval with a lower limit of VE at 41.0%. We note that there is a need to establish the effect of dosing interval on VE in order to establish the optimum dosing interval. The vaccine may provide more benefit for the population with mild to moderate, stable comorbidities with a VE of 73.4%. While there is insufficient direct evidence regarding efficacy and safety for ages 56 years and older, protection is expected given the immunogenicity profile seen in this age group and based on the experience of other countries with other vaccines, according to the European Medicines Agency (EMA). Using *COVID-19 Vaccine AstraZeneca* for the	

		population aged 56 years and above is thus deemed acceptable. Further findings are expected from ongoing studies, which include a greater number of elderly participants. Lastly, we note that there is insufficient evidence on the efficacy and safety of this vaccine for those with severe and/or uncontrolled comorbidities given that this population was excluded from the trial.	
	What is the duration of protection of the COVID-19 Vaccine AstraZeneca in terms of reducing the incidence and/or severity of COVID-19?	Current interim evidence shows protection against laboratory-confirmed symptomatic COVID-19 infection based on a minimum median follow up period of two months after receiving two doses. Data on the duration of protection will be reassessed as more evidence becomes available. **HTAC Judgment:** Cannot be assessed based on current data	**Minimum acceptable duration of protection:** confers at least 6 months protection **Preferred:** ≥1-year protective immunity *Reference: WHO Target Product Profile for COVID-19 Vaccines, 2020*
	What are the safety issues and incidence of adverse events caused by the COVID-	Based on the same randomized clinical trial (Voysey et al., 2020) cited above, with the four sub-trials included in the safety analyses:	Local and systemic reactions are tolerable, self-limiting and do not require hospitalization.

	19 Vaccine AstraZeneca?	<u>Short-term outcomes:</u> Using *COVID-19 Vaccine AstraZeneca*, compared to MenACWY or placebo, increases the risk for: ● Systemic reactogenicity by 1.22 (95% CI: 1.18 to 1.27) [moderate certainty of evidence] ● Local reactogenicity by 1.48 (95% CI: 1.42 to 1.56) [moderate certainty of evidence] <u>Long-term outcomes:</u> *COVID-19 Vaccine AstraZeneca* increases the risk for ● Adverse events (unsolicited) by 1.36 (95% CI 1.31 to 1.41) [moderate certainty of evidence] *COVID-19 Vaccine AstraZeneca* shows inconclusive safety against the following: ● Serious adverse events RR: 0.87 (95% CI: 0.64 to 1.17), [low certainty of evidence] ● Death (all-cause mortality) RR: 0.24 (95% CI: 0.03 to 2.18), [low certainty evidence] Only 17.5% of the trial participants were <u>≥</u>56 of age (4,155 out of 23, 745) based on the published interim analysis by Voysey et al. The UK Medicines and Healthcare products Regulatory Agency (UK MHRA) noted that while limited data are available for the older age groups, current evidence still supports a broad indication on the basis of the	No serious adverse events were caused by the vaccine. **Short term outcomes** (e.g., reactogenicity and allergic reactions): at least 2 months **Long term outcomes** (e.g., serious AEs): at least 1 year *Note: Pending legal provision allowing the use of evidence based on Phase III interim results*

		following: ● The frequency and severity of solicited adverse events was lower in subjects ≥ 65 years. ● The incidence of serious adverse events and adverse events of special interest was similar between subjects less than and ≥ 65 years. ● No clinically relevant difference was seen in the larger population of subjects that had at least one comorbidity. **HTAC Judgment:** Short-term safety is acceptable. However, further follow-up data is needed to establish longer-term safety. We note that there is insufficient evidence for safety among the population aged 56 years and above, and those with severe and/or uncontrolled comorbidities. It should not be given to individuals below 18 years old and to those with a known history of severe allergic reaction to any component of the vaccine. While vaccination is not contraindicated in other special populations who were excluded in the analysis/trials (i.e., immunocompromised patients, pregnant and lactating women), close medical supervision will be required.	

	Does the COVID-19 Vaccine AstraZeneca provide a highly favorable benefit/risk profile in the context of observed vaccine efficacy?	The current evidence shows that likely clinical benefits such as the decreased risk of symptomatic COVID-19 infection after 2 standard doses in the overall study population by 62.1%, symptomatic COVID-19 infection in population with well-controlled comorbidities after dose 2 by 73.4%, and hospitalization due to COVID-19 after at least one dose by 87.5%, outweigh the known short term risks based on data available at the time of evaluation. Evidence on the vaccine efficacy on severe COVID-19 infection and asymptomatic COVID-19 infection, and evidence on long term safety outcomes are still inconclusive, thus we cannot determine the benefit/risk profile in terms of the long term outcomes. **HTAC Judgment:** PASSED	Favorable benefit/risk profile The benefit of preventing morbidity of at least 50% far outweighs the reported risk of adverse events *Note: Pending legal provision allowing the use of evidence based on Phase III interim results*
3. Affordability and viability	*Is COVID-19 Vaccine AstraZeneca affordable?*	Based on the projected calculations, the total cost of rolling out vaccination with *COVID-19 Vaccine AstraZeneca* for 28M Filipinos in 2021 (i.e., target vaccinees for this vaccine profile identified in the vaccination roll out plan) will amount to about Php 17.7 billion. **HTAC Judgment:** Yes. The vaccine is affordable since the budget for the purchase and use of	Affordability will be measured using the sufficiency of the allocated amount to achieve vaccination targets.

		COVID-19 Vaccine AstraZeneca for the target number of vaccinees has been allocated.	
	What are the budget implications of using the COVID-19 Vaccine AstraZeneca?	The total cost of vaccination per individual, which accounts for other costs such as consumables, hauling and storage, and operations, was computed at Php 632.07. The potential budget impact of the use of *COVID-19 Vaccine AstraZeneca* to the national government to cover 28 million Filipinos was calculated at about Php 17.7 billion. It is estimated that 21.45% of the total allocated budget for vaccination will go to 40% of the 70 million target vaccinees for 2021. **HTAC Judgment:** The share of the cost of the *COVID-19 Vaccine AstraZeneca* to the total vaccine budget is considered proportionate to the share of the population to be vaccinated using the said vaccine.	The share of the cost to implement the COVID-19 vaccine within the total vaccination budget is not too disproportionate to the share of the population to be vaccinated using the said vaccine in the total population to be vaccinated. **The vaccine unit cost is comparable with those in other ASEAN countries.*
	Does the COVID-19 Vaccine AstraZeneca represent good value for money in terms of: *a. preventing COVID-19 mortality* *b. lowering hospitalization (moderate, severe*	Whether *COVID-19 Vaccine AstraZeneca* represents good value for money in terms of preventing COVID-19 mortality, lowering hospitalization (moderate, severe, and critical cases), and lowering the incidence of symptomatic (mild) and asymptomatic cases (RT-PCR confirmed cases) cannot be fully assessed at the moment.	The health, economic, and social benefits of the vaccination program outweigh the costs. The vaccine is likely cost-effective and represents an efficient allocation of

	and critical cases) *c. lowering incidence of symptomatic (mild) and asymptomatic cases (RT-PCR confirmed cases)*	Rough estimates of the vaccination cost per case averted are high. However, HTAC has bases to conclude that these will be offset by averted healthcare costs (i.e., total COVID-19-related PhilHealth claims, out of pocket expenditures), economic gains (i.e., in terms of recovery in GDP), and social gains. **HTAC Judgment:** Yes. The HTAC deems that the health, economic, and social benefits of the vaccination program using *COVID-19 Vaccine AstraZeneca* outweigh the negative impacts such as deaths due to COVID-19, medical costs, loss of productivity, social disruption and unprecedented challenges in the health system.	resources Note: A full-blown cost-effectiveness analysis is currently not done for rapid reviews under a pandemic situation due to its emergency nature. A full-blown cost-effectiveness analysis that takes on a societal perspective (i.e., including the economic and social impacts) will be performed once sufficient evidence is available and when full market authorization has been granted.
	Are there significant barriers to vaccine implementation in terms of vaccine storage and transport, handling; adequacy, skills and training of vaccinators; and access of the target population to the health care facility? Are there plans to overcome significant barriers?	The vaccine can be readily stored in a refrigerator at 2 to 8 degrees Celsius. UK MHRA also noted that splitting of packs to aid deployment can be implemented at less than 25 degrees Celsius if completed within 2 hours, immediately prior to final pre-use distribution (at 2 to 8 degrees Celsius). Given this, it is expected that the *COVID-19 Vaccine AstraZeneca* can be widely distributed to facilities with the said equipment. Like any vaccine implementation, there is still a	There are no significant barriers and if there are, the plans to address the barriers are clearly reflected in the vaccine roadmap and other relevant documents.

		need for training on vaccine storage and handling to ensure product integrity across the entire supply chain. Trained personnel in handling unreported or rare adverse reactions that could occur following vaccination should also be in place. Further, training on medical supervision and management of special populations such as pregnant and lactating women and immunocompromised individuals should be conducted. **HTAC Judgment:** The HTAC notes that there are no significant barriers in vaccine implementation using *COVID-19 Vaccine AstraZeneca* in terms of storage, transport, and handling. However, there is still a need for training to: ensure product integrity across the entire supply chain; and, close monitoring of adverse events with emphasis on medical supervision and management on special populations.	
4. Household Financial Impact	*Will the COVID-19 Vaccine AstraZeneca reduce or not add further to the out-of-pocket expenses of Filipino households?*	Interim results from the clinical trial showed vaccine efficacy to reduce risk for hospitalization due to COVID-19 by 87.6%, based on low certainty of evidence. PhilHealth data shows that the median amount spent by patients with moderate and severe COVID-19 pneumonia is at Php 290,058.50. On the other hand, PhilHealth claims for moderate and severe COVID-19 amounted to a median of Php 143,267.00.	The adoption of the vaccine can reduce out-of-pocket spending of individuals and families due to averted COVID-19 disease and/or hospitalization.

		Out-of-pocket spending for patients with moderate and severe pneumonia can reach as high as Php 2.6M and Php 5M, respectively. **HTAC Judgment**: Based on current evidence, *COVID-19 Vaccine AstraZeneca* has the potential to reduce out-of-pocket expenses of Filipino households due to averted hospitalizations.	
5. Social Impact	*Does the COVID-19 vaccine AstraZeneca possess the characteristics desired by key stakeholders (i.e., policy- and decision makers, health workers, program managers and/or implementers, patient groups, CSOs, communities, general public)?* ● *Safety* ● *Efficacy* ● *Transparency in the regulatory/approval process and information on the vaccines* ● *Availability* ● *Potential for high and equitable*	Based on the results of the focus group discussions conducted by the HTAC among *healthcare workers, patient groups, civil society organizations and community leaders* from low- and high-prevalence areas, the results from the deliberations in congressional inquiries on the COVID-19 vaccination roadmap, public hearings, and consultations with government decision-makers and implementers, the following are the important and desirable attributes of COVID-19 vaccines and the corresponding evidences for the *COVID-19 Vaccine AstraZeneca*: 1) Safe and efficacious for the general population (18 years old and older) and for some vulnerable groups like the older population and individuals with comorbidities. - Evidence: Clinical trial shows acceptable safety profile for known short-term risks and significant efficacy to reduce risk for symptomatic COVID-19 and hospitalization	The vaccine possesses all or most of the characteristics desired by key stakeholders Qualitative responses will contextualize the Filipino experience and may impact on implementation strategy

	coverage ● *Ease in logistical and implementation requirements* ● *Cost-efficiency to the government* ● *Public acceptability* ● *Availability of mechanisms to compensate vaccine recipients for any untoward event following vaccination* ● *Appropriateness of the vaccine to special at-risk groups and patients with comorbidities*	due to COVID-19 after at least 1 dose. We note however that there is insufficient efficacy and safety data for populations aged 56 and older and those with severe and uncontrolled comorbidities. Trials are ongoing to provide more conclusive evidence on the efficacy and safety for older adults. 2) Underwent a transparent regulatory process of being evaluated and approved by health authorities - Evidence: The Philippine FDA has issued an EUA for *COVID-19 Vaccine AstraZeneca*. Other stringent regulatory authorities such as the UK MHRA and the European Medicines Agency (EMA) have issued EUA for this vaccine as well. 3) Potential for high and equitable coverage across the population - Evidence: *COVID-19 Vaccine AstraZeneca* can be made more available since vaccine handling and storage are within the capacity of the RHUs . 4) Ease in logistics and administration - Evidence: *COVID-19 Vaccine AstraZeneca* can be stored at 2-8 degrees Celsius which is present in most RHUs.	

		5) Cost-effective - Evidence: The health, economic, and social benefits of implementing vaccination program using *COVID-19 Vaccine AstraZeneca* outweigh the negative impact of COVID-19 such as deaths due to COVID-19, medical costs, loss of productivity, social disruption and unprecedented challenges in the health system 6) Public acceptability - Evidence: No brand-specific study has been conducted to provide evidence for this characteristic. 7) Availability of mechanisms to compensate vaccine recipients for any untoward event following vaccination - Evidence: There has been no official issuance yet but the DOH already announced that all untoward events following vaccination shall be covered by PhilHealth. Likewise, Senate Bill No. 2015 was filed to establish the government vaccine indemnification program and provide funds for such.	

		8) Appropriateness of the vaccine to special at-risk groups and patients with comorbidities - Evidence: The *COVID-19 Vaccine AstraZeneca* has a vaccine efficacy of 73.4% in the population with well-controlled comorbidities. Evidence for efficacy and safety are insufficient for the following populations: individuals aged 56 years and above, and those who are immunocompromised, with uncontrolled comorbidities, pregnant, and lactating women. Trials are ongoing to provide more conclusive evidence on the efficacy and safety for older adults. **HTAC Judgment:** Based on short-term outcomes, *COVID-19 Vaccine AstraZeneca* possesses most of the characteristics desired by key stakeholders.	
6. Responsiveness to equity	*How will the COVID-19 vaccine AstraZeneca and its use impact pre-COVID and COVID-generated health and socioeconomic inequities?* *Which groups might be unfairly disadvantaged in relation to the COVID-19*	*COVID-19 vaccine AstraZeneca* has been shown to have a wide range of efficacy from 62% to 73% in the general population and those with well-controlled comorbidities in the published trial. There may be issues/gaps in access for special and vulnerable populations such as individuals below 18 years old and those with allergy to one of the components of the vaccine.	Ideally, health interventions can be fairly adopted and distributed/ implemented for eligible populations without aggravating existing health inequities especially for vulnerable sectors of our society.

	disease burden and delivery of the COVID-19 vaccine AstraZeneca?	*COVID-19 Vaccine AstraZeneca* can be stored at normal cold storage conditions (2 to 8 degrees Celsius). This will make vaccine distribution more logistically feasible which in turn does not aggravate inequities for patients living in geographically isolated and disadvantaged areas. Compared to other new vaccines, the price per dose and the logistical and operational cost of *COVID-19 Vaccine AstraZeneca* allow it to be utilized widely. **HTAC Judgment:** Because of non-stringent logistic requirements, *COVID-19 Vaccine AstraZeneca* does not aggravate health inequities related to inoculation of recipients residing in isolated and disadvantaged locations. However, the results on the efficacy and safety of the vaccine among individuals aged 56 years and above are insufficient. Trials are ongoing to provide more conclusive evidence on the efficacy and safety for older adults. We also note that the trial population did not include important vulnerable groups such as individuals with any confirmed or suspected immunosuppressive or immunodeficient state, including people with HIV infection, pregnant and lactating women.	

Appendix 1. Evidence for criterion 2 - Clinical Efficacy and Safety

Study characteristics

The appraisal of clinical evidence for the *AstraZeneca COVID-19 Vaccine* was limited to the latest published interim pooled results encompassing all four ongoing blinded, randomised controlled sub trials of this vaccine (i.e., Clinical Trial ISRCTN89951424, NCT04324606, NCT04400838, and NCT04444674) (Voysey et al., 2020; published 08 December 2020). The trial was primarily supported by AstraZeneca and the University of Oxford. The manuscript declared the following: AstraZeneca reviewed the data from the study and the final manuscript before submission, but the academic authors from the University of Oxford retained editorial control. AstraZeneca also facilitated and funded the manufacture of the ChAdOx1 nCoV-19 (AZD1222) clinical trial candidate. The recombinant adenovirus was manufactured and vialed at Advent (Pomezia, Italy), COBRA Biologics (Keele, UK), and Symbiosis (Sterling, UK). Both UK manufacturers were approved for Good Manufacturing Practice by the UK Medicines and Healthcare products Regulatory Agency (UK MHRA). All other funders declared in the study (i.e. UK Research and Innovation, National Institutes for Health Research [NIHR], Coalition for Epidemic Preparedness Innovations, Bill & Melinda Gates Foundation, Lemann Foundation, etc.) had no role in the study design, data collection, data analysis, data interpretation, or writing of the report. All authors had full access to all the data in the study and had final responsibility for the decision to submit for publication. The full text articles and trial protocols are published at the Lancet medical journal.

Apart from the latest published interim results in Voysey et al., 2020, preliminary reports from the phase I/II (Folegatti et al., 2020; published 15 August 2020) and phase II/III (Ramasamy et al., 2020; published 18 November 2020) safety and immunogenicity trials of the *AstraZeneca COVID-19 Vaccine*, and other supporting references such as the published trial protocols, statistical analysis plan, the UK MHRA Public Assessment Report, EMA Committee for Medical Products for Human Use (CHMP) Product Information, and AstraZeneca's report to the Advisory Council on Immunization Practices (ACIP) for this vaccine were also referred to for some key details.

The study is a multinational, ongoing, blinded, randomized controlled trial which aims to study the efficacy and safety of the *COVID-19 Vaccine AstraZeneca*. The study enrolled and vaccinated a total of 23,848 patients between April 23 and November 4, 2020 across

four sub-trials COV001 (UK- Phase I/II), COV002 (UK-Phase II/II), COV003 (Brazil-Phase III), and COV005 (South Africa- Phase I/II). COV005 is a double-blinded trial while the others are all single-blinded trials. Of these, only 23,745 patients were included in the safety analysis as participants from non-randomized open label groups and HIV cohorts were excluded. COV001 included participants aged 18 years to 55 years. COV002 and COV003 enrolled participants 56 years and older. COV005 enrolled participants aged 15-65 years old. With regards to underlying health conditions, COV001 was restricted to healthy individuals while the other trials allowed the inclusion of people with well-controlled, mild to moderate comorbidities. The trial excluded pregnant and breastfeeding women, individuals with history of confirmed COVID-19, anaphylaxis or angioedema, treatment with immunosuppressive therapy or diagnosis with an immunocompromising condition, and severe and/or uncontrolled comorbidities. Across the four sub-trials, participants assigned to the intervention group were given 2 doses of the *AstraZeneca COVID-19 Vaccine*, intramuscularly, 4 to 12 weeks apart. Participants assigned in the control group were given either meningococcal A,C,W, and Y conjugate vaccine (MenACWY) or normal saline (0.9% NaCl) at the same dosing interval as their intervention counterpart. Due to a discrepancy in the spectrophotometric reading of viral particles in COV002, a lower dose was administered to some patients at dose 1 in this subtrial - these were referred to as the low dose (LD) cohort group. After the UK MHRA's review of the incident, quantitative PCR was determined as the more accurate reading and was used in succeeding dose measurements. The detailed characteristics of the four sub-trials are summarized in Table 1.1 below.

Table 1.1 Characteristics of the Four Sub-trials of the AstraZeneca COVID-19 Vaccine

	COV001	**COV002**	**COV003**	**COV005**
Population	18-55 years old	≥ 18 years old	≥ 18 years old	18-65 years old
Number of subjects:				
a. Planned	1,122	12,390	10,300	2,070
b. Vaccinated	1,077	10,673	10,002	2,096
c. Included in the safety analysis	1,067	10,663	10,002	2,013

d. Included in the primary efficacy analysis	-	7,548	4,088	-
Intervention	2 doses Standard Dose (SD): 5×10^{10} vp; 4 and 8 weeks apart	2 doses [LD/SD group; SD/SD group] Low Dose (LD): 2.2 -2.5 x 10^{10} vp SD:5 x 10^{10} vp	2 doses SD: 3·5–6·5 × 10^{10} vp; up to 12 weeks apart	2 doses SD: 3.5–6.5 × 10^{10} vp; 4 weeks apart
Comparator	MenACWY (Dose 1 & 2)	MenACWY (Dose 1 & 2)	Dose 1: MenACWY Dose 2: Placebo (0.9% NaCl)	Normal saline (0.9% NaCl) (Dose 1 & 2)

For this interim analysis, the median safety follow up was 3.4 months after dose 1 and 2 months after dose 2. The overall median efficacy follow up period was at least 2 months according to the UK MHRA report. The primary and secondary outcomes of interest in the trial are as follows:

- *Primary efficacy endpoint:* Efficacy of the *COVID-19 Vaccine AstraZeneca* against *virologically confirmed, symptomatic COVID-19 occuring ≥15 days post second dose*
    - *Confirmed COVID-19 defined as nucleic acid amplification test (NAAT) positive swab combined the presence of at least one of the following symptoms: fever ≥37.8°C, cough, shortness of breath, or anosmia or ageusia*
- *Secondary efficacy endpoints:* Efficacy of the *AstraZeneca COVID-19 Vaccine* against the following outcomes measured post first dose, >22 days post first dose and >15 days post second dose unless stated otherwise:
    - Hospital admissions associated with COVID-19 [WHO Clinical Progression Score ≥ 4]
    - Intensive care unit (ICU) admissions associated with COVID-19

- COVID-19 death
- Severe COVID-19 disease [WHO Clinical Progression Score ≥ 6]
- Asymptomatic COVID-19 (COV002 only)
  - *≥15 days post second dose;*
  - *≥22 days post first dose*
- *Virologically confirmed, symptomatic COVID-19 occuring ≥22 days post first dose* (COV002 only)
- Seroconversion against non-spike SARS-CoV-2 antigens

- *Overall safety profile:* The *AstraZeneca* trial measured for the following outcomes in patients administered with at least one dose of the vaccine:
  - Adverse reaction
    - *any untoward or unintended response to the vaccine, i.e. a causal relationship between the vaccine and the AE is at least a reasonable possibility.*
  - Serious adverse events
    - *any adverse event that results in any of the following, whether or not considered related to the study intervention: death, life-threatening event, disability or incapacity, hospitalization or prolongation of existing hospitalisation, important medical event based upon appropriate medical judgment, congenital anomaly or birth defect.*
  - Solicited systemic adverse events
    - *Occurrence of solicited systemic reactogenicity signs and symptoms (i.e. fever, feverishness, chills, joint and muscle pain, fatigue, headache, malaise, nausea, vomiting) for 7 days following vaccination.*
  - Solicited local adverse events
    - *Occurrence of solicited local reactogenicity signs and symptoms (i.e. pain, tenderness, redness, warmth, itch, swelling, induration, bruising) for 7 days following vaccination*
  - Unsolicited adverse events
    - *Occurrence of unsolicited AEs for 28 days following vaccination. All AEs are unsolicited AEs unless categorized as solicited AEs.*
  - Disease enhancement following vaccination
    - *induction of disease enhancement and lung immunopathology in the event of COVID-19 disease following vaccination.*

Vaccine efficacy (VE) was calculated using the formula: 100 x (1 -adjusted relative risk) derived from a Poisson regression model. A combined independent data safety monitoring board reviewed safety data from all four trials.

Generally, the reviewers utilized a per protocol (PP) analysis for all efficacy outcomes except for three, namely: VE against hospitalization due to COVID-19 after dose 1, VE against severe COVID-19 after at least dose 1, VE against symptomatic COVID-19 after

at least dose 1 (SD/SD) which employed intention-to-treat (ITT) analysis. For safety outcomes, serious adverse events, deaths (all-cause mortality), and unsolicited adverse events utilized ITT analysis, while PP analysis was used for systematic and local reactogenicity.

Methodology

The HTAC's clinical research question elements are as follows:

Population: General and vulnerable population

Intervention: COVID-19 Vaccine AstraZeneca

Comparator: Placebo (Saline) OR Active Control

Outcomes: Vaccine efficacy (VE) and safety (see table below for details)

Table 1.2 Definitions and rating of importance of efficacy outcomes of interest

Name of outcome	Definition	HTAC rating of outcome importance
Vaccine efficacy (VE) against symptomatic COVID-19 after dose 2	Positive Nucleic Acid Amplification Test (NAAT) and the following symptoms after dose 2: ● Acute onset of any of three or more signs and symptoms: fever, cough, general weakness/fatigue, headache, myalgia, sore throat, coryza, dyspnea, anorexia/nausea/vomiting, diarrhea, altered mental status ● Anosmia (loss of smell), ageusia (loss of taste) in the absence of any other identified cause *Reference: WHO COVID-19 case definitions*	**CRITICAL** to decision making Subgroup analyses: **IMPORTANT** but not critical to decision-making
VE against Hospitalization due to COVID-19	Hospital admission for the management of COVID-19	**CRITICAL** to decision making
VE Severe COVID-19 Occurrence after at least 1 dose ~~1~~	Symptomatic COVID-19 after dose 1 with the addition of the following clinical manifestations: pneumonia, severe acute respiratory syndrome, multi-organ failure, and death *Reference: US FDA*	**CRITICAL** to decision making
VE Severe COVID-19	Symptomatic COVID-19 after dose 2 with the addition of the following clinical manifestations: pneumonia, severe acute	**CRITICAL** to decision making

Occurrence after dose 2	respiratory syndrome, multi-organ failure, and death *Reference: US FDA*	
VE against symptomatic COVID-19 after at least 1 d~~D~~ose ~~1~~	Positive Nucleic Acid Amplification Test (NAAT) and the following symptoms after dose 1: ● Acute onset of any of three or more signs and symptoms: fever, cough, general weakness/fatigue, headache, myalgia, sore throat, coryza, dyspnea, anorexia/nausea/vomiting, diarrhea, altered mental status ● Anosmia (loss of smell), ageusia (loss of taste) in the absence of any other identified cause *Reference: WHO COVID-19 case definitions*	**IMPORTANT** but not critical to decision-making
VE against symptomatic COVID-19 among older adults after dose 2	Positive Nucleic Acid Amplification Test (NAAT) and the following symptoms after dose 2 in older adults as defined in the trials: ● Acute onset of any of three or more signs and symptoms: fever, cough, general weakness/fatigue, headache, myalgia, sore throat, coryza, dyspnea, anorexia/nausea/vomiting, diarrhea, altered mental status ● Anosmia (loss of smell), ageusia (loss of taste) in the absence of any other identified cause *Reference: WHO COVID-19 case definitions*	**IMPORTANT** but not critical to decision-making
VE against symptomatic COVID-19 among population with comorbidities after dose 2	Positive Nucleic Acid Amplification Test (NAAT) and the following symptoms after dose 2 in population with comorbidities: ● Acute onset of any of three or more signs and symptoms: fever, cough, general weakness/fatigue, headache, myalgia, sore throat, coryza, dyspnea, anorexia/nausea/vomiting, diarrhea, altered mental status ● Anosmia (loss of smell), ageusia (loss of taste) in the absence of any other identified cause *Reference: WHO COVID-19 case definitions*	**IMPORTANT** but not critical to decision-making
VE against symptomatic COVID-19	Positive Nucleic Acid Amplification Test (NAAT) and the following symptoms after dose 2 in Asian population:	**IMPORTANT** but not critical to decision-making

among Asians, after dose 2	● Acute onset of any of three or more signs and symptoms: fever, cough, general weakness/fatigue, headache, myalgia, sore throat, coryza, dyspnea, anorexia/nausea/vomiting, diarrhea, altered mental status ● Anosmia (loss of smell), ageusia (loss of taste) in the absence of any other identified cause *Reference: WHO COVID-19 case definitions*	
VE against asymptomatic COVID-19	Absence of COVID-19 symptoms but with positive NAAT results	**IMPORTANT** but not critical to decision-making

Table 1.3 Definitions and rating of importance of safety outcomes of interest

Name of outcome	Definition	HTAC rating of outcome importance
Serious adverse events	An adverse event is any undesirable experience associated with the use of a vaccine. The event is serious when the patient outcome is: ● Death ● Life threatening ● Hospitalization (initial or prolonged) ● Disability of permanent damage ● Congenital anomaly/ birth defect ● Required intervention to prevent permanent impairment of damage ● Other serious events which may jeopardize the patient and may require medical or surgical intervention to prevent one of the other outcomes *Reference: US FDA*	**CRITICAL** to decision making
Death (All-cause mortality)	Reported deaths regardless of cause	**CRITICAL** to decision making
Systemic reactogenicity (Dose 1)	General systemic reactions to injectable products such as vaccines include nausea/vomiting, diarrhea, headache, fatigue, and myalgia *Reference: US FDA*	**CRITICAL** to decision making
Systemic reactogenicity (Dose 2)		
Local reactogenicity (Dose 1)	Local reaction to injectable products such as vaccines include pain, tenderness, erythema/redness, and induration/ swelling	**IMPORTANT** but not critical to decision-making

Local reactogenicity (Dose 2)	*Reference: US FDA*	
Adverse Events, Unsolicited	Any untoward medical occurrence associated with the use of a vaccine in humans, whether or not considered vaccine-related. *Reference: US FDA*	**IMPORTANT** but not critical to decision-making

The risk of bias for each outcome was assessed through Version 2 of the Cochrane risk-of-bias tool for randomized trials (RoB2 tool). Two reviewers independently appraised the risk of bias. Any disagreements between reviewers were resolved through consensus. Quality of evidence was then appraised by two reviewers through the Grading of Recommendations, Assessment, Development and Evaluations (GRADE) Approach.

Appraisal of findings

Efficacy and Safety from the Interim Results of Phase III trial

The interim results covered data gathered from 23 April 2020 to 4 November 2020. Overall, there were 23,848 participants enrolled in the trial across three countries (UK, Brazil, South Africa). The primary efficacy population of 11,636 participants was taken from the COV002 (UK) and COV003 (Brazil) trials. Of the primary efficacy population, 5,807 participants were assigned to receive the *COVID-19 Vaccine Astrazeneca* and 5,829 participants were assigned to receive control (COV002: MenACWY; COV003: MenACWY and saline). The participants were mostly White which comprised 82.7% of the primary efficacy population. Meanwhile, Asians comprised 4.4% of the efficacy population. Majority of the primary efficacy population was 18-55 years old (87.8%) while participants aged 56-69, and 70 and older comprised 8.4% and 3.8% of the efficacy population respectively.

Of the nine efficacy outcomes and five safety outcomes of interest to the HTAC, the current trial measured and reported all of the outcomes except for VE against symptomatic COVID-19 in older adults (>65 years old), VE against symptomatic COVID-19 in older adults (>75 years old), VE against symptomatic COVID-19 in population with comorbidities, and VE against symptomatic COVID-19 in Asians. Note however, that VE against symptomatic COVID-19 in the population with comorbidities was reported in the UK Medicines and Healthcare products Regulatory Agency (UK MHRA) report. Below are the outcomes measured and reported by the trial that match the outcomes of interest in our research question:

Table 1.4 HTAC outcomes of interest and the corresponding outcomes reported by Voysey et al., 2020

HTAC outcome of interest	**Matching reported outcome from the *COVID-19 Vaccine* AstraZeneca trial**	**Definition of outcome from the *COVID-19 Vaccine AstraZeneca* trial** *(Voysey et al., 2020)*

	(Voysey et al., 2020)	
Efficacy outcomes		
VE against symptomatic COVID-19 after dose 2	VE against symptomatic COVID-19 more than 14 days after dose 2 (SD/SD)	Virologically confirmed (NAAT positive) SARS-CoV-2 and at least one of the following symptoms: objective fever (defined as ≥ 37.8 °C), cough, shortness of breath, anosmia, or ageusia more than 14 days after dose 2 in participants who received two standard doses
	● VE against symptomatic COVID-19 more than 14 days after dose 2, with < 6 weeks interval (SD/SD)	Virologically confirmed (NAAT positive) SARS-CoV-2 and at least one of the following symptoms: objective fever (defined as ≥ 37.8 °C), cough, shortness of breath, anosmia, or ageusia more than 14 days after dose 2 in participants who received two standard doses less than 6 weeks apart
	● VE against symptomatic COVID-19 more than 14 days after dose 2, with ≥ 6 weeks interval (SD/SD)	Virologically confirmed (NAAT positive) SARS-CoV-2 and at least one of the following symptoms: objective fever (defined as ≥ 37.8 °C), cough, shortness of breath, anosmia, or ageusia more than 14 days after dose 2 in participants who received two standard doses 6 weeks apart or longer
	● VE against symptomatic COVID-19 more than 14 days after dose 2 (LD/SD+SD/SD)	Virologically confirmed (NAAT positive) SARS-CoV-2 and at least one of the following symptoms: objective fever (defined as ≥ 37.8 °C), cough, shortness of breath, anosmia, or ageusia more than 14 days after dose 2

		in participants who received either low dose or standard dose as their first dose.
VE against hospitalization due to COVID-19	VE against hospitalization due to COVID-19 after at least 1 dose (LD/SD+SD/SD)	Hospitalization due to COVID-19 defined as WHO clinical progression score ≥ 4 after receiving at least one dose in participants who received either low dose or standard dose as their first dose.
	VE against hospitalization due to COVID-19 more than 14 days after dose 2 (LD/SD+SD/SD)	Hospitalization due to COVID-19 defined as WHO clinical progression score ≥ 4 more than 14 days after receiving dose 2 in participants who received either low dose or standard dose as their first dose.
VE against severe COVID-19 after at least 1 dose ~~1~~	VE against severe COVID-19 after at least 1 dose (LD/SD+SD/SD)	Virologically-confirmed SARS-CoV-2 infection (NAAT positive) with WHO grade ≥ 6 in WHO clinical progression scale after at least 1 dose in participants who received either low dose or standard dose as their first dose.
VE against severe COVID-19 after dose 2	VE against severe COVID-19 more than 14 days after dose 2 (LD/SD+SD/SD)	Virologically-confirmed SARS-CoV-2 infection (NAAT positive) with WHO grade ≥ 6 in WHO clinical progression scale more than 14 days after receiving dose 2 in participants who received either low dose or standard dose as their first dose.
VE against symptomatic COVID-19 after at least 1 dose ~~1~~	VE against symptomatic COVID-19 after at least 1 dose (SD/SD)	Virologically confirmed (NAAT positive) SARS-CoV-2 and at least one of the following symptoms: objective fever (defined as ≥ 37.8 °C), cough, shortness of breath, anosmia, or ageusia more than 21 days

		after the first standard dose in seronegative participants who received/will receive only standard doses
VE against symptomatic COVID-19 after dose 2 in older adults	VE against symptomatic COVID-19 in older adults (≥56 years old) more than 14 days after dose 2 (SD/SD)	Virologically confirmed (NAAT positive) SARS-CoV-2 and at least one of the following symptoms: objective fever (defined as ≥ 37.8 °C), cough, shortness of breath, anosmia, or ageusia more than 14 days after dose 2 in participants aged 56 years and older who received two standard doses.
VE against symptomatic COVID-19 after dose 2 in population with comorbidities	VE against symptomatic COVID-19 in population with comorbidities more than 14 days after dose 2 (LD/SD+SD/SD)	Virologically confirmed (NAAT positive) SARS-CoV-2 and at least one of the following symptoms: objective fever (defined as ≥ 37.8 °C), cough, shortness of breath, anosmia, or ageusia more than 14 days after dose 2 in participants with mild/moderate, well-controlled comorbidities who received either low dose or standard dose as their first dose.
VE against COVID-19 infection in Asians	VE against symptomatic COVID-19 in Asian population more than 14 days after dose 2 (LD/SD+SD/SD)	Virologically confirmed (NAAT positive) SARS-CoV-2 and at least one of the following symptoms: objective fever (defined as ≥ 37.8 °C), cough, shortness of breath, anosmia, or ageusia more than 14 days after dose 2 in Asians who received either low dose or standard dose as their first dose.
VE against asymptomatic COVID-19	VE against asymptomatic COVID-19 after dose 2 (LD/SD+SD/SD)	Absence of any of the symptoms contributing to COVID-19 outcome, but virologically confirmed (NAAT positive) SARS-CoV-2 infection based on samples collected via home kits (nose and throat swab for NAAT testing) provided by UK Department of Health

		and Social Care more than 14 days after dose 2 in participants who received either low dose or standard dose as their first dose.
Safety outcomes		
Serious adverse events	Serious adverse events after at least one dose (LD/SD+SD/SD)	An AE that results in any of the following, whether or not considered related to the study intervention: death, life-threatening event, disability or incapacity, hospitalisation or prolongation of existing hospitalisation, important medical event based upon appropriate medical judgment, congenital anomaly or birth defect in participants who received at least one dose, either low dose or standard dose.
Death (all-cause mortality)	Death (all-cause mortality) after at least one dose (LD/SD+SD/SD)	All deaths due to COVID-19 and all other causes
Systemic reactogenicity	Systemic reactogenicity after at least one dose (subset of SD/SD)	Occurrence of solicited systemic reactogenicity signs and symptoms (i.e. fever, feverishness, chills, joint and muscle pain, fatigue, headache, malaise, nausea, vomiting) within 7 days of each vaccination in participants who were given at least their first dose (standard dose).
Local reactogenicity	Local reactogenicity after at least 1 dose (subset of SD/SD)	Occurrence of solicited local reactogenicity signs and symptoms (i.e. pain, tenderness, redness, warmth, itch, swelling, induration, bruising) within 7 days of each vaccination in participants who were given at least their first dose (standard dose).
Adverse events	Adverse events, unsolicited after at least one dose (LD/SD+SD/SD)	Occurrence of unsolicited AEs for 28 days following each vaccination in participants who received at least one dose, either low dose or standard dose. All AEs are unsolicited AEs unless categorized as solicited AEs.

A total of 168 participants in the safety population experienced serious adverse events (79 from the intervention group and 89 from the control group). In the UK MHRA Public Assessment Report, the investigators considered five serious adverse events as possibly related to the treatment or control vaccine. Three of these serious adverse events occurred in the intervention group: pyrexia, increase in C-reactive protein, and transverse myelitis. After the data cut-off, the investigator notified that the increase in C-reactive protein is not related to the experimental vaccine and that

only two of the serious adverse events was reported by Voysey et al., as possibly related to the treatment:

- Pyrexia
    - Fever of 40.5°C, increased sweating, shortness of breath, weakness, and loss of sense of smell and taste occurring two days after the first dose of the COVID-19 Vaccine AstraZeneca
- Transverse myelitis
    - Idiopathic, short segment, spinal cord demyelination

A total of 6 deaths were reported by UK MHRA Public Assessment Report - 2 in the intervention arm (fungal pneumonia, metastatic ovarian cancer) and 4 in the control arm (COVID-19 pneumonia, craniocerebral injury, injury, and homicide). None of the deaths were considered by the investigators as related to the intervention. It was also noted in the report that fewer than 1% of the participants reported a serious adverse event with reporting rates balanced between the intervention and control groups. The most frequently reported serious adverse events were 'Infections and Infestations' (0.1% in the intervention group vs 0.2% in the control group) and 'Injury, poisoning and procedural complications' (<0.1% in the intervention group vs 0.1% in the control group).

The results of our appraisal of the clinical evidence for the efficacy and safety of the *COVID-19 Vaccine AstraZeneca* using GRADE approach are shown in *Table 1.5 and Table 1.6*, respectively. Links to the risk of bias appraisal sheets are provided in *Table 1.12*.

Overall, *COVID-19 Vaccine AstraZeneca* showed benefit for the following outcomes of interest ranging from 62.1 to 87.6%:

- VE against symptomatic COVID-19 after dose 2 (SD/SD)
- VE against symptomatic COVID-19 after dose 2 (LD/SD+SD/SD)
- VE against symptomatic COVID-19 after dose 2, with ≥ 6 weeks interval (SD/SD)
- VE against hospitalization due to COVID-19 after at least 1 dose (LD/SD+SD/SD)
- VE against symptomatic COVID-19 after at least 1 dose (SD/SD)
- VE against symptomatic COVID-19 after dose 2 in population with comorbidities (LD/SD+SD/SD)

Of these outcomes, the reported VE was highest for the VE against hospitalization due to COVID-19 after at least 1 dose [LD/SD+SD/SD] (*critical outcome*) at 87.59% (95% CI: 46.0 to 97.2). Meanwhile, the lowest reported VE with conclusive results was for the VE against symptomatic COVID-19 after dose 2 [SD/SD] with a VE of 62.1% (95% CI: 41.0 to 75.7). We noted that all critical outcomes with conclusive results have wide confidence intervals with lower limits that fall below the minimum acceptable vaccine efficacy set by the HTAC, hence they were rated serious for imprecision.

The effect size for the critical outcomes of VE against hospitalization due to COVID-19 after dose 2 and VE against severe COVID-19 after at least 1 dose and after dose 2 cannot be estimated since there were no cases of these outcomes reported in the intervention arm. It is also noted that the VE against symptomatic COVID-19 after dose 2 with less than 6 weeks interval (SD/SD) [VE: 53.4 (95% CI: -2.5 to 78.8)] and VE against asymptomatic COVID-19 [VE: 27.3 (95% CI: -17.2 to 54.9)] are inconclusive based on their confidence intervals.

The median follow-up period was deemed too short to ascertain the VE against symptomatic COVID-19 after dose 2 (SD/SD) *(critical outcome)* and its subgroups; VE against symptomatic COVID-19 after dose 2 at less than 6 weeks interval (SD/SD) *(important outcome*) and VE against symptomatic COVID-19 after dose 2 at least 6 weeks interval (SD/SD) *(important outcome)*. Indirectness for the critical outcomes VE against hospitalization due to COVID-19 after at least 1 dose, VE against hospitalization due to COVID-19 after dose 2, VE against severe COVID-19 after at least 1 dose , and VE against severe COVID-19 after dose 2 was rated serious due to the insufficient follow-up period. VE against symptomatic COVID-19 in the population with comorbidities after dose 2 (*important outcome)* was given a rating of serious for the risk of bias since no raw data was reported in the trial despite a reported efficacy in the UK Medicines and Healthcare products Regulatory Agency's (UK MHRA) assessment report.

Further, we also note that the VE appears to be higher if the dosing interval is ≥ 6 weeks [VE: 65.4% (41.1 to 79.6)] versus if the dosing interval is < 6 weeks [VE: 53.4% (-2.5 to 78.8], although there is little data at this point to state this conclusively. There is a need for more evidence to establish the effect of dosing interval on VE in order to establish the appropriate/ recommended dosing interval.

As mentioned above, *COVID-19 Vaccine AstraZeneca* has no reported VE specific for Asians (4.4% of the study population) and older adults (≥56 years old, 12.2% of the efficacy population). The only data available for older adults came from a product information document approved by the EU Committee for Medical Products for Human Use (CHMP) (pending endorsement by the European Commission) which has reported that among participants aged between 56 and 65 years old, there were 8 cases of COVID-19 reported in the intervention group (≥15 days post dose 2) compared with 9 cases for the control group. Meanwhile, there were 2 and 6 cases of COVID-19 reported in participants older than 65 years of age, for the intervention (≥15 days post dose 2) and control groups, respectively.

As for vaccine safety, participants who received at least one dose of the *COVID-19 Vaccine AstraZeneca* and followed up for a median period of 3.4 months were noted to have higher risk for systemic reactogenicity *(critical outcome)* by 1.22 times (95% CI: 1.18 to 1.27) compared to those who received MenACWY or placebo. For local reactogenicity *(important outcome),* the relative risk was higher by 1.48 times (95% CI: 1.42 to 1.55). Lastly, the risk for adverse events *(important outcome)* is 1.36 times higher (95% CI: 1.31 to 1.41) for participants in the intervention group compared to the participants in the control group. The relative risk for the critical outcomes serious adverse events (RR: 0.87 95% CI: 0.64 to 1.17) and death (all-cause mortality) (RR: 0.24 95% CI: 0.03 to 2.18) remain inconclusive owing to the confidence intervals that cross the null value.

As regards its safety among older adults, only 17.5% of the trial participants were ≥56 of age (4,155 out of 23, 745) based on the published interim analysis by Voysey et al. Further, the trial did not report a subgroup analysis on safety outcomes for older

adults. While limited data are available for the older age groups, the UK MHRA still supports a broad indication on the basis of the following:

- The frequency and severity of solicited adverse events was lower in subjects ≥ 65 years.
- The incidence of serious adverse events and adverse events of special interest was similar between subjects less than and ≥ 65 years.
- No clinically relevant difference was seen in the larger population of subjects that had at least one comorbidity.

Lastly, we note here that COVID-19 Vaccine AstraZeneca should not be given to individuals below 18 years old and to those with a known history of severe allergic reaction to any component of the vaccine.

While vaccination is not contraindicated in other special populations who were excluded in the analysis/trials (i.e., immunocompromised patients, pregnant and lactating women), close medical supervision will be required.

Table 1.5. Summary of findings for efficacy outcomes

	EFFICACY OUTCOMES									
	OUTCOME	**Quality Assessment** *Note: The study design and number of studies column were collapsed since the input for these columns are the same across all outcomes*					**Summary of Findings**			**Certainty**	**Importance**
		Risk of bias	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**ChAdOx1 n/N**	**Control n/N**	**Effect Size (95% CI)**		
1	**VE against symptomatic COVID-19** *(after dose **2**, **SD/SD**)*	Not serious	NA	Cannot be assessed[a]	Serious[b]	None	27/4440	71/4455	VE 62.1% (41.0 to 75.7)	⊕⊕⊕◯ **MODERATE**	CRITICAL
1A	**VE against symptomatic COVID-19** *(after dose **2**, with **<6 weeks interval,** SD/SD)*	Not serious	NA	Cannot be assessed[a]	Serious[c]	None	9/1702	19/1698	VE 53.4 (-2.5 to 78.8)	⊕⊕⊕◯ **MODERATE**	IMPORTANT
1B	**VE against symptomatic COVID-19** *(after dose **2**, with **≥6 weeks interval,** SD/SD)*	Not serious	NA	Cannot be assessed[a]	Serious[b]	None	18/2738	52/2757	VE 65.4 (41.1 to 79.6)	⊕⊕⊕◯ **MODERATE**	IMPORTANT
2	**VE against symptomatic COVID-19** *(after dose **2**, all **LD/SD+SD/SD**)*	Not serious	NA	Not serious	Not Serious	None	30/5807	101/5829	VE 70.4% (54.8 to 80.6)*	⊕⊕⊕⊕ **HIGH**	IMPORTANT
3A	***VE against hospitalization due to COVID-19*** *(after at least 1 dose, all LD/SD+SD/SD)*	Not serious	NA	Serious[d]	Serious[b]	None	*2/12021*	16/11724	VE 87.59 (46.0 to 97.2)	⊕⊕◯◯ **LOW**	CRITICAL

3B	***VE against hospitalization due to COVID-19*** *(after dose **2**, all LD/SD+SD/SD)*	Not serious	NA	Serious[d]	Serious[e]	None	0/5807	5/5829	VE 100% *(cannot be computed)*	⨁⨁◯◯ **LOW**	CRITICAL
4A	**VE against severe COVID-19** *(after at least 1 dose, all LD/SD+SD/SD)*	Not serious	NA	Serious[d]	Serious[e]	None	0/12021	2/11724	VE 100 *(cannot be computed)*	⨁⨁◯◯ **LOW**	CRITICAL
4B	**VE against severe COVID-19** *(14 days after dose 2, all LD/SD+SD/SD)*	Not serious	NA	Serious[d]	Serious[e]	None	0/5807	1/5829	VE 100 *(cannot be computed)*	⨁⨁◯◯ **LOW**	CRITICAL
5	**VE against symptomatic COVID-19** *(after at least 1 dose, SD/SD)*	Not serious	NA	Not serious	Not serious	None	51/6307	141/6297	VE 64.1 (50.5 to 73.9)	⨁⨁⨁⨁ **HIGH**	IMPORTANT
6A	**VE against symptomatic COVID-19 in <u>older adults (>65 yo)</u>** *(after dose 2, all LD/SD+SD/SD)*	No data	No data	No data	No data	No data	No data	No data	No data	No data	No data
6B	**VE against symptomatic COVID-19 in <u>older adults (>75 yo)</u>** *(after dose 2, all LD/SD+SD/SD)*	No data	No data	No data	No data	No data	No data	No data	No data	No data	No data
7	**VE against symptomatic COVID-19 in <u>population with comorbidities</u>** *(after dose 2, all LD/SD+SD/SD)* *(Data taken from UK MHRA Public Assessment Report dated 31 December 2020)*	Serious[f]	NA	Not serious	Not serious	None	No data	No data	VE 73.4 (48.5 to 86.3) *Estimates were provided by UK MHRA (21 Dec 2020) without reporting the*	⨁⨁⨁◯ **MODERATE**	IMPORTANT

									actual numbers for the events and number of participants for intervention and control groups		
8	**VE against symptomatic COVID-19, <u>Asians</u>** *(after dose 2, all LD/SD+SD/SD)*	No data	No data	No data	No data	No data	No data	No data	No data	No data	No data
9	**VE against asymptomatic COVID-19** *(after dose 2, LD/SD+SD/SD)*	Serious[g]	NA	Not serious	Serious[c]	None	29/3288	40/3350	VE 27.3 (-17.2 to 54.9)	⨁⨁◯◯ **LOW**	CRITICAL

Notes:
NA- not applicable, cannot be assessed at the moment
*the reported confidence interval was 95.8% CI

a. Cannot be assessed: in the UK MHRA report, it was explicitly stated that the median follow-up was at least 2 months. We note that the primary analysis pooled the vaccine efficacy for the population which received either LD/SD or SD/SD. Further, we note that the LD/SD population were observed for a longer period due to delays in administering doses in the SD/SD population. With this, we cannot assume that the SD/SD only population reached a median follow up period of 2 months.
b. Wide confidence interval and lower limit of the CI falls below the minimum acceptable VE set by the HTAC (50% efficacy).
c. The confidence interval crosses the null value.
d. Serious concern is due to the insufficient follow-up period. Severe COVID-19 and COVID-19 cases leading to hospitalization may not have had time to occur during the median 2-month follow-up period in the trial.
e. The trial did not report the VE and the 95% CI; instead, the trial only reported the number of cases that occurred before the data cutoff date. The number of events in both the vaccine and control groups is too low to be certain of the precision in the results for this outcome.
f. Serious concern on the risk of bias due to missing outcome data. The vaccine efficacy for this outcome was reported in the UK MHRA report; however, the estimate cannot be validated because the number of events was not reported in the clinical trial (Voysey et al., 2020).
g. Serious concern on the risk of bias due to measurement of the outcome. The measurement of asymptomatic cases was based on the results of the swabs done via home test kits. Participants might not have been able to do the swab properly, thus resulting in false negatives.

Table 1.6. Summary of findings for safety outcomes

	SAFETY OUTCOMES										
	OUTCOME	**Quality Assessment** *Note: The study design and number of studies column were collapsed since the input for these columns are the same across all outcomes*					**Summary of Findings**			**Certainty**	**Importance**
		Risk of bias	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**ChAdOx 1 n/N (% risk)**	**Control n/N (% risk)**	**Effect Size (95% CI**		
1	**Serious adverse events** *(after at least one dose, all LD/SD+SD/SD)*	Not Serious	NA	Serious[a]	Serious[b]	None	79/12021 (0.7)	89/11724 (0.8)	RR 0.87 (0.64 to 1.17)	⨁⨁◯◯ **LOW**	CRITICAL
1A	**Death (all-cause mortality)** *(after at least one dose, all LD/SD+SD/SD)*	Not serious	NA	Serious[a]	Serious[b]	None	1/12021 (0.0)	4/11724 (0.0)	RR 0.24 (0.03 to 2.18)	⨁⨁◯◯ **LOW**	CRITICAL
2	**Systemic reactogenicity** *(after at least one dose, SD/SD)*	Serious[c]	NA	Not serious	Not serious	None	1932/2648 (73.0)	1488/2497 (59.6)	RR 1.22 (1.18 to 1.27)	⨁⨁⨁◯ **MODERATE**	IMPORTANT
3	**Local reactogenicity** *(after at least one dose , SD/SD)*	Serious[c]	NA	Not Serious	Not Serious	None	1979/2648 (74.7)	1258/2497 (50.4)	RR 1.48 (1.42 to 1.55)	⨁⨁⨁◯ **MODERATE**	IMPORTANT
4	**Adverse events, unsolicited** *(after at least one dose, all LD/SD+SD/SD)*	Not Serious	NA	Serious[a]	Not Serious	None	4539/12021 (37.8)	3266/11724 (27.9)	RR 1.36 (1.31 to 1.41)	⨁⨁⨁◯ **MODERATE**	IMPORTANT

Notes:

a. Serious concern is due to the insufficient follow-up period. Serious adverse events and deaths (all-cause mortality) may not have had time to occur during the median 3.4-month follow-up period in the trial.

b. The confidence interval crosses the null value.
c. Serious concern on the risk of bias due to missing outcome data and measurement of outcome. The systemic and local reactogenicity were only solicited to an identified subgroup which were given e-diaries to report adverse reactions for 7 days. Measurement of outcome also differed across the sub trials e.g. in South Africa, adverse events were only solicited for 6 days and options for severity or category of AEs were also limited which may lead to underreporting

Immunogenicity in Older Adults

In view of the limited efficacy and safety data specific for older adults as discussed above, we also reviewed the immunogenicity data as a surrogate outcome for protection against clinical disease for older adults, which were reported in Ramasamay et al (2020) and the UK MHRA report.

The immunogenicity of *COVID-19 Vaccine AstraZeneca* was evaluated in a subset of participants across all clinical trials. Ramasamay et al (2020) enrolled a total of 560 participants classified in three age groups: 18-55 years old (N=160), 56-69 years old (N=160), and ≥70 years old (N=240). However, only a subset of this population was included in the analysis to assess the cellular and humoral response after vaccination. Meanwhile, the UK MHRA reported neutralizing antibody (nAbs) levels which were pooled from COV001, COV002, COV003, and COV005. These data were classified in two age groups: 18-64 years old (N=1,022) and ≥65 years (N=152). Overall, both analyses show the increase in immune response levels after receiving two standard doses of *COVID-19 Vaccine AstraZeneca* regardless of age when compared to control (MenACWY).

Seroconversion rates

The UK MHRA computed seroconversion rates by S-binding antibodies. They reported high seroconversion rates by S-binding antibodies in older adults (≥65 years) after the first SD (97.8% [N=136, 95% CI: 93.7; 99.5]) and the second SD (100.0% [N=111, 95% CI: 96.7; NE]). Disaggregated data on seroconversion rates for other age groups were not presented. However, the agency noted that the overall rate of seroconversion was ≥ 98% at 28 days after the dose 1 and >99% at 28 days after dose 2 for participants who are seronegative at baseline.

Anti-spike SARS-CoV-2 IgG responses

The analysis on immunogenicity data from COV002 subtrial as reported by Ramasamy et al (2020) compared the anti-spike SARS-CoV-2 IgG responses of participants using a multiplex immunoassay (*Table 1.7*) and standardized ELISA (*Table 1.8).* Using a multiplex immunoassay, at day 28 after the first standard dose, there is a significant decrease in antibody titres with increasing age (p=0.0044 using Kruskal-Wallis test). However, at day 28 after the second standard dose, findings show similar antibody titres across all three age groups (p=0.6834 using Kruskal-Wallis test). We noted that antibody titres were consistently higher across age groups in the intervention group compared to the control 28 days after dose 1 and dose 2. Similar IgG response to the spike protein is observed using standardized ELISA.

Table 1.7 SARS-CoV-2 IgG response to spike protein detected using multiplex immunoassay 28 days after dose 1 and dose 2 (Reference: Ramasamy et al, 2020)

Age Group	Timepoint	Population (I = N; C = N)	IgG Response in AU/mL Median [IQR]	
			Standard Dose Vaccine	Standard Dose Control (MenACWY)
18 - 55 years	after dose 1	I = 43 C = 7	9807 [5847 to 17220]	31 [23 to 57]
	after dose 2	I = 39 C= 7	20713 [13898 to 33550]	45 [22 to 64]
56 - 69 years	after dose 1	I = 27 C = 10	4474 [2256 to 8486]	35 [14 to 64]
	after dose 2	I = 26 C = 8	16170 [10233 to 40353]	28 [15 to 72]
≥ 70 years	after dose 1	I = 48 C = 10	4603 [2321 to 13322]	48 [21 to 68]
	after dose 2	I = 47 C= 10	17561 [9705 to 37796]	48 [20 to 65]

Notes:
N - total number of participants whose IgG against spike proteins levels were included in the analysis
AU- arbitrary units
IQR- interquartile range

Table 1.8 SARS-CoV-2 IgG response to spike protein detected using standardised ELISA 28 days after dose 1 and dose 2 (Reference: Ramasamy et al, 2020)

Age Group	Timepoint	Population (I = N; C = N)	IgG Response in AU/mL Median [IQR]		Geometric Mean Titer (95% CI)	
			Standard Dose Vaccine	Control (MenACWY)	Standard Dose Vaccine	Control (MenACWY)
18 - 55 years	after dose 1	I = 48 C = 9	174 [133 to 341]	1 [1 to 4]	214.10 (156.26 to 293.36)	1.80 (0.99 to 3.26)
	after dose 2	I=43 C=7	705 [314 to 1052]	3 [1 to 4]	627.88 (475.82 to 828.53)	2.08 (0.95 to 4.56)
56 - 69 years	after dose 1	I=29 C=10	119 [69 to 212]	1 [1 to 1]	115.46 (78.60 to 169.62)	1.51 (0.6 t, 3.61)
	after dose 2	I = 29 C = 10	394 [243 to 1130]	3 [1 to 7]	522.69 (368.79 to 740.81)	3.26 (1.25 to 8.68)
≥ 70 years	after dose 1	I = 47 C = 10	149 [74 to 260]	1 [1 to 1]	139.48 (87.17 to 223.18)	1.50 (0.77 to 2.93)
	after dose 2	I = 48 C = 10	405 [236 to 940]	1 [1 to 2]	471.51 (344.75 to 644.87)	1.66 (0.84 to 3.29)

Notes:

N - total number of participants whose IgG against spike proteins levels were included in the analysis
IQR - interquartile range

Neutralizing Antibody Titres

The COV002 subtrial also used a live SARS-CoV-2 microneutralization assay (MNA_{80}) to assess the neutralizing antibody responses induced by vaccination with the standard dose. Comparison of the neutralization titers at 14 days after dose 2 showed no significant difference across age groups (p=0.400 using ANOVA applied to log-transformed titers). Further, at 14 days after dose 2, all participants included in the analysis who received standard dose vaccines achieved neutralizing levels, regardless of age. The median neutralization level in the three age groups is summarized in *Table 1.9*.

Table 1.9 SARS-CoV-2 neutralizing antibody titre detected using live microneutralization assay (MNA_{80}) in recipients of standard dose vaccines (Reference: Ramasamy et al, 2020)

Age Group	Timepoint	Population (N)	Neutralization Titers Median [IQR]
18 - 55 years	28 days after dose 1	43	47 [5 to 124]
	14 days after dose 2	39	193 [113 to 238]
	28 days after dose 2	37	185 [129 to 359]
56 - 69 years	28 days after dose 1	15	72 [35 to 102]
	14 days after dose 2	20	144 [119 to 347]
	28 days after dose 2	22	178 [124 to 416]
≥70 years	28 days after dose 1	42	48 [21 to 121]
	14 days after dose 2	47	161 [73 to 323]
	28 days after dose 2	43	146 [56 to 239]

Notes:
N - total number of participants whose median neutralizing titers were included in the analysis
IQR - interquartile range

The UK MHRA reported the geometric mean titres (GMT) of the neutralizing antibodies (nAbs) for participants in COV001, COV002, COV003, and COV005 aged 18-64 and ≥ 65 years. The pooled analyses show that the antibody response 28 days after dose 2 is lower for older adults than in younger adults which is different from the findings of the analysis in COV002 (Ramasamy, et al., 2020) wherein similar immune responses were seen across age groups. We noted

that nAbs levels were consistently higher in participants in the intervention arm compared to the control arm after dose 1 and after dose 2 across all age groups. Further, there is also an observed consistent increase in nABs levels after dose 2 compared to after dose 1. The reported geometric mean titers in the three age groups 28 days after dose 1 and dose 2 are shown in *Table 1.10*

Table 1.10 SARS-CoV-2 neutralizing antibody titre detected by Pseudoneutralizing Assay after 28 days dose 1 and dose 2 (Reference: UK MHRA, 2020)

Age Group	Timepoint	Population (I = N; C = N)	Geometric Mean Titer (95% CI)	
			Standard Dose Vaccine	Control (MenACWY and/or saline)
18 - 64 years	after dose 1	I = 500 C = 522	59.026 (52.87 to 65.90)	20.374 (19.99 to 20.76)
	after dose 2	I = 497 C = 501	173.708 (156.52 to 192.78)	21.487 (20.67 to 22.33)
≥65 years	after dose 1	I = 75 C = 77	37.103 (29.26 to 47.05)	21.105 (18.96 to 23.49)
	after dose 2	I = 52 C = 54	109.212 (77.58 to 153.73)	21.066 (18.98 to 23.28)

Notes:
N - total number of participants whose nAbs levels were included in the analysis

Cellular responses

Cellular responses measured as spot-forming cells per million peripheral blood mononuclear cells were also reported using the data of COV002 trial (Ramasamy et al). Results across age groups show that cellular response was at its highest 14 days after the first dose and does not significantly change 14 days after dose 2 ($p=0.46$ using paired Student T test). In terms of age group, the cellular response 14 days after dose 2 is significantly higher in the 56-69 age group compared to the 18-55 years and ≥70 years age group ($p<0.001$ using Kruskal-Wallis test). The median cellular response [SFCs/PBMCs] in the three age groups is summarized in *Table 1.11*.

Table 1.11 Cellular responses assessed using IFN-γ enzyme-linked immunospot (ELISpot) assay (Reference: Ramasamy et al, 2020)

Age Group	Timepoint	Population(N)	SFCs/PBMCs Median [IQR]
18 - 55 years	14 days after dose 1	24	1187 [841 to 2428]
	28 days after dose 1	10	292 [178 to 803]
	14 days after dose 2	23	413 [245 to 675]
56 - 69 years	14 days after dose 1	29	797 [383 to 1817]
	28 days after dose 1	30	591 [238 to 922]
	14 days after dose 2	28	798 [462 to 1186]
≥70 years	14 days after dose 1	48	977 [458 to 1914]
	28 days after dose 1	49	300 [157 to 492]
	14 days after dose 2	47	307 [161 to 516]

Note:
SFCs/PBMCs- spot-forming cells per million peripheral blood mononuclear cells
N - total number of participants whose SFCs/PBMC were included in the analysis
IQR- interquartile range

Table 1.12 Links to Risk of Bias 2 appraisal sheets for Voysey et al., 2020

Outcome of Interest	Link to RoB sheets
Efficacy outcomes	
1. VE against symptomatic COVID-19 *(after dose 2, SD/SD)*	https://drive.google.com/file/d/1QzTsyePPhObWakpJanTEm2W5kjR1QumH/view?usp=sharing
1a. VE against symptomatic COVID-19 *(after dose 2, with <6 weeks interval, SD/SD)*	https://drive.google.com/file/d/1Ayqu_OAU_VcA4thkxSjymu72ay-ltX1C/view?usp=sharing
1b. VE against symptomatic COVID-19 *(after dose 2, with ≥6 weeks interval, SD/SD)*	https://drive.google.com/file/d/16cYgGsO9KObsVtBo8FecQgXUA-YmQS8T/view?usp=sharing
2. VE against symptomatic COVID-19 *(after dose 2, all LD/SD+SD/SD)*	https://drive.google.com/file/d/1QvPjIKIEGLUyRvPQ3wzEnxEbj_GKhxlD/view?usp=sharing
3a. VE against hospitalization due to COVID-19 *(after at least 1 dose, all LD/SD+SD/SD)*	https://drive.google.com/file/d/1o6iDiZjr0yeY79xCIDiWU1IdtvqTxPcN/view?usp=sharing
3b. VE against hospitalization due to COVID-19 *(after dose 2, all LD/SD+SD/SD)*	https://drive.google.com/file/d/1eIqYOguzVst78yf94QpeL4A-pBLmy8kG/view?usp=sharing
4a. VE against severe COVID-19 *(after at least 1 dose, all LD/SD+SD/SD)*	https://drive.google.com/file/d/1Wd4ZYMRwtRKksHXNNnkyLNdDME1Bh_cF/view?usp=sharing
4b. VE against severe COVID-19 *(>14 days after dose 2, all LD/SD+SD/SD)*	https://drive.google.com/file/d/1Wd4ZYMRwtRKksHXNNnkyLNdDME1Bh_cF/view?usp=sharing
5. VE against symptomatic COVID-19 *(after at least 1 dose, SD/SD)*	https://drive.google.com/file/d/1LVfXetpnNBZvVhLfbQ4yrVODTOAfi2xl/view?usp=sharing

6a. VE against symptomatic COVID-19 in older adults (>65 yo) *(after dose 2, all LD/SD+SD/SD)*	Not performed
6b. VE against symptomatic COVID-19 in older adults (>75 yo) *(after dose 2, all LD/SD+SD/SD)*	Not performed
7. VE against symptomatic COVID-19 in population with comorbidities *(after dose 2, all LD/SD+SD/SD)*	https://drive.google.com/file/d/14LsOT5BSLzQB_Gt04gRyqyVMnyQmU7AU/view?usp=sharing
8. VE against symptomatic COVID-19, Asians *(after dose 2, all LD/SD+SD/SD)*	Not performed
9. VE against asymptomatic COVID-19 *(after dose 2, LD/SD+SD/SD)*	https://drive.google.com/file/d/19sDY_p0JKs_sWYtRZKohTfURHV6VLjQw/view?usp=sharing
Safety outcomes	
1.Serious adverse event *(after at least one dose, all LD/SD+SD/SD)*	https://drive.google.com/file/d/1ARZYtO91hr8x5dH1NuniSKp1dAtliodK/view?usp=sharing
1a. Death (all-cause mortality) *(after at least one dose, all LD/SD+SD/SD)*	https://drive.google.com/file/d/1WcyaGLg20KhSfbTJcu2tOe68O3MdcftO/view?usp=sharing
2. Systemic reactogenicity *(after at least one dose, SD/SD)*	https://drive.google.com/file/d/1k2-bVcuL7df74S2oulGfAkKf0zcPYCpY/view?usp=sharing
3. Local reactogenicity *(after at least one dose, SD/SD)*	https://drive.google.com/file/d/1mCnPSncY0y-5koRy7RFkuR3_GiuYVmNL/view?usp=sharing
4. Adverse event, unsolicited *(after at least one dose, all LD/SD+SD/SD)*	https://drive.google.com/file/d/1RatGYknrfyRGor6GaGx08UPwBOwr-mpE/view?usp=sharing

Real world data

As of this writing, only the UK has started administering *COVID-19 Vaccine AstraZeneca.* We have requested real world data from AstraZeneca. These data shall be incorporated in this document as soon as it is available.

Appendix 2. Evidence for Criteria 3 - Affordability and viability

Cost of Implementing *COVID-19 Vaccine AstraZeneca*

The following cost items were identified in calculating for the total resource requirement in implementing *COVID-19 Vaccine AstraZeneca* to the Philippine government: the *COVID-19 Vaccine AstraZeneca* and vaccine consumables; logistics (hauling and storage); and operations (recruitment and training of vaccinators). The source of these costs was derived from the DOH - Disease Prevention and Control Bureau's (DPCB) overall vaccine budget plan. Overall, the projected cost of vaccine and consumables, logistics and operations based on the data is Php17,697,849,013.33. The paragraphs below will detail the costing calculation for cost components.

Vaccine and Consumables

The total cost of vaccines and consumables for 28 million Filipinos will amount to Php 15,085,248,000.00. This amount takes into account 5% estimated wastage of vaccines and cost of two doses of *COVID-19 Vaccine AstraZeneca* for every vaccinee. Vaccine consumables include personal protective equipment (PPE) of the vaccination team and injection devices.

Logistics

Included under logistics are hauling and storage costs. Hauling cost includes the procurement of transport boxes that can contain 1,000 vials each box. Given a weight of 31.4 kg per box, the total cost for hauling *COVID-19 Vaccine AstraZeneca* is estimated at Php 745,913,280. This amount also includes a 1% valuation cost. For storage, the transport boxes are assumed to be stored in warehouses with storage capacity of 100 boxes per warehouse which will be used as temporary location before distribution to vaccination sites. The storage of the vaccines is assumed to last for a month at most, and is estimated to cost Php 2,800 per warehouse occupied, resulting in a storage cost of Php 1,646,400 per month. The overall cost for logistics is estimated to be at Php 747,559,680.

Operations

Operations cost includes mobilization, hiring costs, as well as training for vaccine implementation. Since it is projected that 28,000,000 Filipino will receive *COVID-19 Vaccine AstraZeneca*, it is assumed that 200,000 vaccinators will be needed for

the rollout. Further, the number of supervisors needed is estimated at 66,667, with the assumption that one supervisor is needed per three vaccinators. The duration of the activity provided by DPCB was seven (7) days. With a salary of Php 500 per day for 7 days, the cost of mobilization of these individuals is estimated to be Php 933,333,333.33. For the training of the vaccinators and supervisors, two days are allotted to train them with a cost of Php 1,200 per head per day. We note that in the training costing, DPCB included an input quantity of 121,545 on top of the total number of trainees (i.e., 200,000) multiplied by the cost (in peso) of training per day. This input value is currently being validated with DPCB. In total, the operations cost is computed at Php 1,865,041,333.33. Excluded in the operations cost are the cost of conducting routine RT-PCR tests among vaccination teams, as well as their transportation or any other costs necessary for mobilization and service delivery.

Table 2.1 elaborates the resource requirement costs and assumptions in the roll-out of the *COVID-19 Vaccine AstraZeneca* in the Philippines in 2021.

Table 2.1 Resource requirement costs in the roll-out of COVID-19 Vaccine AstraZeneca in the Philippines in 2021

Description	Cost	Assumptions/Notes	Source
Vaccine and Vaccine Consumables	**Php 15,085,248,000.00**	For 2 doses, with 5% wastage; consumables include syringes, personal protective equipment, hand rub, cotton *(estimated costs for vaccinating 28,000,000 Filipinos based on identified target vaccinees for this brand)*	DPCB
Logistics	**Php 747,559,680.00**	For 2°C to 8°C vaccine storage temperature only. This includes hauling and storage costs. *(estimated costs for vaccinating 28,000,000 Filipinos based on identified target vaccinees for this brand)*	DPCB

Operations	**Php 1,865,041,333.33**	This does not include yet cost of their testing, transportation of vaccinators, or any other costs necessary for mobilization and service delivery. Note that the duration of activity provided by DPCB was 7 days. *(estimated costs for vaccinating 28,000,000 Filipinos based on identified target vaccinees for this brand)*	DPCB
TOTAL COST	**Php 17,697,849,013.33**		
TOTAL VACCINATION COST PER INDIVIDUAL	**Php 632.07**		

Acronym: **DPCB:** Disease Prevention and Control Bureau

Based on the projected calculations, the total cost of rolling out vaccination with *COVID-19 Vaccine AstraZeneca* for 28,000,000 Filipinos would amount to Php 17,697,849,013.33 (which translates to Php 632.07 per individual). This would entail utilization of 21.45% of the total allocated budget for vaccination while the roll out using *COVID-19 Vaccine AstraZeneca* will cover 40% of the target vaccinees for 2021.

Deployment and Feasibility

The COVID-19 Vaccine Deployment Plan outlines the prioritization of eligible populations in receiving the COVID-19 vaccine which includes *COVID-19 Vaccine AstraZeneca*. For Stage 1 of the Vaccine Deployment Plan of COVID-19 vaccines, 22.8% (24,668,128) of the Philippine population is targeted to receive the vaccine under Priority Eligible Population A. This group includes frontline health workers (1.6% or 1,762,994), indigent senior citizens (3.5% or 3,789,874), senior citizens (5.3% or 5,678,544), indigent populations (12.0% or 12,911,193), and uniformed personnel (0.5% or 525,523). On the other hand, Stage 2 of the Vaccine Deployment Plan will increase coverage to 32.95% of the population that will include teachers and social workers (0.95% or 1,179,097), other government workers (1.66% or 1,728,641), other essential workers (1.63% or 1,690,206), other socio-demographic groups with a significantly higher risk (1.72% or 1,785,000), overseas Filipino workers or OFWs (1.66% or

1,728,641), and other remaining members of the workforce (1.25% or 1,298,729) will be inoculated with the vaccine. Finally, in Stage 3 of the Vaccine Deployment Plan, the remaining Filipinos (67.05% or 73,888,198) will be vaccinated. In terms of the priority areas for the deployment of the COVID-19 vaccine, regions determined to have a higher prevalence would be prioritized for the vaccine rollout (i.e., NCR and Region III – Central Luzon).

In the rollout of the vaccine deployment plan, the logistics involved must be taken into consideration. The required storage temperature for the *COVID-19 Vaccine AstraZenec*a is at 2 to 8 degrees Celsius and the shelf-life of the vaccine after first use is 6 hours at 20-25 degrees Celsius, or 48 hours at 2 to 8 degrees Celsius. This temperature requirement can be addressed by use of refrigerators. It is expected that the *COVID-19 Vaccine AstraZeneca* can be widely distributed to facilities with the said equipment; examples of which include tertiary hospitals, Rural Health Units, Municipal Health Offices, and City Health Offices. *COVID-19 Vaccine AstraZeneca* can be accessible at the rural level.

Even though there is anticipated easier and wider distribution brought about by the storage temperature requirements, there is still a need for training on vaccine storage and handling to ensure product integrity across the entire supply chain, and a need to ensure the availability of trained personnel in handling unreported or rare adverse reactions that could occur following vaccination.

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