World Health Organization

# **Evidence Assessment**:
# ChAdOx1-S [recombinant] vaccine (AZD1222) vaccine against COVID-19 developed by Oxford University and Astra Zeneca

**FOR RECOMMENDATION BY THE STRATEGIC ADVISORY GROUP OF EXPERTS (SAGE) ON IMMUNIZATION**

Prepared by the SAGE Working Group on COVID-19 vaccines

# EVIDENCE ASSESSMENT: AZD1222 COVID-19 vaccine

Key evidence to inform policy recommendations on the use of AZD1222 COVID-19 vaccine

**Evidence retrieval**

- Based on WHO and Cochrane living mapping and living systematic review of Covid-19 trials (www.covid-nma.com/vaccines)

**Retrieved evidence**

Majority of data considered for policy recommendations on AZD1222 vaccine are published in scientific peer reviewed journals:

- Safety and immunogenicity of ChAdOx1 nCoV-19 vaccine administered in a prime-boost regimen in young and old adults COV002): a single-blind, randomised, controlled, phase 2/3 trial. Ramasamy,M.N.; Minassian,A.M.; Ewer,K.J., et al. Lancet. 2021 Dec 19;396(10267):1979-1993.
- Safety and immunogenicity of the ChAdOx1 nCoV-19 vaccine against SARS-CoV-2: a preliminary report of a phase 1/2, single-blind, randomised controlled trial. Folegatti,P.M.; Ewer,K.J.; Aley,P.K., et al. Lancet. 2020 Aug 15;396(10249):467-478.
- T cell and antibody responses induced by a single dose of ChAdOx1 nCoV-19 (AZD1222) vaccine in a phase 1/2 clinical trial. Ewer,K.J.; Barrett,J.R.; Belij-Rammerstorfer,S. et al. Nat Med. 2020 Dec 17.
- Single Dose Administration, And The Influence Of The Timing Of The Booster Dose On Immunogenicity and Efficacy Of ChAdOx1 nCoV-19 (AZD1222) Vaccine. Voysey, M.;Clemens, S.; Madhi, S., et al. Lancet. Preprint. (https://papers.ssrn.com/sol3/papers.cfm?abstract_id=3777268)
- Data provided to the Working Group (see vaccine-specific background paper)

**Quality assessment**

- Voysey M. et al.

| Type of bias | Randomization | Deviations from intervention | Missing outcome data | Measurement of the outcome | Selection of the reported results | **Overall risk of bias** |
|---|---|---|---|---|---|---|
| Working Group judgment | Low | Some concerns | Low | Low | Low | **SOME CONCERNS** |

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1. What is the evidence for recommending a longer inter-dose interval between two doses?
2. What is the evidence of the vaccine impact transmission?
3. What is the evidence for use in older age groups?
4. What is the evidence for efficacy and safety for certain comorbidities and health states?
5. GRADEing of the evidence assessment

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2. What is the evidence of the vaccine impact transmission? Peter Smith
3. What is the evidence for use in older age groups? Peter Smith, Sonali Kochhar, Adam Finn, Nick Grassly, Annelies Wilder-Smith
4. What is the evidence for efficacy and safety for certain comorbidities and health states? Annelies Wilder-Smith
5. GRADEing of the evidence assessment—Melanie Marti

# Efficacy ≥ 15days after D2 by interval between D1 and D2

| Analysis set<br>Time interval between Dose 1 and Dose 2 | Participants with events | | VE (%) | 95% CI (%) | P-value |
|---|---|---|---|---|---|
| | AZD1222 n / N (%) | Control n / N (%) | | | |
| **SDSD seronegative for efficacy analysis set** | | | | | |
| < 4 weeks | 1 / 206 (0.49) | 3 / 203 (1.48) | 66.56 | (-221.83, 96.53) | 0.343 |
| ≥ 4 to 8 weeks | 54 / 4796 (1.13) | 117 / 4662 (2.51) | 56.42 | (39.86, 68.43) | <0.001 |
| 9 to 12 weeks | 11 / 1053 (1.04) | 39 / 1101 (3.54) | 70.48 | (42.41, 84.87) | <0.001 |
| > 12 weeks | 8 / 1146 (0.70) | 38 / 1213 (3.13) | 77.62 | (51.98, 89.57) | <0.001 |

**Approx. test for trend P=0.035**

# Efficacy ≥ 22 days after D1 up to D2 by interval between D1 and D2

| Symptomatic COVID-19 Cases > 21 days after a single SD dose | N cases | ChAdOx1 nCoV-19 | Control | Vaccine Efficacy (95% CI) |
|---|---|---|---|---|
| **Time since first standard dose** | | | | |
| 22 to 30 days | 37 | 7/ 9257 | 30/ 9237 | 77% (47%, 90%) |
| 31 to 60 days | 28 | 6/ 7147 | 22/ 7110 | 73% (33%, 89%) |
| 61 to 90 days | 23 | 4/ 2883 | 19/ 2974 | 78% (36%, 93%) |
| 90 to 120 days | 10 | 4/ 1368 | 6/ 1404 | 32% (-142%, 81%) |
| **22 to 90 days** | **88** | **17** | **71** | **76% (59%, 86%)** |



*Voysey et al: Single dose administration, and the influence of the timing of the booster dose on immunogenicity and efficacy of ChAdOx1 nCoV-19 (AZD1222) vaccine*

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# Potential effect of vaccine on transmission

## Efficacy against PCR+ infection between D1 and D2 ≥22 days after D1

| COVID 19 infection 22 to 90 days after Dose 1 | ChAdOx1 nCoV-19 | Control | Vaccine efficacy (95% CI) |
|---|---|---|---|
| **Asymptomatic** | 11 | 13 | 16% (-88%, 62%) |
| **Symptomatic + asymptomatic** | 28 | 84 | 67% (49%, 78%) |

## Efficacy against PCR+ infection ≥15 days after D2

| COVID 19 infection ≥ 15 days After Dose 2 | ChAdOx1 nCoV-19 | Control | Vaccine efficacy (95% CI) |
|---|---|---|---|
| **Asymptomatic** | 41 | 42 | 2% (-50%, 36%) |
| **Symptomatic +asymptomatic** | 132 | 258 | 49% (38%, 59% |



*Voysey et al: Single dose administration, and the influence of the timing of the booster dose on immunogenicity and efficacy of ChAdOx1 nCoV-19 (AZD1222) vaccine*

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World Health Organization

**Strategic Advisory Group of Experts (SAGE) on Immunization Evidence to recommendations framework**[i]

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| **Question:**<br>**Population:**<br>**Intervention:**<br>**Comparison(s):**<br>**Outcome:** | | | | | | | |
| **Background:** | | | | | | | |
| | **CRITERIA** | **JUDGEMENTS** | | | | **RESEARCH EVIDENCE** | **ADDITIONAL INFORMATION** |
| **PROBLEM** | Is the problem a public health priority? | *No* ☐ | *Un-certain* ☐ | *Yes* ☐ | *Varies by setting* ☐ | | |
| **BENEFITS & HARMS OF THE OPTIONS** | Benefits of the intervention<br><br>Are the desirable anticipated effects large? | *No* ☐ | *Un-certain* ☐ | *Yes* ☐ | *Varies* ☐ | | |

Questions which were considered in SAGE evidence-to-recommendation tables:

1. Should AZD1222 vaccine be administered to adults (18-64 years) to prevent COVID-19?
2. Should AZD1222 vaccine be administered to older adults (≥65 years) to prevent COVID-19?
3. Should AZD1222 vaccine be administered to individuals with comorbidities or health states that increase risk for severe COVID-19 to prevent COVID-19?

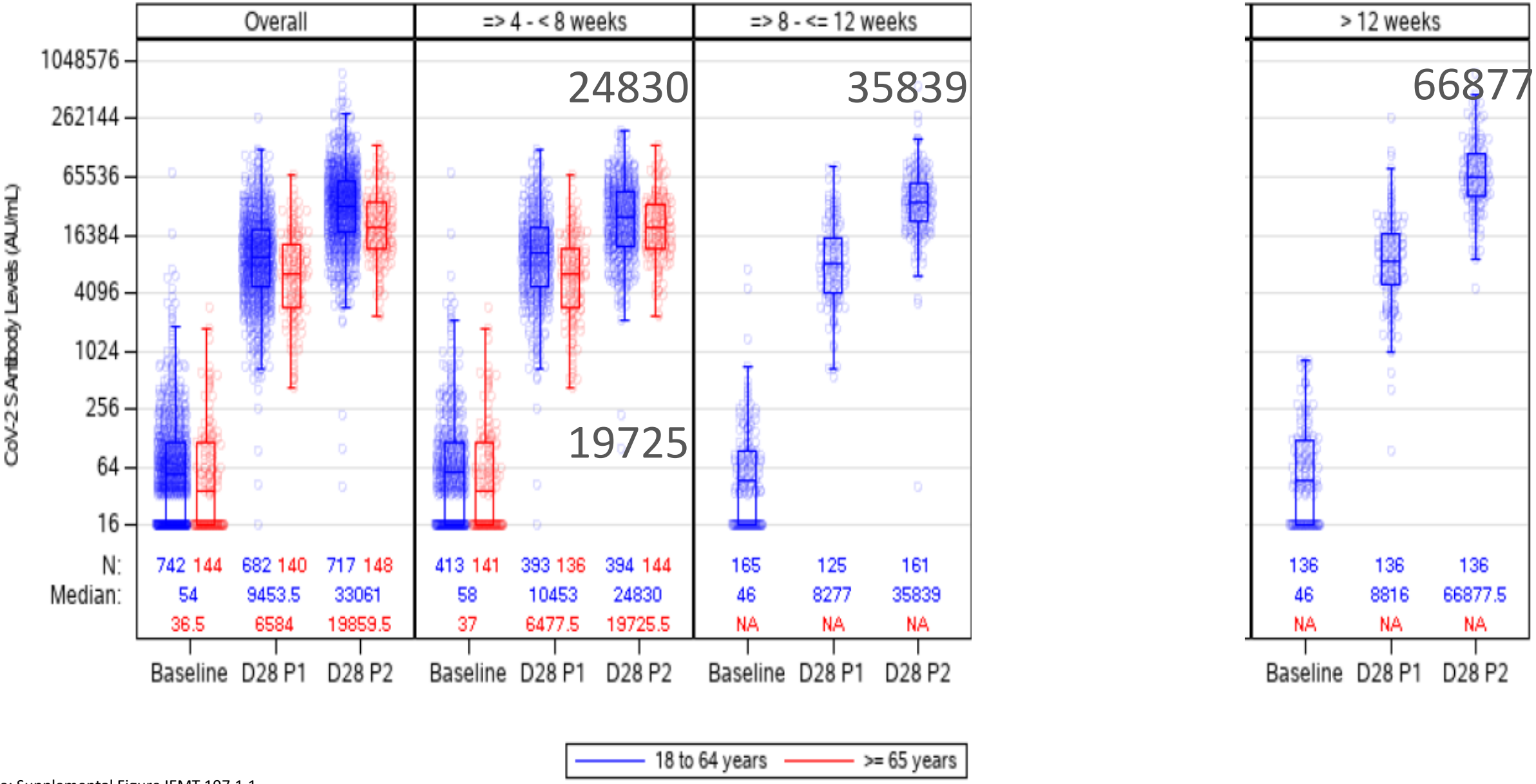
# Vaccine efficacy in older persons aged 65 years and over

| | AZD1222 n/N (%) | Control n/N (%) | Vaccine Efficacy (95% CI) | P-value |
|---|---|---|---|---|
| **≥15 days post-dose 2 (primary efficacy)** | 4/703 (0.57) | 8/680 (1.18) | 51.91 (-59.98,-85.54) | 0.233 |
| **≥ 22 days post-dose 1 (standard dose)** | 6/945 (0.63) | 13/896 (1.45) | 55.87 (-16.08, 83.22) | 0.097 |
| **Post-dose 1 (any dose for efficacy)** | 10/1038 (0.96) | 20/973 (2.06) | 52.99 (-0.45, 78.00) | 0.051 |
| - Hospitalisations | 0/1038 | 4/973 (0.41) | - | - |



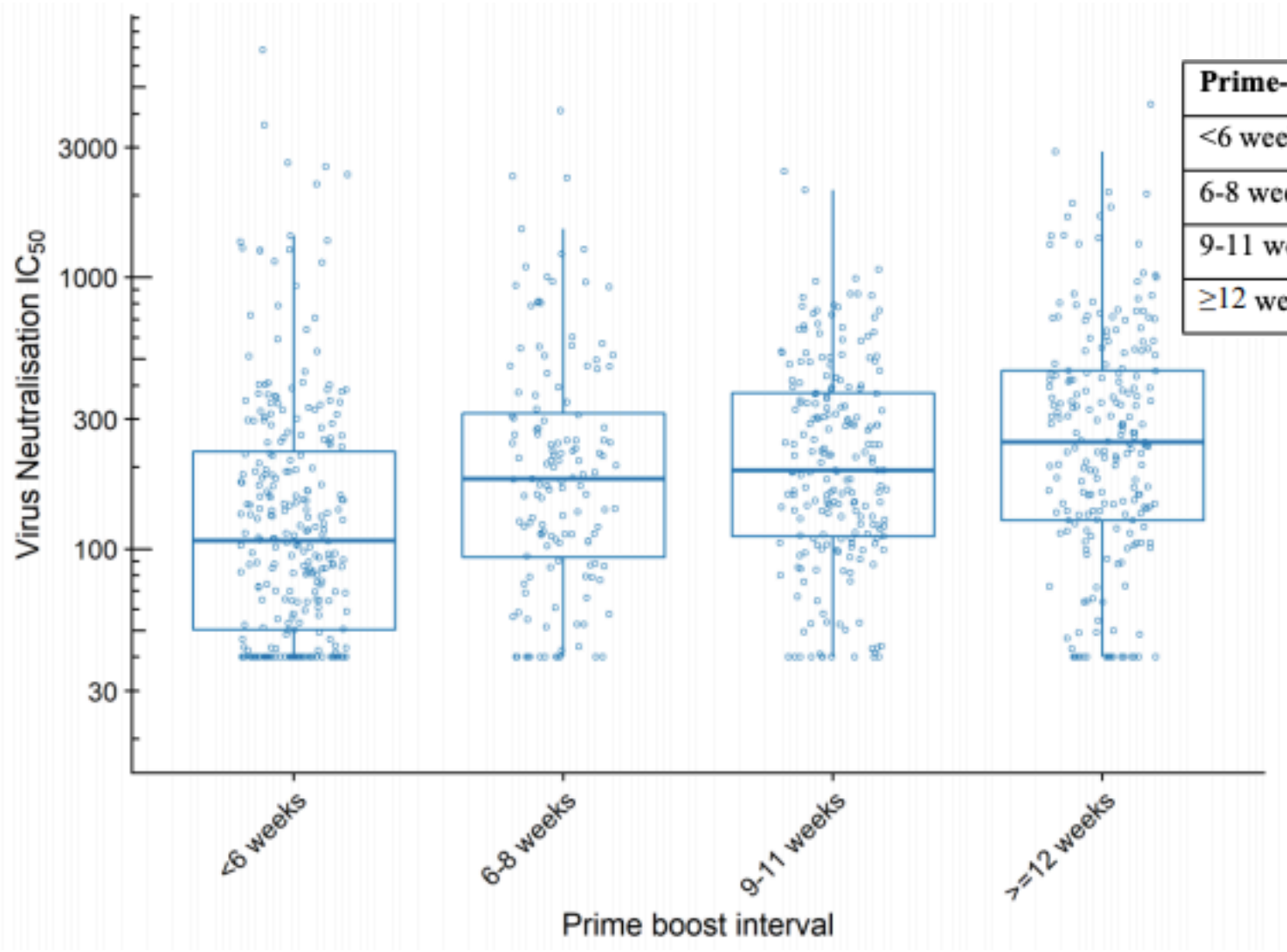
Source: Tables 4.3.1.2, 4.4.8.1, 4.4.10.1, 4.4.13.2, 4.4.14.1, 4.4.15.1.

# Post dose 2 anti-S binding antibody concentrations increase with increasing dose interval




Source: Supplemental Figure IEMT 197.1.1.

# Pseudovirus IC50 neutralising AB titres increase with increasing dose interval
# 18-64y 469 ≥65y 313

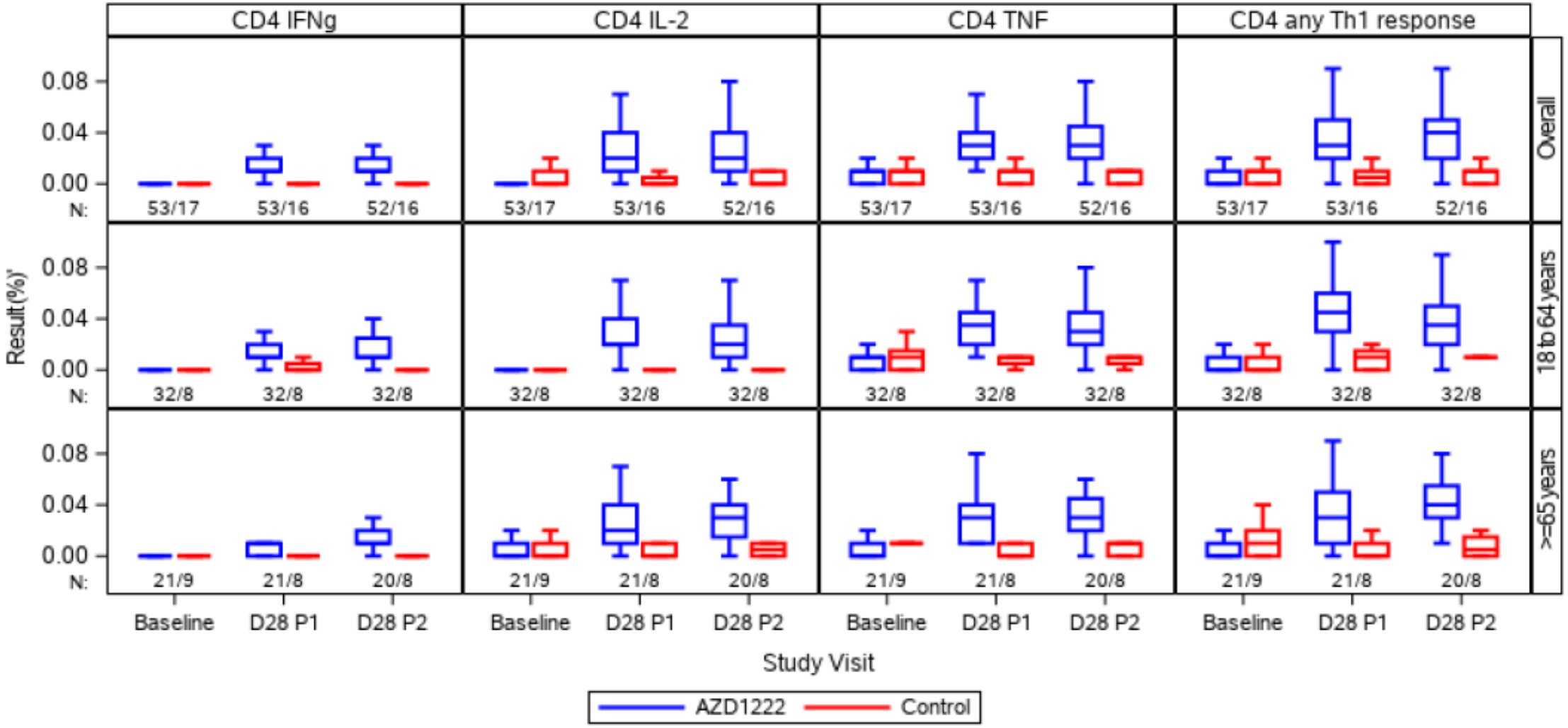



| Prime-boost interval | N | Median [IQR] | GMT (95% CI) |
|---|---|---|---|
| <6 weeks | 272 | 107 [50, 228] | 125 (110, 141) |
| 6-8 weeks | 136 | 181 [93, 315] | 188 (158, 223) |
| 9-11 weeks | 210 | 194 [111, 375] | 203 (181, 228) |
| ≥12 weeks | 217 | 248 [128,452] | 240 (210, 276) |



Lancet pre-print at https://papers.ssrn.com/sol3/papers.cfm?abstract_id=3777268

# Vaccine-induced CD4 T-cell responses – TH1 intra-cellular cytokine staining – S1 peptide panel




Boxplots display the median and 1st and 3rd quartiles. Whiskers extend to the minimum and maximum values, excluding outliers. Baseline is defined as the last non-missing measurement taken prior to the first dose of study intervention. Background percentage was subtracted from the stimulated percentage prior to analysis. Stimulated percentages less than the background percentage were set to 0%.
Abbreviations: D28 P1 = Day 28 post Dose 1; D28 P2 = Day 28 post Dose 2.
Source: Supplemental Figure IEMT 194.1.1.1.; Supplemental Figure IEMT 194.1.1.2



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**Exploratory analysis, Unpublished results**

# Safety Overview

- Overall safety based on interim analysis of pooled data from four clinical trials (UK (phase I/II; phase II/ III), Brazil (phase III), South Africa (phase I/II))
- Safety data available for 23,745 participants ≥18 years
- 12,021 subjects received at least one dose, and **8,266 received 2 doses**
- 59.6% subjects had a dose schedule of 4-8 weeks, 21.6 % 9-12 weeks, and 15.9% > 12 weeks
- Median follow-up post dose 1 was 105 days
- In the vaccine group
    - 90.3% (18- 64 years)
    - **9.7% (≥65 years)**
- 36% had at least one **comorbidity** at baseline (i.e. obesity, cardiovascular disease (mainly HT), respiratory disease (mainly asthma) or diabetes)
- 55.8% female vs 44.2% male
- White (75.5%), Black (10.1%), Asian (3.5%)
- 3% were seropositive at baseline (South Africa (14.8%), Brazil (2.3%), UK (1.6%))

# Safety in Older Adults

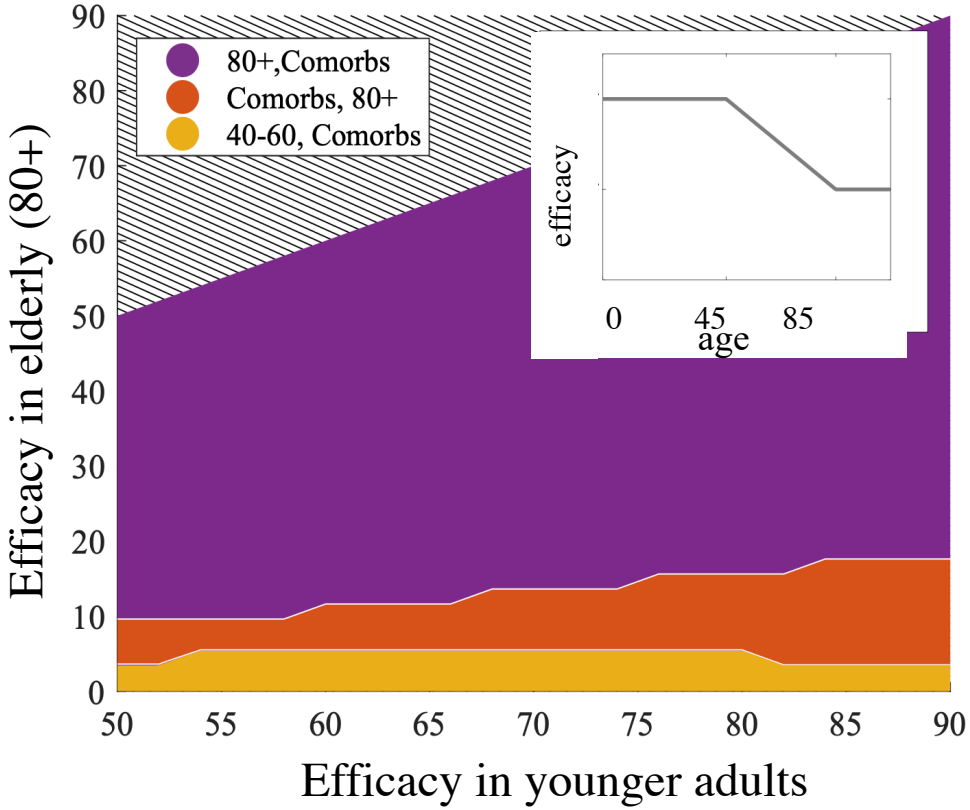
- Majority of the adverse reactions (ARs) were mild to moderate, usually resolved within a few days
- Adverse reactions after dose 2 were milder and less frequent, compared to dose 1
- Reactogenicity was generally milder and less frequent in older adults (≥65 years old) compared to younger adults (18-64 years)
- Incidence of SAE and AESI was similar between <65 and ≥ 65 years
- Analyses of safety data by age, comorbidity, baseline seropositivity and country did not raise any specific concerns
- Based on this, it was considered that the available evidence supports a broad indication

# Vaccine prioritization and efficacy in older adults: public health and modeling considerations

SAGE WG modelling subgroup previously reviewed models of the health impacts of different vaccine prioritization schemes in the context of limited supply

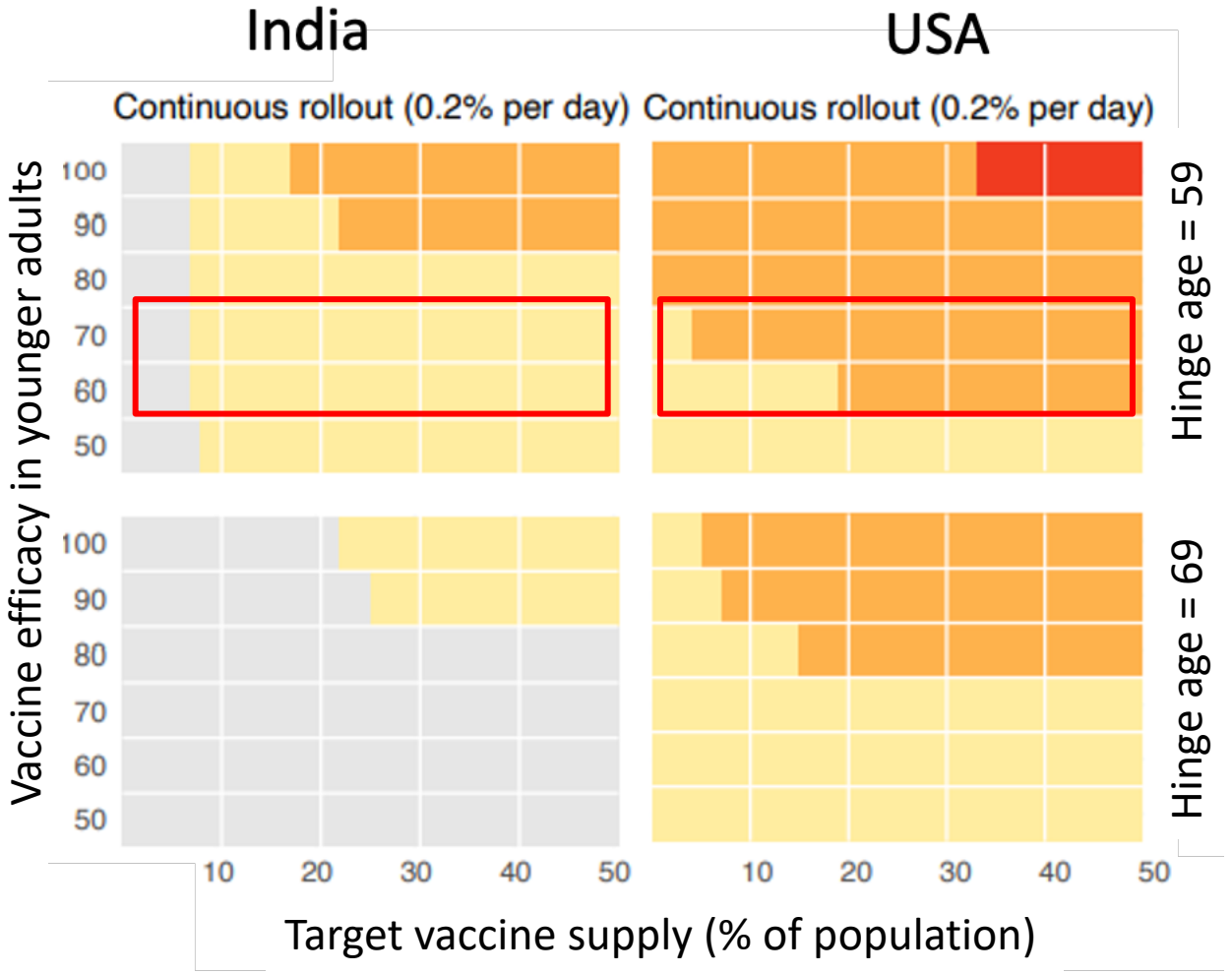
Prioritisation of older adults ‘shown to be optimal for minimizing COVID-19 deaths even for vaccines with substantially lower efficacy in older adults…, when age is the only prioritization dimension considered’ [SAGE WG background paper; Moore et al. 2020, Bubar et al. 2020, Hogan et al. 2020, Buckner et al. 2020]

Prioritisation of younger adults only optimal if the vaccine prevents transmission (infection) and the reproduction number is close to 1

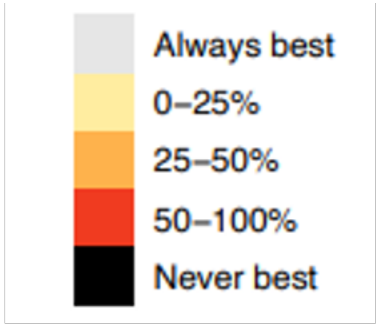



Model of optimal sequence of priority groups for vaccination in the UK (Moore et al. 2020 medrxiv)

# Conclusion continues to be supported by modelling: multi-country model update (Bubar et al. 2021 *Science*)


threshold efficacy in 80+ at which prioritization of 60+ no longer best



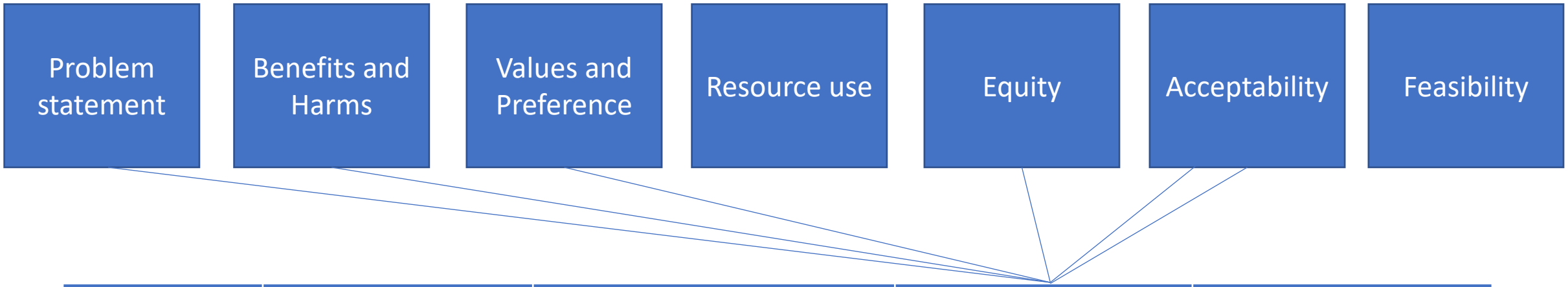

$R_0$=1.5
all-or-nothing vaccine prevents infection

“we conclude that for mortality reduction, prioritization of older adults is a robust strategy that will be optimal or close to optimal to minimize mortality for virtually all plausible vaccine characteristics”

| Criteria for Persons aged 65 and above | | JUDGMENT BY THE WORKING GROUP |
|---|---|---|
| **PROBLEM** | Is the problem a public health priority? | **YES** |
| **BENEFITS & HARMS OF THE OPTIONS** | Are the desirable anticipated effects large? | **UNCERTAIN** |
| | Are the undesirable anticipated effects small? | **YES** |
| | Balance between benefits and harms | **FAVOURS INTERVENTION** |
| **VALUES & PREFERENCES** | How certain is the relative importance of the desirable and undesirable outcomes? | **POSSIBLY IMPORTANT UNCERTAINTY OR VARIABILITY** |
| | Values and preferences of the target population: Are the desirable effects large relative to undesirable effects? | **PROBABLY YES** |
| **RESOURCE USE** | Are the resources required small? | **NO** |
| | Is the intervention cost-effective? | **PROBABLY** |
| **EQUITY** | What would be the impact on health inequities? | **REDUCED** |
| **ACCEPTABILITY** | Which option is acceptable to key stakeholders (e.g. ministries of health, immunization managers)? | **INTERVENTION** |
| | Which option is acceptable to target group? | **INTERVENTION** |
| **FEASIBILITY** | Is the intervention feasible to implement? | **YES** |

# EVIDENCE ASSESSMENT: AZD1222 COVID-19 vaccine on the use in persons aged 65 and older

Key evidence to inform policy recommendations on the use of AZD1222 COVID-19 vaccine




| Undesirable consequences clearly outweigh desirable consequences in most settings | Undesirable consequences probably outweigh desirable consequences in most settings | The balance between desirable and undesirable consequences is closely balanced or uncertain | Desirable consequences probably outweigh undesirable consequences in most settings | Desirable consequences clearly outweigh undesirable consequences in most settings |
|---|---|---|---|---|
| ☐ | ☐ | ☐ | ☒ | ☐ |

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# Vaccine efficacy in participants with stable co-morbidities

Comorbidity was defined as having a BMI ≥30 kg/m$^2$, cardiovascular disorder, respiratory disease or diabetes

- Proportion of subjects vaccinated with AZD1222 with comorbidities at baseline : **36%**
  - Obesity (19.6%)
  - Cardiovascular disease (13.5%)
    - Mainly hypertension (9.9%)
  - Respiratory disease (10.2%)
    - Mainly asthma (6.2%)
  - Diabetes (3.3%)
- Results in this subgroup were consistent with the overall vaccine efficacy result

| Comorbidity at baseline: Yes | Participants with events | | Vaccine Efficacy (%) | 95% CI (%) | P-value |
|---|---|---|---|---|---|
| | AZD1222 n / N (%) | Control n / N (%) | | | |
| Dose 1 SD seronegative | 28 / 2592 (1.08) | 76 / 2631 (2.89) | 62.20 | 41.71, 75.49 | <0.001 |

Source: table 1.1.4.5, , Supplemental Tables IEMT 175.2.a, 175.2.b, IEMT175.1.a, and IEMT175.1.b

# Efficacy and safety with certain comorbidities or health states

- No HIV patients included in the primary analyses
- No pregnant and lactating women included
- No patients with immune deficiencies
- No patients with autoimmune disease
- Patients with history of allergic reactions excluded

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**Vaccine Efficacy: 63.47 % (95% CI: 51.95- 72.23)**

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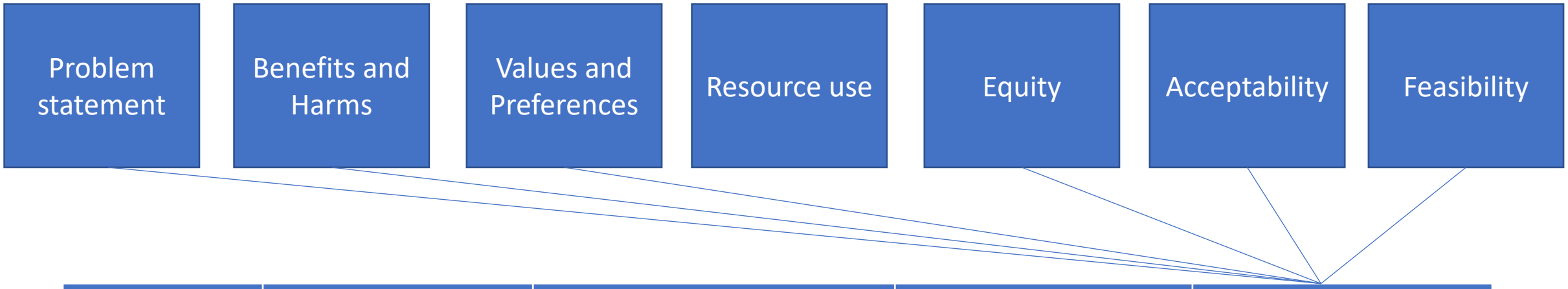


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|---|---|---|---|---|
| ☐ | ☐ | ☐ | ☐ | ☒ |

Specific recommendations: NEXT PRESENTATION

| GRADEing of Evidence | Statement on quality of evidence | SAGE Working Group Judgement |
|---|---|---|
| Efficacy against PCR confirmed COVID-19 (Adults) | **High level of confidence** | We are very confident that 2 doses of AZD1222 vaccine are efficacious in preventing PCR confirmed COVID-19 in adults (18-64 years). |
| Safety-serious adverse events (Adults) | **Moderate level of confidence** | We are moderately confident that the risk of serious adverse events following one or two doses of AZD1222 vaccine in adults (18-64 years) is low. |
| Efficacy PCR confirmed COVID-19 (Older adults) | **Low level of confidence** | We have low confidence in the quality of evidence that 2 doses of AZD1222 vaccine are efficacious in preventing PCR confirmed COVID-19 in older adults (≥65 years). |
| Safety-serious adverse events (Older adults) | **Low level of confidence** | We have low confidence in the quality of evidence that the risk of serious adverse events following one or two doses of AZD1222 vaccine in older adults (≥65 years) is low. |
| Efficacy PCR confirmed COVID-19 (*Individuals with comorbidities or health states that increase risk for severe COVID-19*) | **Moderate level of confidence** | We are moderately confident that 2 doses of AZD1222 vaccine are efficacious in preventing PCR confirmed COVID-19 in individuals with comorbidities or health states that increase risk for severe COVID-19 as included in the clinical trial. No data were obtained on vaccination of pregnant or breastfeeding women, and persons who were immunocompromised. |
| Safety-serious adverse events (*Individuals with comorbidities or health states that increase risk for severe COVID-19*) | **Low level of confidence** | We have low confidence in the quality of evidence that the risk of serious adverse events in individuals with comorbidities or health states that increase risk for severe COVID-19 following one or two doses of AZD1222 vaccine is low. |