Background document on the Janssen Ad26.COV2.S (COVID-19) vaccine

Background document to the WHO Interim recommendations for use of Ad26.COV2.S (COVID-19) vaccine

17 March 2021

World Health Organization

Contents

Background

This background document was prepared by the Strategic Advisory Group of Experts (SAGE) on Immunization Working Group on COVID-19 Vaccines to inform the discussions of SAGE at its 15 March 2021 meeting, which resulted in the issuance of the WHO interim recommendations for use of the Ad26.COV2.S (COVID-19) vaccine. Both the recommendations and the background document are available on the SAGE COVID-19 webpage: https://www.who.int/groups/strategic-advisory-group-of-experts-on-immunization/covid-19-materials.

Declarations of interests were collected from all external contributors and assessed for any conflicts of interest. Summaries of the reported interests can be found on the SAGE meeting webpage and SAGE Covid-19 Working Group webpage.

Context

The Janssen vaccine is a recombinant vector vaccine that uses a human adenovirus to express the SARS-CoV-2 spike protein and is based on the Ad26 vector platform. The adenoviruses are a group of viruses that cause infections in the respiratory and gastrointestinal tracts; the adenovirus vector used in the experimental vaccine has been modified, so that it can no longer replicate in humans and cause illness. In developing the vaccine, Janssen employed the same vector used in the first dose of its prime–boost vaccine regimen against Ebola virus disease (Ad26 ZEBOV and MVN-BN-Filo). As of 31 December 2020, Ad26-based vaccines have been used to vaccinate 193 831 participants in clinical studies and vaccination programmes. These more than 193 000 participants included people from different age groups (elderly, adults, children and infants), individuals positive for human immunodeficiency virus (HIV), and pregnant and breastfeeding women, and the data show a favourable safety profile. Ad26-based vaccines elicit strong humoral immune responses with both neutralizing activity and non-neutralizing antibody functionalities, and cellular immune responses involving both CD8+ T cells and CD4+ T-cells, the latter with a predominantly Th1 phenotype, irrespective of the transgene encoded immunogens (1-4). Overall, these vaccines have been shown to have an acceptable clinical safety profile to date.

Data taken into consideration are those included in the US Food and Drug Administration *Vaccines and Related Biological Products Advisory Committee (VRBPAC)* meeting documentation, available under the following links: www.fda.gov/media/146217/download and www.fda.gov/media/146218/download.

Characteristics of Ad26.COV2.S (COVID-19) vaccine

The Janssen COVID-19 Vaccine is a replication-incompetent adenovirus type 26 (Ad26)-vectored monovalent vaccine encoding the SARS-CoV-2 spike (S) protein from the Wuhan-Hu-1 isolate (GenBank accession number MN908947), stabilized in its prefusion conformation. The vector cannot replicate in human cells because the E1 gene was deleted from the genome. To manufacture vaccines that are based on replication incompetent adenoviral vectors, a specific cell line is used that complements for the missing E1 gene. This cell line is derived from a single human primary cell, obtained in 1985 from fetal retina tissue (at 18 weeks of gestation adhering to the Dutch laws that were in effect). The cell line was established by transformation of the primary cells using the Adenovirus E1 gene which resulted in a cell line that constitutively expresses E1, and that is thus able to complement the adenoviral vector that misses E1, allowing the vector to replicate during the manufacturing process. Another consequence of the E1 transformation is that the cell line can be propagated indefinitely and as a result, there is no need to go back to the primary cells in any part of the scientific discovery or manufacturing process. The Ad26 vector expressing the S protein is grown in PER.C6G TetR cell line, in media containing amino acids and no animal-derived proteins. After propagation, the vaccine is processed through several purification steps, formulated with inactive ingredients and filled into vials.

Composition

One dose (0.5 ml) contains 5 x 10^{10} AD26.COV2.S viral particles (vp).

The vaccine also contains the following inactive ingredients: citric acid monohydrate, trisodium citrate dihydrate, ethanol, 2-hydroxypropyl-beta-cyclodextrin (HBCD), polysorbate 80, sodium chloride, sodium hydroxide, and hydrochloric acid.

The vaccine does not contain preservatives.

Dosing regimen

Ad26.COV2.S is administered as a single intramuscular injection (0.5 ml dose).

Stability and shelf-life

The vaccine is provided to country at -20°C with a shelf life of 24 months in a multi-dose vial containing 5 doses (0.5ml each). The vaccine could be stored at 2°C to 8°C for 3 months. Once thawed the vaccine should not be re-frozen. The vials should be protected from light. After the first dose has been withdrawn, the vial should be held between at 2°C to 8°C for up to 6 hours in compliance with WHO Multidose open vial policy. Any remaining dose of opened vial must be discarded after 6 hours or at the end of the immunization session, whichever comes first.

Drug product description

The Janssen Ad26.COV2.S vaccine is a colourless to slightly yellow, clear to very opalescent sterile suspension for intramuscular injection.

Container

Each multidose vial contains a fill volume of 3.1 ml to allow for an extractable volume of 2.5 ml, as 5 extractions of 0.5 ml.

The vaccine does not require reconstitution.

Preclinical studies

Nonclinical immunogenicity and efficacy

A single dose of Ad26.COV2.S induced a rapid onset of SARS-CoV-2 neutralizing and S protein-binding antibodies in all species tested (mice, rabbits, Syrian hamsters, and nonhuman primates). Cellular immunity was seen in mice and nonhuman primates, with CD4+ T cells, predominantly of the Th1 phenotype, and IgG-producing CD8+ T cells.

In Syrian hamsters, a single dose of Ad26.COV2.S significantly reduced viral load in the lungs after SARS-CoV-2 challenge, in comparison with mock-vaccinated and challenged controls. In nonhuman primates, undetectable viral load in the nose was observed in the majority, and undetectable viral load in the lungs was recorded for all animals. (5, 6).

Duration of protection: Almost all vaccinated macaques had undetectable lung viral load after challenge 6 months after vaccination (7).

Vaccine enhanced respiratory disease (VAERD): In all Syrian hamsters and nonhuman primates vaccinated with Ad26.COV.2S and subsequently challenged with SARS-CoV-2, no increased lung histopathology, infectious viral load, or clinical signs were observed, indicating the absence of any signs of VAERD (8).

Biodistribution

The biodistribution profile of the Ad26 vector platform was evaluated in New Zealand White rabbits. The Ad26 vector did not widely distribute following intramuscular administration. Vector DNA was detected at the site of injection, in draining lymph nodes, and (to a lesser extent) in the spleen. The Ad26 vector showed clearance from these tissues.

Toxicology

In a repeat-dose toxicity and local tolerance study in New Zealand White rabbits, IM administration of Ad26.COV2.S at 1×10^{11} vp/dose on three occasions, with a 14-day interval period, was well tolerated. There were no adverse vaccine-related effects noted.

Developmental and reproductive toxicity

In a combined embryo-fetal and pre- and postnatal development toxicity study, 3 doses of Ad26.COV2.S at $1x10^{11}$ vp/dose were administered at $1x10^{11}$ intramuscularly to female New Zealand White rabbits during the premating and gestation period. There was no adverse effect of Ad26.COV2.S on fertility, or embryo-fetal and postnatal development.

Clinical studies

The pivotal safety, efficacy and immunogenicity data informing registration of the vaccine are derived from five ongoing studies:

- COV1001: a phase 1/2 trial in 1045 adults (1-dose and 2-dose regimens, with booster in 1 cohort);
- COV1002: a phase 1 safety and immunogenicity study in 250 adults (2-dose regimen);
- COV2001: a phase 1a safety and immunogenicity study involving 550 adults and 660 adolescents (1-dose and 2-dose regimens) (enrolment of adolescents has not yet started);
- COV3001: a phase 3 efficacy and safety trial in 40 000 adults (1-dose regimen) (enrolment complete);
- COV3009: a phase 3 efficacy and safety trial in 30 000 adults (2-dose regimen) (enrolment ongoing);

The primary analysis of vaccine efficacy from the study COV3001 is used here as the main source of data.

Studies in other populations (i.e, pregnant women, children with and without comorbidities) are planned in the near future.

Immunogenicity studies in humans

Study COV1001 (healthy adults ages 18 to 55 in the United States and Belgium): A single dose of Ad26.COV2.S elicited a SARS-CoV-2 neutralizing antibody (wtVNA) and SARS-CoV-2 spike binding antibody response that was detected by Day 15 and is increased by Day 57. Ad26.COV2.S was able to elicit cellular responses in participants with a Th-1 phenotype. Ad26.COV2.S, given as a single dose was found to have an acceptable safety and reactogenicity profile in adults aged 18 years and above and did not raise safety concerns in any of the assessed populations.

Study COV1002 (healthy adults ages 20-55, and ≥65 years of age and above in good health, in Japan): Two doses were given at a 56-day interval. Neutralizing antibody responses by day 29 post-vaccination with a single dose were similar to Study COV1001.

Study COV2001 is an ongoing, randomized, double-blind, placebo-controlled Phase 2a study, conducted in Germany, Spain, and the Netherlands in healthy adults ⩾18 to ⩽55 years of age, and adults in good or stable health ⩾65 years of age. The primary objectives of this study are to assess safety and reactogenicity and humoral immune response of Ad26.COV2.S across different doses and intervals (for 2-dose regimens). Recently, adolescents aged 12 to 17 years were included.

Across Phase 1 and 2 studies at Day 29, a SARS-CoV-2 neutralizing antibody response was observed in at least 88% of participants aged 18 to 55 years and at least 93% of participants aged 65 and above. Neutralizing and binding antibody responses continued to increase from Day 29 to Day 57 and were maintained to at least Day 85, with very high responder rates across the age groups. A single dose of Ad26.COV2.S elicited SARS-CoV-2 CD4+ and CD8+ T cell responses by Day 15 and up to Day 29 in the majority of adult participants aged 18 to 55, and aged 65 and above.

Efficacy studies

Study COV3001, which used a 1-dose regimen, provides the primary analyses for this background paper. Study COV3001 is an ongoing, multicentre, randomized, double-blind, placebo-controlled phase 3 study to assess the efficacy, safety and immunogenicity of a single dose (5×10^{10} vp) of Ad26.COV2.S for the prevention of COVID-19 in adults aged 18 years and older. The study is being conducted in Argentina, Brazil, Chile, Colombia, Mexico, Peru, South Africa and the USA. A total of 44 325 participants were randomized, of whom 43 783 were given either Ad26.COV2.S or placebo. The study was well balanced among subgroups with regard to age, comorbidities, sex, region, race, and ethnicity. The study was initiated at sites expected to experience high incidence of COVID-19 on 21 September 2020. The time of study enrollment coincided with a marked increase of incidence of COVID-19 and the emergence of new SARS-CoV-2 variants, which were emerging in some of the countries where study COV3001 was being conducted. Efficacy results were based on the primary analysis, which included 19 630 participants who received the vaccine and 19 691 participants who received placebo.

At the time of the primary analysis, 464 central laboratory-confirmed primary endpoint cases with an onset at least 14 days after vaccination included in the per protocol analysis set, of which 259 cases occurred at least 28 days after vaccination. The primary analysis included centrally confirmed cases only. Because of the high in-study incidence of COVID-19 and the time needed for central laboratory confirmation of the local polymerase chain reaction (PCR) test, not all cases could be confirmed by the central laboratory at the time of the primary analysis. As a result, there were two data sets: a data set of centrally confirmed primary endpoint COVID-19 cases (464 after day 14, 259 after day 28) and a data set including all primary endpoint COVID-19 cases with a positive PCR from any source, regardless of central confirmation (682 after day 14, 437 after day 28). Vaccine efficacy (VE) estimates based on the two data sets differed by less than 1% and had similar confidence intervals (CIs). Among the cases that were centrally confirmed, a high concordance was observed (90.3%). For subgroup analyses, COVID-19 requiring medical intervention, and COVID-19-related deaths, the data set including non-centrally confirmed cases was used to increase the robustness of the conclusions. The primary analysis included centrally confirmed cases only.

The co-primary endpoints in study COV3001 were the first occurrence of PCR-confirmed COVID-19, including both moderate and severe/critical COVID-19 cases according to their case definitions, with onset at least 14 days or at least 28 days after vaccination. All other efficacy endpoints were also evaluated in relation to cases that occurred at least 14 days or at least 28 days after vaccination. The primary efficacy analysis was performed after 50% of the participants had been followed for 8 weeks from the day of vaccination, on 22 January 2021, with 464 primary endpoint cases at least 14 days after vaccination and 259 primary endpoint cases at least 28 days after vaccination. Because of the limited number of mild COVID-19 cases, the co-primary endpoints capture almost all observed symptomatic COVID-19 cases. The total number of symptomatic cases (468 at least 14 days after vaccination and 261 at least 28 days after vaccination) was very similar to the total number of moderate and severe/critical COVID-19 cases. Participants will continue to be followed up for up to 24 months, for assessments of both safety and efficacy of the vaccine against COVID-19. Following emergency use authorization, Janssen proposes to change the study design, offering a single dose of Ad26.COV2.S to participants who initially received placebo, resulting in de facto unblinding of participants and investigators.

Table 1. Participant disposition by age group and comorbidities, full analysis set, study COV3001.

Participant group Follow-up	Ad26.COV2.S (21 895)	Placebo (21 888)	All participants (43 783)
18–59 years, total	14 564	14 547	29 111
Participants with at least 8 weeks follow- up	62.8%	63.1%	63.0%
Median follow-up after vaccination (days)	61.0	61.0	61.0
18–59 years, no comorbidities	9332	9371	18 703
Participants with at least 8 weeks follow- up	70.0%	69.9%	70.0%
Median follow-up after vaccination (days)	64.0	64.0	64.0
18–59 years, with comorbidities	232	5176	10 408
Participants with at least 8 weeks follow- up	49.9%	50.8%	50.4%
Median follow-up after vaccination (days)	56.0	57.0	57.0
≥60 years, total	7331	7341	14672
Participants with at least 8 weeks follow- up	38.2%	37.8%	38.0%
Median follow-up after vaccination (days)	52.0	52.0	52.0
⩾60 years, no comorbidities	3627	3595	7222
Participants with at least 8 weeks follow- up	47.6%	49.0%	48.3%
Median follow-up after vaccination (days)	54.0	55.0	54.0

≥60 years, with comorbidities	3704	3746	7450
Participants with at least 8 weeks follow- up	29.0%	27.1%	28.0%
Median follow-up after vaccination (days)	50.0	50.0	50.0

Boxes 1 and 2 provide respectively the primary endpoint case definitions for moderate and severe/critical COVID-19 cases used in the efficacy studies.

Box 1: Case definition for moderate COVID-19[1]

The **case definition for moderate COVID-19** was a positive SARS-CoV-2 reverse transcription (RT)-PCR or molecular test result from any available respiratory tract sample (e.g. nasal, throat, sputum, saliva) or other sample,

and at any time during the course of observation,

either:

- any one of the following new or worsening signs or symptoms:
  - respiratory rate ≥20 breaths/minute,
  - abnormal saturation of oxygen (SpO2) but still >93% on room air at sea level,
  - clinical or radiological evidence of pneumonia,
  - radiological evidence of deep vein thrombosis,
  - shortness of breath or difficulty breathing

or:

- any two of the following new or worsening signs or symptoms:
  - fever (≥38.0°C or ≥100.4°F),
  - heart rate ≥90 beats/minute,
  - shaking chills or rigors,
  - sore throat,
  - cough,
  - malaise, as evidenced by loss of appetite, fatigue, physical weakness, and/or feeling unwell,
  - headache,
  - muscle pain (myalgia),
  - gastrointestinal symptoms (diarrhoea, vomiting, nausea, abdominal pain),
  - new or changing olfactory or taste disorders,
  - red or bruised-looking feet or toes.

[1] The case definitions used were developed by Janssen and differ from WHO standard definitions of COVID-19 disease severity which can be found in: COVID-19 Clinical management: living guidance (https://www.who.int/publications/i/item/WHO-2019-nCoV-clinical-2021-1, accessed 16 March 2021).

Box 2: Case definition for severe/critical COVID-19[2]

The ***case definition for severe/critical COVID-19*** was an RT-PCR or molecular test result from samples described above and any one of the following at any time during the course of observation:

- clinical signs at rest indicative of severe systemic illness (respiratory rate ≥30 breaths/minute, heart rate ≥125 beats/minute, oxygen saturation (SpO2) ≤93% on room air at sea level, or partial pressure of oxygen/fraction of inspired oxygen (PaO_2/FiO_2) <300 mmHg),
- respiratory failure (defined as needing high-flow oxygen, non-invasive ventilation, mechanical ventilation, or extracorporeal membrane oxygenation (ECMO)),
- evidence of shock (defined as systolic blood pressure <90 mmHg, diastolic blood pressure <60 mmHg, or requiring vasopressors),
- significant acute renal, hepatic, or neurological dysfunction,
- admission to the intensive care unit (ICU),
- death.

Box 3 provides the list of secondary endpoints considered.

Box 3: Secondary efficacy endpoints

Secondary efficacy endpoints included vaccine efficacy to prevent or vaccine impact on:

- Severe/critical COVID-19
- COVID-19 requiring medical intervention
- COVID-19 related death
- Any asymptomatic COVID-19
- Asymptomatic COVID-19 as inferred through seroconversion
- COVID-19 per the U.S. Food and Drug Administration harmonized COVID-19 case definition

All cases meeting the severe/critical criteria were adjudicated by the Clinical Severity Adjudication Committee. Classification of a case as severe/critical by the Clinical Severity Adjudication Committee was considered definitive.

Efficacy against COVID-19

COV3001 demonstrated vaccine efficacy for both co-primary endpoints. A single dose of Ad26.COV2.S protected against moderate to severe/critical COVID-19 in adults ⩾18 years of age, including adults ⩾60 years of age, with an efficacy that was consistent across age groups but with some variability across countries (Table 2). Vaccine efficacy against first occurrence of moderate to severe/critical COVID-19, including non-centrally confirmed cases, was 66.9% (95% CI 59.0-73.4), 14 days after vaccination, and 66.1% (55.0-74.8%) 28 days after vaccination.

Efficacy against severe COVID-19 (WHO clinical progression scale ≥ 6)

The vaccine was highly efficacious against severe/critical COVID-19. Efficacy was consistently high across age groups, regions, and countries. As a prespecified secondary endpoint, the vaccine also prevented COVID-19 requiring medical intervention (defined as hospitalization, ICU admission, mechanical ventilation, ECMO linked to objective measures, such as decreased oxygenation, X-ray or computerized tomography (CT) findings) and COVID-19-related deaths, with all hospitalizations and deaths after day 28 occurring in the placebo group.

[2] The case definitions used were developed by Janssen and differ from WHO standard definitions of COVID-19 disease severity which can be found in: COVID-19 Clinical management: living guidance (https://www.who.int/publications/i/item/WHO-2019-nCoV-clinical-2021-1, accessed 16 March 2021).

The case splits for severe/critical COVID-19 in the vaccine and placebo groups virtually eliminate the risk of VAED, consistent with the Th1-skewed immunological response.

Efficacy against COVID-19 hospitalization

In the per protocol analysis set, 14 days or more after vaccination, there were 2 COVID-19-related hospitalizations in the vaccinated group and 29 in the placebo group (VE 93.1%, 95%CI 72.74–99.20%).

In the per-protocol analysis set, 28 days or more after vaccination, there were no COVID-19-related hospitalizations in the vaccinated group and 16 in the placebo group (VE 100%, 95%CI 74.26–100.00%).

Efficacy against deaths related to COVID-19

There were no COVID-19-related deaths in the Ad26.COV2.S group and 6 COVID-19-related deaths in the placebo group.

Vaccine impact on symptom severity

A post-hoc analysis found that the participants with moderate COVID-19 who received Ad26.COV2.S most frequently reported 4 to 6 symptoms, while participants in the placebo group reported 7 to 9 symptoms.

Efficacy in persons with previous SARS-CoV-2 infection (based on seropositivity at baseline)

Only 7 symptomatic cases of COVID-19 were observed in participants who were SARS-CoV-2 seropositive at baseline, so it is not possible to provide meaningful comments on the VE in these participants.

Efficacy against asymptomatic infections

Preliminary data, based on serology results on day 71, suggest a vaccine effect against asymptomatic infection, based on the data cut-off for the primary analysis of 22 January 2021 (updated analysis submitted to FDA on 12 February 2021). Among 2650 individuals for whom day 71 results were available, 50 in the placebo group had evidence of an asymptomatic or undetected infection versus 18 in the Ad26.COV2.S group (VE 65.5%, 95%CI 39.91–81.08%). A sensitivity analysis, which removed all participants who had had symptoms at any time since screening prior to the SARS-CoV-2 N IgG positive result, found 10 and 37 seroconversions in the vaccinated and placebo group, respectively (VE 74.2%, 95%CI 47.13–88.57%).

Onset of efficacy after a single dose

The onset of VE against moderate to severe/critical COVID-19 was observed at 14 days after vaccination; efficacy persisted for the duration of follow-up (median 58 days). The onset of efficacy against severe/critical COVID-19 was observed at 7 days after vaccination, with a clear trend of increasing VE that persisted for the duration of follow-up (median 58 days). This rise in VE is consistent with available immunogenicity results from phase 1/2a studies. Participants with moderate COVID-19 in the Ad26.COV2.S group experienced fewer and less severe symptoms than those in the placebo group.

Efficacy against new variants of concern

In the USA, VE against moderate to severe/critical COVID-19 and against severe/critical COVID-19 was consistent with the global VE findings. In South Africa, where the 20H/501Y.V2 variant (B.1.351 lineage) was the predominant strain (96.3% of sequenced cases thus far), high efficacy was observed against severe/critical COVID-19 (81.7%, 95%CI 46.2–95.4% at least 28 days after vaccination) and robust VE was observed for moderate to severe/critical COVID-19 (64.0%, 95%CI 41.2–78.7% at least 28 days after vaccination). In Brazil, where a variant from the P.2 lineage was the predominant strain (70.7% of sequenced cases thus far), VE estimates were similar to the USA and South Africa. No differences were observed in S-specific binding antibody levels and responder rates induced by Ad26.COV2.S between participants from Brazil, South Africa, and the USA.

Table 2. Vaccine efficacy >day 28 against COVID-19 disease according to severity endpoint in the United States, Brazil and South Africa

Country (% Variant)	Disease severity endpoint	No. of events/ N		VE% (95% CI) >Day 28
		Vaccine group N= 19 306	Placebo group N=19 178	
United States D614G (96%) CAL.20C (3%)	Moderate to Severe/Critical	32 / 8 958	112 / 8 835	72.0% (58.2–81.7)
	Severe/Critical	1 / 8 958	7 / 8 835	85.9% (-9.4–99.7)
Brazil P.2 lineage (69%) D614G (31%)	Moderate to Severe/Critical	24 / 3 354	74 / 3 312	68.1% (48.8–80.7)
	Severe/Critical	1 / 3 354	8 / 3 312	87.6% (7.8–99.7)
South Africa B.1.351 (95%) D614G (3%)	Moderate to Severe/Critical	23 / 2 449	64 / 2 463	64.0% (41.2–78.7)
	Severe/Critical	4 / 2 449	22 / 2 463	81.7% (46.2–95.4)

Summary of all vaccine efficacy results

Tables 3 summarizes the vaccine efficacy results.

Table 3. Vaccine efficacy against first occurrence of moderate to severe/critical COVID-19, including non-centrally confirmed cases

	Onset at least 14 days after vaccination			Onset at least 28 days after vaccination		
Subgroup	**No. of cases/N (Total person–years)**		**VE[3] (95% CI)**	**No. of cases/N (Total person-years)**		**VE% (95% CI)**
	Vaccine group	**Placebo group**		**Vaccine group**	**Placebo group**	
All	116/19 514 (3116.6)	348/19 544 3096.1	66.9% (59.0–73.4%)	66/19 306 (3102.0)	193/19 178 (3070.7)	66.1% (55.0–74.8%)
Sex						
Male	85/10 861 (1739.0)	269/10 832 (1715.9)	68.8% (60.1–75.9%)	54/10 764 (1732.4)	176/10 649 (1704.2)	69.8% (58.9–78.2%)
Female	88/8649 (1374.2)	240/8708 (1372.6)	63.4% (53.1–71.7%)	59 (8538) 1367.1	148/8525 (1361.1)	60.3% (46.0–71.2%)
Age group (years)						
18–64	157/15 544 (2527.8)	441/15 552 (2504.8)	64.7% (57.6–70.8%)	101/15 378 (2517.1)	286/15 253 (2485.9)	65.1% (56.1–72.5%)
≥65	16/3970 (586.1)	68/3992 (584.3)	76.5% (59.1–87.3%)	12/3928 (583.1)	38/3925 (580.0)	68.6% (38.6–85.1%)
≥75	1/751 (107.3)	9/690 (99.1)	89.7% (26.0–99.8%)	0/740 (106.4)	4/673 (98.0)	
Race						

[3] If fewer than 6 cases were observed for an endpoint, the VE is not shown

	Onset at least 14 days after vaccination			Onset at least 28 days after vaccination		
	No. of cases/N (Total person–years)		VE[3] (95% CI)	No. of cases/N (Total person-years)		VE% (95% CI)
Subgroup	**Vaccine group**	**Placebo group**		**Vaccine group**	**Placebo group**	
American Indian/ Alaskan	21/1634 (279.0)	41/1621 (275.4)	49.4% (12.4–71.6%)	18/1628 (278.4)	26/1604 (274.4)	31.7% (–29.4–64.8%)
Asian	6/714 (99.5)	12/649 (90.6)	54.4% (–31.1–86.0%)	2/689 (97.9)	7/626 (89.1)	74.0% (–36.5–97.4%)
Black or African American	37/3362 (495.7)	101/3361 (491.4)	63.7% (46.6–75.8%)	21/3330 (493.7)	66/3300 (487.3)	68.6% (48.0–81.8%)
Native Hawaiian/ Other	1/54 (8.0)	0/44 (6.6)		1/54 (8.0)	0/43 (6.6)	
White	94/12 123 (1975.4)	288/12 133 (1958.3)	67.6% (59.0–74.6%)	64/11 994 (1967.0)	187/11 912 (1944.4)	66.2% (54.8–74.9%)
Multiple	10/1028 (166.6)	48/1080 (170.8)	78.6% (57.3–90.4%)	4/1018 (166.0)	28/1055 (169.2)	85.4% (58.4–96.3%)
Ethnicity						
Hispanic/Latino	81/8733 (1418.6)	237/8869 (1429.3)	65.6% (55.5–73.6%)	59/8688 (1415.7)	153/8741 (1421.4)	61.3% (47.4–71.8%)
Not Hispanic/ Latino	88/10 289 (1620.3)	257/10 184 (1587.7)	66.4% (57.1–74.0%)	52/10 131 (1610.1)	163/9957 (1573.1)	68.8% (57.2–77.6%)
Region						
North America (USA)	51/9119 (1414.0)	196/9086 (1391.3)	74.4% (65.0–81.6%)	32/8958 (1403.4)	112/8835 (1375.6)	72.0% (58.2–81.7%)
SouthernAfrica (South Africa)	43/2473 (377.6)	90/2496 (379.2)	52.0% (30.3–67.4%)	23/2449 (376.1)	64/2463 (376.9)	64% (41.2–78.7%)
LatinAmerica	79/7922 (1322.2)	223/7962 (1318.5)	64.7% (54.1–73.0%)	58/7899 (1320.8)	148/7880 (1313.3)	61.0% (46.9–71.8%)
Presence of comorbidity						
Yes	70/7777 (1138.8)	194/7798 (1130.9)	64.2% (52.7–73.1%)	44/7684 (1133.0)	105/7626 (1120.0)	58.6% (40.6–71.6%)
No	103/11 737 (1975.1)	315/11 746 (1958.2)	67.6% (59.4–74.3%)	69/11 622 (1967.3)	219/11 552 (1945.9)	68.8% (59.0–76.6%)
Age group and comorbidity						
18–59 years, no comorbidity	89/8346 (1433.5)	258/8411 (1428.2)	65.6% (56.1–73.3%)	58/8267 (1428.2)	180/8254 (1418.3)	68.0% (56.8–76.6%
18-59 years, comorbidity	48/4404 (671.5)	131/4371 (661.0)	63.9% (49.4–74.7%)	29/4350 (668.1)	79/4273 (654.8)	64.0% (44.3–77.3%)
≥60 years, no comorbidity	14/3391 (541.6)	57/3335 (530.0)	76.0% (56.3–87.6)	11/3355 (539.0)	39/3298 (527.6)	72.4% (45.0–87.3%)
≥60 years, comorbidity	22/3373 (467.4)	63/3427 (469.9)	64.9% (42.2–79.4%)	15/3334 (464.9)	26/3353 (465.2)	42.3% (–13.1–71.6%)
Type of comorbidity						
Asthma	1/238 (34.3)	9/278 (39.5)	87.2% (7.6–99.7%)	0/235 (34.1)	4/270 (38.9)	-
Cancer	0/104 (14.2)	2/108 (15.0)	-	0/102 (14.1)	0/105 (14.8)	-
Chronic kidney disease	0/106 (15.1)	1/109 (15.3)	-	0/102 (14.8)	0/106 (15.1)	-

	Onset at least 14 days after vaccination			Onset at least 28 days after vaccination		
	No. of cases/N (Total person–years)		VE[3] (95% CI)	No. of cases/N (Total person-years)		VE% (95% CI)
Subgroup	**Vaccine group**	**Placebo group**		**Vaccine group**	**Placebo group**	
Chronic obstructive pulmonary disease (COPD)	1/213 (30.2)	5/195 (28.0)	81.5% (–65.2–99.6%)	1/211 (30.1)	3/192 (27.8)	-
Serious heart condition	3/460 (65.3)	13/487 (67.7)	76.1% (12.9–95.6%)	1/455 (64.9)	5/472 (66.8)	79.4% (–83.7–99.6%)
HIV infection	5/467 (69.1)	5/498 (72.4)	–4.8% (–355.2–75.9%)	2/461 (68.7)	4/493 (72.2)	47.5% (–266.0–95.3%)
Hypertension	14/1999 (283.3)	38/2019 (282.8)	63.2% (30.6–81.6%)	11/1978 (281.9)	17/1977 (280.2)	35.7% (–45.6–72.8%)
Immuno-compromisedfrom bloodtransplant	2/38 (4.9)	0/33 (4.6)	-	1/35 (4.7)	0/32 (4.5)	-
Liver disease	1/97 (14.5)	2/100 (14.7)	-	1/96 (14.4)	0/98 (14.6)	-
Neurological conditions	0/77 (11.1)	1/115 (16.5)	-	0/77 (11.1)	1/114 (16.5)	-
Obesity	51/5383 (794.1)	151/5352 (780.3)	66.8% (54.1–76.3%)	30/5318 (790.0)	86/5223 (772.0)	65.9% (47.8–78.3%)
Type 2 diabetes mellitus	15/1399 (198.7)	32/1410 (199.5)	52.9% (10.5–76.3%)	10/1380	13/1378	23.0%
Baseline SARS-CoV-2 status						
Total	176/21 636 (3450.2)	513/21 574 (3409.8)	66.1% (59.7–71.6%)	114/21 424 (3436.3)	326/21 199 (3385.9)	65.5% (57.2–72.4%)
Positive	3/2122 (336.3)	4/2030 (320.8)	28.5% (–322.8–89.5%)	1/2118 (336.1)	2/2021 (320.0)	
Negative	173/19 514 (3113.9)	509/19 544 (3089.1)	66.3% (59.9–71.8%)	113/19 306 (3100.3)	324/19 178 (3065.9)	65.5% (57.2–72.4%)

Safety

This section draws on the safety findings of the phase 3 COV3001 study. Ad26.COV2.S demonstrated an acceptable safety and reactogenicity profile in adults ≥18 years of age, and in adults ≥60 years of age, including those with comorbidities associated with an increased risk of progressing to severe/critical COVID-19. In line with other Ad26-based vaccines, hypersensitivity reactions following immunization with Ad26.COV2.S were rare and usually nonserious. In COV3001, no cases were observed that met the Brighton Collaboration criteria for anaphylaxis. However, in an open-label trial in South Africa, one case of anaphylaxis occurred which met the Brighton Collaboration criteria. 77 events of hypersensitivity were reported in COV 3001.

In general, lower reactogenicity was observed in older adults than in younger adults. Otherwise, no clinically relevant difference in the reactogenicity profile of Ad26.COV2.S was observed by sex, race, ethnicity, geography, comorbidity, or SARS-CoV-2 or HIV serostatus at baseline (although numbers in some of these subgroups were too low to allow firm conclusions to be drawn). Reactogenicity was transient and most solicited adverse events (AEs) resolved in one to two days after vaccination. No grade 4 solicited local AEs were reported.

Among the 43 783 participants who received a single dose of Ad26.COV2.S at 5×10^{10} vp, the median follow-up after vaccination was 58 days, and 23 903 (54.6%) participants had at least 2 months (8 weeks) of follow-up at the time of the primary analysis. In the safety subset of 6736 participants, 99.9% of the participants in each group completed the post-vaccination follow-up period (days 1–29). A longer safety follow-up of 2 months or more is available for more than

23 000 participants in the full analysis set (FAS) (11 948 participants in the Ad26.COV2.S group and 11 955 in the placebo group).

The safety subset data included both solicited AEs collected from the day of vaccination until 7 days afterwards and unsolicited AEs collected from the day of vaccination until 28 day afterwards. Data on medically-attended adverse events (MAAEs), serious adverse events (SAEs) and deaths were collected from all 43 783 participants who received a study vaccination (21 895 in the Ad26.COV2.S $5x10^{10}$ vp group and 21 888 in the placebo group) and will continue to be collected until end of the study.

Frequencies of solicited and unsolicited AEs

In general, solicited AEs (both local and systemic) occurred at a higher frequency in participants in the Ad26.COV2.S group than in the placebo group. Regardless of the group, most solicited AEs were grade 1 or 2 in severity and were transient in nature. No grade 4 (serious) solicited AEs were reported during the study. The most frequently reported grade 3 solicited local AE was pain at the vaccination site, which was reported by 11 (0.3%) participants in the Ad26.COV2.S group.

Grade 3 solicited systemic AEs were reported by fewer than 2.0% of participants in the Ad26.COV2.S group. Pyrexia of any grade was reported by 302 participants (9.0%) and grade 3 pyrexia was reported by 8 (0.2%) participants in the Ad26.COV2.S group, of which the majority occurred in the younger age group (below 35 years of age). A total of 5.2% of participants in the Ad26.COV2.S group used analgesics or antipyretics up to 7 days after vaccination.

Overall, there was no apparent difference in unsolicited AEs reported in the Ad26.COV2.S group and the placebo group. The most frequently reported unsolicited AEs by preferred term (PT) (1.0% of participants in the Ad26.COV2.S group) were headache, fatigue, myalgia, and vaccination site pain, which were also recorded as solicited AEs. The most frequently reported unsolicited AEs (1.0% of participants in the Ad26.COV2.S group), not recorded as solicited AEs were chills, arthralgia, cough, nasal congestion, and diarrhoea. Most were of mild or moderate severity and most were considered by the investigator not to be related to the study vaccine. Other unsolicited AEs were reported in <1.0% of participants in the Ad26.COV2.S group.

The frequency of unsolicited AEs that were considered by the investigator to be related to the study vaccine was higher in participants in the Ad26.COV2.S group (242/440, 55%) than in the placebo group (154/407, 37.8%).

There were no notable patterns or numerical imbalances between the vaccine and placebo group for specific categories of AEs of interest (including neurological, neuroinflammatory and cardiovascular events) that would suggest a causal relationship to the vaccine. There were numerically more cases of tinnitus, convulsions/seizures, and pulmonary embolism/deep vein thrombosis in the Ad26.COV2.S group. However, in the majority of the cases the participants had one or more underlying medical conditions that were known risk factors for the event in question, and these events were most likely not causally related to the vaccine.

Solicited and unsolicited adverse events are summarized in Tables 4 and 5.

Table 4. Frequency of solicited local adverse reactions within 7 days following vaccination, safety subset

Adverse reaction	18–59 years		≥60 years	
	Vaccine group N=2036	Placebo group N=2049	Vaccine group N=1320	Placebo group N=1331
Any local reaction	1218 (59.8%)	413 (20.2%)	467 (35.4%)	244 (18.3%)
Grade 3	18 (0.9%)	4 (0.2%)	5 (0.4%)	2 (0.2%)
Pain	1193 (58.6%)	357 (17.4%)	439 (33.3%)	207 (15.6%)
Grade 3[a]	8 (0.4%)	0	3 (0.2%)	2 (0.2%)
Erythema	184 (9.0%)	89 (4.3%)	61 (4.6%)	42 (3.2%)
Grade 3[b]	6 (0.3%)	2 (0.1%)	1 (0.1%)	0
Swelling	142 (7.0%)	32 (1.6%)	36 (2.7%)	21 (1.6%)
Grade 3[b]	5 (0.2%)	2 (0.1%)	2 (0.2%)	0

[a] Grade 3 pain is pain requiring use of prescribed pain reliever or that prevents daily activity.
[b] Grade 3: >100 mm.
Note: No grade 4 solicited local adverse reactions were reported.

Table 5. Unsolicited adverse events occurring in ≥1% of vaccine group participants within 28 days following vaccination, by MedDRA primary system organ class and preferred term, safety subset

Unsolicited adverse events	Vaccine group N=3356		Placebo group N=3380	
	Any grade	≥Grade 3	Any grade	≥Grade 3
General disorders	211 (6.3%)	5 (0.1%)	134 (4.0%)	2 (0.1%)
Chills	67 (2.0%)	1 (<0.1%)	19 (0.6%)	0
Fatigue	64 (1.9%)	1 (<0.1%)	77 (2.3%)	1 (<0.1%)
Vaccination site pain	42 (1.3%)	1 (<0.1%)	22 (0.7%)	0
Musculoskeletal and connective tissue disorders	103 (3.1%)	3 (0.1%)	89 (2.6%)	4 (0.1%)
Myalgia	49 (1.5%)	0	58 (1.7%)	2 (0.1%)
Arthralgia	35 (1.0%)	1 (<0.1%)	24 (0.7%)	2 (0.1%)
Nervous system disorders	98 (2.9%)	3 (0.1%)	108 (3.2%)	5 (0.1%)
Headache	72 (2.1%)	1 (<0.1%)	82 (2.4%)	1 (<0.1%)
Respiratory, thoracic and mediastinal disorders	93 (2.8%)	3 (0.1%)	88 (2.6%)	4 (0.1%)
Nasal congestion	40 (1.2%)	1 (<0.1%)	38 (1.1%)	2 (0.1%)
Cough	33 (1.0%)	1 (<0.1%)	33 (1.0%)	0
Gastrointestinal disorders	87 (2.6%)	2 (0.1%)	90 (2.7%)	2 (0.1%)
Diarrhoea	33 (1.0%)	2 (0.1%)	35 (1.0%)	0
Infections and infestations	57 (1.7%)	3 (0.1%)	87 (2.6%)	6 (0.2%)

Special considerations

Pregnancy

Up to the cutoff date of 31 December 2020, 8 pregnancy were reported in this study. In 3 cases, vaccine exposure occurred within 3 months preceding the date of conception with pregnancy outcomes reported as continuing/ongoing or unknown/not reported. In 5 cases, vaccine exposure occurred during the first trimester of pregnancy with pregnancy

outcomes reported as continuing/ongoing (3), elective abortion (1), or spontaneous abortion (1; assessed as not related to blinded vaccine/placebo). No additional pregnancies were reported between 31 December 2020 and 22 January 2021.

A combined developmental and perinatal/postnatal reproductive toxicity study in rabbits concluded that Ad26.COV.2 given prior to mating and during gestation periods at double the human dose did not have any adverse effects on female reproduction, fetal/embryonal development or postnatal development.

A pregnancy substudy and pregnancy registry are planned.

Ad26 vector platform (non-COVID-19) in pregnancy:

There is some experience with use of the Ad26 vector platform in pregnancy (9).

Janssen has prepared an ad hoc safety report (21 Jan 2021) on the pregnancy experience across the *entire* Ad-based vaccine program. Included in this report is the experience obtained from EBL3008 (also known as DRC-EB-001) as the single largest contributor to the report. EBL3008 deliberately allowed pregnant women to be included in the study, whereas for the other Ad-based studies, inclusion of pregnant women was not permitted. EBL3008 was open-label study sponsored by the London School of Hygiene and Tropical Medicine and thus there is no control comparison group to establish a country-specific background rate of events.

With that understanding, the summary data includes a safety review of adenovirus type 26 (Ad26) vectored vaccines exposure during pregnancy from ongoing and completed clinical trials as well as post-market mass vaccination campaign (47 studies) for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2, COVID-19) vaccine, Ebola vaccine, Human Immunodeficiency Virus (HIV) vaccine, Filovirus vaccine, Human Papilloma Virus (HPV) vaccine, Respiratory Syncytial Virus (RSV) vaccine, and Zika vaccine. Of these 47 studies, pregnancy cases were reported in 22 studies, 4 of which are still blinded.

Cumulative searches through 31 December 2020 were performed in the Global Medical Safety (GMS) global safety database for all the pregnancy cases reported from completed and ongoing trials for Ad26 vectored vaccines which included COVID-19 vaccine, Ebola vaccine, HIV vaccine, Filovirus vaccine, HPV vaccine, RSV vaccine, and Zika vaccine.

The search of the GMS global safety database retrieved 2 061 cases involving exposure during pregnancy in participants who received an Ad26 vectored vaccine or control. Data from 430 cases are not presented below as these cases (and outcomes) were reported either more than 3 months before vaccine exposure or 9 months after vaccine exposure, or with no history of exposure to vaccine or male partner exposure.

The remaining 1 631 cases reported unique pregnancies and were included for further review. Of these 1 631 pregnancies, 1 522 reported exposure to Ebola vaccine or placebo in the Ebola program, 101 reported exposure to HIV vaccine or placebo in the HIV program and 8 reported exposure to COVID-19 vaccine or placebo in COVID-19 program. None of the cases reported exposure to HPV vaccine, RSV vaccine, Filovirus vaccine, or Zika vaccine. Of the 1 522 pregnancies reported from the Ebola vaccine trials with reported exposure to Ad26.ZEBOV vaccine, most cases were reported in VAC52150EBL3008 with 1 062 reported pregnancies.

Of the 1 631 unique pregnancies, outcome was reported with 939 final pregnancy outcomes: healthy baby for 781 and various other outcomes for 158 pregnancies including 102 spontaneous abortions, 19 stillbirths, 9 elective abortions, 7 intrauterine deaths, 6 induced abortions, 5 premature babies/labours, 3 congenital malformations, 3 ectopic pregnancies, 2 abortion incompletes, 1 abortion, and 1 termination; there are also 243 ongoing pregnancies, and unknown/not reported for 449.

Of these 1 631 pregnancies, caesarean section delivery was reported as delivery method in 193 pregnancies and 61 reported normal delivery.

Of the 1 522 pregnancies reported from the Ebola vaccine trials with reported exposure to Ad26.ZEBOV vaccine, most cases were reported in VAC52150EBL3008 with 1 062 reported pregnancies.

Spontaneous abortion was reported in 5.8% (88/1 522) of pregnancies, whereas all other types of abortions (i.e., induced abortion [6], elective abortion [5], abortion, abortion incomplete and incomplete abortion [each reported once] were reported in 0.9% (14/1 522) of pregnancies. Congenital malformations reported in 3 cases were lingula frenulum, cleft lip and evisceration on exomphalos, none of which were considered related to the study vaccine. In addition, none of the reported adverse pregnancy outcomes and SAEs was considered related to the study vaccine.

Of the 101 pregnancies reported from the HIV vaccine trials with exposure to Ad26.Mos4.HIV candidate vaccine, the most frequently reported study protocol was VAC89220HPX2008 with 90 reported pregnancies. In this study, only women are recruited. Spontaneous abortion was reported in 12.9% (13/101) and elective abortion in 3% (3/101) pregnancies. None of the pregnancies reported any congenital malformations. None of the reported adverse pregnancy outcomes and SAEs were considered related to the study vaccine.

All 8 pregnancies reported from COVID-19 vaccine trials were from protocol VAC31518COV3001. There was 1 case each for spontaneous abortion and elective abortion 12.5% (1/8). None of the pregnancies reported any congenital malformations. None of the reported adverse pregnancy outcomes and SAEs were considered related to the study vaccine.

The reported spontaneous abortion rates are within the expected abortion rates during pregnancy which could range anywhere from 10% to 30%. (10)

Overall, the review of the available data is not suggestive of a pregnancy related safety concern.

Breastfeeding

It is unknown whether the vaccine is excreted in human milk.

Pediatric population

No data are available in subjects under 18 years of age.

Immunosuppression

No data are currently available from immunocompromised subjects, including those receiving immunosuppressant therapy. The efficacy of the vaccine may be lower in immunosuppressed individuals.

Safety related to vaccine interactions

No data are available on use of the vaccine with concomitant vaccines, including influenza vaccines. Licensed seasonal influenza and pneumococcal vaccinations were permitted at least 7 days before or after the study vaccine.

References

1. Anywaine Z, Whitworth H, Kaleebu P, Praygod G, Shukarev G, Manno D, et al. Safety and immunogenicity of a 2-dose heterologous vaccination regimen with Ad26.ZEBOV and MVA-BN-Filo Ebola vaccines: 12-month data from a phase 1 randomized clinical trial in Uganda and Tanzania. J Infect Dis. 2019; 220(1):46-56.
2. Baden LR, Liu J, Li H, Johnson JA, Walsh SR, Kleinjan JA, et al. Induction of HIV-1-specific mucosal immune responses following intramuscular recombinant adenovirus serotype 26 HIV-1 vaccination of humans. J Infect Dis. 2015; 211(4):518-28.
3. van der Fits L, Bolder R, Heemskerk-van der Meer M, Drijver J, van Polanen Y, Serroyen J, et al. Adenovector 26 encoded prefusion conformation stabilized RSV-F protein induces long-lasting Th1-biased immunity in neonatal mice. NPJ Vaccines. 2020; **5**(1)49.

4. Williams K, Bastian AR, Feldman RA, Omoruyi E, de Paepe E, Hendriks J, et al. Phase 1 safety and immunogenicity study of a respiratory syncytial virus vaccine with an adenovirus 26 vector encoding prefusion F (Ad26.RSV.preF) in adults aged ≥60 years. J Infect Dis. 2020; 222(6):979-988.

5. He X, Chandrashekar A, Zahn R, Wegmann F, Yu J, Mercado NB, et al. Low-dose Ad26.COV2.S protection against SARS-CoV-2 challenge in rhesus macaques. bioRxiv [Preprint]. 2021 Jan 27:2021.01.27.428380. doi: 10.1101/2021.01.27.428380.

6. Solforosi L, Kuipers H, Rosendahl Huber SK, van der Lubbe JEM, Dekking L, Czapska-Casey DN, et al. Immunogenicity of one-and two-dose regimens of the Ad26.COV2.S COVID-19 vaccine candidate in adult and aged rhesus macaques. bioRxiv [Preprint] 2020.11.17.368258; doi: https://doi.org/10.1101/2020.11.17.368258.

7. Roozendaal R, Solforosi L, Stieh1 D, Serroyen J,Straetemans R, Wegmann F, et al. SARs-CoV-2 binding and neutralizing antibody levels after vaccination with Ad26.COV2.S predict durable protection in rhesus macaques. bxRxiv [Preprint], 2021. doi:https://doi.org/10.1101/2020.11.17.368258.

8. van der Lubben JE, Rosendahl Huber SK, Vijayan A, Dekking L, van Huizen E, et al. Ad26.COV2.S-elicited immunity protects against G614 spike variant SARS-CoV-2 infection in Syrian hamsters and does not enhance respiratory disease in challenged animals with breakthrough infection after sub-optimal vaccine dosing. BioRxiv, 2021. doi: https://doi.org/10.1101/2021.01.08.425915

9. Custers J, Kim D, Leyssen M, Gurwith M, Tomaka F, Robertson J, et al.; Brighton Collaboration Viral Vector Vaccines Safety Working Group (V3SWG). Vaccines based on replication incompetent Ad26 viral vectors: Standardized template with key considerations for a risk/benefit assessment. Vaccine. 2020 Oct 3:S0264-410X(20)31160-9. doi: 10.1016/j.vaccine.2020.09.018.

10. Alves C, Rapp A. Spontaneous Abortion. 2020 Jul 20. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2021 Jan–. PMID: 32809356.

Annexes

Annexes 1–6 contain tables that summarize the grading of recommendations, assessment, development and evaluations (GRADE). Annexes 7–9 contain the SAGE evidence-to-recommendation framework tables (ETR tables). The ETR tables are based on the DECIDE Work Package 5: Strategies for communicating evidence to inform decisions about health system and public health interventions. Evidence to a recommendation (for use by a guideline panel) (www.decide-collaboration.eu/, accessed 11 January 2021).

Annex 1. GRADE table: Efficacy of Janssen AD26.COV2.S COVID-19 vaccine in adults

Population : Adults (18–59 years)

Intervention: Single dose of Janssen AD26.COV2.S vaccine

Comparison: Placebo/active control
Outcome : Moderate to severe/critical COVID-19 (PCR-confirmed)

What is the efficacy of a single dose of Janssen AD26.COV2.S vaccine compared with placebo/active control in preventing moderate to severe/critical PCR-confirmed COVID-19 in adults (18–59 years)?				
			Rating	Adjustment to rating
Quality Assessment	No. of studies/starting rating		1/ RCT(1;2)	4
	Factors decreasing confidence	Limitation in study design[a]	Not serious[b]	0
		Inconsistency	Not serious	0
		Indirectness	Not serious	0
		Imprecision	Not serious	0
		Publication bias	Not serious	0
	Factors increasing confidence	Large effect	Not applicable	0
		Dose-response	Not applicable	0
		Antagonistic bias and confounding	Not applicable	0
	Final numerical rating of quality of evidence			**4**
Summary of Findings	**Statement on quality of evidence**			**Evidence supports a high level of confidence that the true effect lies close to the estimate of the effect on the health outcome (level 4, or ⊕⊕⊕⊕).**
	Conclusion			We are very confident that a single dose of Janssen AD26.COV2.S vaccine is efficacious in preventing moderate to severe/critical PCR-confirmed COVID-19 in adults (18–59 years).

References

1. FDA Briefing Document. Janssen Ad26.COV2.S vaccine for the prevention of COVID-19. (https://www.fda.gov/media/146217/download, accessed 25 February 2021).
2. Sadoff J, Le GM, Shukarev G, Heerwegh D, Truyers C, de Groot AM et al. Interim results of a phase 1-2a trial of Ad26.COV2.S covid-19 vaccine. N Engl J Med. 2021; Jan 13.

[a] For the risk of bias assessments using the revised Cochrane risk-of-bias tool for randomized trials (RoB 2), please see www.covid-nma.com/vaccines.

[b] Data on long-term protection emerging from the ongoing phase 3 clinical trial remain limited, as trial data have so far been reported only for a follow-up of approximately 2 months. This was considered as not constituting a limitation that would lead to downgrading of the evidence. SAGE will continue to review any emerging data and adjust its quality assessment as required.

Annex 2. GRADE table: Safety of Janssen AD26.COV2.S COVID-19 vaccine in adults

Population : Adults (18–59 years)

Intervention: Single dose of Janssen AD26.COV2.S vaccine

Comparison: Placebo/active control

Outcome : Serious adverse events following immunization

What is the risk of serious adverse events following Janssen AD26.COV2.S vaccination compared with placebo/active control in adults (18–59 years)?				
			Rating	Adjustment to rating
Quality Assessment	No. of studies/starting rating		2/ RCT (1;2)	4
	Factors decreasing confidence	Limitation in study design[a]	Serious[b]	-1
		Inconsistency	Not serious	0
		Indirectness	Not serious	0
		Imprecision	Not serious	0
		Publication bias	Not serious	0
	Factors increasing confidence	Large effect	Not applicable	0
		Dose-response	Not applicable	0
		Antagonistic bias and confounding	Not applicable	0
	Final numerical rating of quality of evidence			**3**
Summary of Findings	**Statement on quality of evidence**			**Evidence supports a moderate level of confidence that the true effect lies close to the estimate of the effect on the health outcome (level 3, or ⊕⊕⊕).**
	Conclusion			We are moderately confident that the risk of serious adverse events following a single dose of Janssen AD26.COV2.S vaccine in adults (18–59 years) is low.

References

1. FDA Briefing Document. Janssen Ad26.COV2.S vaccine for the prevention of COVID-19. (https://www.fda.gov/media/146217/download, accessed 25 February 2021).
2. Sadoff J, Le GM, Shukarev G, Heerwegh D, Truyers C, de Groot AM et al. Interim results of a phase 1-2a trial of Ad26.COV2.S covid-19 vaccine. N Engl J Med. 2021; Jan 13.

[a] For the risk of bias assessments using the revised Cochrane risk-of-bias tool for randomized trials (RoB 2), please see www.covid-nma.com/vaccines.

[b] Downgraded for the following limitations. The trial was not adequately powered to detect rare adverse events (i.e. fewer than about 1 in 2000). These may emerge only when large populations have been vaccinated. The limited follow-up time of the clinical trial may not allow detection of adverse events occurring several months after vaccination.

Annex 3. GRADE table: Efficacy of Janssen AD26.COV2.S COVID-19 vaccine in older adults

Population : Older adults (≥60 years)
Intervention: Single dose of Janssen AD26.COV2.S vaccine
Comparison: Placebo/active control
Outcome : Moderate to severe/critical COVID-19 (PCR-confirmed)

What is the efficacy of a single dose of Janssen AD26.COV2.S vaccine compared with placebo/active control in preventing moderate to severe/critical PCR-confirmed COVID-19 in older adults (≥60 years)?				
			Rating	Adjustment to rating
Quality Assessment	No. of studies/starting rating		1/ RCT (1;2)	4
	Factors decreasing confidence	Limitation in study design[a]	Not serious	0
		Inconsistency	Not serious	0
		Indirectness	Not serious	0
		Imprecision	Not serious[b]	0
		Publication bias	Not serious	0
	Factors increasing confidence	Large effect	Not applicable	0
		Dose-response	Not applicable	0
		Antagonistic bias and confounding	Not applicable	0
	Final numerical rating of quality of evidence			**4**
Summary of Findings	**Statement on quality of evidence**			**Evidence supports a high level of confidence that the true effect lies close to the estimate of the effect on the health outcome (level 4, or ⊕⊕⊕⊕).**
	Conclusion			We are confident that a single dose of JANSSEN AD26.COV2.S vaccine is efficacious in preventing moderate to severe/critical PCR-confirmed COVID-19 in older adults (≥60 years).

References

1. FDA Briefing Document. Janssen Ad26.COV2.S vaccine for the prevention of COVID-19. (https://www.fda.gov/media/146217/download, accessed 25 February 2021).
2. Sadoff J, Le GM, Shukarev G, Heerwegh D, Truyers C, de Groot AM et al. Interim results of a phase 1-2a trial of Ad26.COV2.S covid-19 vaccine. N Engl J Med. 2021; Jan 13.

[a] For the risk of bias assessments using the revised Cochrane risk-of-bias tool for randomized trials (RoB 2), please see www.covid-nma.com/vaccines.

[b] Approximately 40% of the trial participants were aged 60 years or over. Data on long-term protection emerging from the ongoing phase 3 clinical trial remain limited, as trial data have so far been reported only for a follow-up of approximately 2 months. This was considered as not constituting a limitation that would lead to downgrading of the evidence. SAGE will continue to review any emerging data and adjust its quality assessment as required.

Annex 4. GRADE table: Safety of Janssen AD26.COV2.S COVID-19 vaccine in older adults

Population : Older adults (≥60 years)
Intervention: Single dose of Janssen AD26.COV2.S vaccine
Comparison: Placebo/active control
Outcome : Serious adverse events following immunization

What is the risk of serious adverse events following Janssen AD26.COV2.S vaccination compared with placebo/active control in older adults (≥60 years)?				
			Rating	Adjustment to rating
Quality Assessment	No. of studies/starting rating		2/ RCT(1;2)	4
	Factors decreasing confidence	Limitation in study design[a]	Serious[b]	-1
		Inconsistency	Not serious	0
		Indirectness	Not serious	0
		Imprecision	Not serious[c]	0
		Publication bias	Not serious	0
	Factors increasing confidence	Large effect	Not applicable	0
		Dose-response	Not applicable	0
		Antagonistic bias and confounding	Not applicable	0
	Final numerical rating of quality of evidence			**3**
Summary of Findings	**Statement on quality of evidence**			**Evidence supports a moderate level of confidence that the true effect lies close to the estimate of the effect on the health outcome (level 3, or ⊕⊕⊕).**
	Conclusion			We are moderately confident that the risk of serious adverse events following a single dose of Janssen AD26.COV2.S vaccine in older adults (≥60 years) is low.

References

1. FDA Briefing Document. Janssen Ad26.COV2.S vaccine for the prevention of COVID-19. (https://www.fda.gov/media/146217/download, accessed 25 February 2021).
2. Sadoff J, Le GM, Shukarev G, Heerwegh D, Truyers C, de Groot AM et al. Interim results of a phase 1-2a trial of Ad26.COV2.S covid-19 vaccine. N Engl J Med. 2021; Jan 13.

[a] For the risk of bias assessments using the revised Cochrane risk-of-bias tool for randomized trials (RoB 2), please see www.covid-nma.com/vaccines.

[b] Downgraded for the following limitations. The trial was not adequately powered to detect rare adverse events (i.e. about 1 in 250). These may emerge only when large populations have been vaccinated. The limited follow-up time of the clinical trial may not allow detection of adverse events occurring several months after vaccination.

[c] Approximately 40% of the trial participants were aged 60 years or over. This was not considered as constituting a limitation that leads to downgrading of the evidence.

Annex 5. GRADE table: Efficacy of Janssen AD26.COV2.S COVID-19 vaccine in individuals with underlying conditions

Population : Individuals with comorbidities or health states that increase risk for severe COVID-19
Intervention: Single dose of Janssen AD26.COV2.S vaccine
Comparison: Placebo/active control
Outcome : Moderate to severe/critical COVID-19 (PCR-confirmed)

What is the efficacy of a single dose of Janssen AD26.COV2.S vaccine compared with placebo/active control in preventing moderate to severe/critical PCR-confirmed COVID-19 in individuals with comorbidities or health states that increase risk for severe COVID-19?

			Rating	Adjustment to rating
Quality Assessment	No. of studies/starting rating		1/ RCT (1;2)	4
	Factors decreasing confidence	Limitation in study design[a]	Not serious	0
		Inconsistency	Not serious	0
		Indirectness	Serious[b]	-1
		Imprecision	Not serious[c]	0
		Publication bias	Not serious	0
	Factors increasing confidence	Large effect	Not applicable	0
		Dose-response	Not applicable	0
		Antagonistic bias and confounding	Not applicable	0
	Final numerical rating of quality of evidence			**3**
Summary of Findings	**Statement on quality of evidence**			**Evidence supports a moderate level of confidence that the true effect lies close to the estimate of the effect on the health outcome (level 3, or ⊕⊕⊕).**
	Conclusion			We are moderately confident that a single dose of Janssen AD26.COV2.S vaccine is efficacious in preventing moderate to severe/critical 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, or persons who were immunocompromised.

References

1. FDA Briefing Document. Janssen Ad26.COV2.S vaccine for the prevention of COVID-19. (https://www.fda.gov/media/146217/download, accessed 25 February 2021).
2. Sadoff J, Le GM, Shukarev G, Heerwegh D, Truyers C, de Groot AM et al. Interim results of a phase 1-2a trial of Ad26.COV2.S covid-19 vaccine. N Engl J Med. 2021; Jan 13.

[a] For the risk of bias assessments using the revised Cochrane risk-of-bias tool for randomized trials (RoB 2), please see www.covid-nma.com/vaccines.

[b] Trial excluded pregnant and breastfeeding women, and persons who were immunocompromised. This was considered as constituting a limitation that leads to downgrading of the evidence.

[c] Underlying comorbidities included BMI ≥ 30 kg/m^2, cardiovascular disorder, respiratory disease and diabetes. Approximately 40% of the trial population had at least one comorbidity. This was considered as not constituting a limitation that would lead to downgrading of the evidence. Data on long-term protection emerging from the ongoing phase 3 clinical trial remain limited, as trial data have so far been reported only for a follow-up of approximately 2 months. This was considered as not constituting a limitation that would lead to downgrading of the evidence. SAGE will continue to review any emerging data and adjust its quality assessment as required.

Annex 6. GRADE table: Safety of Janssen AD26.COV2.S COVID-19 vaccine in individuals with underlying conditions

Population : Individuals with comorbidities or health states that increase risk for severe COVID-19
Intervention: Single dose of Janssen AD26.COV2.S vaccine
Comparison: Placebo/active control
Outcome : Serious adverse events following immunization

What is the risk of serious adverse events following Janssen AD26.COV2.S vaccination compared with placebo/active control in individuals with comorbidities or health states that increase risk for severe COVID-19?				
			Rating	Adjustment to rating
Quality Assessment	No. of studies/starting rating		2/ RCT(1;2)	4
	Factors decreasing confidence	Limitation in study design[a]	Serious[b]	-1
		Inconsistency	Not serious	0
		Indirectness	Serious[c]	-1
		Imprecision	Not serious	0
		Publication bias	Not serious	0
	Factors increasing confidence	Large effect	Not applicable	0
		Dose-response	Not applicable	0
		Antagonistic bias and confounding	Not applicable	0
	Final numerical rating of quality of evidence			**2**
Summary of Findings	**Statement on quality of evidence**			**Evidence supports a limited level of confidence that the true effect lies close to the estimate of the effect on the health outcome (level 2, or ⊕⊕).**
	Conclusion			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 a single dose of Janssen AD26.COV2.S vaccine is low.

References

1. FDA Briefing Document. Janssen Ad26.COV2.S vaccine for the prevention of COVID-19. (https://www.fda.gov/media/146217/download, accessed 25 February 2021).
2. Sadoff J, Le GM, Shukarev G, Heerwegh D, Truyers C, de Groot AM et al. Interim results of a phase 1-2a trial of Ad26.COV2.S covid-19 vaccine. N Engl J Med. 2021; Jan 13.

[a] For the risk of bias assessments using the revised Cochrane risk-of-bias tool for randomized trials (RoB 2), please see www.covid-nma.com/vaccines.

[b] Downgraded for the following limitations. The trial was not adequately powered to detect rare adverse events (i.e. fewer than about 1 in 800). These may emerge only when large populations have been vaccinated. The limited follow-up time of the clinical trial may not allow detection of adverse events occurring several months after vaccination.

[c] Trial excluded pregnant and breastfeeding women and persons who were immunocompromised. This was considered as constituting a limitation that leads to downgrading of the evidence.

Annex 7. SAGE evidence-to-recommendation framework: Janssen AD26.COV2.S vaccine use in adults

Question: Should Janssen AD26.COV2.S vaccine be administered to adults to prevent moderate to severe/critical COVID-19?

Population: Adults (18–59 years)

Intervention: Single dose of JANSSEN AD26.COV2.S vaccine

Comparison(s): Active control/placebo

Outcome: Moderate to severe/critical COVID-19 (PCR-confirmed)

Background: On 31 December 2019, WHO was alerted to several cases of pneumonia of unknown origin in Wuhan City, Hubei Province, China. The cause was found to be a novel coronavirus, SARS-CoV-2. The disease caused by this novel virus has been named COVID-19. The outbreak of COVID-19 was declared a public health emergency of international concern in January 2020. The disease has since spread, with an enormous impact on the health and well-being of individuals and populations worldwide. It has further caused major disruptions to various sectors of society and the economy across the globe.

Vaccines are a critical tool in combating the pandemic. In the rapidly evolving field of COVID-19 vaccines, WHO has to date issued interim recommendations on the use of Pfizer–BioNTech, Moderna and AstraZeneca vaccines (3-5).

	CRITERIA	JUDGEMENTS				RESEARCH EVIDENCE	ADDITIONAL INFORMATION
PROBLEM	Is the problem a public health priority?	*No*	*Uncertain*	*Yes*	*Varies by setting*	The cumulative number of COVID-19 cases globally has surpassed 111 762 965 with more than 2 479 678 deaths. Cases have been found in 190 different countries or territories throughout the world (status 25 February 2021). There has been collateral damage to other public health programmes.	The COVID-19 situation is evolving rapidly; the most recent epidemiological situation can be found on the following website: https://covid19.who.int/table
		☐	☐	☒	☐		

BENEFITS & HARMS OF THE OPTIONS	Benefits of the intervention Are the desirable anticipated effects large?	*No* ☐	*Un-certain* ☐	*Yes* ☒	*Varies* ☐	The phase 3 study COV3001 demonstrated 63.7% efficacy (95%CI 53.9–71.6%) in people aged 18–59 years against confirmed moderate to severe/critical COVID-19 from 14 days after vaccination. In all participants, as from 14 days after vaccination, 2 COVID-19-related hospitalizations were observed in the vaccinated group compared with 29 in the placebo group (VE 93.1%, 95%CI 72.74–99.20).	
	Harms of the intervention Are the undesirable anticipated effects small?	*No* ☐	*Un-certain* ☐	*Yes* ☒	*Varies* ☐	Ad26.COV2.S demonstrated an acceptable safety and reactogenicity profile in adults ≥18 years of age and in adults ≥60 years of age, including those with comorbidities associated with an increased risk of progressing to severe/critical COVID-19. All local and systemic adverse reactions were reported more frequently among younger (18–59 years) than among older (≥60 years) participants. In those aged 18–59 years, 4/14 564 (<0.1%) in the vaccine group reported related serious adverse events compared with 1/14 547 (<0.1%) in the placebo group.	
	Balance between benefits and harms	***Favours inter-vention***	***Favours com-parison***	***Favours both***	***Favours neither***	**Unclear**	Efficacy data suggest benefit, and short-term safety data suggest minimal harms. Further ongoing studies will need to be undertaken as part of post-marketing surveillance.	

		☒ ☐ ☐ ☐ ☐		
	What is the overall quality of this evidence for the critical outcomes?	Effectiveness of the intervention ***No included studies*** ☐ ***Very low*** ☐ ***Low*** ☐ ***Moderate*** ☐ ***High*** ☒ Safety of the intervention ***No included studies*** ☐ ***Very low*** ☐ ***Low*** ☐ ***Moderate*** ☒ ***High*** ☐	Please see the related GRADE tables.	
VALUES & PREFERENCES	How certain is the relative importance of the desirable and undesirable outcomes?	***Important uncertainty or variability*** ☐ ***Possibly important uncertainty or variability*** ☒ ***Probably no important uncertainty or variability*** ☐ ***No important uncertainty or variability*** ☐ ***No known undesirable outcomes*** ☐	Available scientific evidence on the relative importance of the intervention, as well as the relative weights that the target population attributes to the desirable (i.e. protection conferred by the vaccine) and the undesirable outcomes (i.e. the currently reported safety signals), varies. Different population groups may have different opinions regarding the weights assigned to desirable and undesirable outcomes.	
	Values and preferences of the target population: Are the desirable	*No* *Probably No* *Uncertain* *Probably Yes* *Yes* *Varies*	Available scientific evidence suggests that the target population probably assigns more weight to the desirable effects than to the undesirable effects related to COVID-19 vaccination.	

	effects large relative to undesirable effects?	☐	☐	☐	☒	☐	☐	Targeted information campaigns should assess this aspect.	
RESOURCE USE	Are the resources required small?	*No*	*Un-certain*	*Yes*		*Varies*	Janssen AD26.COV2.S vaccine can be distributed and stored using existing cold-chain infrastructure and does not require ultra-cold-chain capacity. Nevertheless, considerable resources will be needed to ensure the implementation of a COVID-19 vaccination programme, especially given: (i) that COVID-19 vaccination is likely to be prioritized for populations (e.g. health care workers, older adults) without pre-existing robust immunization programmes in many settings, and (ii) the urgency of vaccination roll-out worldwide, which may necessitate additional surge resources to accelerate implementation with adequate infection prevention and control procedures in the context of COVID-19. Resources required include, but are not restricted to, human resources, vaccine costs, logistics, planning and coordination, training, social mobilization and communications, and immunization safety surveillance.	An estimated US$15.9 billion is needed for the vaccines pillar (COVAX) of the Access to COVID-19 Tools Accelerator (ACT-A) for 2020–21, in order to deliver 2 billion doses. This does not include all delivery costs in all countries participating in COVAX, bilateral procurement deals, or research and development investments outside of COVAX (6). The World Bank has approved a financing window of up to US$12 billion to support low- and middle-income countries in purchasing and distributing vaccine (7).
		☒	☐	☐		☐		
	Cost-effectiveness	*No*	*Un-certain*	*Yes*		*Varies*	Formal global cost-effectiveness analyses have not been conducted, but the emerging evidence indicates that the benefits, including the impact on recovery of the global economy, are likely to outweigh the cost of COVID-19 vaccination in general at global level.	The global economy is estimated to be losing US$375 billion per month because of the coronavirus pandemic. G20 countries have invested approximately US$10 trillion in domestic economic stimulus to mitigate the economic consequences of reduced business activity and unemployment due to the pandemic. Initial estimates suggest that COVID-19 vaccination will provide substantial economic value in terms of averted morbidity and mortality costs and averted losses in gross domestic product (GDP) (6;9-15).
		☐	☐	☐		☒	No formal cost-effectiveness analyses of Janssen AD26.COV2.S vaccine compared with other vaccines have been conducted. The Janssen AD26.COV2.S vaccine is expected to be less costly than other COVID-19 vaccines (see previous subcriterion).(8) Individual-level efficacy against COVID-19 may be lower than that of	

					some other COVID-19 vaccines; more data are needed to assess efficacy against other endpoints (see main text). The ability to use Janssen AD26.COV2.S in existing cold-chain infrastructure in all country settings may allow higher population-level coverage. Cost-effectiveness analyses should be conducted at country level; cost-effectiveness of COVID-19 vaccination may vary by country depending on COVID-19 burden, comparator interventions assessed, analysis perspective, and local cost-effectiveness thresholds used.	
EQUITY	What would be the impact on health inequities?	*Increa-sed* ☐	*Un-certain* ☐	*Reduced* ☒	*Varies* ☐	Equity and ethical considerations are critical. SAGE has produced a Values Framework (16), which offers guidance on the fair allocation of COVID-19 vaccines based on six core ethical principles that should guide distribution. If distributed fairly, COVID-19 vaccines may have considerable impact on reducing health inequities. Storage and distribution requirements of the Janssen AD26.COV2.S vaccine are the same as those of many other vaccines currently in use globally. Existing vaccine cold-chain capacity, available in almost all countries, could be leveraged for vaccine distribution.	Vaccine nationalism is seen as a threat to reducing health inequity, in particular as high-income countries have arranged bilateral contracts with manufacturers. This has led to the establishment of the Access to COVID-19 Tools (ACT) Accelerator and, within this, the COVAX facility, which aims to ensure equitable access to vaccines for its participating member states (17).
ACCEPTABILITY	Which option is acceptable to key stakeholders (e.g. ministries of health, immunization managers)?	*Inter-vention*	*Com-parison*	*Both*	*Neither*	*Un-clear*	No scientific evidence is available. As vaccination is an eagerly awaited tool to combat COVID-19, it is assumed that key stakeholders, in particular ministries of health and immunization managers, are strongly in favour of it.	The fact that 190 economies are participating in COVAX suggests a very high acceptability of COVID-19 vaccination in general, though not necessarily of this vaccine in particular.

		☒	☐	☐	☐	☐		
	Which option is acceptable to target group?	*Inter-vention*	*Com parison*	*Both*	*Neither*	*Un-clear*	Single-dose administration of this product may be favourable to the target group. COVID-19 vaccine acceptability in general varies between (sub)population groups and may be correlated with the perceived risk posed by the disease. In a global survey (19 countries) of acceptance rates in the general population of any COVID-19 vaccine product, 71.5% of participants reported that they would be very or somewhat likely to take a COVID-19 vaccine. Acceptance rates ranged from almost 55% to 87% (18). Representative multicountry surveys are carried out periodically to assess the percentage of those willing to receive (or of those who have already received) COVID-19 vaccination (non-product-specific). While these polls are limited to selected countries, they provide a certain degree of insight into vaccine acceptance and trends over time (19;20)	
		☒	☐	☐	☐	☐		
FEASIBILITY	Is the intervention feasible to implement?	*No*	*Probably No*	*Un-certain*	*Probably Yes*	*Yes*	*<u>Varies</u>*	Single-dose administration of this vaccine is assumed to be easily implementable in settings – including low- and middle-income-countries – with existing vaccine logistics and delivery infrastructure. Ad26.COV2.S can be stored for at least 3 months at normal refrigerator temperatures of 2°C to 8°C (36°F to 46°F), and its shipping and storage fit	
		☐	☐	☐	☐	☒	☐		

			into the existing medical supply infrastructure (21). Administration of the vaccine to target groups that are currently not reached by national immunization programmes may pose a challenge in certain settings.		
Balance of consequences	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 ☒
Type of recommendation	We recommend the intervention ☐	We suggest considering recommendation of the intervention ☐ Only in the context of rigorous research ☒ Only with targeted monitoring and evaluation ☐ Only in specific contexts or specific (sub)populations		We recommend the comparison ☐	We recommend against the intervention and the comparison ☐
Recommendation (text)	Ad26.COV2.S is recommended for use in persons aged 18 years and above. The recommended schedule is one dose (0.5 ml) given intramuscularly into the deltoid muscle.				

Implementation considerations	
Monitoring, evaluation and research priorities	WHO recommends the following post-authorization monitoring activities and research. • Safety surveillance and monitoring: – anaphylaxis, thromboembolic events and other serious adverse events, cases of COVID-19 following vaccination that result in hospitalization or death; – background rates of AESIs, maternal and neonatal outcomes, and mortality in groups prioritized for vaccination. • Vaccine effectiveness: – vaccine effectiveness in relation to new virus variants; – vaccine effectiveness over time and whether protection can be prolonged by booster doses; – booster studies with a second dose, heterologous or variant-adjusted vaccines; – studies to investigate whether this vaccine reduces SARS-CoV-2 transmission and viral shedding; – assessment and reporting of breakthrough infections and virus sequence information; – head-to-head studies with other vaccines on extent and duration of immunity using standardized neutralization, T-cell and mucosal immunity assays; – vaccine effectiveness against Post-Acute Sequelae of SARS-CoV-2 infection (PASC), chronic COVID syndrome (CCS) and long-haul COVID. • Subpopulations: – prospective studies on the safety of Ad26.COV2.S vaccine in pregnant and lactating women; – immunogenicity and safety of vaccination in persons below the age of 18 years; – safety data on vaccination in immunocompromised persons, including persons living with HIV and persons with autoimmune disease. • Vaccination logistics: – immunogenicity and safety studies of co-administration with other vaccines, including influenza and pneumococcal vaccines, to adults and older persons; – interchangeability and “mix and match” studies for boosters within and across COVID-19 vaccine platforms. • Virus variants: – global surveillance of virus evolution and the impact of virus variants on vaccine effectiveness to support update of vaccines; – modelling to determine the trade-offs for the use of vaccines with reduced effectiveness against emergent variants; – booster studies with updated vaccine formulations.

References

(1) FDA Briefing Document. Janssen Ad26.COV2.S Vaccine for the Prevention of COVID-19. (https://www.fda.gov/media/146217/download, accessed 25 February 2021).

(2) Sadoff J, Le GM, Shukarev G, Heerwegh D, Truyers C, de Groot AM, et al. Interim Results of a Phase 1-2a Trial of Ad26.COV2.S Covid-19 Vaccine. N Engl J Med 2021 Jan 13.

(3) Interim recommendations for use of the Moderna mRNA-1273 vaccine against COVID-19- (www.who.int/publications/i/item/interim-recommendations-for-use-of-the-moderna-mrna-1273-vaccine-against-covid-19, accessed 31 January 2021).

(4) Interim recommendations for use of the Pfizer-BioNTech COVID-19 vaccine. (www.who.int/publications/i/item/WHO-2019-nCoV-vaccines-SAGE_recommendation-BNT162b2-2021.1, accessed 31 January 2021).

(5) Interim recommendations for use of the AZD1222 (ChAdOx1-S [recombinant]) vaccine against COVID19 developed by Oxford University and AstraZeneca. Interim guidance. 10 February 2021 (https://apps.who.int/iris/bitstream/handle/10665/339477/WHO-2019-nCoV-vaccines-SAGE-recommendation-AZD1222-2021.1-eng.pdf, accessed 25 February 2021).

(6) ACT Accelerator: An economic investment case & financing requirements. (www.who.int/docs/default-source/coronaviruse/act-accelerator/economic-investment-case-final-v2.pdf?sfvrsn=91d67ff6_4&download=true, accessed 13 December 2020).

(7) World Bank (2020) COVID-19 Strategic Preparedness and Response Program (SPRP) using the Multiphase Programmatic Approach (MPA) Project : Additional Financing (English).Washington, D.C. : World Bank Group. (http://documents.worldbank.org/curated/en/882781602861047266/World-COVID-19-Strategic-Preparedness-and-Response-Program-SPRP-using-the-Multiphase-Programmatic-Approach-MPA-Project-Additional-Financing, accessed 21 December 2020).

(8) Wouters OJ, Shadlen KC, Salcher-Konrad M, Pollard AJ, Larson HJ, Teerawattananon Y, et al. Challenges in ensuring global access to COVID-19 vaccines: production, affordability, allocation, and deployment. Lancet 2021 Feb 12.

(9) Cutler DM, Summers LH. The COVID-19 Pandemic and the $16 Trillion Virus. JAMA 2020 Oct 20;324(15):1495-6.

(10) Eurasia Group. 2020. Ending the COVID-19 Pandemic: The Need for a Global Approach. New York: Eurasia Group. (www.who.int/publications/m/item/ending-the-covid-19-pandemic-the-need-for-a-global-approach, accessed 13 December 2020).

(11) Hafner, Marco; Yerushalmi, Erez; Fays, Celment; Dufresne, Eliane; Van Stolk, Christian. 2020. COVID-19 and the cost of vaccine nationalism. Cambridge, UK: RAND Europe. (www.rand.org/t/RRA769-1, accessed 13 December 2020).

(12) International Monetary Fund. 2020. World Economic Outlook: A Long and Difficult Ascent. Washington, DC: October 2020. (www.imf.org/en/Publications/WEO/Issues/2020/09/30/world-economic-outlook-october-2020#Full%20Report%20and%20Executive%20Summary, accessed 13 November 2020).

(13) Bartsch SM, O'Shea KJ, Ferguson MC, Bottazzi ME, Wedlock PT, Strych U, et al. Vaccine Efficacy Needed for a COVID-19 Coronavirus Vaccine to Prevent or Stop an Epidemic as the Sole Intervention. Am J Prev Med 2020 Oct;59(4):493-503.

(14) Cakmakli C, Demiralp S, Kalemli-Ozcan, Yesiltas S, Yildirim M. (2021) The Economic Case for Global Vaccinations: An Epidemiological Model with International Production Networks. Paris: International Chamber of Commerce. (https://iccwbo.org/publication/the-economic-case-for-global-vaccinations/, accessed 1 February 2021).

(15) Sandmann F, Davies NG, CMMID COVID-19 Working Group, Vassall A, Edmunds JW, Jit M. (2020) The potential health and economic value of SARS-CoV-2 vaccination alongside physical distancing in the UK: transmission model-based future scenario analysis and economic evaluation; https://www.medrxiv.org/content/10.1101/2020.09.24.20200857v1.

(16) WHO SAGE values framework for the allocation and prioritization of COVID-19 vaccination. www.who.int/publications/i/item/who-sage-values-framework-for-the-allocation-and-prioritization-of-covid-19-vaccination.

(17) ACT Accelarator and COVAX facility. www.who.int/initiatives/act-accelerator. 11-23-2020.

(18) Lazarus JV, Ratzan SC, Palayew A, Gostin LO, Larson HJ, Rabin K, et al. A global survey of potential acceptance of a COVID-19 vaccine. Nat Med 2020 Oct 20.

(19) YouGov.(https://yougov.co.uk/topics/international/articles-reports/2021/01/12/covid-19-willingness-be-vaccinated, accessed 31 January 2021).

(20) Global Attitudes on COVID-19 vaccine. Ipsos survey. (www.ipsos.com/en/global-attitudes-covid-19-vaccine-december-2020, accessed 31 January 2021).

(21) SPONSOR BRIEFING DOCUMENT. COVID-19 Vaccine Ad26.COV2.S VAC31518 (JNJ-78436735) (www.fda.gov/media/146219/download, accessed 26 February 2021).

(22) COVID-19 Clinical management: living guidance. (www.who.int/publications/i/item/WHO-2019-nCoV-clinical-2021-1, accessed February 2021).

Annex 8. SAGE evidence-to-recommendation framework: Janssen AD26.COV2.S vaccine use in older adults

Question: Should Janssen AD26.COV2.S vaccine be administered to older adults to prevent moderate to severe/critical COVID-19?

Population: Older adults (≥60 years)

Intervention: Single dose of Janssen AD26.COV2.S vaccine

Comparison(s): Active control/placebo

Outcome: Moderate to severe/critical COVID-19 (PCR-confirmed)

Background: On 31 December 2019, WHO was alerted to several cases of pneumonia of unknown origin in Wuhan City, Hubei Province, China. The cause was found to be a novel coronavirus, SARS-CoV-2. The disease caused by this novel virus has been named COVID-19. The outbreak of COVID-19 was declared a public health emergency of international concern in January 2020. The disease has since spread with an enormous impact on the health and well-being of individuals and populations worldwide. It has further caused major disruptions to various sectors of society and the economy across the globe.

Vaccines are a critical tool in combating the pandemic. In the rapidly evolving field of COVID-19 vaccines, WHO has to date issued interim recommendations on the use of Pfizer–BioNTech, Moderna and AstraZeneca vaccines (3-5).

	CRITERIA	JUDGEMENTS				RESEARCH EVIDENCE	ADDITIONAL INFORMATION
PROBLEM	Is the problem a public health priority?	*No*	*Uncertain*	*Yes*	*Varies by setting*	The cumulative number of COVID-19 cases globally has surpassed 111 762 965 with more than 2 479 678 deaths. Cases have been found in 190 different countries or territories throughout the world (status 25 February 2021). There has been collateral damage to other public health programmes. Older adults are particularly affected by COVID-19 and bear a significantly higher risk of severe COVID-19 outcomes and death.	The COVID-19 situation is evolving rapidly; the most recent epidemiological situation can be found on the following website: https://covid19.who.int/table
		☐	☐	☒	☐		

BENEFITS & HARMS OF THE OPTIONS	Benefits of the intervention Are the desirable anticipated effects large?	*No* ☐	*Un-certain* ☐	*Yes* ☒	*Varies* ☐	Around 40% of the study population in the primary analysis were aged 60 years or older. The phase 3 study COV3001 demonstrated 76.3% efficacy (95%CI 61.1–86.0%) in those aged 60 years and above against confirmed moderate to severe/critical COVID-19 as from 14 days after vaccination. In all participants, as of 14 days after vaccination, there were 2 COVID-19-related hospitalizations in the vaccinated group compared with 29 in the placebo group (VE 93.1%, 95%CI 72.74–99.20).	
	Harms of the intervention Are the undesirable anticipated effects small?	*No* ☐	*Un-certain* ☐	*Yes* ☒	*Varies* ☐	Ad26.COV2.S demonstrated an acceptable safety and reactogenicity profile in adults ≥18 years of age, and adults ≥60 years of age, including those with comorbidities associated with an increased risk of progressing to severe/critical COVID-19. All local and systemic adverse reactions were reported more frequently among younger (18–59 years) than among older (≥60 years) participants. In those aged 60 years and over, 3/7331 (<0.1%) in the vaccine group reported related serious adverse events compared with 1/7341 (<0.1%) in the placebo group.	
	Balance between benefits and harms	***Favours intervention*** ☒	***Favours comparison*** ☐	***Favours both*** ☐	***Favours neither*** ☐	**Unclear** ☐	Efficacy data benefit of the intervention, and short-term safety data suggest limited harm. Further ongoing studies will need to be undertaken as part of post-marketing surveillance.	
		Effectiveness of the intervention					Please see the related GRADE tables.	

	What is the overall quality of this evidence for the critical outcomes?	***No included studies*** ☐	***Very low*** ☐	***Low*** ☐	***Moderate*** ☐	***High*** ☒			
		Safety of the intervention							
		No included studies ☐	***Very low*** ☐	***Low*** ☐	***Moderate*** ☒	***High*** ☐			
VALUES & PREFERENCES	How certain is the relative importance of the desirable and undesirable outcomes?	***Important uncertainty or variability*** ☐	***Possibly important uncertainty or variability*** ☒	***Probably no important uncertainty or variability*** ☐	***No important uncertainty or variability*** ☐	***No known undesirable outcomes*** ☐		The majority of severe disease occurs in older individuals. Available scientific evidence suggests that the target population probably considers the desirable effects, i.e. the potential protection conferred by the vaccine, more important than the undesirable effects, i.e. the currently reported safety signals related to COVID-19 vaccination. Different population groups may have different opinions regarding the weights assigned to desirable and undesirable outcomes.	
	Values and preferences of the target population: Are the desirable	*No*	*Probably No*	*Uncertain*	*Probably Yes*	*Yes*	*Varies*	Available scientific evidence suggests that the target population probably assigns more weight to the desirable effects than the undesirable effects related to COVID-19 vaccination.	

	effects large relative to undesirable effects?	☐	☐	☐	☒	☐	☐	Targeted information campaigns should assess this aspect. As more data on vaccine efficacy in older adults are generated, the uncertainty around the importance of the desirable effects of the intervention will probably be reduced.	
RESOURCE USE	Are the resources required small?	*No*		*Un-certain*		*Yes*	*Varies*	Janssen AD26.COV2.S can be distributed and stored using existing cold-chain infrastructure and does not require ultra-cold-chain capacity. Nevertheless, considerable resources will be needed to ensure the implementation of a COVID-19 vaccination programme, especially given: (i) that COVID-19 vaccination is likely to be prioritized for populations (e.g. health care workers, older adults) without pre-existing robust immunization programmes in many settings, and (ii) the urgency of vaccination roll-out worldwide, which may necessitate additional surge resources to accelerate implementation with adequate infection prevention and control procedures in the context of COVID-19. Resources required include, but are not restricted to, human resources, vaccine costs, logistics, planning and coordination, training, social mobilization and communications, and immunization safety surveillance.	An estimated US$15.9 billion is needed for the vaccines pillar (COVAX) of the Access to COVID-19 Tools Accelerator (ACT-A) for 2020–21, in order to deliver 2 billion doses. This does not include all delivery costs in all countries participating in COVAX, bilateral procurement deals, or research and development investments outside of COVAX (6). The World Bank has approved a financing window of up to US $12 billion to support low- and middle-income countries in purchasing and distributing vaccine (7).
		☒		☐		☐	☐		
	Cost-effectiveness	*No*		*Un-certain*		*Yes*	*Varies*	Formal global cost-effectiveness analyses have not been conducted, but the emerging evidence indicates that the benefits, including the impact on recovery of the global economy, are likely to outweigh the cost of COVID-19 vaccination in general at global level. No formal cost-effectiveness analyses of Janssen AD26.COV2.S vaccine compared with other vaccines have been conducted. The Janssen AD26.COV2.S vaccine is expected to be less costly than other COVID-19 vaccines (see previous subcriterion). (8) Individual-level efficacy against	The global economy is estimated to be losing US$375 billion per month because of the coronavirus pandemic. G20 countries have invested approximately US$10 trillion in domestic economic stimulus to mitigate the economic consequences of reduced business activity and unemployment due to the pandemic. Initial estimates suggest that COVID-19 vaccination will provide substantial economic value in terms of averted morbidity and mortality
		☐		☐		☐	☒		

					COVID-19 may be lower than that of some other COVID-19 vaccines; more data are needed to assess efficacy against other endpoints (see main text). The ability to use Janssen AD26.COV2.S in existing cold-chain infrastructure in all country settings may allow higher population-level coverage. Cost-effectiveness analyses should be conducted at country level; cost-effectiveness of COVID-19 vaccination may vary by country depending on COVID-19 burden, comparator interventions assessed, analysis perspective, and local cost-effectiveness thresholds used.	costs and averted losses in gross domestic product (GDP) (6;9-15).
EQUITY	What would be the impact on health inequities?	*Increa-sed* ☐	*Un-certain* ☐	*Reduced* ☒	*Varies* ☐	Equity and ethical considerations are critical. SAGE has produced a Values Framework (16), which offers guidance on the fair allocation of COVID-19 vaccines based on six core ethical principles that should guide distribution. If distributed fairly, COVID-19 vaccines may have considerable impact on reducing health inequities. Storage and distribution requirements of Janssen AD26.COV2.S vaccine are the same as those of many other vaccines currently in use globally. Existing vaccine cold-chain capacity, which is available in almost all countries, could be leveraged for vaccine distribution.	Vaccine nationalism is seen as a threat to reducing health inequity, in particular as high-income countries have arranged bilateral contracts with manufacturers. This has led to the establishment of the Access to COVID-19 Tools (ACT) Accelerator and, within this, the COVAX facility, which aims to ensure equitable access to vaccines for its participating member states (17).
ACCEPTABILITY	Which option is acceptable to key stakeholders (e.g. ministries of health, immunization managers)?	*Inter-vention* ☒	*Com-parison* ☐	*Both* ☐	*Neither* ☐	*Un-clear* ☐	No scientific evidence is available. As vaccination is an eagerly awaited tool to combat COVID-19, it is assumed that key stakeholders, in particular ministries of health and immunization managers, are strongly in favour of COVID-19 vaccination.	The fact that 190 economies are participating in COVAX suggests a very high acceptability of COVID-19 vaccination in general, though not necessarily of this vaccine in particular.

	Which option is acceptable to target group?	*Inter-vention*: ☒ *Comparison*: ☐ *Both*: ☐ *Neither*: ☐ *Un-clear*: ☐	Single-dose administration of this product may be favourable to the target group. COVID-19 vaccine acceptability varies between (sub)population groups and may be correlated with the perceived risk posed by the disease. In a global survey (19 countries) of acceptance rates in the general population of any COVID-19 vaccine product, 71.5% of participants reported that they would be very or somewhat likely to take a COVID-19 vaccine. Acceptance rates ranged from almost 55% to 87% (18). Representative multicountry surveys are carried out periodically to assess the percentage of those willing to receive (or of those who have already received) COVID-19 vaccination (non-product specific). While these polls are limited to selected countries, they provide a certain degree of insight into vaccine acceptance and trends over time (19;20)	
FEASIBILITY	Is the intervention feasible to implement?	*No*: ☐ *Probably No*: ☐ *Un-certain*: ☐ *Probably Yes*: ☐ *Yes*: ☒ *Varies*: ☐	Single-dose administration of this vaccine is assumed to be easily implementable in settings – including low- and middle-income-countries – with existing vaccine logistics and delivery infrastructure. Ad26.COV2.S can be stored for at least 3 months at normal refrigerator temperatures of 2°C to 8°C (36°F to 46°F), and its shipping and storage fit into the existing medical supply infrastructure (21)	

Balance of consequences	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 ☒

<table>
<tr><td>Type of recommendation</td><td>We recommend the intervention

☐</td><td>We suggest considering recommendation of the intervention

☐ Only in the context of rigorous research
☒ Only with targeted monitoring and evaluation
☐ Only in specific contexts or specific (sub)populations</td><td>We recommend the comparison

☐</td><td>We recommend against the intervention and the comparison

☐</td></tr>
<tr><td>Recommendation (text)</td><td colspan="4">The risk of severe COVID-19 and death increases steeply with age. Data from the phase 3 trial indicate that the efficacy and safety of the vaccine are comparable across all age groups (above the age of 18). Vaccination is recommended for older persons.</td></tr>
<tr><td>Implementation considerations</td><td colspan="4"></td></tr>
<tr><td>Monitoring, evaluation and research priorities</td><td colspan="4">WHO recommends the following post-authorization monitoring activities and research.

• Safety surveillance and monitoring:
– anaphylaxis, thromboembolic events and other serious adverse events, cases of COVID-19 following vaccination that result in hospitalization or death;
– background rates of AESIs, maternal and neonatal outcomes, and mortality in groups prioritized for vaccination.
• Vaccine effectiveness:
– vaccine effectiveness in relation to new virus variants;
– vaccine effectiveness over time and whether protection can be prolonged by booster doses;
– booster studies with a second dose, heterologous or variant-adjusted vaccines;
– studies to investigate whether this vaccine reduces SARS-CoV-2 transmission and viral shedding;
– assessment and reporting of breakthrough infections and virus sequence information;
– head-to-head studies with other vaccines on extent and duration of immunity using standardized neutralization, T-cell and mucosal immunity assays;
– vaccine effectiveness against Post-Acute Sequelae of SARS-CoV-2 infection (PASC), chronic COVID syndrome (CCS) and long-haul COVID.
• Subpopulations:
– prospective studies on the safety of Ad26.COV2.S vaccine in pregnant and lactating women;</td></tr>
</table>

	– immunogenicity and safety of vaccination in persons below the age of 18 years; – safety data on vaccination in immunocompromised persons, including persons living with HIV and persons with autoimmune disease. • Vaccination logistics: – immunogenicity and safety studies of co-administration with other vaccines, including influenza and pneumococcal vaccines, to adults and older persons; – interchangeability and "mix and match" studies for boosters within and across COVID-19 vaccine platforms. • Virus variants: – global surveillance of virus evolution and the impact of virus variants on vaccine effectiveness to support update of vaccines; – modelling to determine the trade-offs for the use of vaccines with reduced effectiveness against emergent variants; – booster studies with updated vaccine formulations.

References

(1) FDA Briefing Document. Janssen Ad26.COV2.S Vaccine for the Prevention of COVID-19. (https://www.fda.gov/media/146217/download, accessed 25 February 2021).

(2) Sadoff J, Le GM, Shukarev G, Heerwegh D, Truyers C, de Groot AM, et al. Interim Results of a Phase 1-2a Trial of Ad26.COV2.S Covid-19 Vaccine. N Engl J Med 2021 Jan 13.

(3) Interim recommendations for use of the Moderna mRNA-1273 vaccine against COVID-19- (www.who.int/publications/i/item/interim-recommendations-for-use-of-the-moderna-mrna-1273-vaccine-against-covid-19, accessed 31 January 2021).

(4) Interim recommendations for use of the Pfizer-BioNTech COVID-19 vaccine. (www.who.int/publications/i/item/WHO-2019-nCoV-vaccines-SAGE_recommendation-BNT162b2-2021.1, accessed 31 January 2021).

(5) Interim recommendations for use of the AZD1222 (ChAdOx1-S [recombinant]) vaccine against COVID19 developed by Oxford University and AstraZeneca. Interim guidance. 10 February 2021 (https://apps.who.int/iris/bitstream/handle/10665/339477/WHO-2019-nCoV-vaccines-SAGE-recommendation-AZD1222-2021.1-eng.pdf, accessed 25 February 2021).

(6) ACT Accelerator: An economic investment case & financing requirements. (www.who.int/docs/default-source/coronaviruse/act-accelerator/economic-investment-case-final-v2.pdf?sfvrsn=91d67ff6_4&download=true, accessed 13 December 2020).

(7) World Bank (2020) COVID-19 Strategic Preparedness and Response Program (SPRP) using the Multiphase Programmatic Approach (MPA) Project : Additional Financing (English).Washington, D.C. : World Bank Group. (http://documents.worldbank.org/curated/en/882781602861047266/World-COVID-19-Strategic-Preparedness-and-Response-Program-SPRP-using-the-Multiphase-Programmatic-Approach-MPA-Project-Additional-Financing, accessed 21 December 2020).

(8) Wouters OJ, Shadlen KC, Salcher-Konrad M, Pollard AJ, Larson HJ, Teerawattananon Y, et al. Challenges in ensuring global access to COVID-19 vaccines: production, affordability, allocation, and deployment. Lancet 2021 Feb 12.

(9) Cutler DM, Summers LH. The COVID-19 Pandemic and the $16 Trillion Virus. JAMA 2020 Oct 20;324(15):1495-6.

(10) Eurasia Group. 2020. Ending the COVID-19 Pandemic: The Need for a Global Approach. New York: Eurasia Group. (www.who.int/publications/m/item/ending-the-covid-19-pandemic-the-need-for-a-global-approach, accessed 13 December 2020).

(11) Hafner, Marco; Yerushalmi, Erez; Fays, Celment; Dufresne, Eliane; Van Stolk, Christian. 2020. COVID-19 and the cost of vaccine nationalism. Cambridge, UK: RAND Europe. (www.rand.org/t/RRA769-1, accessed 13 December 2020).

(12) International Monetary Fund. 2020. World Economic Outlook: A Long and Difficult Ascent. Washington, DC: October 2020. (www.imf.org/en/Publications/WEO/Issues/2020/09/30/world-economic-outlook-october-2020#Full%20Report%20and%20Executive%20Summary, accessed 13 November 2020).

(13) Bartsch SM, O'Shea KJ, Ferguson MC, Bottazzi ME, Wedlock PT, Strych U, et al. Vaccine Efficacy Needed for a COVID-19 Coronavirus Vaccine to Prevent or Stop an Epidemic as the Sole Intervention. Am J Prev Med 2020 Oct;59(4):493-503.

(14) Cakmakli C, Demiralp S, Kalemli-Ozcan, Yesiltas S, Yildirim M. (2021) The Economic Case for Global Vaccinations: An Epidemiological Model with International Production Networks. Paris: International Chamber of Commerce. (https://iccwbo.org/publication/the-economic-case-for-global-vaccinations/, accessed 1 February 2021).

(15) Sandmann F, Davies NG, CMMID COVID-19 Working Group, Vassall A, Edmunds JW, Jit M. (2020) The potential health and economic value of SARS-CoV-2 vaccination alongside physical distancing in the UK: transmission model-based future scenario analysis and economic evaluation; https://www.medrxiv.org/content/10.1101/2020.09.24.20200857v1.

(16) WHO SAGE values framework for the allocation and prioritization of COVID-19 vaccination. www.who.int/publications/i/item/who-sage-values-framework-for-the-allocation-and-prioritization-of-covid-19-vaccination.

(17) ACT Accelarator and COVAX facility. www.who.int/initiatives/act-accelerator. 11-23-2020.

(18) Lazarus JV, Ratzan SC, Palayew A, Gostin LO, Larson HJ, Rabin K, et al. A global survey of potential acceptance of a COVID-19 vaccine. Nat Med 2020 Oct 20.

(19) YouGov.(https://yougov.co.uk/topics/international/articles-reports/2021/01/12/covid-19-willingness-be-vaccinated, accessed 31 January 2021).

(20) Global Attitudes on COVID-19 vaccine. Ipsos survey. (www.ipsos.com/en/global-attitudes-covid-19-vaccine-december-2020, accessed 31 January 2021).

(21) SPONSOR BRIEFING DOCUMENT. COVID-19 Vaccine Ad26.COV2.S VAC31518 (JNJ-78436735) (www.fda.gov/media/146219/download, accessed 26 February 2021).

(22) COVID-19 Clinical management: living guidance. (www.who.int/publications/i/item/WHO-2019-nCoV-clinical-2021-1, accessed February 2021).

Annex 9. SAGE evidence-to-recommendation framework: Janssen AD26.COV2.S vaccine use in individuals with comorbidities

Question: Should Janssen AD26.COV2.S vaccine be administered to individuals with comorbidities or health states that increase risk for severe COVID-19[a] to prevent moderate to severe/critical COVID-19?

Population: Individuals with comorbidities or health states that increase risk for severe COVID-19

Intervention: Single dose of JANSSEN AD26.COV2.S vaccine

Comparison(s): Active control/placebo

Outcome: Moderate to severe/critical COVID-19 (PCR-confirmed)

Background: On 31 December 2019, WHO was alerted to several cases of pneumonia of unknown origin in Wuhan City, Hubei Province, China. The cause was found to be a novel coronavirus, SARS-CoV-2. The disease caused by this novel virus has been named COVID-19. The outbreak of COVID-19 was declared a public health emergency of international concern in January 2020. The disease has since spread, with an enormous impact on the health and well-being of individuals and populations worldwide. It has further caused major disruptions to various sectors of society and the economy across the globe.

Vaccines are a critical tool in combating the pandemic. In the rapidly evolving field of COVID-19 vaccines, WHO has to date issued interim recommendations on the use of Pfizer–BioNTech, Moderna and AstraZeneca vaccines (3-5).

	CRITERIA	JUDGEMENTS				RESEARCH EVIDENCE	ADDITIONAL INFORMATION
PROBLEM	Is the problem a public health priority?	*No*	*Uncertain*	*Yes*	*Varies by setting*	The cumulative number of COVID-19 cases globally has surpassed 111 762 965 with more than 2 479 678 deaths. Cases have been found in 190 different countries or territories throughout the world (status 25 February 2021). There has been collateral damage to other public health programmes. Individuals with certain comorbidities are particularly affected by COVID-19 and bear a higher risk of severe COVID-19 outcomes and death. Identified risk factors include comorbidities such as diabetes, hypertension, cardiac disease, chronic lung disease, cerebrovascular disease, dementia, mental disorders, chronic kidney	The COVID-19 situation is evolving rapidly; the most recent epidemiological situation can be found on the following website: https://covid19.who.int/table
		☐	☐	☒	☐		

[a] Comorbidity in the phase 3 trial was defined as asthma, cancer, chronic kidney disease, cardiovascular disorder, respiratory disease, obesity, neurological conditions, immunocompromised from blood transplant, HIV infection or diabetes type 2.

				disease, immunosuppression, obesity and cancer. People with multiple comorbidities are at a higher risk of COVID-19-related adverse outcomes (22) Although the relative risk may be high for some conditions, the absolute risk for younger adults with comorbidities is typically lower than for healthy older adults (>75 years).	
BENEFITS & HARMS OF THE OPTIONS	Benefits of the intervention Are the desirable anticipated effects large?	*No* ☐	*Un-certain* ☐	*Yes* ☒	*Varies* ☐	At least one comorbidity was present for 39.9% of participants. The phase 3 study COV3001 demonstrated 64.2% efficacy (95%CI 52.7–73.1) in those with comorbidities against confirmed moderate to severe/critical COVID-19 as from 14 days after vaccination.	
	Harms of the intervention Are the undesirable anticipated effects small?	*No* ☐	*Un-certain* ☐	*Yes* ☒	*Varies* ☐	Ad26.COV2.S demonstrated an acceptable safety and reactogenicity profile in adults ≥18 years of age, and adults ≥60 years of age, including those with comorbidities associated with an increased risk of progressing to severe/critical COVID-19.	
	Balance between benefits and harms	***Favours inter-vention*** ☒	***Favours com-parison*** ☐	***Favours both*** ☐	***Favours neither*** ☐	**Unclear** ☐	Efficacy data suggest benefit, and the short-term safety data suggest minimal harm. Further studies will need to be undertaken as part of post-marketing surveillance.	
	What is the overall quality of this evidence for the critical outcomes?	Effectiveness of the intervention ***No included studies***	***Very low***	***Low***	***Mod-erate***	***High***	Please see the related GRADE tables.	

		☐ ☐ ☐ ☒ ☐ Safety of the intervention ***No included studies*** ☐ ***Very low*** ☐ ***Low*** ☒ ***Moderate*** ☐ ***High*** ☐		
VALUES & PREFERENCES	How certain is the relative importance of the desirable and undesirable outcomes?	***Important uncertainty or variability*** ☐ ***Possibly important uncertainty or variability*** ☒ ***Probably no important uncertainty or variability*** ☐ ***No important uncertainty or variability*** ☐ ***No known undesirable outcomes*** ☐	There is possibly important uncertainty regarding how the target population weighs the desirable and undesirable effects (i.e. the protection conferred by the vaccine weighed against the currently reported safety signals) related to COVID-19 vaccination. Different population groups may have different opinions regarding the relative weights attributed to desirable and undesirable outcomes.	
	Values and preferences of the target population: Are the desirable effects large relative to undesirable effects?	*No* ☐ *Probably No* ☐ *Uncertain* ☐ *Probably Yes* ☒ *Yes* ☐ *Varies* ☐	It is assumed that target population probably attaches more weight to the desirable effects than the undesirable effects related to COVID-19 vaccination. Targeted information campaigns should assess this aspect.	
RESOUR		*No* *Un-certain* *Yes* *Varies*	Janssen AD26.COV2.S can be distributed and stored using existing cold-chain infrastructure	An estimated US$15.9 billion is needed for the vaccines pillar

	Are the resources required small?	☒	☐	☐	☐	and does not require ultra-cold-chain capacity. Nevertheless, considerable resources will be needed to ensure the implementation of a COVID-19 vaccination programme, especially given: (i) that COVID-19 vaccination is likely to be prioritized for populations (e.g. health care workers, older adults) without pre-existing robust immunization programmes in many settings, and (ii) the urgency of vaccination roll-out worldwide, which may necessitate additional surge resources to accelerate implementation with adequate infection prevention and control procedures in the context of COVID-19. Resources required include, but are not restricted to, human resources, vaccine costs, logistics, planning and coordination, training, social mobilization and communications, and immunization safety surveillance.	(COVAX) of the Access to COVID-19 Tools Accelerator (ACT-A) for 2020–21, in order to deliver 2 billion vaccine doses. This does not include all delivery costs in all countries participating in COVAX, bilateral procurement deals, or research and development investments outside of COVAX (6). The World Bank has approved a financing window of up to US$12 billion to support low- and middle-income countries in purchasing and distributing vaccine (7).
	Cost-effectiveness	*No* ☐	*Un-certain* ☐	*Yes* ☐	*Varies* ☒	Formal global cost-effectiveness analyses have not been conducted, but the emerging evidence indicates that the benefits, including the impact on recovery of the global economy, are likely to outweigh the cost of COVID-19 vaccination in general at global level. No formal cost-effectiveness analyses of Janssen AD26.COV2.S compared with other vaccines have been conducted. The Janssen AD26.COV2.S vaccine is expected to be less costly than other COVID-19 vaccines (see previous subcriterion). (8)Individual-level efficacy against COVID-19 may be lower than for some other COVID-19 vaccines; more data are needed to assess efficacy against other endpoints (see main text). The ability to use Janssen AD26.COV2.S in existing cold-chain infrastructure in all country settings may allow higher population-level coverage. Cost-effectiveness analyses should be conducted at country level; cost-effectiveness of COVID-19 vaccination may vary by country depending on COVID-19 burden, comparator	The global economy is estimated to be losing US$375 billion per month because of the coronavirus pandemic. G20 countries have invested approximately US$10 trillion in domestic economic stimulus to mitigate the economic consequences of reduced business activity and unemployment due to the pandemic. Initial estimates suggest that COVID-19 vaccination will provide substantial economic value in terms of averted morbidity and mortality costs and averted losses in gross domestic product (GDP) (6;9-15).

					interventions assessed, analysis perspective, and local cost-effectiveness thresholds used.	
EQUITY	What would be the impact on health inequities?	*Increa-sed* ☐	*Un-certain* ☐	*Reduced* ☒	*Varies* ☐	Equity and ethical considerations are critical. SAGE has produced a Values Framework (16), which offers guidance on the fair allocation of COVID-19 vaccines based on six core ethical principles that should guide distribution. If distributed fairly, COVID-19 vaccines may have considerable impact on reducing health inequities. Storage and distribution requirements of Janssen AD26.COV2.S vaccine are the same as for many other vaccines currently in use globally. Existing vaccine cold-chain capacity, available in almost all countries worldwide, could be leveraged for vaccine distribution.	Vaccine nationalism is seen as a threat to reducing health inequity, in particular as high-income countries have arranged bilateral contracts with manufacturers. This has led to the establishment of the Access to COVID-19 Tools (ACT) Accelerator and, within this, the COVAX facility, which aims to ensure equitable access to vaccines for its participating member states (17).
ACCEPTABILITY	Which option is acceptable to key stakeholders (e.g. ministries of health, immunization managers)?	*Inter-vention* ☒	*Com-parison* ☐	*Both* ☐	*Neither* ☐	*Un-clear* ☐	No scientific evidence is available. As vaccination is an eagerly awaited tool to combat COVID-19, it is assumed that key stakeholders, in particular ministries of health and immunization managers, are strongly in favour of COVID-19 vaccination.	The fact that 190 economies are participating in COVAX suggests a very high acceptability of COVID-19 vaccination in general, though not necessarily of this vaccine in particular.
	Which option is acceptable to target group?	*Inter-vention*	*Com-parison*	*Both*	*Neither*	*Un-clear*	Single-dose administration of this product may be favourable to the target group. COVID-19 vaccine acceptability in general varies between (sub)population groups and may be	

		☒ ☐ ☐ ☐ ☐	correlated with the perceived risk posed by the disease. In a global survey (19 countries) of acceptance rates in the general population of any COVID-19 vaccine product, 71.5% of participants reported that they would be very or somewhat likely to take a COVID-19 vaccine. Acceptance rates ranged from almost 55% to 87% (18). Representative multicountry surveys are carried out periodically to assess the percentage of those willing to receive (or of those who have already received) COVID-19 vaccination (non-product specific). While these polls are limited to selected countries, they provide a certain degree of insight into vaccine acceptance and trends over time (19;20).	
FEASIBILITY	Is the intervention feasible to implement?	*No* ☐ *Probably No* ☐ *Uncertain* ☐ *Probably Yes* ☐ *Yes* ☒ *Varies* ☐	Single-dose administration of this vaccine is assumed to be easily implementable in settings – including low- and middle-income countries – with existing vaccine logistics and delivery infrastructure. Ad26.COV2.S can be stored for at least 3 months at normal refrigerator temperatures of 2°C to 8°C (36°F to 46°F), and its shipping and storage fit into the existing medical supply infrastructure (21).	

Balance of consequences	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 ☐

Type of recommendation	We recommend the intervention ☐	We suggest considering recommendation of the intervention ☐ Only in the context of rigorous research ☒ Only with targeted monitoring and evaluation ☒ Only in specific contexts or specific (sub)populations	We recommend the comparison ☐	We recommend against the intervention and the comparison ☐
Recommendation (text)	**Persons with comorbidities** Certain comorbidities have been identified as increasing the risk of severe COVID-19 disease and death. The phase 3 clinical trial demonstrated that the vaccine has similar safety and efficacy profiles in persons with various underlying medical conditions, including those that place them at increased risk for severe COVID-19. The comorbidities studied in the phase 3 clinical trial included hypertension, chronic lung disease, significant cardiac disease, obesity, diabetes, and human immunodeficiency virus (HIV) infection. Vaccination is recommended for persons with such comorbidities that have been identified as increasing the risk of severe COVID-19. **Pregnant women** Pregnant women are at higher risk of severe COVID-19 compared with women of childbearing age who are not pregnant, and COVID-19 has been associated with an increased risk of preterm birth. The available data on Ad26.COV2.S of pregnant women are insufficient to assess vaccine-associated risks in pregnancy. However, it should be noted that Ad26.COV2.S is a nonreplicating vaccine. No safety issues in more than 1 600 pregnant women were identified using the Ad26 vaccine platform for other pathognes including Ebola virus. Animal developmental and reproductive toxicity studies show no harm to the development of the foetus. Further studies are planned in pregnant women in the coming months, including a pregnancy sub-study and a pregnancy registry. As data from these studies become available, recommendations on vaccination will be updated accordingly. In the interim, pregnant women should receive Ad26.COV2.S only if the benefit of vaccination to the pregnant woman outweighs the potential vaccine risks, such as if they are health workers at high risk of exposure or have comorbidities that place them in a high-risk group for severe COVID-19. Information and, if possible, counselling on the lack of safety data for pregnant women and the potential benefit of vaccination should be provided. WHO does not recommend pregnancy testing prior to vaccination. WHO does not recommend delaying pregnancy because of vaccination. **Lactating women** Breastfeeding offers substantial health benefits to lactating women and their breastfed children. Vaccine efficacy is expected to be similar in lactating women as in other adults. It is unknown whether Ad26.COV2.S is excreted in human milk. As the Ad26.COV2.S vaccine is a nonreplicating vaccine, it is unlikely to pose a risk to the breastfeeding child. On the basis of these considerations, a lactating woman who is part of a group recommended for vaccination, e.g., health workers, should be offered vaccination on an equivalent basis. WHO does not recommend discontinuing breastfeeding after vaccination.			

	Persons living with HIV Persons living with human immunodeficiency virus (HIV) may be at higher risk of severe COVID-19. Persons living with HIV who were well controlled were included in the trials and no safety concern was observed. Data on administration of the vaccine are currently insufficient to allow assessment of vaccine efficacy for persons living with HIV. It is possible that the immune response to the vaccine may be reduced, which may lower its clinical effectiveness. In the interim, given that the vaccine is nonreplicating, persons living with HIV who are part of a group recommended for vaccination may be vaccinated. Information and, where possible, counselling should be provided to inform individual benefit–risk assessment. It is not necessary to test for HIV infection prior to vaccine administration. **Immunocompromised persons** Immunocompromised persons are at higher risk of severe COVID-19. Available data are currently insufficient to assess vaccine efficacy or vaccine-associated risks in severely immunocompromised persons, including those receiving immunosuppressant therapy. It is possible that the immune response to the vaccine may be reduced, which may lower its clinical effectiveness. In the interim, given that the vaccine is nonreplicating, immunocompromised persons who are part of a group recommended for vaccination may be vaccinated. Information and, where possible, counselling about vaccine safety and efficacy profiles in immunocompromised persons should be provided to inform individual benefit–risk assessment.
Implementation considerations	
Monitoring, evaluation and research priorities	WHO recommends the following post-authorization monitoring activities and research. • Safety surveillance and monitoring: – anaphylaxis, thromboembolic events and other serious adverse events, cases of COVID-19 following vaccination that result in hospitalization or death; – background rates of AESIs, maternal and neonatal outcomes, and mortality in groups prioritized for vaccination. • Vaccine effectiveness: – vaccine effectiveness in relation to new virus variants; – vaccine effectiveness over time and whether protection can be prolonged by booster doses; – booster studies with a second dose, heterologous or variant-adjusted vaccines; – studies to investigate whether this vaccine reduces SARS-CoV-2 transmission and viral shedding; – assessment and reporting of breakthrough infections and virus sequence information; – head-to-head studies with other vaccines on extent and duration of immunity using standardized neutralization, T-cell and mucosal immunity assays;

	– vaccine effectiveness against Post-Acute Sequelae of SARS-CoV-2 infection (PASC), chronic COVID syndrome (CCS) and long-haul COVID. • Subpopulations: – prospective studies on the safety of Ad26.COV2.S vaccine in pregnant and lactating women; – immunogenicity and safety of vaccination in persons below the age of 18 years; – safety data on vaccination in immunocompromised persons, including persons living with HIV and persons with autoimmune disease. • Vaccination logistics: – immunogenicity and safety studies of co-administration with other vaccines, including influenza and pneumococcal vaccines, to adults and older persons; – safety, immunogenicity, and impact of a delayed second dose, as currently implemented by certain countries; – interchangeability and “mix and match” studies for boosters within and across COVID-19 vaccine platforms. • Virus variants: – global surveillance of virus evolution and the impact of virus variants on vaccine effectiveness to support update of vaccines; – modelling to determine the trade-offs for the use of vaccines with reduced effectiveness against emergent variants; – booster studies with updated vaccine formulations.

References

(1) FDA Briefing Document. Janssen Ad26.COV2.S Vaccine for the Prevention of COVID-19. (https://www.fda.gov/media/146217/download, accessed 25 February 2021).

(2) Sadoff J, Le GM, Shukarev G, Heerwegh D, Truyers C, de Groot AM, et al. Interim Results of a Phase 1-2a Trial of Ad26.COV2.S Covid-19 Vaccine. N Engl J Med 2021 Jan 13.

(3) Interim recommendations for use of the Moderna mRNA-1273 vaccine against COVID-19- (www.who.int/publications/i/item/interim-recommendations-for-use-of-the-moderna-mrna-1273-vaccine-against-covid-19, accessed 31 January 2021).

(4) Interim recommendations for use of the Pfizer-BioNTech COVID-19 vaccine. (www.who.int/publications/i/item/WHO-2019-nCoV-vaccines-SAGE_recommendation-BNT162b2-2021.1, accessed 31 January 2021).

(5) Interim recommendations for use of the AZD1222 (ChAdOx1-S [recombinant]) vaccine against COVID19 developed by Oxford University and AstraZeneca. Interim guidance. 10 February 2021 (https://apps.who.int/iris/bitstream/handle/10665/339477/WHO-2019-nCoV-vaccines-SAGE-recommendation-AZD1222-2021.1-eng.pdf, accessed 25 February 2021).

(6) ACT Accelerator: An economic investment case & financing requirements. (www.who.int/docs/default-source/coronaviruse/act-accelerator/economic-investment-case-final-v2.pdf?sfvrsn=91d67ff6_4&download=true, accessed 13 December 2020).

(7) World Bank (2020) COVID-19 Strategic Preparedness and Response Program (SPRP) using the Multiphase Programmatic Approach (MPA) Project : Additional Financing (English).Washington, D.C. : World Bank Group. (http://documents.worldbank.org/curated/en/882781602861047266/World-COVID-19-Strategic-Preparedness-and-Response-Program-SPRP-using-the-Multiphase-Programmatic-Approach-MPA-Project-Additional-Financing, accessed 21 December 2020).

(8) Wouters OJ, Shadlen KC, Salcher-Konrad M, Pollard AJ, Larson HJ, Teerawattananon Y, et al. Challenges in ensuring global access to COVID-19 vaccines: production, affordability, allocation, and deployment. Lancet 2021 Feb 12.

(9) Cutler DM, Summers LH. The COVID-19 Pandemic and the $16 Trillion Virus. JAMA 2020 Oct 20;324(15):1495-6.

(10) Eurasia Group. 2020. Ending the COVID-19 Pandemic: The Need for a Global Approach. New York: Eurasia Group. (www.who.int/publications/m/item/ending-the-covid-19-pandemic-the-need-for-a-global-approach, accessed 13 December 2020).

(11) Hafner, Marco; Yerushalmi, Erez; Fays, Celment; Dufresne, Eliane; Van Stolk, Christian. 2020. COVID-19 and the cost of vaccine nationalism. Cambridge, UK: RAND Europe. (www.rand.org/t/RRA769-1, accessed 13 December 2020).

(12) International Monetary Fund. 2020. World Economic Outlook: A Long and Difficult Ascent. Washington, DC: October 2020. (www.imf.org/en/Publications/WEO/Issues/2020/09/30/world-economic-outlook-october-2020#Full%20Report%20and%20Executive%20Summary, accessed 13 November 2020).

(13) Bartsch SM, O'Shea KJ, Ferguson MC, Bottazzi ME, Wedlock PT, Strych U, et al. Vaccine Efficacy Needed for a COVID-19 Coronavirus Vaccine to Prevent or Stop an Epidemic as the Sole Intervention. Am J Prev Med 2020 Oct;59(4):493-503.

(14) Cakmakli C, Demiralp S, Kalemli-Ozcan, Yesiltas S, Yildirim M. (2021) The Economic Case for Global Vaccinations: An Epidemiological Model with International Production Networks. Paris: International Chamber of Commerce. (https://iccwbo.org/publication/the-economic-case-for-global-vaccinations/, accessed 1 February 2021).

(15) Sandmann F, Davies NG, CMMID COVID-19 Working Group, Vassall A, Edmunds JW, Jit M. (2020) The potential health and economic value of SARS-CoV-2 vaccination alongside physical distancing in the UK: transmission model-based future scenario analysis and economic evaluation; https://www.medrxiv.org/content/10.1101/2020.09.24.20200857v1.

(16) WHO SAGE values framework for the allocation and prioritization of COVID-19 vaccination. www.who.int/publications/i/item/who-sage-values-framework-for-the-allocation-and-prioritization-of-covid-19-vaccination.

(17) ACT Accelarator and COVAX facility. www.who.int/initiatives/act-accelerator. 11-23-2020.

(18) Lazarus JV, Ratzan SC, Palayew A, Gostin LO, Larson HJ, Rabin K, et al. A global survey of potential acceptance of a COVID-19 vaccine. Nat Med 2020 Oct 20.

(19) YouGov.(https://yougov.co.uk/topics/international/articles-reports/2021/01/12/covid-19-willingness-be-vaccinated, accessed 31 January 2021).

(20) Global Attitudes on COVID-19 vaccine. Ipsos survey. (www.ipsos.com/en/global-attitudes-covid-19-vaccine-december-2020, accessed 31 January 2021).

(21) SPONSOR BRIEFING DOCUMENT. COVID-19 Vaccine Ad26.COV2.S VAC31518 (JNJ-78436735) (www.fda.gov/media/146219/download, accessed 26 February 2021).

(22) COVID-19 Clinical management: living guidance. (www.who.int/publications/i/item/WHO-2019-nCoV-clinical-2021-1, accessed February 2021).

WHO reference number: WHO/2019-nCoV/vaccines/SAGE_recommendation/Ad26.COV2.S/background/2021.1