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Evidence Assessment

STRATEGIC ADVISORY GROUP OF EXPERTS (SAGE) ON IMMUNIZATION

Meeting 15 March 2021

FOR RECOMMENDATION BY SAGE

Prepared by the SAGE Working Group on COVID-19 vaccines

EVIDENCE ASSESSMENT: Ad26.COV2.S COVID-19 vaccine

Key evidence to inform policy recommendations on the use of Ad26.COV2.S COVID-19 vaccine

Evidence retrieval

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

Retrieved evidence

Majority of data considered for policy recommendations on Ad26.COV2.S Covid-19 vaccine are published in scientific peer reviewed journals:

- Interim Results of a Phase 1–2a Trial of Ad26.COV2.S Covid-19 Vaccine. NEJM. February 2021. DOI: 10.1056/NEJMoa2034201. Jerald Sadoff, Mathieu Le Gars, Georgi Shukarev, et al.
- FDA briefing document Janssen Ad26.COV2.S (COVID-19) Vaccine
- Ad26 platform literature: Custers et al. Vaccines based on the Ad26 platform; Vaccine 2021

Quality assessment

Type of bias	Randomization	Deviations from intervention	Missing outcome data	Measurement of the outcome	Selection of the reported results	**Overall risk of bias**
Working Group judgment	Low	Low	Low	Low	Low	**LOW**

EVIDENCE ASSESSMENT

The SAGE Working Group specifically considered the following issues:

1. Trial endpoints used in comparison with other vaccines *Saad Omer*
2. Evidence on vaccine efficacy in the total population and in different subgroups *Cristiana Toscano*
3. Evidence of vaccine efficacy against asymptomatic infections, reducing severity, hospitalisations, deaths, and efficacy against virus variants of concern *Annelies Wilder-Smith*
4. Vaccination after SARS-CoV2 infection.
5. Evidence on vaccine safety in the total population and in different subgroups *Sonali Kochhar*
6. Frequently asked questions - Annelies Wilder-Smith
7. GRADEing of the evidence assessment *Melanie Marti*

Protocol specific definitions for COVID-19

moderna NIH National Institutes of Health

Positive RT-PCR **AND**
- **Any ≥1** of: cough, dyspnoea, or clinical/radiographic pneumonia **OR**
- **Any ≥2** of: fever, chills, myalgia, headache, sore throat, anosmia, or ageusia

Pfizer BIONTECH FOSUN PHARMA

Positive SARS-CoV-2 NAAT **AND**
- **Any ≥1** of: fever, cough dyspnoea, chills, myalgia, anosmia or ageusia, sore throat, diarrhoea, or vomiting

AstraZeneca UNIVERSITY OF OXFORD

Positive RT-PCR **AND**
- **Any ≥1** of: dyspnoea, SpO2 ≤ 93% or requiring supplemental O2, clinical/radiographic pneumonia **OR**
- **Any ≥2** of: fever, cough, myalgia, fatigue, anosmia or ageusia, vomiting, or diarrhoea

Johnson & Johnson Beth Israel Lahey Health Beth Israel Deaconess Medical Center

Molecularly confirmed C-19 with:
- **Any ≥1** of fever (≥38.0°C), sore throat, malaise, headache, myalgia, GI symptoms, cough, chest congestion, runny nose, wheezing, skin rash, eye irritation or discharge, chills, anosmia, ageusia, red or bruised looking feet or toes, or shaking chills or rigors

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Primary efficacy endpoint

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Any symptomatic COVID-19 disease based on protocol definition

Pfizer BIONTECH FOSUN PHARMA

Any symptomatic COVID-19 disease based on protocol definition in those without prior infection

Assessed separately for with/without prior infection

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Any symptomatic COVID-19 disease based on protocol definition

Johnson & Johnson Beth Israel Lahey Health Beth Israel Deaconess Medical Center

Prevention of moderate or severe COVID-19 disease

Moderate C-19 (**Any ≥1** of: RR>20/min, abnormal SpO2 > 93%, pneumonia, DVT, or dyspnoea **OR** **Any ≥2** of: fever, chills/rigors, cough, malaise, headache, myalgia, Gastrointestinal symptoms, anosmia/ageusia, or limb rashes)

Severe: ≥1 of: RR ≥30/min, HR ≥125 BPM,SpO2 ≤93% or PaO2/FIO2 <300 **OR** respiratory failure **OR** shock **OR** organ failure **OR** ICU/CCU admission **OR** death

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Triggers for investigation*

moderna / NIH National Institutes of Health	Pfizer BIONTECH / FOSUN PHARMA	AstraZeneca / University of Oxford	Johnson & Johnson / Beth Israel Lahey Health Beth Israel Deaconess Medical Center
o Respiratory symptoms or fever of any duration (cough, dyspnoea, temp ≥38ºC) o Defined C-19 symptoms ≥ 48 hrs (chills, myalgia, headache, sore throat, anosmia, ageusia, rhinorrhoea, nasal congestion, fatigue, nausea, vomiting, or diarrhoea)	o Fever o New or increased cough o New or increased dyspnoea o Chills o New or increased myalgia o New ageusia/anosmia o Sore throat o Diarrhoea o Vomiting o A diagnosis of C-19 outside the trial	o Symptoms of any duration: tachypnoea, dyspnoea, fever o Additional CDC-defined C-19 symptoms lasting ≥ 48 hrs: chills, cough, myalgia, body ache, headache, sore throat, anosmia, ageusia, rhinorrhoea, nasal congestion, fatigue, nausea, vomiting, or diarrhoea	Any ≥1 fever, sore throat, malaise, headache, myalgia, GI symptoms, cough, chest congestion, dyspnoea, runny nose, wheezing, skin rash, eye irritation or discharge, chills, anosmia/ageusia, red or bruised looking feet or toes, SpO2 ≤95%, HR ≥ 90 BPM, neurological symptoms, skin rash, confusion, bluish lips or face, thrombosis, or clinically suspected C-19

*Starting points for further investigation for COVID-19 using RT-PCR/NAAT

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EVIDENCE ASSESSMENT: Ad26.COV2.S COVID-19 vaccine

Key evidence to inform policy recommendations on the use of Ad26.COV2.S COVID-19 vaccine

Benefits of the intervention (vaccine overall efficacy against COVID-19)

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

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

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

1. Should Ad26.COV2.S COVID-19 vaccine be administered to adults (18-59 years) to prevent COVID-19?

2. Should Ad26.COV2.S COVID-19 vaccine be administered to older adults (≥60 years) to prevent COVID-19?

3. Should Ad26.COV2.S COVID-19 vaccine be administered to individuals with comorbidities or health states that increase risk for severe COVID-19 to prevent COVID-19?

EVIDENCE ASSESSMENT: Ad26.COV2.S COVID-19 vaccine

Key evidence to inform policy recommendations on the use of Ad26.COV2.S COVID-19 vaccine

Benefits of the intervention (vaccine efficacy against moderate to severe/critical, overall and by sub-groups)

Group/subgroup	VE% (95% CI)	
	14 days after vaccination	28 days after vaccination
Overall	66.9% (59.0, 73.4)	66.1% (55.0, 74.8)
Sex		
MALE	68.8% (60.1, 75.9)	69.8% (58.9, 78.2)
FEMALE	63.4% (53.1, 71.7)	60.3% (46.0, 71.2)
Age group (years)		
18-64	64.7% (57.6, 70.8)	65.1% (56.1, 72.5)
65+	76.5% (59.1, 87.3)	68.6% (38.6, 85.1)
Comorbidities		
YES	64.2% (52.7, 73.1)	58.6% (40.6, 71.6)
NO	67.6% (59.4, 74.3)	68.8% (59.0, 76.6)

EVIDENCE ASSESSMENT: Ad26.COV2.S COVID-19 vaccine

Key evidence to inform policy recommendations on the use of Ad26.COV2.S COVID-19 vaccine

Benefits of the intervention (vaccine efficacy against other endpoints)

- **Efficacy against COVID-19 hospitalization**
  - 14 days after vaccination → 2 vs 29, VE: 93.1% (95% CI 72.7-99.20)
  - 28 days after vaccination → 0 vs 16, VE: 100% (95% CI 74.26; 100.00)
- **Efficacy against severe/critical COVID-19 (WHO clinical progression scale ≥ 6)**
  - 14 days after vaccination → 14 vs 60, VE: 76.7 (95% CI 54.56, 89.09)
  - 28 days after vaccination → 5 vs 34, VE: 85.4% (95% CI 54.15, 96.90)
- **Efficacy against deaths related to COVID-19**
  - 0 vs 6

  - **Onset of efficacy:** 7 days after single dose for severe/critical COVID-19,
    - 14 days after single dose for moderate-severe COVID-19

EVIDENCE ASSESSMENT: Ad26.COV2.S COVID-19 vaccine

Key evidence to inform policy recommendations on the use of Ad26.COV2.S COVID-19 vaccine

Benefits of the intervention (vaccine efficacy against other endpoints)

- **Efficacy against asymptomatic infection**
  - 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%).
  - **Efficacy in terms of disease 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**

  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.

Given global vaccine supply constraints, should vaccination of persons with known SARS-CoV2 infection be delayed?

Considerations:

With almost 120 million laboratory confirmed SARS-CoV-2 infections in the context of limited vaccine supplies, delaying vaccination of persons with known infections could be justified.

Programmatic ease:

Vaccinating all persons eligible according to the WHO prioritization roadmap will facilitate rapid roll-out. Pre-screening would be a major programmatic hurdle.

Evidence assessment:

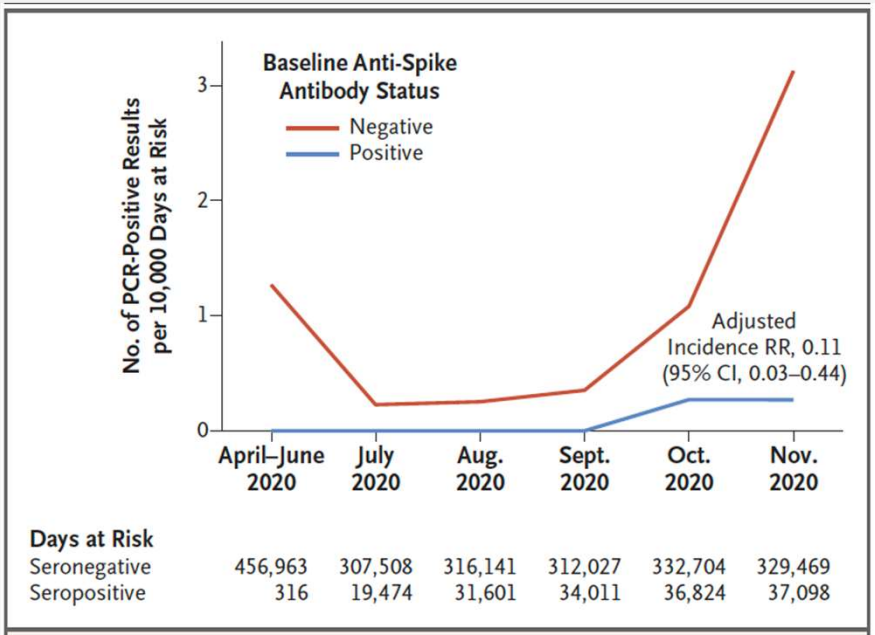
What is the evidence of the duration and extent of natural protection against re-infection?
What is the impact of variants of concern?

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Antibody Status and Incidence of SARS-CoV-2 Infection in Health Care Workers

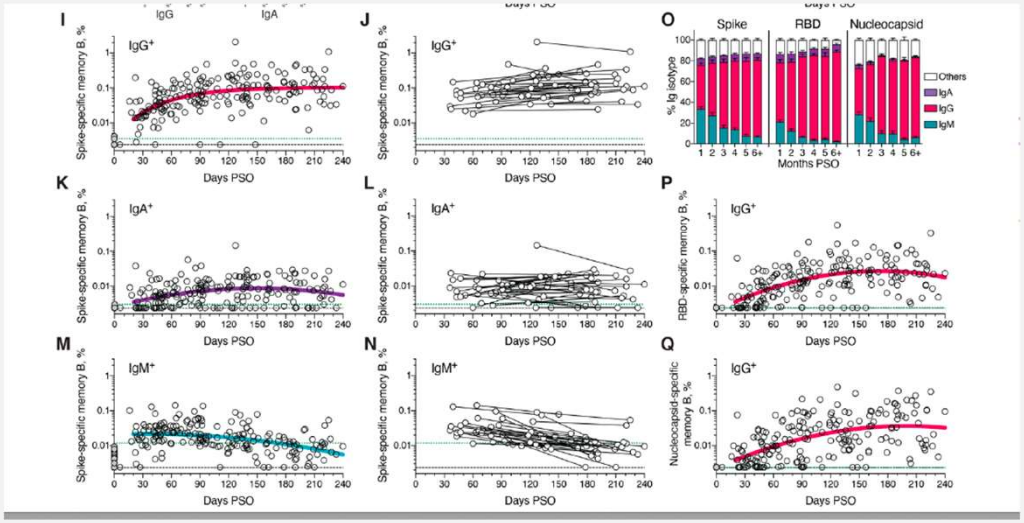
S.F. Lumley, D. O'Donnell, N.E. Stoesser, P.C. Matthews, A. Howarth, S.B. Hatch, B.D. Marsden, S. Cox, T. James, F. Warren, L.J. Peck, T.G. Ritter, Z. de Toledo, L. Warren, D. Axten, R.J. Cornall, E.Y. Jones, D.I. Stuart, G. Screaton, D. Ebner, S. Hoosdally, M. Chand, D.W. Crook, A.-M. O'Donnell, C.P. Conlon, K.B. Pouwels, A.S. Walker, T.E.A. Peto, S. Hopkins, T.M. Walker, K. Jeffery, and D.W. Eyre, for the Oxford University Hospitals Staff Testing Group*



Days at Risk						
Seronegative	456,963	307,508	316,141	312,027	332,704	329,469
Seropositive	316	19,474	31,601	34,011	36,824	37,098

Figure 1. Observed Incidence of SARS-CoV-2–Positive PCR Results According to Baseline Anti-Spike IgG Antibody Status.

The incidence of polymerase-chain-reaction (PCR) tests that were positive for SARS-CoV-2 infection during the period from April through November 2020 is shown per 10,000 days at risk among health care workers according to their antibody status at baseline. In seronegative health care workers, 1775 PCR tests (8.7 per 10,000 days at risk) were undertaken in symptomatic persons and 28,878 (141 per 10,000 days at risk) in asymptomatic persons; in seropositive health care workers, 126 (8.0 per 10,000 days at risk) were undertaken in symptomatic persons and 1704 (108 per 10,000 days at risk) in asymptomatic persons. RR denotes rate ratio.



Science

RESEARCH ARTICLES

Cite as: J. M. Dan *et al.*, *Science* 10.1126/science.abf4063 (2021).

Immunological memory to SARS-CoV-2 assessed for up to 8 months after infection

Jennifer M. Dan[1,3]*, Jose Mateus[1]*, Yu Kato[1]*, Kathryn M. Hastie[1], Esther Dawen Yu[1], Caterina E. Faliti[1], Alba Grifoni[1], Sydney I. Ramirez[1,3], Sonya Haupt[1], April Frazier[1], Catherine Nakao[1], Vamseedhar Rayaprolu[1], Stephen A. Rawlings[3], Bjoern Peters[1,2], Florian Krammer[4], Viviana Simon[4,5,6], Erica Ollmann Saphire[1,3], Davey M. Smith[3], Daniela Weiskopf[1]†, Alessandro Sette[1,3]†, Shane Crotty[1,3]†

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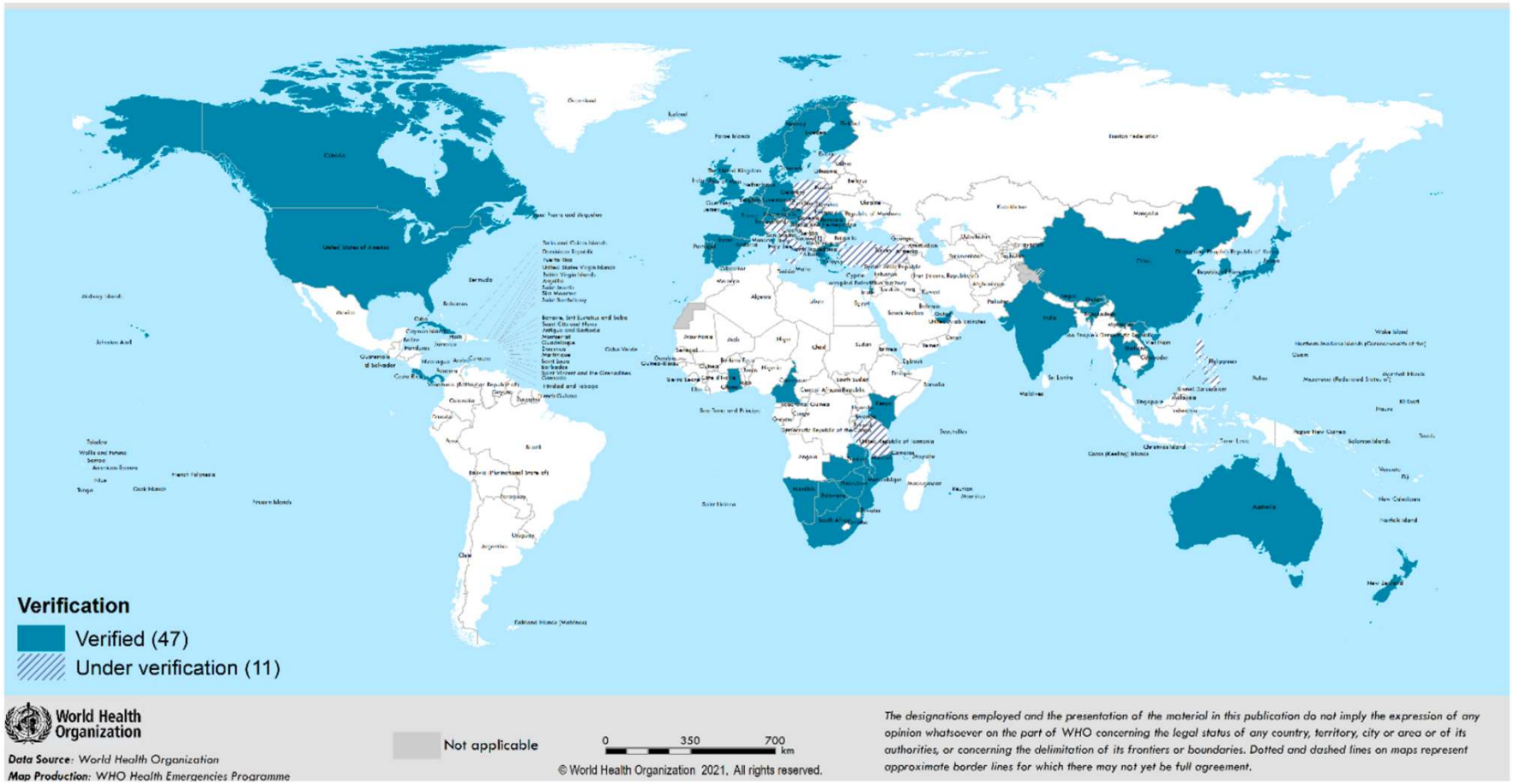
Understanding immune memory to SARS-CoV-2 is critical for improving diagnostics and vaccines, and for assessing the likely future course of the COVID-19 pandemic. We analyzed multiple compartments of circulating immune memory to SARS-CoV-2 in 254 samples from 188 COVID-19 cases, including 43 samples at ≥ 6 months post-infection. IgG to the Spike protein was relatively stable over 6+ months. Spike-specific memory B cells were more abundant at 6 months than at 1 month post symptom onset. SARS-CoV-2-specific CD4⁺ T cells and CD8⁺ T cells declined with a half-life of 3-5 months. By studying antibody, memory B cell, CD4⁺ T cell, and CD8⁺ T cell memory to SARS-CoV-2 in an integrated manner, we observed that each component of SARS-CoV-2 immune memory exhibited distinct kinetics.

Table 3: Overview of emerging information on key variants of concern, as of 9 March 2021*

Nextstrain clade	20I/501Y.V1	20H/**501Y.V2**†	20J/501Y.V3
PANGO lineage	B.1.1.7	B.1.351	B.1.1.28.1, alias **P.1**†
GISAID clade	GR	GH	GR
Alternate names	**VOC 202012/01**†	VOC 202012/02	-
First detected by	United Kingdom	South Africa	Brazil / Japan
First appearance	20 September 2020	Early August 2020	December 2020
Key spike mutations	H69/V70 deletion; Y144 deletion; N501Y; A570D; and P681H	L242/A243/L244 deletion; K417N E484K, N501Y	K417N, E484K; N501Y
Key mutation in common	S106/G107/F108 deletion in Non-Structural Protein 6 (NSP6)		
Transmissibility*	Increased[1] (36%-75%)[2], increased secondary attack rate[3] (10% to 13%)	Increased [1.50 (95% CI: 1.20-2.13) times more transmissible than previously circulating variants][4, 5]	Increased, more transmissible than previous circulating variants[6]
Severity*	Possible increased risk of hospitalization[7], severity and mortality[3]	No impact reported to date[4, 5], no significant change in-hospital mortality[8]	Under investigation, limited impact[6]
Neutralization capacity*	Slight reduction but overall neutralizing titers still remained above the levels expected to confer protection[9]	Decreased, suggesting potential increased risk of reinfection[4, 10, 11]	Decreased, reinfections reported[12-14]

Figure 6. Countries, territories and areas reporting SARS-CoV-2 501Y.V2 as of 9 March 2021



Screenshot

EVIDENCE ASSESSMENT: Ad26.COV2.S COVID-19 vaccine

Key evidence to inform policy recommendations on the use of Ad26.COV2.S COVID-19 vaccine

Vaccine efficacy against SARS-CoV-2 variants

Country (main strains detected)	Disease severity endpoint	No. of cases		VE% (95% CI)
		Vaccine group	Placebo group	
United States D614G (96%); CAL.20C (3%)	Moderate or 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 or 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 or 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)

Impact Of Anti-Vector Immunity Against Ad26

- Experience across Janssen clinical development programs
- **Ad26 seropositivity at baseline** (before vaccination) - **No major impact on Ag-specific immune response.** Evidence from
  - **HIV prophylactic vaccine program**: naturally occurring Ad26 neutralizing antibody titers or Ad26-targeting T cell responses at baseline were not associated with decreased immune responses against the vaccine antigen [3,4]
  - **Ebola vaccine program**: Ad26-specific seroprevalence rate of 93- 94% observed in a study in Sierra Leone → negligible correlation between the baseline Ad26-specific neutralizing antibody titers and the vaccine-induced EBOV GP-specific binding antibody response. Also observed in 2 other Ebola clinical trials [5, 6, 7]

1. Geisbert Ad26 and Ad35 vaccine vector. J Virol, 2011
2. Majhen adenovector vaccine 2014
3. Barouch APPROACH and NHP 13-19. Lancet. 2018
4. Baden IPCAVD 004. Ann Intern Med. 2016
5. Ishola Ad26.ZEBOV, MVA-BN-Filo adults Sierra Leone. Submitted Lancet Inf Dis, 2020
6. Afolabi vaccine regimen against Ebola children Sierra Leone. Submitted Lancet Inf Dis , 2020
7. Barry Ad26.ZEBOV, MVA-BN-Filo in healthy and HIV-infected adults. Submitted

Impact Of Anti-Vector Immunity Against Ad26

- **Ad26-specific immunity after repeated vaccination with a vaccine containing the same antigen has no major impact on Ag-specific immune response**
  - **HIV prophylactic vaccine program**: Ad26-based heterologous vaccinations showed that a second or subsequent doses of the same vectored vaccine were able to boost humoral and cellular immune responses to HIV antigens even in the presence of high Ad26 neutralizing antibody titers induced by the first dose [3, 8]
  - **Ebola vaccine program**: Response to Ad26.ZEBOV booster not impaired by presence of Ad26 neutralizing antibodies, with anamnestic responses elicited in all participants by a booster dose[9]
  - **RSV vaccine program**: In phase 1, with Ad26.preF adenovirus-26-specific neutralizing GMTs were 19- to 35-fold higher at Day 365 than at baseline, but no interference with RSV-A2 neutralizing responses or IFN-γ-secreting T cell responses to 2nd vaccine dose[10]

8. Baden IPCAVD 001. J Infect Dis. 2013
9. Goldstein JID 2020
10. Williams JID 2020

Safety Overview

- Safety data from the Phase 3 trial with 43,783 participants who received a single dose of vaccine with median follow-up post vaccination of 58 days, 23,903 (54.6%) participants had ≥ 2 months of follow-up
- Most AEs were mild to moderate, transient, generally resolved in 1-2 days post vaccination
- No Grade 4 AEs reported
- Lower reactogenicity in older adults (≥60 years) compared to younger adults (18- 59 years of age)
- Most frequently reported AEs were injection site pain (48.7%), erythema and swelling (<8%), headache (39%), fatigue (38.2%), myalgia (33.2%), pyrexia (9%)
- No clinically relevant difference in the reactogenicity profile observed by sex, race, ethnicity, geography, comorbidity, SARS-CoV-2 or HIV serostatus at baseline (numbers in some subgroups very low)
- Participants with one or more comorbidity at baseline (i.e. asthma, cerebrovascular disease, chronic kidney disease, COPD, serious heart conditions, hypertension, and obesity) had higher frequencies of AEs in the vaccine vs placebo group

Safety Overview

SAEs considered to be vaccine related included

- Grade 4 Guillain-Barré syndrome (ongoing for 29 days at time of reporting)
- Grade 3 Type IV hypersensitivity
- 2 cases of Grade 2 Bell's Palsy (ongoing for 43 and 24 days at time of reporting)
- Grade 4 pericarditis
- Grade 3 brachial radiculitis - ongoing for 75 days at the time of reporting, based on investigations, Janssen assessed it as an injection site pain secondary to injection
- Grade 3 post-vaccination syndrome – Janssen assessed it as vaccine reactogenicity (asthenia)

- Hypersensitivity reactions were rare, non serious (i.e. rash and urticarial), no anaphylaxis reported

- Numerically more cases of tinnitus, convulsions/seizures, and pulmonary embolism/deep vein thrombosis in the vaccine group- Not considered causally related to the vaccine as
  - One or more underlying medical conditions that are known risk factors for the events
  - Total number of cases in the study low, within the rates observed in the general population
  - Absence of safety signal in the Ad-26 safety database for these events of interest

Safety Overview

- 3 deaths in the vaccine group (lung abscess, non-COVID-19 pneumonia, and unknown cause (onset on Day 45) versus 16 in the placebo group. None of the deaths were considered vaccine related
- 8 pregnancies reported - 5 ongoing, 1 elective abortion, 1 spontaneous abortion, 1 unknown
- Available nonclinical and clinical data suggest that the theoretical risk of VAED, including VAERD, for Ad26.COV2.S is low as
  - Case splits for COVID-19 associated SAEs and deaths were higher in the placebo vs vaccine group
  - Symptoms of moderate and severe/critical COVID-19 cases reported in the vaccine group were milder than the placebo group
  - Consistent with the Th1-skewed immunologic response and high level of neutralizing antibodies induced
- Vaccine has an acceptable safety and reactogenicity profile
- No significant safety issues identified to date

Ad26 Vaccine Safety Database - Dec. 21, 2020 Update

- Data from 49 completed/ongoing trials (Ebola, HIV, Malaria, RSV, Zika, HPV, COVID-19 and Filovirus Ad26-based vaccine programs) and a government-lead Ebola vaccination campaign in Rwanda
    - >193,000 subjects (as of Feb 1, 2021 over 200,000) (including comparator/placebo)
    - Children: >67,000
    - Pregnant women: >1,000
    - Elderly: >10,000
- Follow up duration- 6 months up to 4.5 years
- Safety monitoring- SAEs, Solicited AEs, Unsolicited AEs
- Active Surveillance
    - Ebola - list of neuro-inflammatory disorders categorized as Immediate Reportable Events
    - HIV - confirmed HIV and potential immune disorders categorized as AESIs
- Three suspected unexpected serious adverse reactions (SUSARs) reported (related or possibly related)- Hypersensitivity [severe allergic reaction], small fiber neuropathy and rheumatoid arthritis

Ad26 Vaccine Safety Database

- Most frequently reported **local AEs-** injection-site pain (58.8% vaccine vs 21.9% placebo recipients), injection-site warmth (20.4% vs 9.9%) and injection site swelling (10.1% vs 4.8%)
- Most frequently reported **systemic AEs-** malaise (53.8%), fatigue (49.0%), headache (46.2%), myalgia (38.9%), pyrexia (10.7%), all more frequent than placebo group
- **Sex**- systemic AEs related to vaccine higher in adults females compared to males (71.6% vs 62.7%)
- **Elderly**- No safety concerns identified
- **AESI**- 3 cases of incident HIV infection, assessed to be not related to vaccine
- **HIV positive –** 118 HIV positive on ART with CD4+ counts of >350 and 221 with counts >200 cells/µL- no safety concerns identified
- **Pregnancy**- EMA May 2020 review of 72 safety reports: "no safety concern"; but all vaccinated prior to pregnancy
- **Lactation** - Unknown whether the vaccine is excreted in human milk, but considered unlikely due to the limited biodistribution observed in nonclinical studies
- No indication that **pre-existing antibodies** against Ad26 result in increased reactogenicity
- No risk of **shedding and transmission** – Ad26 vector is non-replicating

Safety in Children and Pregnancy from the Ebola Vaccine Deployment Program in Rwanda

Children - vaccine indicated from one year of age

- Nine children ≤ 7 years of age reported febrile seizures 5-12 hours post-vaccination
- Six reported recurrent seizures within a 24 hour period, "rare" frequency (0.04%)
- These cases were reported to FDA, EMA, Rwanda authorities
- RCT (Ebola vaccine versus comparator) is ongoing to evaluate the safety, reactogenicity, and immunogenicity in infants (4-11 months) in Guinea and Sierra Leone (NCT03929757)

Pregnancy

- Vaccine given to pregnant women in any trimester of pregnancy as considered high risk population
- 1,522 pregnancies reported- spontaneous abortion in 88 (5.8%) of pregnancies, other types of abortions (induced, elective and incomplete) in 14 (0.9%) of pregnancies, congenital malformations in 3 cases (lingula frenulum, cleft lip and evisceration on exomphalos)
- No reported adverse pregnancy outcomes and SAEs considered related to the vaccine
- RCT (Ebola vaccination during pregnancy versus Ebola vaccination 6 weeks after pregnancy termination) has started in Rwanda (NCT04556526), assessing adverse maternal/fetal outcomes

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Conclusion - Ad26 Vaccine Safety Database

- Overall, acceptable tolerability profile and no safety concerns observed so far
- Mostly mild to moderate AEs of rapid onset and short duration
- Fever is not a prominent AE but reported more frequently for younger children
- Rare febrile seizures in post-approval Ebola vaccination program in children
- Related SAEs were reported in 3 adult participants after vaccination with Ad26
- No significant safety issues and safety signals have been identified to date

Thrombotic and Thromboembolic Events

Full Analysis Set	Ad26.COV2.S N = 21,895 n	Placebo N = 21,888 n
Venous Thromboembolic events		
DVT	6*	2
PE	4	1
Transverse sinus thrombosis	1	0
Thrombosed hemorrhoid	0	1
Total Venous Events	11	4
Arterial Thromboembolic Events		
Cerebrovascular events	3**	3
Cardiovascular events	2	3
Total Arterial Events	5	6
Total number of patients with any event	14	10

*Includes one case with deep vein thrombosis and pulmonary embolism

**Includes one case with transverse sinus thrombosis with secondary cerebral hemorrhage, which led to the temporary study pause

Thrombotic/thromboembolic event: Pulmonary Embolism and other thromboembolic events

Pulmonary Embolism and other thromboembolic events

Study Vaccine	Age Gender	PT	Serious	TTO (Days)	Outcome	Relationship (PI)	Relevant Family / Medical History	Case notes
Ad26.Cov2.S 5x10e10 vp	30 Female	Pulmonary Embolism	Yes	2	Recovered	Not related	Drug and alcohol abuse, contraceptive use (medroxyprogesterone)	
	72 Male	Pulmonary Embolism	Yes	35	Not recovered	Not related	Hypertension, obesity	Positive COVID-19 test Developed kidney failure and PE in hospital
	52 Male	Pulmonary Embolism	Yes	44	Recovered	Not related	Obesity, Hypertension, Hereditary hemochromatosis	
	68 Male	Pulmonary Embolism	No	20	Not recovered	Not related	COPD, Hypertension, Dyslipidaemia, Gout, Hypothyroidism, Insulin resistance, Tonsillitis, Urinary tract infection	
Placebo	53 Male	Pulmonary Embolism	Yes	29	Recovering	Not related	Obesity, Obstructive sleep apnea, Hyperlipidemia, Hypertension	Positive COVID-19 test
	42 Female	Hemorrhoidal Thrombosis	No	24	Recovered	Not related	Vitamin D deficiency Pancreatic cyst rupture Hemorrhoids Insulin resistance	

COV3001: Thrombotic/thromboembolic Events

Overall incidence of thrombotic and thromboembolic events, arterial and venous, are similar across arms

Numerical imbalance observed for venous subtypes, 11 cases in Ad26 group, 4 cases in placebo group

- One nonserious AE of DVT in Ad26 group considered related to study vaccine by investigator. Event began 27 days after vaccination. Participant has medical history of obesity
- Serious AE of DVT reported in placebo group deemed related by the investigator, not related by the Company

Imbalance observed in vaccine arm for Deep Vein Thrombosis (6 vs 2 cases) and Pulmonary Embolism (4 vs 1 case)

No imbalances observed for cerebrovascular events (3 vs 3 cases) and cardiovascular events (2 vs 3)

Many of the participants had underlying medical conditions that predisposed to DVT and PE

Ad26 platform: No clustering or other trend was observed for thromboembolic events.

EVIDENCE ASSESSMENT: Ad26 platform

Questions	Response
Are adjuvants, preservatives or animal sources used	No
Does the vaccine contain fetal tissue	No. Grown in PER.C6 cell lines.
Does the wild type virus establish a latent or persistent infection?	Biodistribution studies is limited to injection site and draining lymph nodes, occasionally in spleen. Persistent infection or transmission of the Ad26 vector is highly unlikely as the vector is replication-incompetent
Does the vaccine replicate in the nucleus?	The vector is replication-incompetent. The vector genome (linear ds-DNA) travels to the nucleus of the host cell where antigen expression occurs, in the absence of vaccine vector replication
Has disease enhancement been shown with the wild type vector?	No
What is the background prevalence of natural immunity to the virus?	Varies; 10-90%. Neutralization titers are low-intermediate compared to other human adenovirus types
What is known about the effect of pre-existing immunity to the vector?	Data acquired to date, in more than 6000 vaccinated participants, have not revealed impact of pre-existing vector immunity on the vaccine specific humoral or cellular response. Repeated administration with the Ad26 vector leads to an increase in antigen specific humoral and cellular responses
What is the risk of reversion to virulence or recombination with wild type virus?	Low due to biodistribution

Custers et al. Vaccines based on the Ad26 Platform-Brighton publication. Vaccine 2021

GRADEing of Evidence	Statement on quality of evidence
Efficacy against moderate to severe/critical COVID-19 (PCR-confirmed) (Adults)	**High level of confidence**
Safety-serious adverse events (Adults)	**Moderate level of confidence**
Efficacy against moderate to severe/critical COVID-19 (PCR-confirmed) (Older adults)	**High level of confidence**
Safety-serious adverse events (Older adults)	**Moderate level of confidence**
Efficacy against moderate to severe/critical COVID-19 (PCR-confirmed) (*Individuals with comorbidities or health states that increase risk for severe COVID-19*)	**Moderate level of confidence**
Safety-serious adverse events (*Individuals with comorbidities or health states that increase risk for severe COVID-19*)	**Low level of confidence**

EVIDENCE ASSESSMENT: JANSSEN Ad26.COV2.S COVID-19 vaccine

Key evidence to inform policy recommendations on the use of Ad26.COV2.S COVID-19 vaccine

Adults and older adults

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
☐	☐	☐	☐	☒

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

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
☐	☐	☐	☒	☐