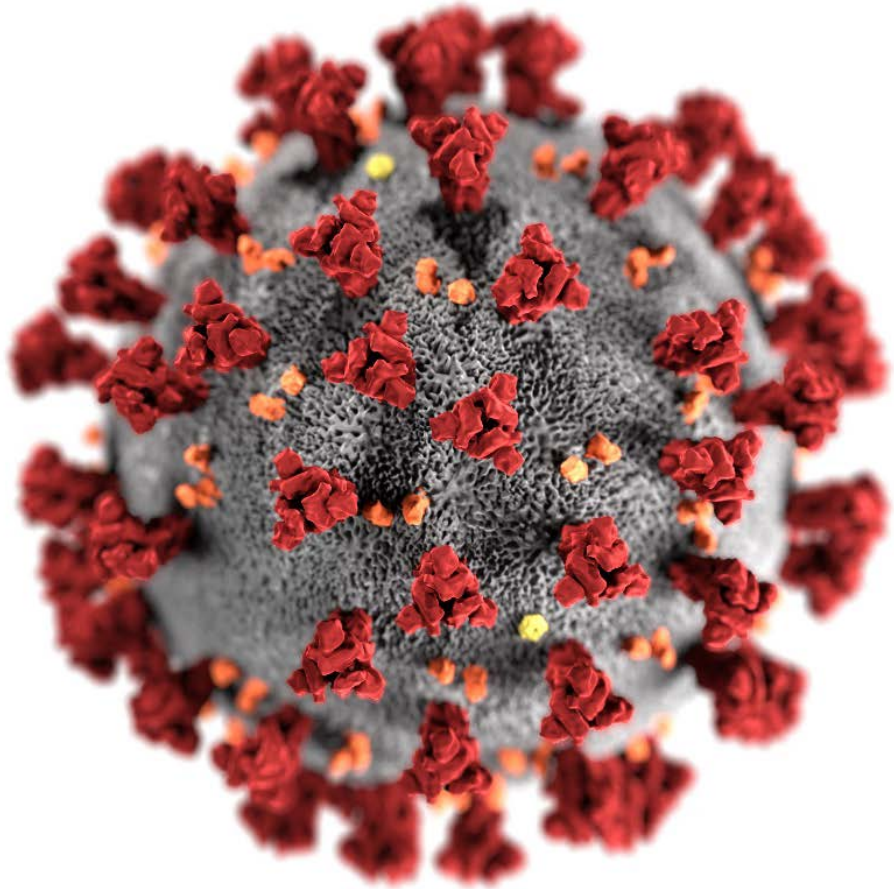
Grading of Recommendations, Assessment, Development, and Evaluation (GRADE): Janssen COVID-19 Vaccine



Dr. Julia Gargano
ACIP Meeting
28 February 2021

CONFIDENTIAL DRAFT

Policy Question

- Should vaccination with Janssen COVID-19 vaccine (single-dose, IM) be recommended for persons 18 years of age and older under an emergency use authorization?

PICO Question

Population	Persons aged ≥18 years
Intervention	Janssen COVID-19 vaccine Ad26.COV2.S (5×10^{10} viral particles, single-dose IM)
Comparison	No COVID-19 vaccine
Outcomes	Symptomatic lab-confirmed COVID-19 Hospitalization due to COVID-19 All-cause death SARS-CoV-2 seroconversion to a non-spike protein Asymptomatic SARS-CoV-2 infection Serious Adverse Events Reactogenicity

Outcomes

Outcome	Importance[a]	Description
Benefits		
Symptomatic lab-confirmed COVID-19	Critical	Primary outcome; current studies use PCR + specific symptoms
Hospitalization due to COVID-19	Critical	COVID-19 requiring medical intervention
All-cause death	Important	Death from all causes
SARS-CoV-2 seroconversion	Important	Measured using antibodies to non-spike protein to differentiate seroconversion due to natural infection from immunogenicity to vaccine
Asymptomatic SARS-CoV-2 infection	Important	No serial PCR; no systematic PCR after day 1 – not assessed
Harms		
Serious adverse events	Critical	Evaluating balance of events between arms; also reporting on number deemed vaccine-related
Reactogenicity	Important	Evaluating grade ≥ 3 severity of systemic events and local reactions

[a]Three options: Critical; Important but not critical; Not important for decision making

Outcomes

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Less common outcomes

[a]Three options: Critical; Important but not critical; Not important for decision making

Outcomes

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Benefits		
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Hospitalization due to COVID-19	Critical	COVID-19 requiring medical intervention
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Harms		
Serious adverse events	Critical	Evaluating balance of events between arms; also reporting on number deemed vaccine-related
Reactogenicity	Important	Evaluating grade ≥ 3 severity of systemic events and local reactions

Partial data available from day 29 and day 71

[a]Three options: Critical; Important but not critical; Not important for decision making

Outcomes

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Harms		
Serious adverse events	Critical	Evaluating balance of events between arms; also r… vaccine-related
Reactogenicity	Important	Evaluating grade ≥ 3 severity of systemic events and local reactions

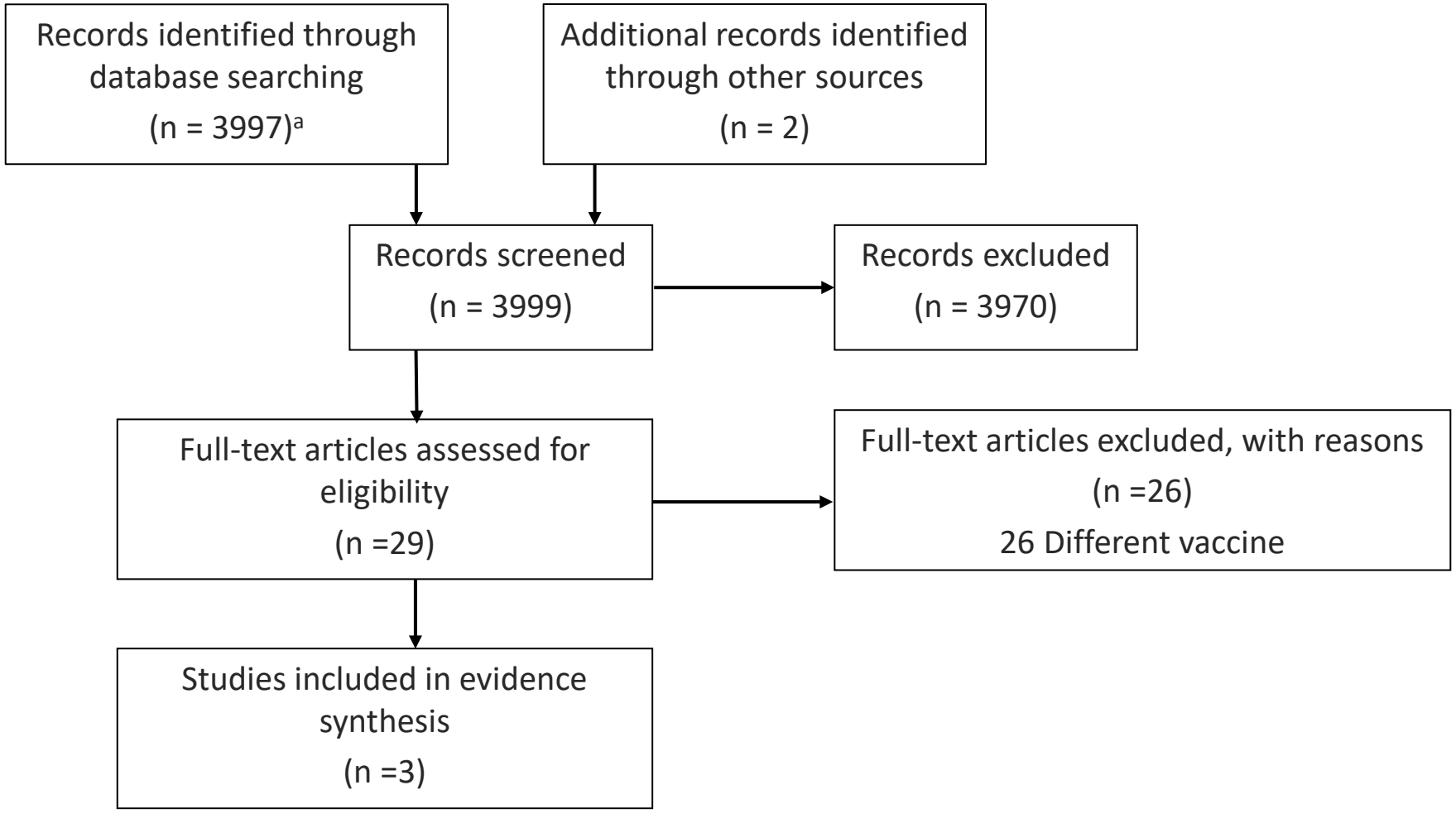
No data available; not included in evidence profile

[a]Three options: Critical; Important but not critical; Not important for decision making

Evidence Retrieval

- **Databases**: Medline, Embase, and Cochrane Library, written in English, restricted to 2020
- **Search terms**: coronavirus, COVID-19, SARS-CoV-2, respiratory (symptom, disease, illness, condition), vaccine, immunization, trial, double blind, single blind, placebo, comparative study, phase 3, immunogenicity, efficacy, effective, adverse, evidence, and variations on these terms
- **Inclusion:** provided data on vaccination with Ad26.COV2.S and 1) involved human subjects; 2) reported primary data; 3) included adults (ages 18 and older) at risk for SARS-CoV-2 infection; 4) included data relevant to the efficacy and safety outcomes being measured; and 5) included data for the dosage and timing being recommended (5×10^{10} viral particles, single-dose IM)
- **Additional resources:** unpublished and other relevant data by hand-searching reference lists, and consulting with vaccine manufacturers and subject matter experts
- Title and abstracts were screened independently by two separate reviewers.

Evidence Retrieval



a. Search results as of 2/8/2021

GRADE Evidence Type

- **Type 1 (high certainty):** We are very confident that the true effect lies close to that of the estimate of the effect.
- **Type 2 (moderate certainty):** We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
- **Type 3 (low certainty):** Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect.
- **Type 4 (very low certainty):** We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect.

NOTE: Evidence type is not measuring the quality of individual studies, but how much certainty we have in the estimates of effect across each outcome.

GRADE Criteria

- **Initial evidence type** (certainty level) determined by study design
  - Initial evidence type 1 (high certainty): A body of evidence from randomized controlled trials
  - Initial evidence type 3 (low certainty): A body of evidence from observational studies
- **Risk of bias:** Can include failure to conceal allocation, failure to blind, loss to follow-up. Risk of bias may vary across outcomes.
- **Inconsistency:** Criteria for evaluating include similarity of point estimates, extent of overlap of confidence intervals, and statistical criteria including tests of heterogeneity and I^2.
- **Indirectness:** Considers the generalizability of the evidence to the original PICO components (e.g., patients, intervention, comparison, or outcomes differ from those of interest[1]).
- **Imprecision:** Considers the fragility of the relative and absolute effect measures based on the interpretation of the 95% CIs and the optimal information size.
- **Other considerations:** Includes publication bias or indications of dose-response gradient, large or very large magnitude of effect, and opposing residual confounding.

Guyatt GH, Oxman AD, Kunz R et al. GRADE guidelines: 8. Rating the quality of evidence--indirectness. *J Clin Epidemiol.* 2011. DOI:10.1016/j.jclinepi.2011.04.014

Benefits

Outcome 1: Symptomatic Lab-confirmed COVID-19
Studies with Unvaccinated Comparator (n=1)

- Janssen phase III randomized controlled trial (RCT) (unpublished, data obtained from sponsor)
- Persons aged ≥18 years in United States, Argentina, Brazil, Chile, Colombia, Peru, and South Africa
- Data evaluated: final scheduled analysis, data cut-off Jan 22, 2021
- Full analysis set: 21,895 vaccine; 21,888 placebo (used for serious adverse events)
- Per-protocol set: 19,630 vaccine, 19,691 placebo (used for most efficacy estimates)
  - No immunologic or virologic evidence of prior SARS-CoV-2 infection, no major protocol deviations
- Safety subset: 3,356 vaccine, 3,380 placebo
  - Subset of full analysis set for the analysis of solicited, unsolicited, and immediate adverse events

PCR testing and molecular confirmation

- SARS-CoV-2 positive RT-PCR or molecular test result from any available respiratory tract sample
- Specimens from suspect COVID cases tested with FDA-approved PCR assay locally
- All positive specimens also sent to central laboratory (U. Washington) for confirmatory PCR testing
  - Protocol required molecular confirmation for primary endpoints
  - Not all specimens had been tested at central laboratory at time of interim analysis; 90% of re-tested specimens were confirmed
  - Analyses reported using any PCR-positive and centrally confirmed

Staggered clinical trial enrollment

- Enrollment stratified by age group (18-59 years, ≥60 years); age groups concurrently enrolled
- In each age group, protocol specified initial enrollment of 2000 persons without comorbidities
  - Data Safety and Monitoring Board reviewed safety data before persons with comorbidities were enrolled
- Median follow-up time varied by subgroup:
  - **≥60 year-olds with comorbidities : 50 days**
  - ≥60 year-olds without comorbidities: 54 days
  - 18-59 year-olds with comorbidities: 57 days
  - **18-59 year-olds without comorbidities: 64 days**

Symptomatic COVID-19 case definition

- "Moderate to severe/critical COVID-19"
- PCR-positive[a] (± centrally confirmed[b]) AND
- ≥1 of: respiratory rate ≥ 20 breaths/min, abnormal SpO_2, pneumonia, DVT, shortness of breath/difficulty breathing OR
- ≥2 of: Fever (38°C), Heart rate ≥90, shaking chills, sore throat, cough, malaise, headache, myalgia, GI symptoms (nausea, vomiting, diarrhea, abdominal pain), olfactory/taste disorder, red/bruised toes
- Timing of outcome ascertainment: co-primary
  - ≥14 days post vaccination
  - ≥28 days post vaccination

a. PCR could have been performed at local labs, central lab at U Washington, Covance, or labs external to study. All PCR assays FDA approved assays.
b. According to Phase III protocol, "Molecular confirmation of SARS-CoV-2 infection by a central laboratory will be used for the analysis of the case definition"

4 options for symptomatic COVID-19 case definition

- Timing of outcome ascertainment

	≥14 days post vaccine	≥28 days post vaccine
PCR+ at central laboratory	n = 464	n = 259
PCR + from any source	n = 682	n = 437

- Confirmation at central lab incomplete at time of analysis; of samples tested at central lab, 90% were confirmed (“centrally confirmed”)
- Case numbers limited post 28 days; limited follow-up time
- ≥14 days, PCR+ from any source selected for GRADE

Outcome 1: Symptomatic Lab-confirmed COVID-19 Studies with Unvaccinated Comparator (n=1)

Population	Events/Vaccine[a] (n/N)	Events/Placebo[a] (n/N)	Vaccine efficacy (95% CI)
Primary Outcome[b,c]			
Aged ≥18 years	173/19,514	509/19,544	66.3% (59.9%, 71.8%)
Aged 18–64 years	157/15,544	441/15,552	64.7% (57.6, 70.8)
Aged ≥65 years	16/3,970	68/3,992	76.5% (59.1, 87.3)
Aged ≥75 years	1/751	9/690	89.7% (26.0, 99.8)
Any comorbidity	70/7,777	194/7798	64.2% (52.7, 73.1)

[a]21,895 and 21,888 persons were randomized to vaccine and placebo

[b]Cases diagnosed ≥14 days post vaccination among persons without evidence of prior SARS-CoV-2 infection

[C] Primary efficacy population (per protocol); includes a total of 3113 person-years of observation in vaccine group and 3089 person-years in placebo group

CI: confidence interval

Outcome 1: Symptomatic Lab-confirmed COVID-19 Studies with Unvaccinated Comparator (n=1)

Population	Events/Vaccine[a] (n/N)	Events/Placebo[a] (n/N)	Vaccine efficacy (95% CI)
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Aged 18–64 years	157/15,544	441/15,552	64.7% (57.6, 70.8)
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Outcome 1: Symptomatic Lab-confirmed COVID-19 Studies with Unvaccinated Comparator (n=1)

Population	Events/Vaccine[a] (n/N)	Events/Placebo[a] (n/N)	Vaccine efficacy (95% CI)
Aged ≥18 years[b,c]	173/19,514	509/19,544	66% (60%, 72%)
By geography			
United States[c,d] (96.4% D614G)	51/9,119	196/9,086	74% (65%, 82%)
South Africa[c,d] (94.5% B.1.351)	43/2,473	90/2,496	52% (30%, 67%)
Brazil[c,d] (69.4% P.2 lineage)	39/3,370	114/3,355	66% (51%, 77%)
Other Latin American countries[c]	40/4,552	109/4,607	63% (47%, 74%)[e]

a. 21,895 and 21,888 persons were randomized to vaccine and placebo
b. Cases diagnosed ≥14 days post vaccination among persons without evidence of prior SARS-CoV-2 infection
c. Primary efficacy population (per protocol); includes a total of 3113 person-years of observation in vaccine group and 3089 person-years in placebo group
d. Sequencing was performed on a subset of centrally confirmed cases to determine lineage. In South Africa, 94.5% of cases were from B.1.351 lineage. In Brazil, 69.4% of cases represented P.2 lineage. In US, 96.4% were D614G variant, and 3% were CAL.20C.
e. Calculated using country-specific n/N supplied by sponsor.

CI: confidence interval

Outcome 1: Symptomatic Lab-confirmed COVID-19 Studies with Unvaccinated Comparator (n=1)

Population	Events/Vaccine (n/N)	Events/Placebo (n/N)	Vaccine efficacy (95% CI)
Co-primary outcomes			
≥14 days after vaccination, all PCR + (any laboratory)	173/19,514	509/19,544	66.3% (59.9, 71.8)
≥14 days after vaccination, centrally confirmed only	116/19,514	348/19544	66.9% (59.0, 73.4)
≥28 days after vaccination, all PCR + (any laboratory)	113/19,306	324/19,178	65.5% (57.2, 72.4)
≥28 days after vaccination, centrally confirmed only	66/19,306	193/19,178	66.1% (55.0, 74.8)

CI: confidence interval

Outcome 1: Symptomatic Lab-confirmed COVID-19 Studies with Unvaccinated Comparator (n=1)

Population	Events/Vaccine (n/N)	Events/Placebo (n/N)	Vaccine efficacy (95% CI)
Primary outcome			
No evidence of prior infection, ≥14 days after vaccination	173/19,514	509/19,544	66.3% (59.9%, 71.8%)
Secondary outcomes			
± evidence of prior infection, ≥14 days after vaccination	176/21,636	513/21,574	66.1% (59.7%, 71.6%)
Including mild[a] cases	181/19,514	516/19,544	65.2% (58.7%, 70.8%)

a. Mild COVID-19 defined as PCR-positive plus one of the symptoms in the moderate COVID-19 symptom list (excluding elevated heart rate) or chest congestion, runny nose, wheezing, skin rash, eye irritation/discharge.

CI: confidence interval

Evidence Table: Symptomatic Lab-confirmed COVID-19

Certainty assessment							№ of patients		Effect	Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Janssen COVID-19 vaccine	No vaccine	Relative (95% CI)		
Vaccine efficacy against symptomatic COVID-19											
1	RCT	Not serious a	Not serious	Serious b,c,d	Not serious	None	173/19514 (0.9%)	509/19544 (2.6%)	RR 0.34 (0.29 to 0.40)	Type 2	CRITICAL

a. Risk of bias related to blinding of participants and personnel was present. Although participants and study staff were blinded to intervention assignments, they may have inferred receipt of vaccine or placebo based on reactogenicity. This was deemed unlikely to overestimate efficacy or underestimate risk of serious adverse events, therefore the risk of bias was rated as not serious.

b. Serious concern for indirectness was noted due to the short duration of observation in the available body of evidence. Vaccine efficacy or adverse events observed at a median 2-month follow-up may differ from those observed with ongoing follow-up.

c. The effects noted are from an analysis of the per protocol population with outcomes assessed at least 14 days post vaccination, who had no evidence of prior SARS-CoV-2 infection, and counting cases who met the case definition with symptoms for moderate to severe COVID-19 and were PCR positive but not necessarily molecularly confirmed at the central laboratory. In an interim analysis using the full analysis set (persons with or without evidence of prior SARS-CoV-2 infection), there were 267 cases among 21,895 persons in the vaccine arm and 621 cases among 21,888 persons in the placebo arm (RR = 0.43 (0.37 to 0.50)).

d. The RCT excluded persons with prior COVID-19 diagnosis, pregnant women or women planning to become pregnant within 3 months of vaccination, and persons who were immunocompromised due to conditions and/or treatments (participants with stable/well-controlled HIV infection were not excluded). The population included in the RCT may not represent all persons aged >=18 years.

CI: confidence interval; **RR:** risk ratio

Outcome 2: Hospitalization for COVID-19 Studies with Unvaccinated Comparator (n=1)

- Janssen Phase III RCT (unpublished, data obtained from sponsor)
- Data on COVID-19 cases needing medical intervention was provided[a]
- Data on **severe COVID-19**: COVID-19 case with ≥1 of following:
  - Clinical signs at rest indicative of severe systemic illness [b]
  - Respiratory failure [b]
  - Evidence of shock [b]
  - Significant acute renal, hepatic, or neurologic dysfunction
  - Admission to an intensive care unit
  - Death

a. Defined as hospitalization, ICU admission, mechanical ventilation and ECMO

b. Severe systemic illness: respiratory rate ≥30, heart rate ≥125, SpO_2 ≤93% on room air at sea level or PaO_2/FiO_2<300 mm Hg; respiratory failure: needing high-flow oxygen, noninvasive ventilation, mechanical ventilation, ECMO; evidence of shock: SBP <90 mm Hg, DBP <60 mm Hg, requiring vasopressors.

Outcome 2: Hospitalization for COVID-19
Studies with Unvaccinated Comparator (n=1)

Outcome	Study/population	Events/Vaccine (n/N)	Events/Placebo (n/N)	Vaccine efficacy (95% CI)
COVID-19 needing medical intervention a	No evidence of prior infection, ≥14 d post vaccination	2/19,514	29/19,544	93% (71%, 98%)
COVID-19 needing medical intervention [a]	No evidence of prior infection, ≥28 d post vaccination	0/19,306	16/19,178	100%[c]
Severe COVID-19, protocol definition [b]	No evidence of prior infection, ≥14 d post vaccination	19/19,514	80/19,544	76% (58%, 88%)
Severe COVID-19, protocol definition [b]	No evidence of prior infection, ≥28 d post vaccination	8/19,306	48/19,178	84% (54%, 97%)

a. Medical intervention defined as hospitalization, ICU admission, mechanical ventilation, and extracorporeal membrane oxygenation (ECMO)

b. Severe COVID-19, defined consistent FDA guidance: clinical signs at rest indicative of severe systemic illness; respiratory failure; evidence of shock; significant acute renal, hepatic, or neurologic dysfunction; admission to an intensive care unit; or death

c. With a standard continuity correction of 0.5 applied, the estimated VE (95% CI) is 97% (50%, 100%)

CI: Confidence interval

Evidence Table: Hospitalization for COVID-19

Certainty assessment							№ of patients		Effect	Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Janssen COVID-19 vaccine	No vaccine	Relative (95% CI)		
Vaccine efficacy against hospitalization due to COVID-19											
1	RCT	Not serious a	Not serious	Serious b,c,d	Not serious	None	2/19,514 (0.0%)	29/19,544 (0.1%) e	**RR 0.07** (0.02 to 0.29)	**Type 2**	CRITICAL

a. Risk of bias related to blinding of participants and personnel was present. Although participants and study staff were blinded to intervention assignments, they may have inferred receipt of vaccine or placebo based on reactogenicity. This was deemed unlikely to overestimate efficacy or underestimate risk of serious adverse events, therefore the risk of bias was rated as not serious.
b. The RCT excluded persons with prior COVID-19 diagnosis, pregnant women or women planning to become pregnant within 3 months of vaccination, and persons who were immunocompromised due to conditions and/or treatments (participants with stable/well-controlled HIV infection were not excluded). The population included in the RCT may not represent all persons aged >=18 years.
c. The effects noted are from a per protocol analysis with outcomes assessed at least 14 days post vaccination, among persons who had no evidence of prior SARS-CoV-2 infection.
d. Serious concern for indirectness was noted due to the short duration of observation in the available body of evidence. Vaccine efficacy or adverse events observed at a median 2-month follow-up may differ from those observed with ongoing follow-up.
e. Includes 15 hospitalized cases in the placebo arm identified from the Serious Adverse Events form rather than from the Medical Resource Utilization form.

CI: Confidence interval; **RR:** Risk ratio

Outcome 3: All-cause Death
Studies with Unvaccinated Comparator (n=1)

- Janssen Phase III RCT (unpublished, data obtained from sponsor)

Outcome 3: All-cause Death
Studies with Unvaccinated Comparator (n=1)

Study/population	Events/Vaccine (n/N)[b]	Events/Placebo (n/N)	Relative Risk (95% confidence interval)
All-cause death, persons aged ≥18 years[a]	5/21,895	20/21,888	0.25 (0.09, 0.67)
COVID-19 related deaths, persons aged ≥18 years	0/21,895	7/21,888[c]	0.07 (0.00, 1.17)[d]

a. Deaths in study participants as of February 5, 2021; denominator is full analysis set.
b. Estimate and confidence interval were calculated based on number of participants.
c. One death due to COVID-19 occurred in a participant who was PCR-positive for SARS-CoV-2 at baseline.
d. Relative risk calculated using the standard continuity correction of 0.5.

Evidence Table: All-cause Death

Certainty assessment							№ of patients		Effect	Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Janssen COVID-19 vaccine	No vaccine	Relative (95% CI)		
Vaccine efficacy against death, all cause											
1	RCT	Not serious	Not serious	Serious a,b	Not serious	None	5/21,895 (0.0%)	20/21,888 (0.1%)	**RR 0.25** (0.09 to 0.67)	**Type 2**	IMPORT-ANT

a. Serious concern for indirectness was noted due to the short duration of observation in the available body of evidence. Vaccine efficacy or adverse events observed at a median 2-month follow-up may differ from those observed with ongoing follow-up.
b. The RCT excluded persons with prior COVID-19 diagnosis, pregnant women or women planning to become pregnant within 3 months of vaccination, and persons who were immunocompromised due to conditions and/or treatments (participants with stable/well-controlled HIV infection were not excluded). The population included in the RCT may not represent all persons aged >=18 years.

CI: Confidence interval; **RR:** Risk ratio

Outcome 4: SARS-CoV-2 seroconversion to a non-spike protein Studies with Unvaccinated Comparator (n=1)

- Janssen Phase III RCT (unpublished, data obtained from sponsor)
- Blood draws on trial days 1, 29, 71, then months 6, 12, 18, 24
- Asymptomatic seroconversion
  - Detect N-binding antibody (non-spike protein)
    - Distinguishes natural infection from vaccine-induced immunity
  - Excluded persons with COVID-19 symptoms or PCR-positive test prior to specimen collection
- Evaluated seroconversion at 2 time points:
  - Between days 1 and 29
  - Between days 29 and 71 (less data but more relevant)

Outcome 4: SARS-CoV-2 seroconversion to a non-spike protein Studies with Unvaccinated Comparator (n=1)

Study/population	Events/Vaccine (n/N)	Events/Placebo (n/N)	Vaccine Efficacy (95% confidence interval)
Asymptomatic seroconversion (Day 1 to 29)[a,b]	84/14,084	108/14,019	22.6% (-3.9%, 42.5%)
Asymptomatic seroconversion (Day 29 to 71)[a,b]	10/1346	37/1304	74.2% (47.1%, 88.6%)

a. Among participants in the serology risk set, which included persons with a non-S protein result available on Day 71 or day 29.
b. Asymptomatic SARS-CoV-2 infection is defined as (1) positive serology (non-S protein), and (2) no COVID-19 symptoms or PCR-positive test prior to specimen collection. Seroconversion to a non-spike protein can distinguish between natural infection and vaccine-induced immunity.

Evidence Table: SARS-CoV-2 seroconversion to a non-spike protein

Certainty assessment							№ of patients		Effect	Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Janssen COVID-19 vaccine	No vaccine	Relative (95% CI)		
Vaccine efficacy against death, all cause											
1	RCT	Not serious	Not serious	Very serious a,b	Not serious	None	10/1346 (1.3%)	37/1304 (3.8%)	**RR 0.26** (0.13 to 0.52)	**Type 3**	IMPORT-ANT

a. The RCT excluded persons with prior COVID-19 diagnosis, pregnant women or women planning to become pregnant within 3 months of vaccination, and persons who were immunocompromised due to conditions and/or treatments (participants with stable/well-controlled HIV infection were not excluded). The population included in the RCT may not represent all persons aged >=18 years.

b. Very serious concern for indirectness was noted. Efficacy against seroconversion based on day 71 serology may not be a direct measure of efficacy over a relevant period of time for an emergency use authorization. Additionally, serology data were only available for a subset of 7% of the per protocol population, likely not representing all ages, comorbidities, geographies, and exposures to circulating variants, raising additional concern for indirectness.

CI: Confidence interval; **RR:** Risk ratio

Harms

Outcome 6: Serious Adverse Events

Studies with Unvaccinated Comparator (n=3)

- Janssen phase III RCT (unpublished, data obtained from sponsor)
- Janssen phase II RCT (unpublished, data obtained from the sponsor)
- Janssen phase I/II RCT (Sadoff, 2021, additional data obtained from sponsor)

Janssen Phase II Randomized Controlled Trial

- Janssen phase II RCT (unpublished, data obtained from the sponsor)
- Population: healthy adults aged ≥18 to ≤55 years and ≥65 years, Germany, Spain, and the Netherlands
- Data evaluated:
  - 276 received 1 dose of 5×10^{10} viral particles of Ad26.COV2.S
  - 78 received 1 dose of placebo
- Primary outcomes: Safety
  - Local and systemic reactions: collected using memory aid 7 days following each dose
  - Adverse events: unsolicited AEs during 28 day follow up period
  - SAEs for duration of study period

Janssen Phase I/II Randomized Controlled Trial

- Janssen phase I/II RCT (Sadoff, 2021, additional data obtained from sponsor)
- Population: healthy adults aged ≥18 years, United States and Belgium
- Data evaluated:
  - 323 received 1 dose of 5×10^{10} viral particles of Ad26.COV2.S
    - 162 aged 18 to 55 years
    - 161 aged ≥65 years
  - 163 received 1 dose of placebo
- Primary outcomes: Safety
  - Local and systemic reactions: collected using memory aid 7 days following each dose
  - Adverse events: unsolicited AEs during 28 day follow up period
  - SAEs for duration of study period

Outcome 6: Serious Adverse Events (SAE)[a]
Studies with Unvaccinated Comparator (n=3)

Study/population[a]	Events/Vaccine (n/N)	% SAE Vaccine	Events/Placebo (n/N)	% SAE Placebo	Associated with vaccination
Janssen, phase III, unpublished[b]	83/21,895	0.4%	96/21,888	0.4%	3[c]
Janssen, phase II, unpublished[d]	0/276	0.0%	0/78	0.0%	
Sadoff 2021; Janssen, phase I/II, unpublished	1/323	0.3%	2/163	1.2%	

a. Excludes COVID-19 related SAEs
b. Proportion of participants who reported at least one SAE from dose 1 to primary analysis cutoff date (January 22, 2021).
c. 9 participants (7 in the vaccine and 2 in the placebo group) were deemed by blinded investigators to have serious adverse events to be related or possibly related to vaccination. Among the 7 vaccine participants, these included: pericarditis, facial paralysis, injection site pain, Guillain-Barre Syndrome, systemic reactogenicity, and hypersensitivity. Through further investigation by the FDA, only 3 were classified as related to vaccination: injection site pain, hypersensitivity, and systemic reactogenicity.
d. Proportion of participants who reported at least one SAE from dose 1 to primary analysis cutoff date (January 11, 2021).

Outcome 6: Serious Adverse Events (SAE): Summary of non-fatal vaccine-related SAEs from phase III trial (n=3)

Age/sex	Comorbidities	SAE	Onset post-vaccination	Duration (days)	Severity
42/M	No	Hypersensitivity	3	31[a]	Grade 3
30/M	No	Injection site pain	1	75[a]	Grade 3
35/M	Yes	Systemic reactogenicity[b]	2	3	Grade 3

a. Ongoing at the time of report
b. Hospitalized due to exacerbated generalized weakness, originally suspected for demyelinating disorder which was subsequently discarded

Evidence Table: Serious Adverse Events

Certainty assessment							№ of patients		Effect	Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Janssen COVID-19 vaccine	No vaccine	Relative (95% CI)		
Serious adverse events											
3 a	RCT	not serious b	not serious	Serious c,d	not serious	none	84/22494 (0.4%)	98/22129 (0.4%)	RR 0.85 (0.63 to 1.13)	**Type 2**	CRITICAL

a. Data were pooled from one Phase III trial, one Phase I/II trial, and one Phase II trial.
b. Risk of bias related to blinding of participants and personnel was present. Although participants and study staff were blinded to intervention assignments, they may have inferred receipt of vaccine or placebo based on reactogenicity. This was deemed unlikely to overestimate efficacy or underestimate risk of serious adverse events, therefore the risk of bias was rated as not serious.
c. The RCT excluded persons with prior COVID-19 diagnosis, pregnant women or women planning to become pregnant within 3 months of vaccination, and persons who were immunocompromised due to conditions and/or treatments (participants with stable/well-controlled HIV infection were not excluded). The population included in the RCT may not represent all persons aged >=18 years.
d. Serious concern for indirectness was noted due to the short duration of observation in the available body of evidence. Vaccine efficacy or adverse events observed at a median 2-month follow-up may differ from those observed with ongoing follow-up.

CI: Confidence interval; **RR:** Risk ratio

Outcome 7: Reactogenicity, Severe (Grade ≥3)[a]

Studies with Unvaccinated Comparator (n=3)

- Janssen phase III RCT (unpublished, data obtained from sponsor)
- Janssen phase II RCT (unpublished, data obtained from sponsor)
- Janssen phase I/II RCT (Sadoff, 2021, additional data obtained from sponsor)

[a]Grade 3: prevents daily routine activity. Grade 4: requires emergency room visit or hospitalization.

Outcome 7: Reactogenicity, Severe (Grade ≥3) Definitions

- All trials collected solicited events through electronic diaries for 7 days following vaccination
- Local reactions (pain at injection site, redness, swelling)
  - Grade 3: pain at injection site that prevents daily activity or use of narcotic pain reliever; redness > 10 cm; and swelling > 10 cm
  - Grade 4: hospitalization for severe pain at the injection site, necrosis (redness and swelling categories) or exfoliative dermatitis (redness category only).
- Systemic events (fever, nausea, headache, fatigue, muscle pain)
  - Grade 3: fever >38.9°C to 40.0°C , nausea, fatigue, headache, or muscle pain that prevents daily activity or use of narcotic pain reliever.
  - Grade 4: fever >40.0°C, nausea, fatigue, headache, or muscle pain that require hospitalization or prevents basic self care.

Outcome 7: Reactogenicity, Severe (Grade ≥3)[a,b]
Studies with and without unvaccinated comparator (n=3)

Study/population	Events/Vaccine (n/N)	% Vaccine	Events/Placebo (n/N)	% Placebo
Janssen, phase III, unpublished	75/3356	2.2%	25/3380	0.7%
Janssen, phase II, unpublished	8/276	2.9%	0/78	0%
Sadoff 2021; Janssen, phase I/II[c]	16/323	5.0%	0/163	0%

a. Grade 3: prevents daily routine activity or requires use of a narcotic pain reliever. Grade 4: requires hospitalization or prevents basic self care. There were no grade 4 adverse reactions reported.
b. Includes local and systemic events, grade ≥3.
c. Additional data provided by sponsor
Note: GRADE was conducted considering pooled phase I/II, II and III available data.

Evidence Table: Reactogenicity, Severe (Grade ≥3)

Certainty assessment							№ of patients		Effect	Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Janssen COVID-19 vaccine	No vaccine	Relative (95% CI)		
Reactogenicity, severe (grade ≥3)											
3 [a]	RCT	not serious	not serious	not serious [b,c]	not serious	none	99/3955 (2.5%)	25/3621 (0.7%)	RR 3.42 (2.20 to 5.31)	**Type 1**	IMPORT-ANT

a. Data were pooled from one Phase III trial, one Phase I/II trial, and one Phase II trial.
b. The RCT excluded persons with prior COVID-19 diagnosis, pregnant women or women planning to become pregnant within 3 months of vaccination, and persons who were immunocompromised due to conditions and/or treatments (participants with stable/well-controlled HIV infection were not excluded). The population included in the RCT may not represent all persons aged >=18 years.
c. Differences in demographic composition were noted between the full analysis set (FAS) and the safety subset used for evaluation of reactogenicity. Notably, compared to the FAS, the safety subset included a higher proportion of White race (83.4% vs. 58.7%), a higher proportion from Brazil (38.5% vs. 16.6%), and a lower proportion who were seropositive for SARS-CoV-2 at baseline (4.5% vs. 9.6%).

CI: Confidence interval; **RR:** Risk ratio

Summary of GRADE

Outcome	Importance	Design (# of studies)	Findings	Evidence type
Benefits				
Symptomatic lab-confirmed COVID-19	Critical	RCT (1)	Janssen COVID-19 vaccine is effective in preventing symptomatic COVID-19	**2**
Hospitalization due to COVID-19	Critical	RCT (1)	Janssen COVID-19 vaccine prevents COVID-19-resulting in hospitalization	**2**
All-cause Death	Important	RCT (1)	Janssen COVID-19 vaccine is associated with a lower risk of both all-cause death and death due to COVID-19	**2**
SARS-CoV-2 seroconversion	Important	RCT (1)	Data from day 71 serology indicates that Janssen COVID-19 vaccine prevents seroconversion during the available follow-up period; data support an effect on prevention of asymptomatic infection	**3**
Asymptomatic SARS-CoV-2 infection	Important	No studies	No systematically collected PCR data are available to develop an estimate for this outcome	**ND**
Harms				
Serious adverse events	Critical	RCT (3)	SAEs were balanced between vaccine and placebo arms. 3 participants had SAEs judged by FDA to be related to study vaccine	**2**
Reactogenicity	Important	RCT (3)	Severe reactions were more common in vaccinated; any grade ≥3 reaction was reported by 2.5% of vaccinated vs. 0.7% of placebo	**1**

Evidence type: 1=high; 2=moderate; 3=low; 4=very low; ND, no data

Conclusion – GRADE for Janssen COVID-19 vaccine

- Phase III RCT conducted on three continents during a time of high COVID-19 incidence while viral variants were emerging.
- Vaccine efficacy estimates: **66%** for symptomatic laboratory-confirmed COVID-19, **93%** for hospitalization due to COVID-19, **75%** for all-cause death, and **74%** for asymptomatic seroconversion.
- No deaths due to COVID-19 were identified among vaccine recipients, and 7 deaths due to COVID-19 were identified among placebo recipients.
- No serious safety concerns identified; balanced reports of serious adverse events between arms (0.4% each).
- Grade ≥3 local or systemic reactions more common among vaccine than placebo recipients, and were reported by <3% of vaccinated subjects.
- Certainty for all **critical** benefits and harms was **type 2** (moderate).

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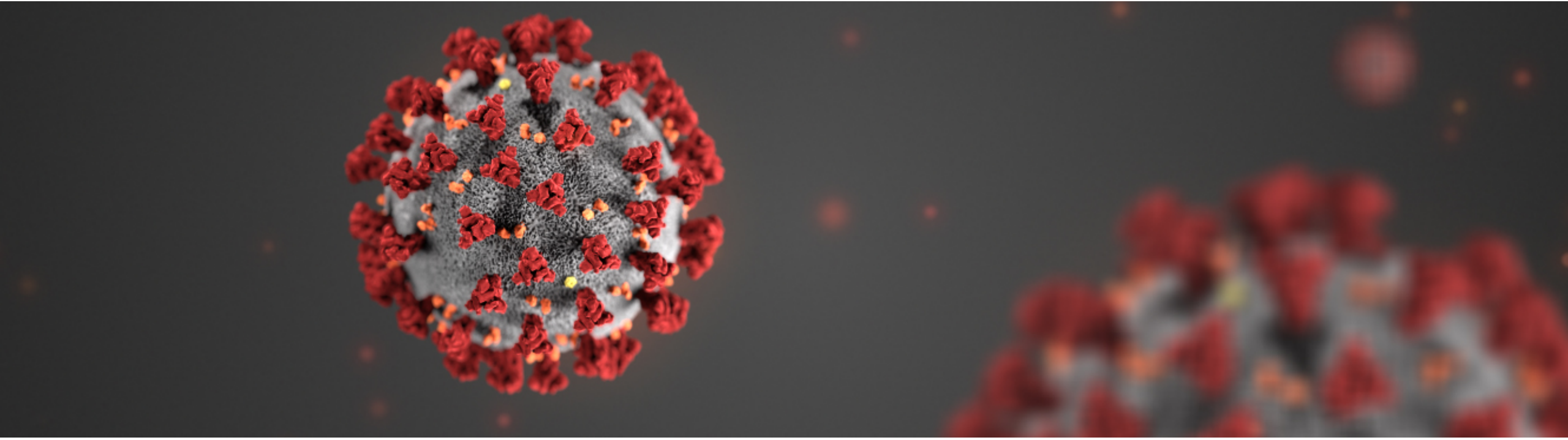


For more information, contact CDC
1-800-CDC-INFO (232-4636)
TTY: 1-888-232-6348 www.cdc.gov

Thank you

The findings and conclusions in this report are those of the authors and do not necessarily represent the official position of the Centers for Disease Control and Prevention.

Comparability of GRADE across trials: indirectness

- For the mRNA vaccines, we were concerned about indirectness for several outcomes due to the median 2-month follow-up
- Certainty in estimates for hospitalization, deaths, and serious adverse events were graded down 1 level for indirectness
- For efficacy against the primary endpoint of symptomatic COVID-19, we did not grade down for indirectness in consideration of the very strong and precise estimate
  - Was not plausible that the efficacy would dip lower than 50% during time period of EUA
  - This exception is not being made for Janssen with 66% overall efficacy

Measures used in COVID-19 vaccine trials: reactogenicity

Solicited symptom	Janssen	Moderna	Pfizer
Local			
Redness	X	X	X
Swelling	X	X	X
Pain, injection site	X	X	X
Axillary swelling/tenderness		X	
Systemic			
Fever	X	X	X
Fatigue	X	X	X
Headache	X	X	X
Chills		X	X
Nausea	X	X	X
Diarrhea			X
Myalgia	X	X	X
Arthralgia		X	X

Measures used in COVID-19 vaccine trials: symptoms required for symptomatic COVID-19

Janssen ("moderate to severe/critical")	Moderna	Pfizer
>=1 of:	>=1 of:	>=1 of:
Respiratory >=20		
Abnormal pulse ox but >93%		
Clinical/Radiological pneumonia	Clinical/Radiological pneumonia	
DVT		
Shortness of breath/difficulty breathing	Shortness of breath	Shortness of breath
	Cough	
OR	**OR**	
>=2 of:	>=2 of:	
Fever >=38C	Fever >=38C	Fever >=38C
Heart rate >=90		
Shaking chills	Chills	Chills
Sore throat	Sore throat	Sore throat
Cough		Cough
Malaise		
Headache	Headache	
Myalgia	Myalgia	Muscle pain
GI sx (N/V/D/abdominal pain)		Diarrhea or vomiting
Olfactory/taste disorder	Olfactory/taste disorder	Loss of taste or smell
Red/bruised toes		

Measures used in COVID-19 vaccine trials: expanded symptom list (more sensitive case definitions)

Janssen	Moderna	Pfizer
Mild COVID-19	**Expanded CDC symptom list**	**Expanded CDC symptom list**
At least 1 symptom from mod/severe list* or:	At least 1 from primary symptom list or :	At least 1 of above or expanded CDC symptom list:
Chest congestion	Fatigue	Fatigue
Runny nose	Nasal congestion	Nasal congestion/runny nose
Wheezing	Nausea/vomiting	
Skin rash	Diarrhea	
Eye irritation/discharge		Headache
"FDA harmonized list"		Nausea
fever or chills		
cough		
shortness of breath/difficulty breathing		
fatigue		
muscle or body aches		
headache		
loss of taste or smell		
sore throat		
congestion		
runny nose		
nausea or vomiting		
diarrhea		

*May exclude elevated heart rate

Note: Janssen's "FDA harmonized list" matches Moderna and Pfizer "Expanded CDC symptom list"

Measures used in COVID-19 vaccine trials: hospitalization due to COVID-19

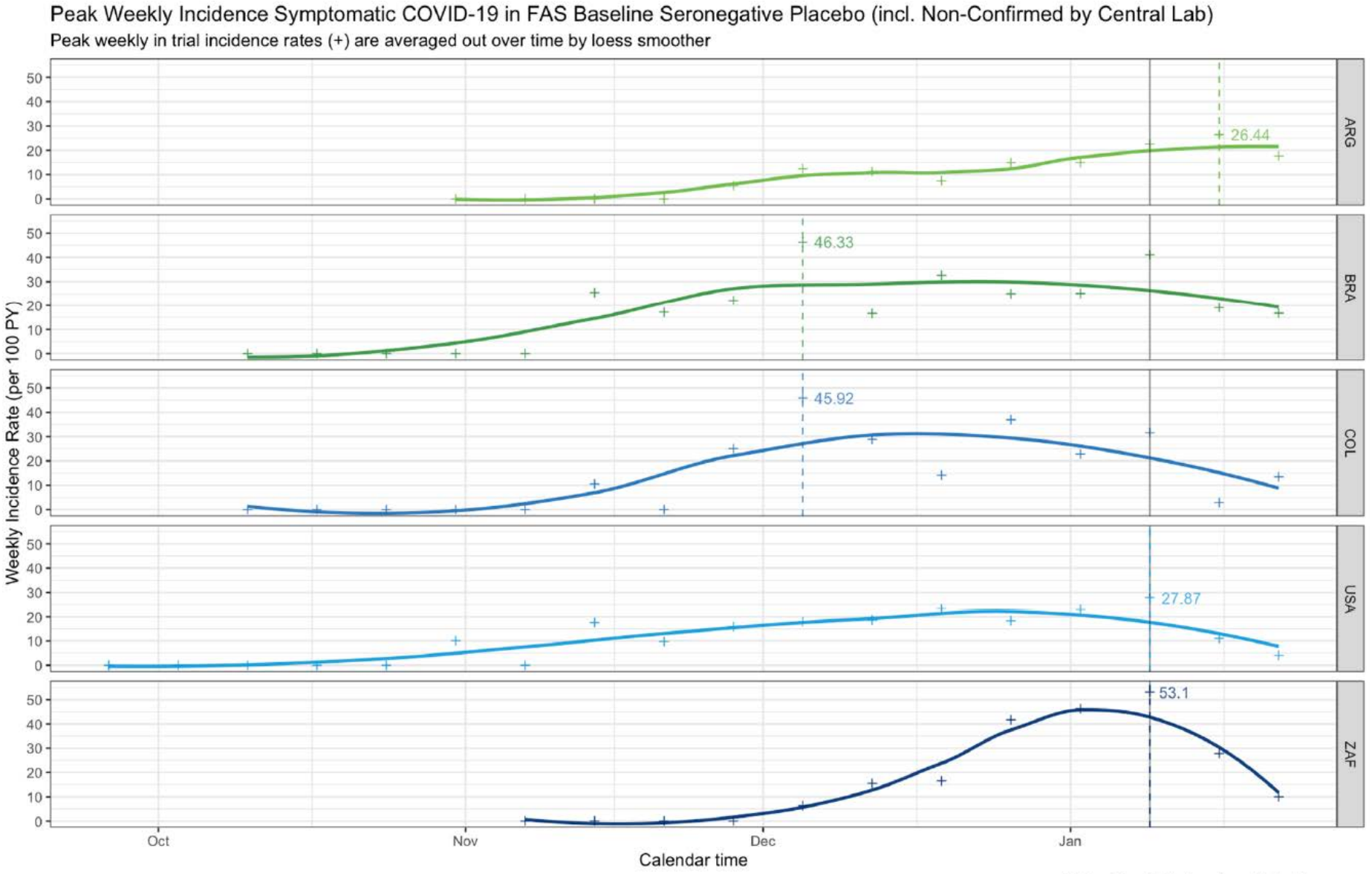
Janssen	Moderna	Pfizer
Hospitalization, ICU admission, mechanical ventilation, or death	Hospitalized subset of cases meeting FDA definition of severe COVID-19	Hospitalization, admission to the ICU, intubation or mechanical ventilation, or death in a participant who met the secondary case definition using expanded CDC symptom list*

*some did not meet FDA definition of severe COVID-19

Measures used in COVID-19 vaccine trials: severe COVID-19 (FDA harmonized)

Janssen	Moderna	Pfizer
"Severe/Critical"	"Severe COVID-19"	"Severe COVID-19"
1 of the following:	any of the following:	at least 1 of the following:
Resp rate >=30 bpm	Resp rate >=30 bpm	Resp rate >=30 bpm
Heart rate >=125 bpm	Heart rate >=125 bpm	Heart rate >=125 bpm
SpO2 93%	SpO2 93%	SpO2 93%
PaO2/FiOs <300 mmHg	PaO2/FiOs <300 mmHg	PaO2/FiOs <300 mmHg
Respiratory failure (needing high-flow O2, non-invasive ventilation, mechanical ventilation, or ECMCO)	Respiratory failure or ARDS (needing high-flow O2, non-invasive ventilation, mechanical ventilation, or ECMO)	Respiratory failure (needing high-flow O2, non-invasive ventilation, mechanical ventilation, or ECMCO)
Shock (SBP <90, DBP <60, or requiring vasopressors)	Shock (SBP <90, DBP <60, or requiring vasopressors)	Shock (SBP <90, DBP <60, or requiring vasopressors)
Significant acute renal, hepatic, or neurologic dysfunction	Significant acute renal, hepatic, or neurologic dysfunction	Significant acute renal, hepatic, or neurologic dysfunction
Admission to ICU	Admission to ICU	Admission to ICU
Death	Death	Death

COVID-19 incidence in the Placebo Group, Seronegative Participants, Phase III trial, FAS



The observed decrease in COVID-19 incidence depicted above, after 7 January 2021, may be partially due to operational reasons: operational time from sampling to PCR confirmation in the central laboratory was estimated to be on average 14 days, with a longer confirmation time in some countries in the Latin America region and South Africa. Therefore some cases after the database cut-off may be pending.

Source: VRBPAC briefing document, Figure 10

Follow-up time, by age and comorbidities

Table 3. Participant Disposition by Age Group and Comorbidities, Full Analysis Set, Study 3001

Participant Group Follow-up	Ad26.COV2.S N=21895	Placebo N=21888	All Participants N=43783
18-59 overall	14564	14547	29111
Participants with at least 8 weeks follow-up	62.8%	63.1%	63.0%
Median follow-up after vaccination in days	61.0	61.0	61.0
18-59, no comorbidities	9332	9371	18703
Participants with at least 8 weeks follow-up	70.0%	69.9%	70.0%
Median follow-up after vaccination in days	64.0	64.0	64.0
18-59, with comorbidities	5232	5176	10408
Participants with at least 8 weeks follow-up	49.9%	50.8%	50.4%
Median follow-up after vaccination in days	56.0	57.0	57.0
≥60 years overall	7331	7341	14672
Participants with at least 8 weeks follow-up	38.2%	37.8%	38.0%
Median follow-up after vaccination in 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 in 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 in days	50.0	50.0	50.0

Source:Sponsor table TSIDS08

Source: FDA briefing document, page 18