Webinar del ciclo “Innovaciones terapéuticas
“Prevención y terapéutica de la infección por COVID-19”

Vacunas frente a COVID-19

Prof. Angel Gil.
Académico correspondiente de la RANME
Catedrático de Medicina Preventiva y Salud Pública
Director del Dpto. de Especialidades Médicas y Salud Pública
Universidad Rey Juan Carlos.

Cómo funcionan las vacunas frente a la COVID-19

VACUNAS DE VIRUS INACTIVADO

Virus completo inactivado

Ejemplo: poliomielitis

VACUNAS BASADAS EN PROTEÍNAS

Fragmentos de proteínas y otros componentes del virus que generan respuesta inmune

Ejemplo: hepatitis B, hepatitis A, gripe

VACUNAS CON VECTORES VÍRICOS

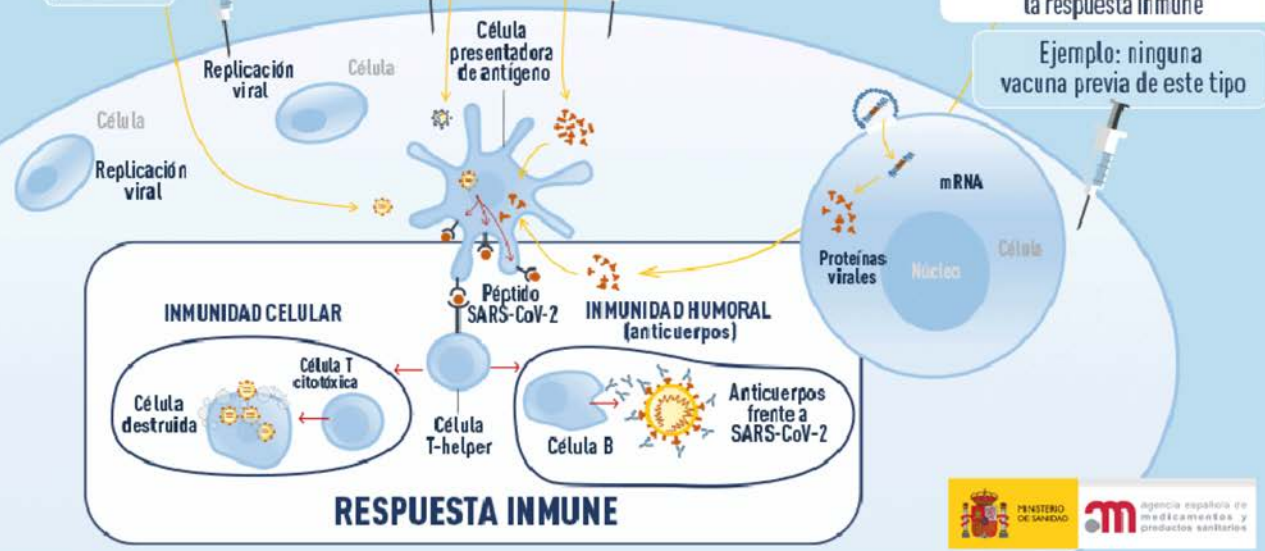
Utilizan virus modificados genéticamente, para que no causen enfermedad, que transportan información para la producción de proteínas que desencadenan la respuesta inmune

Ejemplo: ébola, circovirus porcino recombinante (vacuna veterinaria)

VACUNAS DE ARN MENSAJERO (mRNA)

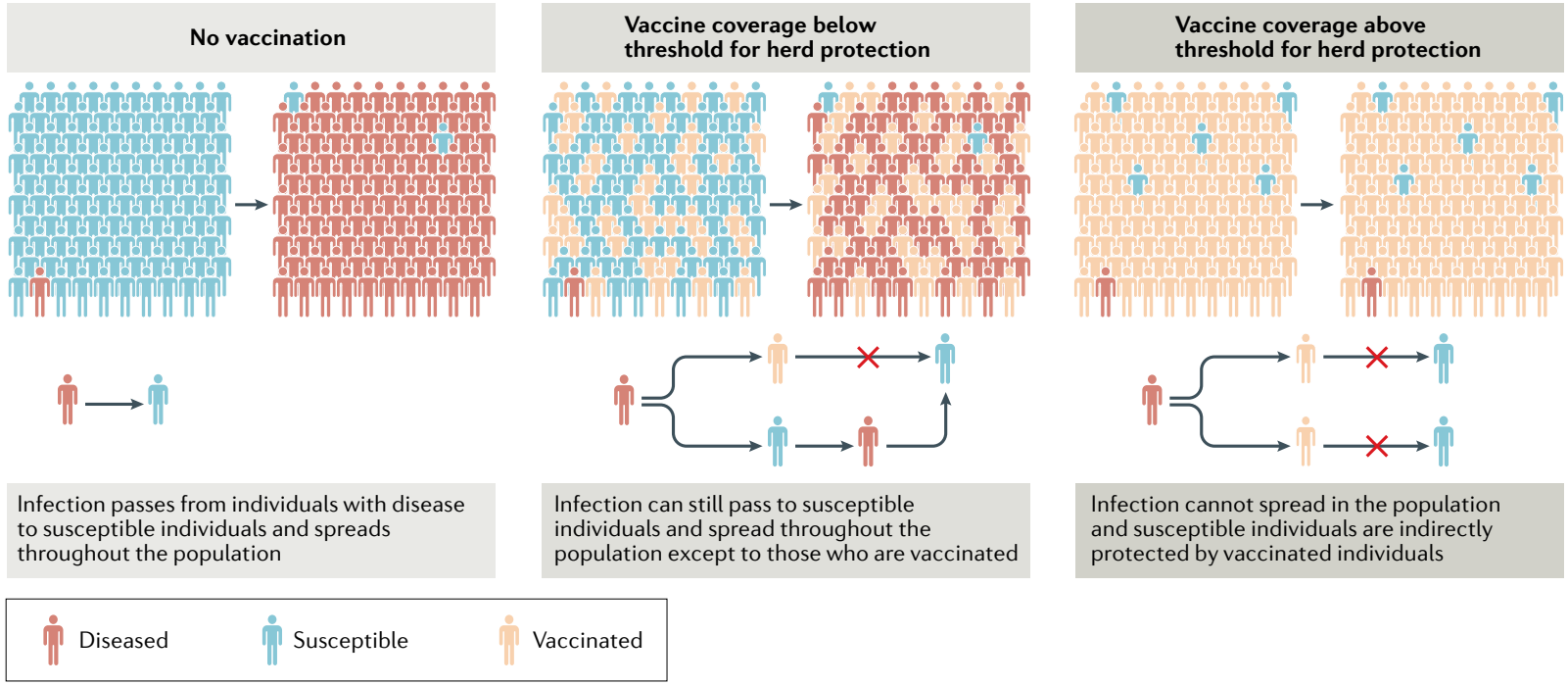
Utilizan ARN diseñado por ingeniería genética que contiene las instruccionespara la producción de proteínas que desencadenan la respuesta inmune

Ejemplo: ninguna vacuna previa de este tipo



MINISTERIO DE SANIDAD

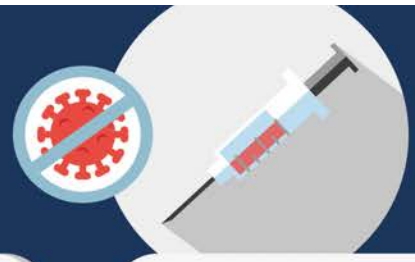
agencia española de medicamentos y productos sanitarios



La inmunidad colectiva es una característica importante de la producción inducida por vacunas.

Pollard AJ, et al. A guide to vaccinology: from basic principles to new developments. Nature Reviews Immunology. 2021;21:83-100.

Pasos para la evaluación y autorización de las vacunas frente a la COVID-19



Solicitud de autorización de comercialización

Evaluación de la EMA

Evaluación de la Comisión Europea y autorizacion

Comercialización en toda la Unión Europea

#VacunasConGarantías

MINISTERIO DE SANIDAD

agencia española de medicamentos y productos sanitarios

Estrategia de vacunación

1. Establecer orden de prioridad en función de la vulnerabilidad y necesidad de reforzar la seguridad y protección.
2. Asegurar la logística para alcanzar a toda la población.
3. Priorizar el seguimiento, evolución e impacto de la vacunación.
4. Estrategia de comunicación interna (profesionales) y externa (población en general) para lograr vencer la resistencia a la vacunación.

El objetivo general de la Estrategia de Vacunación COVID-19 en España es reducir la morbilidad y la mortalidad causada por esta enfermedad mediante la vacunación frente a COVID-19 en un contexto de disponibilidad progresiva de dosis, y protegiendo a los grupos más vulnerables.

Ministerio de Sanidad. Estrategia de vacunación COVID-19 en España. Líneas maestras. Actualizado a 23 de noviembre de 2020.

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

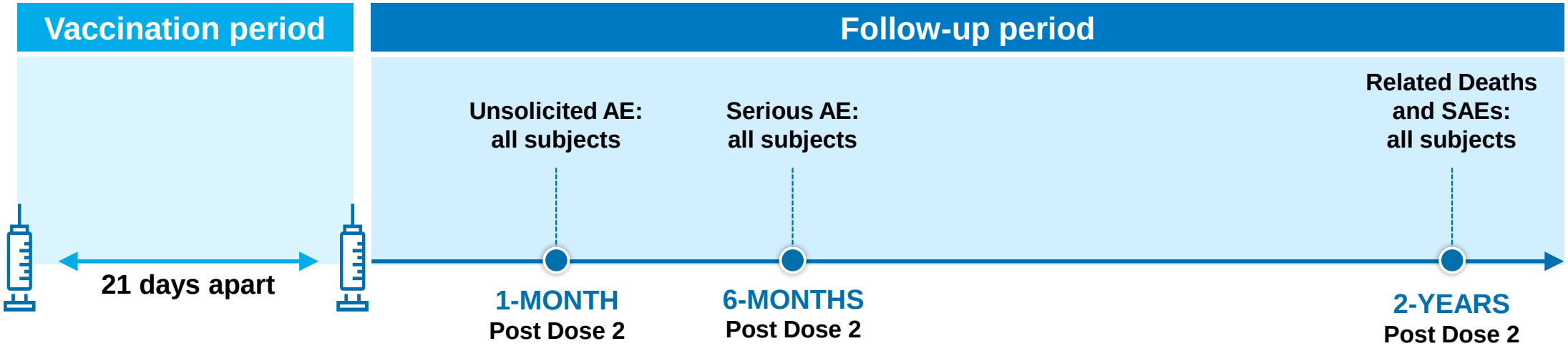
Safety and Efficacy of the BNT162b2 mRNA Covid-19 Vaccine

Fernando P. Polack, M.D., Stephen J. Thomas, M.D., Nicholas Kitchin, M.D., Judith Absalon, M.D., Alejandra Gurtman, M.D., Stephen Lockhart, D.M., John L. Perez, M.D., Gonzalo Pérez Marc, M.D., Edson D. Moreira, M.D., Cristiano Zerbini, M.D., Ruth Bailey, B.Sc., Kena A. Swanson, Ph.D., Satrajit Roychoudhury, Ph.D., Kenneth Koury, Ph.D., Ping Li, Ph.D., Warren V. Kalina, Ph.D., David Cooper, Ph.D., Robert W. Frenck, Jr., M.D., Laura L. Hammitt, M.D., Özlem Türeci, M.D., Haylene Nell, M.D., Axel Schaefer, M.D., Serhat Ünal, M.D., Dina B. Tresnan, D.V.M., Ph.D., Susan Mather, M.D., Philip R. Dormitzer, M.D., Ph.D., Uğur Şahin, M.D., Kathrin U. Jansen, Ph.D., and William C. Gruber, M.D., for the C4591001 Clinical Trial Group*

BNT162b2 Vaccine Candidate Against COVID-19

William Gruber, MD, FAAP, FIDSA
Senior Vice President Vaccine Clinical R&D
Pfizer

Phase 2/3 Safety – Study Start 27 July, 2020



Active surveillance begins after 1st dose
Potential COVID-19 symptoms **TRIGGER** telehealth or in-person visit and nasal swab

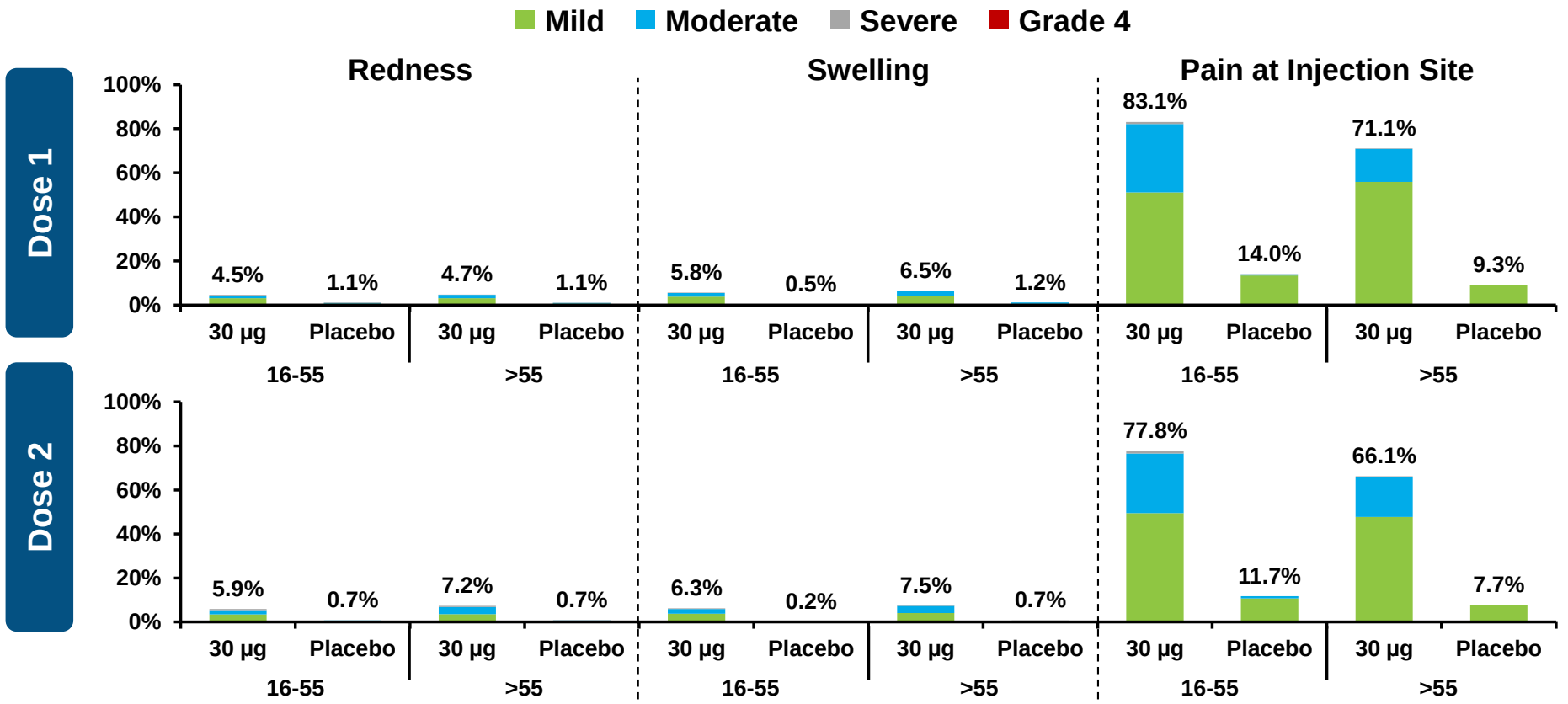
7 DAYS

7 DAYS

Reactogenicity:
at least 6000 subjects, at least 500 in each country

William Gruber, MD, FAAP, FIDSA
Senior Vice President Vaccine Clinical R&D
Pfizer

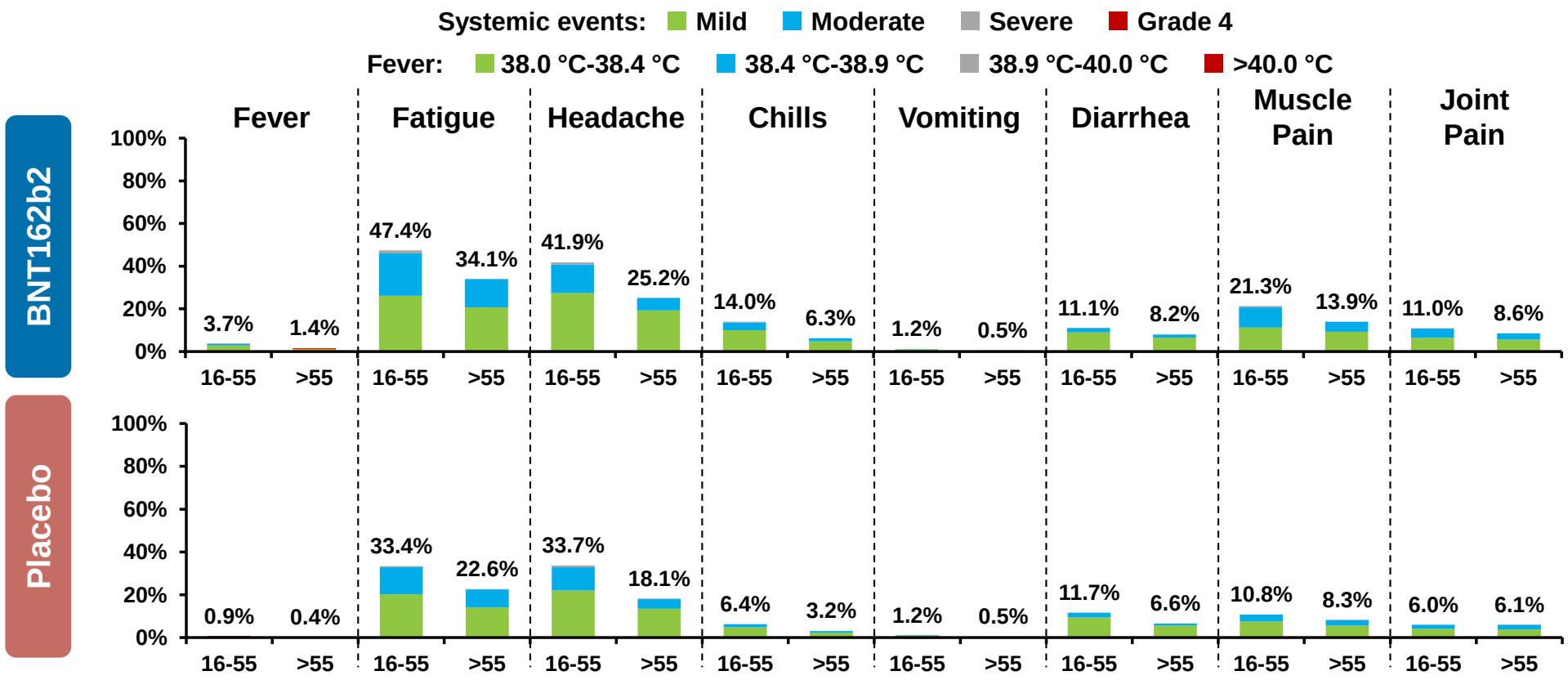
eDiary: Local Events Within 7 Days From Dose 1 and 2 in 16-55 and >55 Year Olds (N=8,183)



Redness and sweeling severity definition: Mild= >2-5cm, Moderate= >5-10 cm; Severe= >10 cm; Grade 4= necrosis
Pain at injection site severity definition: Mild=no interference; Moderate=some interference; Severe=prevents daily activity; Grade 4=ER visit or hospitalization
Dose 1: 16-55 yrs N=4589; >55 yrs N=3594 Dose 2: 16-55 yrs N=4201 >55 yrs N=3306

William Gruber, MD, FAAP, FIDSA
Senior Vice President Vaccine Clinical R&D
Pfizer

eDiary: Systemic Events Within 7 Days From Dose 1 in 16-55 and >55 Year Olds (N=8,183)



Fatigue, headache, chills, muscle pain, joint pain severity definition: Mild=no interference; Moderate=some interference; Severe=prevents daily activity; Grade 4=ER visit or hospitalization
Vomiting severity definition: Mild=1-2 time in 24h; Moderate=>2times in 24h; Severe=Requires IV hydration; Grade 4=ER visit or hospitalization
Diarrhea severity definition: Mild=2-3 times in 24h; Moderate=4-5 times in 24h; Severe=6 or more times in 24h; Grade 4=ER visit or hospitalization
Dose 1: 18-55 yrs N=3529; 56-85 yrs N=3027 Dose 2: 18-55 yrs N=3345; 56-85 yrs N=2899

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First COVID-19 Occurrence From 7 Days After Dose 2

Phase 2/3 Efficacy – Final Analysis

Subjects WITHOUT Evidence of Infection Prior to 7 days after Dose 2

	BNT162b2 (30 µg) N=18,198		Placebo N=18,325				
Efficacy Endpoint	n	Surveillance Time (n)	n	Surveillance Time (n)	VE (%)	(95% CI)	Pr (VE >30%)
First COVID-19 occurrence ≥7 days after Dose 2	8	2.214 (17,411)	162	2.222 (17,511)	95.0	(90.3, 97.6)	>0.9999

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Senior Vice President Vaccine Clinical R&D
Pfizer

First COVID-19 Occurrence From 7 Days After Dose 2

Phase 2/3 Efficacy – Final Analysis: Risk Factor Subgroups

Subjects WITHOUT Evidence of Infection Prior to 7 days after Dose 2

		BNT162b2 N=18,198 n	Placebo N=18,325 n	VE (%)	(95% CI)
Overall		8	162	95.0	(90.0, 97.9)
At risk[1]	Yes	4	86	95.3	(87.7, 98.8)
	No	4	76	94.7	(85.9, 98.6)
Age group at risk	16-64 and not at risk	4	69	94.2	(84.4, 98.5)
	16-64 and at risk	3	74	95.9	(87.6, 99.2)
	≥65 and not at risk	0	7	100.0	(29.0, 100.0)
	≥65 and at risk	1	12	91.7	(44.2, 99.8)
Obese[2]	Yes	3	67	95.4	(86.0, 99.1)
	No	5	95	94.8	(87.4, 98.3)
Age group and obese	16-64 and not obese	4	83	95.2	(87.3, 98.7)
	16-64 and obese	3	60	94.9	(84.4, 99.0)
	≥65 and not at obese	1	12	91.8	(44.5, 99.8)
	≥65 and obese	0	7	100.0	(27.1, 100.0)

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Senior Vice President Vaccine Clinical R&D
Pfizer

First COVID-19 Occurrence From 7 Days After Dose 2 by Comorbidity Status – Evaluable Efficacy (7 Days) Population

Subjects WITHOUT Evidence of Infection Prior to 7 days after Dose 2

	BNT162b2 (30 µg) N=18,198		Placebo N=18,325			
	n	Surveillance Time (n)	n	Surveillance Time (n)	VE (%)	(95% CI)
Overall	8	2.214 (17,411)	162	2.222 (17,511)	95.0	(90.0, 97.9)
Comorbidity						
No comorbidity	4		76		94.7	(85.9, 98.6)
Any comorbidity	4		86		95.3	(87.7, 98.8)
Any malignancy	1		4		75.7	(-145.8, 99.5)
Cardiovascular	0		5		100.0	(-0.8, 100.0)
Chronic pulmonary disease	1		14		93.0	(54.1, 99.8)
Diabetes	1		19		94.7	(66.8, 99.9)
Obese (≥30.0 kg/m^2)	3		67		95.4	(86.0, 99.1)
Hypertension	2		44		95.4	(82.6, 99.5)
Diabetes (including gestational diabetes)	1		20		95.0	(68.7, 99.9)

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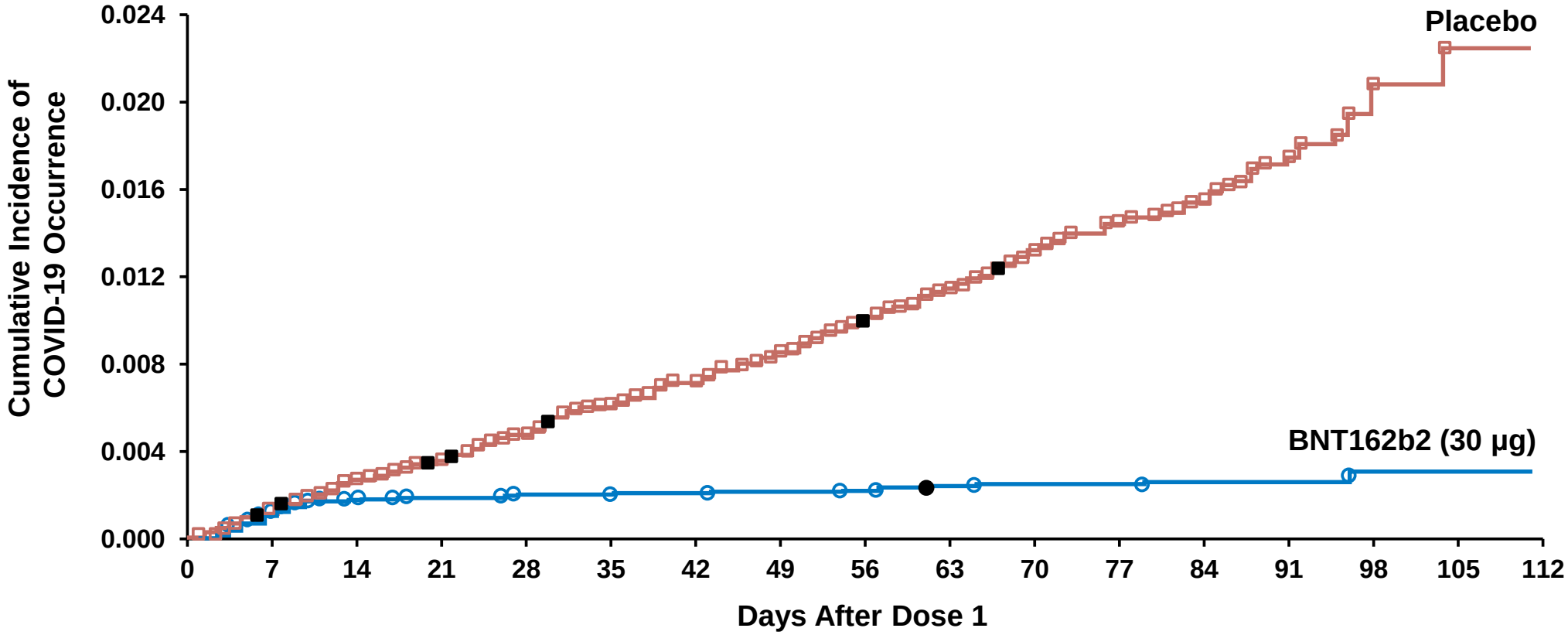
Cumulative Incidence of COVID-19 After Dose 1



Rapid communication

Impact of age, ethnicity, sex and prior infection status on immunogenicity following a single dose of the BNT162b2 mRNA COVID-19 vaccine: real-world evidence from healthcare workers, Israel, December 2020 to January 2021

Kamal Abu Jabal[1,2,3] , Hila Ben-Amram[1,2] , Karine Beiruti[1] , Yunis Batheesh[1] , Christian Sussan[1] , Salman Zarka[1,3] , Michael Edelstein[1,3]
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Citation style for this article:
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Article submitted on 27 Jan 2021 / accepted on 10 Feb 2021 / published on 11 Feb 2021

Table

Geometric mean concentration of anti-SARS-CoV-2 spike IgG antibodies among healthcare workers who responded to the BNT162b2 mRNA COVID-19 vaccine, 21 days post first dose, Israel, December 2020 to January 2021

Characteristics		Individuals in the sample (n=514)	Vaccine responders (n=475)	IgG geometric mean concentration among vaccine responders (AU/mL)[a]	95% CI
All participants with a detectable antibody response		475	475	68.6	64–73.6
Age (years)	<30	11	10	100.4	51.8–194.5
	30–39	161	156	84.2	74.3–95.3
	40–49	146	139	68.2	60.2–77.4
	50–59	101	92	61.5	52.6–71.9
	60+	95	78	49.8	42.6–58.1
Ethnicity	Jewish	322	291	62.4	58.2–66.9
	Arab	114	109	69.9	59.6–82
	Druze	58	57	73.4	58.6–92
	Circassian	2	1	–[b]	–[b]
	Missing	18	17	NA	NA
Sex	Male	193	177	64.6	60.2–69.2
	Female	321	298	75.9	65.6–87.9
Prior disease status[a]	All patients with evidence of prior COVID-19 infection	17	17	573.6	289–1,138.7
	IgG positive at baseline	6	6	747.3	140–3,978.3
	IgG negative with prior positive PCR test	11	11	496.5	217.4–1,134
	IgG negative at baseline and no prior positive PCR test	369	347	61.5	58–65.1
	Unknown (no PCR test and not tested at baseline)	128	111	64.3	60.5–68.3

CI: confidence interval; COVID-19: coronavirus disease; HCW: healthcare workers; SARS-CoV-2: severe acute respiratory coronavirus 2.

[a] Geometric mean concentration calculation includes all HCWs who responded to the vaccine. Those with no detectable antibodies post-vaccination are excluded.

[b] The GMC for Circassian HCWs is not given as only one HCW in this category responded to the vaccine.

The average age of people seriously ill with Covid in Israel's hospitals is falling dramatically as vaccines take effect

Average age of people hospitalised with severe cases of Covid-19

Source: data.gov.il

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Efficacy and Safety of the mRNA-1273 SARS-CoV-2 Vaccine

L.R. Baden, H.M. El Sahly, B. Essink, K. Kotloff, S. Frey, R. Novak, D. Diemert, S.A. Spector, N. Rouphael, C.B. Creech, J. McGettigan, S. Khetan, N. Segall, J. Solis, A. Brosz, C. Fierro, H. Schwartz, K. Neuzil, L. Corey, P. Gilbert, H. Janes, D. Follmann, M. Marovich, J. Mascola, L. Polakowski, J. Ledgerwood, B.S. Graham, H. Bennett, R. Pajon, C. Knightly, B. Leav, W. Deng, H. Zhou, S. Han, M. Ivarsson, J. Miller, and T. Zaks, for the COVE Study Group*

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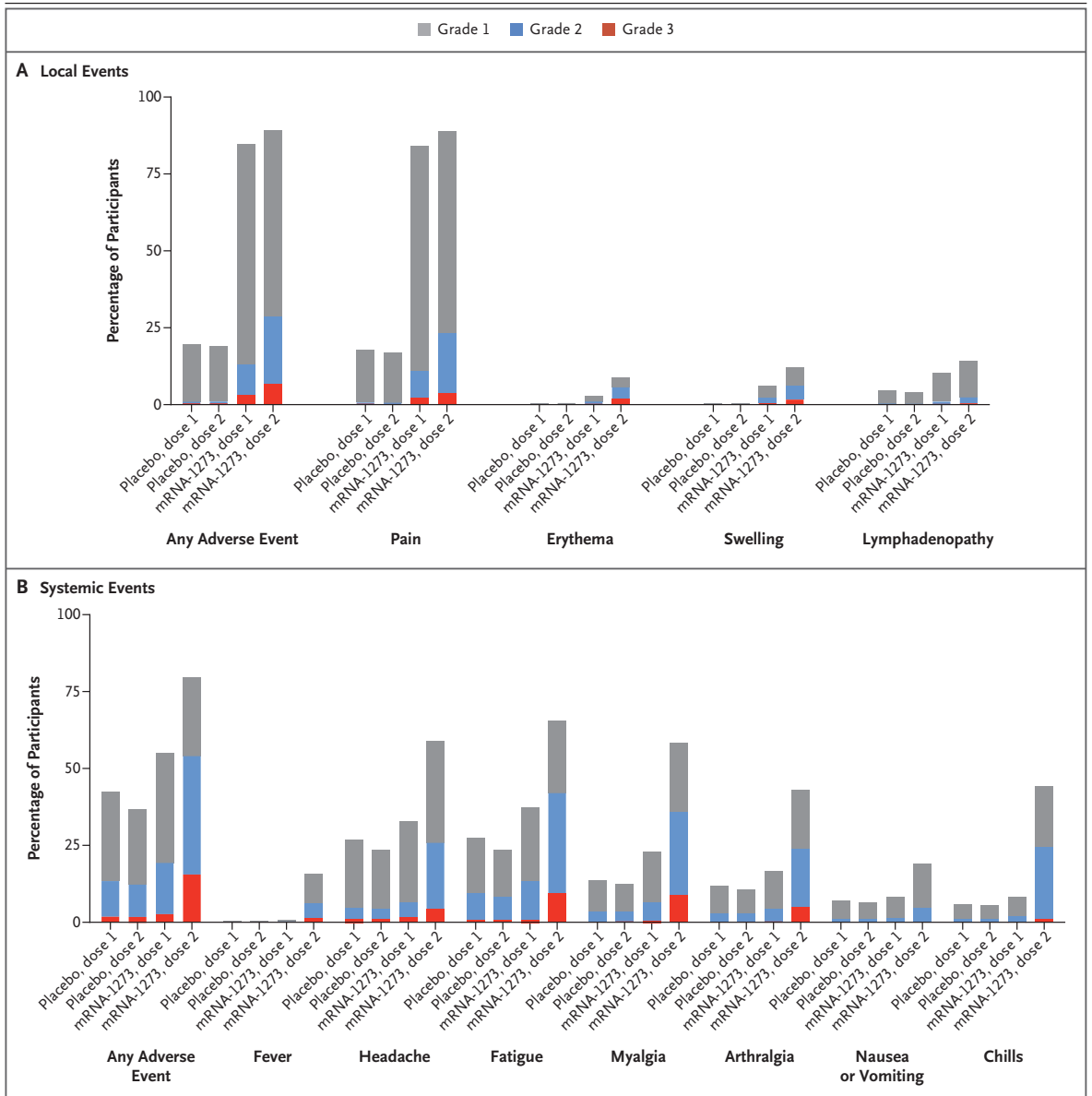

Figure 2. Solicited Local and Systemic Adverse Events.

Shown is the percentage of participants who had a solicited local or systemic adverse event within 7 days after injection 1 or injection 2 of either the placebo or the mRNA-1273 vaccine.

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Subgroup	Placebo (N=14,073)	mRNA-1273 (N=14,134)	Vaccine Efficacy (95% CI)
	no. of events/total no.		
All patients	185/14,073	11/14,134	94.1 (89.3–96.8)
Age			
≥18 to <65 yr	156/10,521	7/10,551	95.6 (90.6–97.9)
≥65 yr	29/3552	4/3583	86.4 (61.4–95.2)
Age, risk for severe Covid-19			
18 to <65 yr, not at risk	121/8403	5/8396	95.9 (90.0–98.3)
18 to <65 yr, at risk	35/2118	2/2155	94.4 (76.9–98.7)
≥65 yr	29/3552	4/3583	86.4 (61.4–95.2)
Sex			
Male	87/7462	4/7366	95.4 (87.4–98.3)
Female	98/6611	7/6768	93.1 (85.2–96.8)
At risk for severe Covid-19			
Yes	43/3167	4/3206	90.9 (74.7–96.7)
No	142/10,906	7/10,928	95.1 (89.6–97.7)
Race and ethnic group			
White	144/8916	10/9023	93.2 (87.1–96.4)
Communities of color	41/5132	1/5088	97.5 (82.2–99.7)

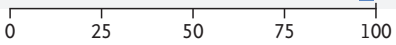

Figure 4. Vaccine Efficacy of mRNA-1273 to Prevent Covid-19 in Subgroups.

The efficacy of the RNA-1273 vaccine in preventing Covid-19 in various subgroups in the per-protocol population was based on adjudicated assessments starting 14 days after the second injection. Vaccine efficacy, defined as 1 minus the hazard ratio (mRNA-1273 vs. placebo), and 95% confidence intervals were estimated with the use of a stratified Cox proportional hazards model, with Efron's method of tie handling and with the treatment group as a covariate, adjusting for stratification factor if applicable. Race and ethnic group categories shown are White (non-Hispanic) and communities of color (all others, including those whose race and ethnicity were both reported as unknown, were not reported, or were both missing at screening). Data for communities of color were pooled owing to limited numbers of participants in each racial or ethnic group, to ensure that the subpopulations would be large enough for meaningful analyses.

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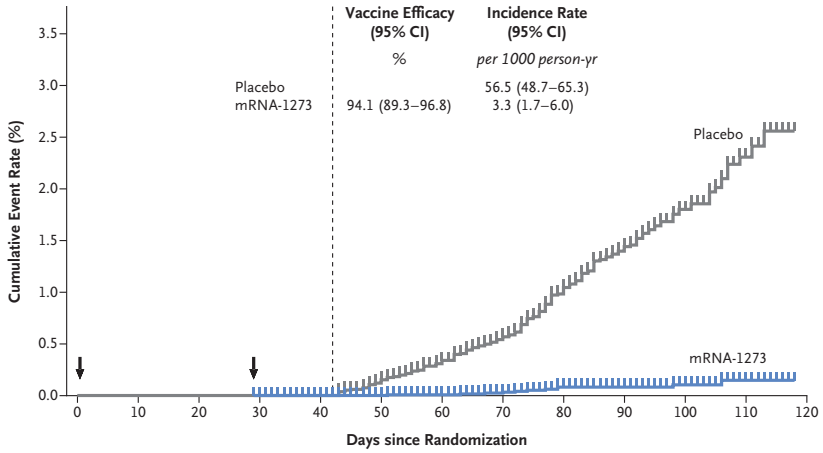
The NEW ENGLAND JOURNAL of MEDICINE

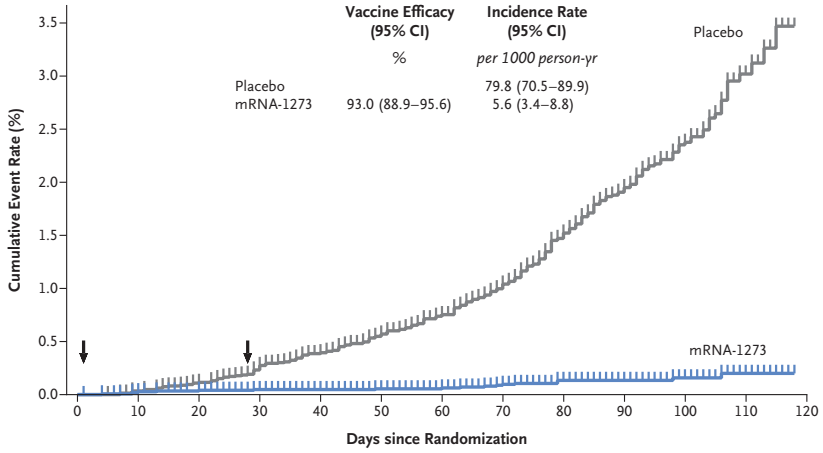
A Per-Protocol Analysis



No. at Risk

Placebo	14,073	14,073	14,073	14,072	13,416	12,992	12,361	11,147	9474	6563	3971	1172	0
mRNA-1273	14,134	14,134	14,134	14,133	13,483	13,073	12,508	11,315	9684	6721	4094	1209	0

B Modified Intention-to-Treat Analysis



No. at Risk

Placebo	14,598	14,590	14,567	14,515	13,806	12,352	12,694	11,450	9736	6729	4067	1200	0
mRNA-1273	14,550	14,543	14,532	14,504	13,825	13,398	12,791	11,573	9911	6871	4179	1238	0

Covid-19 Onset	Placebo (N=14,598)	mRNA-1273 (N=14,550)
Randomization to 14 days after dose 1	11	5
14 Days after dose 1 to dose 2	35	2
Dose 2 to 14 days after dose 2	19	0
Starting 14 days after dose 2	204	12
Total (any time after randomization)	269	19

EMA recommends COVID-19 Vaccine AstraZeneca for authorisation in the EU

News 29/01/2021

Update: COVID-19 Vaccine AstraZeneca is now authorised across the EU. This follows the granting of a conditional marketing authorisation by the European Commission on 29 January 2021.

EMA has recommended granting a conditional marketing authorisation for COVID-19 Vaccine AstraZeneca to prevent coronavirus disease 2019 (COVID-19) in people from 18 years of age. This is the third COVID-19 vaccine that EMA has recommended for authorisation.

EMA's human medicines committee (CHMP) has thoroughly assessed the data on the quality, safety and efficacy of the vaccine and recommended by consensus a formal conditional marketing authorisation be granted by the European Commission. This will assure EU citizens that the vaccine meets EU standards and puts in place the safeguards, controls and obligations to underpin EU-wide vaccination campaigns.

Información importante
COVID-19 Vaccine AstraZeneca

Esta vacuna está sujeta a una monitorización adicional. Esto permitirá la identificación rápida de la información de seguridad.

Aprobación condicional

COVID-19 Vaccine AstraZeneca se ha autorizado bajo un esquema de aprobación condicionada. Esto significa que se espera evidencia adicional sobre esta vacuna próximamente.

La Agencia Europea del Medicamento revisará la nueva información de esta vacuna al menos cada año y la ficha técnica se actualizará si es necesario.

European Commission . Union Register of Medicinal Products for Human Use.
Available at :https://ec.europa.eu/health/documents/community-egister/html/h1529.htm .Consultado Febrero 2021.

Indicación COVID-19 Vaccine AstraZeneca

COVID-19 Vaccine AstraZeneca está indicada para la inmunización activa para prevenir la COVID-19 causada por SARS-CoV-2, en personas de 18 años de edad y mayores.

El uso de esta vacuna debe seguir las recomendaciones oficiales.

European Commission . Union Register of medicinal products for human use. Available at :https://ec.europa.eu/health/documents/community-register/html/h1529.htm .Consultado Febrero 2021.

SARS = severe acute respiratory syndrome; S = spike; SARS-CoV-2 = severe acute respiratory syndrome coronavirus-2.

Cómo se administra la vacuna
Posología y forma de administración (4.2)

Individuos de 18 años de edad y mayores

- **2 dosis separadas,** de 0,5 ml cada una**. La segunda dosis** debe administrarse entre **4 y 12 semanas** (28 a 84 días) tras la primera dosis
    - Una dosis contiene no menos de **2.5 x 10^8 unidades infecciosas**
- No hay datos disponibles sobre la intercambiabilidad de COVID-19 Vaccine AstraZeneca con otras vacunas frente a COVID-19 para completar la pauta de vacunación. Las personas que hayan recibido la primera dosis de COVID-19 Vaccine AstraZeneca deben recibir la segunda dosis de COVID-19 Vaccine AstraZeneca para completar la pauta de vacunación.

Población pediátrica

- No se ha establecido todavía la seguridad y eficacia de COVID-19 Vaccine AstraZeneca en niños y adolescentes (menores de 18 años de edad). No se dispone de datos

Forma de administración

- Inyección intramuscular, preferiblemente en el músculo deltoides en la parte superior del brazo.
- La vacuna no debe mezclarse en la misma jeringa con ninguna otra vacuna o medicamento.
- No inyecte la vacuna por vía intravascular, subcutánea o intradérmica

Población de edad avanzada

- No es necesario un ajuste de la dosis

European Commission . Union Register of Medicinal Products for Human Use.
Available at :https://ec.europa.eu/health/documents/community-egister/html/h1529.htm .Consultado Febrero 2021.

Condiciones de conservación

Precauciones especiales de almacenaje (6.4)

- Conservar en nevera (2°C – 8°C).
- No congelar.
- Conservar los viales en el cartonaje exterior para protegerlos de la luz.
- Puede guardarse y utilizarse a temperaturas de hasta 30ºC durante un único periodo de hasta 6 horas. Después debe ser desechado.

Naturaleza y contenido del envase (6.5)

Vial de 8 dosis

4 ml de suspensión en un vial de 8 dosis (vidrio transparente tipo I) con tapón (elastómero con revestimiento de aluminio). Cada vial contiene 8 dosis de 0,5 ml. Tamaños de envase de 10 viales multidosis.

Vial de 10 dosis

5 ml de suspensión en un vial de 10 dosis (vidrio transparente tipo I) con tapón (elastómero con revestimiento de aluminio). Cada vial contiene 10 dosis de 0,5 ml. Tamaños de envase de 10 viales multidosis.

Analisis combinado de seguridad y eficacia (COV001, COV002, COV003, COV005)

Safety and efficacy of the ChAdOx1 nCoV-19 vaccine (AZD1222) against SARS-CoV-2: an interim analysis of four randomised controlled trials in Brazil, South Africa, and the UK

Merryn Voysey, Sue Ann Costa Clemens*, Shabir A Madhi*, Lily Y Weckx*, Pedro M Folegatti*, Parvinder K Aley, Brian Angus, Vicky L Baillie, Shaun L Barnabas, Qasim E Bhorat, Sagida Bibi, Carmen Briner, Paola Cicconi, Andrea M Collins, Rachel Colin-Jones, Clare L Cutland, Thomas C Darton, Keertan Dheda, Christopher J A Duncan, Katherine R W Emary, Katie J Ewer, Lee Fairlie, Saul N Faust, Shuo Feng, Daniela M Ferreira, Adam Finn, Anna L Goodman, Catherine M Green, Christopher A Green, Paul T Heath, Catherine Hill, Helen Hill, Ian Hirsch, Susanne H C Hodgson, Alane Izu, Susan Jackson, Daniel Jenkin, Carina C D Joe, Simon Kerridge, Anthonet Koen, Gaurav Kwatra, Rajeka Lazarus, Alison M Lawrie, Alice Lelliott, Vincenzo Libri, Patrick J Lillie, Raburn Mallory, Ana V A Mendes, Eveline P Milan, Angela M Minassian, Alastair McGregor, Hazel Morrison, Yama F Mujadidi, Anusha Nana, Peter J O'Reilly, Sherman D Padayachee, Ana Pittella, Emma Plested, Katrina M Pollock, Maheshi N Ramasamy, Sarah Rhead, Alexandre V Schwarzbold, Nisha Singh, Andrew Smith, Rinn Song, Matthew D Snape, Eduardo Sprinz, Rebecca K Sutherland, Richard Tarrant, Emma C Thomson, M Estée Török, Mark Toshner, David P J Turner, Johan Vekemans, Tonya L Villafana, Marion E E Watson, Christopher J Williams, Alexander D Douglas*, Adrian V S Hill*, Teresa Lambe*, Sarah C Gilbert*, Andrew J Pollard* on behalf of the Oxford COVID Vaccine Trial Group†*

Voysey M et al, Lancet published on line December 8, 2020. https://doi.org/10.1016/S0140-6736(20)32661-1.

La vacuna AZD1222 alcanzó el criterio de valoración principal de eficacia

- >23.000 participantes registrados en COV002 y COV003
- Análisis realizado en 11.636 participantes

Se evaluaron dos regímenes de dosificación; media dosis/dosis completa y dosis completa/dosis completa administradas con al menos 4 semanas de diferencia.

No se han confirmado acontecimientos de toxicidad graves relacionados con la vacuna AZD1222. Bien tolerada en ambos regímenes de dosificación, con incluso menos reacciones adversas observadas en el régimen que muestra una eficacia del 90%.

El análisis completo se envía a los reguladores y a la revista científica para su publicación en revisión por pares.

70,4% de eficacia combinada en 131 casos confirmados*
(IC del 95,8%: del 54,8% al 80,6%)

90% MD/DC
62,1% DC/DC

Eficacia

Ausencia de hospitalizaciones o casos graves de COVID-19 entre los participantes de AZD1222*

Dosis completa (DC): ~$5x10^{10}$ partículas virales
Media dosis (MD): ~$2,5x10^{10}$ partículas virales

Voysey M, Lancet published on line December 8, 2020. https://doi.org/10.1016/S0140-6736(20)32661-1.

Más de 21 días después de la primera dosis, ninguno de los participantes que recibieron AZD1222 fue hospitalizado o desarrolló COVID-19 grave

	AZD1222 (n=12,021)	MenACWY or saline control (n=11,724)
Hospitalization (WHO clinical progression score ≥4)		
≤21 days after the first dose	2[a]	6
>21 days after the first dose and ≤14 days after the second dose	0	5
>14 days after the second dose	0	5
Severe COVID-19 (WHO clinical progression score ≥6)		
≤21 days after the first dose	0	0
>21 days after the first dose and ≤14 days after the second dose	0	1
>14 days after the second dose	0	1

- >21 days after first dose, ten participants were hospitalized with COVID-19, two of whom were assessed as having severe disease (WHO score ≥6), including one fatal case
- All ten cases were in the control group

[a]One case on the day of the first vaccination and one case 10 days after the first dose.
COVID-19 = coronavirus disease 2019; MenACWY = meningococcal group A, C, W, and Y conjugate vaccine; WHO = World Health Organization.
Voysey M et al, Lancet published on line December 8, 2020. https://doi.org/10.1016/S0140-6736(20)32661-1.

Nota de Prensa

3 de febrero de 2021 07:00 GMT

La vacuna de AstraZeneca para la COVID-19 confirma un 100% de protección frente a casos graves de la enfermedad, hospitalización y fallecimiento, según ha demostrado un análisis primario de ensayos clínicos en Fase III

Se ha demostrado una mayor eficacia con un mayor intervalo entre dosis

Más del 70% de protección desde la administración de la primera dosis

Primeros indicios de hasta un 67% de reducción en la transmisión de la enfermedad

El análisis primario de los ensayos clínicos en Fase III realizados en Reino Unido, Brasil y Sudáfrica, publicado como prepublicación en The Lancet, confirmó que la vacuna de AstraZeneca para la COVID-19 es segura y eficaz en prevenir la enfermedad, y no se han registrado casos graves ni hospitalizaciones después de más de 22 días tras la administración de la primera dosis.

Los resultados demuestran una eficacia de la vacuna del 76% (IC: 59% a 86%) después de una primera dosis, manteniendo la protección hasta la segunda dosis. Con un intervalo entre dosis de 12 semanas o más, la eficacia de la vacuna aumentó hasta un 82% (IC: 63%, 92%).

Single-dose administration and the influence of the timing of the booster dose on immunogenicity and efficacy of ChAdOx1 nCoV-19 (AZD1222) vaccine: a pooled analysis of four randomised trials

Merryn Voysey, Sue Ann Costa Clemens*, Shabir A Madhi*, Lily Y Weckx*, Pedro M Folegatti*, Parvinder K Aley, Brian Angus, Vicky L Baillie, Shaun L Barnabas, Qasim E Bhorat, Sagida Bibi, Carmen Briner, Paola Cicconi, Elizabeth A Clutterbuck, Andrea M Collins, Clare L Cutland, Thomas C Darton, Keertan Dheda, Christina Dold, Christopher J A Duncan, Katherine R W Emary, Katie J Ewer, Amy Flaxman, Lee Fairlie, Saul N Faust, Shuo Feng, Daniela M Ferreira, Adam Finn, Eva Galiza, Anna L Goodman, Catherine M Green, Christopher A Green, Melanie Greenland, Catherine Hill, Helen C Hill, Ian Hirsch, Alane Izu, Daniel Jenkin, Carina C D Joe, Simon Kerridge, Anthonet Koen, Gaurav Kwatra, Rajeka Lazarus, Vincenzo Libri, Patrick J Lillie, Natalie G Marchevsky, Richard P Marshall, Ana V A Mendes, Eveline P Milan, Angela M Minassian, Alastair McGregor, Yama F Mujadidi, Anusha Nana, Sherman D Padayachee, Daniel J Phillips, Ana Pittella, Emma Plested, Katrina M Pollock, Maheshi N Ramasamy, Adam J Ritchie, Hannah Robinson, Alexandre V Schwarzbold, Andrew Smith, Rinn Song, Matthew D Snape, Eduardo Sprinz, Rebecca K Sutherland, Emma C Thomson, M Estée Török, Mark Toshner, David P J Turner, Johan Vekemans, Tonya L Villafana, Thomas White, Christopher J Williams, Alexander D Douglas*, Adrian V S Hill*, Teresa Lambe*, Sarah C Gilbert*, Andrew J Pollard*, on behalf of the Oxford COVID Vaccine Trial Group†*

Summary

Background The ChAdOx1 nCoV-19 (AZD1222) vaccine has been approved for emergency use by the UK regulatory authority, Medicines and Healthcare products Regulatory Agency, with a regimen of two standard doses given with an interval of 4–12 weeks. The planned roll-out in the UK will involve vaccinating people in high-risk categories with their first dose immediately, and delivering the second dose 12 weeks later. Here, we provide both a further prespecified pooled analysis of trials of ChAdOx1 nCoV-19 and exploratory analyses of the impact on immunogenicity and efficacy of extending the interval between priming and booster doses. In addition, we show the immunogenicity and protection afforded by the first dose, before a booster dose has been offered.

Methods We present data from three single-blind randomised controlled trials—one phase 1/2 study in the UK (COV001), one phase 2/3 study in the UK (COV002), and a phase 3 study in Brazil (COV003)—and one double-blind phase 1/2 study in South Africa (COV005). As previously described, individuals 18 years and older were randomly assigned 1:1 to receive two standard doses of ChAdOx1 nCoV-19 (5×10^{10} viral particles) or a control vaccine or saline placebo. In the UK trial, a subset of participants received a lower dose ($2{\cdot}2\times10^{10}$ viral particles) of the ChAdOx1 nCoV-19 for the first dose. The primary outcome was virologically confirmed symptomatic COVID-19 disease, defined as a nucleic acid amplification test (NAAT)-positive swab combined with at least one qualifying symptom (fever ≥37·8°C, cough, shortness of breath, or anosmia or ageusia) more than 14 days after the second dose. Secondary efficacy analyses included cases occuring at least 22 days after the first dose. Antibody responses measured by immunoassay and by pseudovirus neutralisation were exploratory outcomes. All cases of COVID-19 with a NAAT-positive swab were adjudicated for inclusion in the analysis by a masked independent endpoint review committee. The primary analysis included all participants who were SARS-CoV-2 N protein seronegative at baseline, had had at least 14 days of follow-up after the second dose, and had no evidence of previous SARS-CoV-2 infection from NAAT swabs. Safety was assessed in all participants who received at least one dose. The four trials are registered at ISRCTN89951424 (COV003) and ClinicalTrials.gov, NCT04324606 (COV001), NCT04400838 (COV002), and NCT04444674 (COV005).

Findings Between April 23 and Dec 6, 2020, 24 422 participants were recruited and vaccinated across the four studies, of whom 17 178 were included in the primary analysis (8597 receiving ChAdOx1 nCoV-19 and 8581 receiving control vaccine). The data cutoff for these analyses was Dec 7, 2020. 332 NAAT-positive infections met the primary endpoint of symptomatic infection more than 14 days after the second dose. Overall vaccine efficacy more than 14 days after the second dose was 66·7% (95% CI 57·4–74·0), with 84 (1·0%) cases in the 8597 participants in the ChAdOx1 nCoV-19 group and 248 (2·9%) in the 8581 participants in the control group. There were no hospital admissions for COVID-19 in the ChAdOx1 nCoV-19 group after the initial 21-day exclusion period, and 15 in the control group. 108 (0·9%) of 12 282 participants in the ChAdOx1 nCoV-19 group and 127 (1·1%) of 11 962 participants in the control group had serious adverse events. There were seven deaths considered unrelated to vaccination (two in the ChAdOx1 nCov-19 group and five in the control group), including one COVID-19-related death in one participant in the control group. Exploratory analyses showed that vaccine efficacy after a single standard dose of vaccine from day 22 to day 90 after

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AstraZeneca's COVID-19 vaccine: EMA finds possible link to very rare cases of unusual blood clots with low blood platelets

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News 07/04/2021

EMA confirms overall benefit-risk remains positive

EMA's safety committee (PRAC) has concluded today that unusual blood clots with low blood platelets should be listed as very rare side effects of Vaxzevria (formerly COVID-19 Vaccine AstraZeneca).

In reaching its conclusion, the committee took into consideration all currently available evidence, including the advice from an ad hoc expert group.

EMA is reminding healthcare professionals and people receiving the vaccine to remain aware of the possibility of very rare cases of blood clots combined with low levels of blood platelets occurring within 2 weeks of vaccination. So far, most of the cases reported have occurred in women under 60 years of age within 2 weeks of vaccination. Based on the currently available evidence, specific risk factors have not been confirmed.

People who have received the vaccine should seek medical assistance immediately if they develop symptoms of this combination of blood clots and low blood platelets (see below).

The PRAC noted that the blood clots occurred in veins in the brain (cerebral venous sinus thrombosis, CVST) and the abdomen (splanchnic vein thrombosis) and in arteries, together with low levels of blood platelets and sometimes bleeding.

The Committee carried out an in-depth review of 62 cases of cerebral venous sinus thrombosis and 24 cases of splanchnic vein thrombosis reported in the EU drug safety database (EudraVigilance) as of 22 March 2021, 18 of which were fatal.[1] The cases came mainly from spontaneous reporting systems of the EEA and the UK, where around 25 million people had received the vaccine.

COVID-19 is associated with a risk of hospitalisation and death. The reported combination of blood clots and low blood platelets is very rare, and the overall benefits of the vaccine in preventing COVID-19 outweigh the risks of side effects.

https://www.ema.europa.eu/en/news/astrazenecas-covid-19-vaccine-ema-finds-possible-link-very-rare-cases-unusual-blood-clots-low-blood

1. Updates on safety of Vaxzevria

At its meeting held 3 to 6 May 2021, based on new safety data including the latest Monthly Summary Safety Report (MSSR)[2] from the marketing authorisation holder, PRAC assessed the following:

Embolic and thrombotic events with a focus on thrombosis with thrombocytopenia

Further to the PRAC assessment in April 2021[3] and an assessment by the Committee for Medicinal Products for Human Use (CHMP) of the vaccine's benefits and the risk of thrombosis with thrombocytopenia syndrome (TTS, formation of blood clots in the vessels with low blood platelets)[4], PRAC considered the available evidence, including recent data from the marketing authorisation holder, for an ongoing procedure to further amend the product information regarding:

- a contraindication to not vaccinate individuals with Vaxzevria who have experienced TTS following vaccination with Vaxzevria before;

- advice that individuals diagnosed with thrombocytopenia within 3 weeks of vaccination with Vaxzevria should be actively investigated for signs of thrombosis, and similarly individuals who present with thrombosis following vaccination should be evaluated for thrombocytopenia;

- addition of leg pain, seizures (fits) and mental status change as possible signs and symptoms of TTS (in addition to the signs and symptoms already included in the product information: severe or persistent headache, blurred vision, skin bruising beyond the site of vaccination after a few days, shortness of breath, chest pain, leg swelling, or persistent abdominal pain);

Immune thrombocytopenia (ITP)

PRAC assessed cases of immune thrombocytopenia (ITP, an auto-immune condition of low blood platelet levels that can lead to bruising and bleeding) reported with Vaxzevria. PRAC has requested further data from the marketing authorisation holder to continue its assessment.

Guillain-Barré syndrome (GBS)

PRAC is assessing cases of Guillain-Barré syndrome (GBS) reported after vaccination with Vaxzevria in the context of its regular reviews of the MSSRs. GBS is an immune system disorder that causes nerve inflammation and can result in pain, numbness, muscle weakness and difficulty in walking. PRAC has requested the marketing authorisation holder to provide further detailed data, including an analysis of all the reported cases, in the context of the next MSSR[5].

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[1] The European Centre for Disease Prevention and Control (ECDC) collects these data from EU Member States as well as from the additional countries of the European Economic Area (EEA) Norway, Iceland and Liechtenstein.

[2] Monthly Summary Safety Reports, also referred to as pandemic summary safety reports, will be compiled by the marketing authorisation holders to support timely and continuous benefit-risk evaluations for COVID-19 vaccines used during the pandemic. These reports complement the submission of Periodic Safety Update Reports (PSURs).

[3] See Safety Update for Vaxzevria of 14 April 2021

[4] See EMA Public Health Communication of 23 April 2021

Heterologous prime-boost COVID-19 vaccination: initial reactogenicity data

There is significant international interest in heterologous prime-boost COVID-19 vaccination to mitigate against supply shocks or shortages that might otherwise reduce the speed of vaccine roll-out. Additionally, in light of changing recommendations regarding use of the ChAdOx1 nCoV-19 (ChAd) COVID-19 vaccine (Vaxzevria, AstraZeneca), several countries are now advising that individuals previously primed with this vaccine should now receive an alternative vaccine as their second dose, most commonly mRNA vaccines such as the BNT162b2 (BNT) COVID-19 vaccine (Comirnaty, Pfizer–BioNTech), administered in a heterologous prime-boost schedule.[1–3] To date there are no data on the immunogenicity, reactogenicity, or safety of such schedules. Com-COV (ISRCTN 69254139) is a UK multicentre, participant-masked, randomised heterologous prime-boost COVID-19 vaccination study comparing all four prime-boost permutations of the ChAd and BNT vaccines both at 28-day and 84-day prime-boost intervals. Participants are 50 years and older with no or mild-to-moderate, well controlled comorbidity and were recruited across eight sites. The protocol is available online.

Following consultation with the study trial steering committee, here we present the initial reactogenicity and safety data, ahead of the primary immunological outcome, which is projected to be available in June, 2021. Reactogenicity data presented here consist of self-reported solicited local and systemic symptoms collected in the 7 days after both prime and boost vaccination in participants randomised to receive vaccines at 28-day intervals. Haematology and biochemistry safety monitoring blood results are also reported from the immunology cohort (100 participants with additional visits), at baseline (before the prime dose), at day 28 (before the boost dose) and 7 days post-boost, graded according to a modified US Food and Drug Administration toxicity scale (appendix). All analyses are descriptive, as the study was not powered for reactogenicity, with endpoints reported as frequencies and percentages, together with absolute differences between heterologous and homologous vaccine schedules and corresponding 95% CIs.

Recruitment commenced on Feb 11, 2021, and was completed on Feb 26, 2021, with 830 participants enrolled and randomised from 978 screened (the CONSORT flow diagram is available in the appendix). 463 participants were randomly assigned to the four groups with a 28-day prime-boost interval, and 367 participants randomised to groups with an 84-day prime-boost interval. All 463 participants in the 28-day prime-boost interval group received their prime vaccine, and 461 participants received their boost vaccine. Among the 463 participants, the median age was 57 years (range 50–69), 212 (46%) participants were female, and 117 (25%) from ethnic minorities, with baseline characteristics well balanced across study groups. In groups with homologous vaccine schedules, systemic reactogenicity was greater after the prime dose in the ChAd group, and after the boost dose in the BNT group (figure).

Both heterologous vaccine schedules induced greater systemic reactogenicity following the boost dose than their homologous counterparts, with feverishness reported by 37 (34%) of 110 recipients of ChAd for prime and BNT for boost compared with 11 (10%) of 112 recipients of ChAd for both prime and boost (difference 24%, 95% CI 13–35%). Feverishness was reported by 47 (41%) of 114 recipients of BNT for prime and ChAd for boost, compared with 24 (21%) of 112 recipients of BNT for both prime and boost (difference 21%, 95% CI 8–33%). Similar increases were observed for chills, fatigue, headache, joint pain, malaise, and muscle ache (figure; appendix). There were no hospitalisations due to solicited symptoms, and most of this increase in reactogenicity was observed in the 48 h after immunisation (appendix).

Participants were advised that paracetamol might reduce vaccine side-effects but were not actively counselled to medicate prophylactically. Paracetamol use in the 48 h post-boost vaccine was reported by 40 (36%) of 112 recipients of ChAd for both prime and boost, 63 (57%) of 110 recipients of ChAd for prime and BNT for boost, 48 (41%) of 117 recipients of BNT for both prime and boost, and 68 (60%) of 114 recipients of BNT for prime and ChAd for boost, thereby mirroring the reactogenicity pattern.

Haematology and biochemistry profiles were similar between heterologous and homologous vaccine schedules, with all laboratory adverse events of grade 2 severity or less in the heterologous vaccine schedule, and no thrombocytopenia in any group at day 7 post-boost (appendix).

In this interim safety analysis, we found an increase in systemic reactogenicity after the boost dose reported by participants in heterologous vaccine schedules in comparison to homologous vaccine schedules, and this was accompanied by increased paracetamol usage. Of note, these data were obtained in participants aged 50 years and older, and reactogenicity might be higher in younger age groups[4,5] for whom a mixed vaccination schedule is being advocated in Germany, France, Sweden, Norway, and Denmark among those who have received a ChAd prime dose, in light of concerns regarding thrombotic thrombocytopenia after the first dose of ChAd.[6]

Pending availability of a more complete safety dataset and immunogenicity results for heterologous

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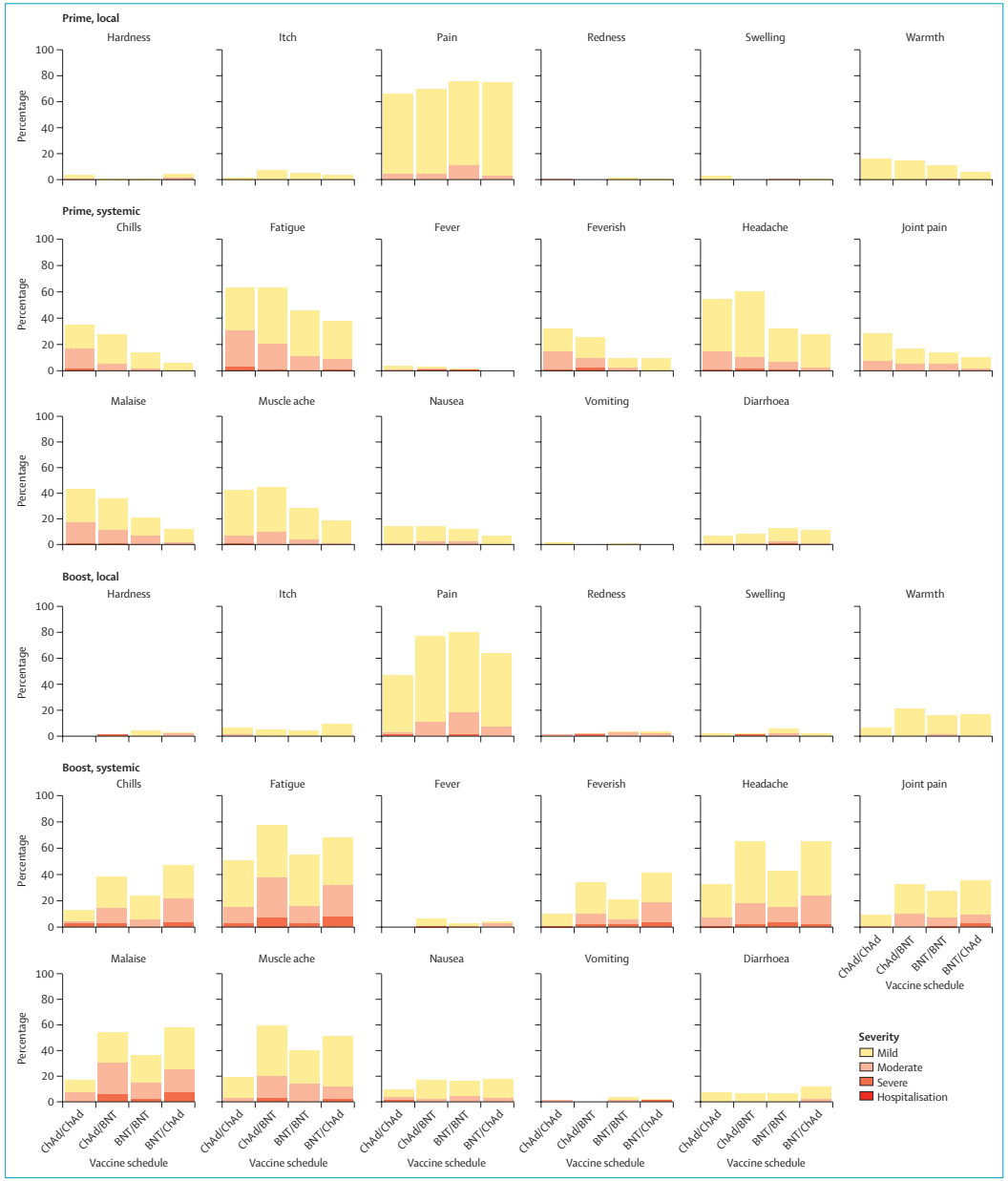
See Online for appendix

For the **Com-COV protocol** see https://comcovstudy.org.uk/study-protocol

Submissions should be made via our electronic submission system at http://ees.elsevier.com/thelancet/



U.S. FOOD & DRUG ADMINISTRATION

Vaccines and Related Biological Products Advisory Committee Meeting

FDA Review of Efficacy and Safety of the Janssen COVID-19 Vaccine Emergency Use Authorization Request

Rachel Zhang, M.D.
Yosefa Hefter, M.D.
FDA/CBER
Office of Vaccines Research and Review
Division of Vaccines and Related Products Applications
February 26, 2021

Janssen COVID-19 Vaccine Ad26.COV2.S

Vaccine composition	• Recombinant, replication-incompetent adenovirus type 26 (Ad26) vectored • Encodes SARS-CoV-2 spike (S) protein • Produced in PER.C6 cells
Dosing regimen	Intramuscular, single-dose regimen $5x10^{10}$ vp
Proposed indication and usage under EUA	For active immunization to prevent COVID-19 caused by SARS-CoV-2 in individuals 18 years of age and older

Clinical Development to Date

Ongoing, randomized, double-blinded, placebo-controlled studies

Study Number	Phase	Vaccination Schedule	No. of Dose Levels	Description
1001	1/2a	1-dose and 2-dose	2	Regimen selection
1002*	1	2-dose	2	Safety and immunogenicity study in Japan
2001	2a	1-dose and 2-dose	4	Dose-ranging; includes adolescents
3001	3	1-dose	1	Efficacy, safety, immunogenicity
3009	3	2-dose	1	Efficacy, safety, immunogenicity

*Non-US IND study

Study 3001 data used to support EUA application

Study 3009

Phase 3 efficacy, safety, and immunogenicity study of 2-dose regimen (N=30,000)

- Multicenter study in US, South Africa, Brazil, Colombia, Philippines, and 5 European countries
- Age cohorts: 18-59 years, ≥60 years
- Randomized 1:1 to 2 doses of vaccine ($5x10^{10}$ vp) or placebo, 56-day interval

- Initiated November 16, 2020
- Enrollment ongoing
- No safety concerns identified based on review of blinded SAE reports to date

Study 3001

Phase 3 efficacy, safety, immunogenicity of 1-dose regimen (N=44,325)

- Multicenter study across US, South Africa, and 6 countries in Latin America
- Age cohorts: 18-59 years, ≥60 years
- Randomized 1:1 to a single dose of vaccine ($5x10^{10}$ vp) or saline placebo

- Initiated September 21, 2020
- Staged enrollment:
  - 18 to <60 years without comorbidities
  - 18 to <60 years with and without comorbidities
  - ≥60 years without comorbidities
  - ≥60 years with and without comorbidities

  Goal of 30% of total study population
- Planned study duration: 2 years

Median Follow-Up Duration

Participant Group Follow-up	Ad26.COV2.S N=21895	Placebo N=21888	All Participants N=43783
18-59 overall	14564	14547	29111
Participants with ≥8 weeks follow-up	62.8%	63.1%	63.0%
Median follow-up after vaccination (days)	61.0	61.0	61.0
18-59, no comorbidities	9332	9371	18703
Participants with ≥8 weeks follow-up	70.0%	69.9%	70.0%
Median follow-up after vaccination (days)	64.0	64.0	64.0
18-59, with comorbidities	5232	5176	10408
Participants with ≥8 weeks follow-up	49.9%	50.8%	50.4%
Median follow-up after vaccination (days)	56.0	57.0	57.0
≥60 years overall	7331	7341	14672
Participants with ≥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 ≥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 ≥8 weeks follow-up	29.0%	27.1%	28.0%
Median follow-up after vaccination (days)	50.0	50.0	50.0

Primary Efficacy Endpoint

	Onset at Least 14 Days			Onset at Least 28 Days		
Co-primary Endpoint Subgroup	**Ad26.COV2.S Cases (N) Person-yrs**	**Placebo Cases (N) Person-yrs**	**VE% (95% CI)**	**Ad26.COV2.S Cases (N) Person-yrs**	**Placebo Cases (N) Person-yrs**	**VE% (95% CI)**
All participants	116 (19514) 3116.6	348 (19544) 3096.1	**66.9%** (59.0, 73.4)	66 (19306) 3102.0	193 (19178) 3070.7	**66.1%** (55.0, 74.8)
Age 18-59 years	95 (12750) 2106.8	260 (12782) 2095.0	**63.7%** (53.9, 71.6)	52 (12617) 2097.6	152 (12527) 2077.0	**66.1%** (53.3, 75.8)
Age ≥60 years	21 (6764) 1009.8	88 (6762) 1001.2	**76.3%** (61.6, 86.0)	14 (6689) 1004.4	41(6651) 993.6	**66.2%** (36.7, 83.0)

Subgroup Analyses of Primary Efficacy Endpoint, by Comorbidity

	Onset at Least 14 Days			Onset at Least 28 Days		
Subgroup	**Ad26.COV2.S Cases (N) Person-yrs**	**Placebo Cases (N) Person-yrs**	**VE% (95% CI)**	**Ad26.COV2.S Cases (N) Person-yrs**	**Placebo Cases (N) Person-yrs**	**VE%[a] (95% CI)**
Comorbidity, presence						
Yes	70 (7777)	194 (7798)	**64.2%**	44 (7684)	105 (7626)	**58.6%**
	1138.8	1130.9	(52.7, 73.1)	1133.0	1120.0	(40.6, 71.6)
No	103 (11737)	315 (11746)	**67.6%**	69 (11622)	219 (11552)	**68.8%**
	1975.1	1958.2	(59.4, 74.3)	1967.3	1945.9	(59.0, 76.6)
Comorbidity, type						
Asthma	1 (238)	9 (278)	**87.2%**	0 (235)	4 (270)	
	34.3	39.5	(7.6, 99.7)	34.1	38.9	
COPD	1 (213)	5 (195)	**81.5%**	1 (211)	3 (192)	
	30.2	28.0	(-65.2, 99.6)	30.1	27.8	
Serious heart	3 (460)	13 (487)	**76.1%**	1 (455)	5 (472)	**79.4%**
conditions	65.3	67.7	(12.9, 95.6)	64.9	66.8	(-83.7, 99.6)
HIV infection	5 (467)	5 (498)	**-4.8%**	2 (461)	4 (493)	**47.5%**
	69.1	72.4	(-355.2, 75.9)	68.7	72.2	(-266.0, 95.3)
Hypertension	14 (1999)	38 (2019)	**63.2%**	11 (1978)	17 (1977)	**35.7%**
	283.3	282.8	(30.6, 81.6)	281.9	280.2	(-45.6, 72.8)
Obesity	51 (5383)	151 (5352)	**66.8%**	30 (5318)	86 (5223)	**65.9%**
	794.1	780.3	(54.1, 76.3)	790.0	772.0	(47.8, 78.3)
Type 2 diabetes	15 (1399)	32 (1410)	**52.9%**	10 (1380)	13 (1378)	**23.0%**
mellitus	198.7	199.5	(10.5, 76.3)	197.5	197.7	(-90.1, 69.8)

Note: Only comorbidities with ≥6 cases at either of the 2 time points are shown

[a] VE not shown if less than 6 cases are observed for an endpoint

Solicited Local Reactions Within 7 Days After Vaccination

Adverse Reaction	18-59 Years Ad26.COV2.S N=2036 n (%)	18-59 Years Placebo N=2049 n (%)	≥60 Years Ad26.COV2.S N=1320 n (%)	≥60 Years Placebo N=1331 n (%)
Any Local	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	8 (0.4%)	0	3 (0.2%)	2 (0.2%)
Erythema (≥25mm)	184 (9.0%)	89 (4.3%)	61 (4.6%)	42 (3.2%)
Grade 3 (≥100mm)	6 (0.3%)	2 (0.1%)	1 (0.1%)	0
Swelling (≥25mm)	142 (7.0%)	32 (1.6%)	36 (2.7%)	21 (1.6%)
Grade 3 (≥100mm)	5 (0.2%)	2 (0.1%)	2 (0.2%)	0

The rate of local ARs among vaccine recipients who were seronegative for SARS-CoV-2 at baseline (n=3,202) was similar to that of those seropositive at baseline (n=154): 50.0% vs. 53.9%.

Solicited Systemic Reactions Within 7 Days After Vaccination

Adverse Reaction	18-59 Years Ad26.COV2.S N=2036 n/N (%)	18-59 Years Placebo N=2049 n/N (%)	≥60 Years Ad26.COV2.S N=1320 n/N (%)	≥60 Years Placebo N=1331 n/N (%)
Any Systemic	1252 (61.5%)	745 (36.4%)	598 (45.3%)	440 (33.1%)
Grade 3	47 (2.3%)	12 (0.6%)	14 (1.1%)	9 (0.7%)
Fatigue	891 (43.8%)	451 (22.0%)	392 (29.7%)	277 (20.8%)
Grade 3	25 (1.2%)	4 (0.2%)	10 (0.8%)	5 (0.4%)
Headache	905 (44.4%)	508 (24.8%)	401 (30.4%)	294 (22.1%)
Grade 3	18 (0.9%)	5 (0.2%)	5 (0.4%)	4 (0.3%)
Myalgia	796 (39.1%)	248 (12.1%)	317 (24.0%)	182 (13.7%)
Grade 3	29 (1.4%)	1 (<0.1%)	3 (0.2%)	5 (0.4%)
Nausea	315 (15.5%)	183 (8.9%)	162 (12.3%)	144 (10.8%)
Grade 3	3 (0.1%)	3 (0.1%)	3 (0.2%)	3 (0.2%)
Fever (≥38.0℃)	261 (12.8%)	14 (0.7%)	41 (3.1%)	6 (0.5%)
Grade 3 (39.0-40℃)	7 (0.3%)	0	1 (0.1%)	0
Antipyretic/Analgesic Use	538 (26.4%)	123 (6.0%)	130 (9.8%)	68 (5.1%)

Among vaccine recipients, rates of systemic ARs by baseline SARS-CoV-2 serostatus were similar: 55.4% vs. 50.0%, for seronegative (n=3,202) and seropositive (n=154) vaccine recipients, respectively.

NÚMERO 5
FECHA DE ELABORACIÓN: 7 DE MAYO DE 2021
FECHA DE PUBLICACIÓN: 11 DE MAYO DE 2021

VACUNAS COVID-19
INFORME DE FARMACOVIGILANCIA

- **Tras la revisión de los datos de seguridad disponibles, se ha establecido lo siguiente:**
  - ✓ Comirnaty (BioNTech/Pfizer): se han incorporado a la ficha técnica y al prospecto como posibles reacciones adversas erupción cutánea y prurito (poco frecuentes) y urticaria (de frecuencia rara). También se incorporará la posible aparición de inflamación localizada después de la vacunación en personas que habían recibido previamente inyecciones de relleno en la cara.
  - ✓ Vaxzevria (AstraZeneca): la aparición de trombosis acompañada de trombocitopenia en lugares poco habituales como los senos venosos cerebrales y venas esplácnicas, es una posible reacción adversa de la vacuna. Su frecuencia de aparición es muy rara y la mayoría de los casos notificados en el momento de la evaluación se presentaron dentro de los 14 días siguientes a la vacunación y en menores de 60 años. Esta información se ha incorporado a la ficha técnica con recomendaciones para profesionales sanitarios y ciudadanos. También se ha incorporado a la ficha técnica y al prospecto la posible aparición de trombocitopenia aislada. Se encuentra en estudio la posible asociación con la aparición de síndrome de fuga capilar tras haberse notificado algunos casos aislados.
  - ✓ COVID-19 Vaccine Janssen: la aparición de trombosis acompañada de trombocitopenia en lugares poco habituales como los senos venosos cerebrales y venas esplácnicas es una posible reacción adversa de la vacuna. Su frecuencia de aparición es muy rara. En el momento de la evaluación, los casos notificados con esta vacuna se presentaron dentro de los 21 días siguientes a la vacunación y, mayoritariamente, en mujeres menores de 60 años. Esta posible reacción adversa se describe en la ficha técnica y el prospecto de esta vacuna, con recomendaciones para profesionales sanitarios y ciudadanos.

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

20 April 2021
EMA/268126/2021
Pharmacovigilance Risk Assessment Committee (PRAC)

Signal assessment report on Embolic and Thrombotic events (SMQ) with COVID-19 Vaccine Janssen (Ad26.COV2-S [recombinant])

EPITT no:19689

Table 1: Thrombotic and Thromboembolic Events in Study COV3001[1]

Full Analysis Set	Ad26.COV2.S N=21,895 n	Placebo N=21,888 n
Total participants with any event (percentage)	29 (0.1)	22 (0.1)
Venous thromboembolic events		
Deep vein thrombosis	11[2]	3
Pulmonary embolism	7	3[3]
Cerebral sinus thrombosis	1	1
Retinal vein thrombosis	1	0
Thrombophlebitis	1	1
Venous stent occlusion	0	1
Thrombosed hemorrhoid	0	1
Total participants with venous events	21	9
Arterial thromboembolic events		
Cerebrovascular events	6[4]	9
Cardiovascular events	3	4
Arterial stent occlusion	0	1[5]
Total participants with arterial events	8	14

[1] Data until March 17th , 2021
[2] Includes one event reported as 'venous thrombosis limb' and one event reported as 'embolism venous'
[3] One patient reported both deep vein thrombosis and pulmonary embolism as separate terms
[4] Two events reported in 1 participant
[5] One participant reported 2 events of stent occlusion (1 venous, 1 arterial)

3.5. Adopted PRAC recommendation

The PRAC has reviewed the available evidence on the occurrence of thromboembolic events following the administration of COVID-19 Vaccine Janssen, including data ascertained from spontaneous case reports identified in EudraVigilance, clinical trials and additional data from the MAH. The evaluation of the data revealed eight reports of interest, which included severe cases of venous thrombosis at unusual sites such as cerebral venous sinus thrombosis, splanchnic vein thrombosis, as well as arterial thrombosis concomitant with thrombocytopenia. Fatal outcome has been reported. These cases occurred within the first three weeks following vaccination, and mostly in women under 60 years of age.

PRAC is of the view that there is sufficient evidence to conclude, with a reasonable possibility, that *thrombosis in combination with thrombocytopenia* can be considered as a very rare adverse drug reaction of the Covid-19 Vaccine Janssen.

Regarding additional risk minimisation measures, a DHPC is warranted to inform health care professionals.

The PRAC recommends that the MAH for Covid-19 Vaccine Janssen (Janssen-Cilag International NV) should submit a variation to amend the product information as described below (new text underlined/text to be removed with strikethrough):

Section 4.4

Thrombocytopenia and coagulation disorders

A combination of thrombosis and thrombocytopenia, in some cases accompanied by bleeding, has been observed very rarely following vaccination with COVID-19 Vaccine Janssen. This includes severe cases of venous thrombosis at unusual sites such as cerebral venous sinus thrombosis, splanchnic vein thrombosis, as well as arterial thrombosis concomitant with thrombocytopenia. Fatal outcome has been reported. These cases occurred within the first three weeks following vaccination, and mostly in women under 60 years of age.

Healthcare professionals should be alert to the signs and symptoms of thromboembolism and/or thrombocytopenia. Those vaccinated should be instructed to seek immediate medical attention if they develop symptoms such as shortness of breath, chest pain, leg swelling, or persistent abdominal pain following vaccination. Additionally, anyone with neurological symptoms including severe or persistent headaches or blurred vision after vaccination, or who experiences skin bruising (petechia) beyond the site of vaccination after a few days, should seek prompt medical attention.

Thrombosis in combination with thrombocytopenia requires specialised clinical management. Healthcare professionals should consult applicable guidance and/or consult specialists (e.g., haematologists, specialists in coagulation) to diagnose and treat this condition.

Risk of bleeding with intramuscular administration

Section 4.8

In the Table

SOC: Vascular disorders: Thrombosis in combination with thrombocytopenia*

* *Severe and very rare cases of thrombosis in combination with thrombocytopenia have been reported post-marketing. These included venous thrombosis such as cerebral venous sinus thrombosis, splanchnic vein thrombosis, as well as arterial thrombosis (see section 4.4).

Frequency: Very rare

RESUMEN VACUNACIÓN FRENTE A LA COVID-19

v01. 26 de abril 2021

INDICACIONES DE VACUNACIÓN EN ATENCIÓN PRIMARIA

GRUPO 4
[SEGÚN DISPONIBILIDAD]

GRANDES DEPENDIENTES	
Pueden acudir al CS	ARNm
Inmovilizados >70 años	ARNm
Inmovilizados 60–69	Janssen /2ª opción: AZ
Inmovilizados <60 años	ARNm

CUIDADORES PROFESIONALES	
60-69 años	Si se va al domicilio de una persona dependiente: utilizar la misma vacuna que se pone al paciente. En el CS: AZ (según disponibilidad)

GRUPO 5
[ARNm]

PERSONAS VULNERABLES POR SU EDAD	
>75 años	Pfizer / Moderna

★ **ANTECEDENTE DE INFECCIÓN CONFIRMADA POR SARS-COV-2 ANTES DE RECIBIR LA PRIMERA DOSIS**

> 65 AÑOS: 2 dosis desde que finalice la infección activa o el periodo de aislamiento..

< 65 AÑOS: 1 sola dosis a los 6 meses del diagnóstico.

★ **INFECCIÓN CONFIRMADA POR SARS-COV-2 TRAS RECIBIR LA PRIMERA DOSIS**

> 65 AÑOS: completar la pauta tras recuperación/fin de aislamiento.

< 65 AÑOS: 2ª dosis a los 6 meses del diagnóstico.

RECUERDA

Identificar al paciente con más de un dato.

Comprobar el estado vacunal frente a la COVID.

Informar sobre posibles efectos secundarios y solicitar consentimiento informado (incapacidad, embarazo, lactancia).

Comprobar si ha habido reacciones adversas anteriores. Está **contraindicado vacunar** si ha presentado una reacción anafiláctica o alérgica inmediata de cualquier gravedad a una dosis previa de la vacuna o a cualquier componente de la misma.

Comprobar si existen situaciones especiales y posponer si cuadro febril agudo, separar al menos 7 días antes o después de la administración de otra vacuna.

Realizar el **registro en el RUV.**

Mantener en observación al paciente al menos 15 minutos tras la vacunación (30 minutos en personas con antecedentes de alergia grave)

Notificar los errores producidos durante la vacunación: **CISEMadrid y a Salud Pública** (isp.prevención@salud.madrid.org. Tel: 91 3700920)

Notificar las incidencias relacionadas con la rotura de **la cadena de frío** a **Salud Pública** (isp.prevención@salud.madrid.org. Tel: 91 3700920)

Notificar los efectos adversos que se producen tras la vacunación a **NotificaRAM**

Historia de alergia	- Alergia a medicamentos orales (incluyendo el equivalente oral de un medicamento inyectable) - Alergias alimentarias, a animales, insectos, venenos, alergenos ambientales, látex etc. - Historia familiar de alergia.	- Antecedente de reacción alérgica a otras vacunas o tratamientos inyectables (diferentes a los componentes de la vacuna).	- **Antecedentes de reacción anafiláctica o alérgica inmediata de cualquier gravedad a una dosis previa de la vacuna o a cualquier componente de la misma**.
Actuación	-Observar 30 minutos si antecedentes de reacciones alérgicas graves por cualquier causa. - Observar durante 15 minutos si antecedentes de reacciones alérgicas no anafilácticas.	- Evaluar el riesgo . - Valorar posponer la vacunación o consulta con especialista. - Observar durante un tiempo de 30 minutos si se decide vacunar.	- **No vacunar.** - Derivar para estudio al Servicio de Alergia.

RESUMEN VACUNACIÓN FRENTE A LA COVID-19

v01. 18 de abril 2021

OTRAS SITUACIONES A CONSIDERAR

INMUNOSUPRESIÓN

- En las **personas inmunodeprimidas o con tratamiento inmunosupresor** (incluyendo los corticoides que pueden utilizarse en el tratamiento de la COIVD) deben **recibir la vacuna a menos que esté contraindicada**.

EMBARAZO

- Se recomienda **posponer la vacunación hasta finalizar el embarazo**.
- Si una **embarazada pertenece a un grupo de riesgo** de la enfermedad por su alta exposición o por alto riesgo de complicaciones debería consultar al profesional que realiza el seguimiento y **valorar el riesgo-beneficio de la vacunación**.
- En los **casos de planificación de embarazo** se recomienda esperar 2 semanas tras la administración de la segunda dosis, como medida de precaución.

LACTANCIA

- Una madre que amamanta puede ser vacunada si forma parte de un grupo en el que se recomienda la vacunación por su alta exposición (p.e.: sanitarias y socio-sanitarias) o que tenga un alto riesgo de complicaciones por COVID-19.
- **No es necesario suspender la lactancia los días posteriores a la vacunación**.

ANTICOAGULACIÓN

- Se puede vacunar a personas con alteraciones de la coagulación o en tratamiento crónico con anticoagulantes o antiagregantes.

AMPLIAR INFORMACIÓN:

- Agencia Española del Medicamento y Productos Sanitarios (AEMPS). Informes de farmacovigilancia
- Sociedad Española de Reumatología
- Comité Asesor de Vacunas. Asociación Española de Pediatría
- Sociedad Española de Trombosis y Hemostasia
- Federación de Asociaciones Científico Médicas de España

POSPONER LA VACUNACIÓN SI EXISTE SOSPECHA DE INFECCIÓN POR SARS-CoV-2 O SI EXISTE INFECCIÓN CONFIRMADA HASTA FINALIZAR EL PERIODO DE AISLAMIENTO.

NO SE RECOMIENDA SOLICITAR PRUEBAS DE LABORATORIO ANTES NI DESPUÉS DE VACUNAR.

LAS PERSONAS CON CONDICIONES DE MUY ALTO RIESGO (GRUPO 7) SON LAS SIGUIENTES:

Trasplante de progenitores hematopoyéticos (TPH) -alo y autotrasplante- en los últimos 2 años, o >50 años y/o < 80% de índice Karnofsky, independientemente del tiempo desde el TPH.

Trasplante de órgano sólido o en lista de espera para trasplante de órgano sólido:

- Trasplante pulmonar.
- Trasplante renal y pancreático.
- Trasplante cardíaco.
- Trasplante hepático.
- Trasplante intestinal.

Tratamiento sustitutivo renal (hemodiálisis y diálisis peritoneal).

Enfermedad oncohematológica en los últimos 5 años o no controlada y/o ECOC 3-4 y/o neutropenia severa (<500 neutrófilos/mm^3) independientemente del tiempo desde el diagnóstico.

Cáncer de órgano sólido:

- Cáncer de órgano sólido en tratamiento con quimioterapia citotóxica.
- Cáncer de órgano sólido metastásico.
- Pacientes que reciben radioterapia por tumores de localización torácica con riesgo de neumonitis (tumor esófago, radioterapia sobre metástasis pulmonares, etc).

Inmunodeficiencias primarias. Todas las inmunodeficiencias primarias, excluyendo el déficit de IgA y el defecto de formación de anticuerpos.

Infección con VIH y con <200 cel/ml (analítica de los últimos 6 meses)

Síndrome de Down con 40 o más años de edad (nacidos en 1981 o antes)

BIBLIOGRAFÍA :

1- Ministerio de Sanidad. 6ª actualización Estrategia de vacunación. 20 de abril 2021

2.- Dirección General de Salud Pública. Documento informativo de vacunación frente a la COVID-19 en la Comunidad de Madrid.

3- Dirección General de Salud Pública. Nota informativa: Indicación de las vacunas actualmente disponibles en la Comunidad de Madrid. 8 de abril 2021.

4.- AEMPS. DHPC: VAXZEVRIA/COVID-19 VACCINE ASTRAZENECA: Actualización sobre el riesgo de trombosis en combinación con trombocitopenia. 13 de abril 2021

Este documento está en revisión permanente en función de la evolución y nueva información que se disponga de la vacunación frente a la COVID-19 en la Comunidad de Madrid

Comunidad de Madrid

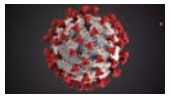
PLAN DE VACUNACIÓN. SEMANA 17 AL 23 DE MAYO

Las vacunas se administran en función de su disponibilidad. Actualizado a 17 de mayo

GRUPO	DÓNDE ME VACUNAN	CÓMO ME CITAN	QUÉ VACUNA
50 a 55 años Nacidos en años 1966 a 1971 (incluidos).	**Hospitales del Servicio Madrileño de Salud** *(ver listado de hospitales).* **Wanda Metropolitano y Wizink Center**	Citación mediante un **SMS**[1] con un enlace para **confirmar la cita en una página web** habilitada al efecto.	Vacuna ARNm (Pfizer o Moderna).
56 a 59 años. Nacidos en años 1962 a 1965 (incluidos).	**Hospitales del Servicio Madrileño de Salud** *(ver listado de hospitales).*	Citación mediante un **SMS**[1] con un enlace para **confirmar la cita en una página web** habilitada al efecto.	Vacuna ARNm (Pfizer o Moderna).
60 a 67 años. Nacidos en años 1954 a 1961 (incluidos).	**Wanda Metropolitano y Wizink Center.**	Citación mediante un **SMS**[1] con un enlace para **confirmar la cita en una página web** habilitada al efecto.	Vacuna AstraZeneca.
68 años y más[2] Nacidos en 1953 y anteriores.	En sus **Centros de Salud.**	**Citación por llamada telefónica** desde el número de teléfono único de Atención Primaria **91 370 00 01** ***(este número NO es para consultar dudas)***	Vacuna ARNm (Pfizer).
MUTUALISTAS (MUFACE, ISFAS, MUGEJU y otros).	- 70 años y más, en el **H.E. Isabel Zendal los fines de semana.** - Menores de 70 años, con sus grupos de población.	**- 74 años y más,** recibiran una llamada desde el Centro de Atención Personalizada (número de teléfono **91 502 60 58**). - **Menores de 74 años**, citación por SMS	Vacuna: la que corresponda según su grupo de edad.
COLECTIVOS ESENCIALES: Docentes, personal de Fuerzas y Cuerpos de Seguridad, Emergencias y Fuerzas Armadas y otros profesionales sociosanitarios**, que aún no han recibido ninguna dosis.**	**H.E. Isabel Zendal.**	Citación mediante un **SMS**[1] con un enlace para **confirmar la cita en** una **página web** habilitada al efecto.	Vacuna ARNm (Pfizer o Moderna).
GRUPOS DE RIESGO[3]	**- Hospitales del Servicio Madrileño de Salud** *(ver listado de hospitales).* **- Varios hospitales privados** *(ver listado de hospitales).*	**Citados directamente** desde los centros hospitalarios en los que son atendidos habitualmente.	Vacuna ARNm (Pfizer o Moderna), preferentemente Moderna.
GRANDES DEPENDIENTES - Grado III Ley 39/2006, de 14 de diciembre) con necesidad de intensas medidas de apoyo, no institucionalizados.	**- En su domicilio o Centro de Salud.** - En sus **Centros de Día**.	Citados desde sus Centros de Salud o Centros de Día.	Vacunas ARNm (Pfizer o Moderna) y Janssen.

AL RECIBIR LA PRIMERA DOSIS DE LA VACUNA QUE LE CORRESPONDA, SE LE INDICARÁ
CUÁNDO RECIBIRÁ LA SEGUNDA DOSIS, SI ÉSTA FUERA NECESARIA.
LA SEGUNDA DOSIS SE ADMINISTRARÁ, EN PRINCIPIO, EN EL LUGAR DONDE SE PUSO LA PRIMERA.

Las personas de **colectivos esenciales que se vacunaron con la primera dosis de AstraZeneca** serán informadas próximamente de qué vacuna, así como dónde y cuándo recibirán la segunda dosis en función de la evidencia científica, las evaluaciones de la Agencia Europea del Medicamento y la coordinación con otros países de la UE.



Efecto de la vacunación en las nuevas variantes

Viceconsejería de Salud Pública y Plan COVID-19
Consejería de Sanidad
Comunidad de Madrid

Comunidad de Madrid

Características de las nuevas variantes

Variante UK

La variante del Reino Unido se propaga más fácil y rápidamente que otras. Hay evidencia que sugiere que esta variante podría estar asociada con mayor gravedad.

Variante Brasil

La variante de Brasil contiene más mutaciones que la cepa del Reino Unido que pueden afectar su capacidad de ser bloqueada por anticuerpos terapéuticos o por la vacuna.

Variante Sudafricana

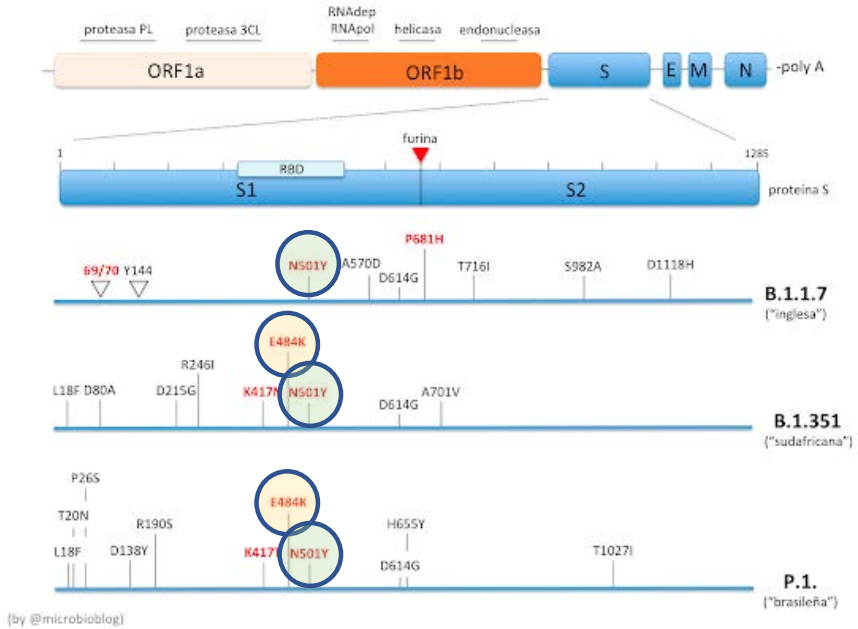
La variante sudafricana comparte algunas mutaciones con la variante de Brasil y comporta riesgos similares.

Variante California

Las variantes de California comparten algunas mutaciones con la variante del Reino Unido y pueden no responder a algunas terapias.

Variante de la India

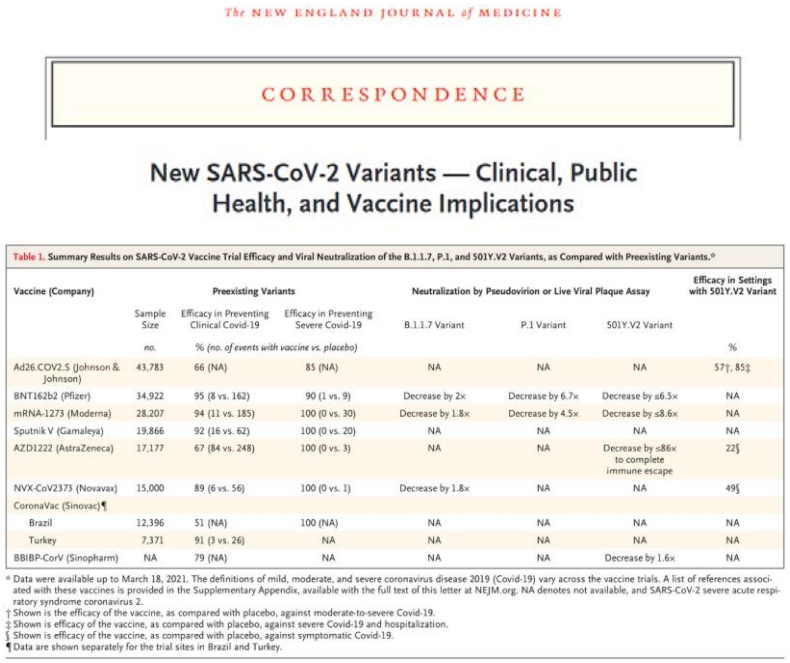
Conocida como "doble variante" por ser portadora de dos mutaciones de preocupación presentes en las cepas de Sudáfrica, Brasil y California.



European Centre for Disease Prevention and Control. SARS-CoV-2 - increased circulation of variants of concern and vaccine rollout in the EU/EEA, 14th update – 15 February 2021. ECDC: Stockholm; 2021.

Comunidad de Madrid

Resumen de la eficacia/efectividad de las vacunas



The NEW ENGLAND JOURNAL of MEDICINE

CORRESPONDENCE

New SARS-CoV-2 Variants — Clinical, Public Health, and Vaccine Implications

Table 1. Summary Results on SARS-CoV-2 Vaccine Trial Efficacy and Viral Neutralization of the B.1.1.7, P.1, and 501Y.V2 Variants, as Compared with Preexisting Variants.*

Vaccine (Company)	Preexisting Variants			Neutralization by Pseudovirion or Live Viral Plaque Assay			Efficacy in Settings with 501Y.V2 Variant
	Sample Size	Efficacy in Preventing Clinical Covid-19	Efficacy in Preventing Severe Covid-19	B.1.1.7 Variant	P.1 Variant	501Y.V2 Variant	
	no.	% (no. of events with vaccine vs. placebo)					%
Ad26.COV2.S (Johnson & Johnson)	43,783	66 (NA)	85 (NA)	NA	NA	NA	57†, 85‡
BNT162b2 (Pfizer)	34,922	95 (8 vs. 162)	90 (1 vs. 9)	Decrease by 2×	Decrease by 6.7×	Decrease by ≤6.5×	NA
mRNA-1273 (Moderna)	28,207	94 (11 vs. 185)	100 (0 vs. 30)	Decrease by 1.8×	Decrease by 4.5×	Decrease by ≤8.6×	NA
Sputnik V (Gamaleya)	19,866	92 (16 vs. 62)	100 (0 vs. 20)	NA	NA	NA	NA
AZD1222 (AstraZeneca)	17,177	67 (84 vs. 248)	100 (0 vs. 3)	NA	NA	Decrease by ≤86× to complete immune escape	22§
NVX-CoV2373 (Novavax)	15,000	89 (6 vs. 56)	100 (0 vs. 1)	Decrease by 1.8×	NA	NA	49§
CoronaVac (Sinovac)¶							
Brazil	12,396	51 (NA)	100 (NA)	NA	NA	NA	NA
Turkey	7,371	91 (3 vs. 26)	NA	NA	NA	NA	NA
BBIBP-CorV (Sinopharm)	NA	79 (NA)	NA	NA	NA	Decrease by 1.6×	NA

* Data were available up to March 18, 2021. The definitions of mild, moderate, and severe coronavirus disease 2019 (Covid-19) vary across the vaccine trials. A list of references associated with these vaccines is provided in the Supplementary Appendix, available with the full text of this letter at NEJM.org. NA denotes not available, and SARS-CoV-2 severe acute respiratory syndrome coronavirus 2.
† Shown is the efficacy of the vaccine, as compared with placebo, against moderate-to-severe Covid-19.
‡ Shown is efficacy of the vaccine, as compared with placebo, against severe Covid-19 and hospitalization.
§ Shown is efficacy of the vaccine, as compared with placebo, against symptomatic Covid-19.
¶ Data are shown separately for the trial sites in Brazil and Turkey.

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	Británica	Sudafricana	Brasileña*
Pfizer			?
Moderna			?
Astra-Zeneca			?
Janssen			?
Novavax			?

*No hay suficiente evidencia sobre el efecto de las vacunas en algunas variantes.

Todas las vacunas han demostrado eficacia frente al riesgo de desarrollar enfermedad grave, hospitalización o muerte por todas las variantes

CORRESPONDENCE

Effectiveness of the BNT162b2 Covid-19 Vaccine against the B.1.1.7 and B.1.351 Variants

TO THE EDITOR: The messenger RNA vaccine BNT162b2 (Pfizer–BioNTech) has 95% efficacy against coronavirus disease 2019 (Covid-19).[1] Qatar launched a mass immunization campaign with this vaccine on December 21, 2020. As of March 31, 2021, a total of 385,853 persons had received at least one vaccine dose and 265,410 had completed the two doses. Vaccination scale-up occurred as Qatar was undergoing its second and third waves of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection, which were triggered by expansion of the B.1.1.7 variant (starting in mid-January 2021) and the B.1.351 variant (starting in mid-February 2021). The B.1.1.7 wave peaked during the first week of March, and the rapid expansion of B.1.351 started in mid-March and continues to the present day. Viral genome sequencing conducted from February 23 through March 18 indicated that 50.0% of cases of Covid-19 in Qatar were caused by B.1.351 and 44.5% were caused by B.1.1.7. Nearly all cases in which virus was sequenced after March 7 were caused by either B.1.351 or B.1.1.7.

Data on vaccinations, polymerase-chain-reaction testing, and clinical characteristics were extracted from the national, federated Covid-19 databases that have captured all SARS-CoV-2–related data since the start of the epidemic (Section S1 of the Supplementary Appendix, available with the full text of this letter at NEJM.org). Vaccine effectiveness was estimated with a test-negative case–control study design, a preferred design for assessing vaccine effectiveness against influenza (see the Supplementary Appendix).[2] A key strength of this design is the ability to control for bias that may result from differences in health care–seeking behavior between vaccinated and unvaccinated persons.[2]

The estimated effectiveness of the vaccine against any documented infection with the B.1.1.7 variant was 89.5% (95% confidence interval [CI], 85.9 to 92.3) at 14 or more days after the second dose (Table 1 and Table S2). The effectiveness against any documented infection with the B.1.351 variant was 75.0% (95% CI, 70.5 to 78.9). Vaccine effectiveness against severe, critical, or fatal disease due to infection with any SARS-CoV-2 (with the B.1.1.7 and B.1.351 variants being predominant within Qatar) was very high, at 97.4% (95% CI, 92.2 to 99.5). Sensitivity analyses confirmed these results (Table S3).

Vaccine effectiveness was also assessed with the use of a cohort study design by comparing the incidence of infection among vaccinated persons with the incidence in the national cohort of persons who were antibody-negative (Section S2). Effectiveness was estimated to be 87.0% (95% CI, 81.8 to 90.7) against the B.1.1.7 variant and 72.1% (95% CI, 66.4 to 76.8) against the B.1.351 variant, findings that confirm the results reported above.

The BNT162b2 vaccine was effective against infection and disease in the population of Qatar, despite the B.1.1.7 and B.1.351 variants being predominant within the country; however, vaccine effectiveness against the B.1.351 variant was approximately 20 percentage points lower than the effectiveness (>90%) reported in the clinical trial[1] and in real-world conditions in Israel[4] and the United States.[5] In Qatar, as of March 31, breakthrough infections have been recorded in 6689 persons who had received one dose of the vaccine and in 1616 persons who had received two doses. Seven deaths from Covid-19 have been also recorded among vaccinated persons: five after the first dose and two after the second dose. Nevertheless, the reduced protection against infection with the B.1.351 variant did not seem to translate into poor protection against

Table 1. Vaccine Effectiveness against Infection and against Disease in Qatar.

Type of Infection or Disease	PCR-Positive Persons		PCR-Negative Persons		Effectiveness (95% CI)*
	Vaccinated	Unvaccinated	Vaccinated	Unvaccinated	
	number of persons				*percent*
Infection					
PCR-confirmed infection with the B.1.1.7 variant†					
After one dose	892	18,075	1241	17,726	29.5 (22.9–35.5)
≥14 days after second dose	50	16,354	465	15,939	89.5 (85.9–92.3)
PCR-confirmed infection with the B.1.351 variant‡					
After one dose	1329	20,177	1580	19,926	16.9 (10.4–23.0)
≥14 days after second dose	179	19,396	698	18,877	75.0 (70.5–78.9)
Disease§					
Severe, critical, or fatal disease caused by the B.1.1.7 variant					
After one dose	30	468	61	437	54.1 (26.1–71.9)
≥14 days after second dose	0	401	20	381	100.0 (81.7–100.0)
Severe, critical, or fatal disease caused by the B.1.351 variant					
After one dose	45	348	35	358	0.0 (0.0–19.0)
≥14 days after second dose	0	300	14	286	100.0 (73.7–100.0)
Severe, critical, or fatal disease caused by any SARS-CoV-2					
After one dose	139	1,966	220	1,885	39.4 (24.0–51.8)
≥14 days after second dose	3	1,692	109	1,586	97.4 (92.2–99.5)

* Vaccine effectiveness was estimated with the use of a test-negative case–control study design,[2] with persons found positive by polymerase-chain-reaction (PCR) testing for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) serving as cases in the analysis and those found negative by PCR serving as controls. PCR-positive and PCR-negative persons were matched one to one according to age, sex, nationality, and reason for PCR testing. Vaccine effectiveness was calculated as described by Jackson and Nelson[2] (see the Supplementary Appendix).

† A B.1.1.7 infection was identified as an S gene "target failure" in an analysis conducted with the TaqPath COVID-19 Combo Kit platform (Thermo Fisher Scientific), with the criteria of a PCR cycle threshold value no higher than 30 for the genes encoding both the nucleocapsid protein (N) and ORF1ab but a negative outcome for the gene encoding the spike protein (S) applied. The median date of vaccination was March 1 for PCR-positive persons and February 28 for the matched PCR-negative persons.

‡ Because only B.1.351 and B.1.1.7 viruses were identified in viral genome sequencing in Qatar after March 7, 2021, the criteria used to identify a B.1.351 infection involved the complement of the criterion for S that was used to identify a B.1.1.7 infection — that is, any infection with a cycle threshold value no higher than 30 for the genes encoding N, ORF1ab, and S between March 8 and March 31 was regarded as a B.1.351 infection. The median date of vaccination was March 7 for the PCR-positive persons and March 1 for the matched PCR-negative persons.

§ Effectiveness against severe, critical, or fatal disease caused by PCR-confirmed SARS-CoV-2 infection was analyzed. The B.1.1.7 and B.1.351 variants were dominant in Qatar during the study period. Severe, critical, and fatal coronavirus disease 2019 (Covid-19) were defined on the basis of the World Health Organization criteria[3] for classifying SARS-CoV-2 infection severity and Covid-19–related death.

Comunidad de Madrid

¿Por qué hay que seguir vacunando?

Las vacunas COVID son altamente eficaces.

- Las vacunas actuales causan una potente respuesta inmune.
- Los anticuerpos no son la única parte de las vacunas que las hace funcionar.
- También hay células T y células B de memoria y otros tipos de anticuerpos.

Las vacunas previenen la hospitalización y la muerte.

Todas las vacunas actuales son eficaces para prevenir la hospitalización y la muerte.

Las vacunas ayudan a detener nuevas variantes.

- A mayor número de personas vacunadas, podemos detener la propagación.
- Una lenta transmisión significa menos riesgo para mutar, puede ayudar a prevenir la aparición de cualquier otra variante.

Las vacunas pueden actualizarse para ser más eficaces.

Es posible modificar las vacunas COVID-19 en el futuro para aumentar si eficacia ante las variantes.