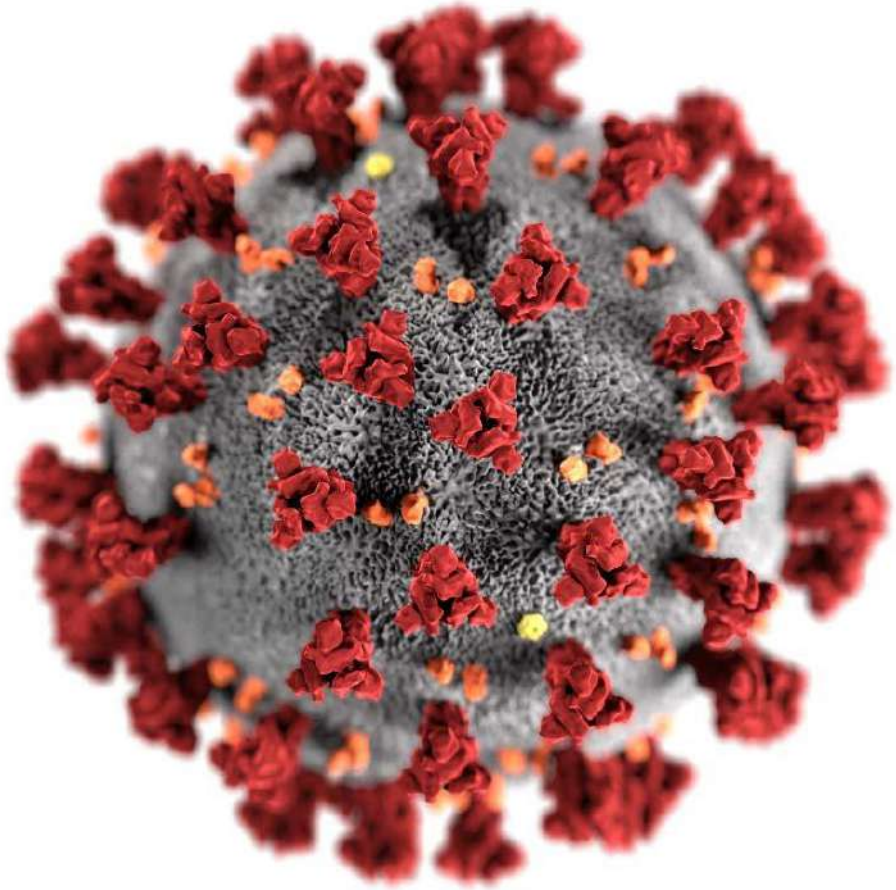
Vacunas SARS-CoV-2

Dr. Luis Miguel Noriega



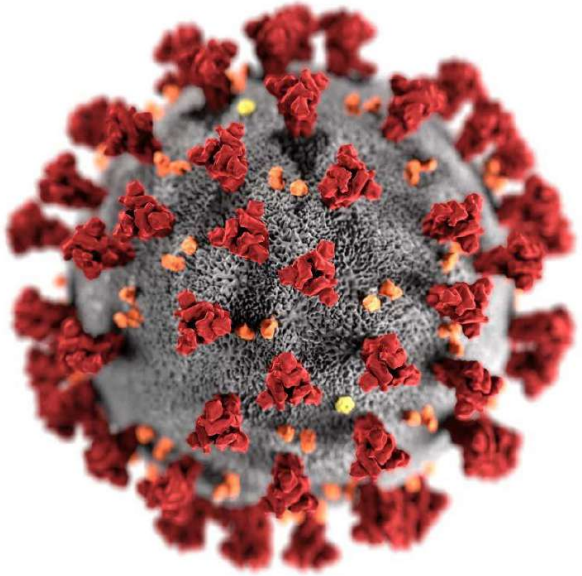
CURSO Universitario
Trienal de Clínica Médica – Medicina Interna 2021

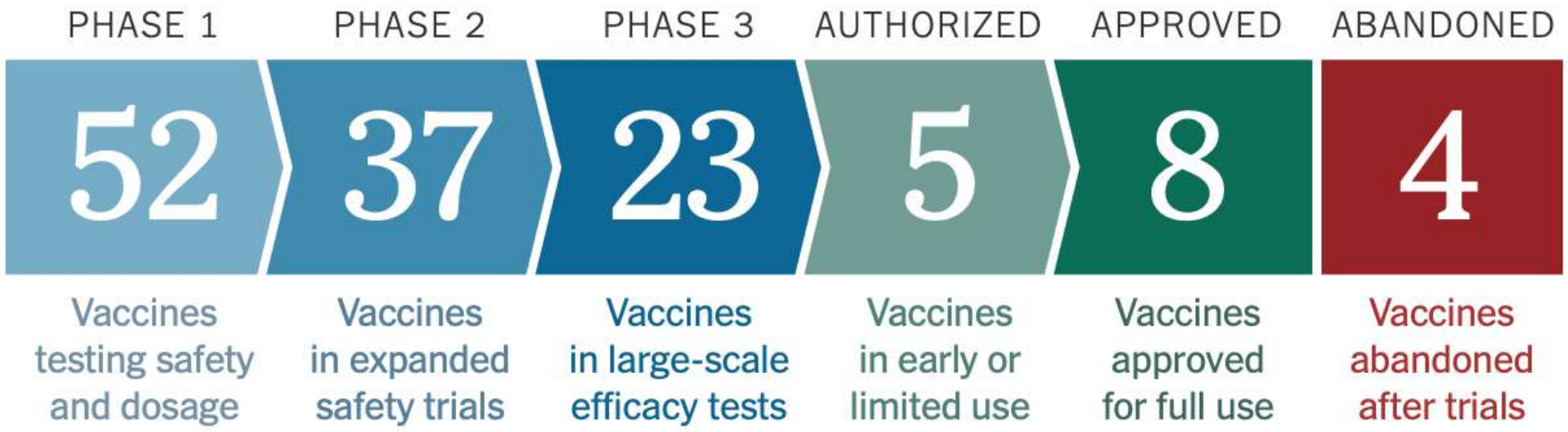
SMI BA Sociedad de MEDICINA INTERNA de Buenos Aires

- Tipos de vacuna
- Estudios de eficacia y efectividad
- Variantes y vacunas
- Efectos adversos

Sin conflictos de interés

Coronavirus Vaccine Tracker



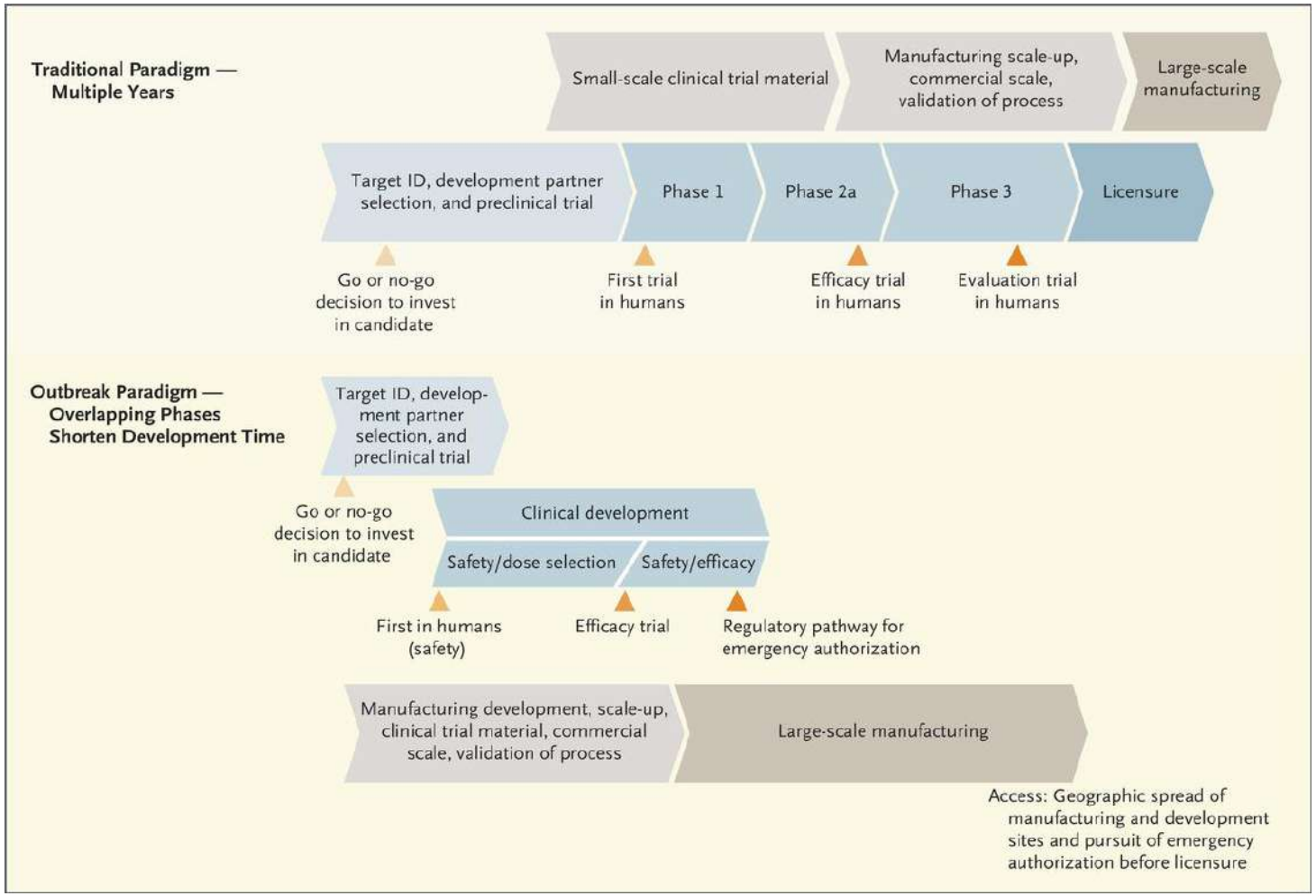


The New York Times, actualizado 20 de abril 2021

Desarrollo tradicional de vacunas vs estrategia en pandemia

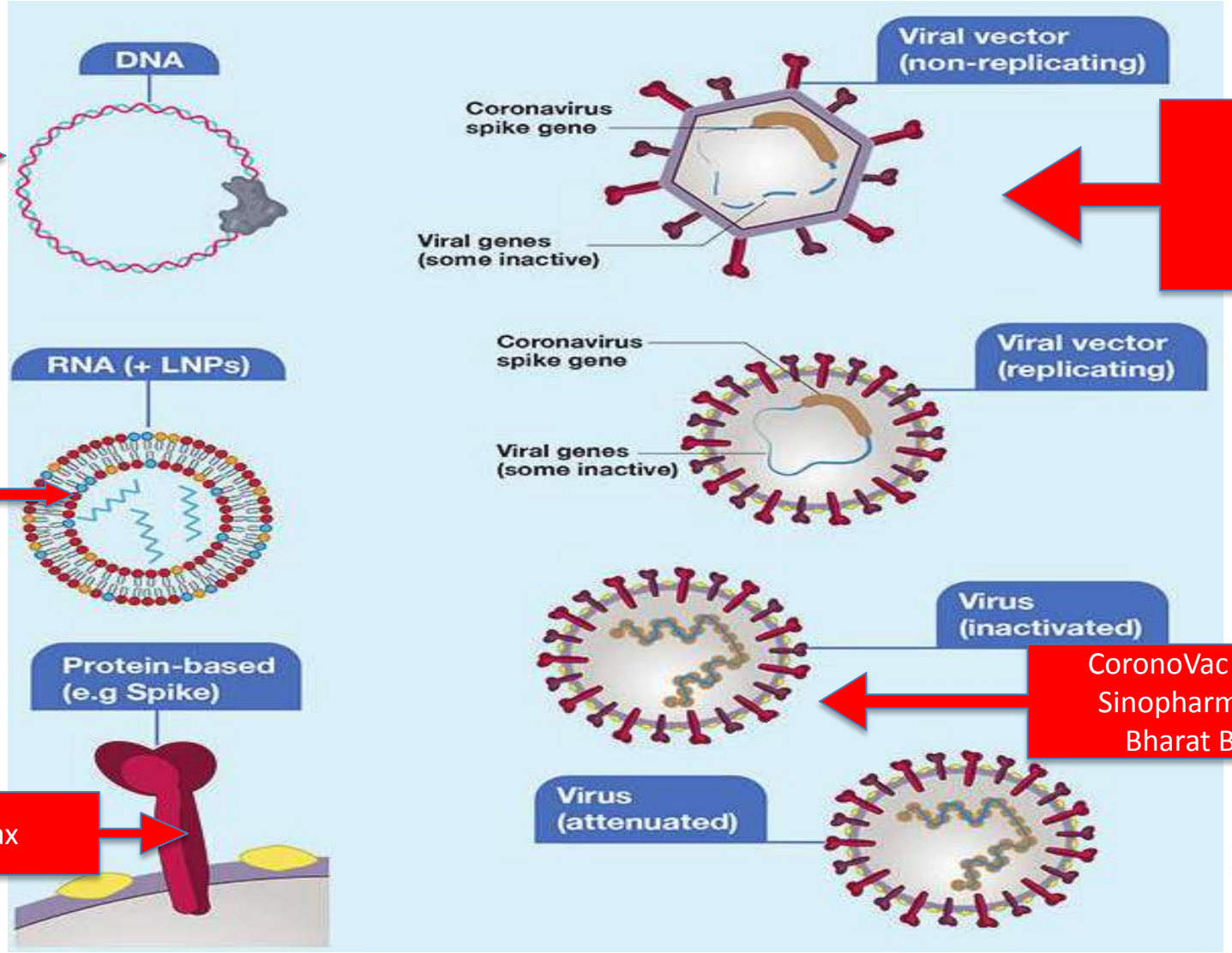
15 años

10 a 18 meses



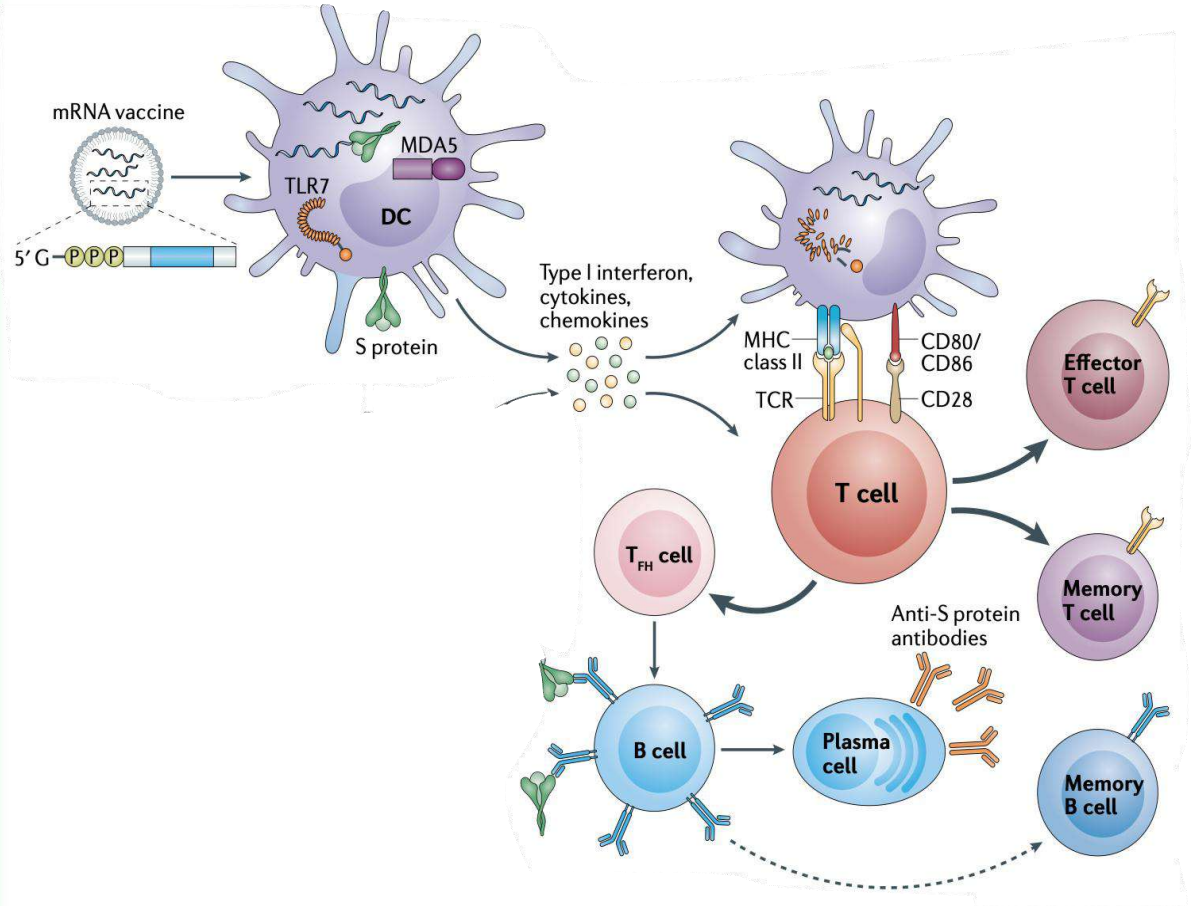
N Lurie et al. N Engl J Med 2020;382:1969-1973.

Vacunas SARS-CoV-2 con fase 3 en curso



Funk. Frontiers in Pharmacology. 2020; 11:937.

Vacunas SARS-CoV-2 mRNA



Tipo de vacuna		Etapa
mRNA Nanoparticulas	BNT 162 Pfizer-BioNTech (USA-Alemania)	Fase 3 Autorización uso emergencia
mRNA Nanoparticulas	mRNA-1273 Moderna (USA)	Fase 3 Autorización uso emergencia

Vacunas mRNA SARS-CoV-2

The NEW ENGLAND JOURNAL of MEDICINE

RESEARCH SUMMARY

Safety and Efficacy of the BNT162b2 mRNA Covid-19 Vaccine

F.P. Polack, et al. DOI: 10.1056/NEJMoa2034577

CLINICAL TRIAL

A randomized, double-blind study of an mRNA vaccine encoding the SARS-CoV-2 spike protein.

43,548 participants ≥16 years old were assigned to receive the vaccine or placebo by intramuscular injection on day 0 and day 21. Participants were followed for safety and for the development of symptomatic Covid-19 for a median of 2 months.

The NEW ENGLAND JOURNAL of MEDICINE

RESEARCH SUMMARY

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

L.R. Baden, et al. DOI: 10.1056/NEJMoa2035389

CLINICAL TRIAL

A randomized, double-blind trial to evaluate the efficacy and safety of mRNA-1273.

30,420 participants ≥18 years old were assigned to receive either the vaccine or placebo in two intramuscular injections 28 days apart. Participants were followed for safety and the development of laboratory-confirmed, symptomatic Covid-19 over a median of 2 months after the second dose.

Vacunas mRNA SARS-CoV-2

The NEW ENGLAND JOURNAL of MEDICINE

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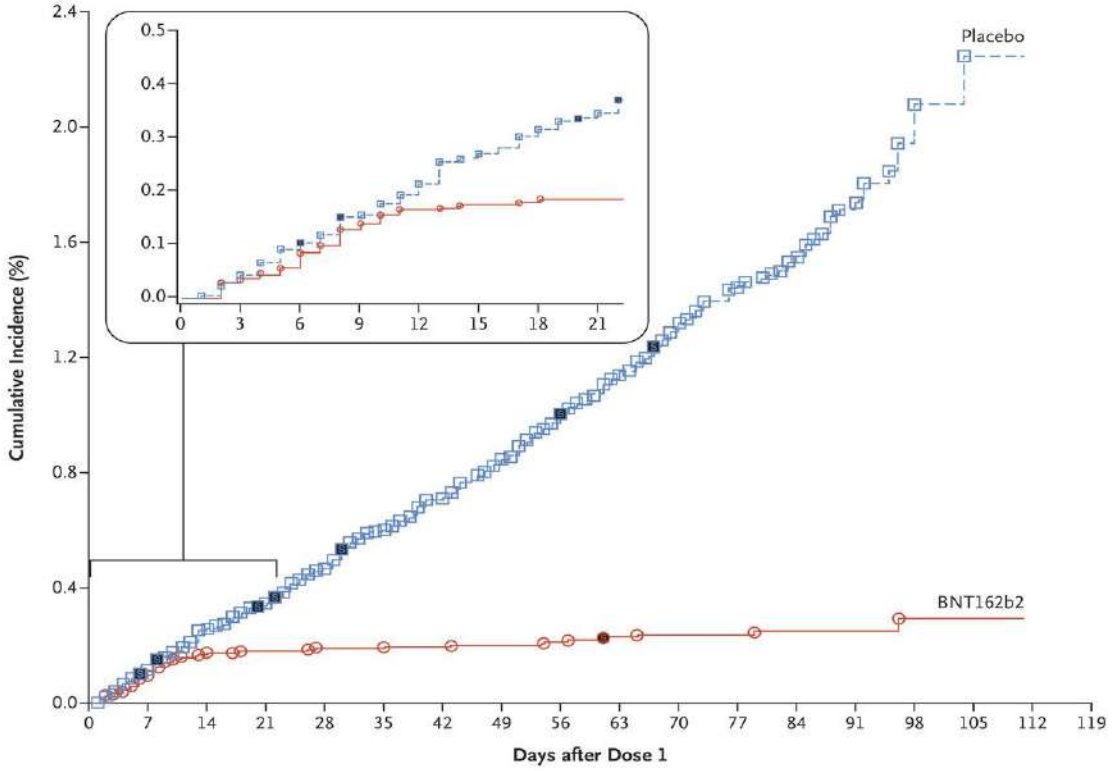
Safety and Efficacy of the BNT162b2 mRNA Covid-19 Vaccine

F.P. Polack, et al. DOI: 10.1056/NEJMoa2034577



Efficacy End-Point Subgroup	BNT162b2, 30 μg (N=21,669) No. of participants	BNT162b2, 30 μg (N=21,669) Surveillance time person-yr (no. at risk)	Placebo (N=21,686) No. of participants	Placebo (N=21,686) Surveillance time person-yr (no. at risk)	VE (95% CI) percent
Covid-19 occurrence					
After dose 1	50	4.015 (21,314)	275	3.982 (21,258)	82.0 (75.6–86.9)
After dose 1 to before dose 2	39		82		52.4 (29.5–68.4)
Dose 2 to 7 days after dose 2	2		21		90.5 (61.0–98.9)
≥7 Days after dose 2	9		172		94.8 (89.8–97.6)

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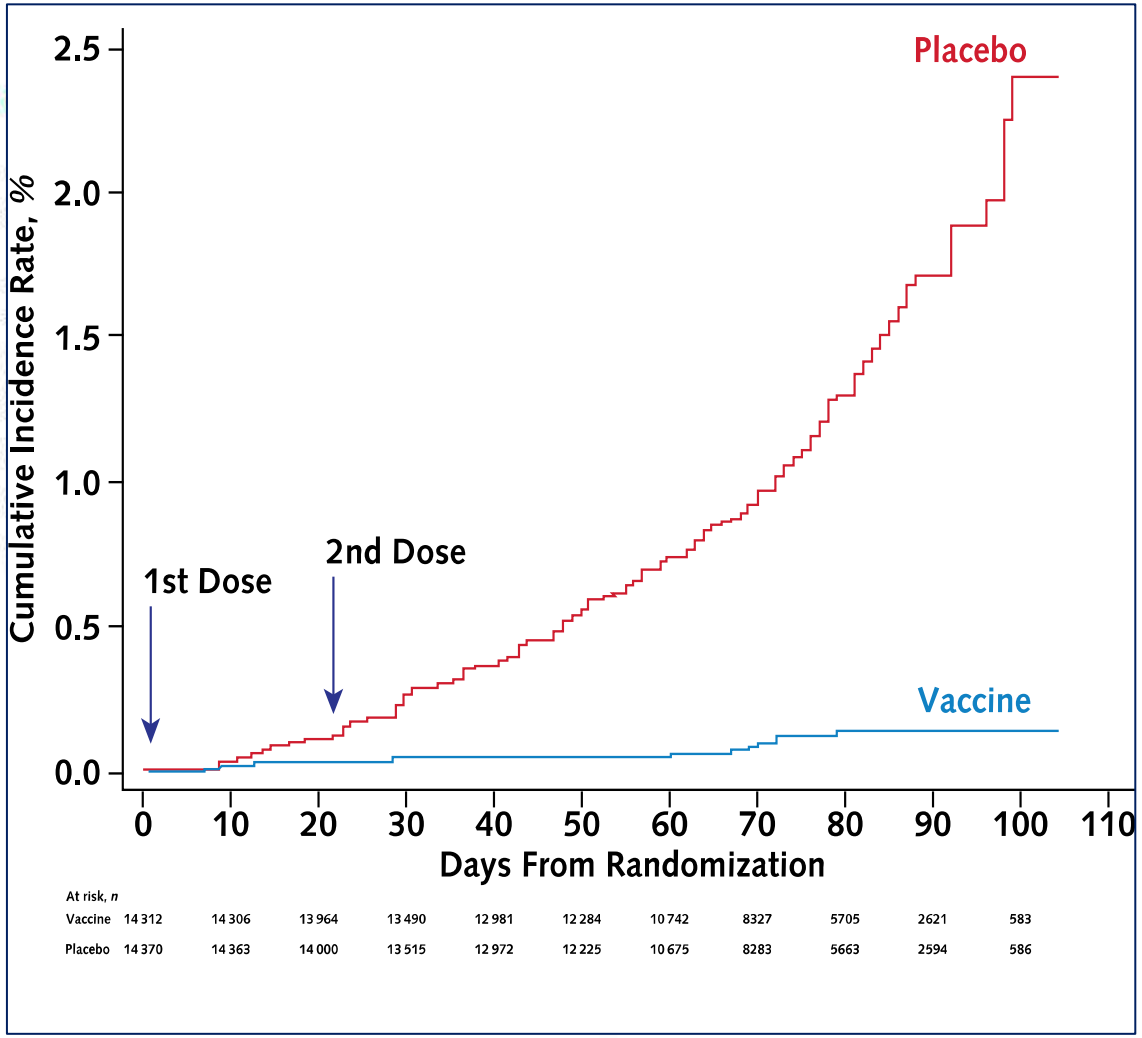

Vacunas mRNA SARS-CoV-2

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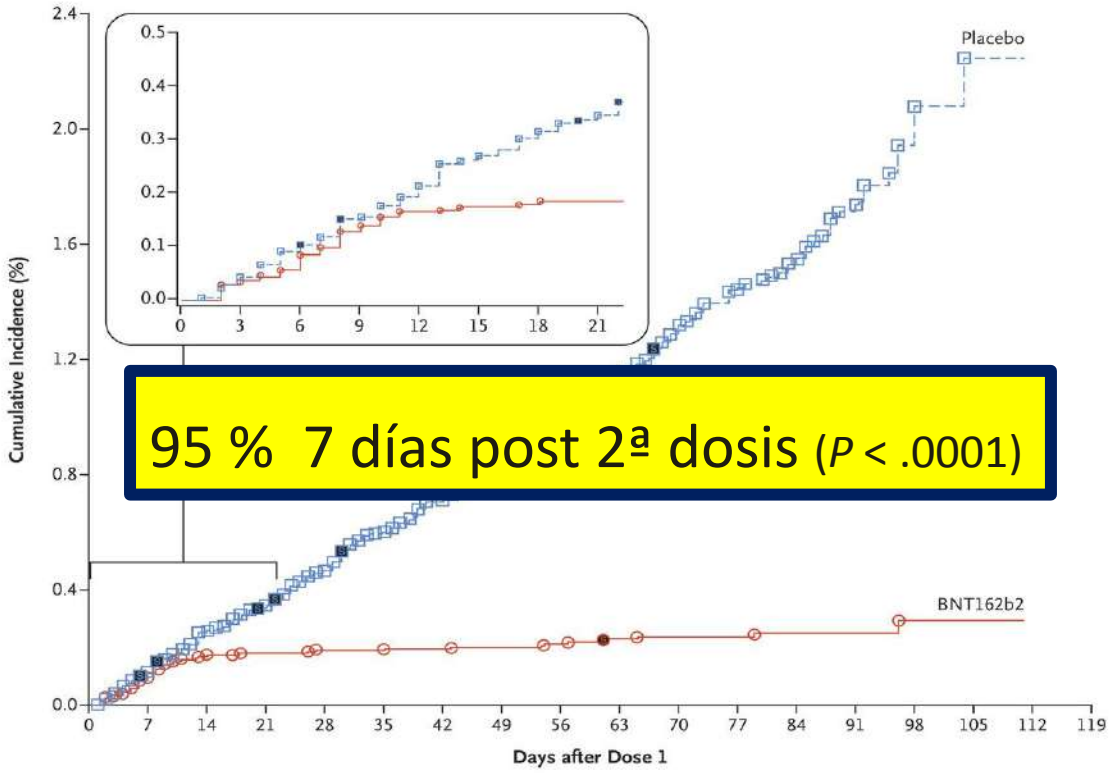

95 % 7 días post 2ª dosis ($P < .0001$)

Efficacy End-Point Subgroup	BNT162b2, 30 μg (N=21,669) No. of participants	BNT162b2, 30 μg (N=21,669) Surveillance time *person-yr (no. at risk)*	Placebo (N=21,686) No. of participants	Placebo (N=21,686) Surveillance time *person-yr (no. at risk)*	VE (95% CI) *percent*
Covid-19 occurrence					
After dose 1	50	4.015 (21,314)	275	3.982 (21,258)	82.0 (75.6–86.9)
After dose 1 to before dose 2	39		82		52.4 (29.5–68.4)
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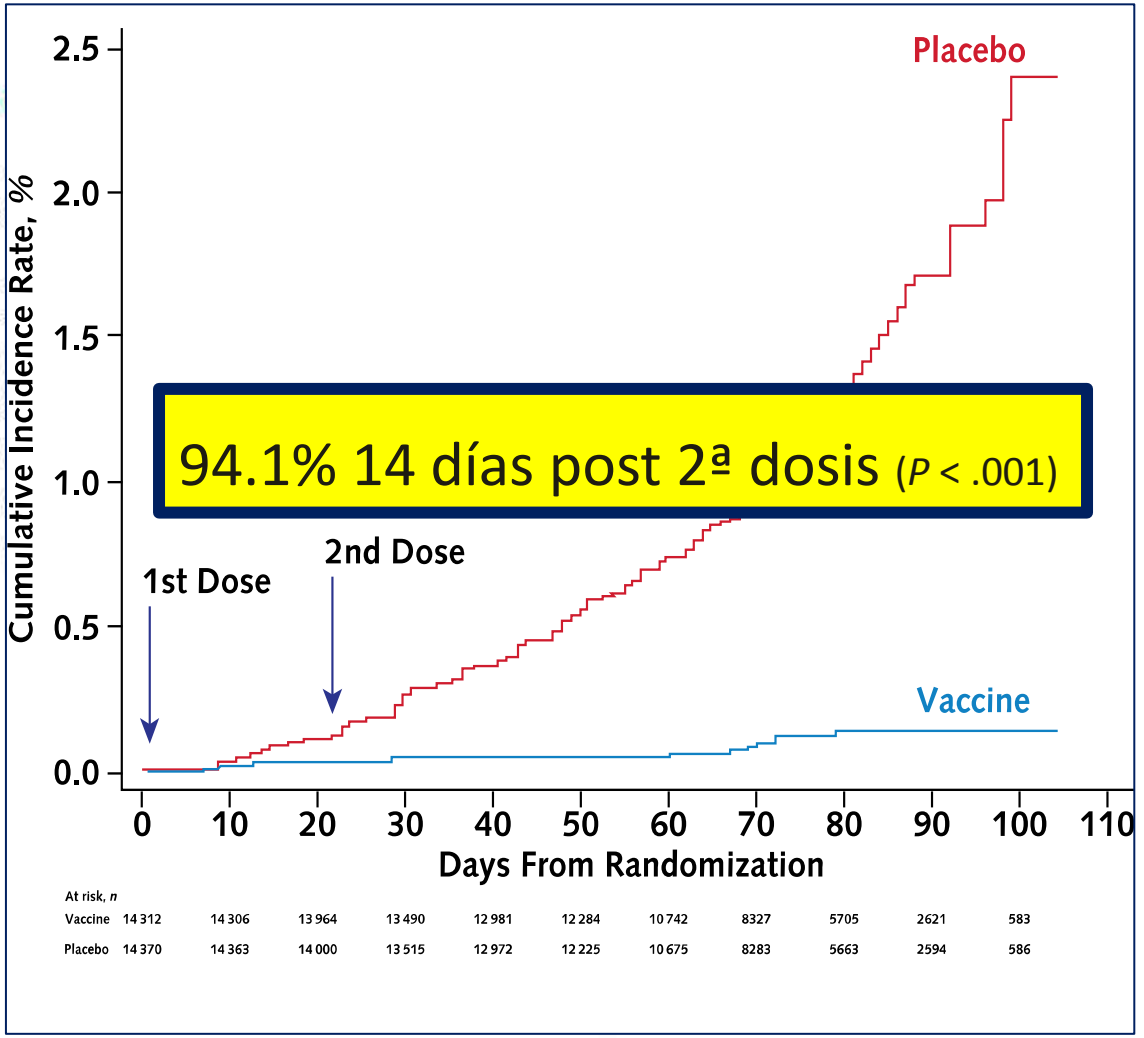
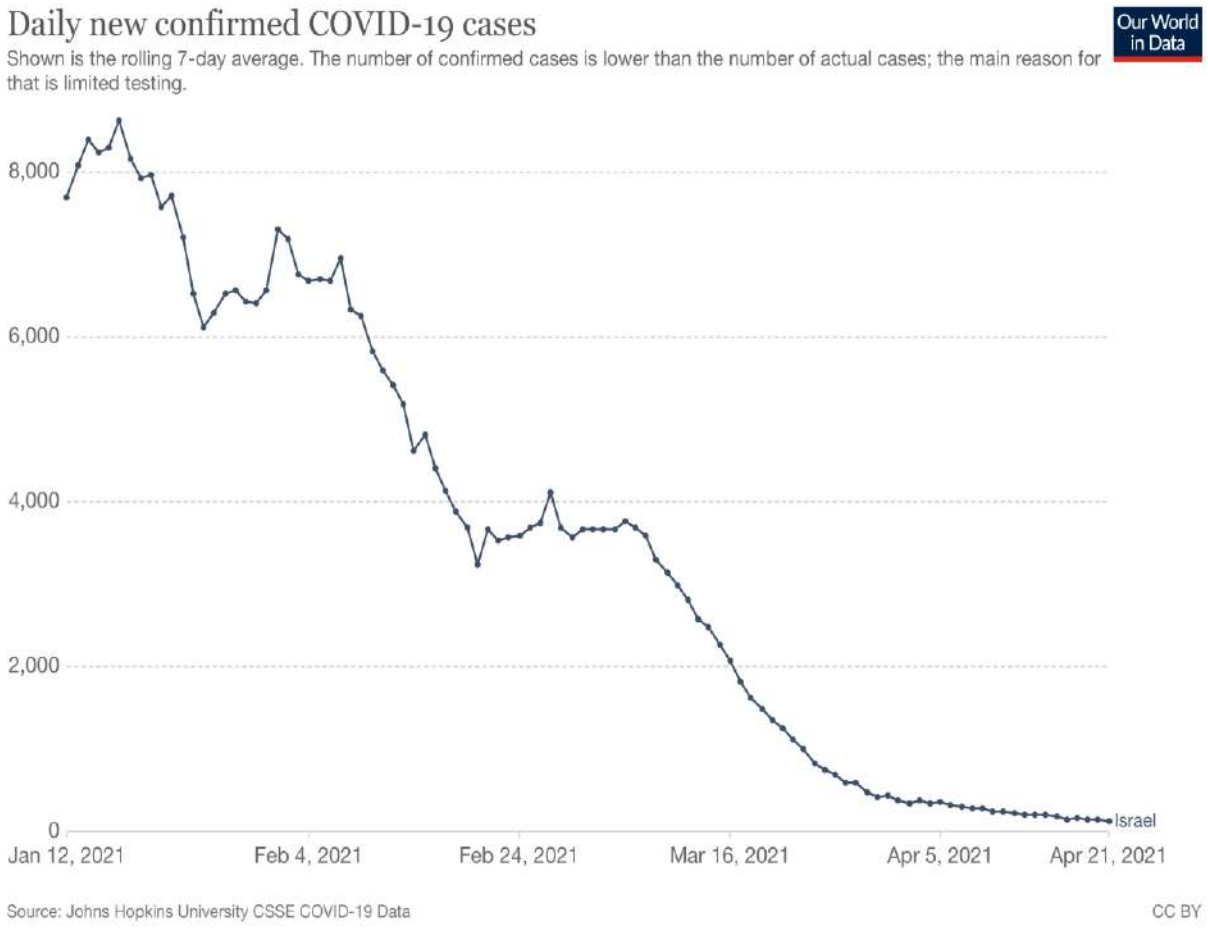
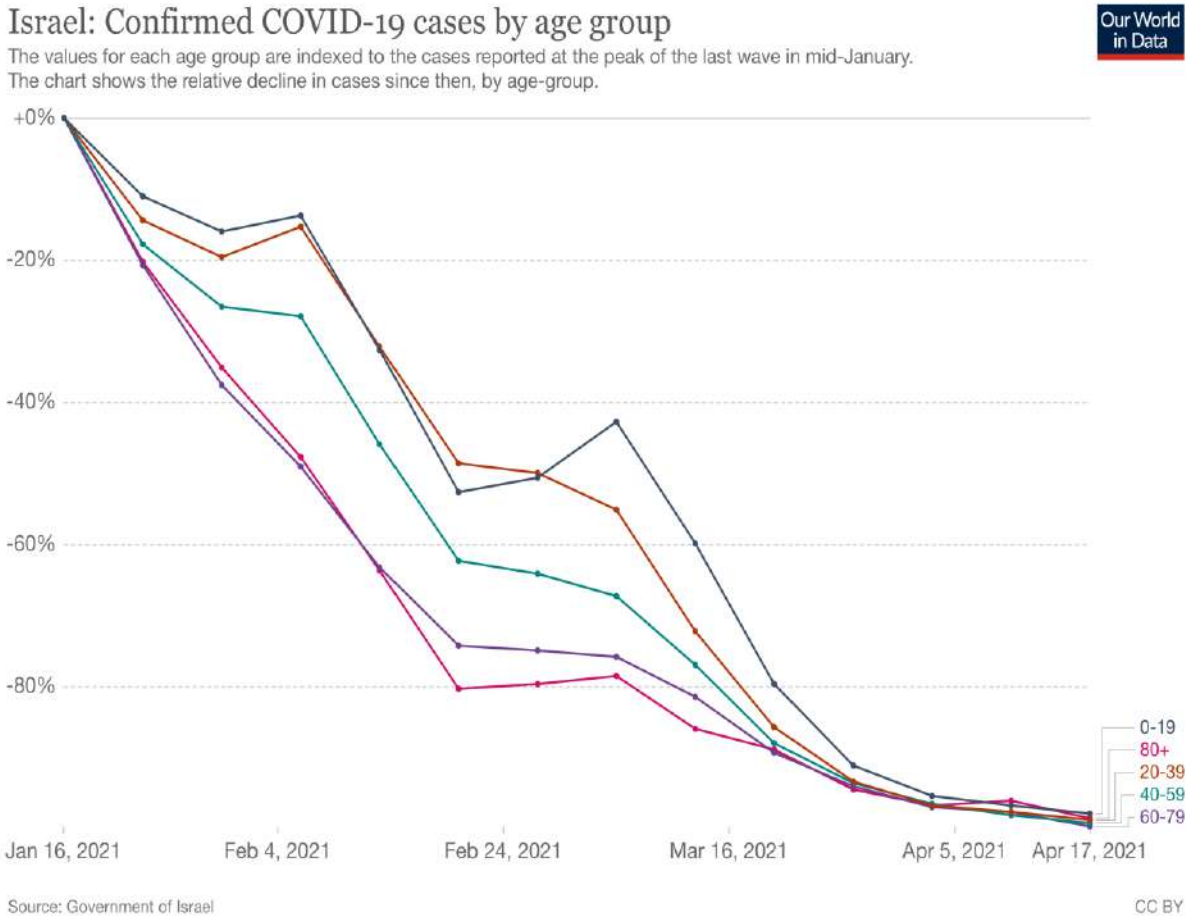


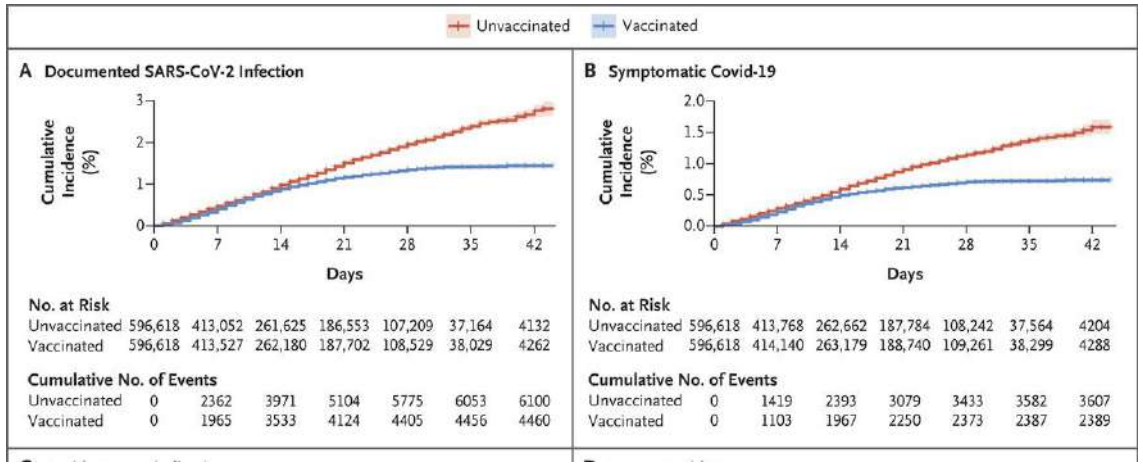
94.1% 14 días post 2ª dosis ($P < .001$)

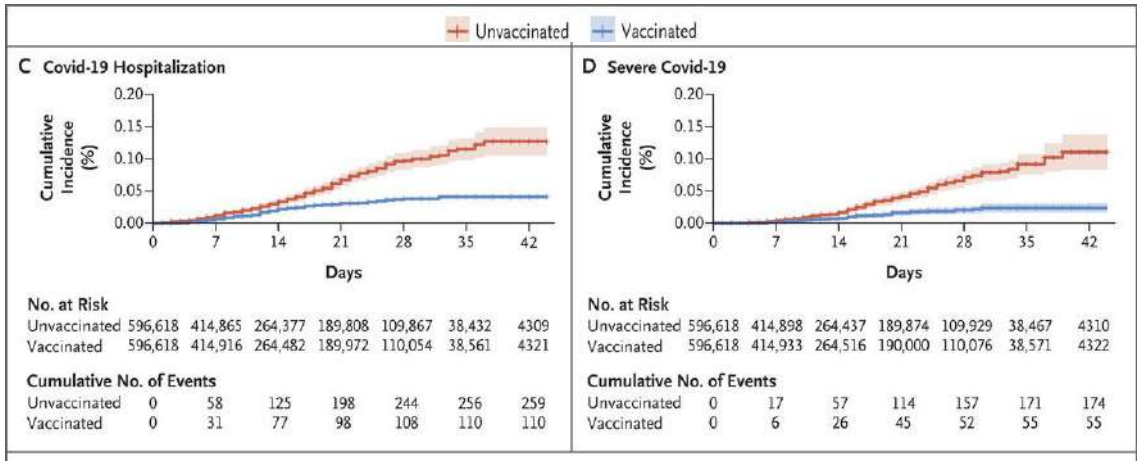
Vacuna BNT162b2 en vida real: Israel

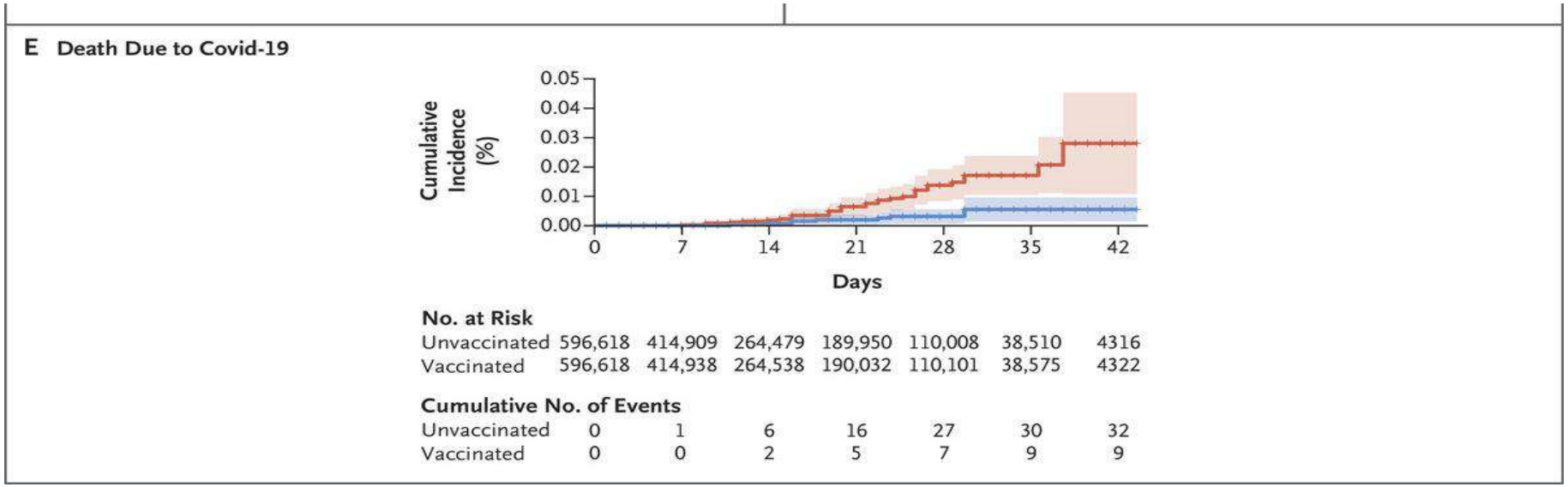




Vacuna BNT162b2 Israel: incidencia acumulativa de 5 outcomes

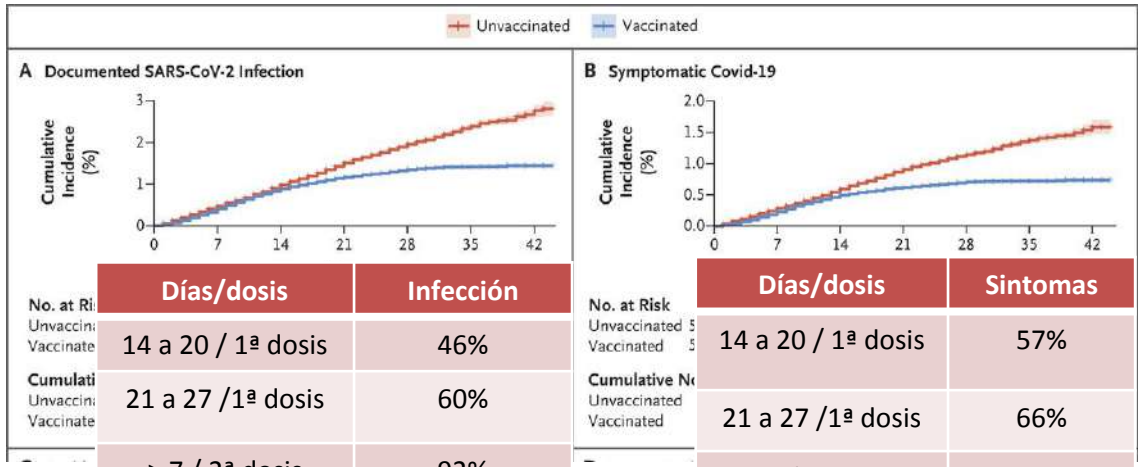






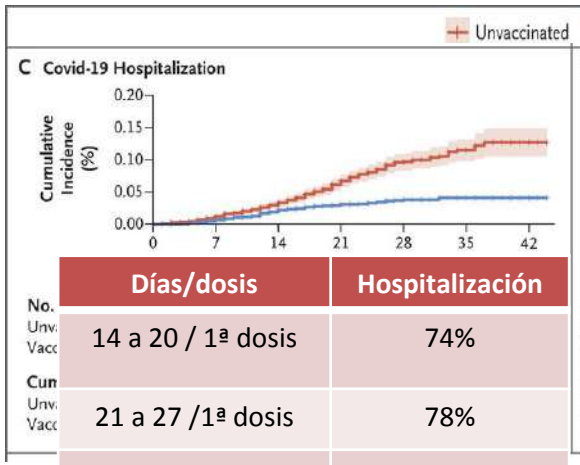
N Dagan et al. N Engl J Med 2021

Vacuna BNT162b2 Israel: incidencia acumulativa de 5 outcomes

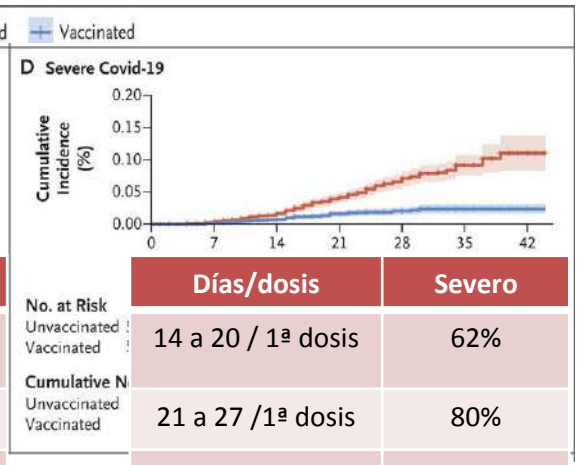


Días/dosis	Infección
14 a 20 / 1ª dosis	46%
21 a 27 /1ª dosis	60%
> 7 / 2ª dosis	92%

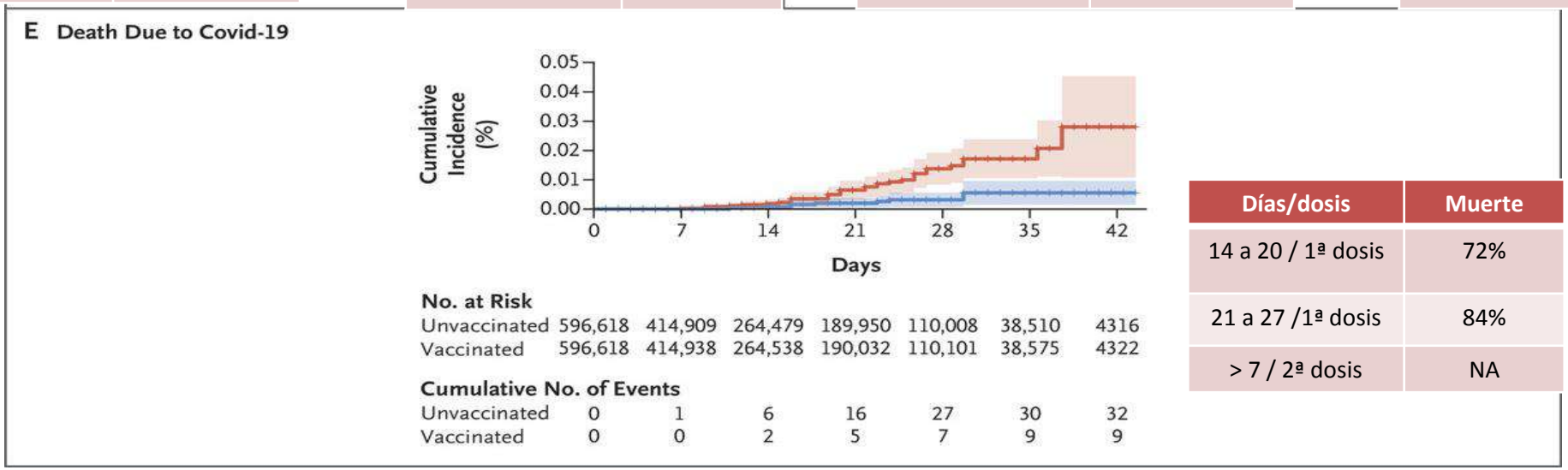
Días/dosis	Sintomas
14 a 20 / 1ª dosis	57%
21 a 27 /1ª dosis	66%
> 7 / 2ª dosis	94%



Días/dosis	Hospitalización
14 a 20 / 1ª dosis	74%
21 a 27 /1ª dosis	78%
> 7 / 2ª dosis	87%



Días/dosis	Severo
14 a 20 / 1ª dosis	62%
21 a 27 /1ª dosis	80%
> 7 / 2ª dosis	92%

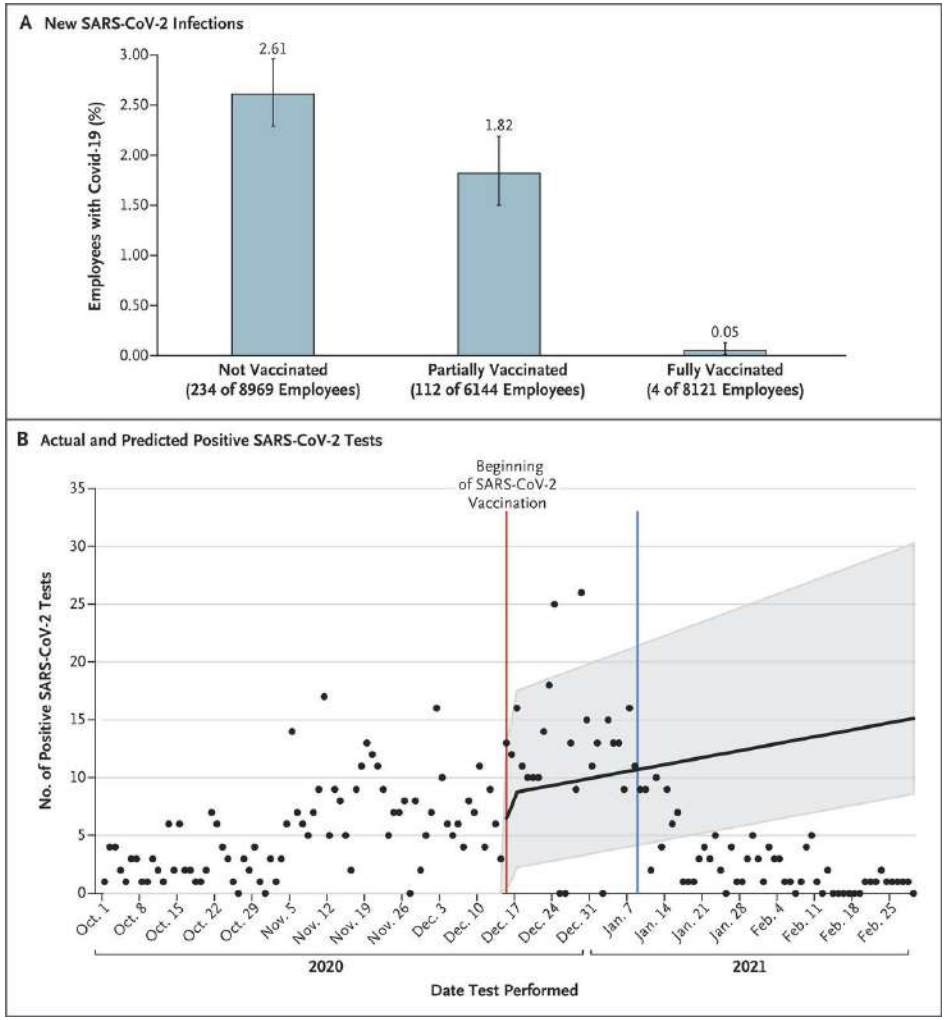


Días/dosis	Muerte
14 a 20 / 1ª dosis	72%
21 a 27 /1ª dosis	84%
> 7 / 2ª dosis	NA

N Dagan et al. N Engl J Med 2021

Vacuna BNT162b2 y mRNA-1273 en vida real

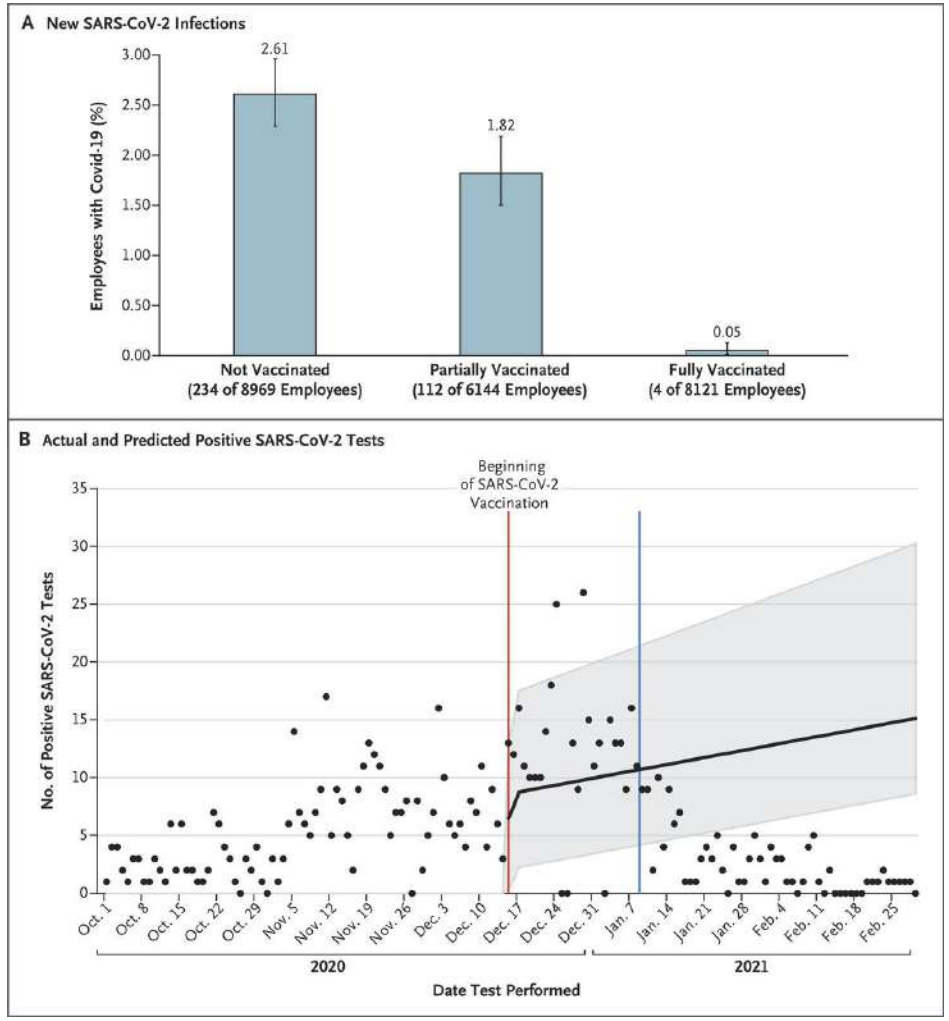
Universidad Texas, N 23234, BNT162b2



W Daniel et al. N Engl J Med 2021, MMWR 2021

Vacuna BNT162b2 y mRNA-1273 en vida real

Universidad Texas, N 23234, BNT162b2



Varios centros, 4000 personal de salud, BNT162b2 and mRNA-1273

TABLE 2. Person-days, SARS-CoV-2 infections, and vaccine effectiveness among health care personnel, first responders, and other essential and frontline workers, by messenger RNA immunization status — eight U.S. locations, December 14, 2020–March 13, 2021

		SARS-CoV-2 infections		Unadjusted vaccine effectiveness*	Adjusted vaccine effectiveness*,†
COVID-19 immunization status	Person-days	No.	Incidence rate per 1,000 person-days	% (95% CI)	% (95% CI)
Unvaccinated	116,657	161	1.38	N/A	N/A
Partially immunized	41,856	8	0.19	82 (62–91)	80 (59–90)
≥14 days after receiving first dose only§	15,868	5	0.32		
≥14 days after first dose through receipt of second dose	25,988	3	0.12		
Fully immunized					
≥14 days after second dose	78,902	3	0.04	91 (73–97)	90 (68–97)

Abbreviations: CI = confidence interval; N/A = not applicable.
* Vaccine effectiveness was estimated using a Cox proportional hazards model accounting for time-varying immunization status.
† Hazard ratio is adjusted for study site.
§ Participants received first dose but had not received second dose by the end of the study period.

W Daniel et al. N Engl J Med 2021, MMWR 2021

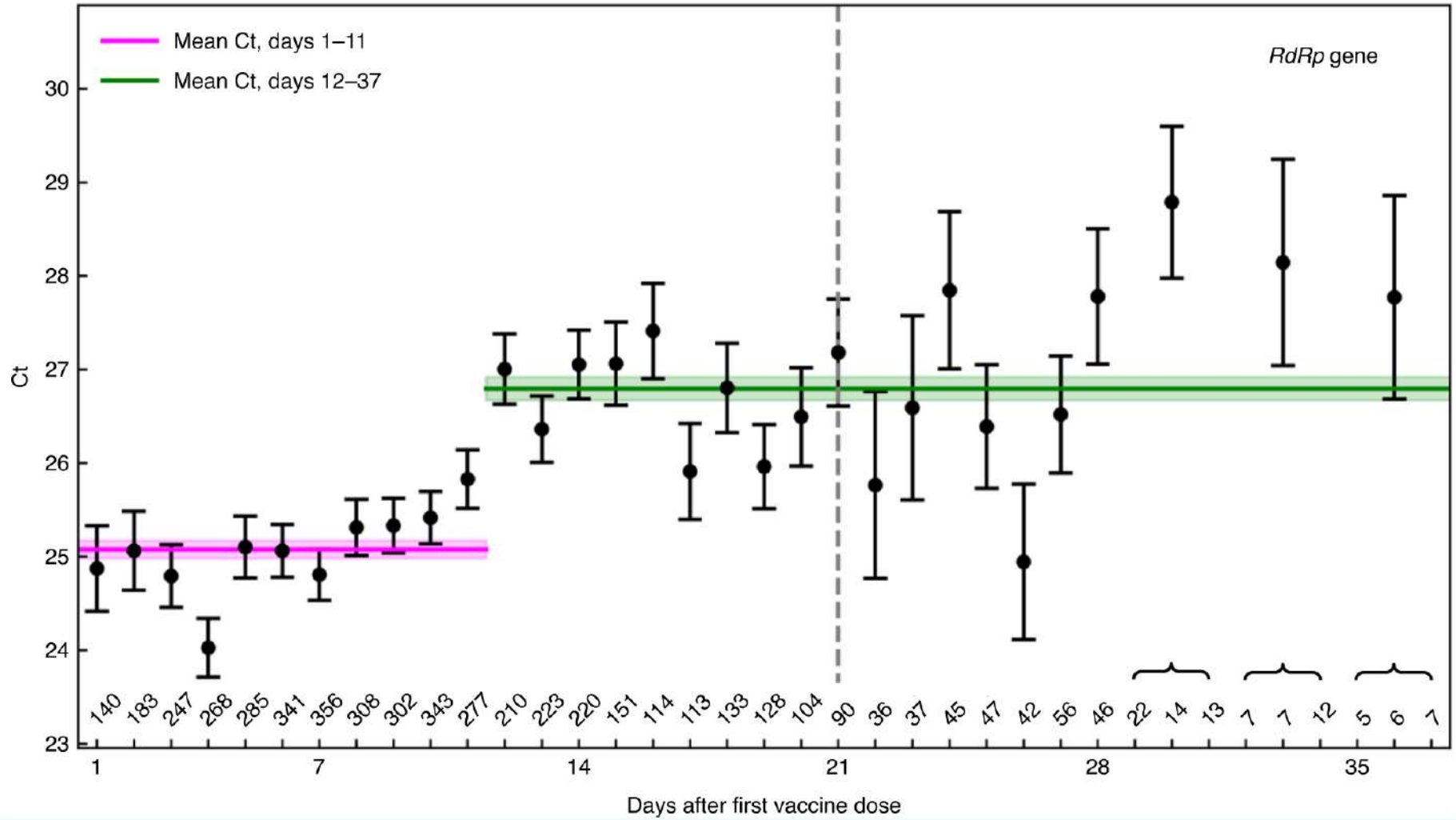
nature medicine

BRIEF COMMUNICATION

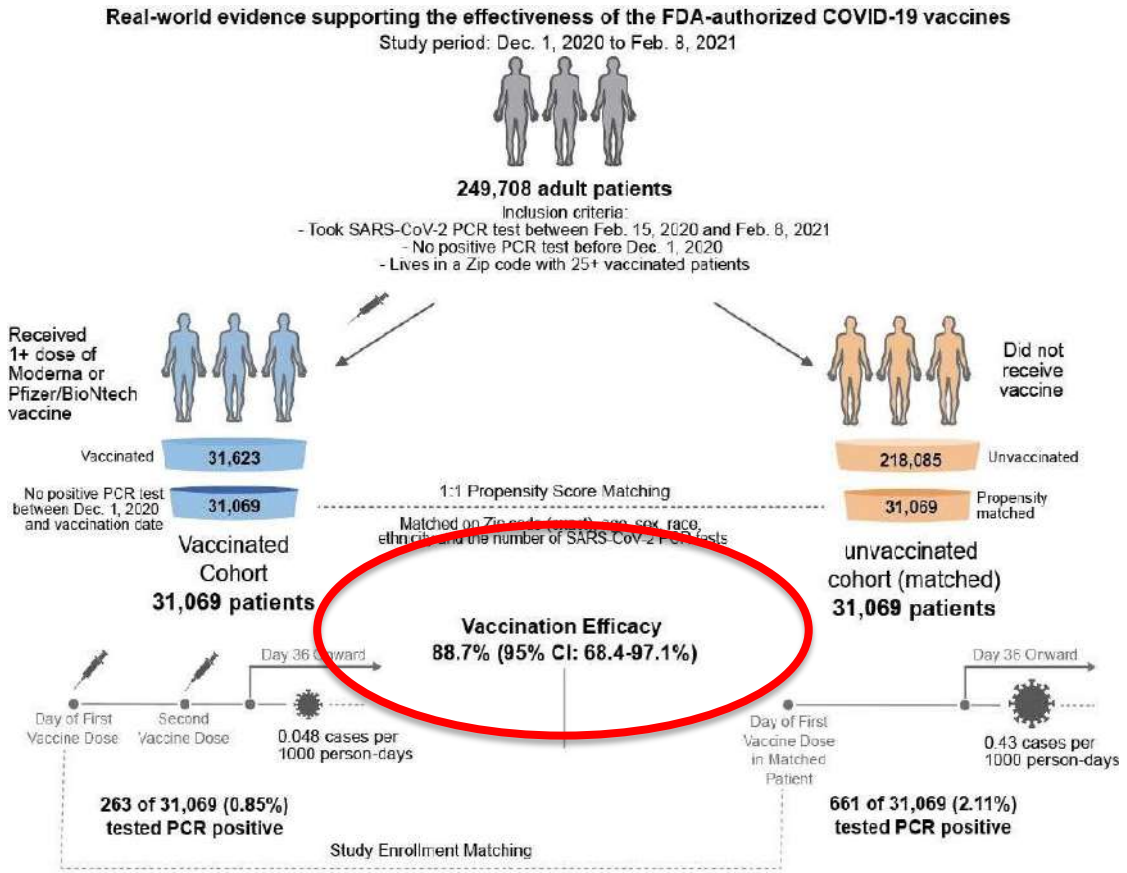
https://doi.org/10.1038/s41591-021-01316-7

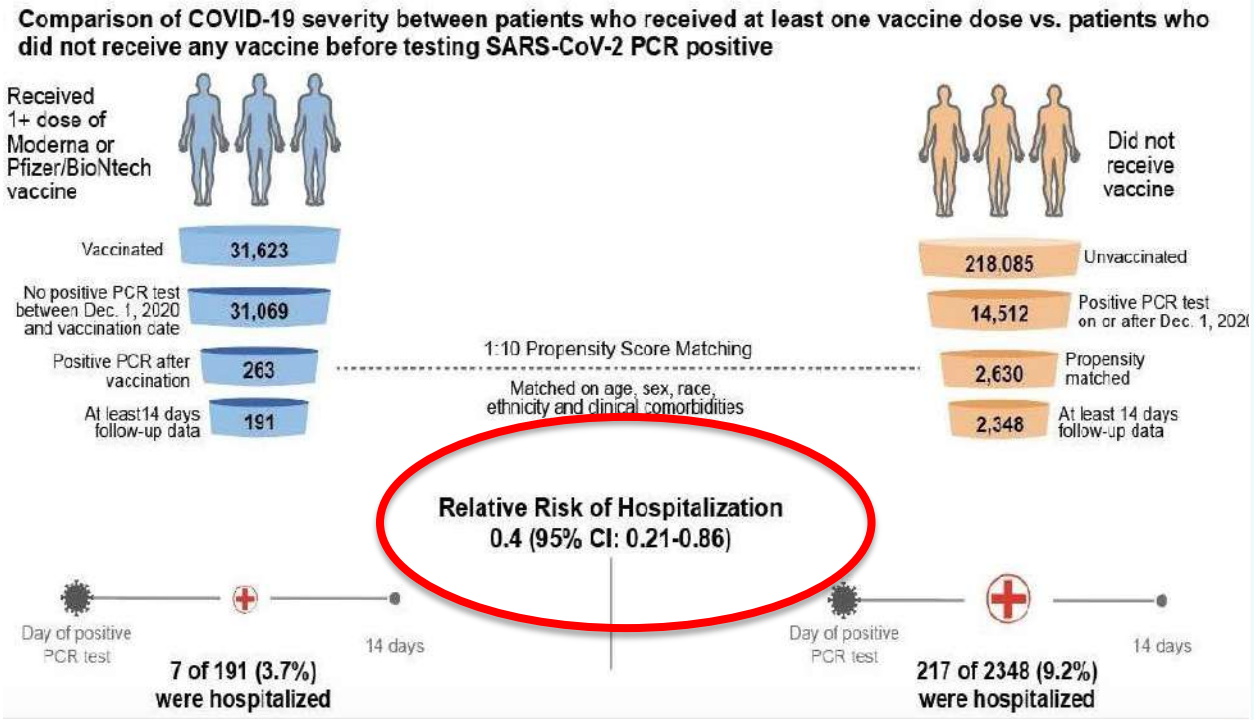
Initial report of decreased SARS-CoV-2 viral load after inoculation with the BNT162b2 vaccine

Matan Levine-Tiefenbrun[1,6], Idan Yelin[1,6]✉, Rachel Katz[2], Esma Herzel[2], Ziv Golan[3], Licita Schreiber[3], Tamar Wolf[3], Varda Nadler[3], Amir Ben-Tov[2,4], Jacob Kuint[2,4], Sivan Gazit[2], Tal Patalon[2], Gabriel Chodick[2,4] and Roy Kishony[1,5]✉



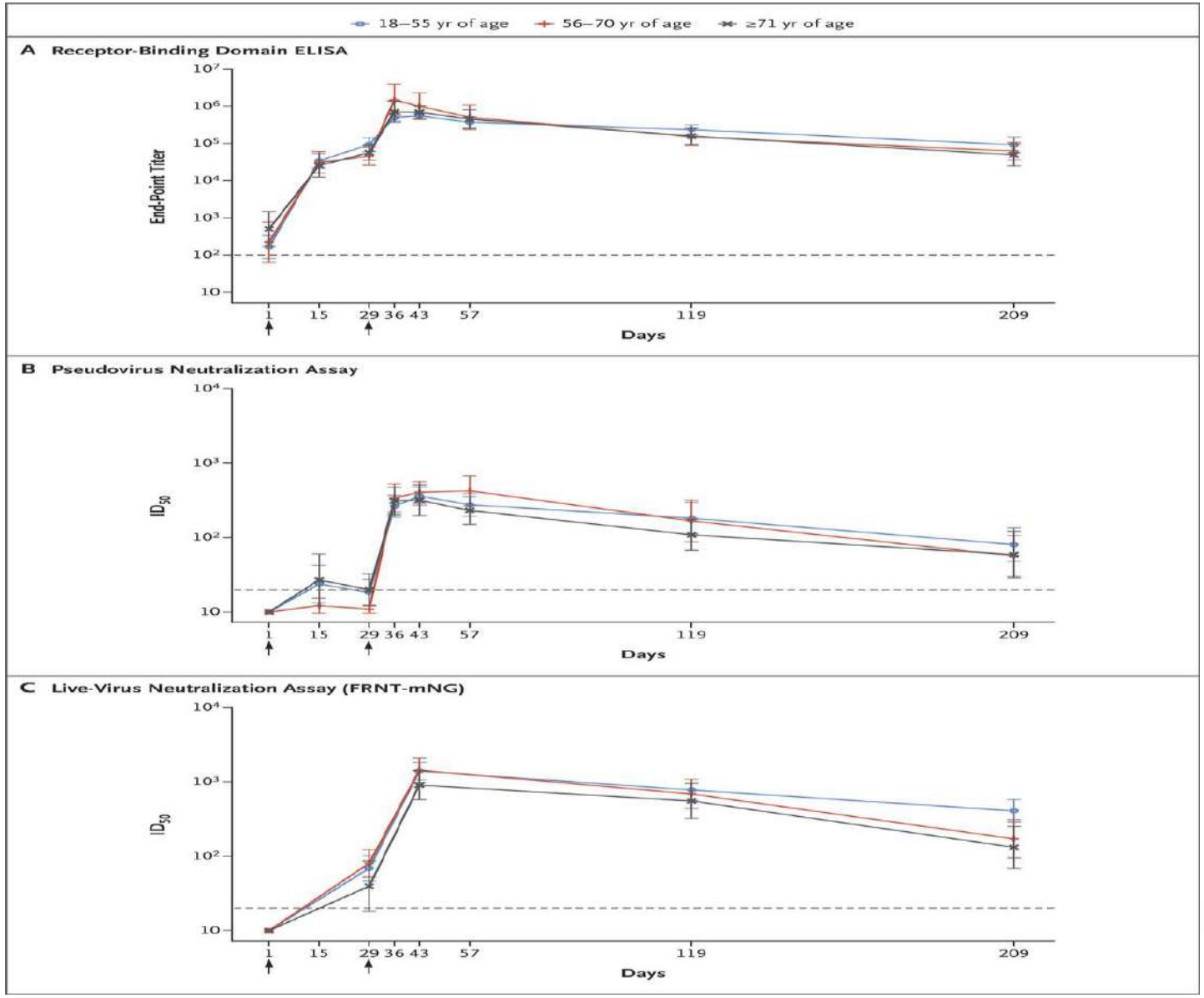
FDA-authorized COVID-19 vaccines are effective per real-world evidence synthesized across a multi-state health system





Pawlowski et al, https://doi.org/10.1101/2021.02.15.21251623

Ac SARS-CoV-2 post vacuna mRNA-1273

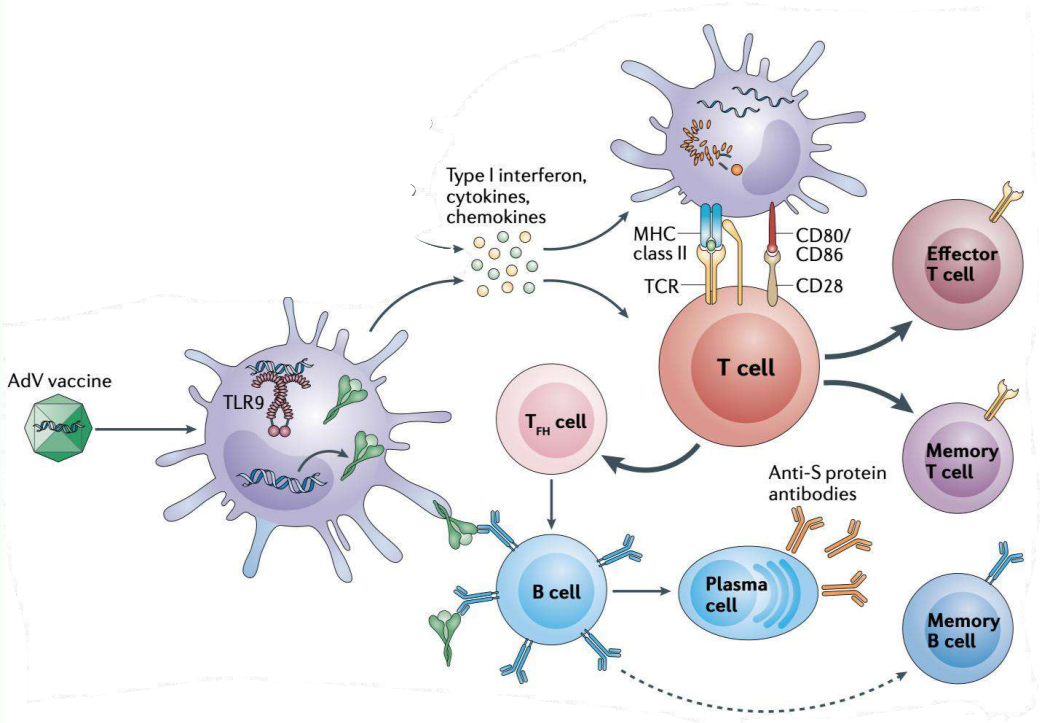


N Doria-Rose et al. N Engl J Med 2021.

Vacunas mRNA en mundo real

Cohort	N	Infection Rate	Reference
Nursing home residents and staff	2,916	0.9%	Teran R,, MMWR, CDC, 2021
Rockefeller University employees	417	0.4%	Hacisuleyman E, NEJM, 2021
University Texas Southwest HCW	8,121	0.05%	Daniel W, NEJM 2021
UCLA and UCSD HCW	4,167	0.17%	Keehner J, NEJM 2021
Mayo Clinic health system	31,069	0.85%	Pawlowski , medRxiv, 2021
CDC Frontline workers	2,479	0.12%	Thompson M, MMWR, CDC, 2021

Vacunas SARS-CoV-2con vectores virales



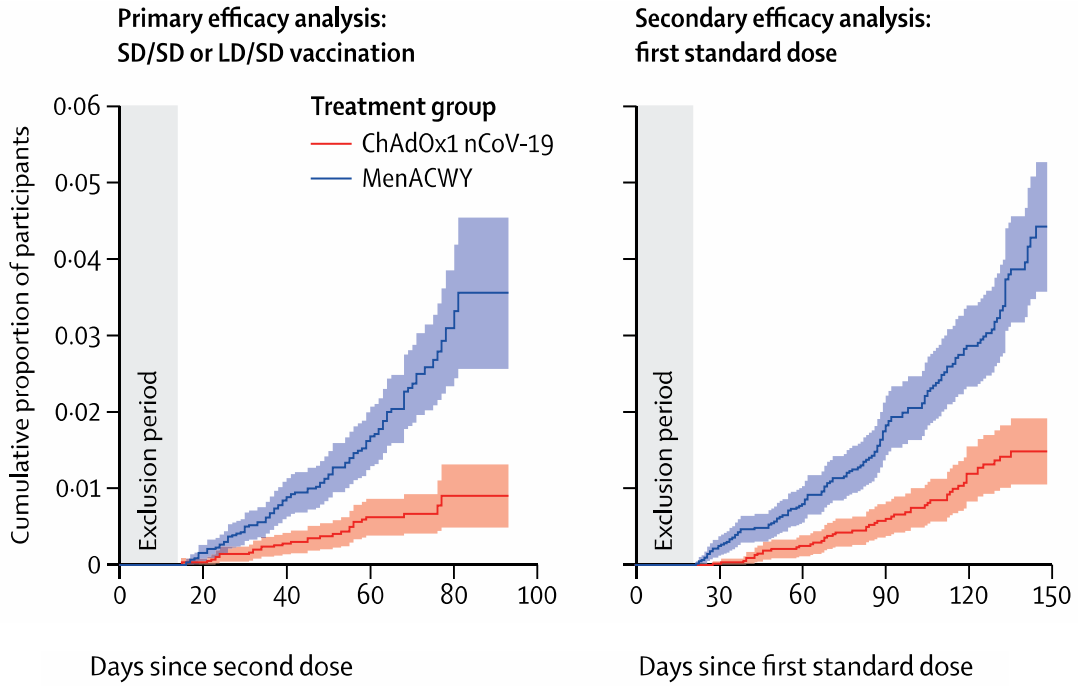
Tipo de vacuna		Etapa
Adenovirus ChAdOx1	Oxford&AZ (Reino Unido) 2 dosis	Fase 3 Autorización uso emergencia
Adenovirus 26 y 5	Sputnik V (Rusia) 2 dosis	Fase 3 Autorización uso emergencia
Adenovirus 5	CanSino / Bio (China/Canada) 1 dosis	Fase 3 Autorización uso emergencia
Adenovirus 26	Janssen&JJ (Belgica) 1 dosis	Fase 3 Autorización uso emergencia

Vacunas SARS-CoV-2 con vectores virales

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

Ensayo	Fase (N)	Casos	Endpoint 1º: Prevención COVID-19 14 días post 2ª dosis	Seguridad*
COV002 UK COV003 Brasil Dia 1/28 ≥ 18 años	II/III RU (10,673) III Brasil (10,002)	131	**Total: 70.4%** (N = 11,636) **1/2 y 1 dosis** **90%** (n = 2741) **2 dosis full (dia 1 y 28)** **62.1%** (n = 8895)	74,341 personas/mes Hospitalizaciones -No en vacuna, -10 en control 1 EA severo posible relacionado

* incluyen además datos de otros 2 ensayos Fase I/II COV001 en RU y Fase I/II COV005 en Sudáfrica.

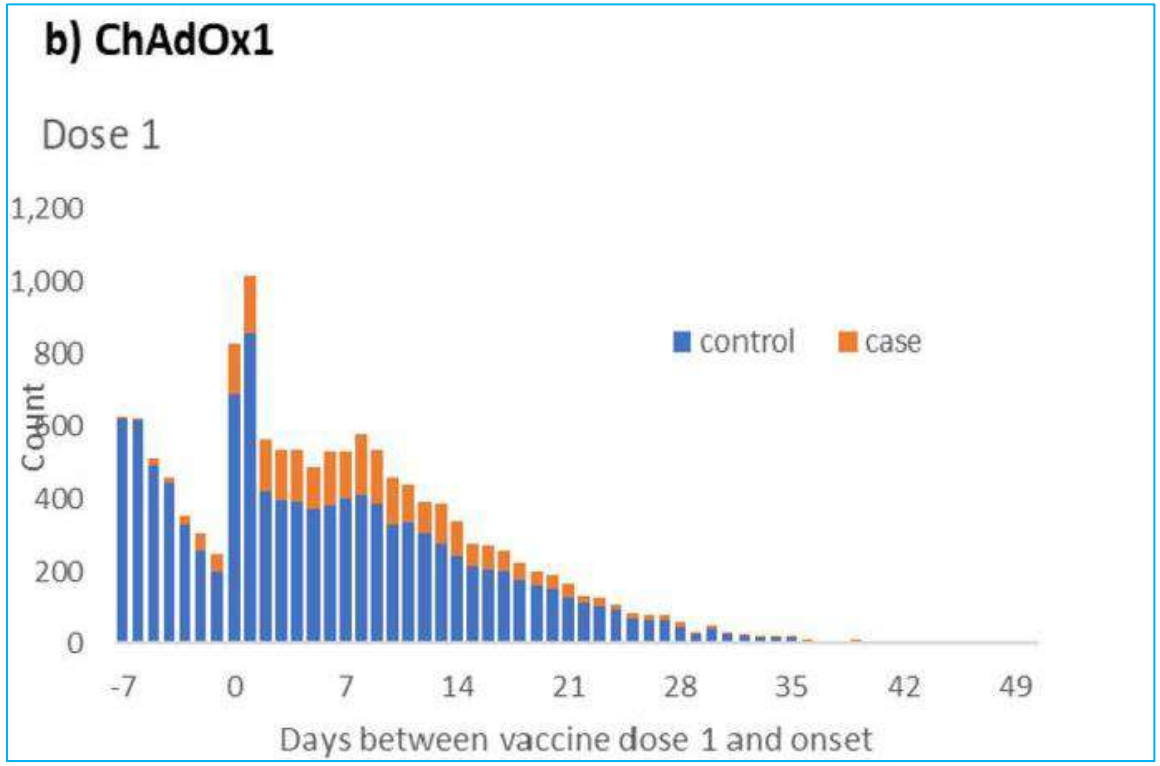


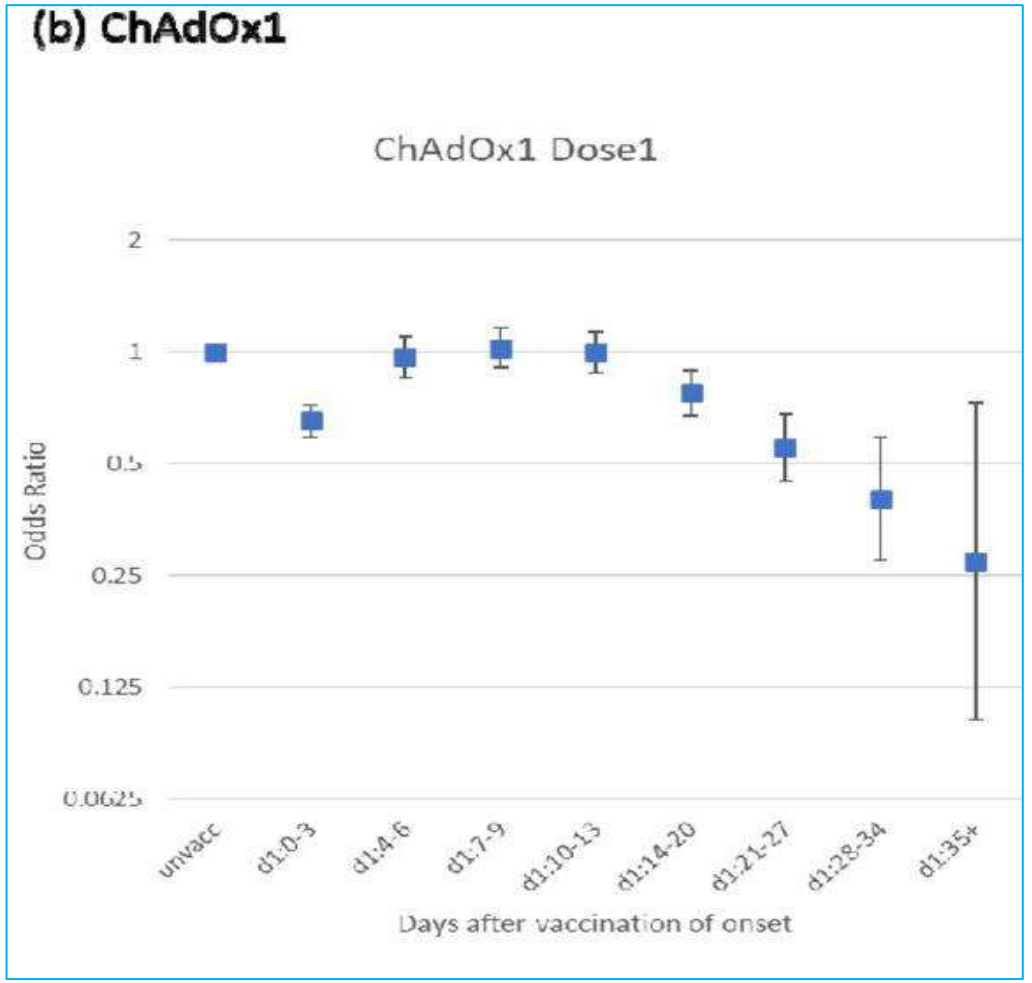
Eficacia Oxford / AstraZeneca
62 a 90 %

Voysey M et al, Lancet 2020,

ChAdOx1 nCoV-19 (Oxford&Astrazeneca)
Mundo real

Early effectiveness of COVID-19 vaccination with BNT162b2 mRNA vaccine and ChAdOx1 adenovirus vector vaccine on symptomatic disease, hospitalisations and mortality in older adults in England





Lopez Bernal J et al, doi: https://doi.org/10.1101/2021.03.01.21252652

Vacunas SARS-CoV-2 con vectores virales

Safety and efficacy of an rAd26 and rAd5 vector-based heterologous prime-boost COVID-19 vaccine: an interim analysis of a randomised controlled phase 3 trial in Russia

25 centros en Rusia (21977) **> 18 años, Dosis dia 1 y 21**	**Endp 1º: COVID-19 21 días post 1ª dosis** **Endp 2ª: casos moderados/severos**
3/1 Vacuna/Placebo rAd26 y rAd5	**21997 (16501/5476)** **19866 2 dosis**

Lagunov D et al, Lancet 2021

Vacunas SARS-CoV-2 con vectores virales

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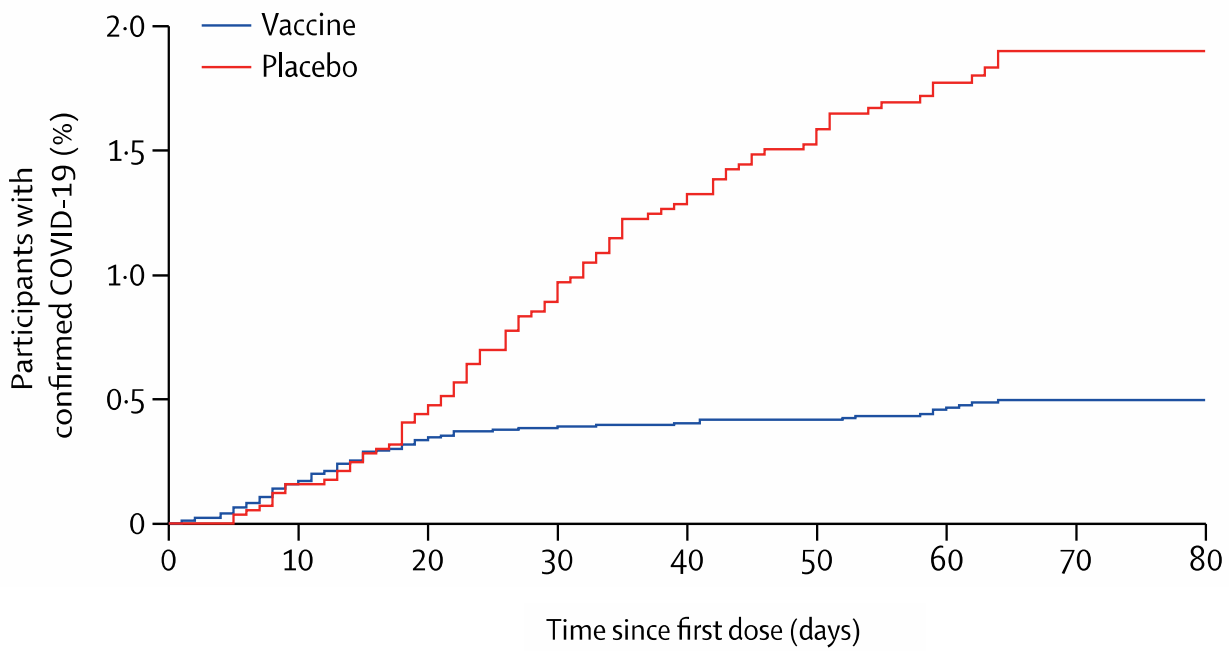

Lagunov D et al, Lancet 2021

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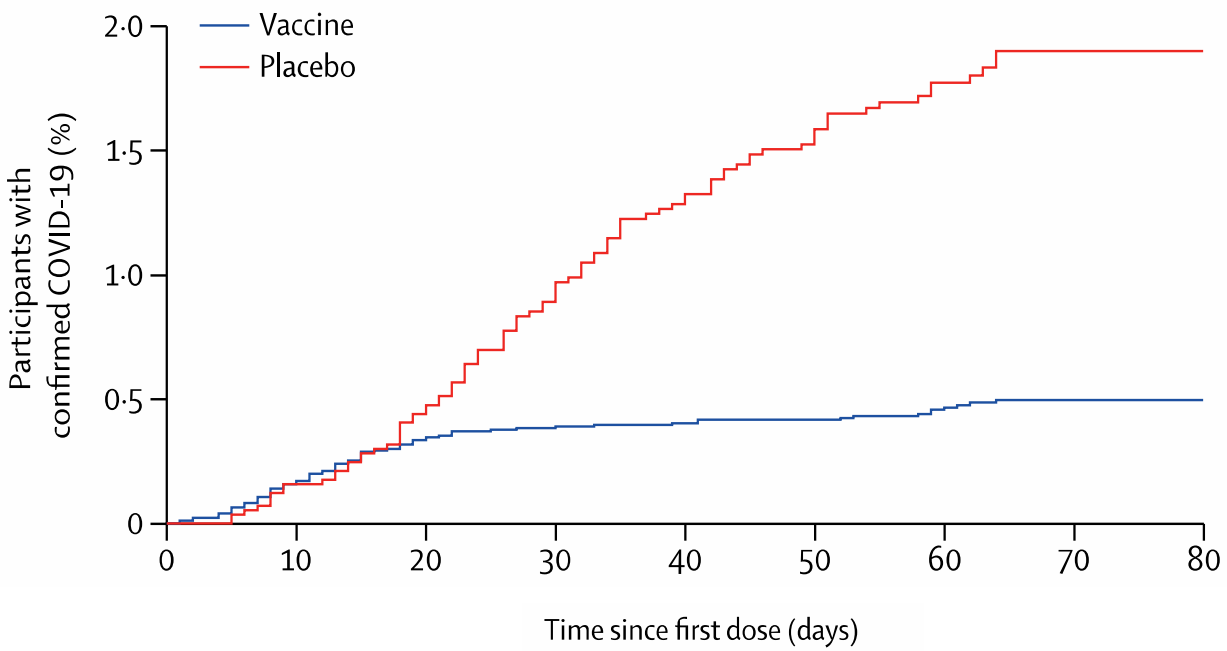
	Total cases	Vaccine group	Placebo group	Vaccine efficacy (95% CI)	p value
First COVID-19 occurrence from 21 days after dose 1 (day of dose 2)*					
Overall	78	16/14 964 (0·1%)	62/4902 (1·3%)	91·6% (85·6–95·2)	<0·0001
Age group (years)					
18–30	5	1/1596 (0·1%)	4/521 (0·8%)	91·9% (51·2–99·3)	0·0146
31–40	17	4/3848 (0·1%)	13/1259 (1·0%)	90·0% (71·1–96·5)	<0·0001
41–50	19	4/4399 (0·1%)	15/1443 (1·0%)	91·3% (73·7–96·9)	<0·0001
51–60	27	5/3510 (0·1%)	22/1146 (1·9%)	92·7% (81·1–97·0)	<0·0001
>60	10	2/1611 (0·1%)	8/533 (1·5%)	91·8% (67·1–98·3)	0·0004
Sex					
Female	32	9/5821 (0·2%)	23/1887 (1·2%)	87·5% (73·4–94·2)	<0·0001
Male	46	7/9143 (0·1%)	39/3015 (1·3%)	94·2% (87·2–97·4)	<0·0001
Moderate or severe cases	20	0/14 964	20/4902 (0·4%)	100% (94·4–100·0)	<0·0001
First COVID-19 occurrence after dose 1†					
Any time after dose 1	175	79/16 427 (0·5%)	96/5435 (1·8%)	73·1% (63·7–80·1)	<0·0001
From 14 days after dose 1	109	30/14 999 (0·2%)	79/4950 (1·6%)	87·6% (81·1–91·8)	<0·0001
First COVID-19 occurrence after dose 2 (28 days after dose 1)*					
All	60	13/14 094 (0·1%)	47/4601 (1·0%)	91·1% (83·8–95·1)	<0·0001

Data are n/N (%), unless otherwise stated. *Includes those who received both doses. †Includes participants who received at least one dose.



Eficacia Sputnik V
91,6 % (16/62)

Lagunov D et al, Lancet 2021

Sputnik V en Rusia

Sputnik V
THE FIRST REGISTERED COVID-19 VACCINE
PROVEN HUMAN ADENOVIRAL VECTOR TECHNOLOGY

РУС ENG 中文 عربي ESP POR FRA TGL MSA

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SPUTNIK V DEMONSTRATES 97.6% EFFICACY ACCORDING TO ANALYSIS OF DATA FROM 3.8 MILLION VACCINATED PERSONS IN RUSSIA MAKING IT THE MOST EFFICIENT COVID-19 VACCINE IN THE WORLD

Moscow, April 19, 2021 – The Gamaleya National Research Center of Epidemiology and Microbiology of the Ministry of Health of the Russian Federation and the Russian Direct Investment Fund (RDIF, Russia's sovereign wealth fund) today announced that the Sputnik V vaccine demonstrated efficacy of 97.6%, based on the analysis of data on the infection rate of coronavirus among those in Russia vaccinated with both components of Sputnik V.

The Ministry of Health of Russia maintains a register of persons who have been vaccinated, as well as citizens who have got infected with COVID as part of the Unified State Information System in Healthcare.

According to the data from 3.8 million Russians vaccinated with both components of Sputnik V from December 5, 2020 to March 31, 2021 as part of the mass-scale civil vaccination program, the infection rate starting from the 35th day from the date of the first injection was only 0.027%.

At the same time, the incidence among the unvaccinated adult population was 1.1% for a comparable period starting from the 35th day after the launch of mass-scale vaccination in Russia.

The following formula was used to calculate the vaccine's efficacy:

$$\frac{\left(\begin{array}{c}\text{Infection rate among}\\ \text{non-vaccinated adult population}\end{array}\right)-\left(\begin{array}{c}\text{Infection rate among the}\\ \text{fully vaccinated population}\end{array}\right)}{\begin{array}{c}\text{Infection rate among}\\ \text{non-vaccinated adult population}\end{array}}=\frac{1{,}1\%-0{,}027\%}{1{,}1\%}=97{,}6\%$$

The data and calculations of the vaccine's efficacy will be published in a peer-reviewed medical journal in May.

Vacunas SARS-CoV-2 con vectores virales

The NEW ENGLAND JOURNAL of MEDICINE

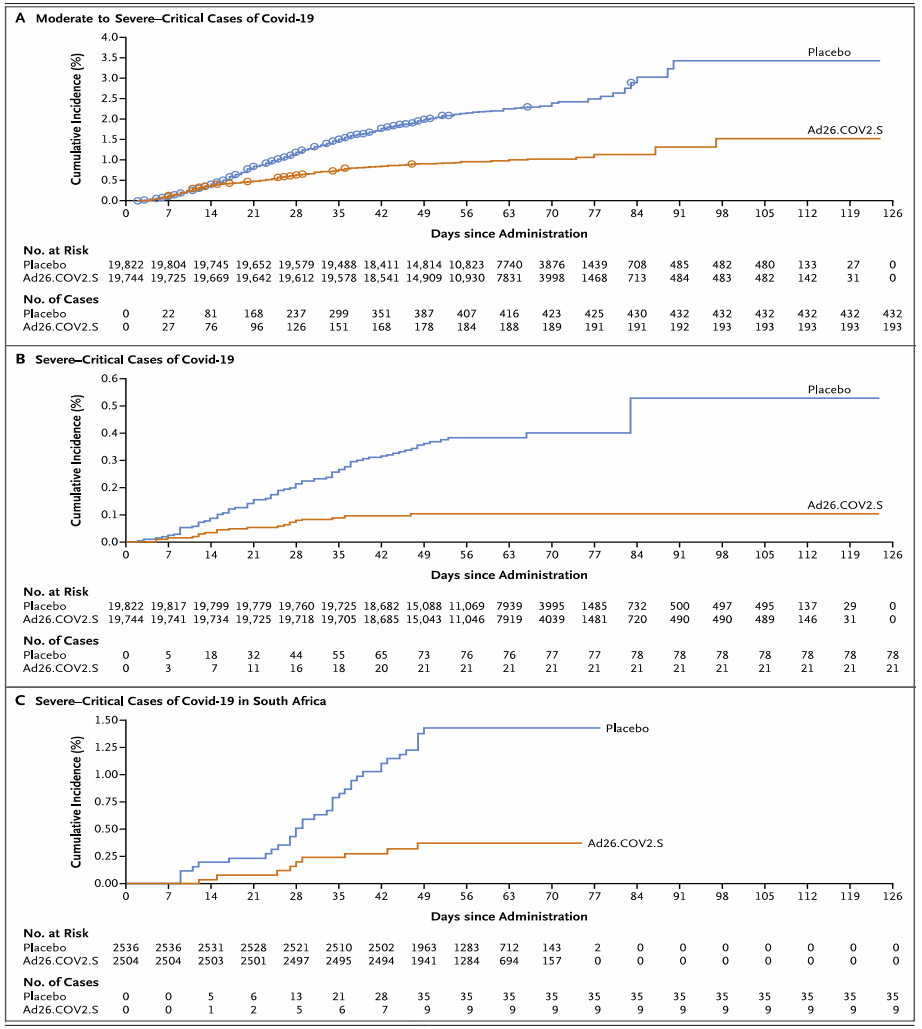
ORIGINAL ARTICLE

Safety and Efficacy of Single-Dose Ad26.COV2.S Vaccine against Covid-19

J. Sadoff, G. Gray, A. Vandebosch, V. Cárdenas, G. Shukarev, B. Grinsztejn, P.A. Goepfert, C. Truyers, H. Fennema, B. Spiessens, K. Offergeld, G. Scheper, K.L. Taylor, M.L. Robb, J. Treanor, D.H. Barouch, J. Stoddard, M.F. Ryser, M.A. Marovich, K.M. Neuzil, L. Corey, N. Cauwenberghs, T. Tanner, K. Hardt, J. Ruiz-Guiñazú, M. Le Gars, H. Schuitemaker, J. Van Hoof, F. Struyf, and M. Douoguih, for the ENSEMBLE Study Group*

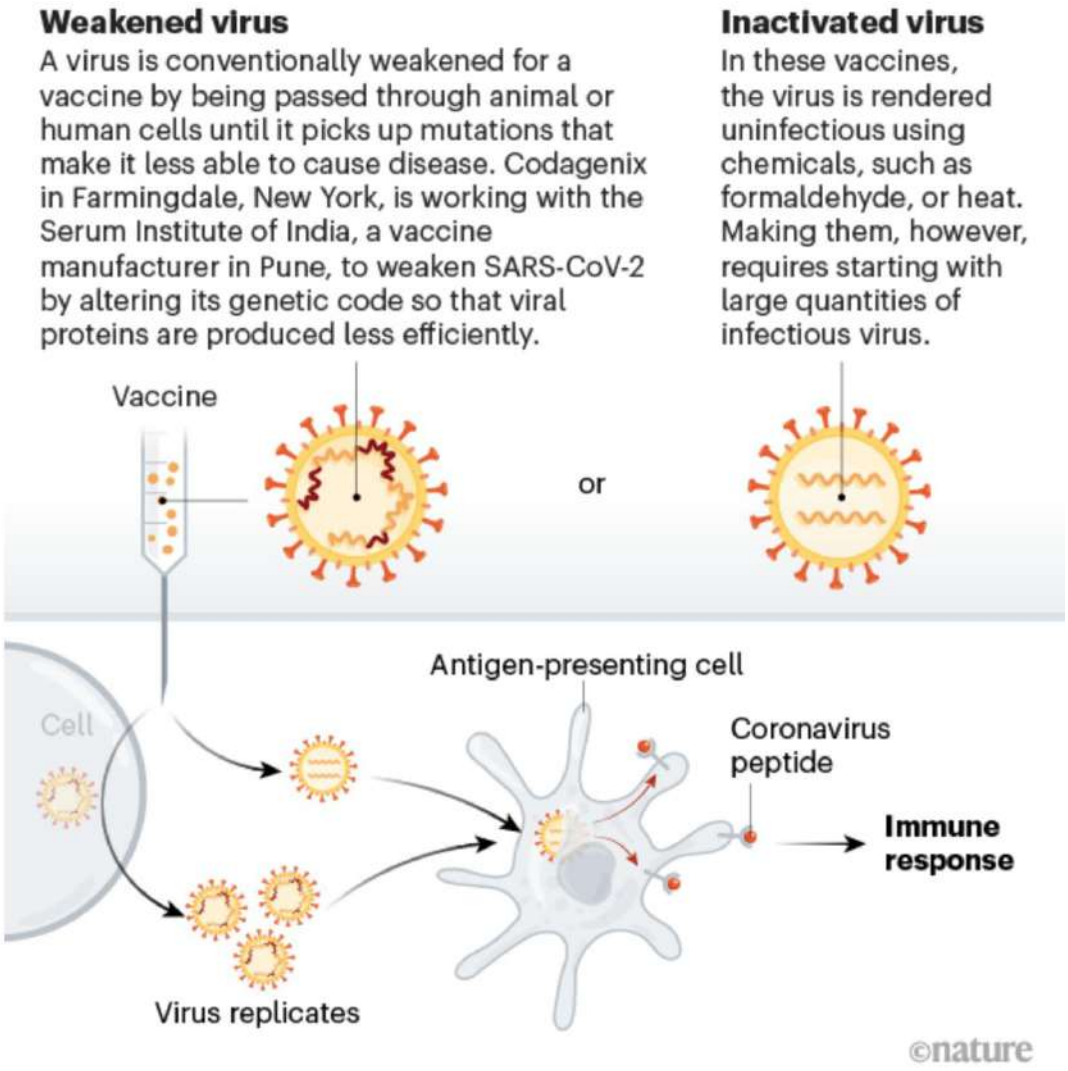
8 países (19630/19691) > 18 años, 1 dosis	Endp 1º: moderado o severo 14 y 28 días de dosis	Alguna alerta de seguridad

	Moderate & Severe (28 days)	Severe (28 days)	Severe (>49 days)
US	72% ⬇	85% ⬇ (100% ⬇ death)	100% ⬇
Latin America	66% ⬇		
South Africa (95% B.1.351 variant)	57% ⬇		



Cumulative Incidence of Covid-19 with Onset at Least 1 Day after Vaccination and Vaccine Efficacy over Time.

Vacuna Virus inactivado



Tipo de vacuna		Etapa
Virus inactivado	Coronavac Sinovac (China)	Fase 3 Uso emergencia
Virus inactivado	WIBP y Sinopharm (Wuham, China)	Fase 3 Uso emergencia
Virus inactivado 5	BBIBP-CorV Sinopharm (Beijing, China)	Fase 3 Uso emergencia

Callaway E, Nature 2020

Vacuna Virus inactivado: CoronaVac Fase I/II

Safety, tolerability, and immunogenicity of an inactivated SARS-CoV-2 vaccine in healthy adults aged 18–59 years: a randomised, double-blind, placebo-controlled, phase 1/2 clinical trial

Yanjun Zhang*, Gang Zeng*, Hongxing Pan*, Changgui Li*, Yaling Hu, Kai Chu, Wenxiao Han, Zhen Chen, Rong Tang, Weidong Yin, Xin Chen, Yuansheng Hu, Xiaoyong Liu, Congbing Jiang, Jingxin Li, Minnan Yang, Yan Song, Xiangpo Wang, Qiang Gao†, Fengcai Zhu†

Summary

Background With the unprecedented morbidity and mortality associated with the COVID-19 pandemic, a vaccine against COVID-19 is urgently needed. We investigated CoronaVac (Sinovac Life Sciences, Beijing, China), an inactivated vaccine candidate against COVID-19, containing inactivated severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), for its safety, tolerability and immunogenicity.

Methods In this randomised, double-blind, placebo-controlled, phase 1/2 clinical trial, healthy adults aged 18–59 years were recruited from the community in Suining County of Jiangsu province, China. Adults with SARS-CoV-2 exposure or infection history, with axillary temperature above 37·0°C, or an allergic reaction to any vaccine component were excluded. The experimental vaccine for the phase 1 trial was manufactured using a cell factory process (CellSTACK Cell Culture Chamber 10, Corning, Wujiang, China) , whereas those for the phase 2 trial were produced through a bioreactor process (ReadyToProcess WAVE 25, GE, Umea, Sweden) . The phase 1 trial was done in a dose-escalating manner. At screening, participants were initially separated (1:1), with no specific randomisation, into two vaccination schedule cohorts, the days 0 and 14 vaccination cohort and the days 0 and 28 vaccination cohort, and within each cohort the first 36 participants were assigned to block 1 (low dose CoronaVac [3 μg per 0·5 mL of aluminium hydroxide diluent per dose) then another 36 were assigned to block 2 (high-dose Coronavc [6 μg per 0·5 mL of aluminium hydroxide diluent per dse]). Within each block, participants were randomly assigned (2:1), using block randomisation with a block size of six, to either two doses of CoronaVac or two doses of placebo. In the phase 2 trial, at screening, participants were initially separated (1:1), with no specific randomisation, into the days 0 and 14 vaccination cohort and the days 0 and 28 vaccination cohort, and participants were randomly assigned (2:2:1), using block randomisation with a block size of five, to receive two doses of either low-dose CoronaVac, high-dose CoronaVac, or placebo. Participants, investigators, and laboratory staff were masked to treatment allocation. The primary safety endpoint was adverse reactions within 28 days after injection in all participants who were given at least one dose of study drug (safety population). The primary immunogenic outcome was seroconversion rates of neutralising antibodies to live SARS-CoV-2 at day 14 after the last dose in the days 0 and 14 cohort, and at day 28 after the last dose in the days 0 and 28 cohort in participants who completed their allocated two-dose vaccination schedule (per-protocol population). This trial is registered with ClinicalTrials.gov, NCT04352608, and is closed to accrual.

Findings Between April 16 and April 25, 2020, 144 participants were enrolled in the phase 1 trial, and between May 3 and May 5, 2020, 600 participants were enrolled in the phase 2 trial. 743 participants received at least one dose of investigational product (n=143 for phase 1 and n=600 for phase 2; safety population). In the phase 1 trial, the incidence of adverse reactions for the days 0 and 14 cohort was seven (29%) of 24 participants in the 3 ug group, nine (38%) of 24 in the 6 μg group, and two (8%) of 24 in the placebo group, and for the days 0 and 28 cohort was three (13%) of 24 in the 3 μg group, four (17%) of 24 in the 6 μg group, and three (13%) of 23 in the placebo group. The seroconversion of neutralising antibodies on day 14 after the days 0 and 14 vaccination schedule was seen in 11 (46%) of 24 participants in the 3 μg group, 12 (50%) of 24 in the 6 μg group, and none (0%) of 24 in the placebo group; whereas at day 28 after the days 0 and 28 vaccination schedule, seroconversion was seen in 20 (83%) of 24 in the 3 μg group, 19 (79%) of 24 in the 6 μg group, and one (4%) of 24 in the placebo group. In the phase 2 trial, the incidence of adverse reactions for the days 0 and 14 cohort was 40 (33%) of 120 participants in the 3 μg group, 42 (35%) of 120 in the 6 μg group, and 13 (22%) of 60 in the placebo group, and for the days 0 and 28 cohort was 23 (19%) of 120 in the 3 μg group, 23 (19%) of 120 in the 6 μg group, and 11 (18%) of 60 for the placebo group. Seroconversion of neutralising antibodies was seen for 109 (92%) of 118 participants in the 3 μg group, 117 (98%) of 119 in the 6 μg group, and two (3%) of 60 in the placebo group at day 14 after the days 0 and 14 schedule; whereas at day 28 after the days 0 and 28 schedule, seroconversion was seen in 114 (97%) of 117 in the 3 μg group, 118 (100%) of 118 in the 6 μg group, and none (0%) of 59 in the placebo group.

Lancet Infect Dis 2020

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See Online/Comment https://doi.org/10.1016/S1473-3099(20)30870-7

For the Chinese translation of the abstract see Online for appendix 1

*Joint first authors

†Contributed equally

Department of Microbiology, Zhejiang Provincial Center for Disease Control and Prevention, Hangzhou, China (Prof Y Zhang PhD); Sinovac Biotech, Beijing, China (G Zeng PhD, W Han MSc, W Yin, M Yang MPH); Jiangsu Provincial Center for Disease Control and Prevention, Nanjing, China (H Pan MSc, K Chu MSc, X Jiang BA, Prof J Li PhD, Prof F Zhu MD); National Institutes for Food and Drug Control, Beijing, China (Prof C Li PhD, Z Chen MSc); Suining County Center for Disease Control and Prevention, Suining, Jiangsu Province, China (X Chen BA, X Liu BA, C Jiang BA, Y Song BA); CAS Key Laboratory of Infection and Immunity, National Laboratory of Macromolecules, Institute of Biophysics, Chinese Academy of Sciences, Beijing, China (M Yang PhD, Prof X Wang PhD) and Sinovac Life Sciences, Beijing, China (Q Gao MSc)

Correspondence to: Dr Qiang Gao, Sinovac Life Sciences, Beijing 100085, China gaoq@sinovac.com

or

Dr Fengcai Zhu, Jiangsu Provincial Center for Disease Control and Prevention, Nanjing 210009, China jsfc@vip.sina.com

Safety, tolerability, and immunogenicity of an inactivated SARS-CoV-2 vaccine (CoronaVac) in healthy adults aged 60 years and older: a randomised, double-blind, placebo-controlled, phase 1/2 clinical trial

Zhiwei Wu*, Yaling Hu*, Miao Xu*, Zhen Chen*, Wangi Yang, Zhiwei Jiang, Minjie Li, Hui Jin, Guoliang Cui, Panpan Chen, Lei Wang, Guoqing Zhao, Yuzhu Ding, Yuliang Zhao†, Weidong Yin†

Summary

Background A vaccine against COVID-19 is urgently needed for older adults, in whom morbidity and mortality due to the disease are increased. We aimed to assess the safety, tolerability, and immunogenicity of a candidate COVID-19 vaccine, CoronaVac, containing inactivated SARS-CoV-2, in adults aged 60 years and older.

Methods We did a randomised, double-blind, placebo-controlled, phase 1/2 clinical trial of CoronaVac in healthy adults aged 60 years and older in Renqiu (Hebei, China). Vaccine or placebo was given by intramuscular injection in two doses (days 0 and 28). Phase 1 comprised a dose-escalation study, in which participants were allocated to two blocks: block 1 (3 μg inactivated virus in 0·5 mL of aluminium hydroxide solution per injection) and block 2 (6 μg per injection). Within each block, participants were randomly assigned (2:1) using block randomisation to receive CoronaVac or placebo (aluminium hydroxide solution only). In phase 2, participants were randomly assigned (2:2:2:1) using block randomisation to receive either CoronaVac at 1·5 μg, 3 μg, or 6 μg per dose, or placebo. All participants, investigators, and laboratory staff were masked to treatment allocation. The primary safety endpoint was adverse reactions within 28 days after each injection in all participants who received at least one dose. The primary immunogenicity endpoint was seroconversion rate at 28 days after the second injection (which was assessed in all participants who had received the two doses of vaccine according to their random assignment, had antibody results available, and did not violate the trial protocol). Seroconversion was defined as a change from seronegative at baseline to seropositive for neutralising antibodies to live SARS-CoV-2 (positive cutoff titre 1/8), or a four-fold titre increase if the participant was seropositive at baseline. This study is ongoing and is registered with ClinicalTrials.gov (NCT04383574).

Findings Between May 22 and June 1, 2020, 72 participants (24 in each intervention group and 24 in the placebo group; mean age 65·8 years [SD 4·8]) were enrolled in phase 1, and between June 12 and June 15, 2020, 350 participants were enrolled in phase 2 (100 in each intervention group and 50 in the placebo group; mean age 66·6 years [SD 4·7] in 349 participants). In the safety populations from both phases, any adverse reaction within 28 days after injection occurred in 20 (20%) of 100 participants in the 1·5 μg group, 25 (20%) of 125 in the 3 μg group, 27 (22%) of 123 in the 6 μg group, and 15 (21%) of 73 in the placebo group. All adverse reactions were mild or moderate in severity and injection site pain (39 [9%] of 421 participants) was the most frequently reported event. As of Aug 28, 2020, eight serious adverse events, considered unrelated to vaccination, have been reported by seven (2%) participants. In phase 1, seroconversion after the second dose was observed in 24 of 24 participants (100·0% [95% CI 85·8–100·0]) in the 3 μg group and 22 of 23 (95·7% [78·1–99·9]) in the 6 μg group. In phase 2, seroconversion was seen in 88 of 97 participants in the 1·5 μg group (90·7% [83·1–95·7]), 96 of 98 in the 3 μg group (98·0% [92·8–99·8]), and 97 of 98 (99·0% [94·5–100·0]) in the 6 μg group. There were no detectable antibody responses in the placebo groups.

Interpretation CoronaVac is safe and well tolerated in older adults. Neutralising antibody titres induced by the 3 μg dose were similar to those of the 6 μg dose, and higher than those of the 1·5 μg dose, supporting the use of the 3 μg dose CoronaVac in phase 3 trials to assess protection against COVID-19.

Funding Chinese National Key Research and Development Program and Beijing Science and Technology Program.

Introduction

The ongoing COVID-19 pandemic, caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), has rapidly spread across the world and led to more than 94 million infections and more than 2 million deaths worldwide as of Jan 19, 2021.[1] Studies have shown that individuals aged 60 years or older, and especially those with underlying chronic conditions, have an

Lancet Infect Dis 2021

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See Online/Comment https://doi.org/10.1016/S1473-3099(21)00020-7

*Contributed equally

†Contributed equally

Hebei Provincial Center for Disease Control and Prevention, Shijiazhuang, Hebei, China (Z Wu MSc, M Li MSc, Prof Y Zhao MSc); Sinovac Biotech, Beijing, China (Y Hu MSc, W Yang MSc, L Wang MBA); National Institutes for Food and Drug Control, Beijing, China (Prof M Xu PhD, Z Chen MSc); Beijing Key Tech Statistics Technology, Beijing, China (Z Jiang PhD, G Zhao PhD); Renqiu City Center for Disease Control and Prevention, Renqiu, Hebei, China (H Jin BA, P Chen MSc, Y Ding BA); Sinovac Life Sciences, Beijing, China (G Cui BA)

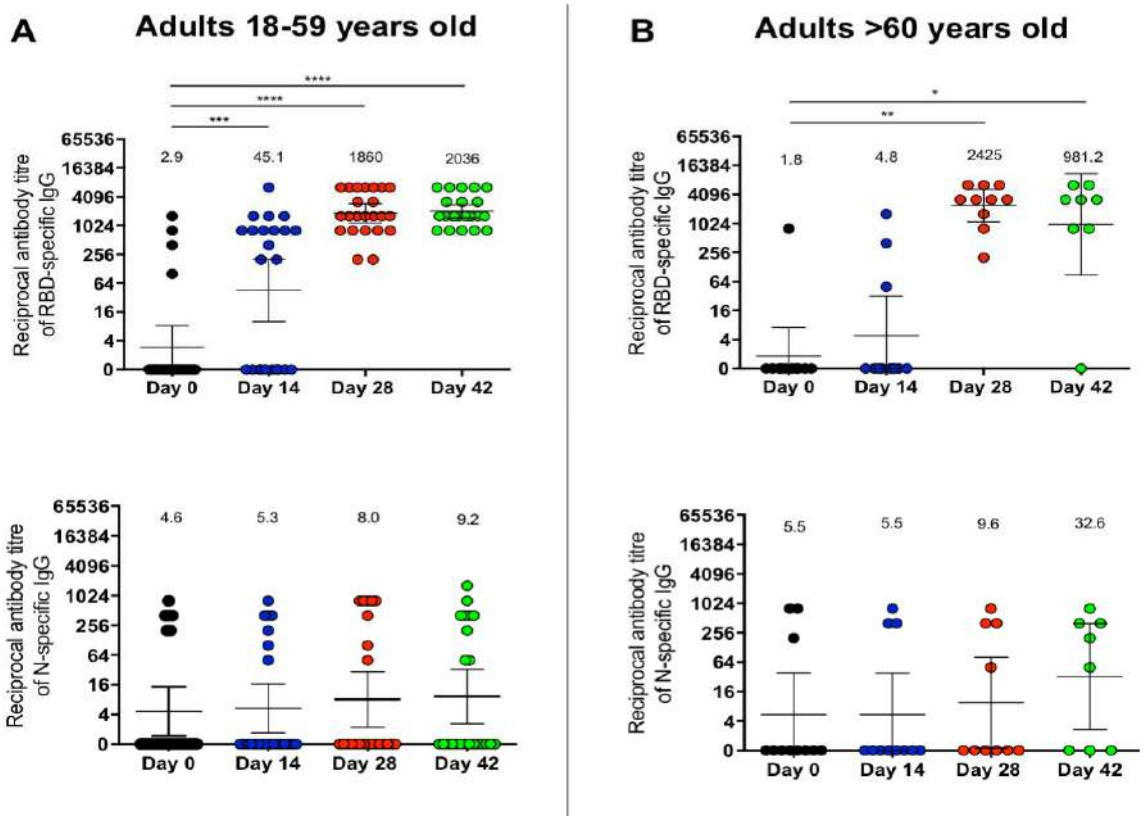
Correspondence to: Dr Yuliang Zhao, Hebei Provincial Center for Disease Control and Prevention, Shijiazhuang, Hebei 050023, China yuliang_zh1@163.com

or

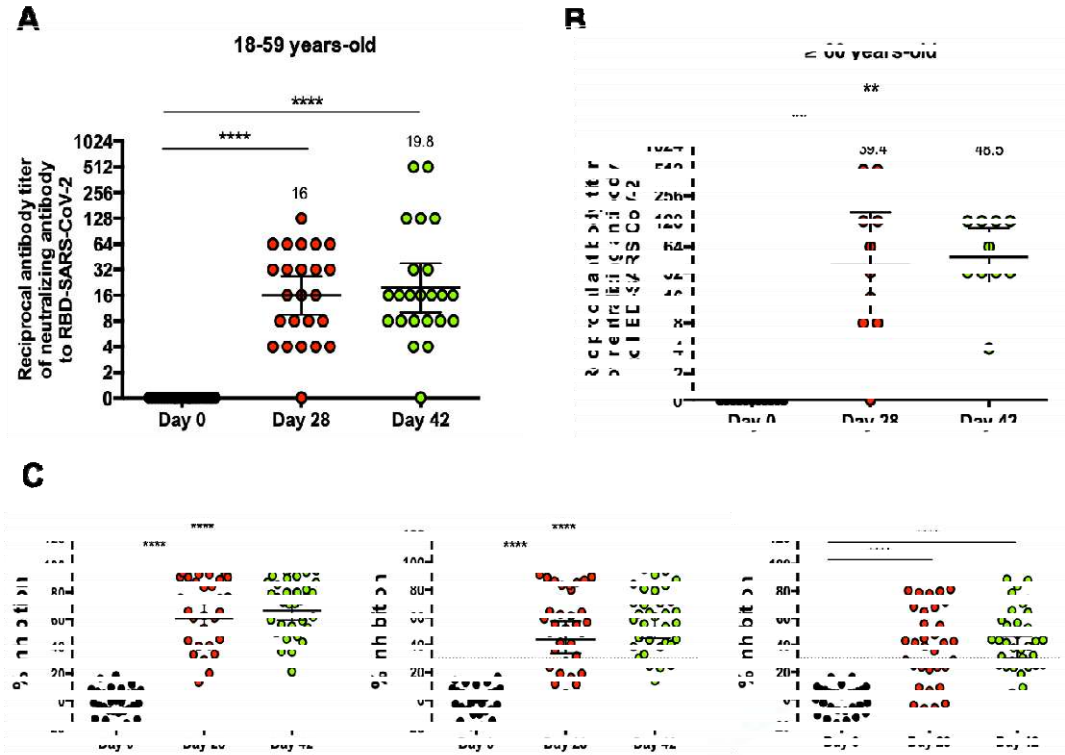
Dr Weidong Yin, Sinovac Biotech, Beijing 100085, China yinwd@sinovac.com

CoronaVac Fase I/II Chile

Anticuerpos anti S y N

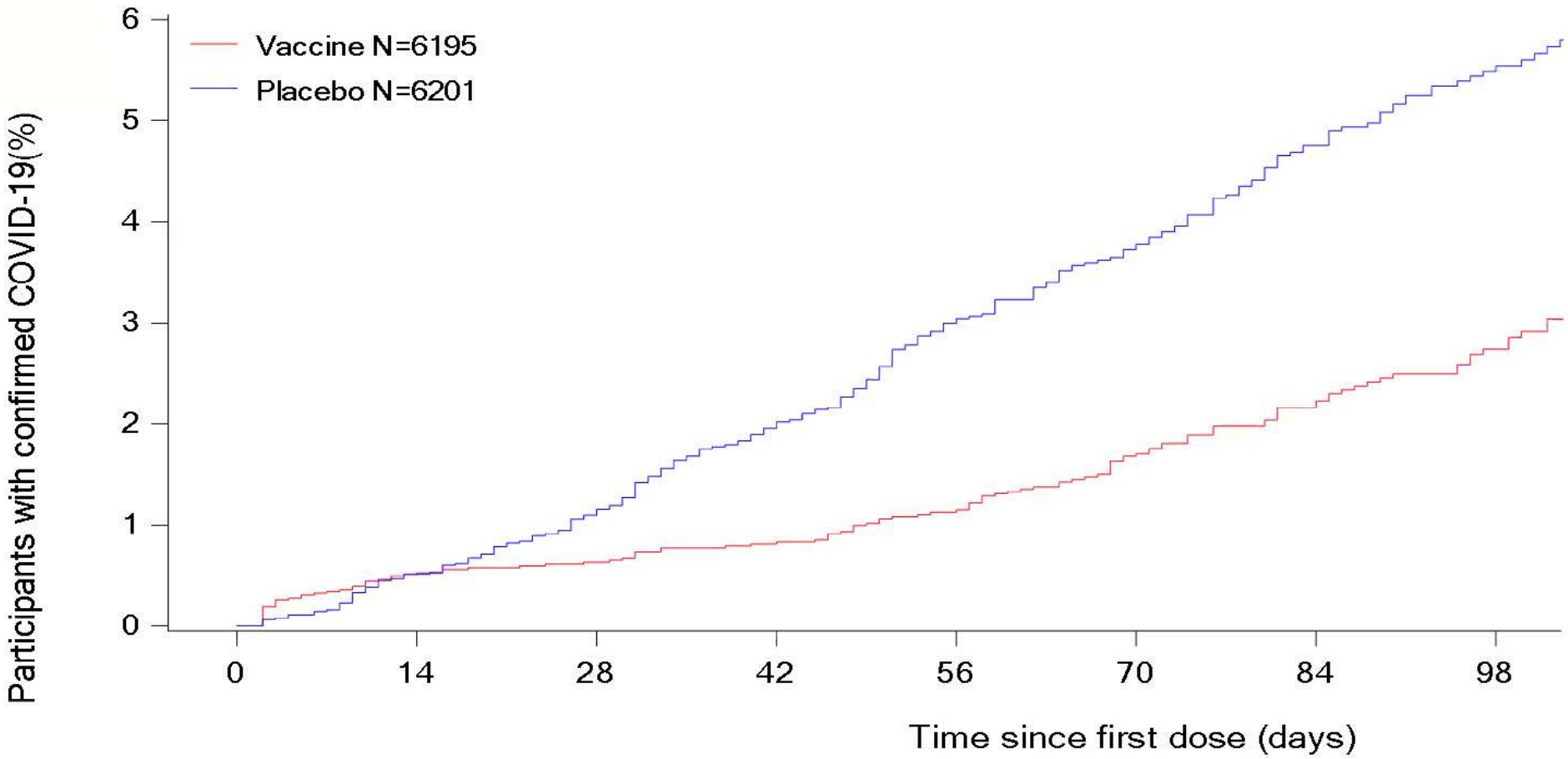


Anticuerpos neutralizantes



medRxiv preprint doi: https://doi.org/10.1101/2021.03.31.21254494, April 1, 2021

Eficacia Coronavac Brasil

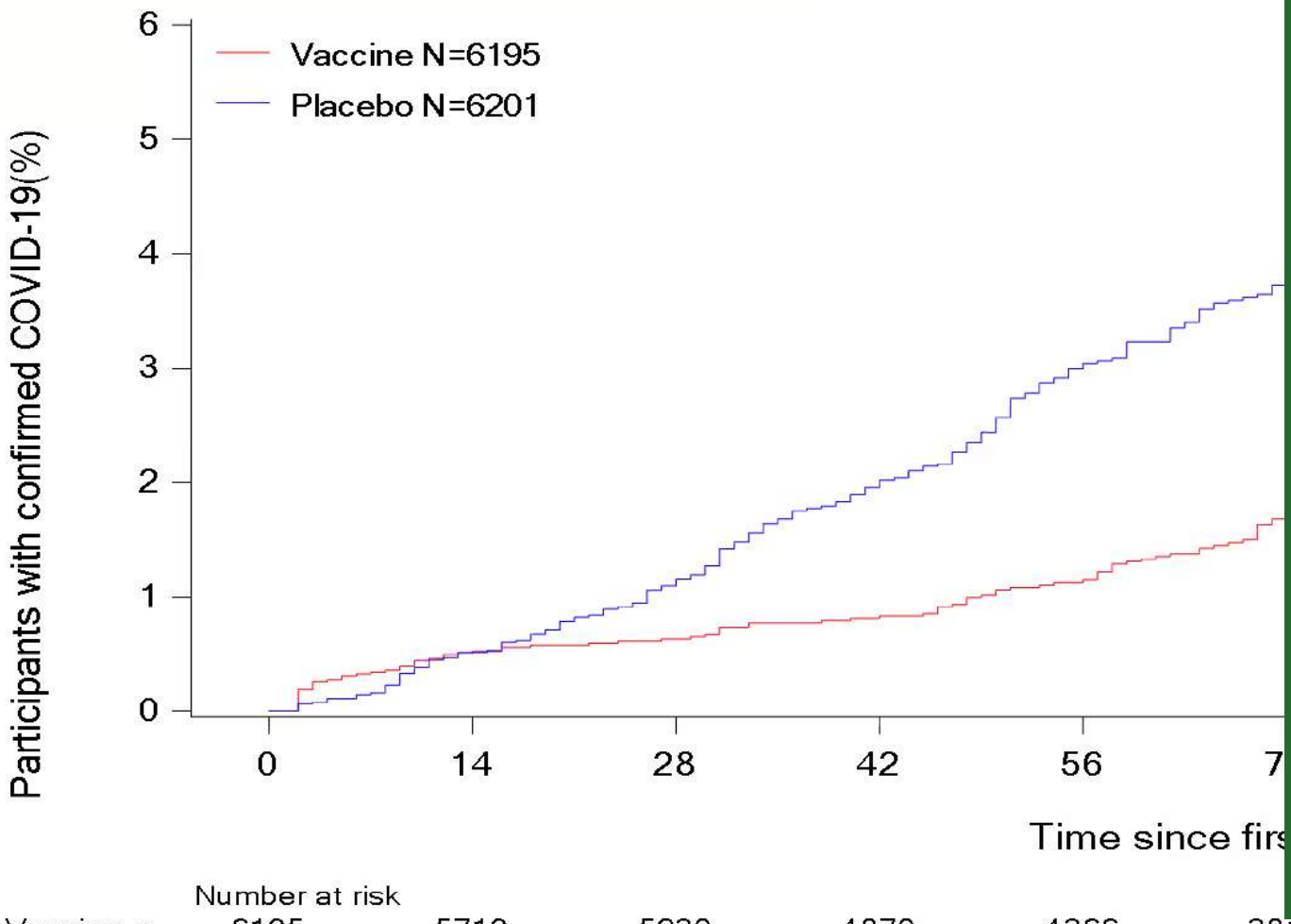


Number at risk								
Vaccine n	6195	5719	5230	4870	4366	3817	2876	1804
Placebo n	6201	5720	5200	4807	4273	3729	2793	1749

INSTITUTO BUTANTAN
A serviço da vida

Palacios R et al, preprint

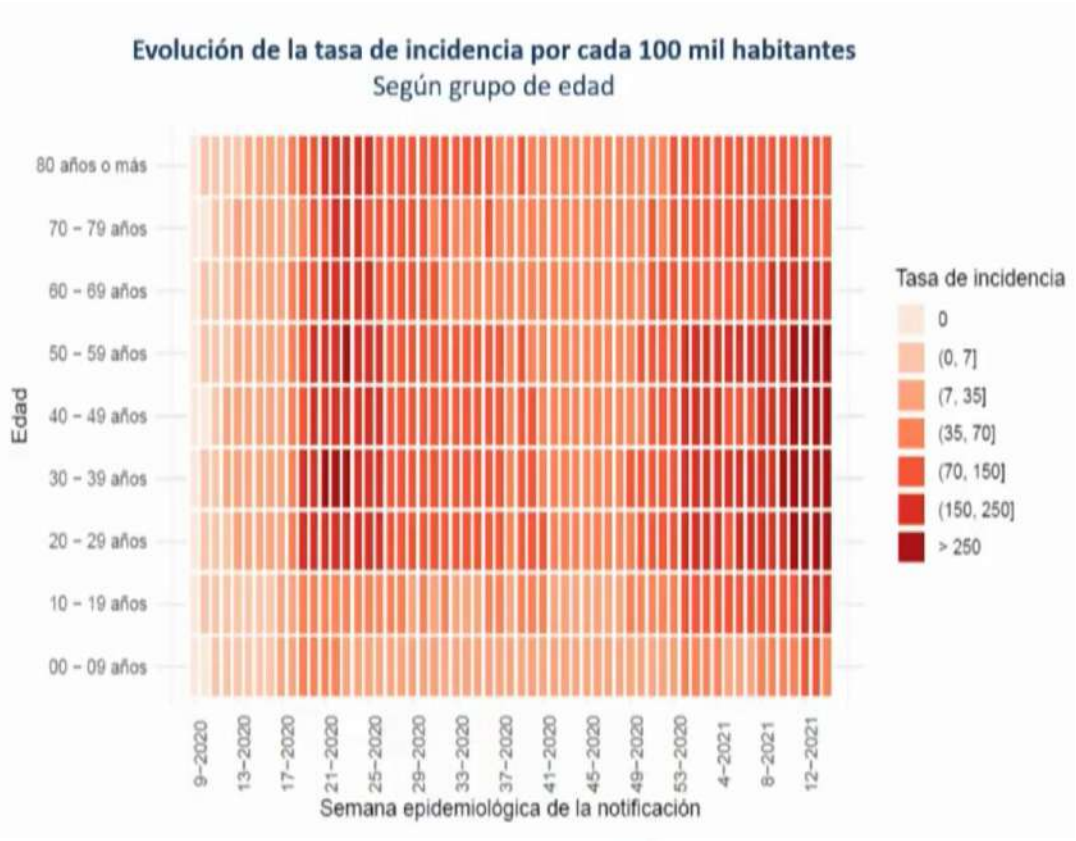
Eficacia Coronavac Brasil



INSTITUTO BUTANTAN
A serviço da vida

Palacios R et al, preprint

Situación Chile durante vacunación 2/2 a 1/4/2021



Efectividad Coronavac > día 14 post 2ª dosis

De 100 que se iban a morir
Lo hacen 20

67% (65% - 69%)
De efectividad para prevenir
Covid-19 sintomático

Estado de inmunización	Efectividad (IC 95%) 100% x 1-HR
Covid-19	
No vacunados	-
Grupo parcialmente inmunizado	16.13
≥ 14 días después de la primera dosis	(14.30 ; 17.92)
Grupo completamente inmunizado	66.96
(≥ 14 días después de la segunda dosis	(65.28 ; 68.55)

85% (83% - 87%)
De efectividad para prevenir
Hospitalización

Estado de inmunización	Efectividad (IC 95%) 100% x 1-HR
Hospitalización	
No vacunados	-
Grupo parcialmente inmunizado	35.65
≥ 14 días después de la primera dosis	(32.13 ; 38.99)
Grupo completamente inmunizado	84.84
≥ 14 días después de la segunda dosis	(82.52 ; 86.85)

89% (84% - 92%)
De efectividad para prevenir
Ingreso a UCI

Estado de inmunización	Efectividad (IC 95%) 100% x 1-HR
Hospitalización	
No vacunados	-
Grupo parcialmente inmunizado	35.65
≥ 14 días después de la primera dosis	(32.13 ; 38.99)
Grupo completamente inmunizado	84.84
≥ 14 días después de la segunda dosis	(82.52 ; 86.85)

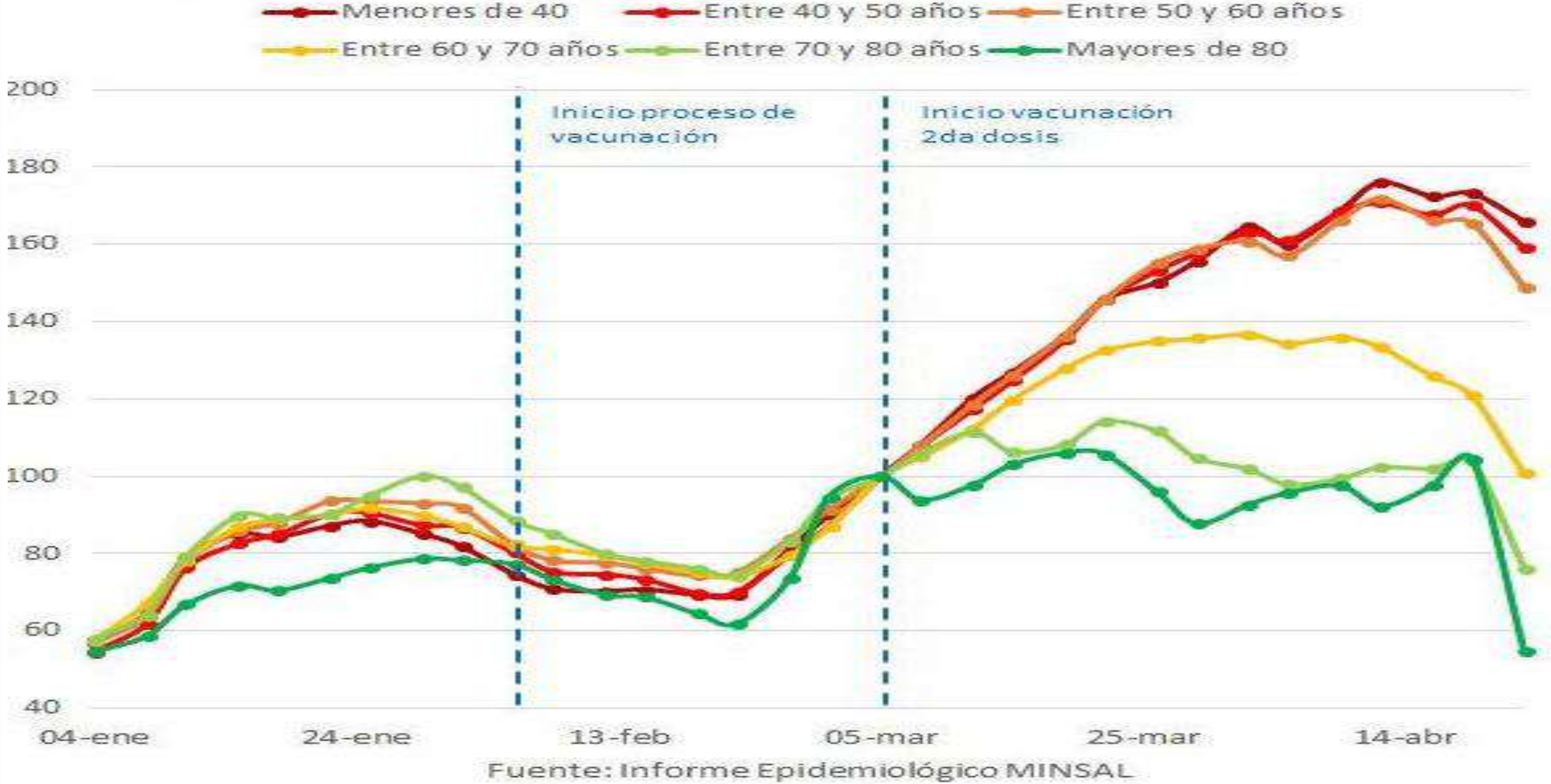
80% (73% - 86%)
De efectividad para prevenir
Muerte

Estado de inmunización	Efectividad (IC 95%) 100% x 1-HR
Muerte debido a Covid-19	
No vacunados	-
Grupo parcialmente inmunizado	40.23
≥ 14 días después de la primera dosis	(32.63 ; 46.97)
Grupo completamente inmunizado	80.44
≥ 14 días después de la segunda dosis	(73.16 ; 85.75)

Araos R at al, Minsal 2021

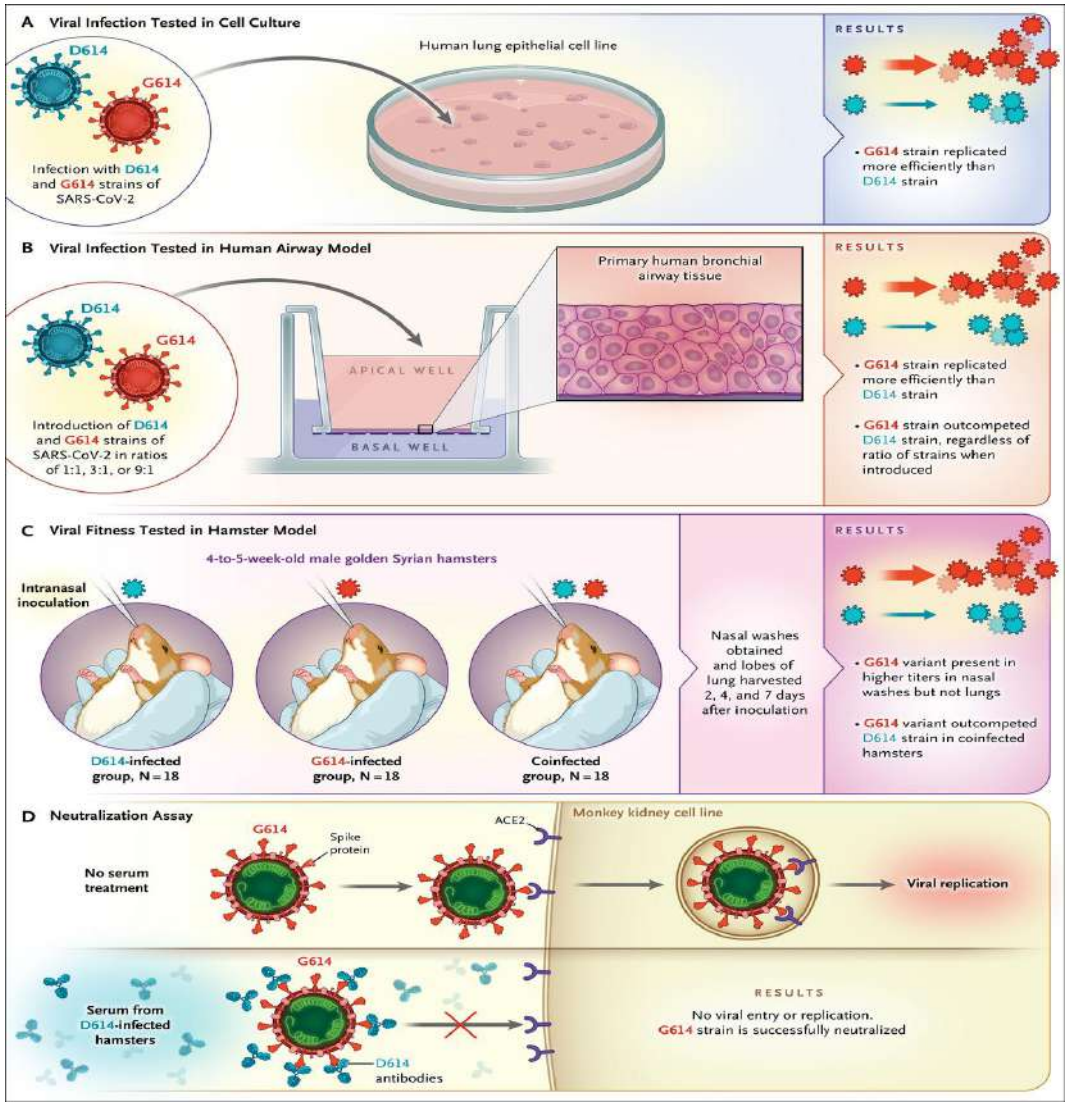
Número de casos COVID-19 semanales, por edad

(Base 100 = número de casos semana 2 al 8 de marzo, para cada grupo etario)



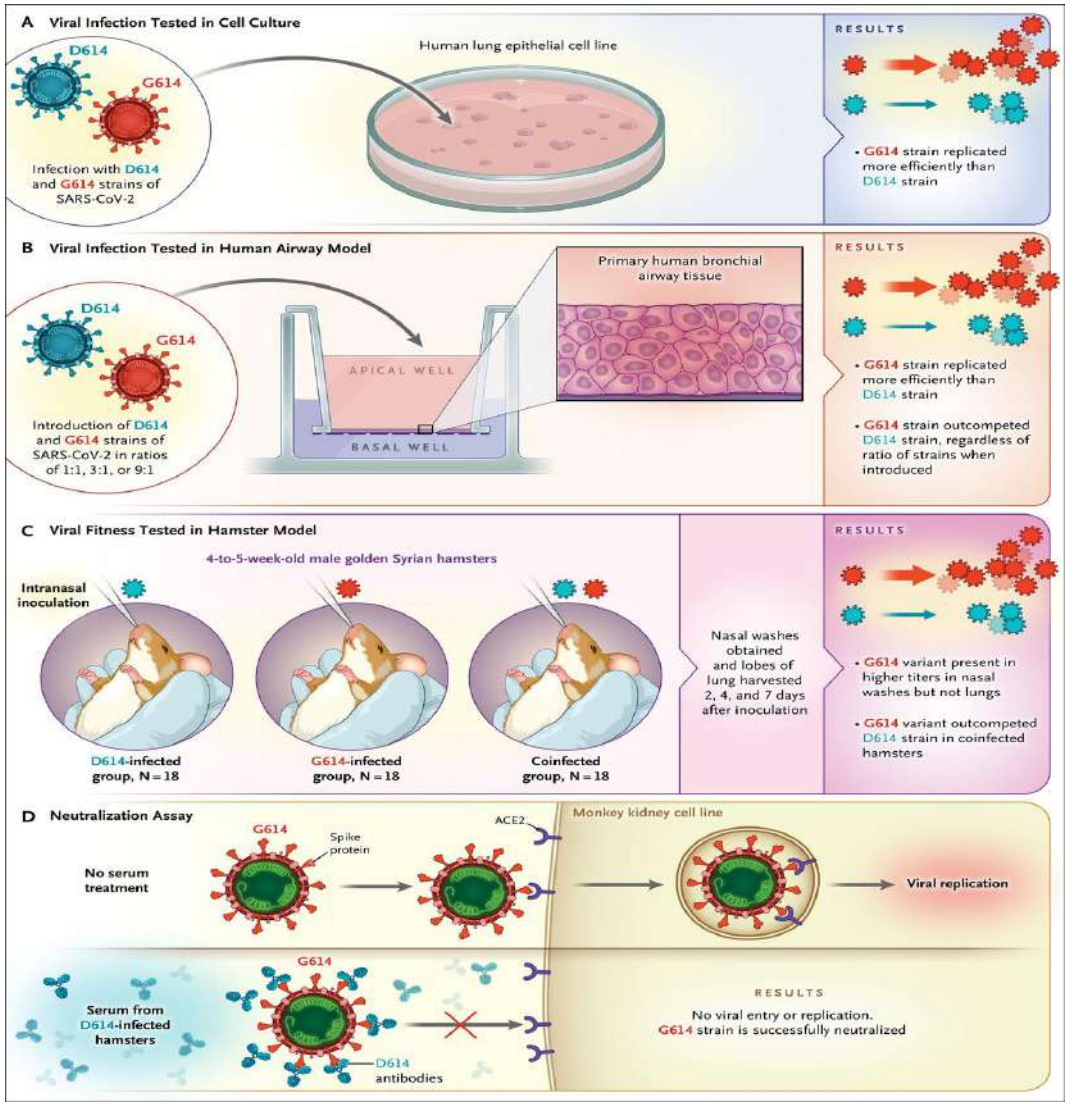
Fuente: Informe Epidemiológico MINSAL

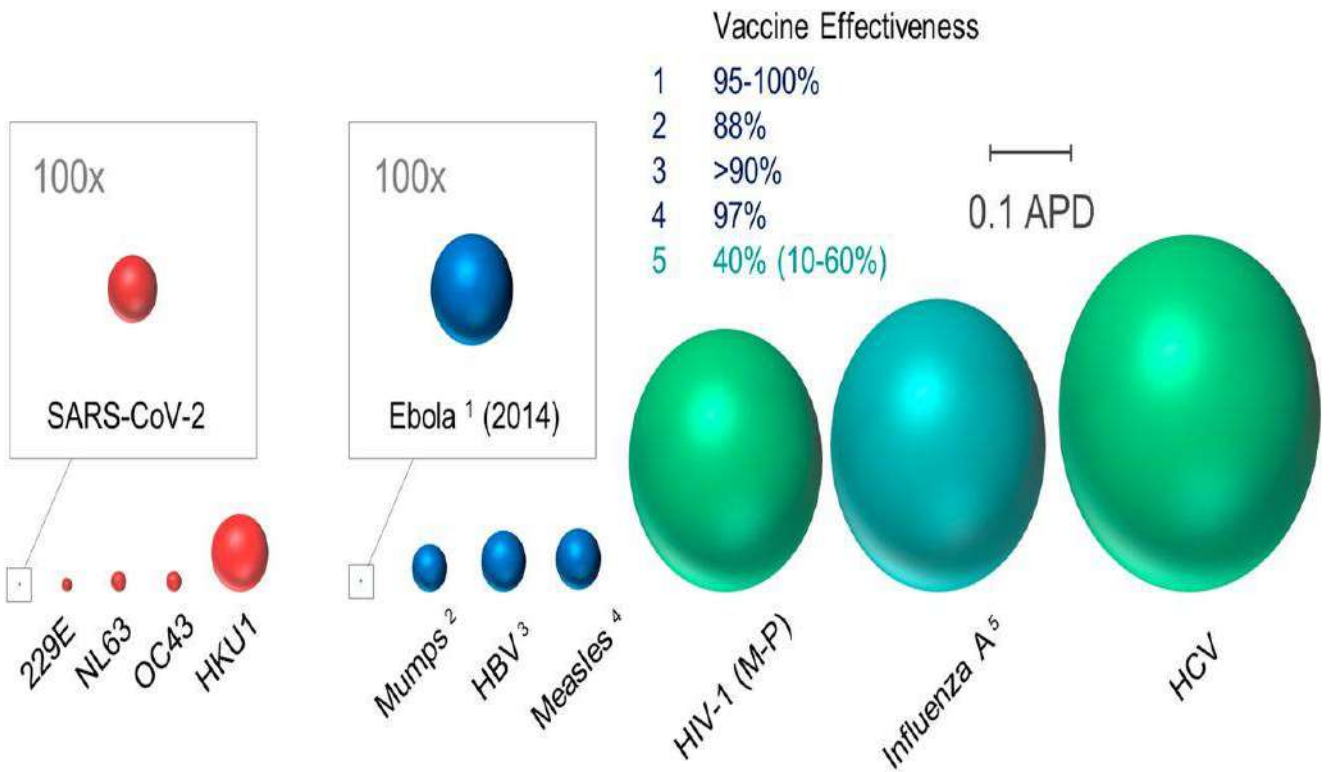
SARS-CoV-2: mutaciones



Jason W. Rausch et al. PNAS 2020, RS Baric. N Engl J Med 2020;, Callaway E Nature 2020

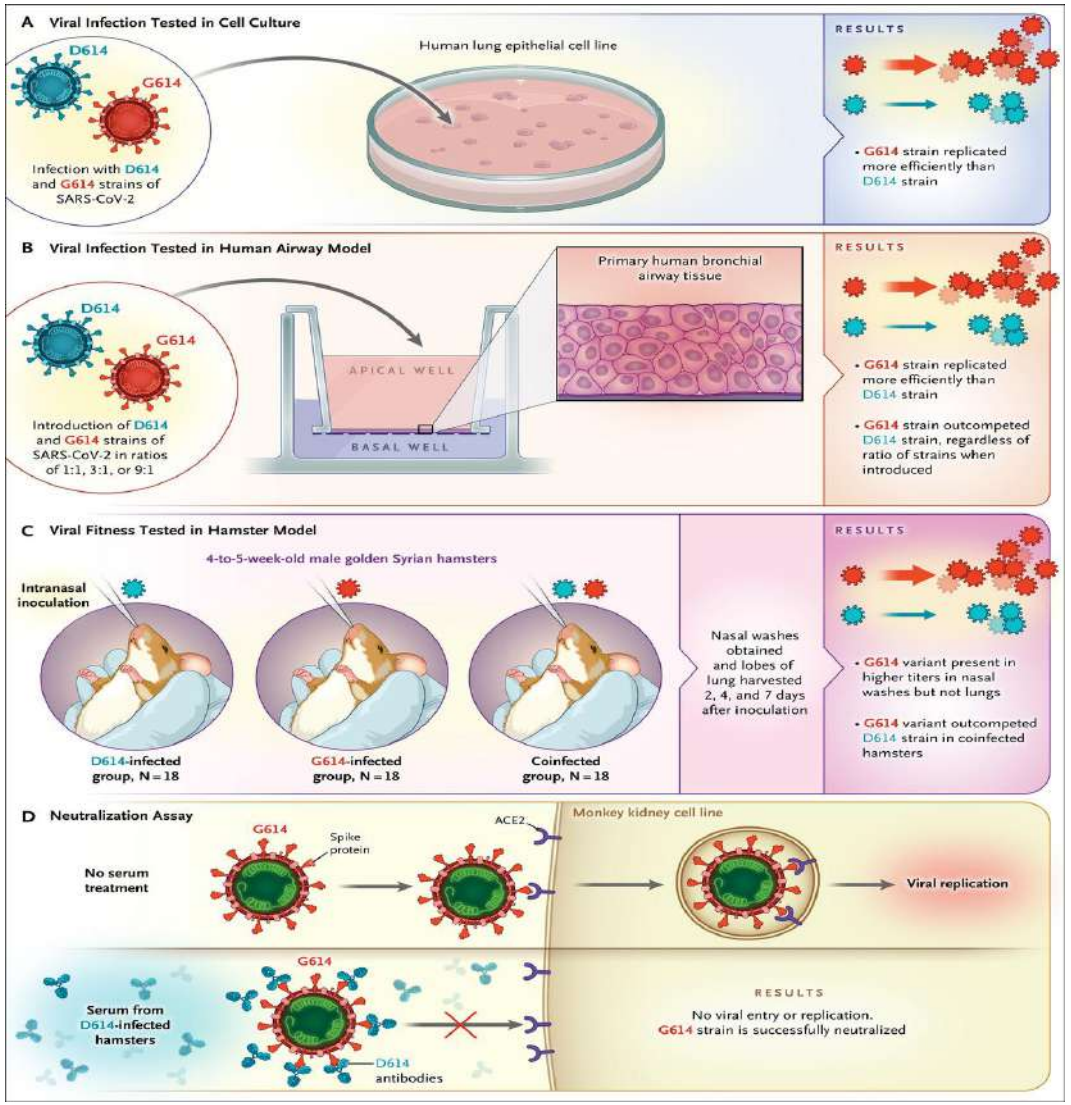
SARS-CoV-2: mutaciones

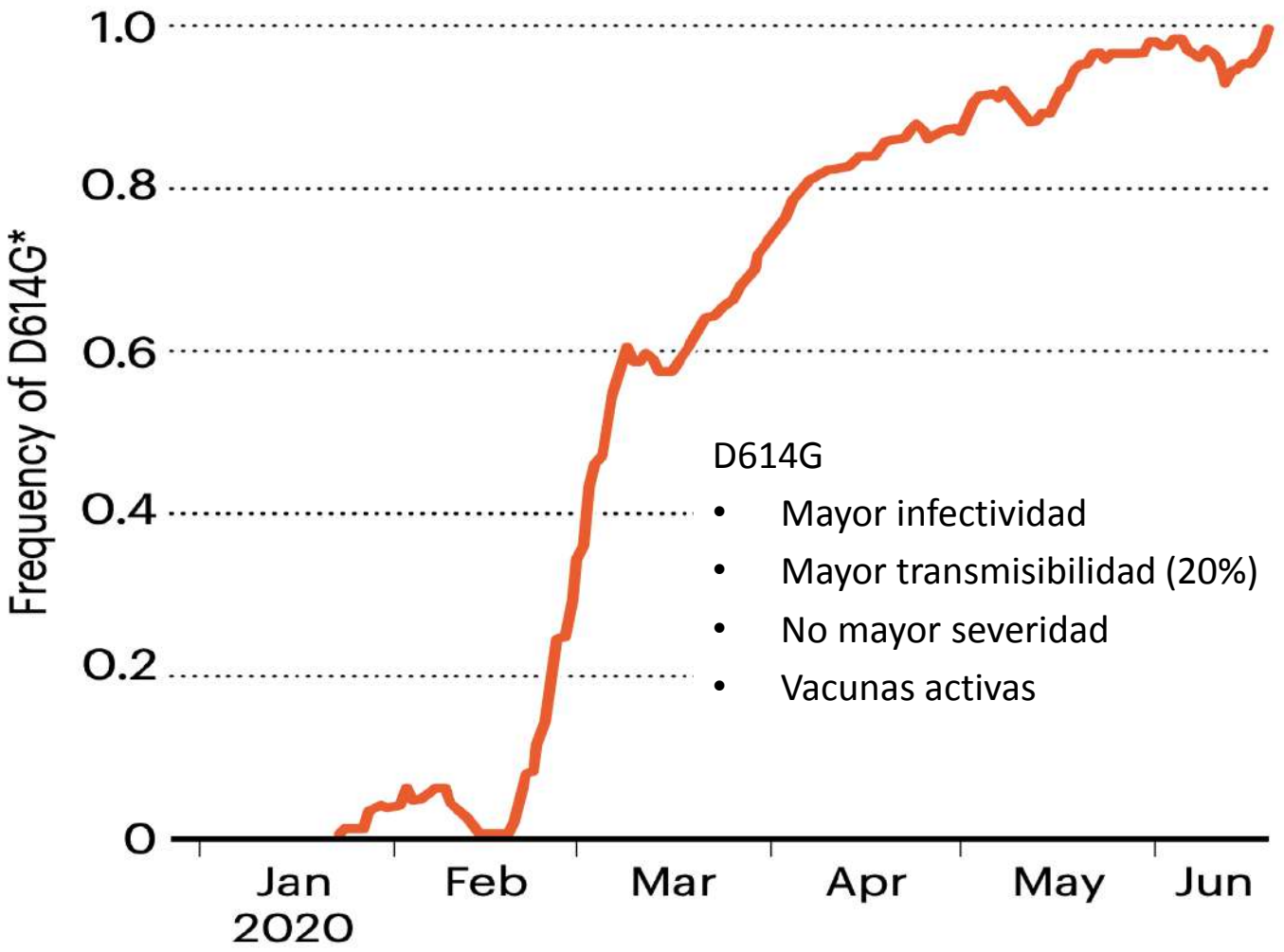




Jason W. Rausch et al. PNAS 2020, RS Baric. N Engl J Med 2020;, Callaway E Nature 2020

SARS-CoV-2: mutaciones



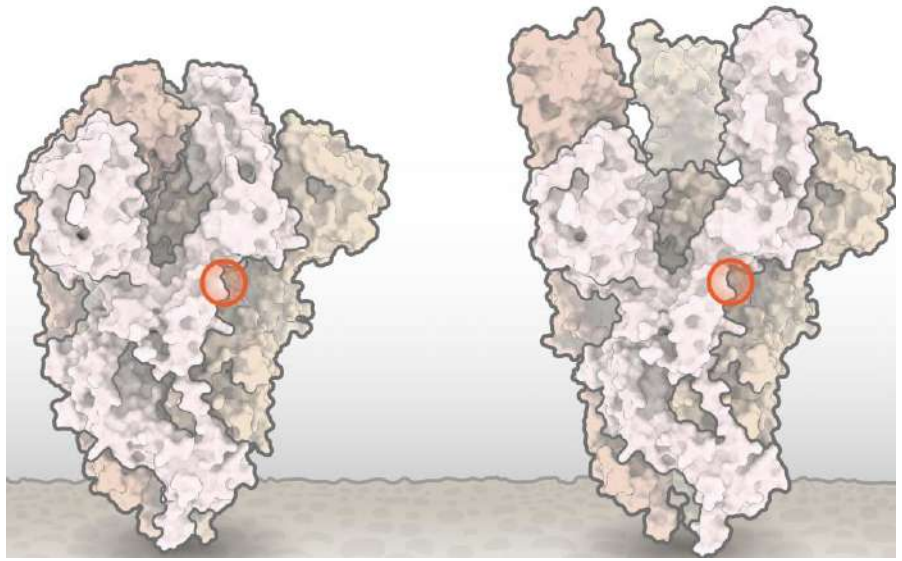


D614G

- Mayor infectividad
- Mayor transmisibilidad (20%)
- No mayor severidad
- Vacunas activas

Jason W. Rausch et al. PNAS 2020, RS Baric. N Engl J Med 2020;, Callaway E Nature 2020

SARS-CoV-2: mutaciones



Variantes de interés

- *Múltiples mutaciones, incremento circulación*

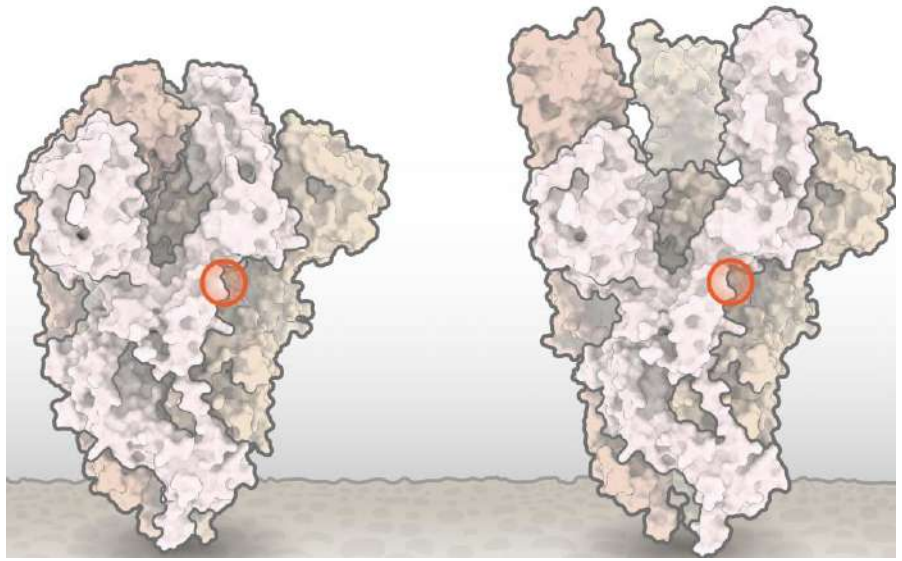
Variantes de preocupación

- *Mayor transmisión, virulencia, y escape inmunológico*

Variantes con consecuencias

- *Falla diagnóstica, falla importante de vacunas, mayor severidad enfermedad*

SARS-CoV-2: mutaciones



Variantes de interés

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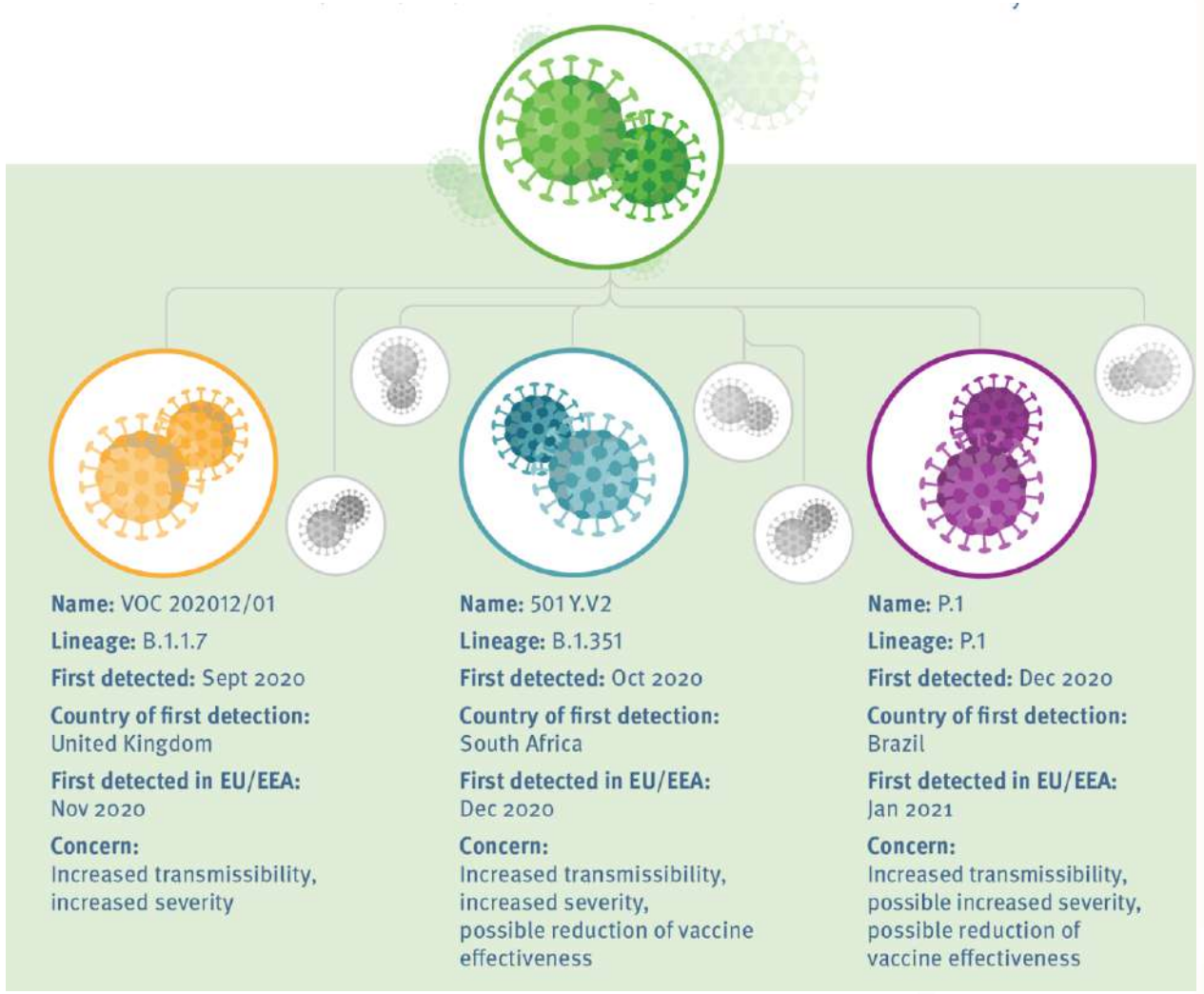
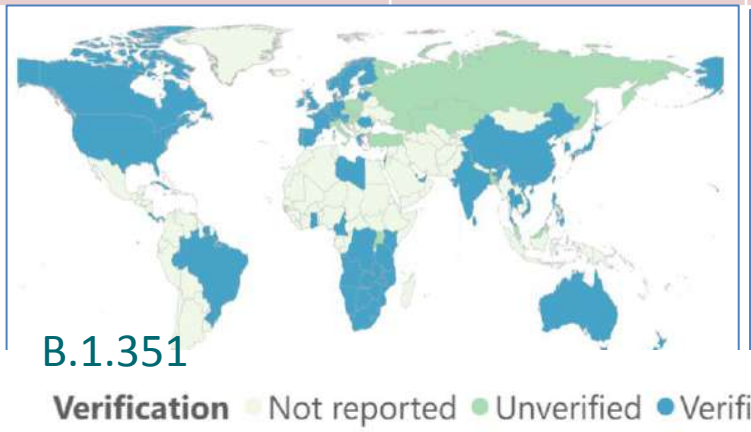
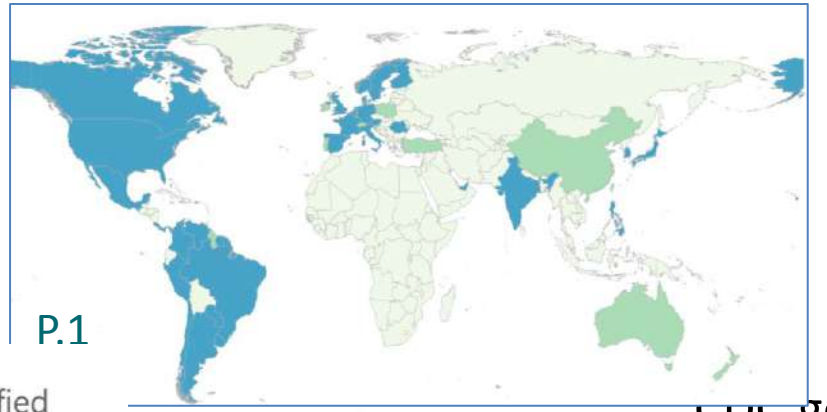
- *Falla diagnóstica, falla importante de vacunas, mayor severidad enfermedad*



Variantes de preocupación SARS-CoV-2

Nombre (Pangolin)	Nombre (Nextstrain)	Detectado	Países con reporte casos	Mutación	Transmisibilidad
B.1.1.7	20I/501Y.V1	Reino Unido	101	Δ69/70 Δ144Y **N501Y** A570D D614G P681H	~50% aumento
B.1.351	20H/501Y.V2	Sudáfrica	51	K417N E484K N501Y D614G	~50% aumento
P.1	20J/501Y.V3	Brasil/ Japón	29	E484K K417N/T **N501Y** D614G	No determinada
B.1.427, B.1.429		USA, California			
B.1.617.1 (VUI)		India			

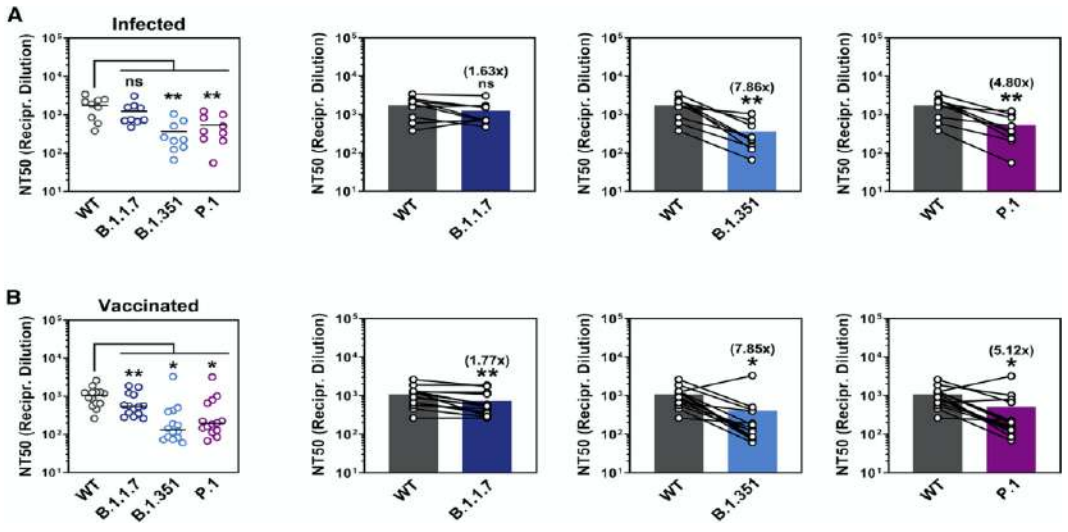




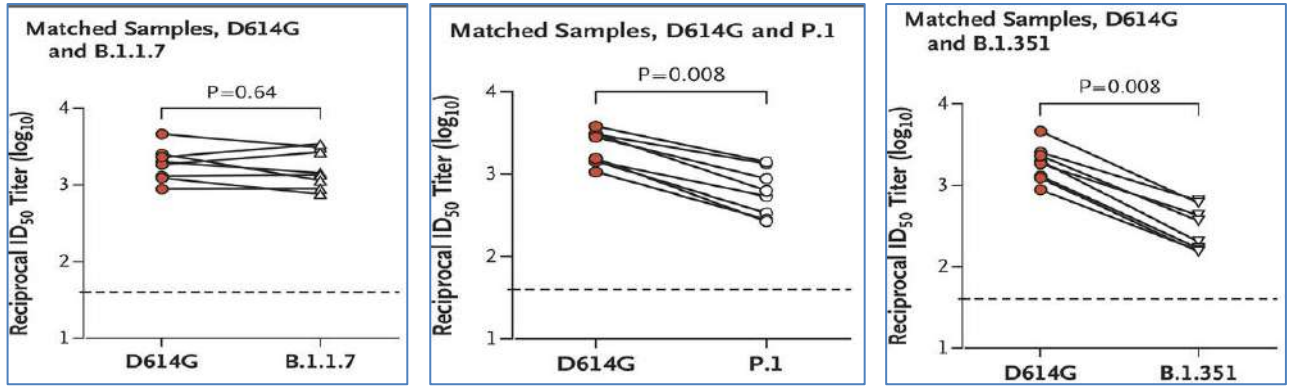
CDC.gov

Variantes y eficacia vacunas mRNA

BNT162b2 (*Pfizer-BioNTech*)



mRNA-1273 (*Moderna*)



K Wu et al. N Engl J Med 2021, Garcia-Beltran W et al, Cell 2021, Hoffmann et al Cell, 2021

Variantes y eficacia vacunas mRNA

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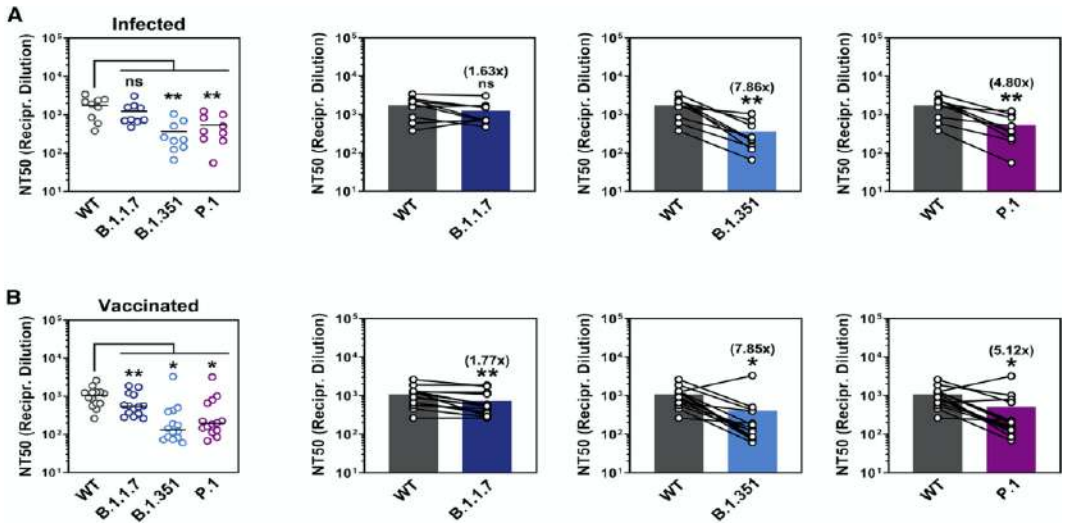

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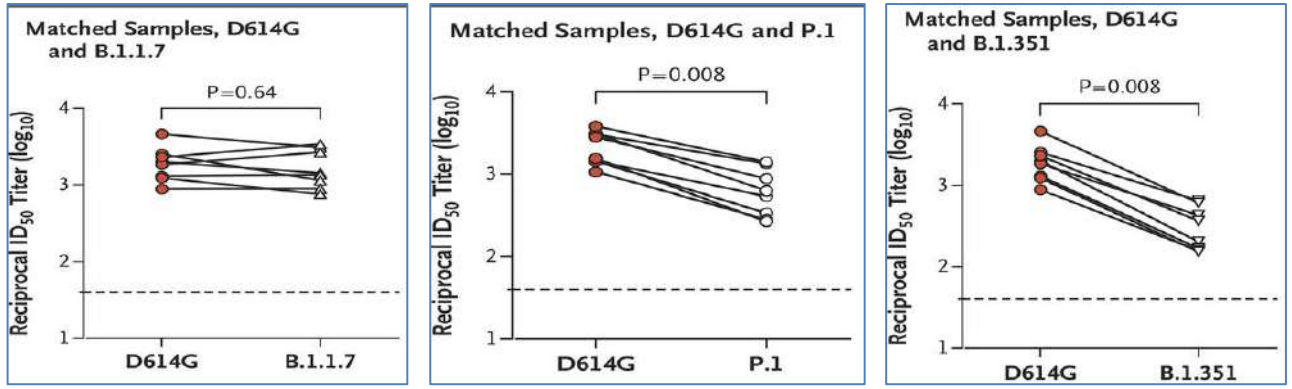
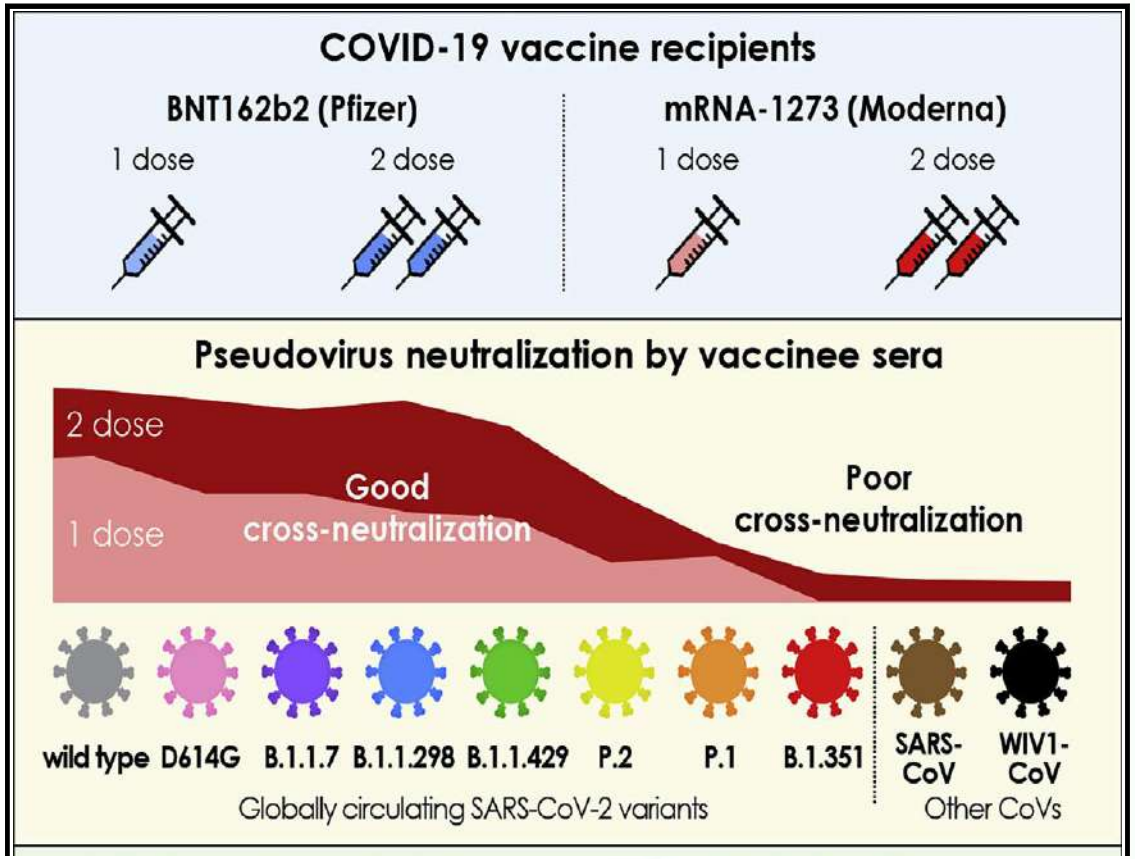
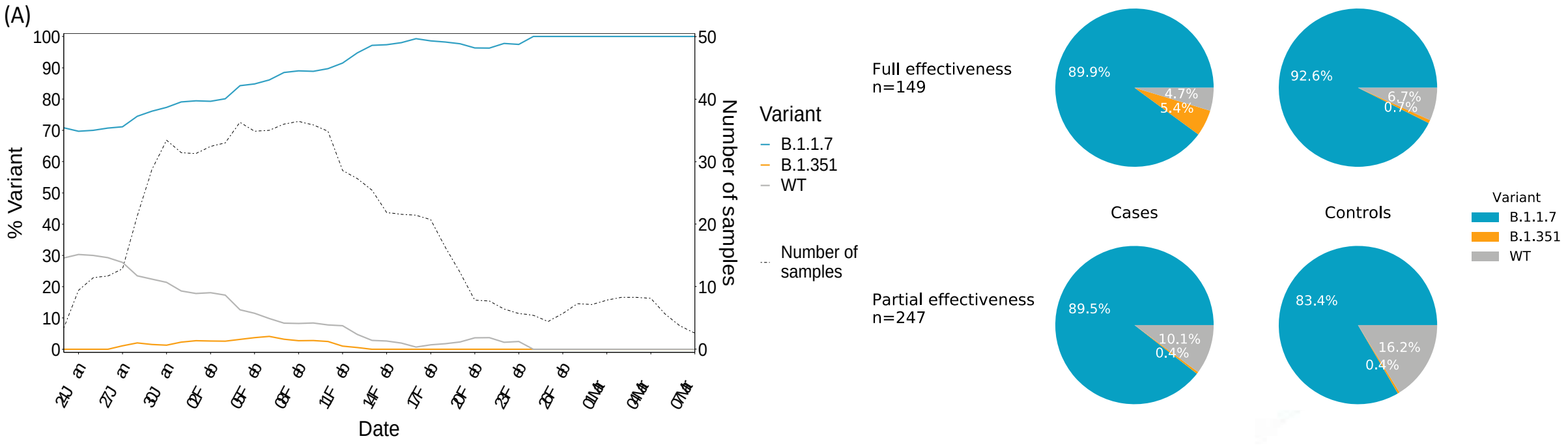




K Wu et al. N Engl J Med 2021, Garcia-Beltran W et al, Cell 2021, Hoffmann et al Cell, 2021

Pfizer versus variantes

- Evidence for increased breakthrough rates of SARS-CoV-2 variants of concern in BNT162b2 mRNA vaccinated individuals



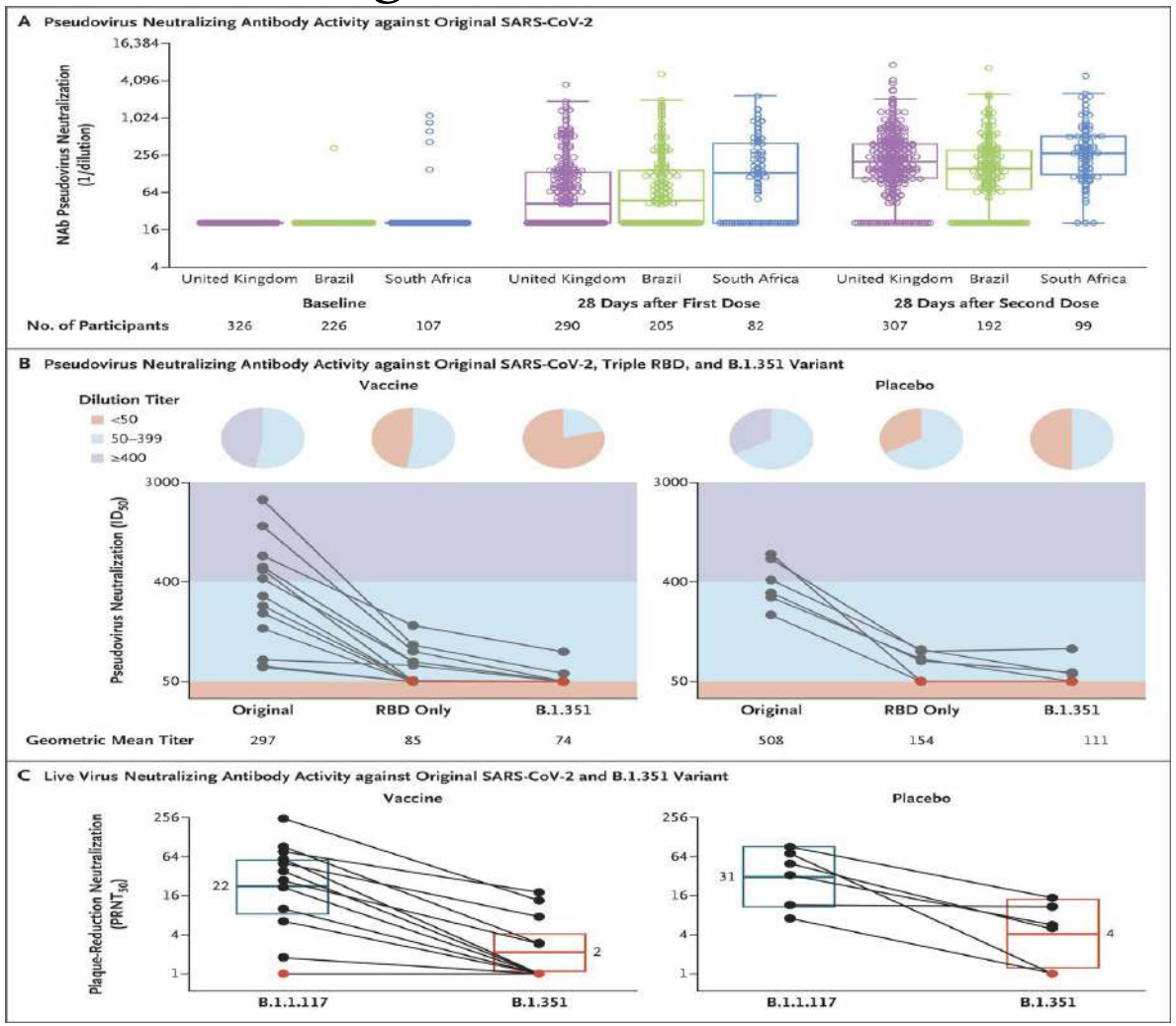
Talia Kustin et al, https://doi.org/10.1101/2021.04.06.21254882

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

SA Madhi et al. N Engl J Med 2021.

Efficacy of the ChAdOx1 nCoV-19 Covid-19 Vaccine against the B.1.351 Variant



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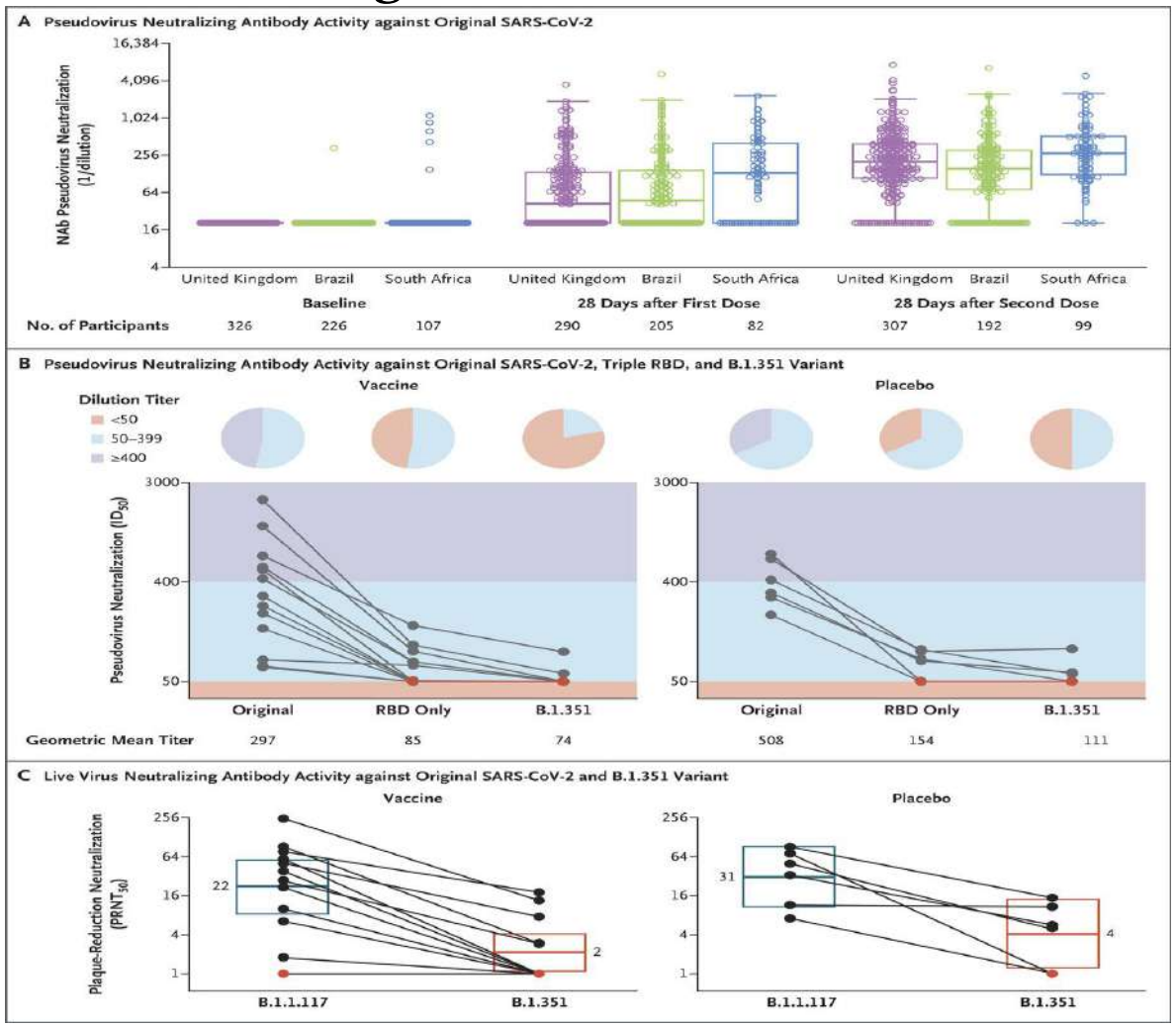
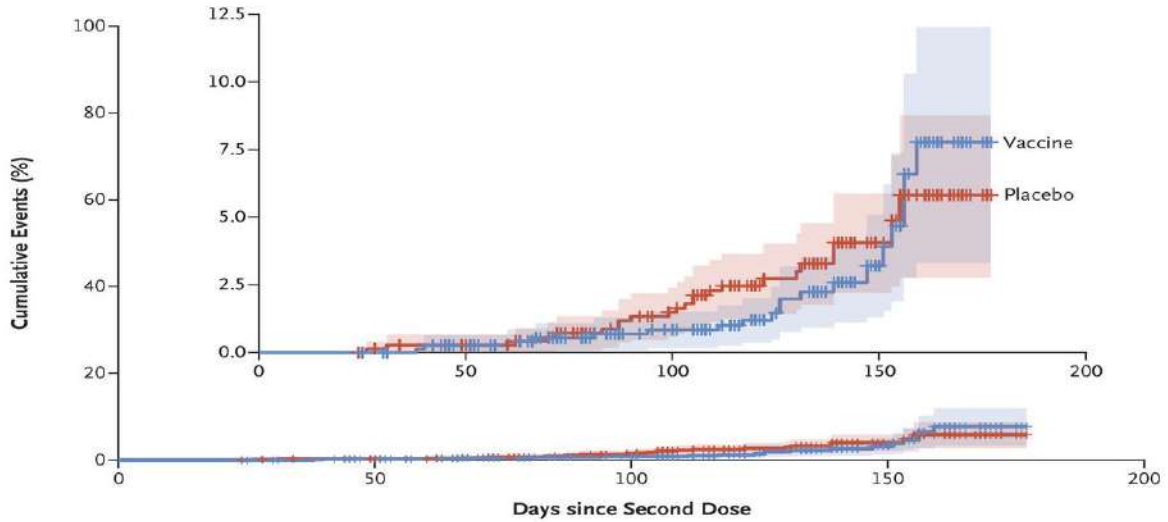




Vaccine Efficacy against Mild-to-Moderate Symptomatic Covid-19 Confirmed by Nucleic Acid Amplification Test.*

End Point	Vaccine Efficacy‡ % (95% CI)
Mild-to-moderate illness with onset >14 days after second injection	21.9 (−49.9 to 59.8)
Mild-to-moderate illness associated with B.1.351 variant with onset >14 days after second injection	10.4 (−76.8 to 54.8)
Mild-to-moderate illness with onset >14 days after second injection, regardless of baseline serostatus	10.6 (−66.4 to 52.2)
Mild-to-moderate illness with onset >14 days after one dose until October 31, 2020, a proxy for non-B.1.351 variant infection	75.4 (8.9 to 95.5)

The NEW ENGLAND JOURNAL of MEDICINE

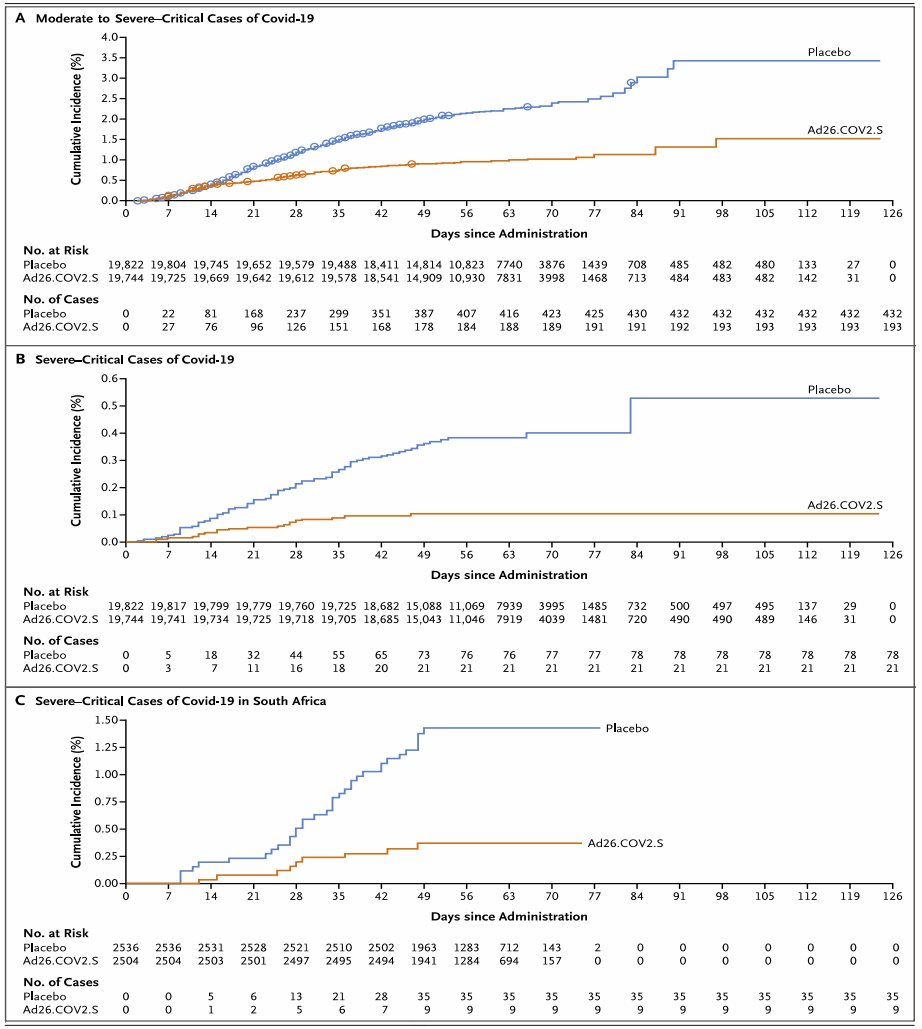
ORIGINAL ARTICLE

Safety and Efficacy of Single-Dose Ad26.COV2.S Vaccine against Covid-19

J. Sadoff, G. Gray, A. Vandebosch, V. Cárdenas, G. Shukarev, B. Grinsztejn, P.A. Goepfert, C. Truyers, H. Fennema, B. Spiessens, K. Offergeld, G. Scheper, K.L. Taylor, M.L. Robb, J. Treanor, D.H. Barouch, J. Stoddard, M.F. Ryser, M.A. Marovich, K.M. Neuzil, L. Corey, N. Cauwenberghs, T. Tanner, K. Hardt, J. Ruiz-Guiñazú, M. Le Gars, H. Schuitemaker, J. Van Hoof, F. Struyf, and M. Douoguih, for the ENSEMBLE Study Group*

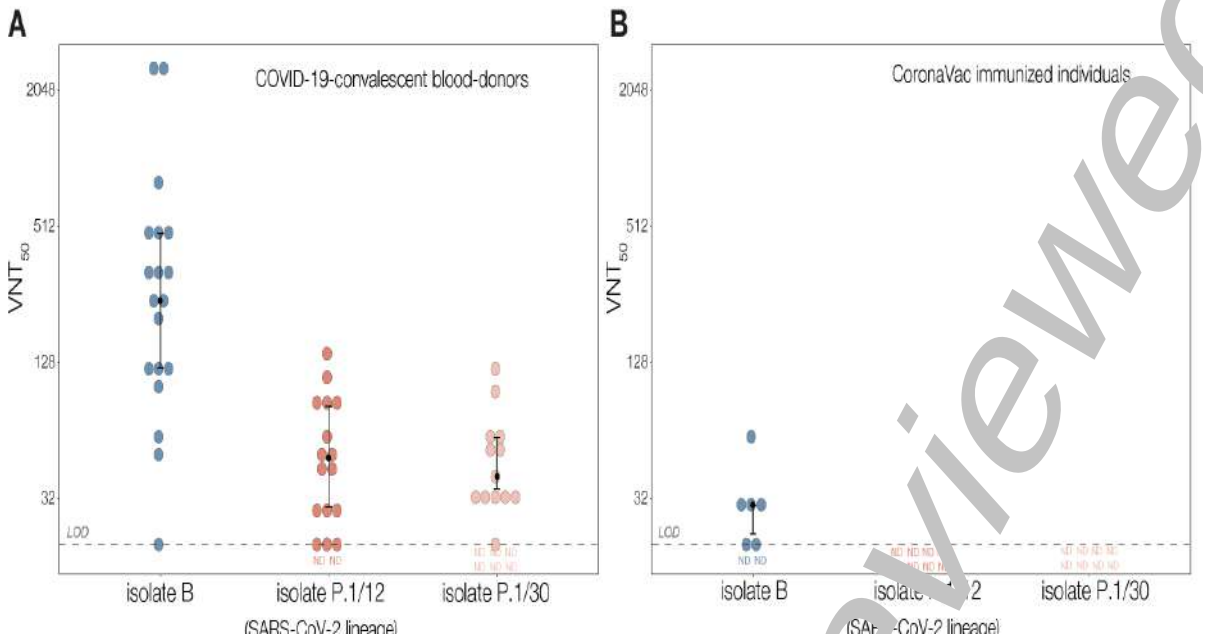
8 países (19630/19691) > 18 años, 1 dosis	Endp 1º: moderado o severo 14 y 28 días de dosis	Alguna alerta de seguridad

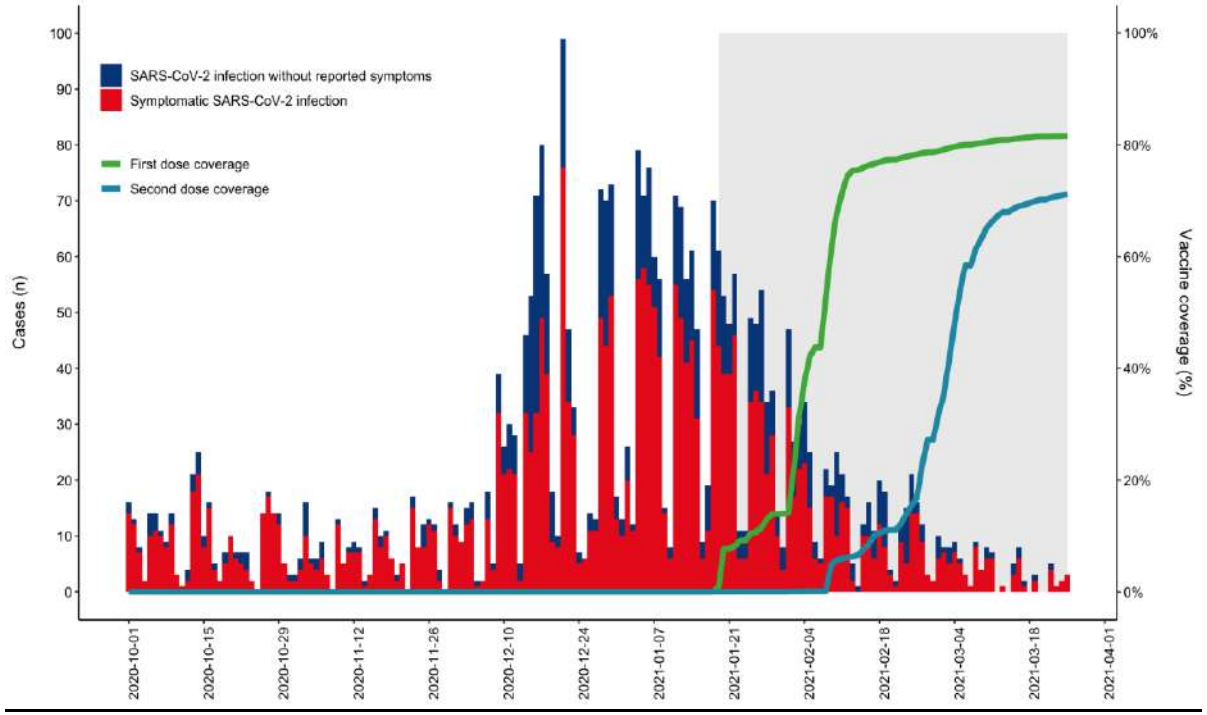
	Moderate & Severe (28 days)	Severe (28 days)	Severe (>49 days)
US	72% ⬇	85% ⬇ (100% ⬇ death)	100% ⬇
Latin America	66% ⬇		
South Africa (95% B.1.351 variant)	57% ⬇		



Cumulative Incidence of Covid-19 with Onset at Least 1 Day after Vaccination and Vaccine Efficacy over Time.

Variantes en vacunas virus atenuado





https://dx.doi.org/10.2139/ssrn.3793486. Hitchings M et al, https://doi.org/10.1101/2021.04.07.21255081

CORRESPONDENCE

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

SS Abdool Karim, T de Oliveira. N Engl J Med 2021.

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

Trombocitopenia y trombosis inducida por vacuna

The NEW ENGLAND JOURNAL of MEDICINE

BRIEF REPORT

Thrombosis and Thrombocytopenia after ChAdOx1 nCoV-19 Vaccination

Nina H. Schultz, M.D., Ph.D., Ingvild H. Sørvoll, M.D., Annika E. Michelsen, Ph.D., Ludvig A. Munthe, M.D., Ph.D., Fridtjof Lund-Johansen, M.D., Ph.D., Maria T. Ahlen, Ph.D., Markus Wiedmann, M.D., Ph.D., Anne-Hege Aamodt, M.D., Ph.D., Thor H. Skattør, M.D., Geir E. Tjønnfjord, M.D., Ph.D., and Pål A. Holme, M.D., Ph.D.

SUMMARY

We report findings in five patients who presented with venous thrombosis and thrombocytopenia 7 to 10 days after receiving the first dose of the ChAdOx1 nCoV-19 adenoviral vector vaccine against coronavirus disease 2019 (Covid-19). The patients were health care workers who were 32 to 54 years of age. All the patients had high levels of antibodies to platelet factor 4–polyanion complexes; however, they had had no previous exposure to heparin. Because the five cases occurred in a population of more than 130,000 vaccinated persons, we propose that they represent a rare vaccine-related variant of spontaneous heparin-induced thrombocytopenia that we refer to as vaccine-induced immune thrombotic thrombocytopenia.

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Pathologic Antibodies to Platelet Factor 4 after ChAdOx1 nCoV-19 Vaccination

Marie Scully, M.D., Deepak Singh, B.Sc., Robert Lown, M.D., Anthony Poles, M.D., Tom Solomon, M.D., Marcel Levi, M.D., David Goldblatt, M.D., Ph.D., Pavel Kotoucek, M.D., William Thomas, M.D., and William Lester, M.D.

ABSTRACT

BACKGROUND

The mainstay of control of the coronavirus disease 2019 (Covid-19) pandemic is vaccination against severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). Within a year, several vaccines have been developed and millions of doses delivered. Reporting of adverse events is a critical postmarketing activity.

METHODS

We report findings in 23 patients who presented with thrombosis and thrombocytopenia 6 to 24 days after receiving the first dose of the ChAdOx1 nCoV-19 vaccine (AstraZeneca). On the basis of their clinical and laboratory features, we identify a novel underlying mechanism and address the therapeutic implications.

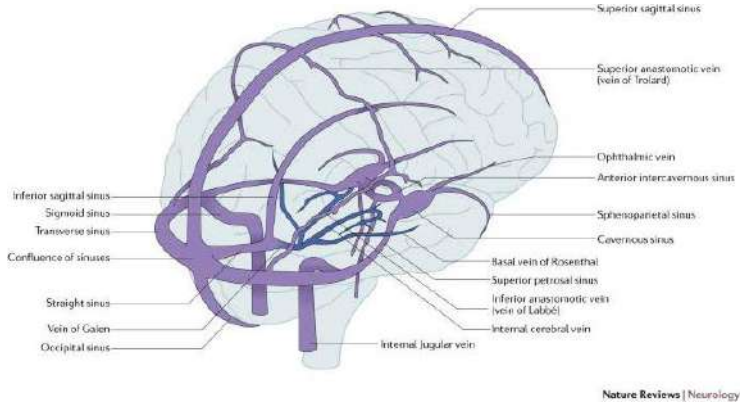
The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Thrombotic Thrombocytopenia after ChAdOx1 nCov-19 Vaccination

Andreas Greinacher, M.D., Thomas Thiele, M.D., Theodore E. Warkentin, M.D., Karin Weisser, Ph.D., Paul A. Kyrle, M.D., and Sabine Eichinger, M.D.

We assessed the clinical and laboratory features of 11 patients in Germany and Austria in whom thrombosis or thrombocytopenia had developed after vaccination with ChAdOx1 nCov-19. We used a standard enzyme-linked immunosorbent assay to detect platelet factor 4 (PF4)–heparin antibodies and a modified (PF4-enhanced) platelet-activation test to detect platelet-activating antibodies under various reaction conditions. Included in this testing were samples from patients who had blood samples referred for investigation of vaccine-associated thrombotic events, with 28 testing positive on a screening PF4–heparin immunoassay.



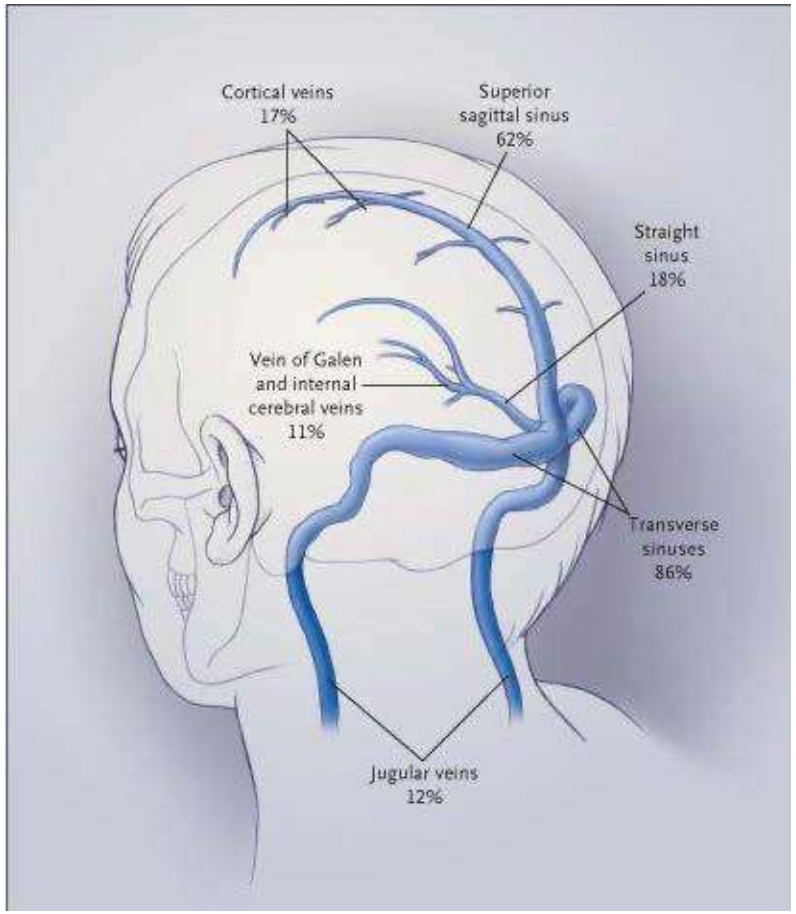
3 reportes simultáneos de VITT relacionado a ChAdOx1

La mayoría con Ac anti factor 4 plaquetario (PFA)

Surge el: “Vaccine-induced immune thrombotic thrombocytopenia” (**VITT**)

Trombosis de senos venosos cerebrales

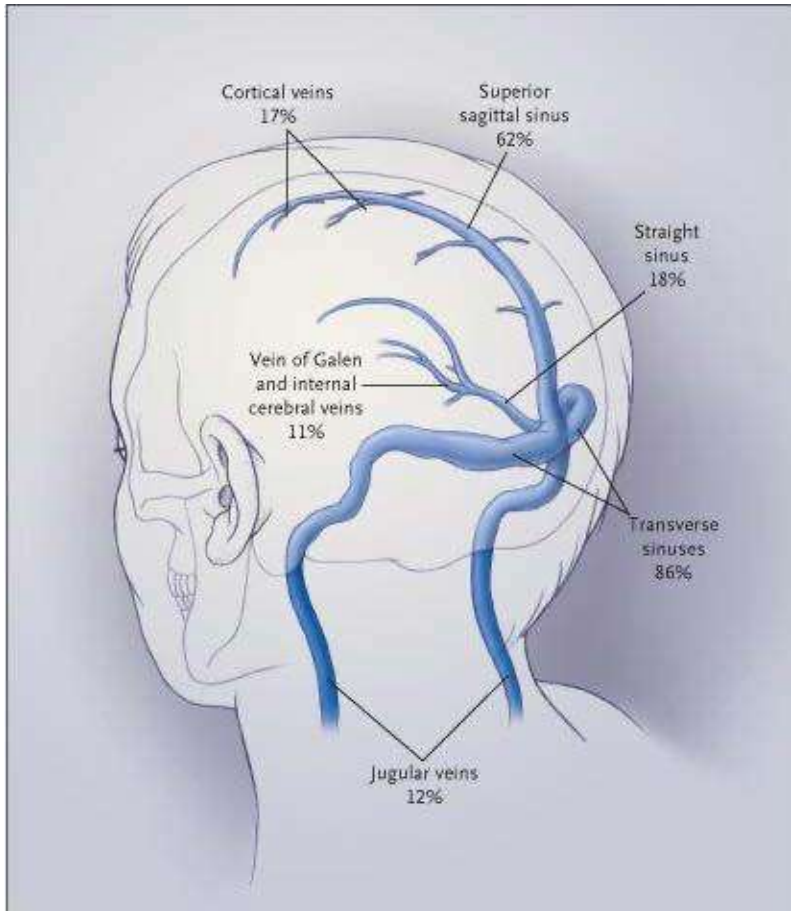
- Trombosis superficiales y profundas en venas cerebrales
- Incidencia: 10-15 casos por millón
- Edad media: 35 años
- Mujeres/hombres: 2,2/1
- Cefalea, convulsiones, alteración conciencia y coma
- FR: anticonceptivos, alteraciones coagulación, embarazo, cáncer, infecciones, cirugía
- Diagnostico: TAC o RM
- Tratamiento: anticoagulación, trombolisis



Capecchi M et al. J Thromb Haemost. 2018 Stam J. N Engl J Med. 2005. Adaptada de Michael Striff, ACIP abril 2021

Trombosis de senos venosos cerebrales y vacunas SARS-CoV-2

- Sin casos confirmados en vacunas mRNA
- Asociada con vacunas Adenovirus modificados
  - Incidencia estimada excede riesgo basal
  - 21-77 años (90% <60)
  - Mujer/hombre: 2,5:1
  - Inicio 5 a 24 días (10)
  - Trombosis: cerebral , abdominal, TVP/TEP, trombosis arterial
  - Plaquetas nivel: 7000-113,000
  - PFA positivo en la mayoria



Greinacher A, et al. N Engl J Med. 2021. Schultz NH, et al. N Engl J Med.. Scully M, et al. N Engl J Med. 2021, Cines D et al, N Engl J Med 2021

VACCINE INDUCED THROMBOTIC THROMBOCYTOPENIA

ACIP Meeting April 14, 2021 and European Medicines Agency

association with viral vector COVID-19 vaccines

this entity has only been reported in relation to viral vector vaccines using adenovirus vectors (AstraZeneca - not currently approved in the US and Johnson and Johnson)
it has not been found amongst individuals receiving mRNA vaccines (Pfizer, Moderna)

AstraZeneca

reported to European Medicines Agency (EMA) as of April 4, 2021
out of ~34 million doses administered
Cerebral venous sinus thrombosis (CVST): n=169
Splanchnic vein thrombosis: n=53

From the EU in-depth review
62 cases of CSVT and 24 cases of splanchnic vein thrombosis were reviewed
Fatal n=18

From the UK (of 20.2 million doses given)
79 cases
CSVT n=44 (14 fatal)
Other thrombosis (5 fatal)

Johnson & Johnson

8 reported from >6.8 million doses administered
7 reported to J&J (6 reported via VAERS), 1 reported in FDA EUA for J&J
6 with CSVT, 1 with extensive DVTs, 1 with details pending

FOAMcast.org

CDC Centers for Disease Control and Prevention
CDC 24/7: Saving Lives, Protecting People™

FDA and CDC Lift Recommended Pause on Johnson & Johnson (Janssen) COVID-19 Vaccine Use Following Thorough Safety Review

Press Release

Embargoed Until: Friday, April 23, 2021, 7:00 p.m. ET
Contact: Media Relations
(404) 639-3286

Following a thorough safety review, including two meetings of the CDC's Advisory Committee on Immunization Practices, the U.S. Food and Drug Administration and the U.S. Centers for Disease Control and Prevention have determined that the recommended pause regarding the use of the Janssen (Johnson & Johnson) COVID-19 Vaccine in the U.S. should be lifted and use of the vaccine should resume.

The pause was recommended after reports of six cases of a rare and severe type of blood clot in individuals following administration of the Janssen COVID-19 Vaccine. During the pause, medical and scientific teams at the FDA and CDC examined available data to assess the risk of thrombosis involving the cerebral venous sinuses, or CVST (large blood vessels in the brain), and other sites in the body (including but not limited to the large blood vessels of the abdomen and the veins of the legs) along with thrombocytopenia, or low blood platelet counts. The teams at FDA and CDC also conducted extensive outreach to providers and clinicians to ensure they were made aware of the potential for these adverse events and could properly manage and recognize these events due to the unique treatment required for these blood clots and low platelets, also known as thrombosis-thrombocytopenia syndrome (TTS).

The two agencies have determined the following:

- Use of the Janssen COVID-19 Vaccine should be resumed in the United States.
- The FDA and CDC have confidence that this vaccine is safe and effective in preventing COVID-19.
- The FDA has determined that the available data show that the vaccine's known and potential benefits outweigh its known and potential risks in individuals 18 years of age and older.
- At this time, the available data suggest that the chance of TTS occurring is very low, but the FDA and CDC will remain vigilant in continuing to investigate this risk.

Weighing up the potential benefits and harms of the Astra-Zeneca COVID-19 vaccine

For 100,000 people with low exposure risk*

Potential benefits: ICU admissions due to COVID-19 prevented every 16 weeks:	Age group	Potential harms: Serious harms due to the vaccine:
0.8	20-29yr	1.1
2.7	30-39yr	0.8
5.7	40-49yr	0.5
10.5	50-59yr	0.4
14.1	60-69yr	0.2

* Based on coronavirus incidence of 2 per 10,000: roughly UK in March

Weighing up the potential benefits and harms of the Astra-Zeneca COVID-19 vaccine

For 100,000 people with medium exposure risk*

Potential benefits: ICU admissions due to COVID-19 prevented every 16 weeks:	Age group	Potential harms: Serious harms due to the vaccine:
2.2	20-29yr	1.1
8.0	30-39yr	0.8
16.7	40-49yr	0.5
31.0	50-59yr	0.4
41.3	60-69yr	0.2

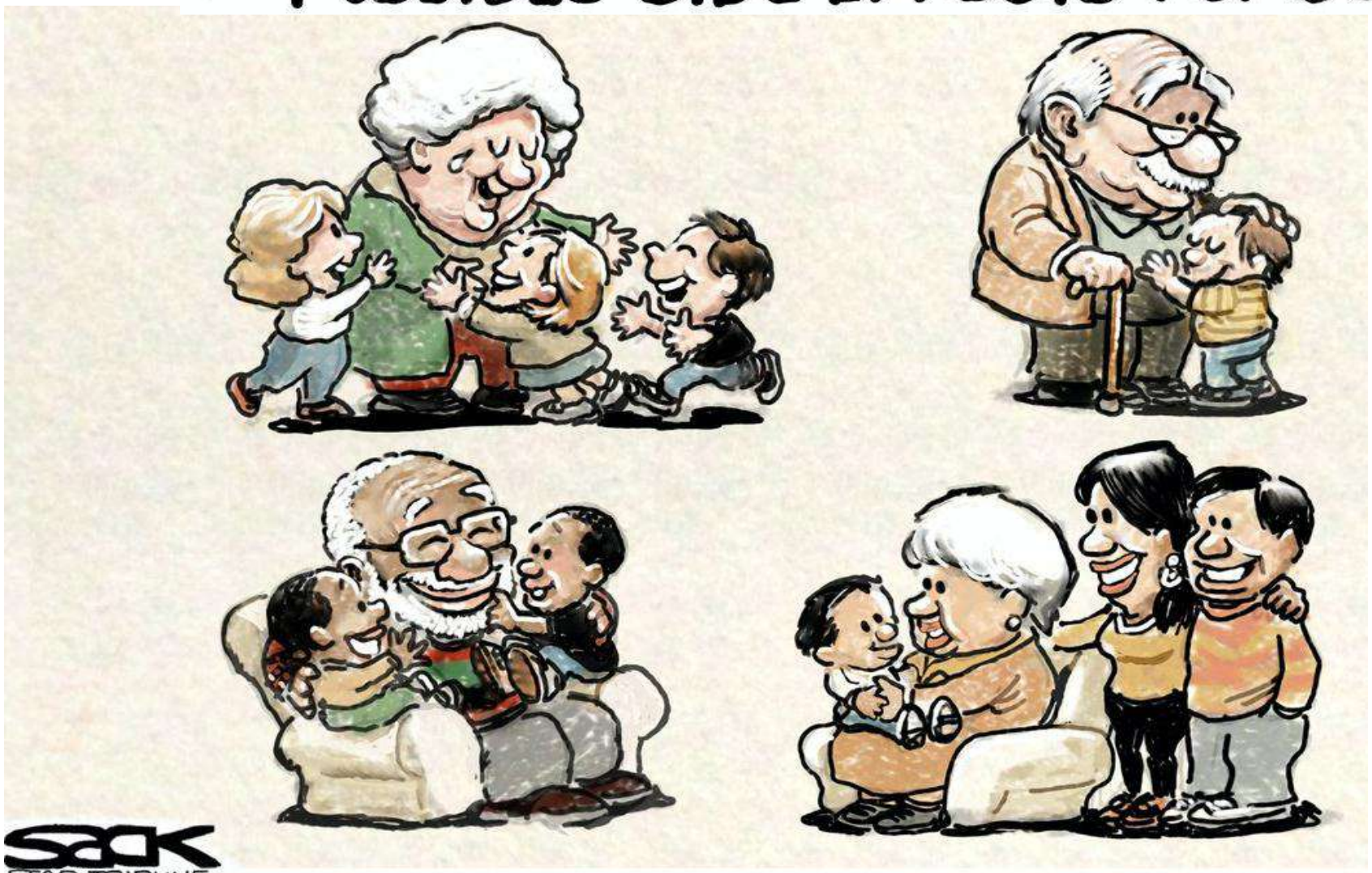
* Based on coronavirus incidence of 6 per 10,000: roughly UK in February

Weighing up the potential benefits and harms of the Astra-Zeneca COVID-19 vaccine

For 100,000 people with high exposure risk*

Potential benefits: ICU admissions due to COVID-19 prevented every 16 weeks:	Age group	Potential harms: Serious harms due to the vaccine:
6.9	20-29yr	1.1
24.9	30-39yr	0.8
51.5	40-49yr	0.5
95.6	50-59yr	0.4
127.7	60-69yr	0.2

* Based on coronavirus incidence of 20 per 10,000: roughly UK at peak of second wave



Muchas gracias

lnoriega@alemana.cl