Universidad de Alcalá

GILEAD

Red Española de Investigación en Sida

CÁTEDRA Red de Investigación en SIDA

¿Por qué somos tan lentos para conseguir una vacuna frente al VIH?

Fotografía de Asís G Ayerbe

Pepe Alcamí
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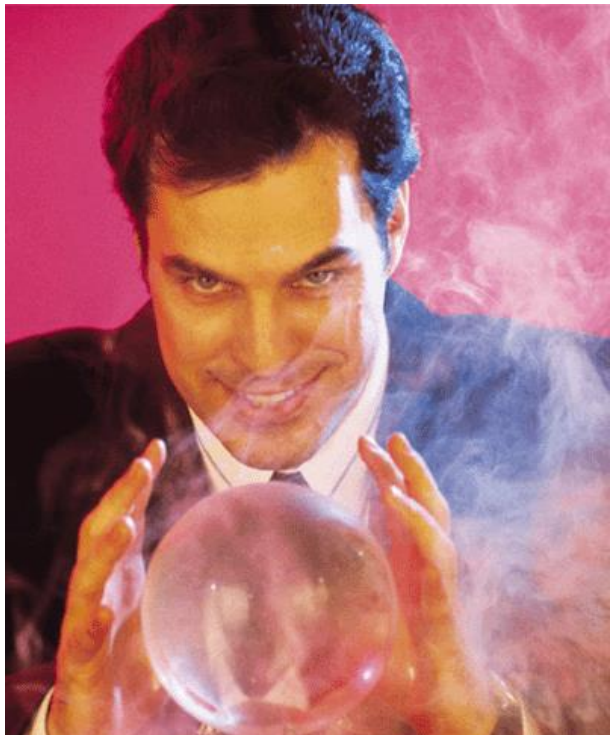
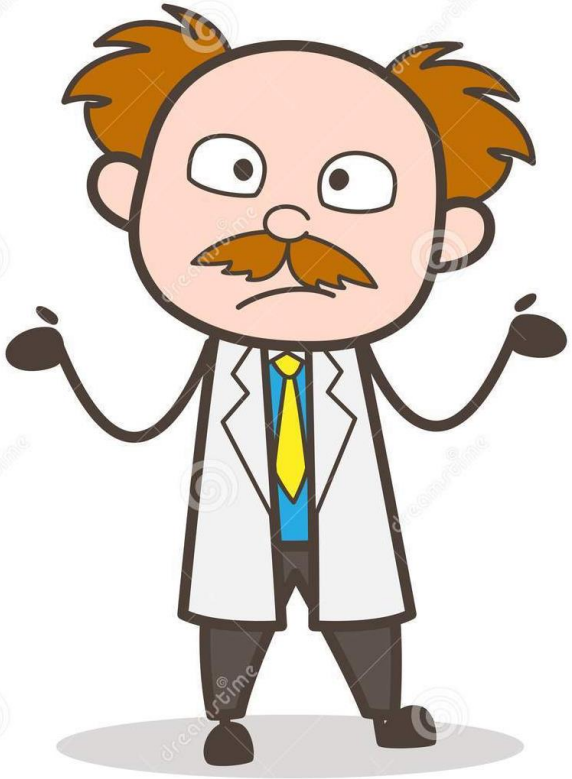
Coordinador de la Red de Investigación en SIDA

¿Cuando tendremos una vacuna preventiva contra el VIH?



¿Por qué se ha conseguido la vacuna frente a SARS-CoV-2 en menos de un año y llevan 40 años sin conseguir la vacuna frente al VIH?

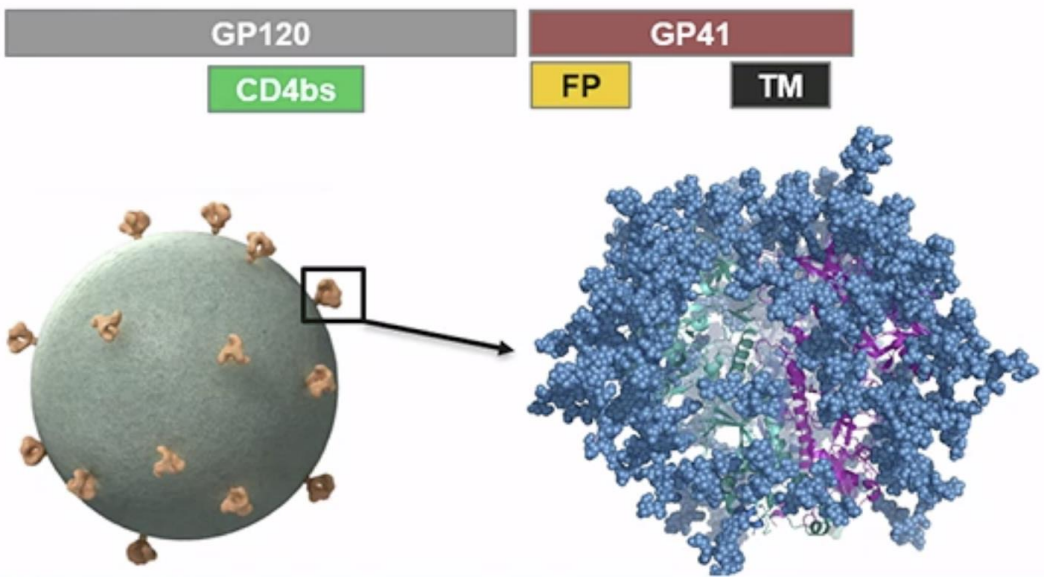


SARS-CoV-2 and HIV: Similarities and differences

HIV-1

Target cell/disease = **CD4+ T cells…..AIDS**
Host receptor = **CD4 and CCR5**
Entry = **Env, 2 subunits (GP120 & GP41)**
→ **trimeric glycoprotein**

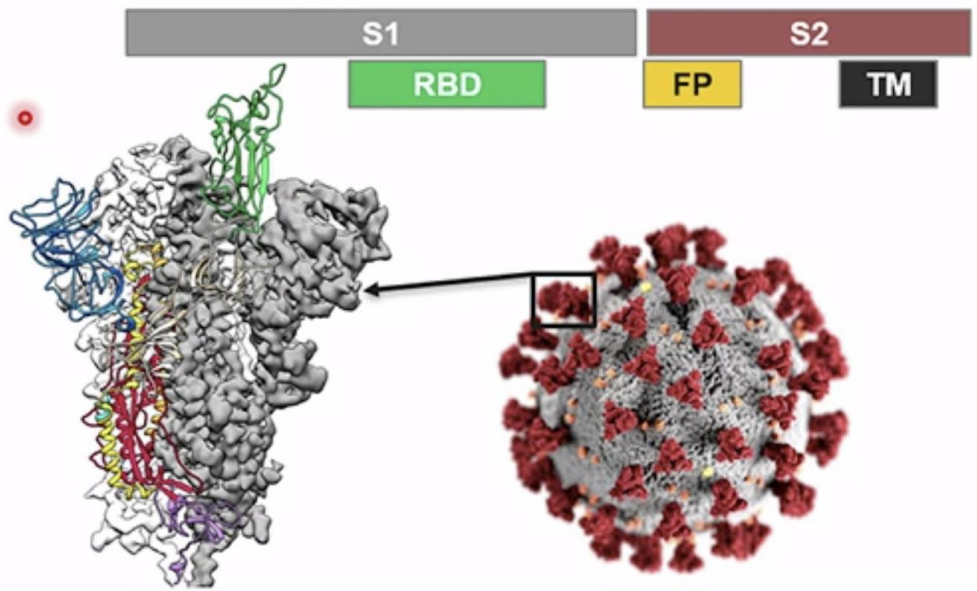
- **Enormous diversity, persistent infection**
- **High level glycosylation of Env**
- **Neutralizing epitopes structurally shielded**
- **Neutralizing antibodies not readily elicited in natural infection, and to date, not by vaccination**



SARS-CoV-2

Target cell/disease = **Epithelial cells lungs….COVID-19**
Host receptor = **ACE2**
Entry = **Spike, 2 subunits (S1 & S2)**
→ **trimeric glycoprotein**

- **More limited diversity, acute infection**
- **More limited glycosylation of S**
- **Neutralizing epitopes readily accessible to Abs**
- **Neutralizing antibodies readily elicited by infection and vaccination**



La carrera por las vacunas frente a SARS-CoV-2

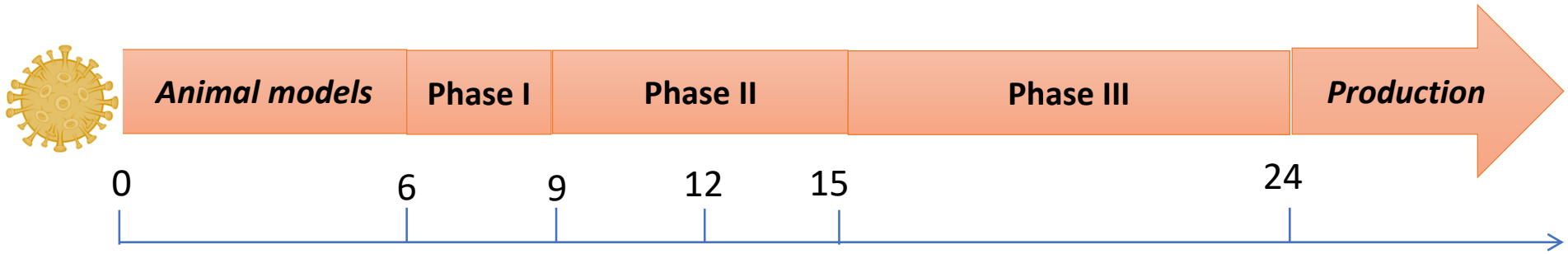
VACUNAS COVID

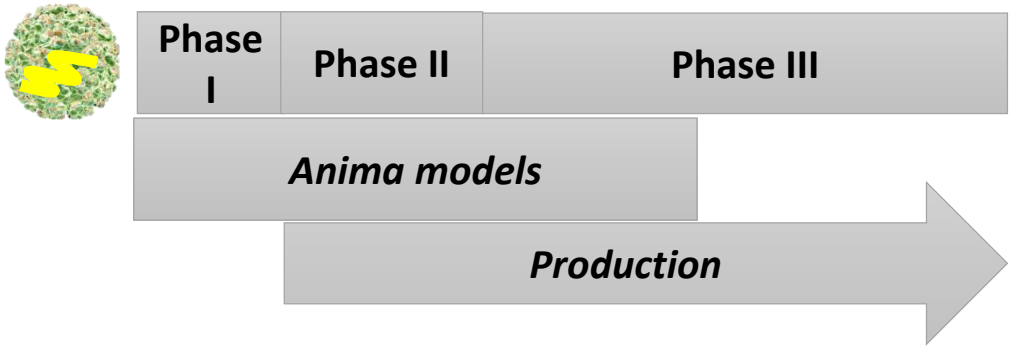
VACUNAS VIH

La carrera por las vacunas frente a SARS-CoV-2

Steps in vaccine development

Classical development

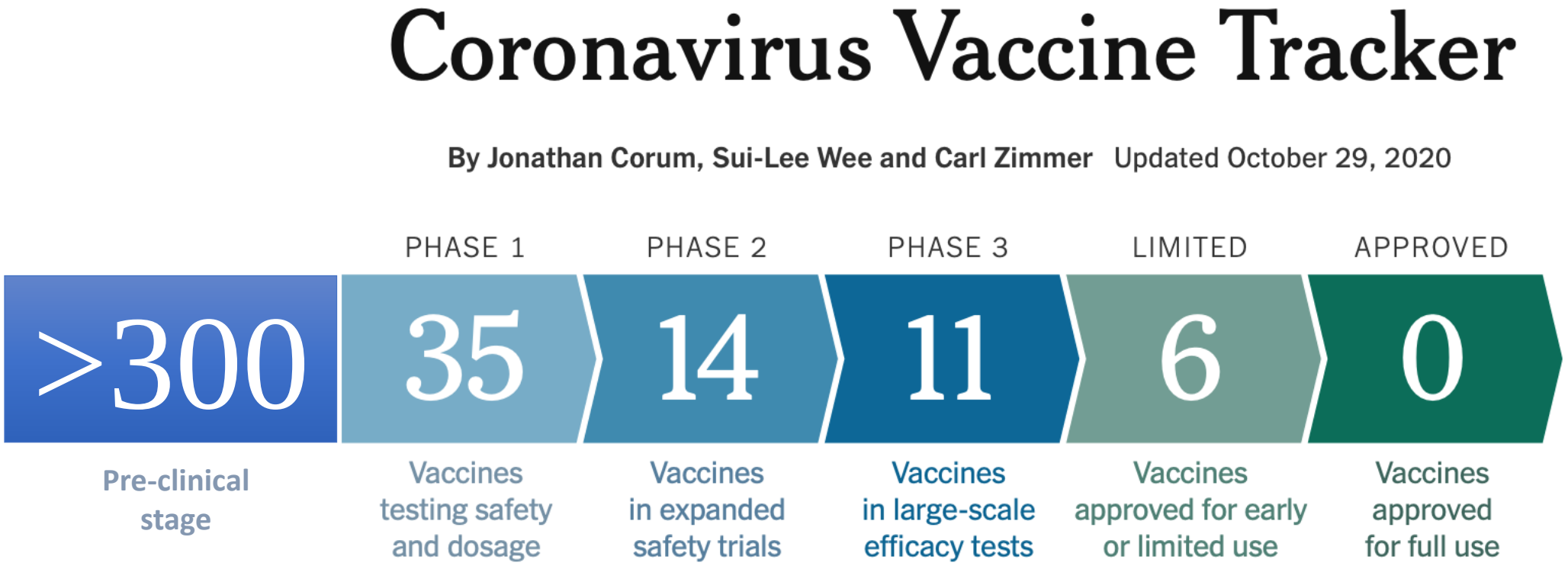




Accelerated development

J. Alcamí y E.López-Collazo. Coronavirus ¿la última Pandemia? Oberón libros, Editorial Anaya 2020

La carrera por las vacunas frente a SARS-CoV-2



New York Times, October 2020

La carrera por las vacunas frente a SARS-CoV-2

Protein Subunit
Anhui Zhifei Longcom
ZF2001
Approved in 3 countries
8 trials in 1 country

Inactivated
Bharat Biotech
Covaxin
Approved in 9 countries
7 trials in 1 country

Non Replicating Viral Vector
CanSino
Ad5-nCoV
Approved in 9 countries
11 trials in 1 country

Non Replicating Viral Vector
Gamaleya
Sputnik Light
Approved in 18 countries
4 trials in 2 countries

Non Replicating Viral Vector
Gamaleya
Sputnik V
Approved in 72 countries
21 trials in 2 countries

Non Replicating Viral Vector
Janssen (Johnson & Johnson)
Ad26.COV2.S
Approved in 75 countries
13 trials in 2 countries

Protein Subunit
Center for Genetic Engineering and Biotechnology (CIGB)
CIGB-66
Approved in 4 countries
5 trials in 1 country

Inactivated
Chumakov Center
KoviVac
Approved in 1 country
2 trials in 1 country

Protein Subunit
FBRI
EpiVacCorona
Approved in 2 countries
3 trials in 1 country

Inactivated
Kazakhstan RIBSP
QazVac
Approved in 2 countries
3 trials in 1 country

Protein Subunit
Medigen
MVC-COV1901
Approved in 1 country
7 trials in 1 country

Inactivated
Minhai Biotechnology Co
SARS-CoV-2 Vaccine (Vero Cells)
Approved in 1 country
5 trials in 1 country

RNA
Moderna
mRNA-1273
Approved in 76 countries
30 trials in 2 countries

Non Replicating Viral Vector
Oxford/AstraZeneca
AZD1222
Approved in 124 countries
45 trials in 2 countries

RNA
Pfizer/BioNTech
BNT162b2
Approved in 103 countries
37 trials in 2 countries

Inactivated
Sinopharm (Wuhan)
Inactivated (Vero Cells)
Approved in 2 countries
8 trials in 7 countries

Inactivated
Sinovac
CoronaVac
Approved in 41 countries
22 trials in 1 country

RNA
Takeda
TAK-919 (Moderna formulation)
Approved in 1 country
2 trials in 1 country

Non Replicating Viral Vector
Serum Institute of India
Covishield (Oxford/AstraZeneca formulation)
Approved in 46 countries
2 trials in 1 country

Inactivated
Shifa Pharmed Industrial Co
COVID-19 Inactivated Vaccine
Approved in 1 country
4 trials in 1 country

Inactivated
Sinopharm (Beijing)
BBIBP-CorV (Vero Cells)
Approved in 66 countries
14 trials in 2 countries

Protein Subunit
Vaxine/CinnaGen Co.
COVAX-19
Approved in 1 country
4 trials in 2 countries

DNA
Zydus Cadila
ZyCoV-D
Approved in 1 country
5 trials in 1 country

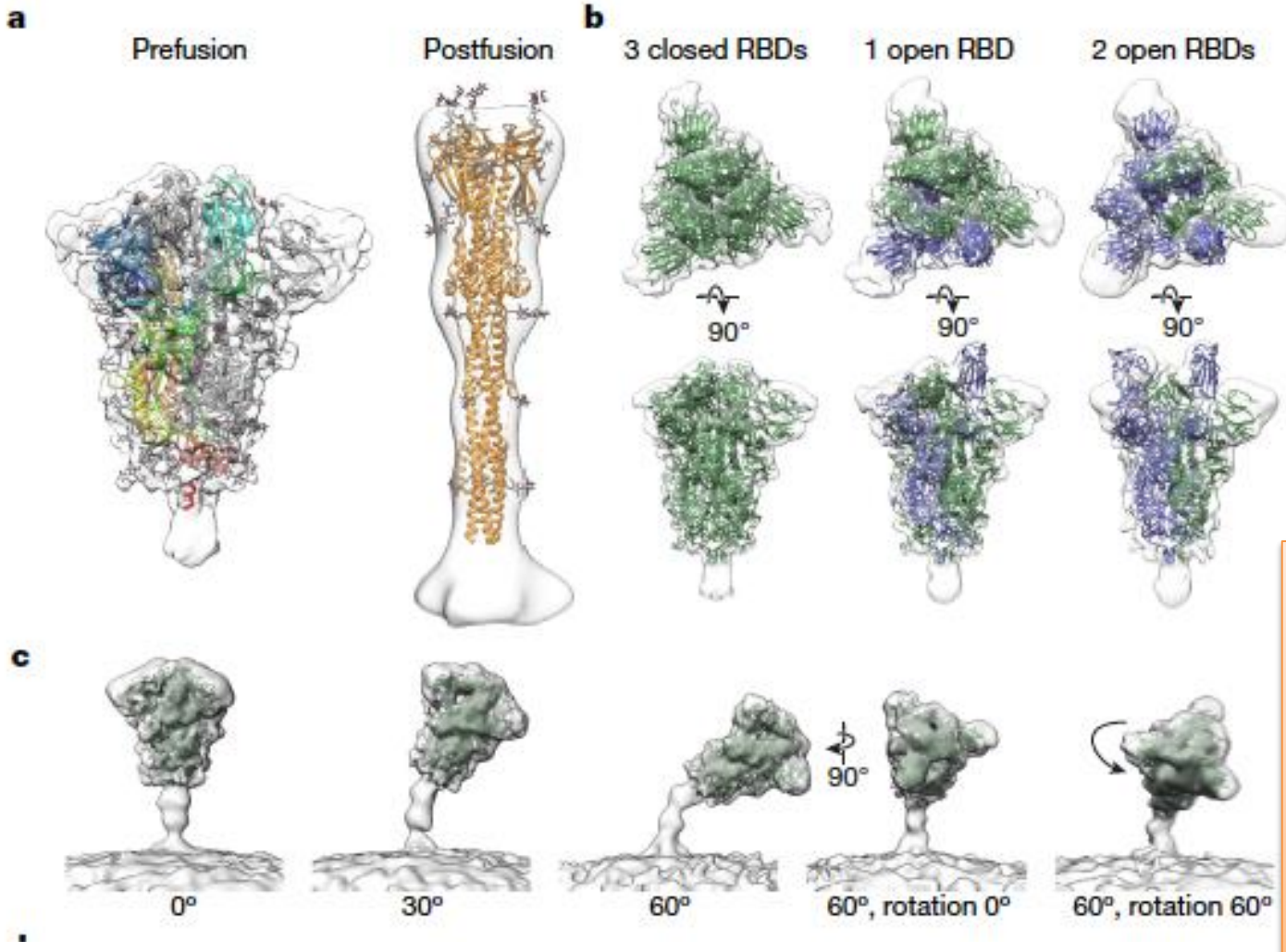
COVID19 VACCINE TRACKER

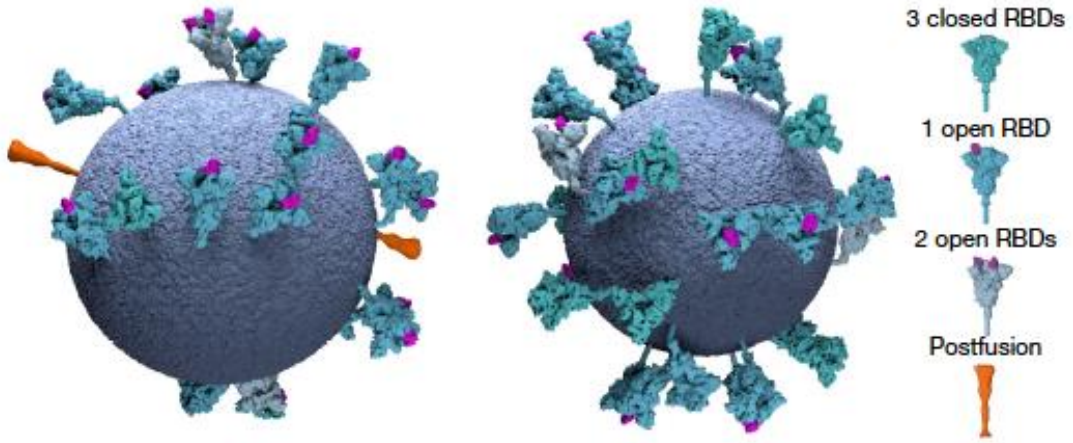
23
Approved Vaccines

- 8 Inactivated
- 6 Non-replicating viral vector
- 5 Protein subunit
- 3 RNA
- 1 DNA

https://covid19.trackvaccines.org/vaccines/approved/#vaccine-list

La carrera por las vacunas frente a SARS-CoV-2

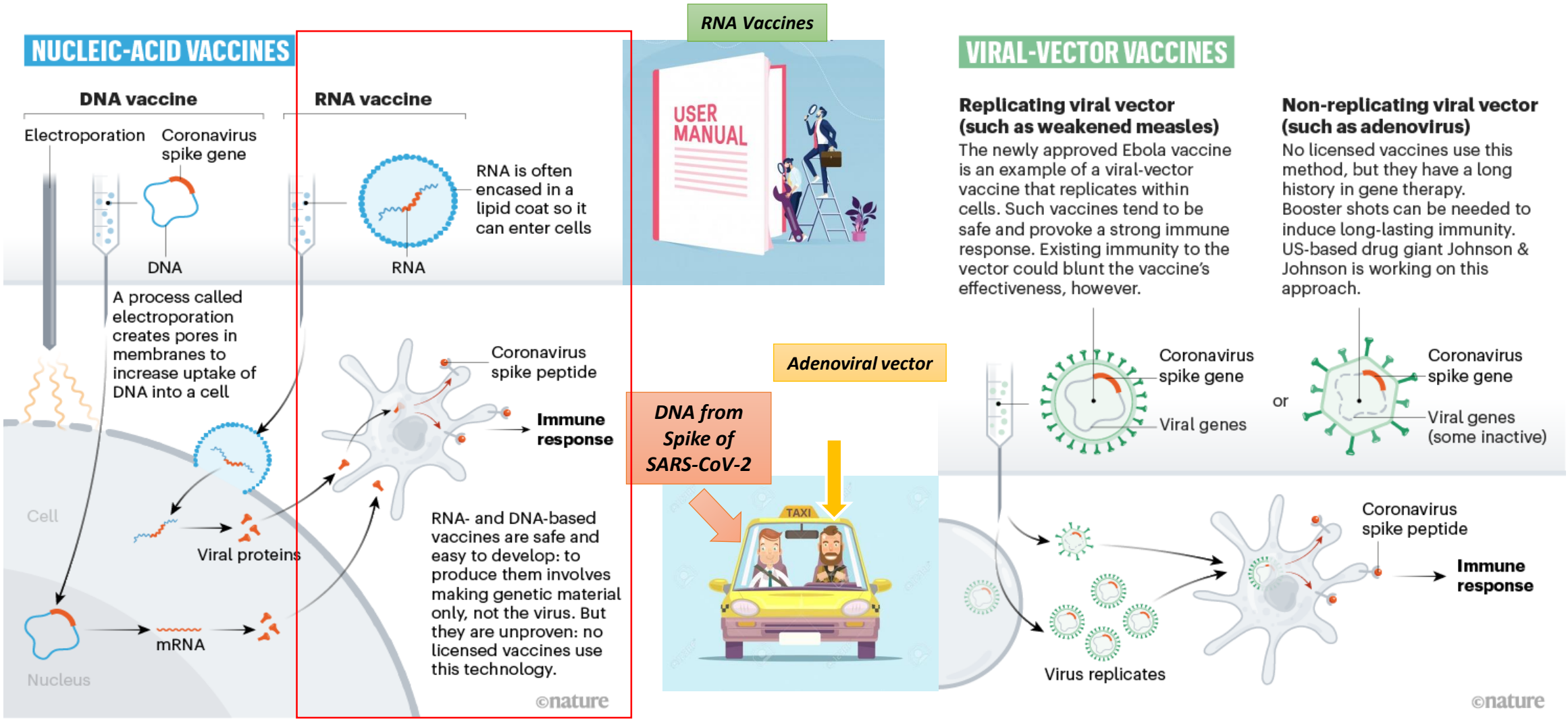




- **Todas las vacunas que funcionan inducen AcN**
- **Respuestas celulares colaboran al control pero pueden no ser protectoras**
- **La reacción cruzada entre coronavirus es a nivel de respuesta celular, no de Ac**
- **Los AcN son el principal marcador surrogado de inmunogenicidad y eficacia**

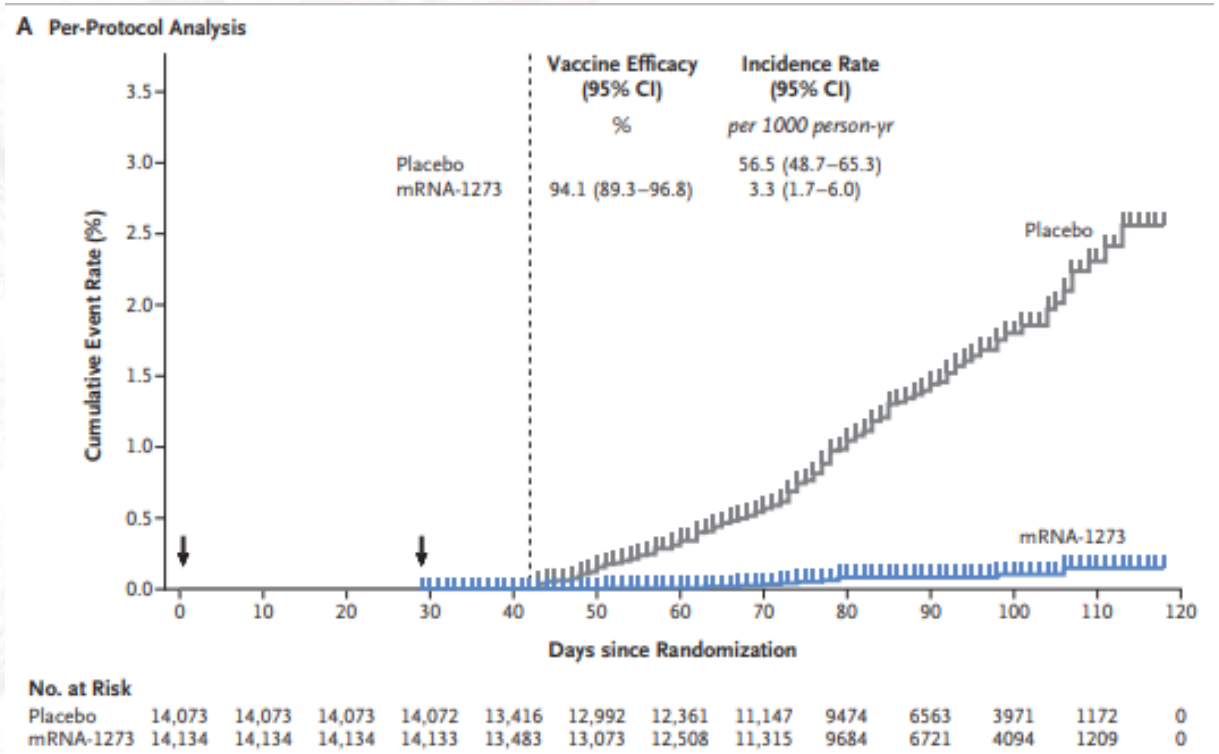
Ke Z et al. Nature 2020, https://doi.org/10.1038/s41586-020-2665-2

La carrera por las vacunas frente a SARS-CoV-2

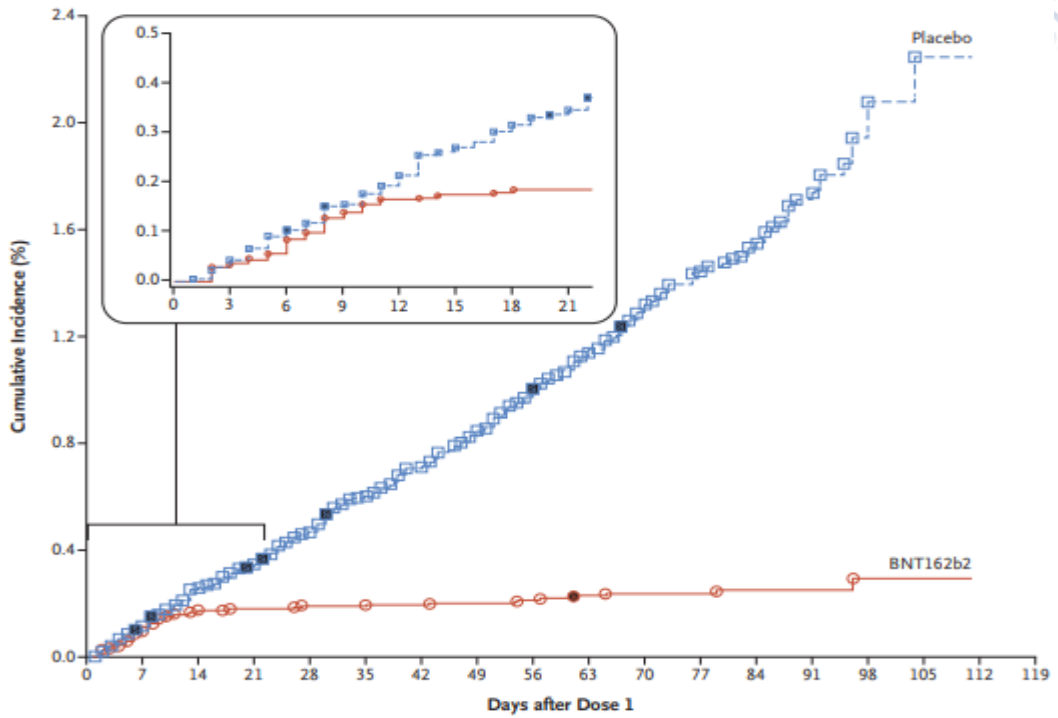


Ewen Callaway and Nik Spencer
Nature 580. April 2020

La carrera por las vacunas frente a SARS-CoV-2



Baden LR et al. NEJM 2020 DOI: 10.1056/NEJMoa2035389



Pplack FP et al. NEJM 2020 DOI: 10.1056/NEJMoa2034577

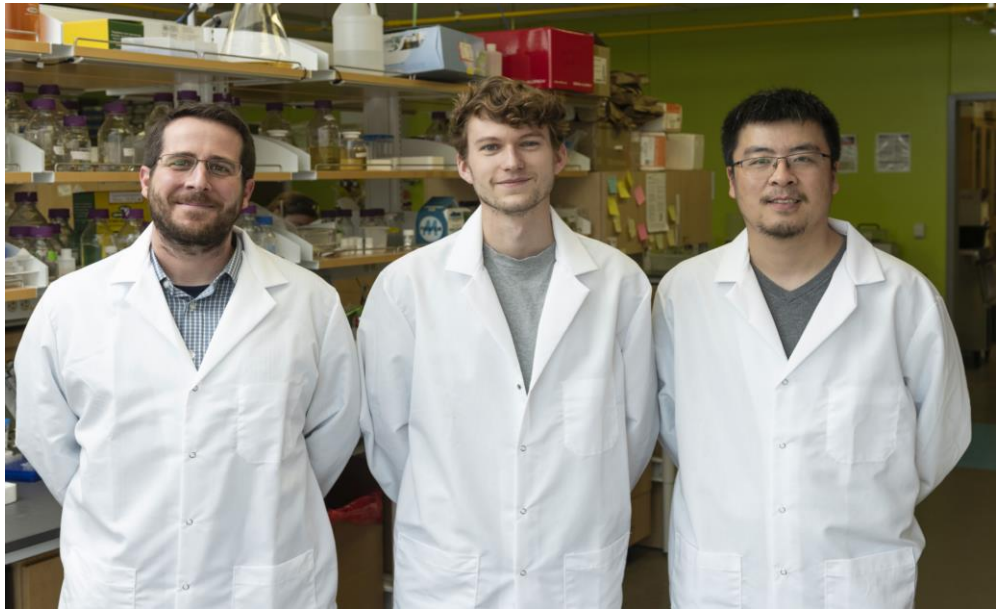
La carrera por las vacunas frente a SARS-CoV-2

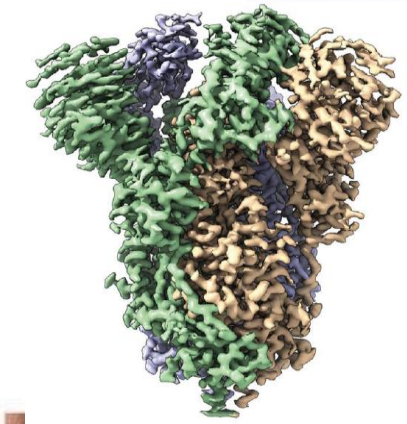
PNAS

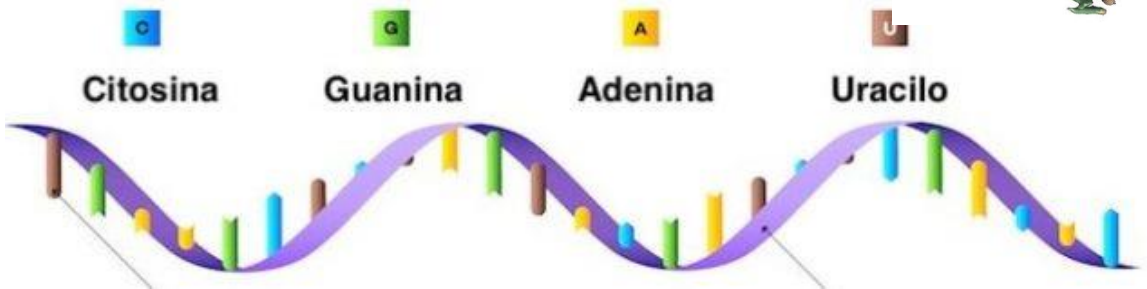
Immunogenicity and structures of a rationally designed prefusion MERS-CoV spike antigen

Jesper Pallesen[a,1], Nianshuang Wang[b,1,2], Kizzmekia S. Corbett[c,1], Daniel Wrapp[b], Robert N. Kirchdoerfer[a], Hannah L. Turner[a], Christopher A. Cottrell[a], Michelle M. Becker[d], Lingshu Wang[e], Wei Shi[e], Wing-Pui Kong[e], Erica L. Andres[d], Arminja N. Kettenbach[b,f], Mark R. Denison[d,g], James D. Chappell[d], Barney S. Graham[c], Andrew B. Ward[a,2], and Jason S. McLellan[b,2]

[a]Department of Integrative Structural and Computational Biology, The Scripps Research Institute, La Jolla, CA 92037; [b]Department of Biochemistry and Cell Biology, Geisel School of Medicine at Dartmouth, Hanover, NH 03755; [c]Viral Pathogenesis Laboratory, Vaccine Research Center, National Institute of Allergy and Infectious Diseases, Bethesda, MD 20892; [d]Department of Pediatrics, Vanderbilt University Medical Center, Nashville, TN 37232; [e]Virology Core, Vaccine Research Center, National Institute of Allergy and Infectious Diseases, Bethesda, MD 20892; [f]Norris Cotton Cancer Center, Geisel School of Medicine at Dartmouth, Lebanon, NH 03756; and [g]Department of Pathology, Microbiology, and Immunology, Vanderbilt University School of Medicine, Nashville, TN 37232







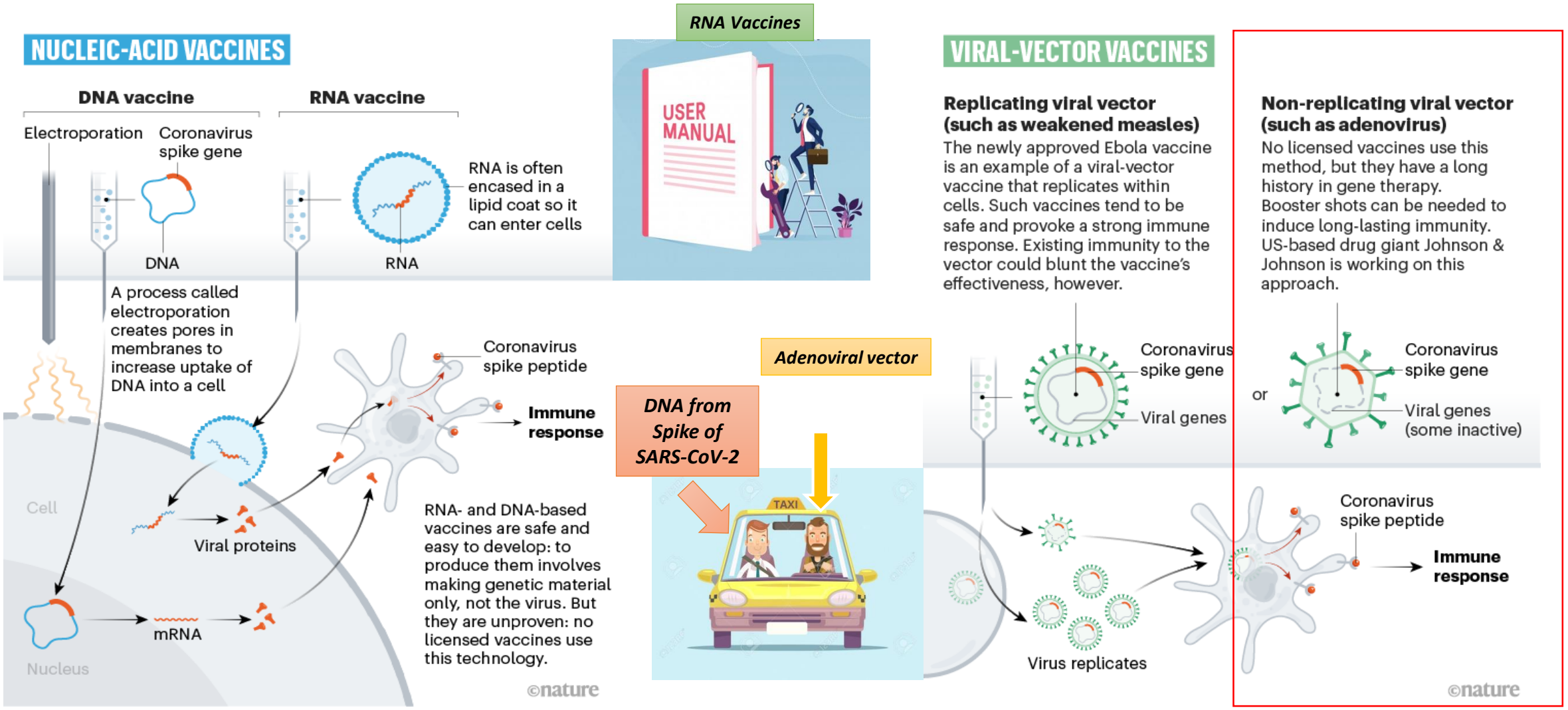
INGENIEROS DEL ARN

ARN, en el jardín de su casa en Filadelfia, el 22 de diciembre. RACHEL WISNIEWSKI / RACHEL WISNIEWSKI

Matrimonio de científicos: Özlem Türeci (dcha.) y Ugur Sahin, fundadores de BioNTech.

La carrera por las vacunas frente a SARS-CoV-2

La carrera por las vacunas frente a SARS-CoV-2

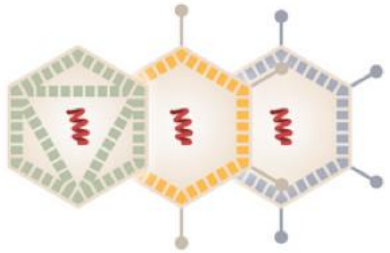


Ewen Callaway and Nik Spencer
Nature 580. April 2020

La carrera por las vacunas frente a SARS-CoV-2

CanSinoBIO

Adenovirus 5



Multivariable analysis showed that high pre-existing Ad5 neutralising antibody titres compromised the seroconversion of neutralising antibody post-vaccination, regardless of the vaccine doses,

and recipients aged 45–60 years seemed to have lower seroconversion of neutralising antibody compared with the younger recipients (appendix p 11). The Ad5 neutralising antibodies were significantly boosted post-vaccination

	Vaccine at 1×10^{11} vp (n=253)	Vaccine at 5×10^{10} vp (n=129)	Placebo (n=126)	p value
GMT	9·6	9·5	4·6	0·028
	(6·9-13·5)	(6·0-15·0)	(3·4-6·4)	
Seroconversion	9, 26%	5, 29%	0	0·055
Neutralization antibodies to pseudovirus				
18-44 years old	n=152	n=80	n=77	
GMT	72·4	58·2	5·5	<0·0001
	(60·0-87·3)	(45·8-74·0)	(4·9-6·1)	
Seroconversion	134, 88%	68, 85%	1, 1%	<0·0001
45-54 years old	n=67	n=32	n=35	
GMT	48·6	56·1	5·1	<0·0001
	(36·6-64·4)	(34·7-90·5)	(4·9-5·4)	
Seroconversion	52, 78%	26, 81%	0	<0·0001
≥55 years old	n=34	n=17	n=14	
GMT	46·6	42·4	6·8	<0·0001
	(30·6-71·0)	(23·9-75·3)	(4·0-11·7)	
Seroconversion	28, 82%	13, 76%	0	<0·0001

Títulos neutralización: 1/160-1/320

Zhu FC et al. Lancet 2020 https://doi.org/10.1016/S0140-6736(20)31208-3

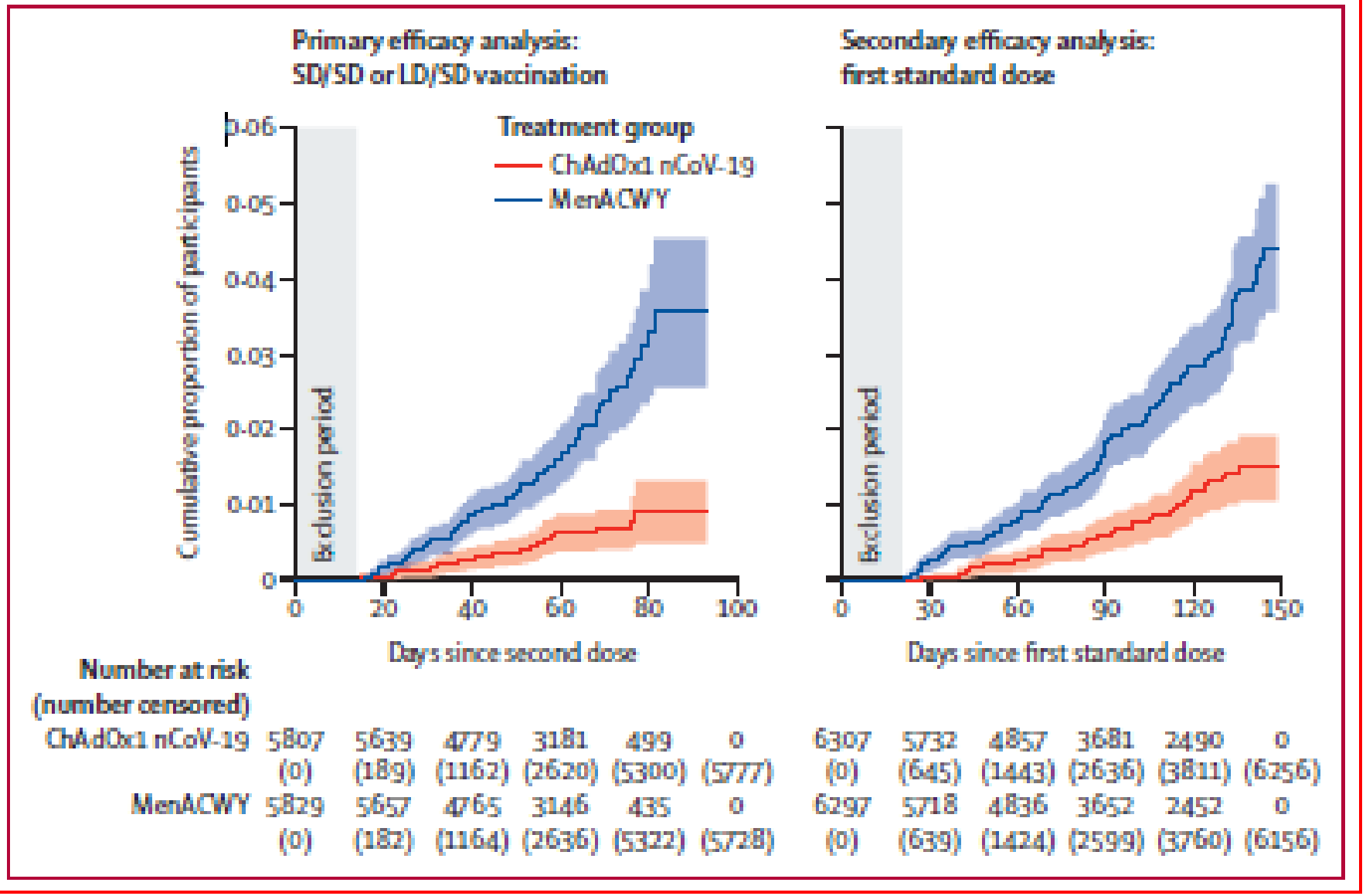
Desarrollo de vacunas frente a SARS-CoV-2

ChimpAdeno

AstraZeneca

University of Oxford

Títulos neutralización 1/160-1/320



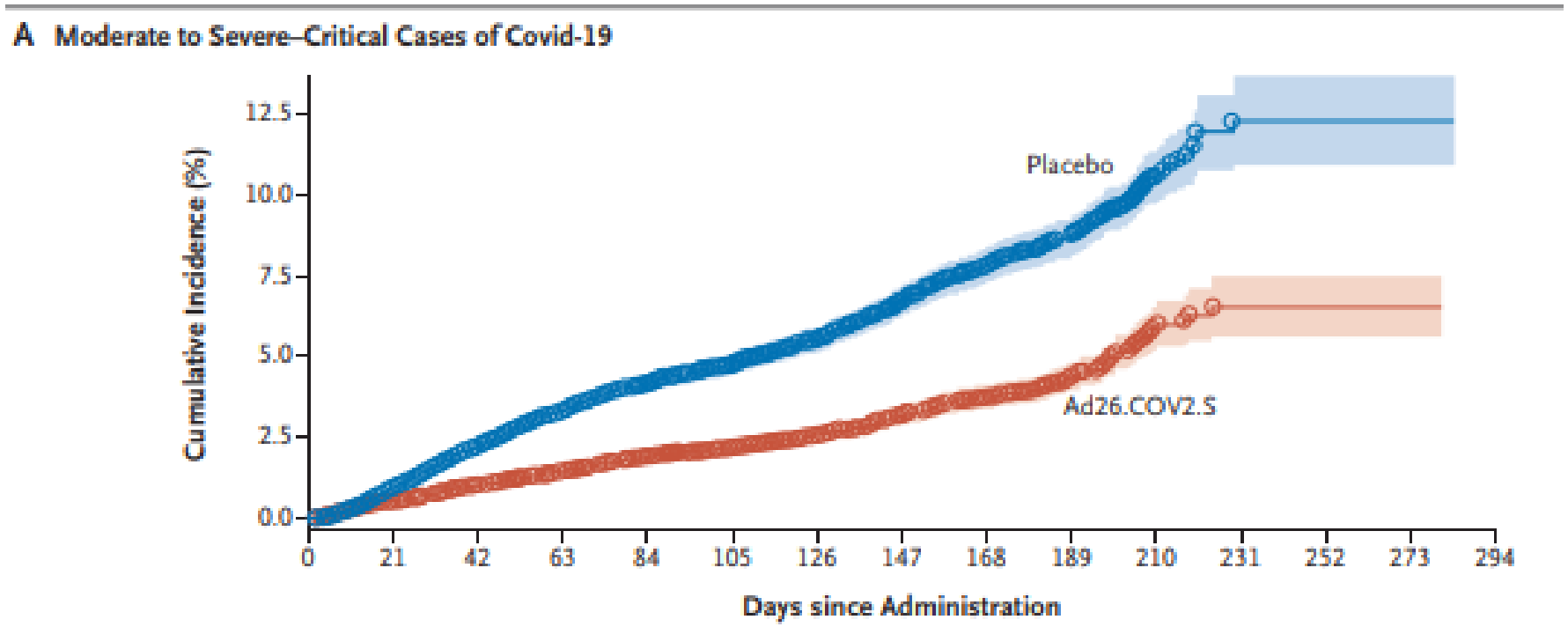
https://doi.org/10.1016/S0140-6736(20)32661-1

Desarrollo de vacunas frente a SARS-CoV-2

Adeno26

AcN
Una dosis.
GMT 288-488
Dos dosis
GMT 827-1266

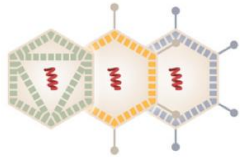
Eficacia 69% una dosis



No. at Risk															
Placebo	19,589	19,265	18,203	16,872	15,086	12,359	8040	5076	4022	2976	1098	199	19	8	0
Ad26.COV2.S	19,562	19,352	18,531	17,386	15,730	13,133	8729	5615	4444	3220	1193	207	18	6	0
No. of Cases															
Placebo	0	185	430	628	769	855	938	1019	1071	1106	1144	1155	1155	1155	1155
Ad26.COV2.S	0	100	197	277	351	393	436	476	505	531	563	566	566	566	566

Sadoff JM et al. NEJM **DOI: 10.1056/NEJMoa2034201**

Desarrollo de vacunas frente a SARS-CoV-2



Adeno 5+ Adeno26

THE GAMALEYA NATIONAL CENTER
OF EPIDEMIOLOGY AND MICROBIOLOGY

Casos COVID
Placebo 62/4902
Vacuna 16/14964
Eficacia 91%

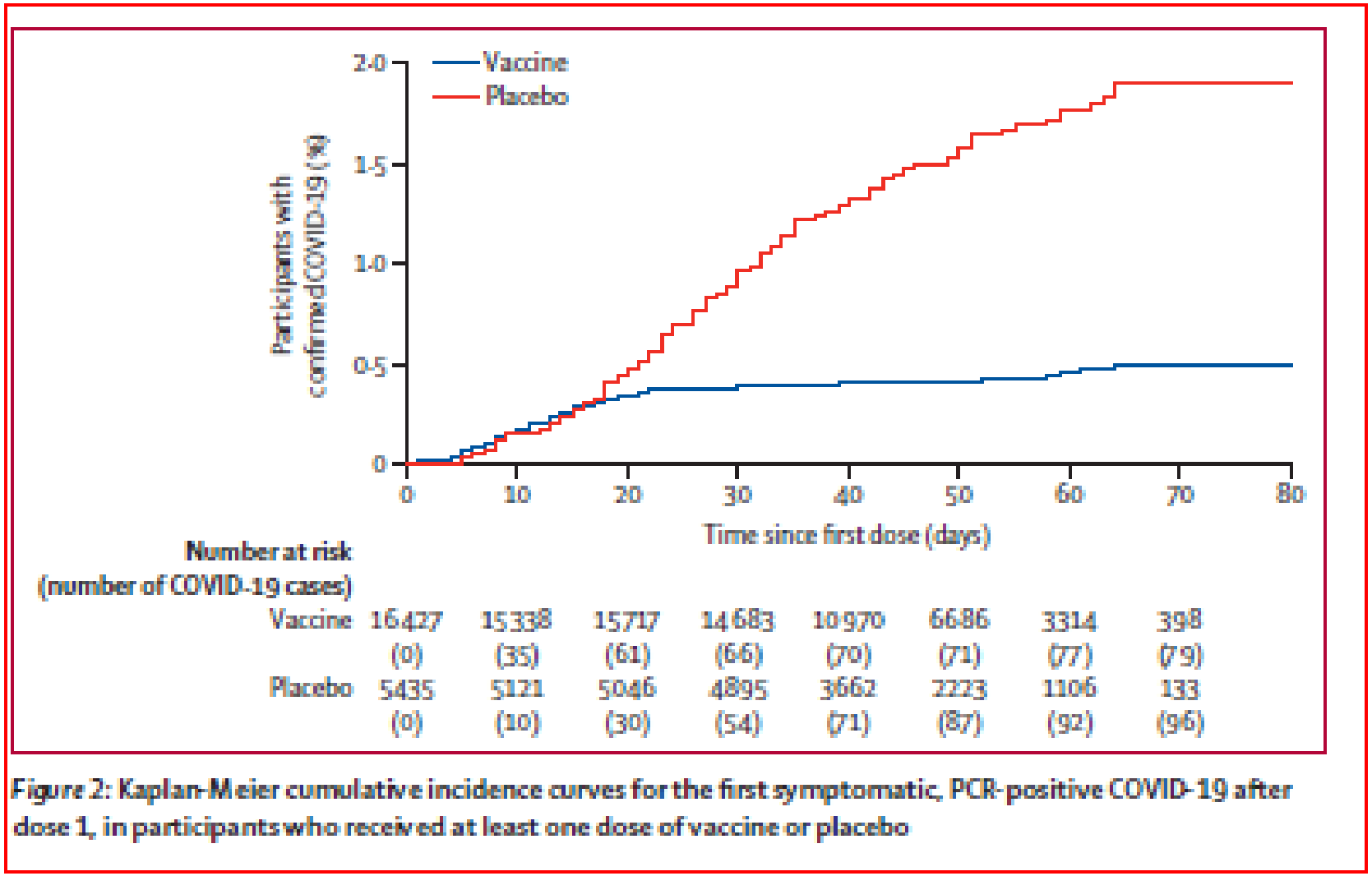
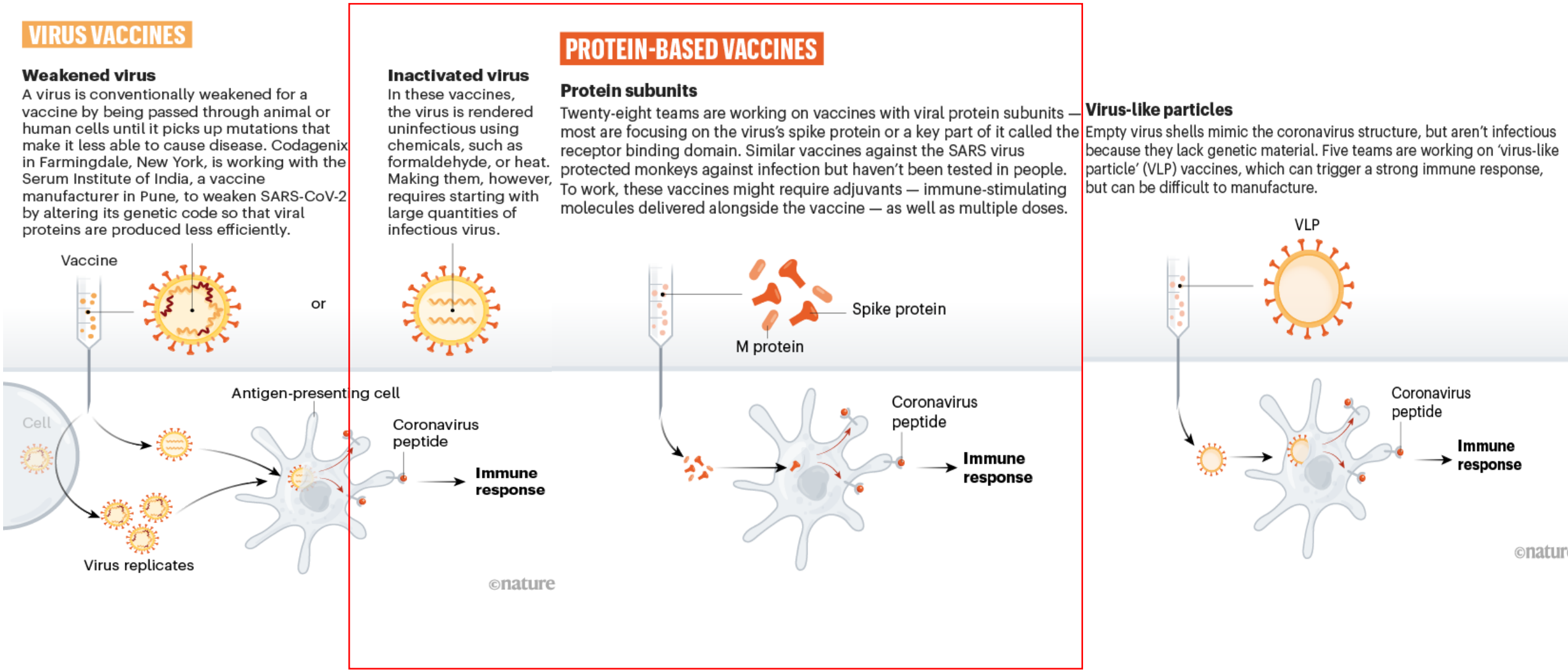


Figure 2: Kaplan-Meier cumulative incidence curves for the first symptomatic, PCR-positive COVID-19 after dose 1, in participants who received at least one dose of vaccine or placebo

Sadoff JM et al. NEJM DOI: 10.1056/NEJMoa2034201

La carrera por las vacunas frente a SARS-CoV-2



Ewen Callaway E and Nik Spencer
Nature 580. April 2020

Desarrollo de vacunas frente a SARS-CoV-2

Sinopharm

Títulos neutralización: 1/160-1/320

Table 3. Antibody Responses 14 Days After 3 Doses in the Phase 1 Trial and 2 Doses in the Phase 2 Trial[a]

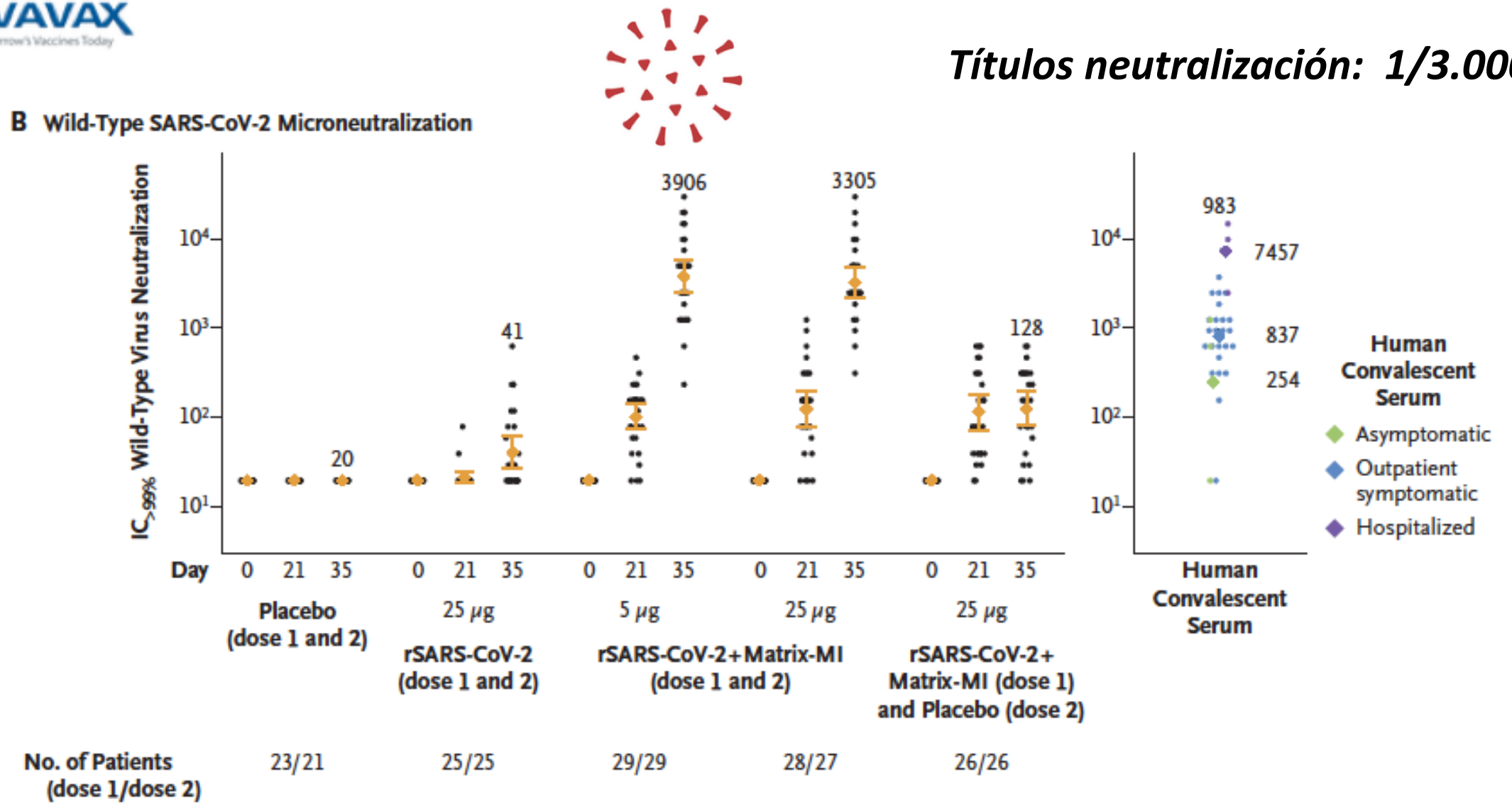
	Phase 1 clinical trial; 0, 28, and 56-d group				Phase 2 clinical trial			
					0 and 14-d Group		0 and 21-d Group	
	Low dose (n = 24)	Medium dose (n = 24)	High dose (n = 24)	Alum only (n = 24)	Medium dose (n = 42)	Alum only (n = 14)	Medium dose (n = 42)	Alum only (n = 14)
Neutralizing antibodies to live SARS-CoV-2								
Geometric mean titer (95% CI)	316 (218-457)	206 (123-343)	297 (208-424)	5 (5-5)	121 (95-154)	5 (5-5)	247 (176-345)	5 (5-5)
Geometric mean ratio (95% CI)[b]	63.1 (43.6-91.5)	41.1 (24.6-68.7)	59.4 (41.5-84.9)	NA	24.1 (19.0-30.7)	NA	49.3 (35.2-69.0)	NA
Seroconversion rate, % (95% CI)[b]	100.0 (60.0-100.0)	95.8 (56.7-100.0)	100.0 (60.0-100.0)	0	97.6 (67.7-100.0)	0	97.6 (67.7-100.0)	0
Specific IgG-binding antibody responses to whole SARS-CoV-2 antigen								
Geometric mean titer (95% CI)	415 (288-597)	349 (258-472)	311 (229-422)	10 (10-10)	74 (56-97)	10 (10-10)	215 (157-296)	10 (10-10)
Geometric mean ratio (95% CI)[b]	41.5 (28.8-59.7)	34.9 (25.8-47.2)	31.1 (22.9-42.2)	NA	7.4 (5.6-9.7)	NA	21.5 (15.7-29.6)	NA
Seroconversion rate, % (95% CI)[b]	100.0 (60.0-100.0)	100.0 (60.0-100.0)	100.0 (60.0-100.0)	0	85.7 (57.7-100.0)	0	100.0 (60.0-100.0)	0

Xla S et al. JAMA 2020 JAMA. doi:10.1001/jama.2020.15543

Desarrollo de vacunas frente a SARS-CoV-2

NOVAVAX
Creating Tomorrow's Vaccines Today

Títulos neutralización: 1/3.000



Keech C et al. N Eng J Med 2020 DOI: 10.1056/NEJMoa2026920

Desarrollo de vacunas frente a SARS-CoV-2

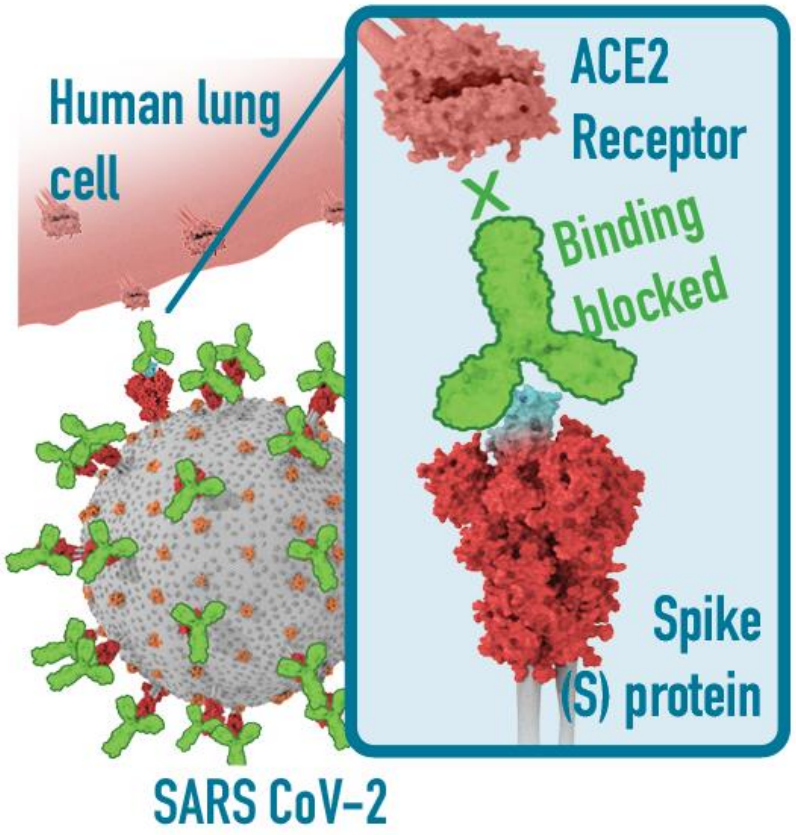
Ventajas

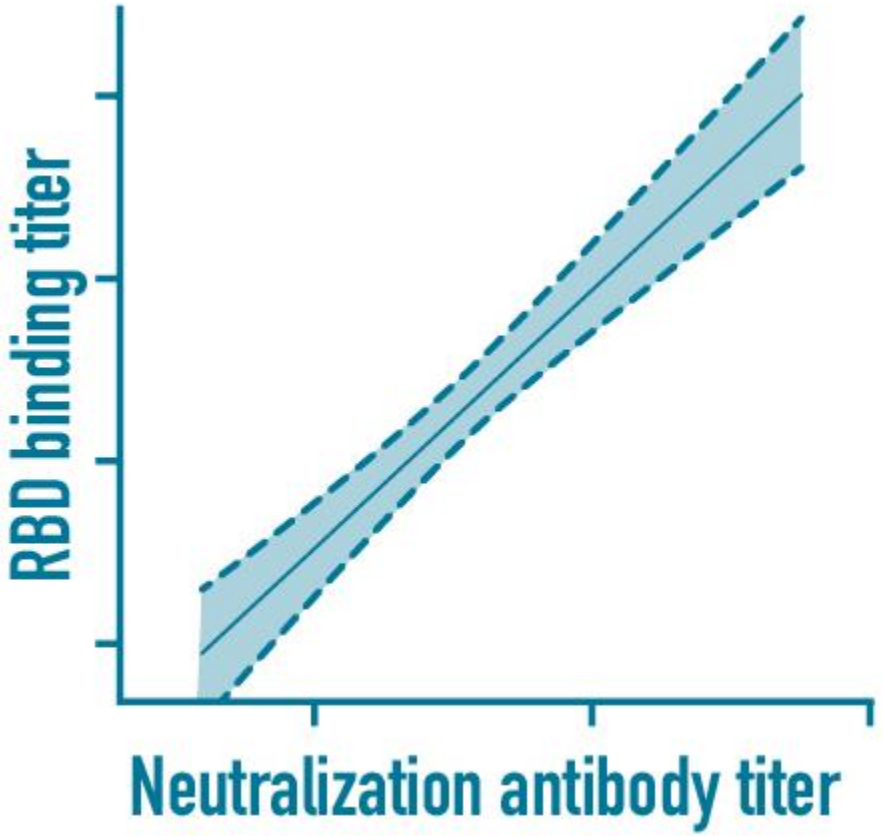
- Vacuna sencilla
- Vacuna barata
- Estrategia inteligente: tercera dosis. No han de hacer ensayo fase III
- Tienen experiencia
- Tienen las factorías para fabricarla
- Combinan dos variantes, una con mutaciones de escape

Inconvenientes

- Llegan tarde
- Incluso para tercera dosis el mercado es pequeño en Europa
- No han incluido el spike de ómicron

Preguntas planteadas
Marcadores subrogados de protección





Suthar MS et al. Cell Reports Medicine (2020) https://doi.org/10.1016/j.xcrm.2020.100040

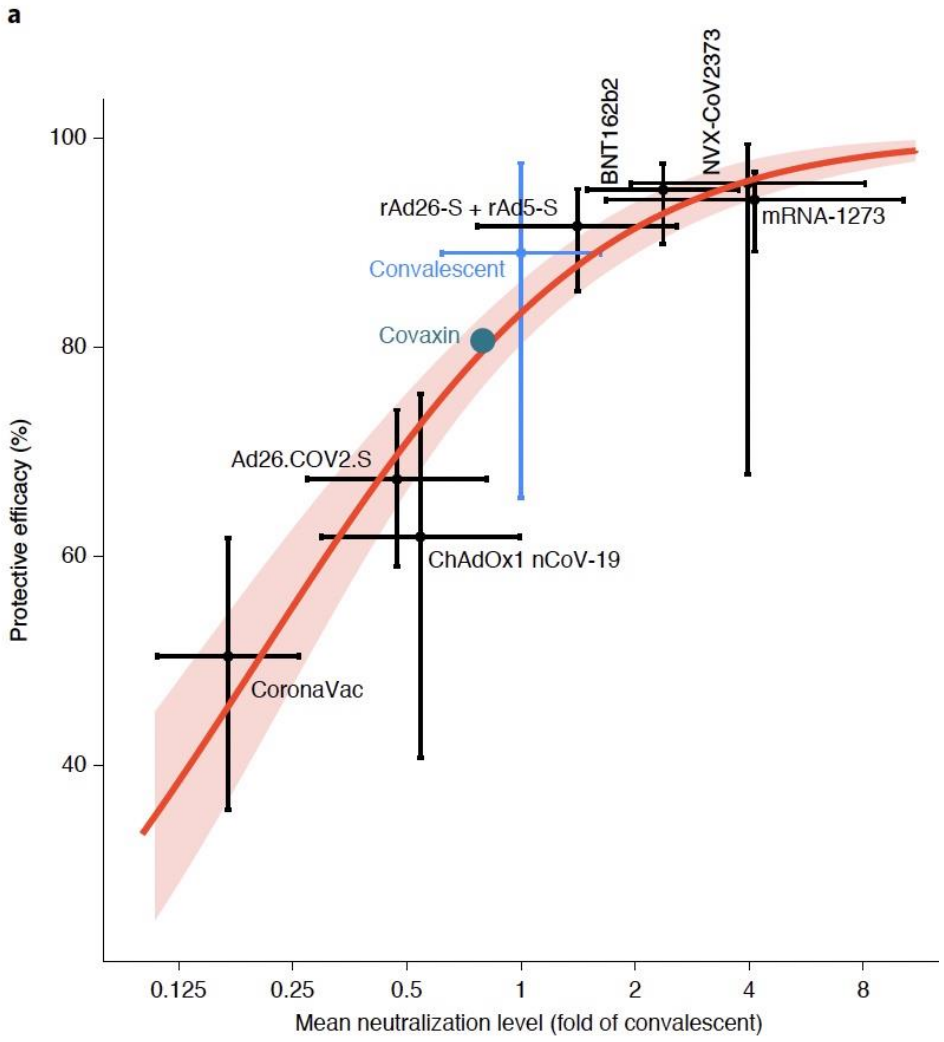
Preguntas planteadas
Marcadores subrogados de protección

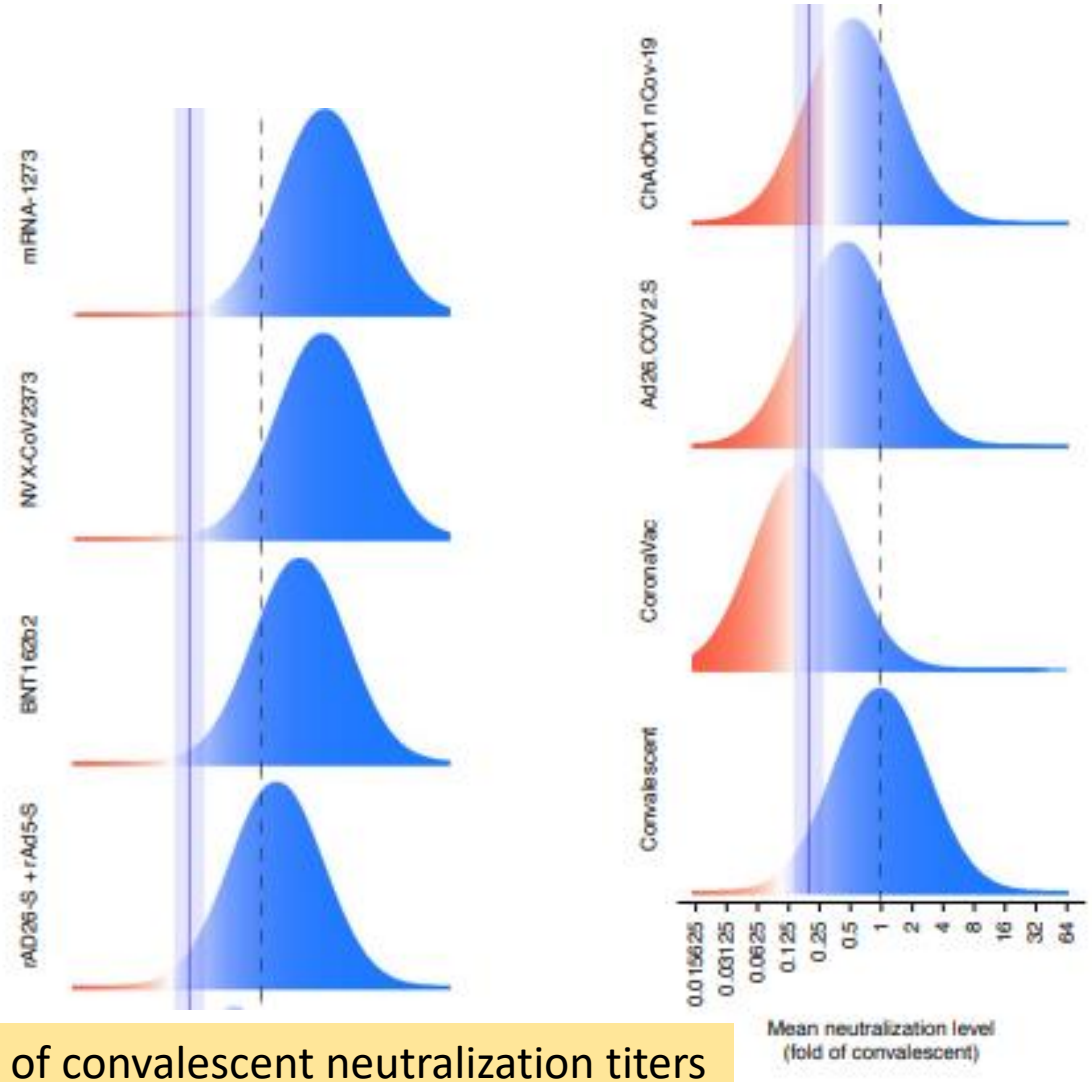
Summary of Neutralization titers against SARS-CoV-2 (pseudotyped viruses unless indicated)

moderna	*1/256-1/512*	
BIONTECH Pfizer	*1/437 (1/200 in >65 years)*	
CanSinoBIO	*1/42-1/72 (only 50% seroconversion >55 years)*	
AstraZeneca UNIVERSITY OF OXFORD	*1/320 – 1/413*	
janssen PHARMACEUTICAL COMPANIES OF Johnson&Johnson	*One dose 1/212 – 1/388* *Two doses 1/827- 1/1266*	*Lower in >65 years*
Sinopharm	*1/121-1/320 (live virus)*	
NOVAVAX Creating Tomorrow's Vaccines Today	*1/3.300 1/3.900 (microneutralization)*	

Fuente: Elaboración propia

Preguntas planteadas
Marcadores subrogados de protección

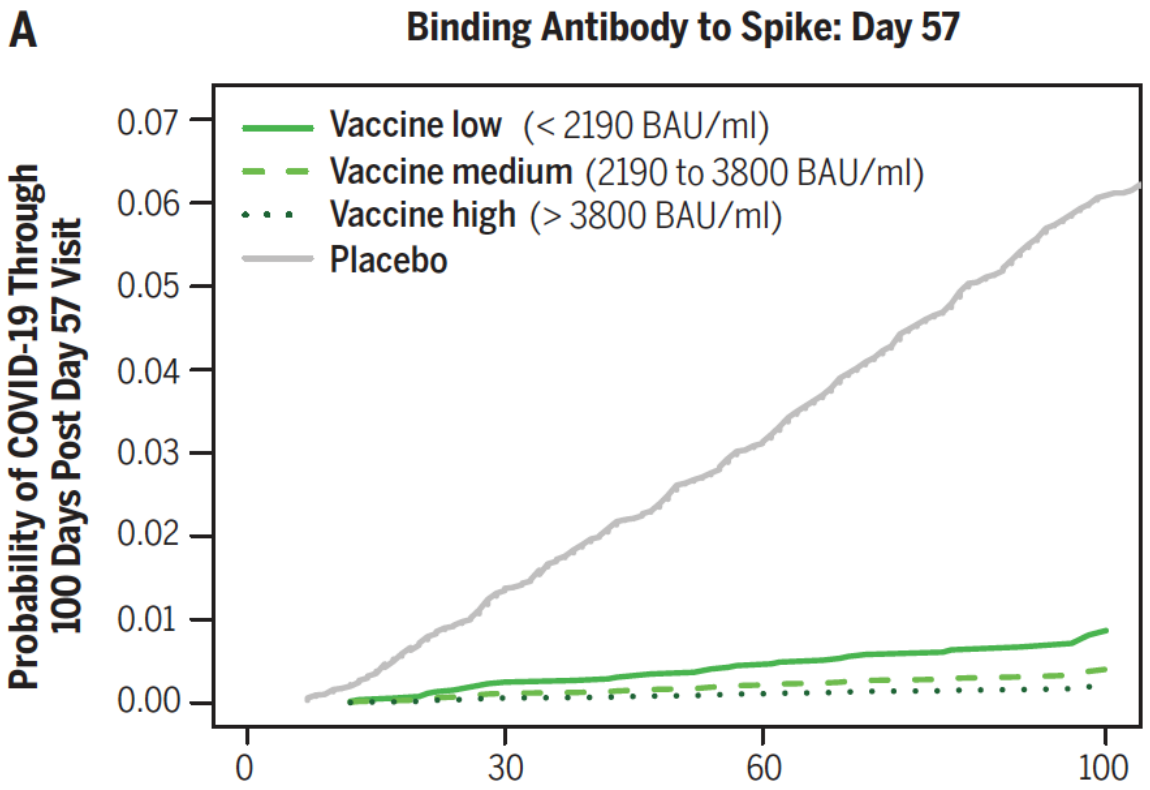


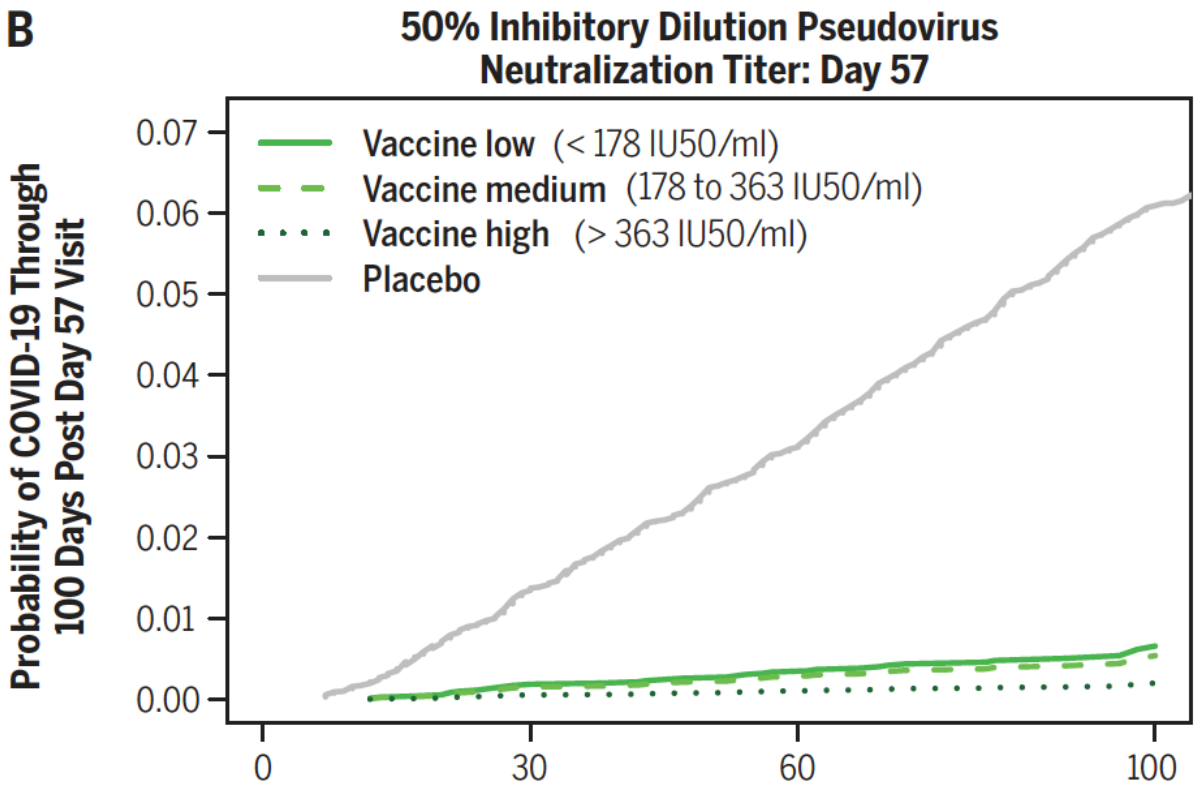


20% of convalescent neutralization titers
- 1/100 NT50
- Detectable NT50 (>32-40 dilution)

Khoury DS et al. https://doi.org/10.1038/s41591-021-01377-8

Preguntas planteadas
Marcadores subrogados de protección

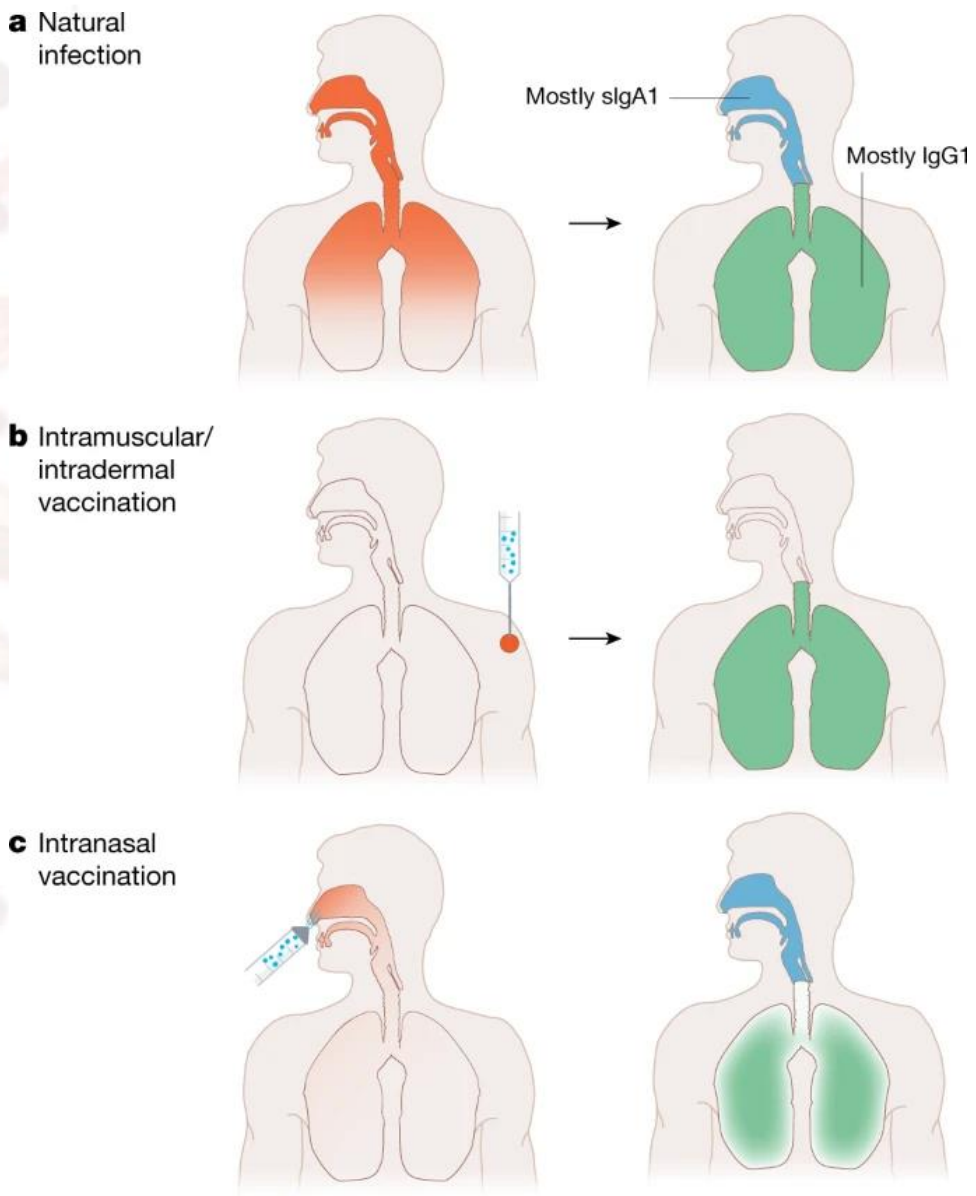




POST-VACCINATION NEUTRALIZATION TITERS	VACCINE EFFICACY
NT50 10	78% (54-89)
NT50 100	91% (87-94)
NT50 1.000	98% (94-98)

Gilbert PB,et al. Science. 2022;375:43-50.

Preguntas planteadas. Protección frente a la infección



Kramer F. Nature 2020; 586:516–527

Preguntas planteadas. Protección frente a la infección

Table 1 | Overview of NHP results

Company (ref.)	Vaccine candidate (type)	Dose range (route)	Neut. titre after prime	Neut. titre after boost	T cell response	Challenge dose (route)	URT protection	LRT protection	Species
Sinovac[34]	PiCoVacc (inactivated virion + aluminium hydroxide)	3–6 μg (i.m.)	None[a]	1:10 range[a] after first boost; 1:50 range[a] after second boost	ND	10^6 $TCID_{50}$ (i.t.)	Partial[b]	Partial (low dose)[b] Complete (high dose)	Rhesus macaques
Beijing Institute of Biological Products[33]	BBIBP-CorV (inactivated virion + aluminium hydroxide)	4–8 μg (i.m.)	1:100 range[a]	1:200 range[a]	ND	10^6 $TCID_{50}$ (i.t.)	Partial[b]	Complete[b]	Cynomolgus macaques
AstraZeneca[49]	ChAdOxnCoV-19 (non-replicating AdV)	2.4×10^{10} VP; 1× or 2× (i.m.)	1:5–1:40 range[a]	1:10–1:160 range[a]	Yes	2.6×10^6 $TCID_{50}$ (i.t., oral, i.n., ocular)	None (1×)[c] None (2×)[c]	Partial (1×)[c] Complete (2×)[c]	Rhesus macaques
Janssen[41]	Ad26COVS1 (non-replicating AdV)	1×10^{11} VP (i.m.)	1:100 range[d]	NA	Low	10^5 $TCID_{50}$ (i.n, i.t.)	Complete in S.PP group[c]	Complete in S.PP group[c]	Rhesus macaques
Moderna[57]	mRNA-1273 (mRNA via LNPs)	2×10–100 μg (i.m.)	ND[e]	1:501–1:3,481 range[d]	Yes, CD4, T_{FH}	7.6×10^5 $TCID_{50}$ (i.n., i.t.)	None (10 μg)[c] Partial (100 μg)[c]	Partial (10 μg)[c] Complete (100 μg)[c]	Rhesus macaques
Novavax[79]	NVX CoV2373 (spike protein + Matrix-M)	2× 2.5–25 μg	Not reported	17,920–23,040 range[a]	ND	10^4 plaque-forming units (i.n., i.t.)	Partial (low dose)[c] Complete (higher doses)[c]	Complete[c]	Cynomolgus macaques

[a]Based on microneutralization assay with CPE as readout.
[b]Based on viral genome RNA copy number.
[c]Based on subgenomic RNA copy number.
[d]Based on microneutralization assay with a SARS-CoV-2 reporter virus; 50% reduction in relative light units as readout.
[e]Not assessed using authentic SARS-CoV-2.
Neut., neutralizing antibody; NA, not applicable; ND, not determined; i.m., intramuscular; i.n., intranasal; i.t., intratracheal; T_{FH}, T follicular helper cells.

Kramer F. Nature 2020; 586:516–527

Preguntas planteadas. Protección frente a la infección

Interim Estimates of Vaccine Effectiveness of BNT162b2 and mRNA-1273 COVID-19 Vaccines in Preventing SARS-CoV-2 Infection Among Health Care Personnel, First Responders, and Other Essential and Frontline Workers — Eight U.S. Locations, December 2020–March 2021

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.

https://preprints.jmir.org/preprint/28925

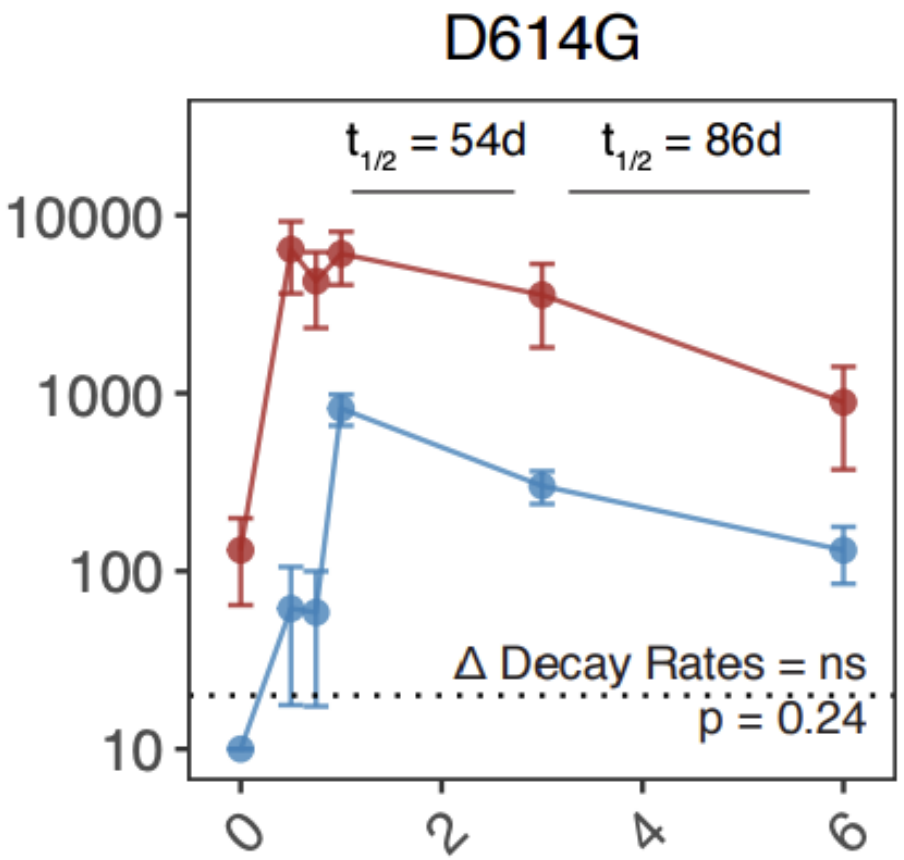
Preguntas planteadas. Protección frente a la infección

	BNT162b2: second dose ≥14 days	ChAdOx1: second dose ≥14 days	Not vaccinated, previously positive*
VE: All infections			
1 Dec 2020 – 16 May 2021 (Alpha)	78% (68-84%)	79% (56-90%)	60% (50-68%)
17 May 2021- (Delta)	80% (77-83%)	67% (62-71%)	72% (58-82%)
Heterogeneity p	0.50	0.23	0.12
VE: Ct<30			
1 Dec 2020 – 16 May 2021 (Alpha)	94% (91-96%)	86% (71-93%)	87% (84-90%)
17 May 2021- (Delta)	84% (82-86%)	70% (65-73%)	77% (66-85%)
Heterogeneity p	<0.0001	0.04	0.02
VE: Self-reported symptoms			
1 Dec 2020 – 16 May 2021 (Alpha)	97% (96-98%)	97% (93-98%)	80% (75-84%)
17 May 2021- (Delta)	84% (82-86%)	71% (66-74%)	82% (73-88%)
Heterogeneity p	<0.0001	<0.0001	0.59

Puwels KB et al. https://www.ndm.ox.ac.uk/files/coronavirus/covid-19-infection-survey/finalfinalcombi

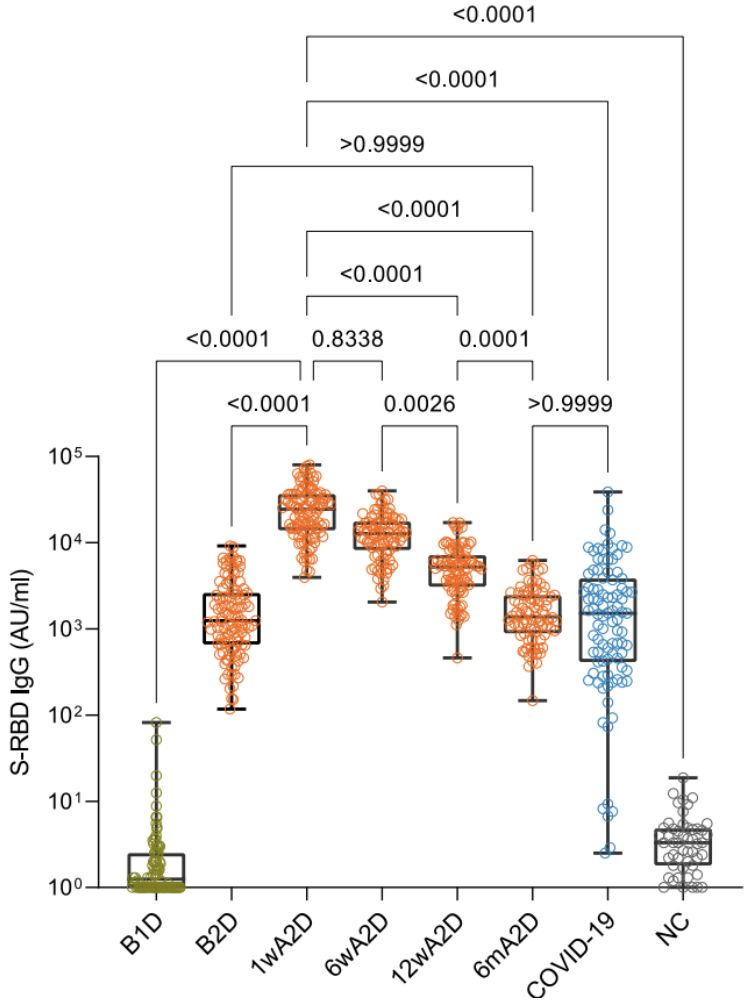
Preguntas planteadas. Duración de la respuesta inmune

DECAY OF NEUTRALIZATION TITERS IN CONVALESCENT AND NAIVE PATIENTS VACCINATED COMIRNATY AND RNAm1273



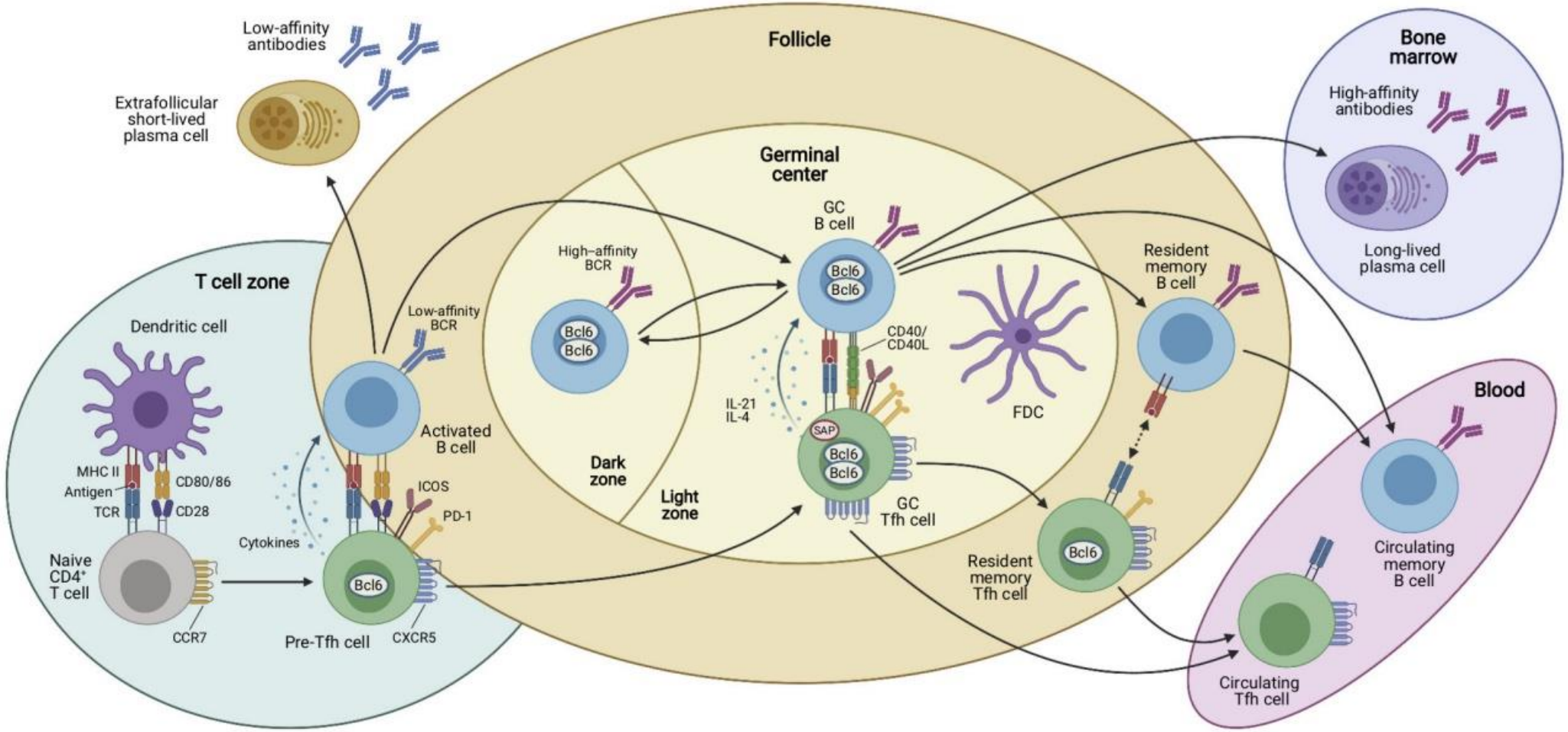
Goel RR, et al. Goel et al., Science 10.1126/science.abm0829 (2021).

DECAY OF ANTI-RBD ANTIBODIES IN PATIENTS VACCINATED WITH COMIRNATY



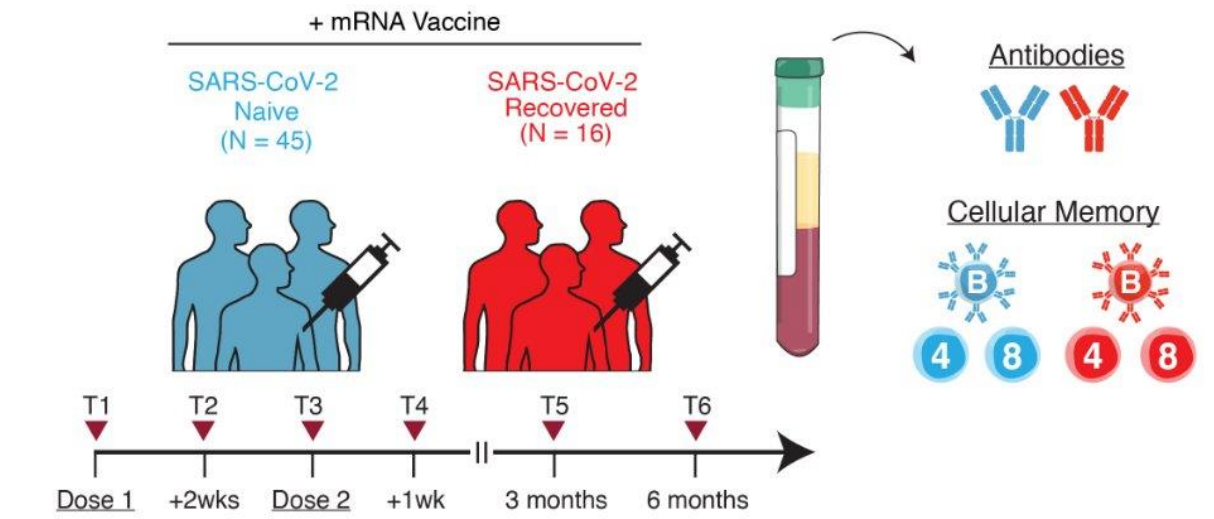
Naaber P et al. Lancet Reg Health Eur. 2021 Sep 6:100208. doi: 10.1016/j.lanepe.2021.100208

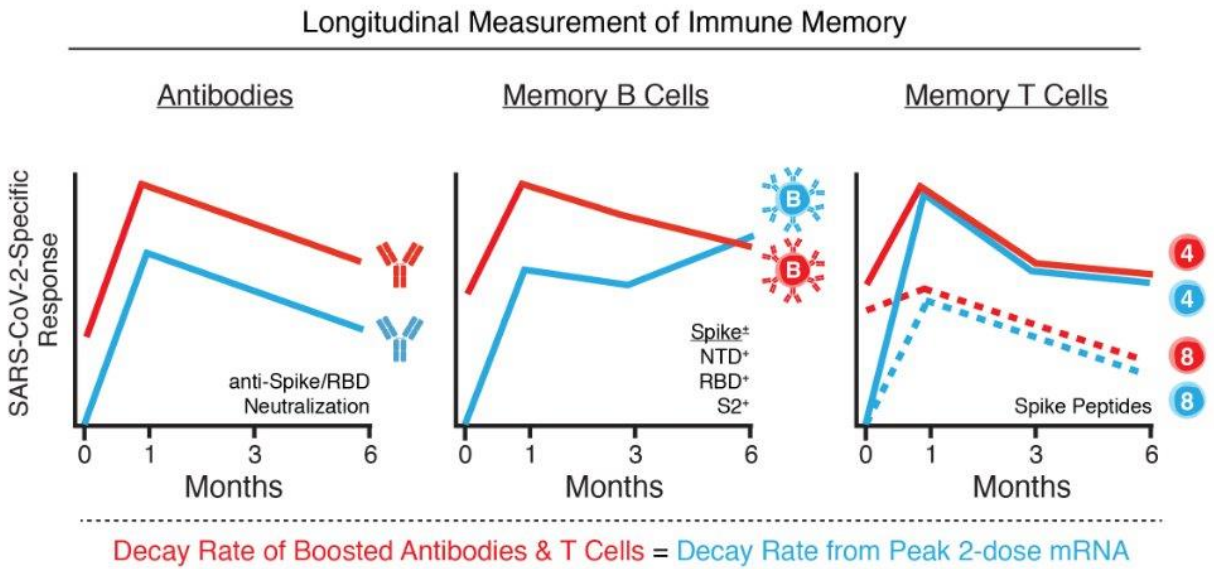
Memoria de linfocitos B y T en la vacunación y la enfermedad



Baumjohann D et al. Eur J Immunol 2021 DOI: 10.1002/eji.202049148

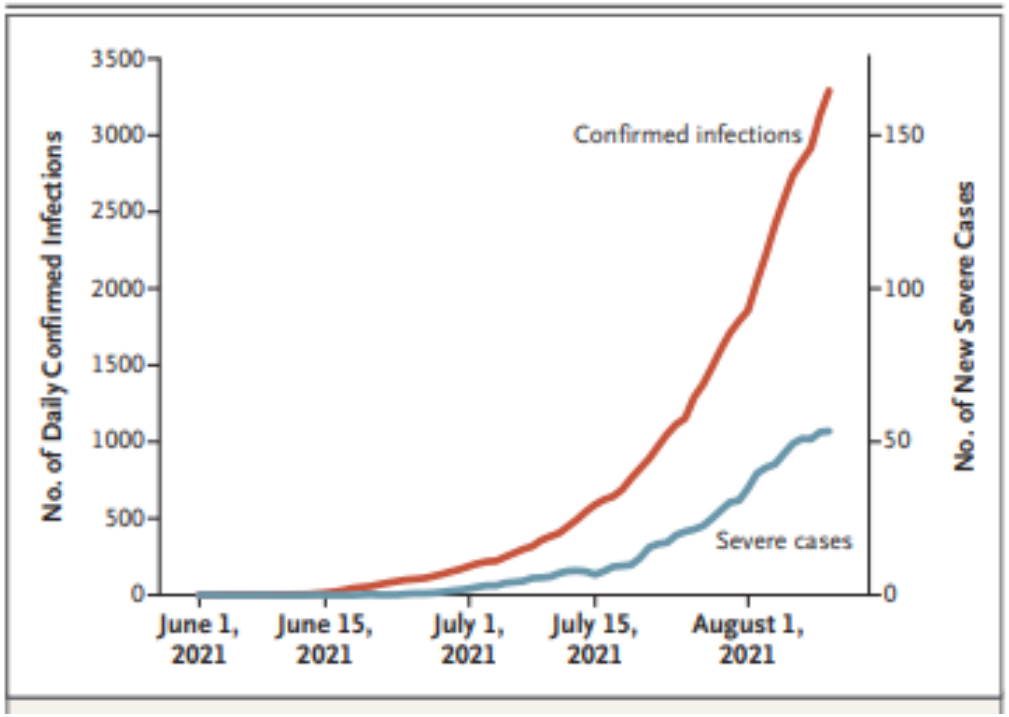
Preguntas planteadas. Duración de la respuesta inmune

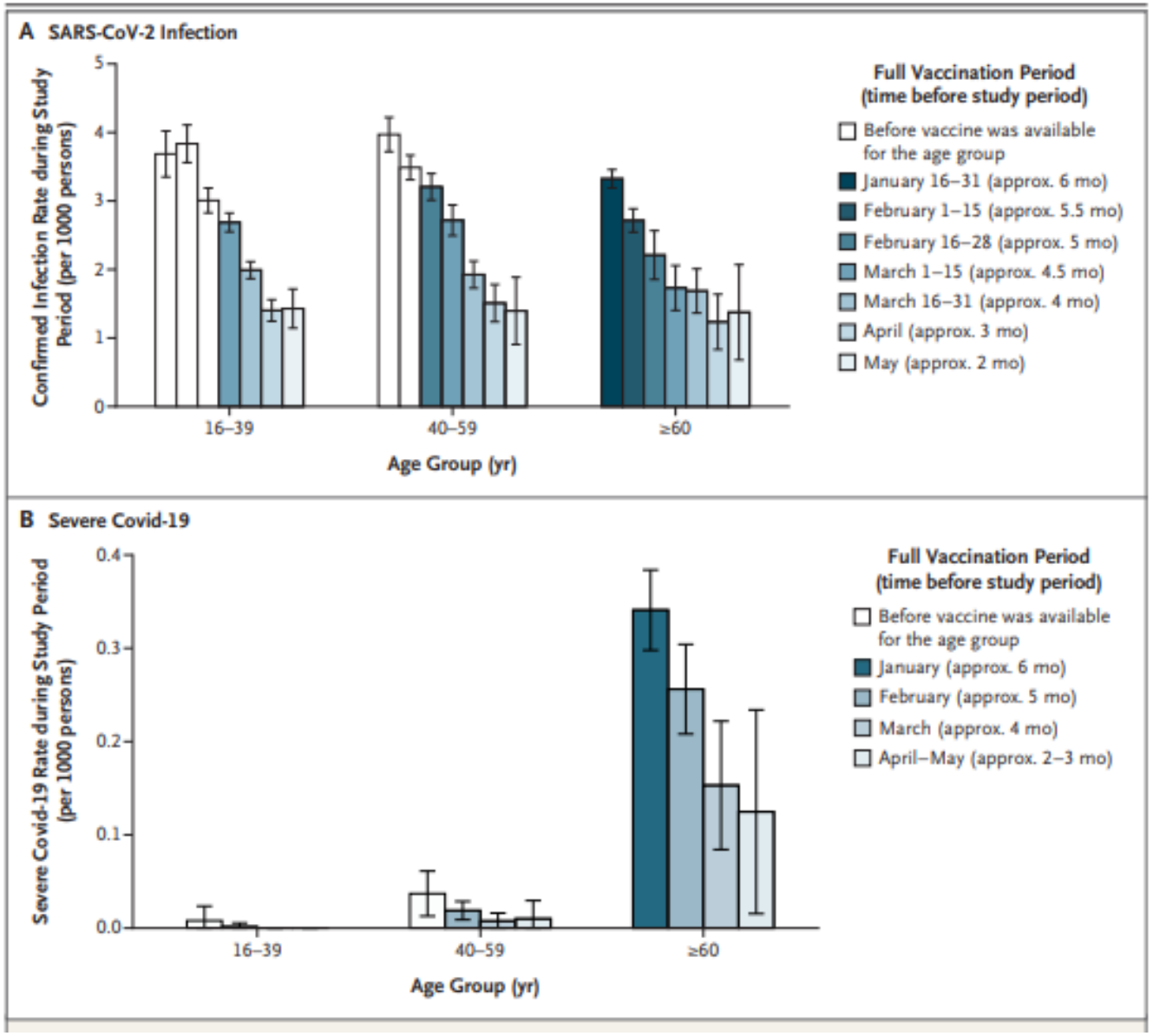




Goel RR, et al. Goel et al., Science 10.1126/science.abm0829 (2021).

Preguntas planteadas. Duración de la respuesta inmune





Goldberg Y et al. N Engl J Med. 2021;385:e85. doi: 10.1056/NEJMoa2114228.

Variantes de SARS-CoV-2

La transmisibilidad y el escape inmune han sido los vectores de selección de las variantes de SARS-CoV-2

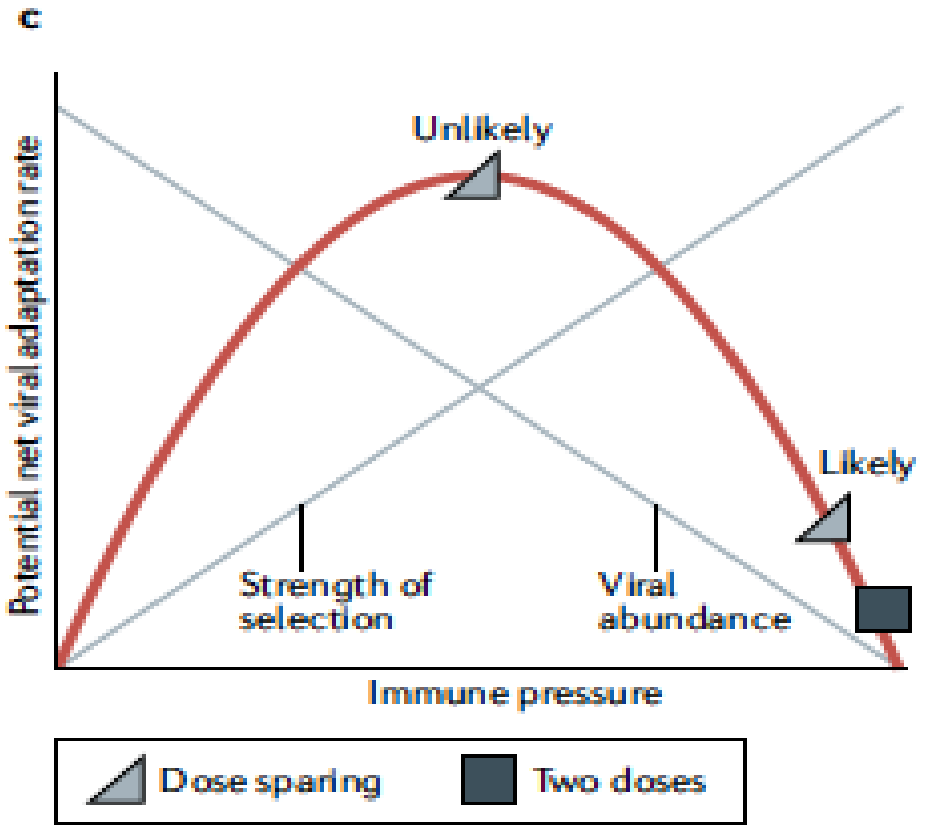
WHO label	Pango lineage•	GISAID clade	Nextstrain clade	Additional amino acid changes monitored°	Earliest documented samples	Date of designation
Alpha	B.1.1.7	GRY	20I (V1)	+S:484K +S:452R	United Kingdom, Sep-2020	18-Dec-2020
Beta	B.1.351	GH/501Y.V2	20H (V2)	+S:L18F	South Africa, May-2020	18-Dec-2020
Gamma	P.1	GR/501Y.V3	20J (V3)	+S:681H	Brazil, Nov-2020	11-Jan-2021
Delta	B.1.617.2	GK	21A, 21I, 21J	+S:417N +S:484K	India, Oct-2020	VOI: 4-Apr-2021 VOC: 11-May-2021
Omicron*	B.1.1.529	GRA	21K, 21L 21M	+S:R346K	Multiple countries, Nov-2021	VUM: 24-Nov-2021 VOC: 26-Nov-2021

Tracking SARS-CoV-2 variants. WHO 25/01/2022

Variantes de SARS-CoV-2

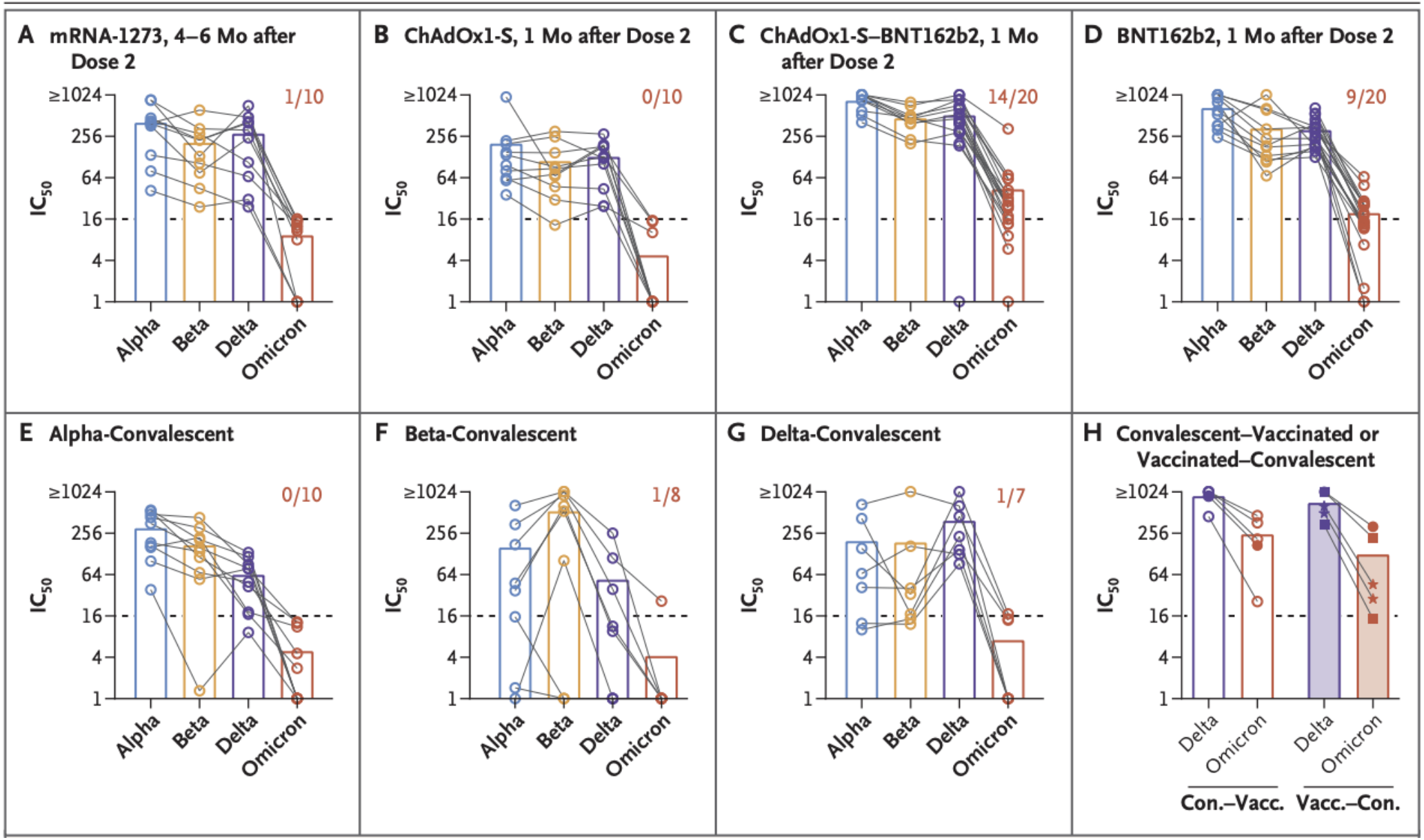
Fuentes de variabilidad

- Replicación crónica
- Saltos interespecie
- Infección masiva de la población
- Presión inmune parcial



https://www.nature.com/articles/s41577-021-00544-9.pdf

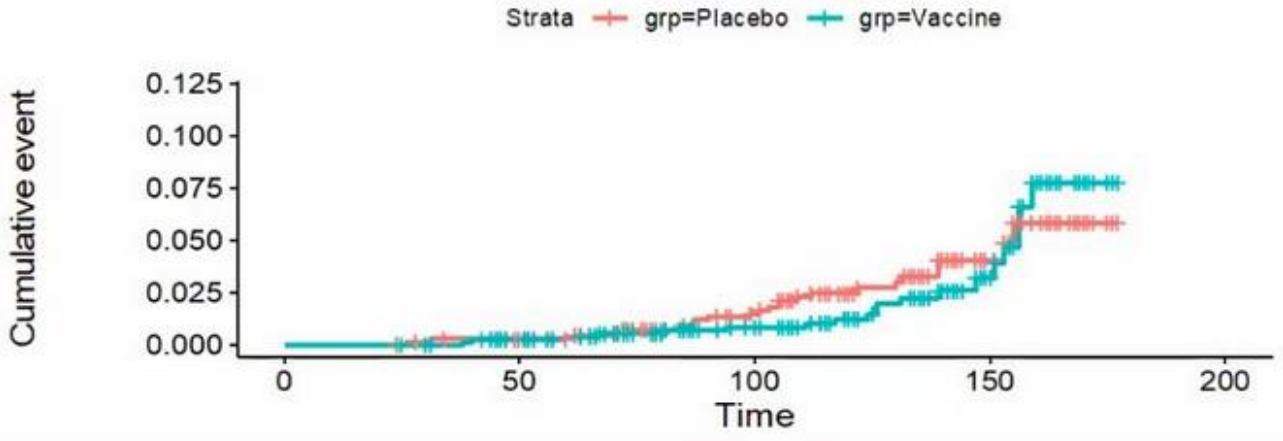
Eficacia de las vacunas frente a las nuevas variantes



Rössler A, et al. N Engl J Med. 2022 Jan 12:NEJMc2119236. doi: 10.1056/NEJMc2119236.

ChAdOx1-nCoV19 not efficacious in protecting against mild to moderate Covid-19 due to the B.1351 variant.

UNIVERSITY OF THE WITWATERSRAND JOHANNESBURG



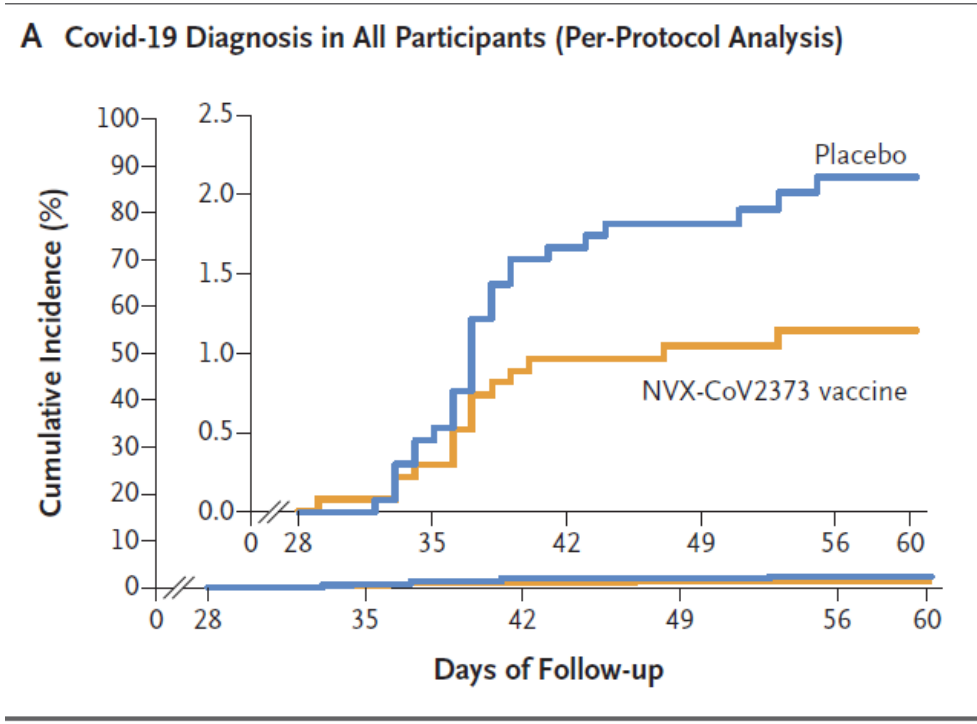
No significant risk reduction in mild-moderate Covid-19 from B.1351 variant occurring at least 14 days after 2nd dose of ChAdOx1/nCoV19.

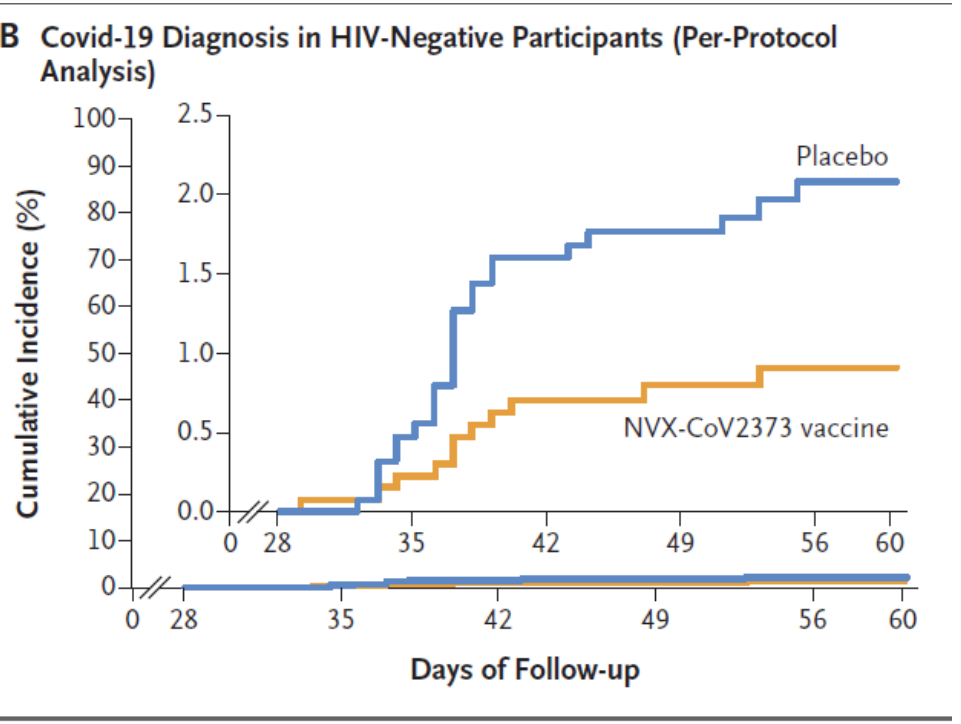
Baseline N-protein IgG	Total number of cases	Placebo n/N (%)	Vaccine n/N (%)	Vaccine efficacy (95%CI)
Primary endpoints: All severity COVID-19 clinical >14 days post-boost				
Negative	42	23/717 (3.2%)	19/750 (2.5%)	21.9% (-49.9 to 59.8)
Secondary endpoint: All severity COVID-19 clinical disease due to B1.351 variant >14 days post-boost				
Negative	39	20/714 (2.3%)	19/748 (2.5%)	10.4% (-78.8 to 54.8)

Submitted for peer review

WITS VIDA
UNIVERSITY OF THE WITWATERSRAND
VACCINES & INFECTIOUS DISEASES ANALYTICS

Eficacia de las vacunas frente a las nuevas variantes





B.1.351 (Identified in South Africa)

Vaccine	N of Participants	Main Efficacy Findings
Novavax	4,422	60% efficacy HIV negative (89% in UK) 49% efficacy HIV positive No hospitalizations or deaths in SA
J&J	~10,900	57% efficacy (72% in US, D614G*) No hospitalizations or deaths in SA
Astra-Zeneca	~2,000	"minimal protection vs mild-moderate infections" details pending

Preguntas planteadas. Mix and match vaccines

Estudio Combivacs

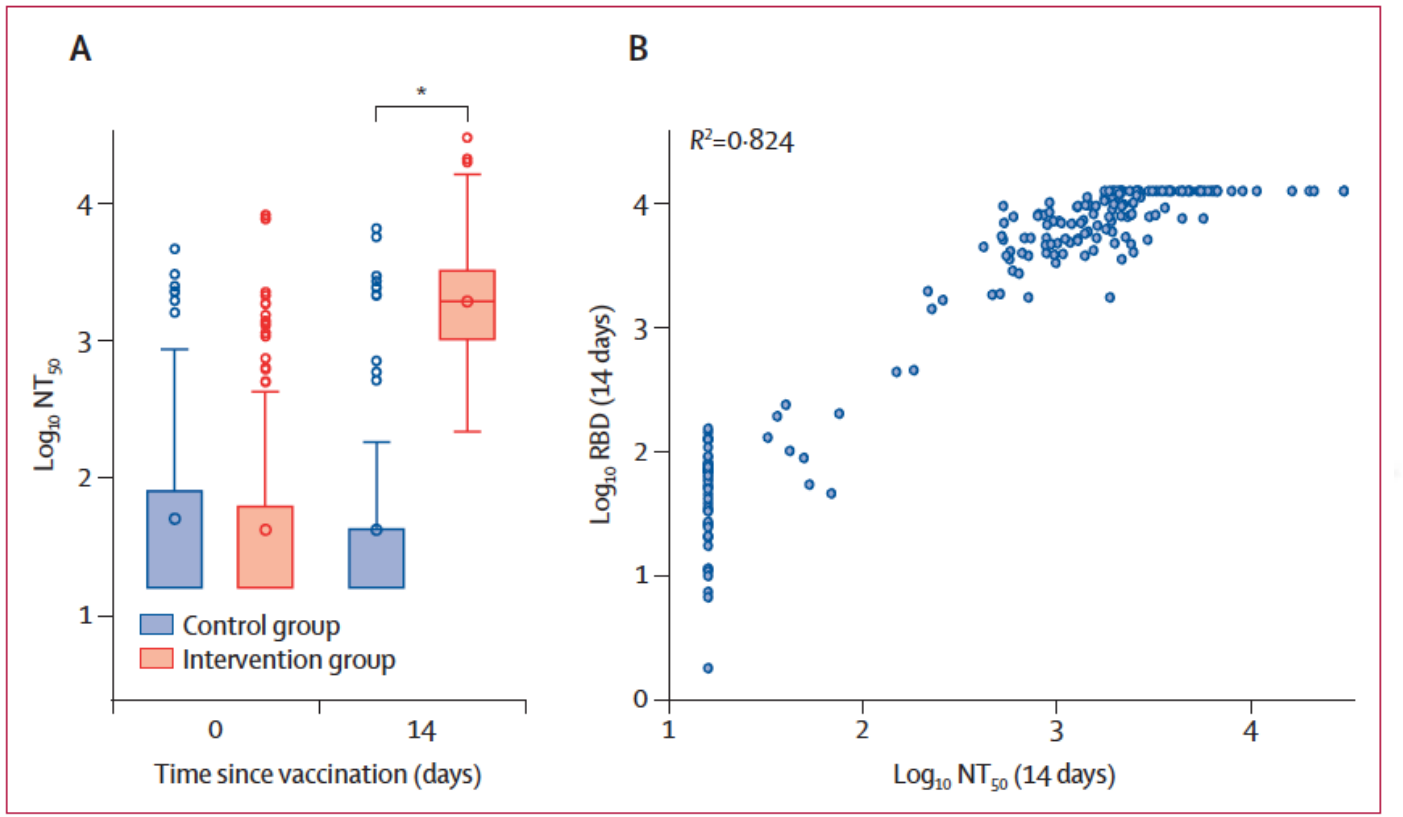
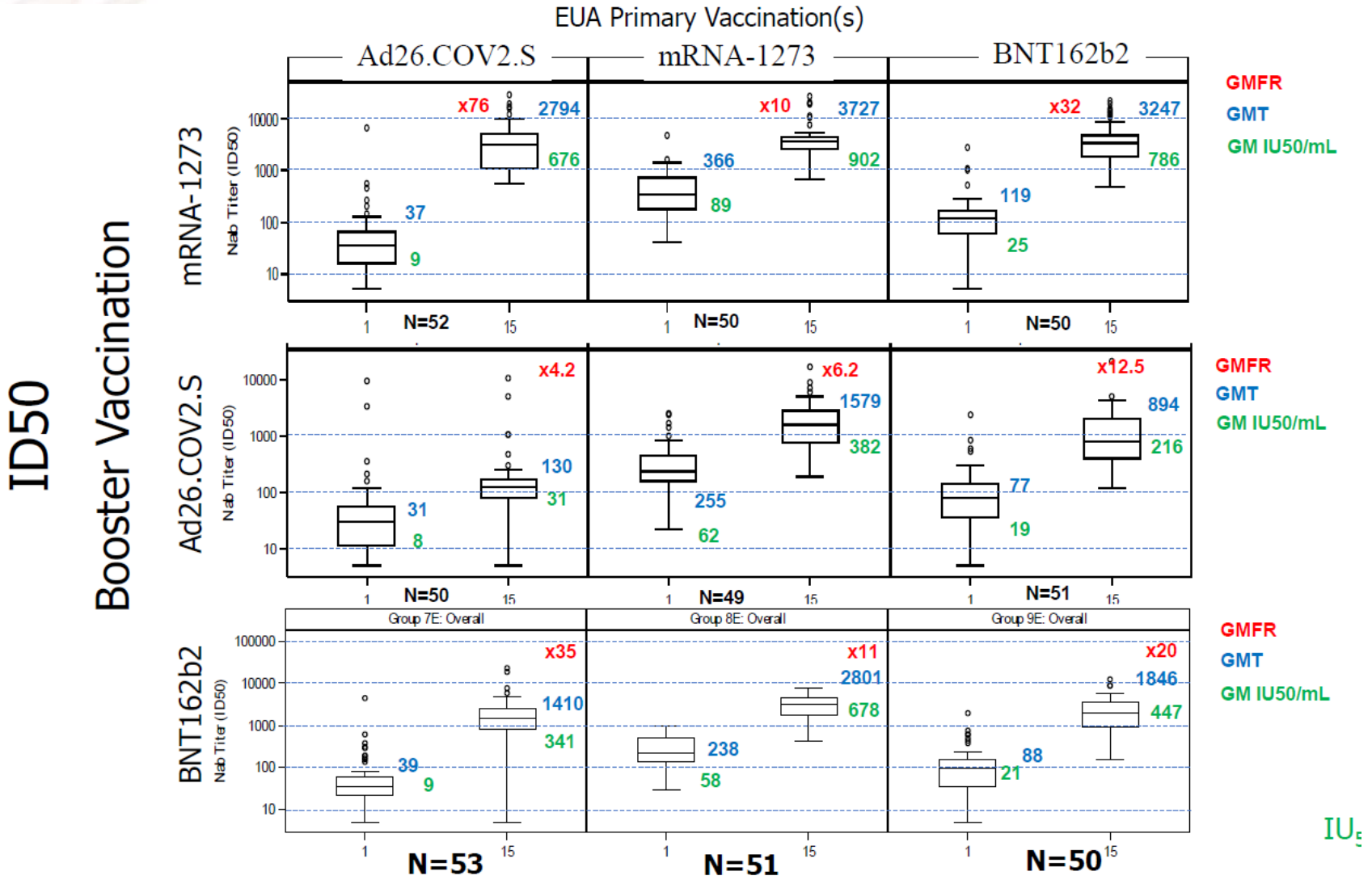


***Figure 3*: Neutralisation responses**

(A) Neutralising antibodies measured in both intervention and control groups on days 0 and 14. (B) Correlation between NT_{50} and RBD (anti-spike protein) antibody titres. NT_{50}=titres that achieved 50% neutralisation. RBD=receptor-binding domain. *p<0·0001.

Lancet 2021; 398: 121–30 https://doi.org/10.1016/ S0140-6736(21)01420-3

Preguntas planteadas. Mix and match vaccines



Lyke KE et al FDA VRBPAC Meeting 14 October 2021

Munro A et al. Lancet. 2021;398:2258-2276. doi: 10.1016/S0140-6736(21)02717-3. 1.

Courtesy of Dan Kuritzkes

Preguntas planteadas. Dos, tres, cuatro...

Table 2. Primary Outcomes of Confirmed Infection and Severe Illness.*

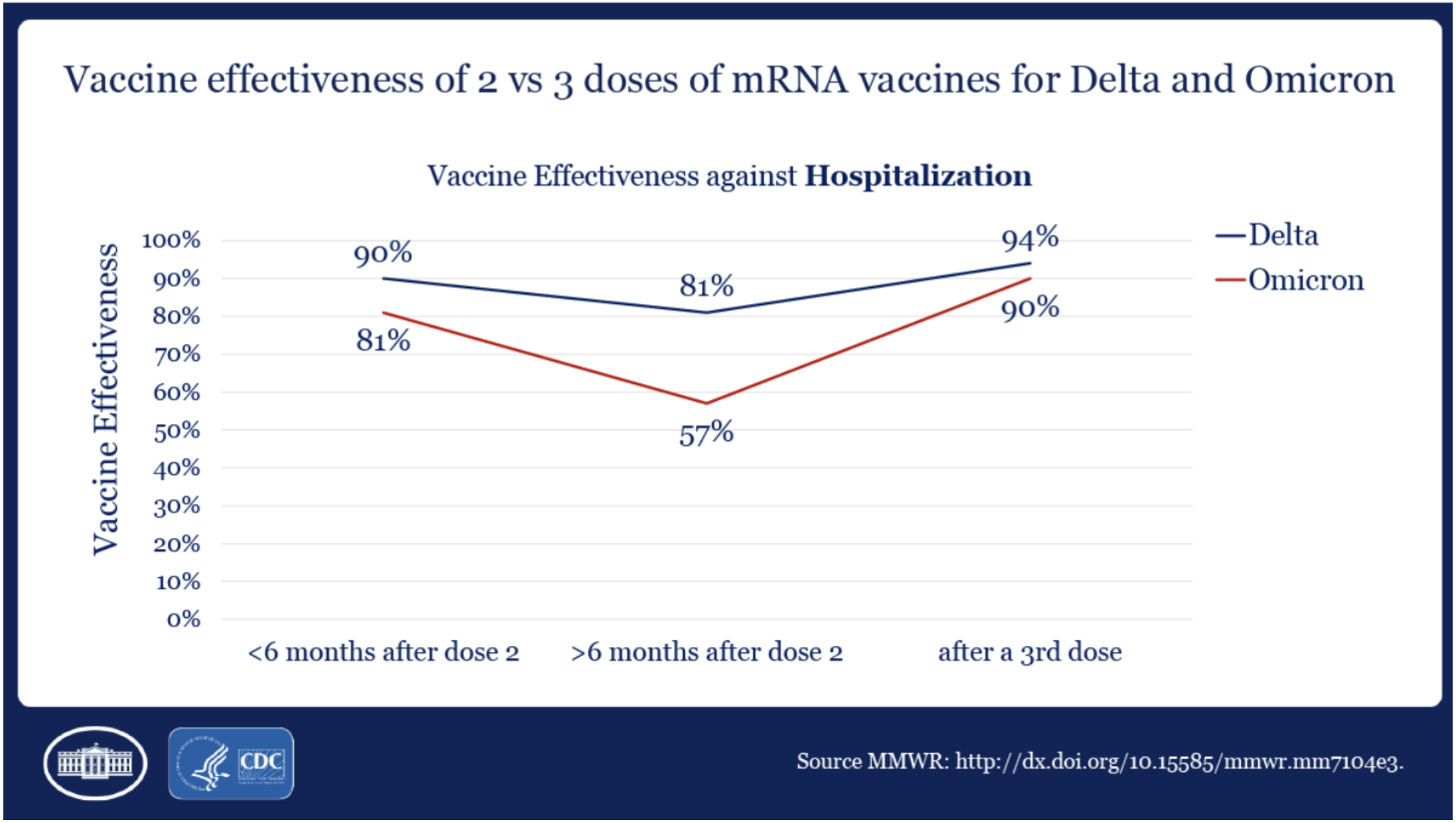
Outcome	Nonbooster Group	Booster Group	Adjusted Rate Ratio (95% CI)†
Confirmed infection			11.3 (10.4 to 12.3)
No. of cases	4439	934	
No. of person-days at risk	5,193,825	10,603,410	
Severe illness			19.5 (12.9 to 29.5)
No. of cases	294	29	
No. of person-days at risk	4,574,439	6,265,361	

* Listed are the results of the Poisson regression analysis in participants who received a booster vaccine and in those who did not receive a booster. The booster group includes data that were obtained at least 12 days after receipt of the booster dose.

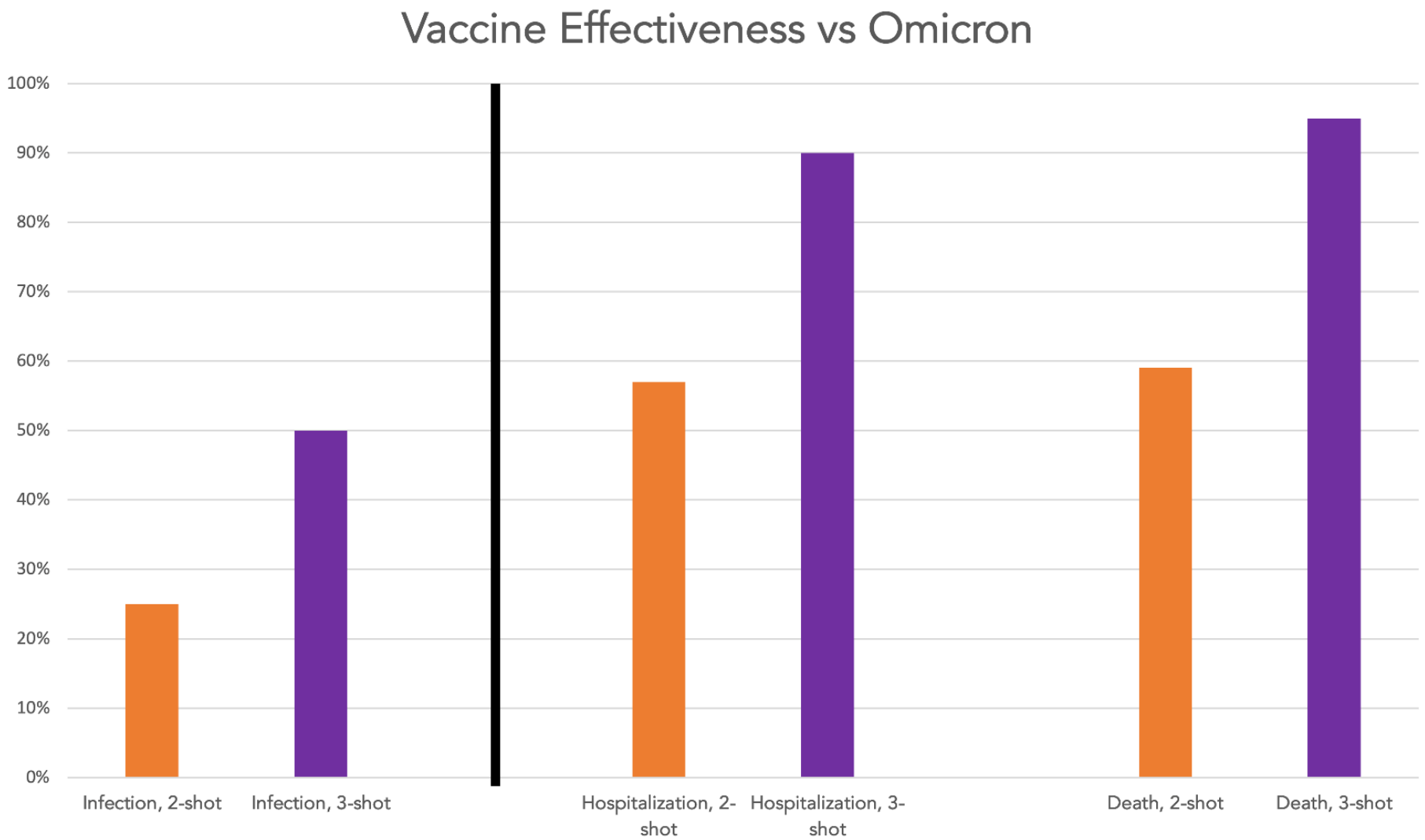
† The rate ratio is the estimated factor reduction in the rate in the booster group as compared with the rate in the non-booster group.

Bar-On YM et al. N Engl J Med. 2021 Sep 15:NEJMoa2114255. doi: 10.1056/NEJMoa2114255

Preguntas planteadas. Dos, tres, cuatro...



Preguntas planteadas. Dos, tres, cuatro…



Ground Truths from Eric Topol. https://erictopol.substack.com/p/humans-2-omicron-1?s=r

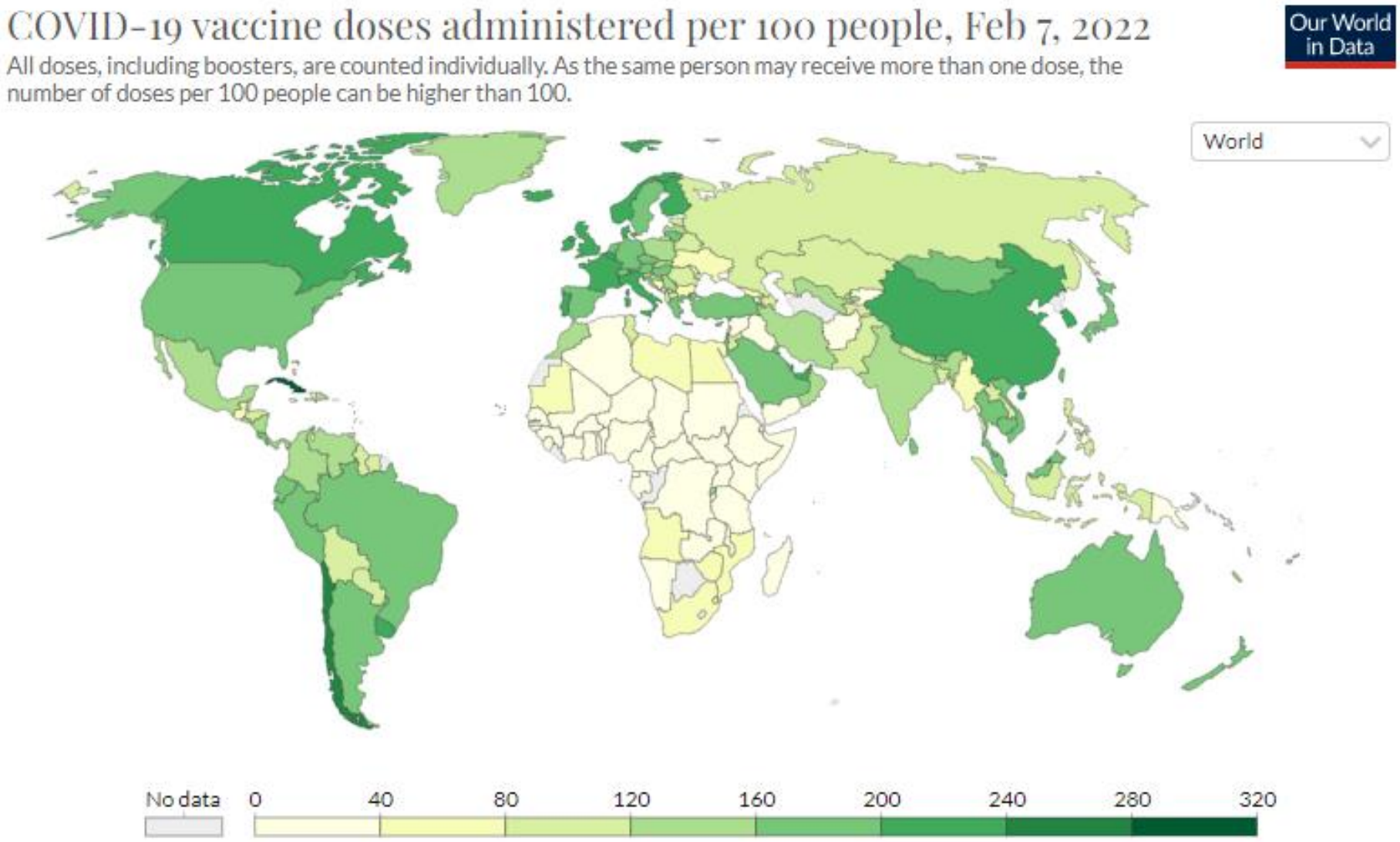
Preguntas planteadas. Nuevos prototipos de vacunas

- Prototipos
  - Actuales: ARN, vectores adenovirales
  - Nuevos: Subunidades de proteínas
  - Novísimos y dudosos
    - Vacunas inhaladas → Riesgos de seguridad
    - Vacunas atenuadas → Riesgos de seguridad
    - Vacunas Pan-coronavirus → Desafío tecnológico
- Composición
  - Específicas de omicron
  - Vacunas Pan-coronavirus

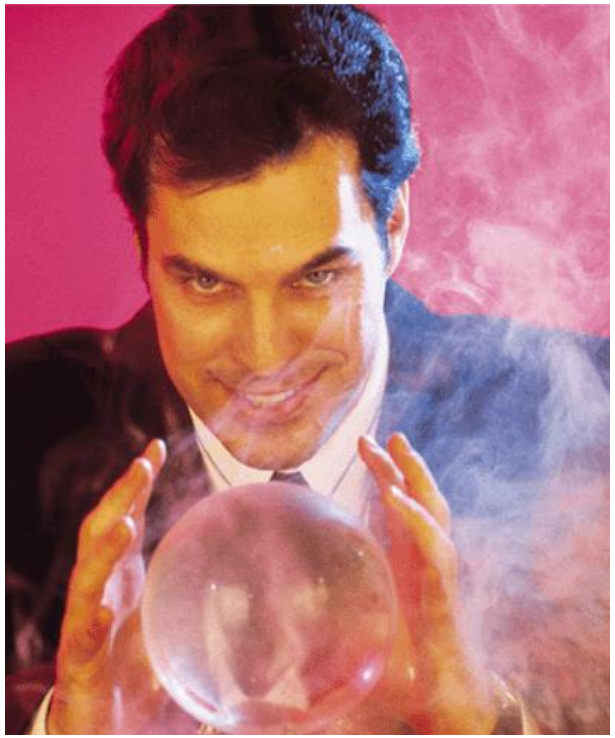
Preguntas planteadas. Una solución global

Solución global para un problema global

61.5% of the world population has received at least one dose of a COVID-19 vaccine.
10.24 billion doses have been administered globally,
and 23.66 million are now administered each day.
Only 10.4% of people in low-income countries have received at least one dose.



¿Cuando tendremos una vacuna preventiva contra el VIH?

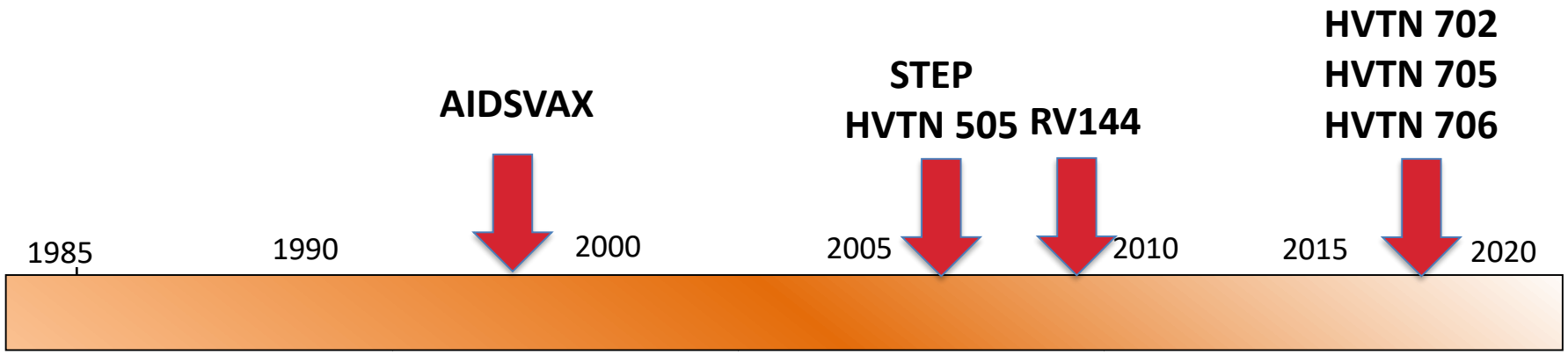


~~¿cuándo tenfremos una vacuna preventiva frente al VIH?~~

¿Es posible conseguir una vacuna frente al VIH?

No lo sabemos

Etapas en el desarrollo de una vacuna VIH



1984-2004.
FRACASO DE LOS MODELOS CLÁSICOS
- **Vacunas inactivadas**
- **Vacunas atenuadas**
- **Vacunas de envueltas recombinantes**

2000-2015
Inducción de respuestas linfocitarias T

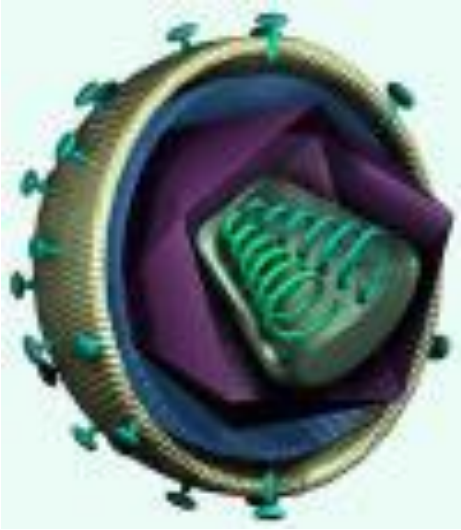
2005-2020
VACUNAS COMBINADAS T+B

2010 -
CARACTERIZACIÓN DE AcN
DISEÑO DE NUEVAS ENVUELTAS
INDUCCION DE Ac NEUTRALIZANTES

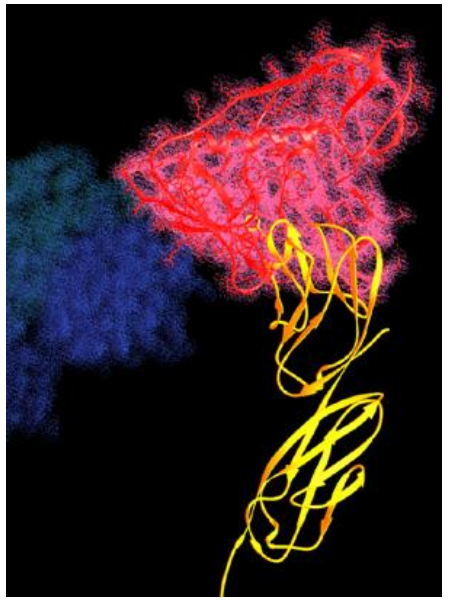
Pepe Alcamí

Steps in the development of an HIV vaccine

1984-2004.
FRACASO DE LOS MODELOS CLÁSICOS
- **Vacunas inactivadas**
- **Vacunas atenuadas**
- **Vacunas de envueltas recombinantes**

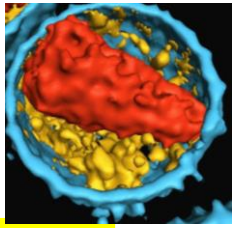


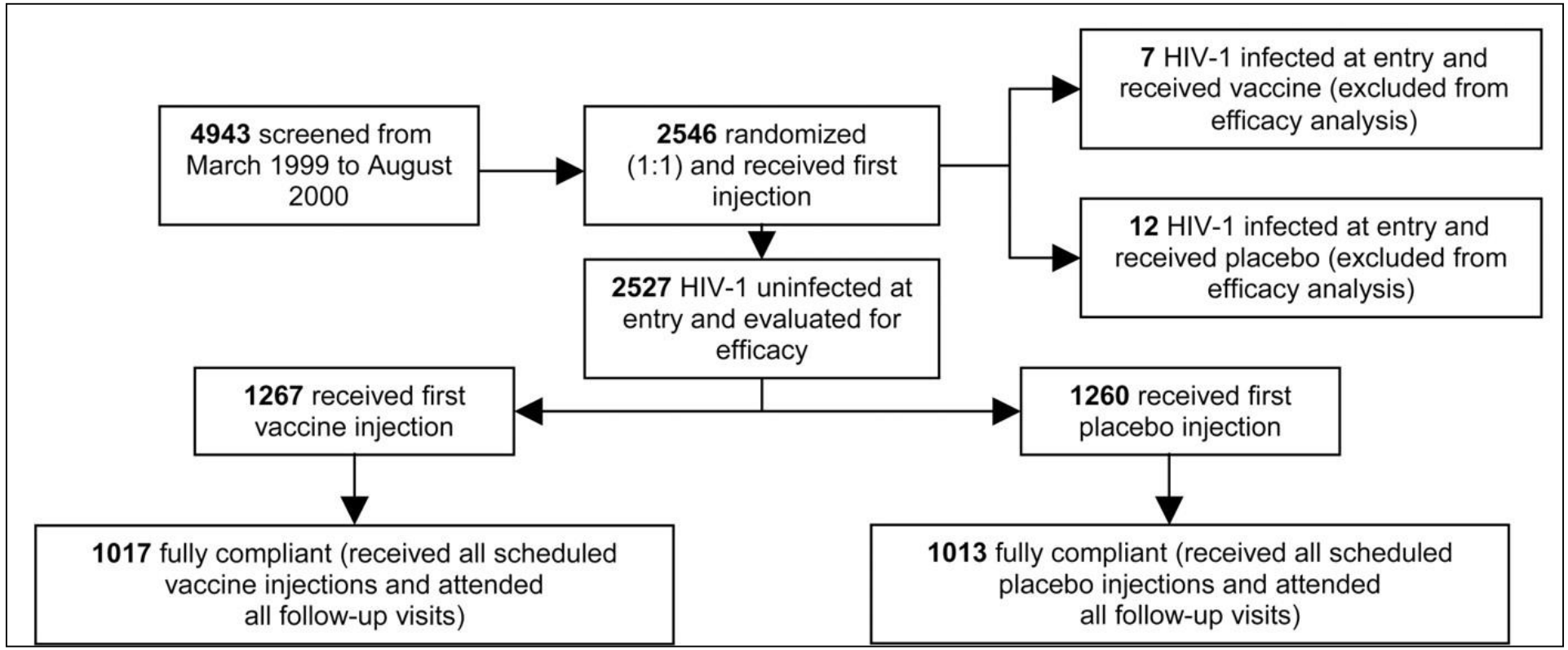
MODELO DE LA HEPATITIS B
- Antigeno de superficie
- Fuerte respuesta humoral
- Protección elevada
- Protección a largo plazo



AIDSVAX TRIAL

Randomized, double-blind, placebo-controlled efficacy trial of a bivalent recombinant glycoprotein 120 HIV-1 vaccine among injection drug users in Bangkok, Thailand.





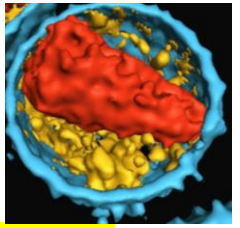
-IVDU

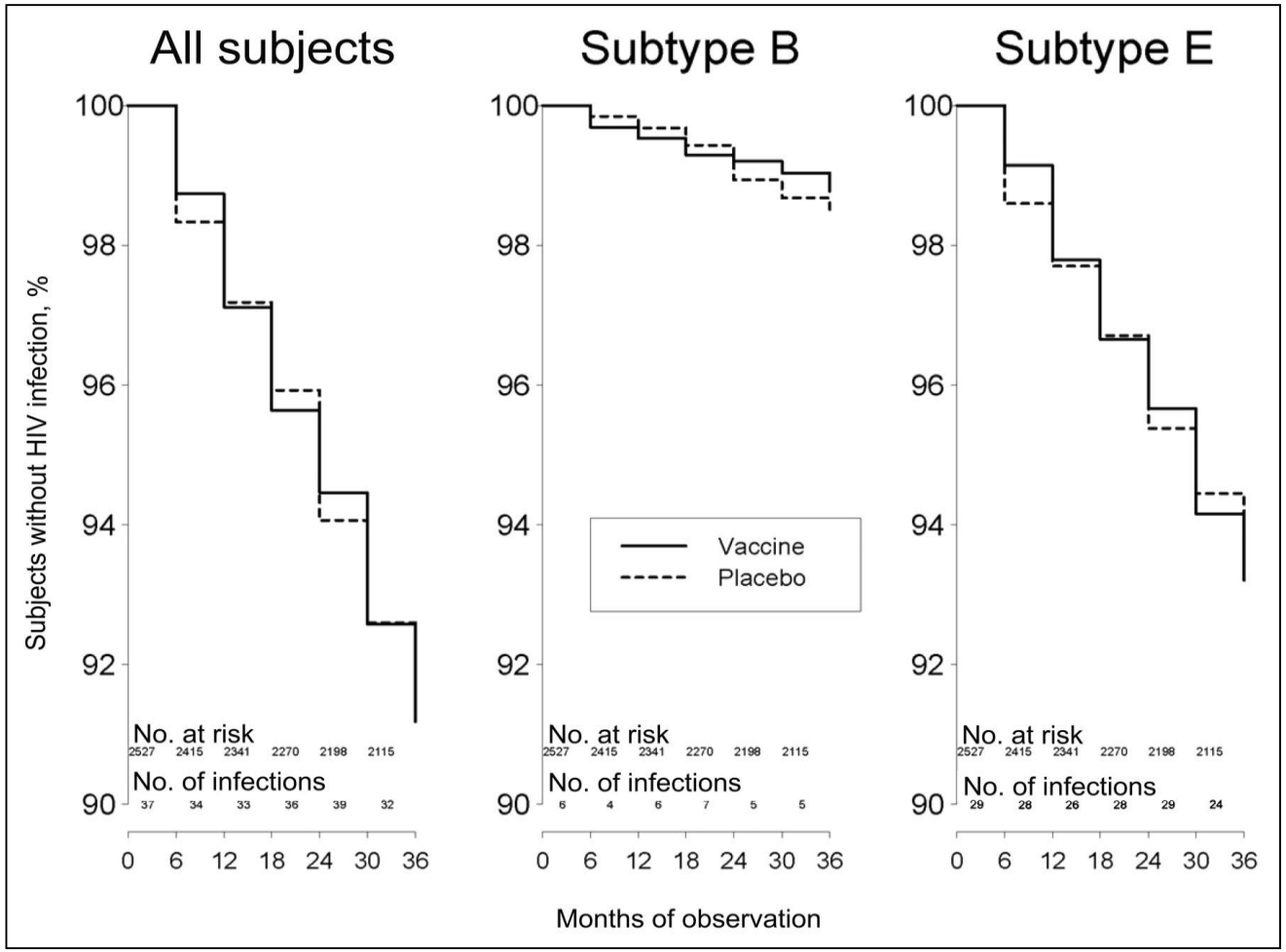
- AIDSVAX B/E contains 2 rgp120 HIV-1 envelope antigens: 1 from a CXCR4-dependent laboratory-adapted subtype B strain (MN), and 1 from a CCR5-dependent primary subtype CRF01_AE isolate (A244)

Pitisuttithum P et al. J Infect Dis. 2006;194:1661-71

AIDSVAX TRIAL

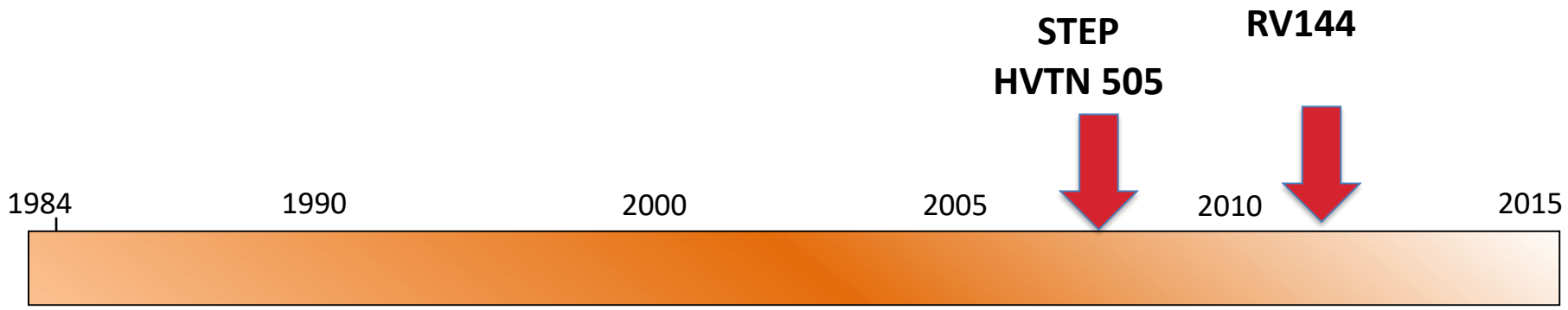
Randomized, double-blind, placebo-controlled efficacy trial of a bivalent recombinant glycoprotein 120 HIV-1 vaccine among injection drug users in Bangkok, Thailand.





Pitisuttithum P et al. J Infect Dis. 2006;194:1661-71

Steps in the development of an HIV vaccine

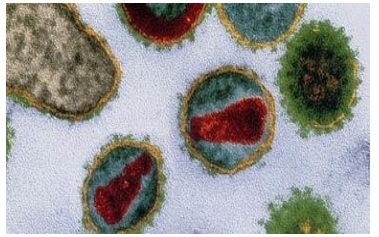


2000-
Inducción de respuestas linfocitarias T

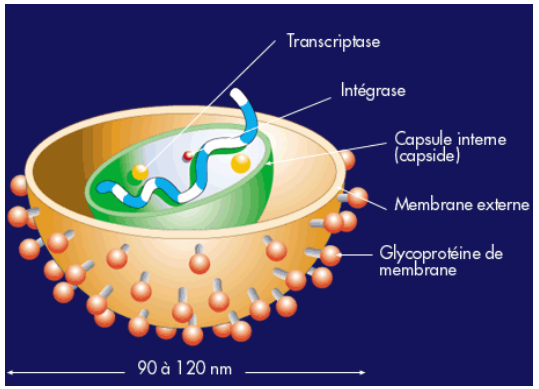
RESPUESTAS CELULARES T POTENTES

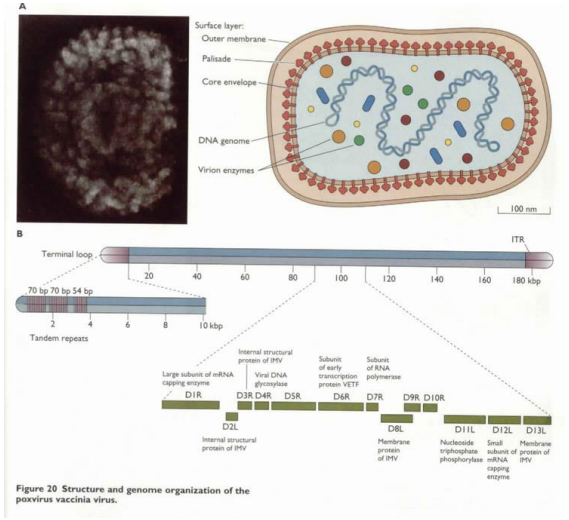
- Controladores de élite
- Infección aguda y crónica
- Interrupción de tratamiento
- Modelos animales

VACUNAS CELULARES

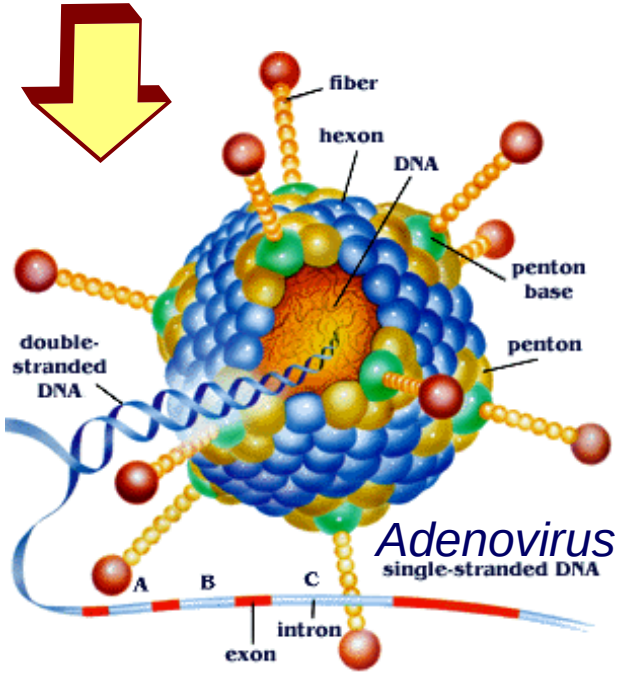


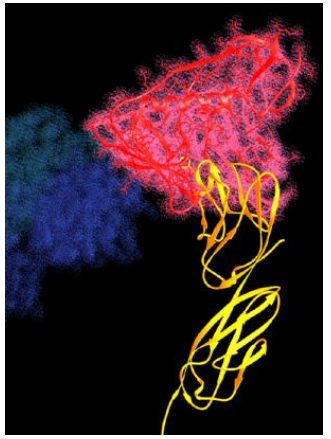
EXPRESION DE GENES DEL VIH EN VECTORES VIRALES





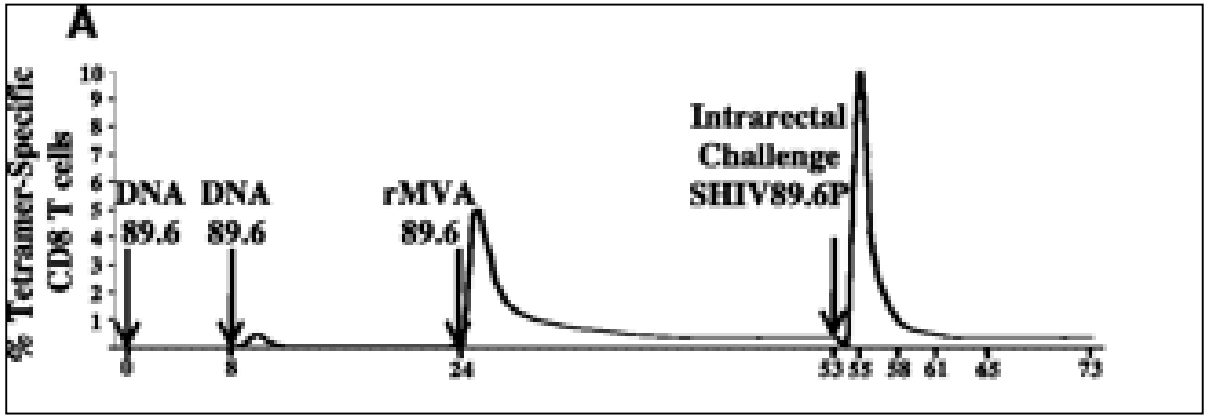
Poxvirus

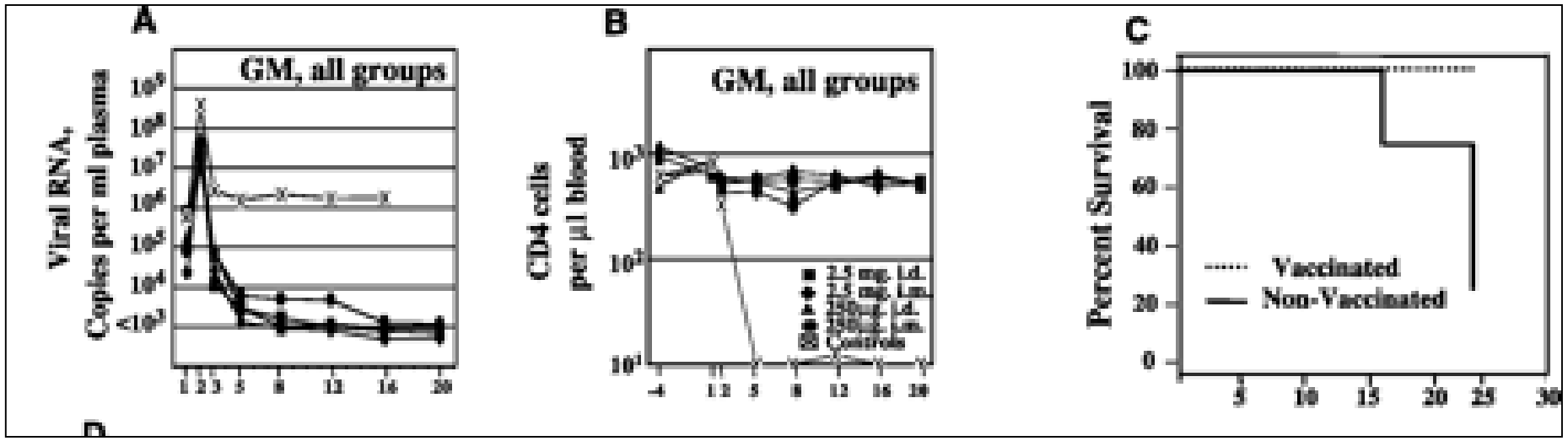




VACUNAS CELULARES

Control of a Mucosal Challenge and Prevention of AIDS by a Multiprotein DNA/MVA Vaccine (Science 2001;292:69-74)

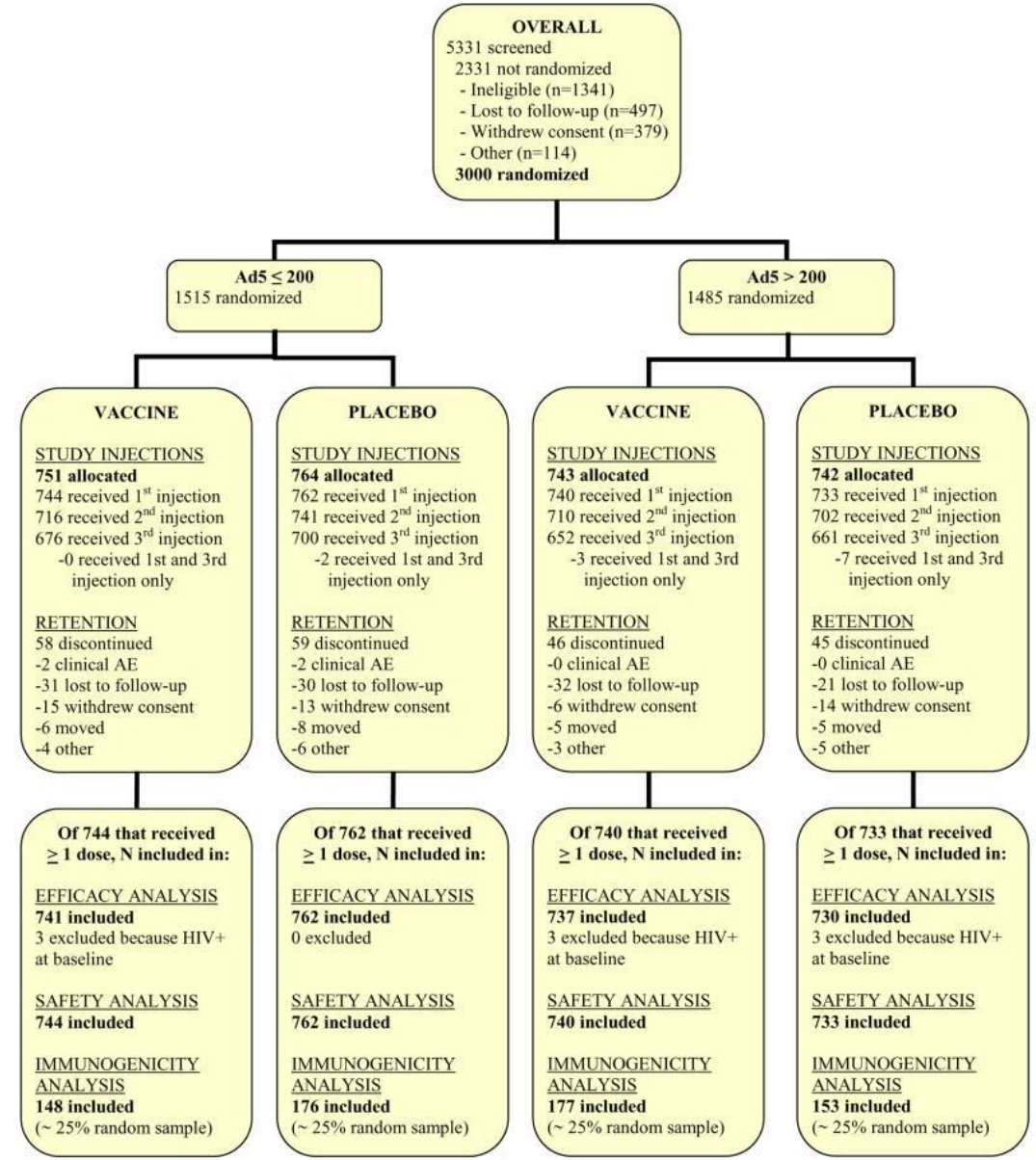




CONTROL OF VIRAL LOAD, STABLE CD4 COUNTS AND SURVIVAL NEVER PROTECTION AGAINST SIV INFECTION

STEP TRIAL (MERCK V520 Protocolo 023/HVTN 502)

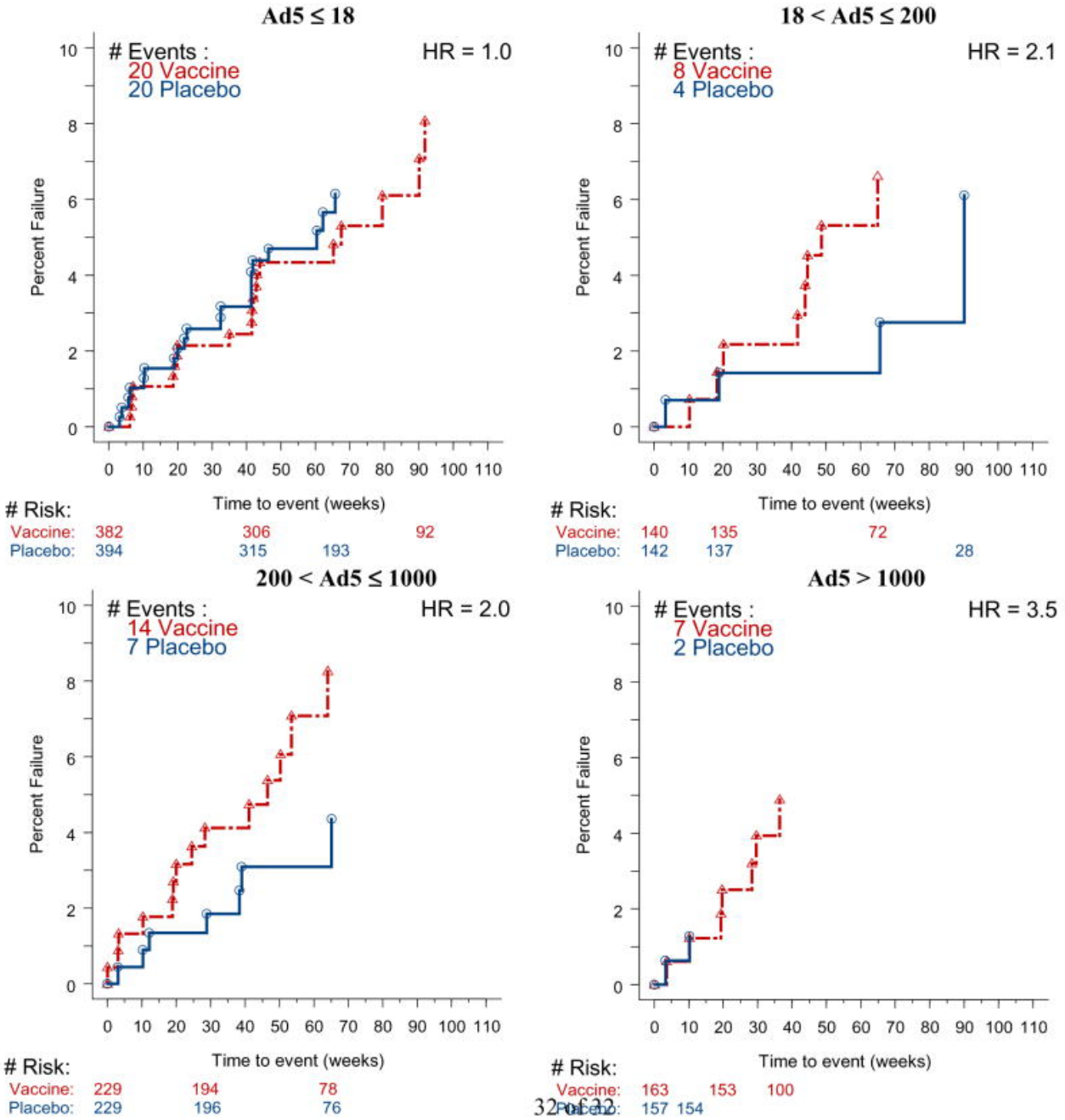
Efficacy assessment of a cell-mediated immunity HIV-1 vaccine (the Step Study): a double-blind, randomised, placebo-controlled, test-of-concept trial Susan P Buchbinder et al. Lancet 2008;372:1881-93



STEP TRIAL (MERCK V520 Protocolo 023/HVTN 502)

RESULTADOS

- Incidence of HIV infection was higher in vaccinated subjects as compared to control **(5.1% versus 2.2% per year)**



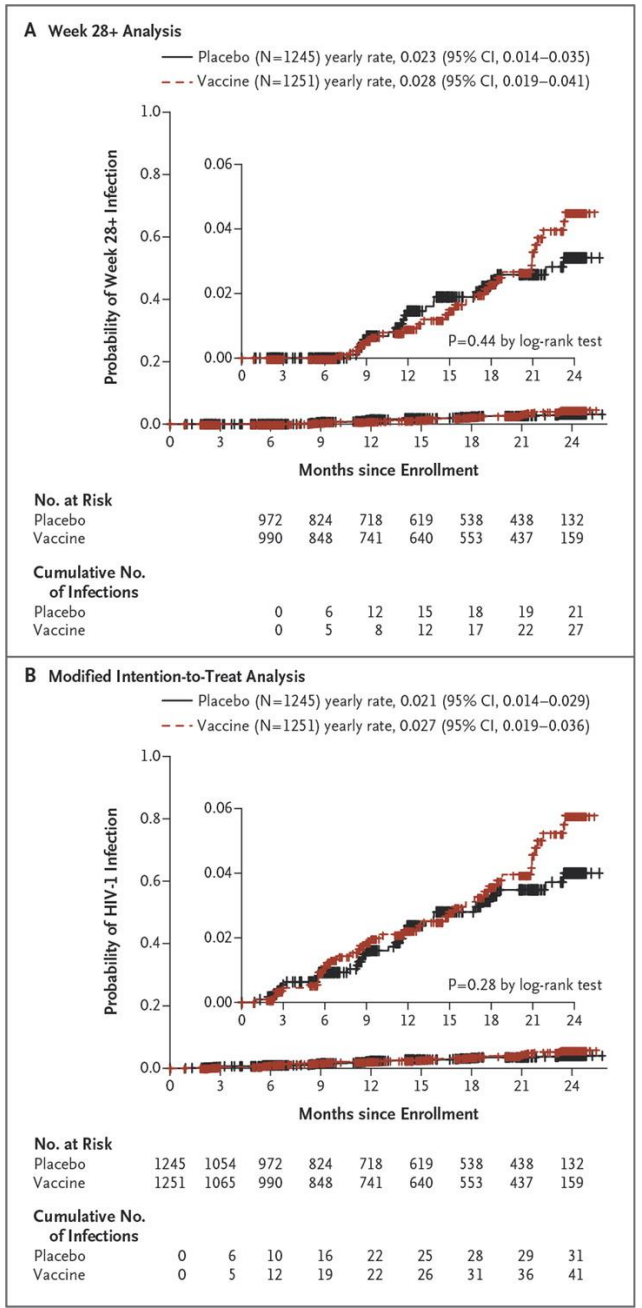
SIMILAR RESULTS IN THE HVTN 505

NIH halts trial of HIV prevention vaccine on lack of efficacy. April 2013

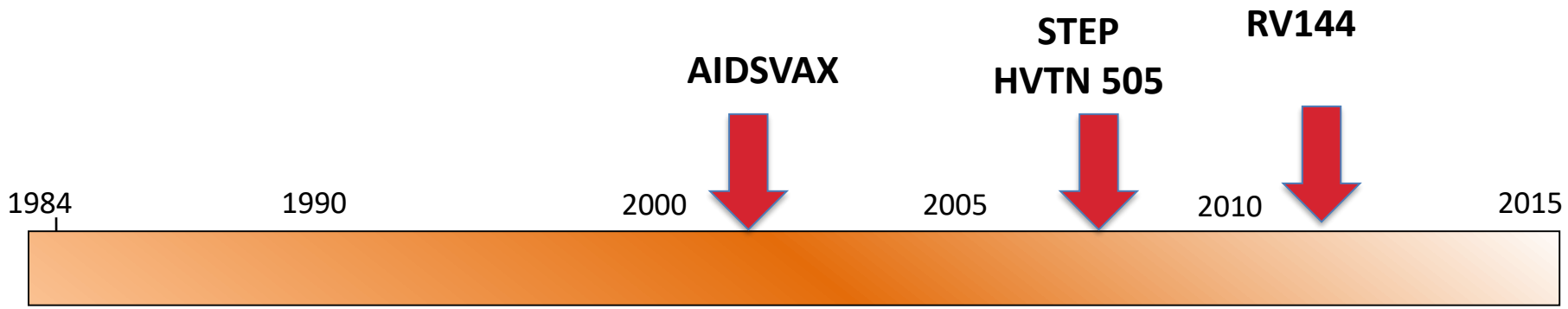
NIH's National Institute of Allergy and Infectious Diseases (NIAID) discontinued the Phase IIb HVTN 505 trial to prevent HIV infection after an interim analysis showed a lack of efficacy of the vaccine regimen in the trial. An independent DSMB found that the VRC DNA/rAd5 HIV vaccine regimen did not prevent HIV infection nor reduce viral load in vaccine recipients who became infected with HIV. The double-blind, placebo-controlled, U.S. trial enrolled 2,504 HIV-uninfected circumcised men who have sex with men and transgender people who have sex with men. All subjects received HIV risk-reduction counseling

A scheduled safety review on April 22 found that slightly more volunteers who had received the vaccine later became infected with HIV. Overall, 41 cases of HIV infection occurred in the volunteers who received the experimental vaccine and 30 cases of HIV infection occurred among the recipients who received the dummy injection.

Efficacy Trial of a DNA/rAd5 HIV-1 Preventive Vaccine
Scott M. Hammer. NEJM 2013 N Engl J Med 2013; 369:2083-2092

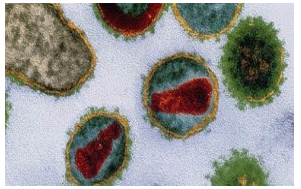


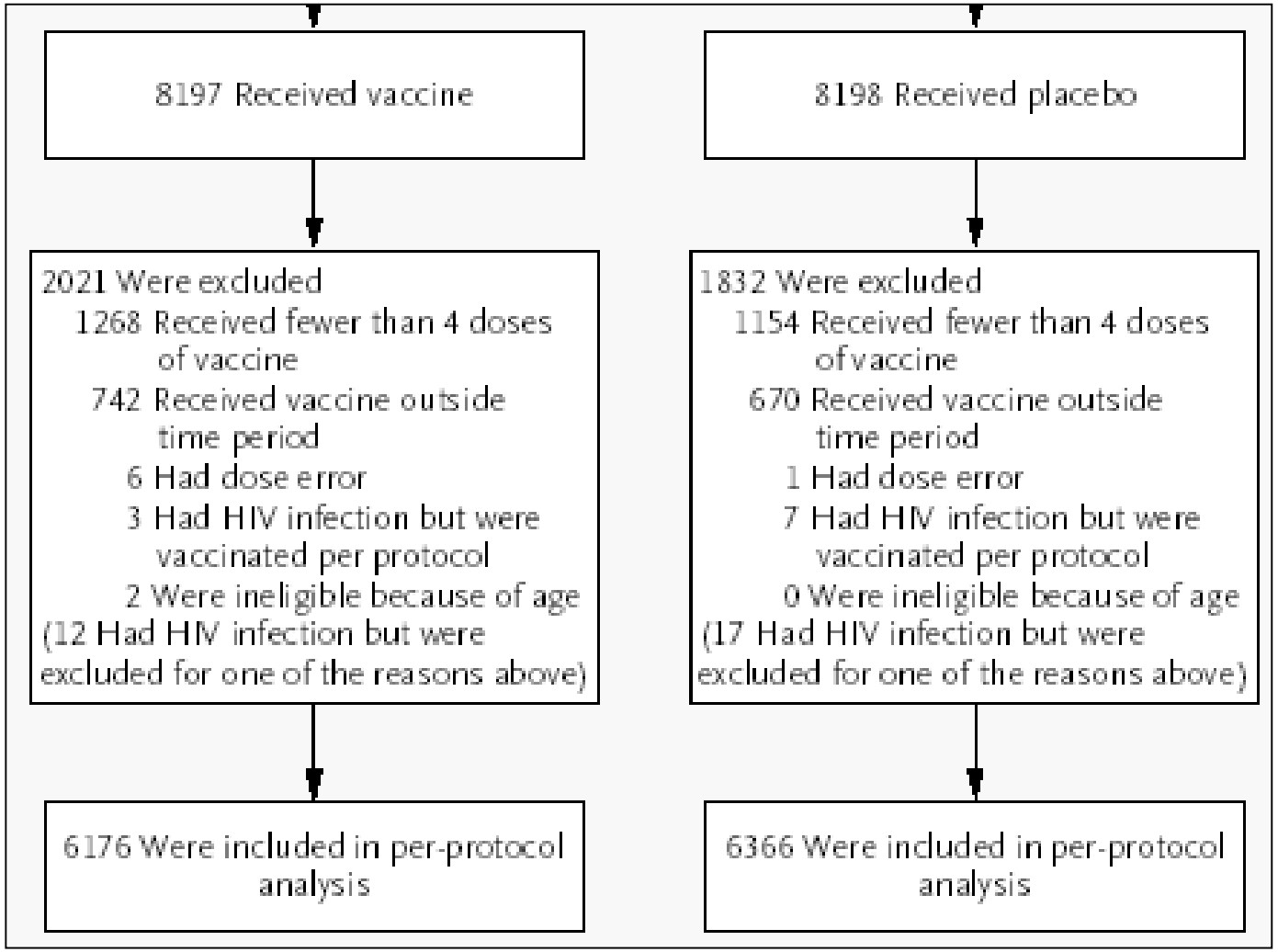
Etapas en el desarrollo de una vacuna VIH



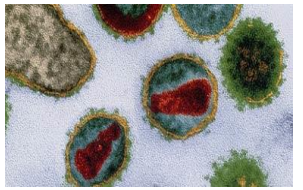
2000-
VACUNAS COMBINADAS T+B
¿Pueden dos fracasos ser una solución de éxito?

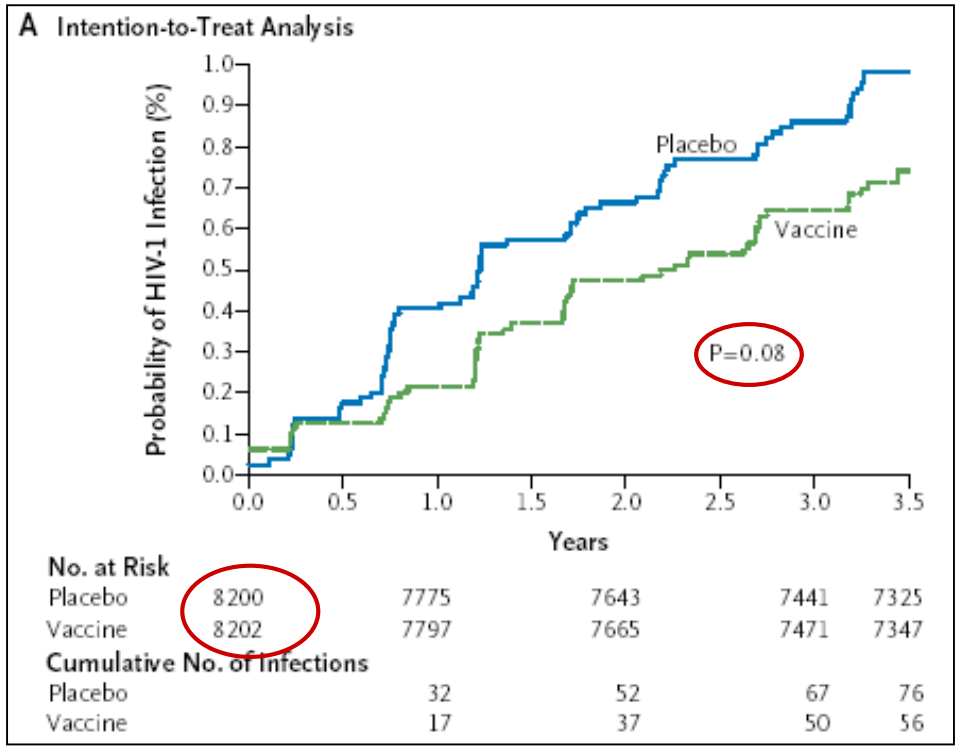
RV144 TRIAL. HUMORAL AND CELLULAR VACCINES COMBINATION OF AIDSVAX AND CANARYPOX.

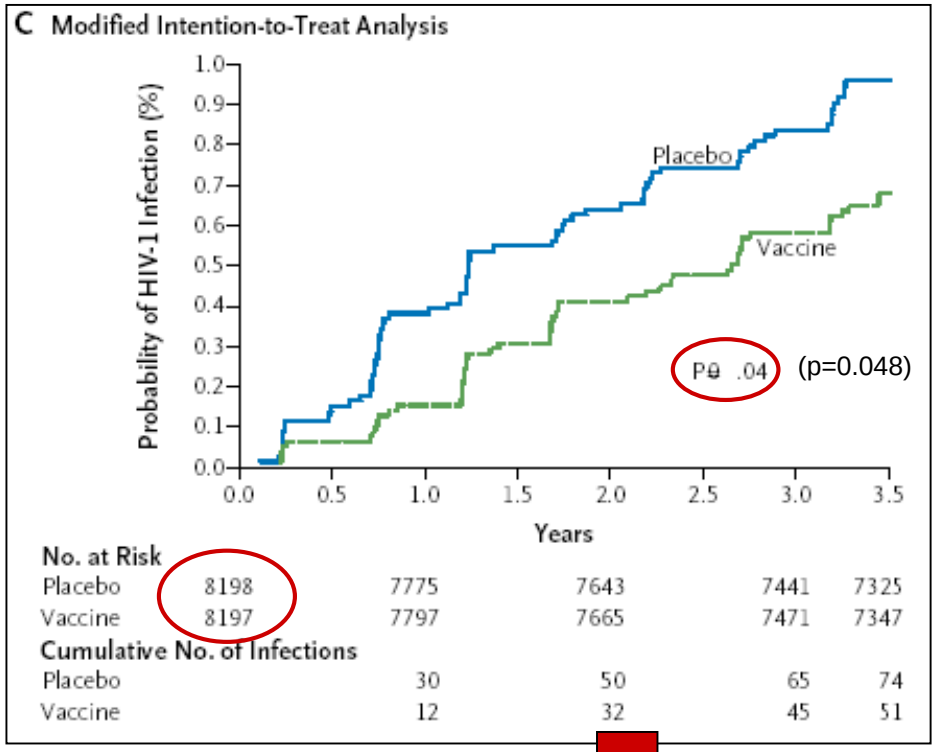




RV144 TRIAL. HUMORAL AND CELLULAR VACCINES COMBINATION OF AIDSVAX AND CANARYPOX.







Cumulative No. of Infections

Placebo	30	50	65	74
Vaccine	12	32	45	51

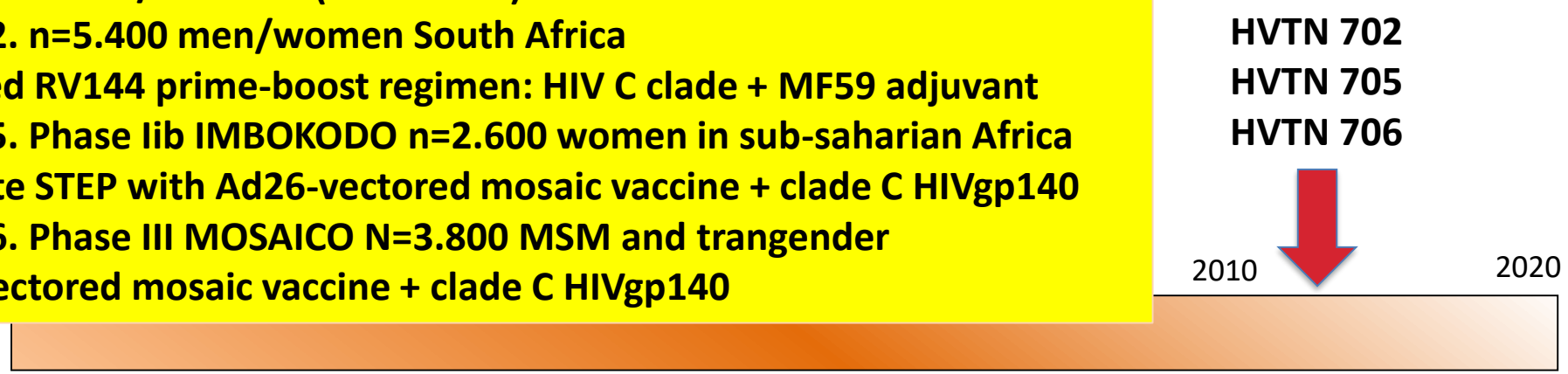
Cumulative No. of Infections

Placebo	32	52	67	76
Vaccine	17	37	50	56

Etapas en el desarrollo de una vacuna VIH

ONGOING PHASE 2B/3 TRIALS (2018-2020)

- **HVTN 702. n=5.400 men/women South Africa**
  Modified RV144 prime-boost regimen: HIV C clade + MF59 adjuvant
- **HVTN 705. Phase Iib IMBOKODO n=2.600 women in sub-saharian Africa**
  Replicate STEP with Ad26-vectored mosaic vaccine + clade C HIVgp140
- **HVTN 706. Phase III MOSAICO N=3.800 MSM and trangender**
  Ad26-vectored mosaic vaccine + clade C HIVgp140



NHP 13-19 STUDY. HUMORAL AND CELLULAR VACCINES COMBINATION OF ADENO 26 Y GP140

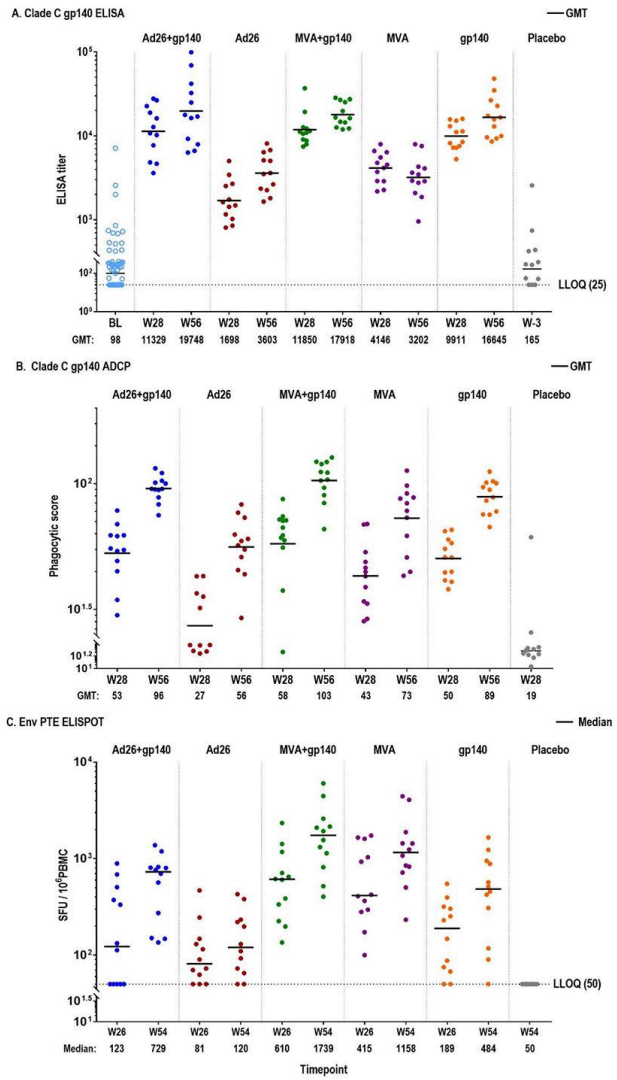
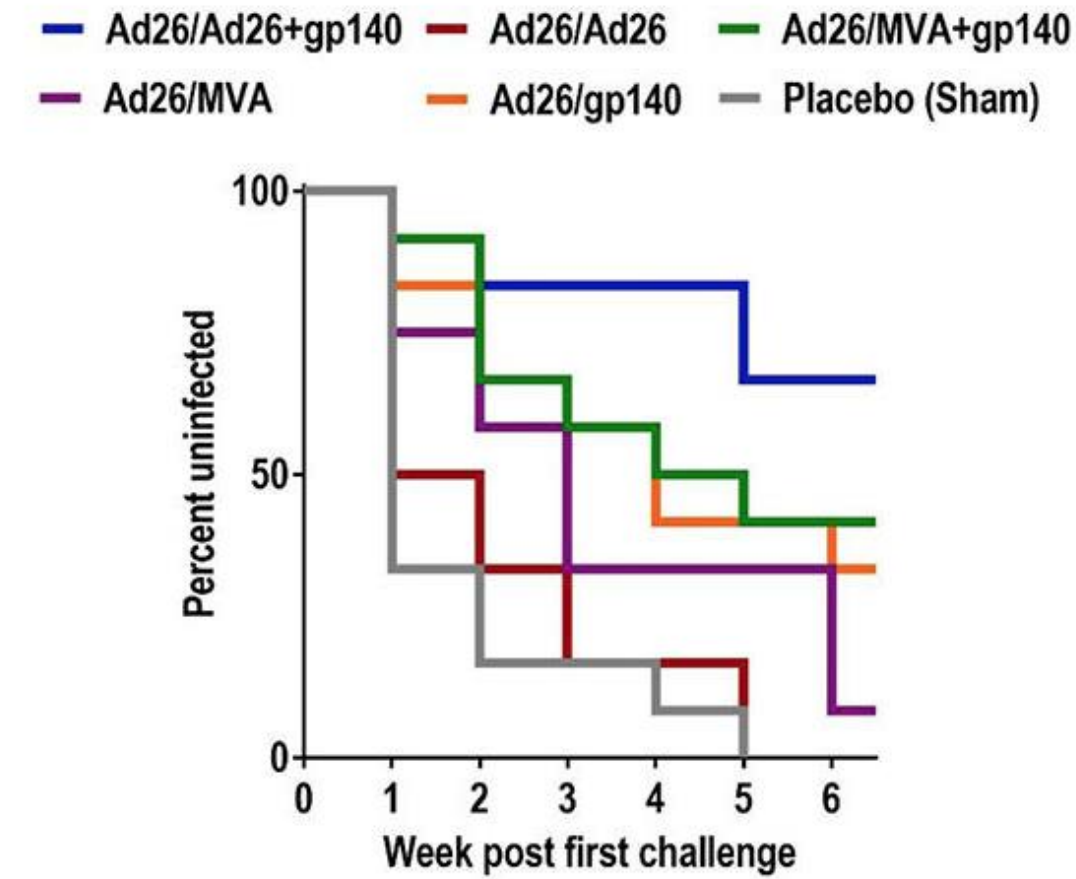


Figure 4A. Kaplan-Meier curve



Barouch D. Lancet 2018

Etapas en el desarrollo de una vacuna VIH

ONGOING PHASE 2B/3 TRIALS (2018-2020)

- ~~HVTN 702. n=5.400 men/women South Africa~~
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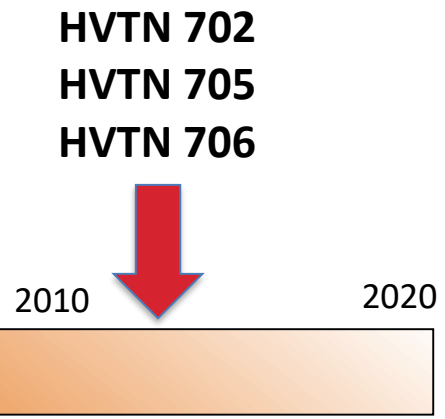

UNAIDS

PRESS STATEMENT

HVTN 702 clinical trial of an HIV vaccine stopped

GENEVA, 4 February 2020—The United States National Institutes of Health has announced that its HVTN 702 clinical trial of an HIV vaccine has been stopped. While no safety concerns were found during the trial, the independent data and safety monitoring board found that the vaccine was ineffective in preventing HIV transmission.

The trial, conducted at 14 sites across South Africa, followed more than 5400 HIV-negative 18–35-year-olds over 18 months. The participants received six injections during the six-month period, either the vaccine or a placebo. An analysis undertaken after at least 60% of the participants had been in the study for more than 18 months showed that there were 129 HIV infections among the people who had the vaccine, while 123 people who had the placebo became infected.

"While we are obviously disappointed with the results, important science has been learned that can be carried forward to future trials. I thank the study team for this important vaccine trial," said Winnie Byanyima, UNAIDS Executive Director.

Etapas en el desarrollo de una vacuna VIH

ONGOING PHASE 2B/3 TRIALS (2018-2020)

- ~~HVTN 702. n=5.400 men/women South Africa~~
  ~~Modified RV144 prime-boost regimen: HIV C clade + MF59 adjuvant~~
- ~~HVTN 705. Phase IIb IMBOKODO n=2.600 women in sub-saharian Africa~~
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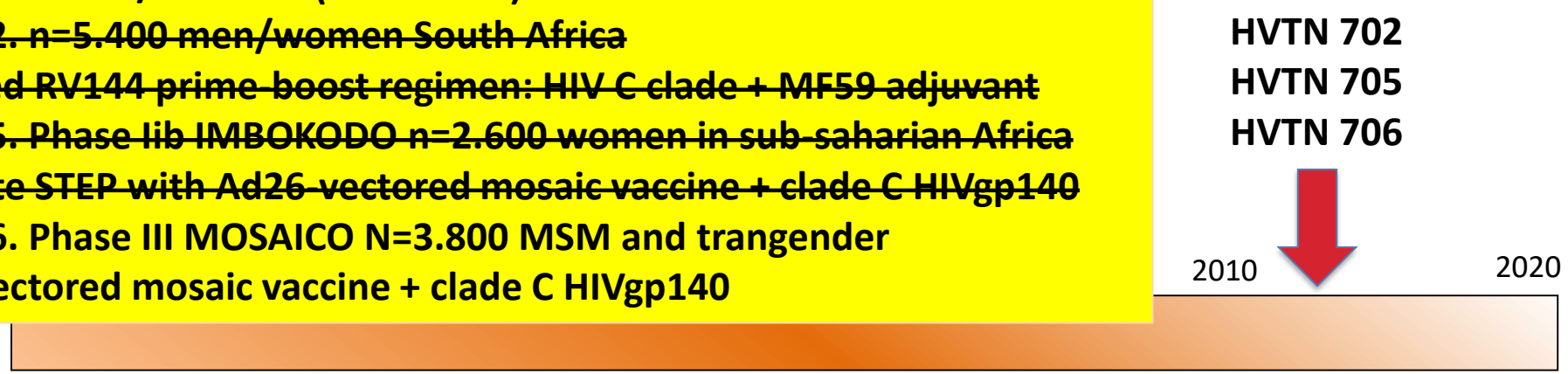


Johnson & Johnson and Global Partners Announce Results from Phase 2b Imbokodo HIV Vaccine Clinical Trial in Young Women in Sub-Saharan Africa

Investigational vaccine candidate did not provide sufficient protection against HIV infection

No vaccine-related safety signals identified

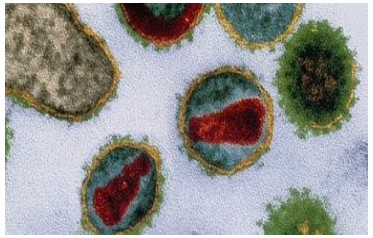
J&J HIV vaccine program continues with global Phase 3 Mosaico HIV study evaluating a different composition of the vaccine regimen in different populations

Johnson & Johnson

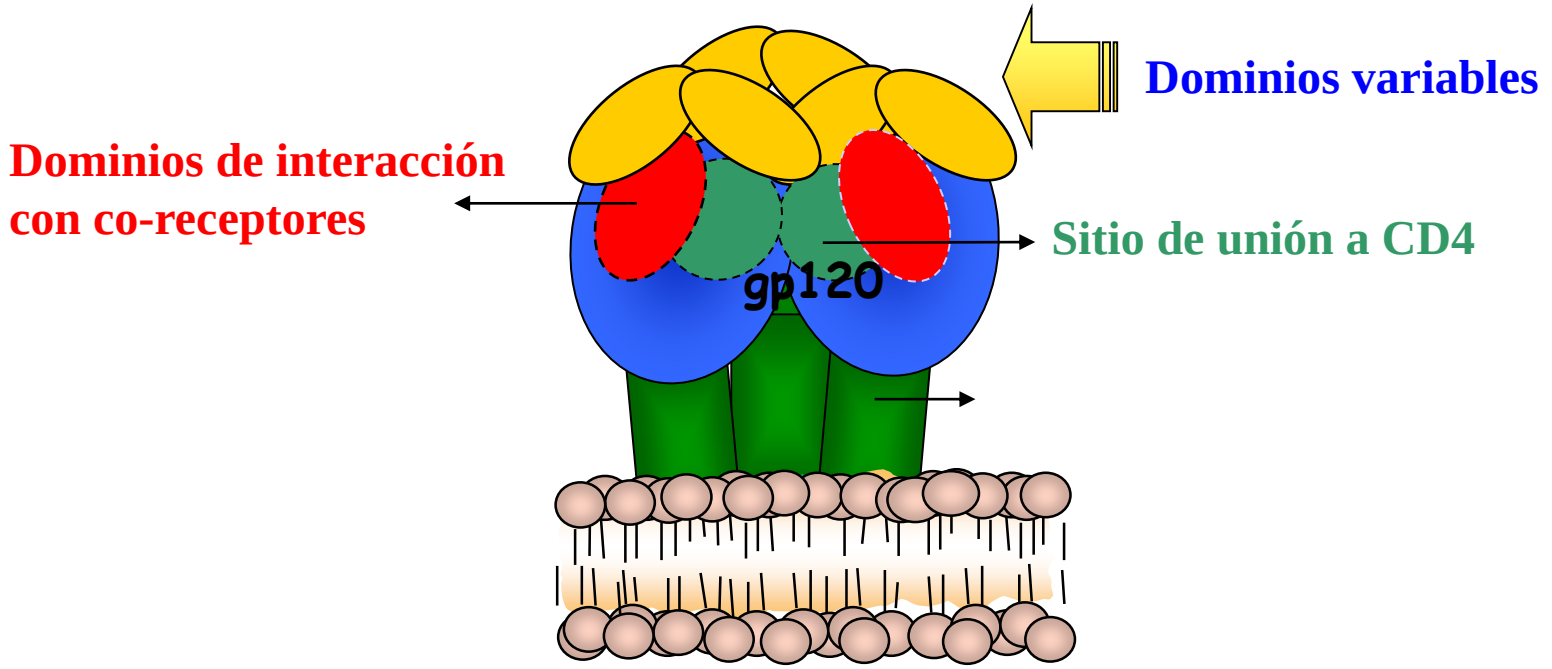
¿Por qué hemos fracasado hasta ahora?

1. **Estructura de la envuelta**
2. **No inducimos los anticuerpos apropiados en el momento apropiado**

ESTRUCTURA DE LA ENVUELTA DEL VIH



1- TRIMERICA
2. CONFORMACIÓN CERRADA QUE OCULTA LOS DOMINIOS DE INTERACCIÓN CON LOS RECEPTORES
3. ALTA CAPACIDAD DE MUTACIÓN EN LOS DOMINIOS EXPUESTOS
4. POTENCIAL DE GLICOSILACIÓN ELEVADA



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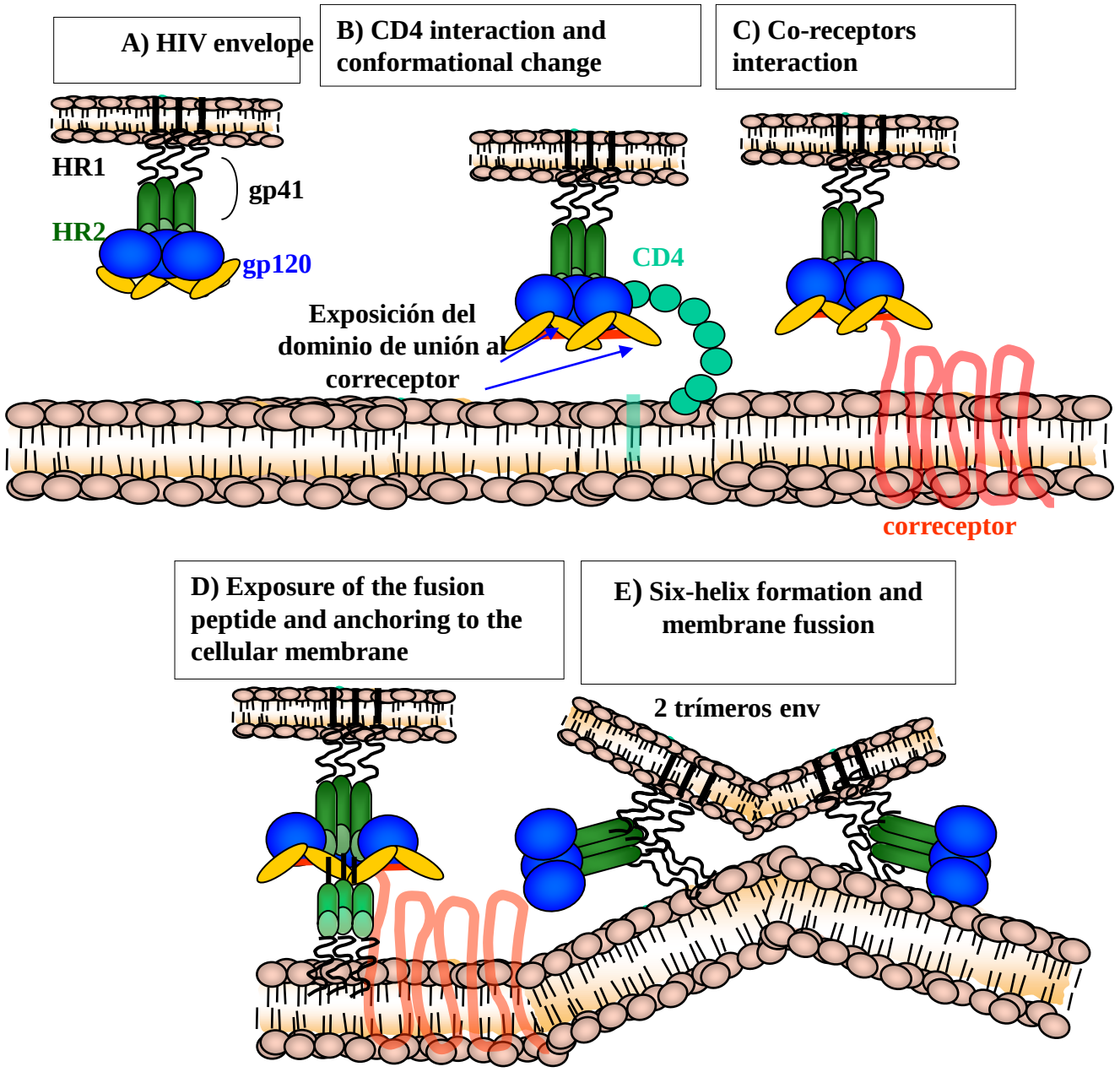
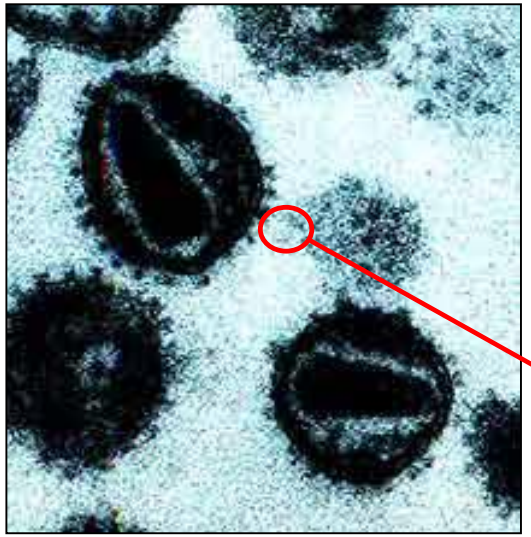
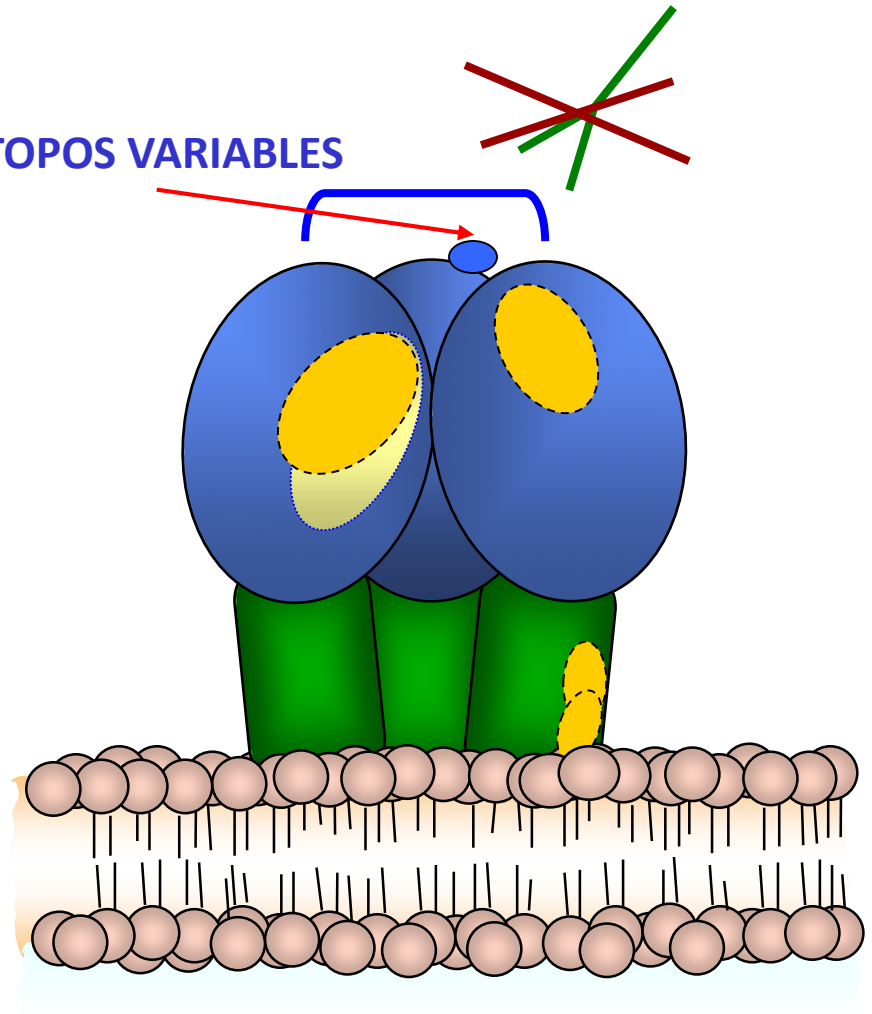


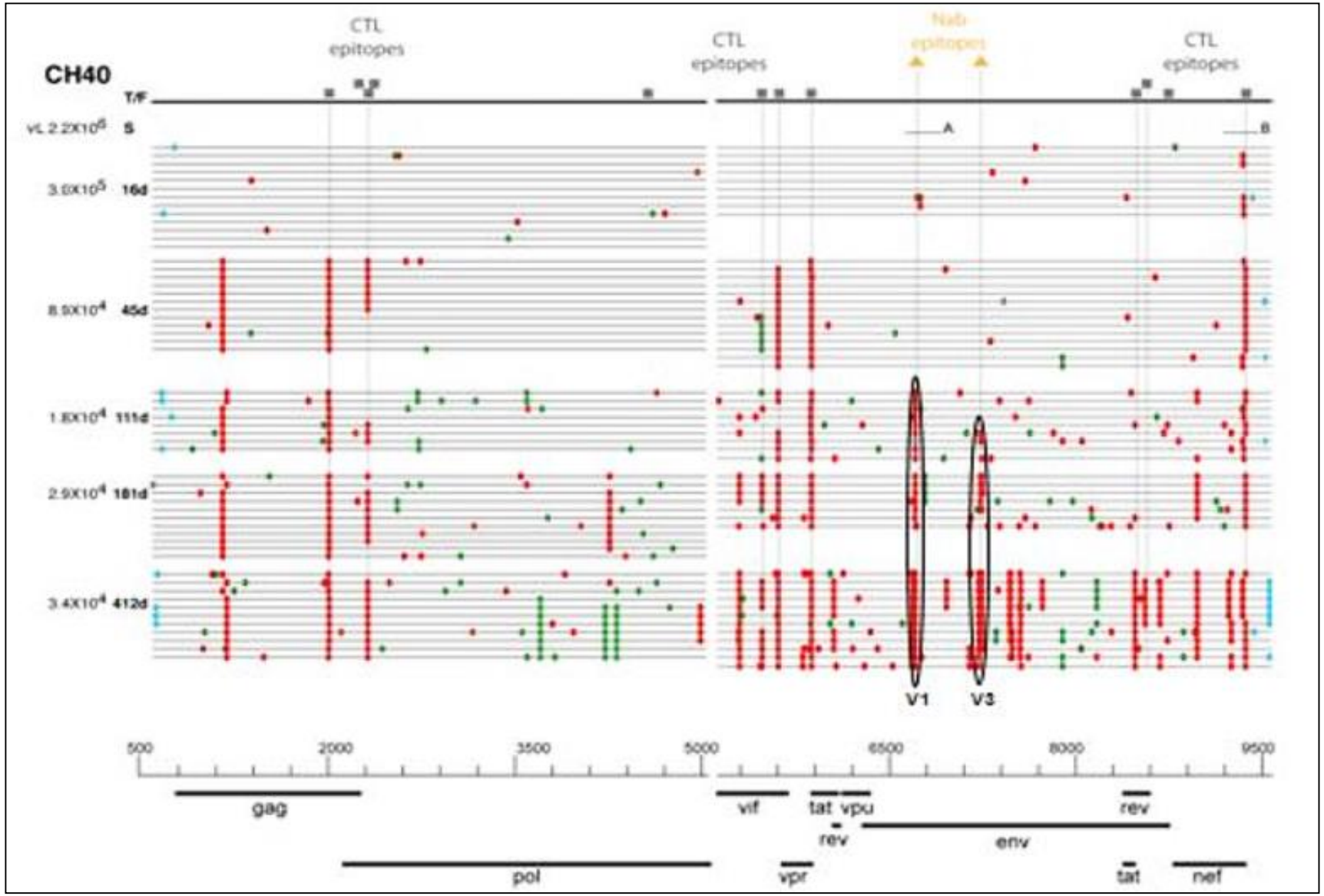
3. ALTA CAPACIDAD DE MUTACIÓN EN LOS DOMINIOS EXPUESTOS





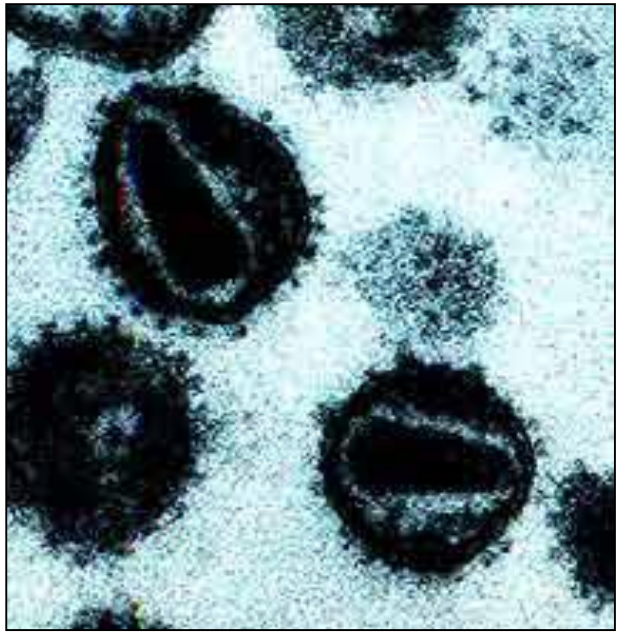
(Burton D. Human neutralizing antibodies and a vaccine for HIV-1. XIV International AIDS Conference [Abstract nº201])

3. ALTA CAPACIDAD DE MUTACIÓN EN LOS DOMINIOS EXPUESTOS

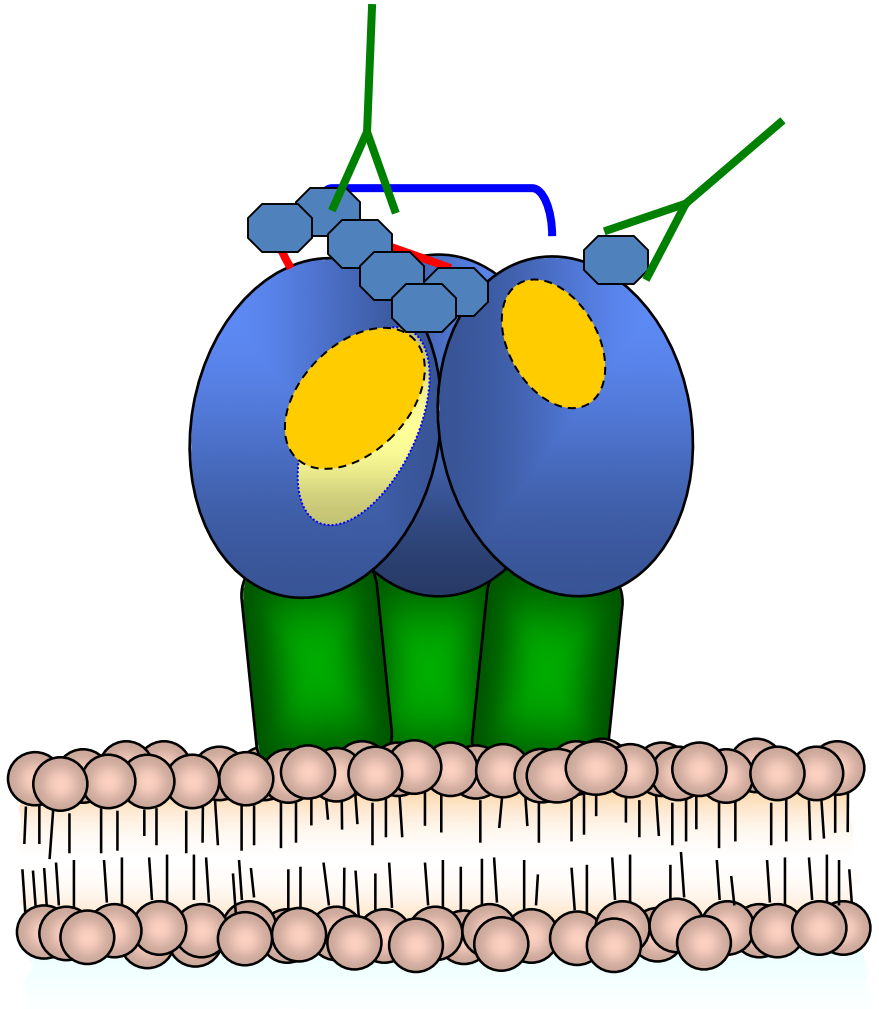


Salazar-Gonzalez JF, et al. J Exp Med. 2009 ;206:1273-89. Keele BF, et al. PNAS 2008;105:7552-7

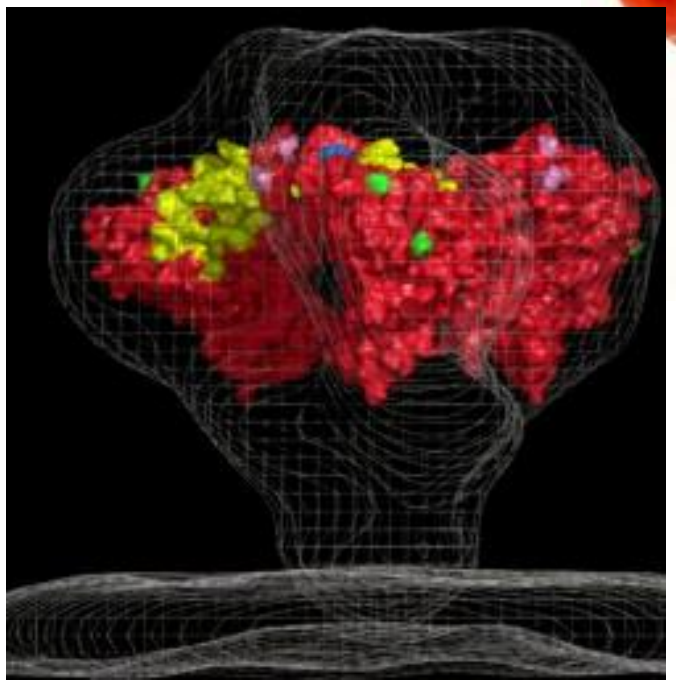
4. GLICOSILACIÓN ELEVADA

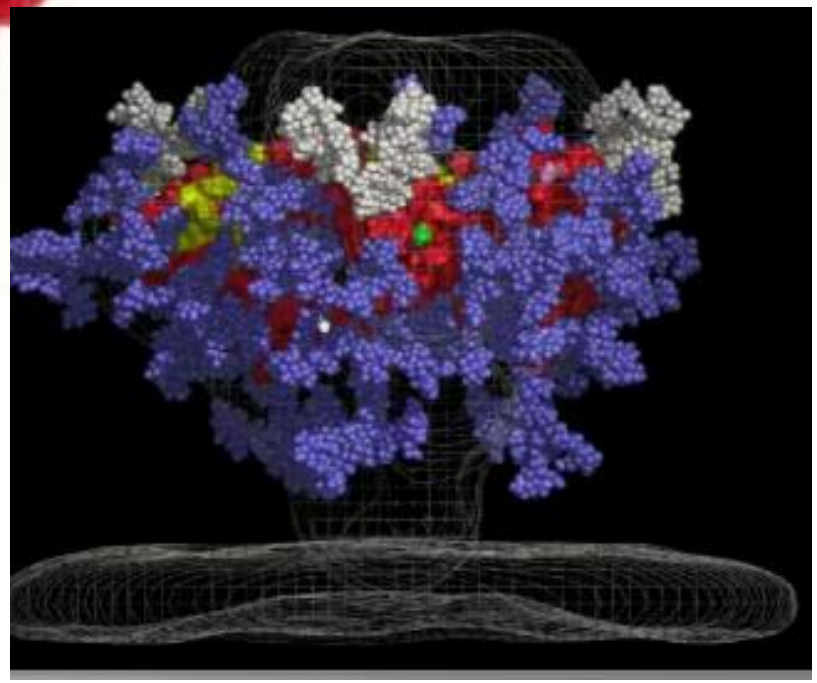


Viral envelope



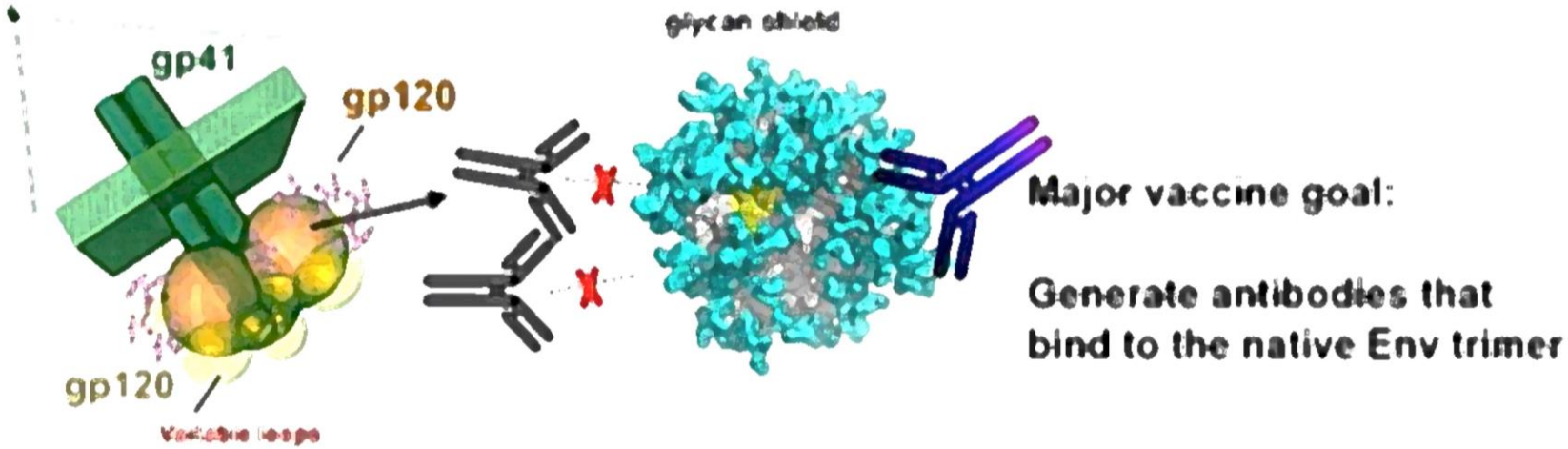
4. GLICOSILACIÓN ELEVADA





¿Por qué hemos fracasado hasta ahora?

No generamos los anticuerpos apropiados

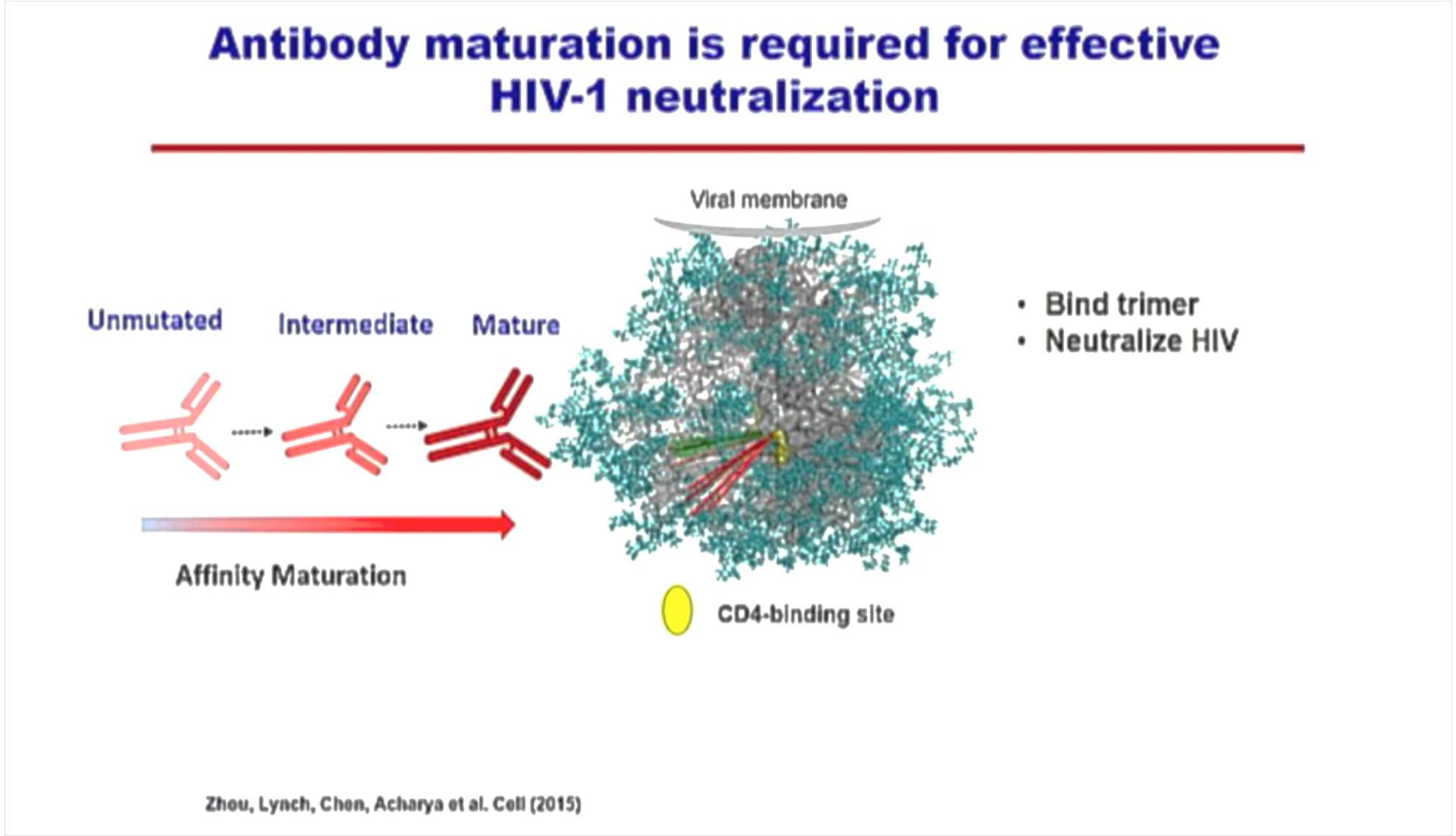


Antibodies elicited by the gp120 immunization do not effectively bind the native trimer and do not neutralize HIV-1

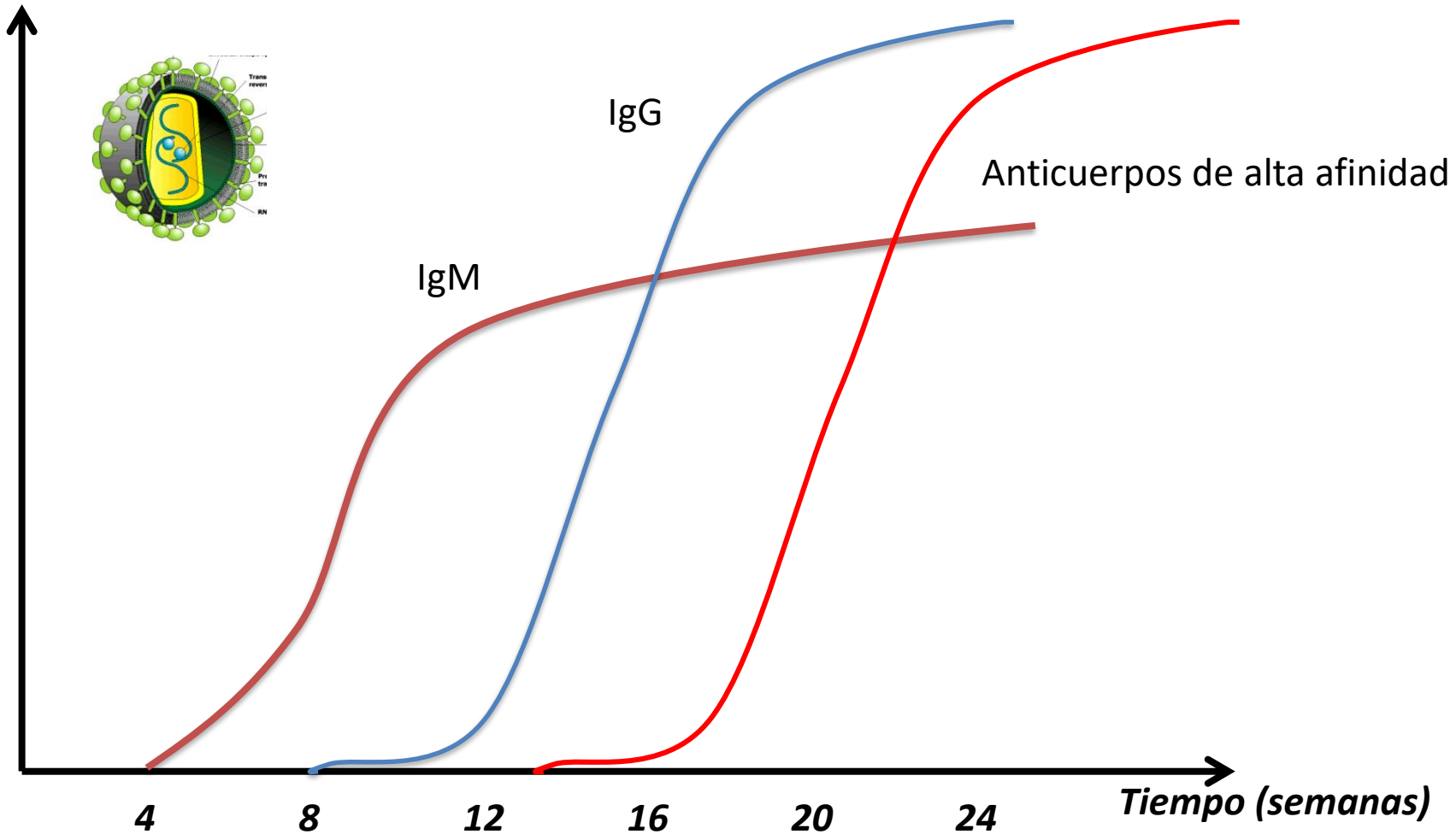
Cortesía de John Mascola

¿Por qué hemos fracasado hasta ahora?

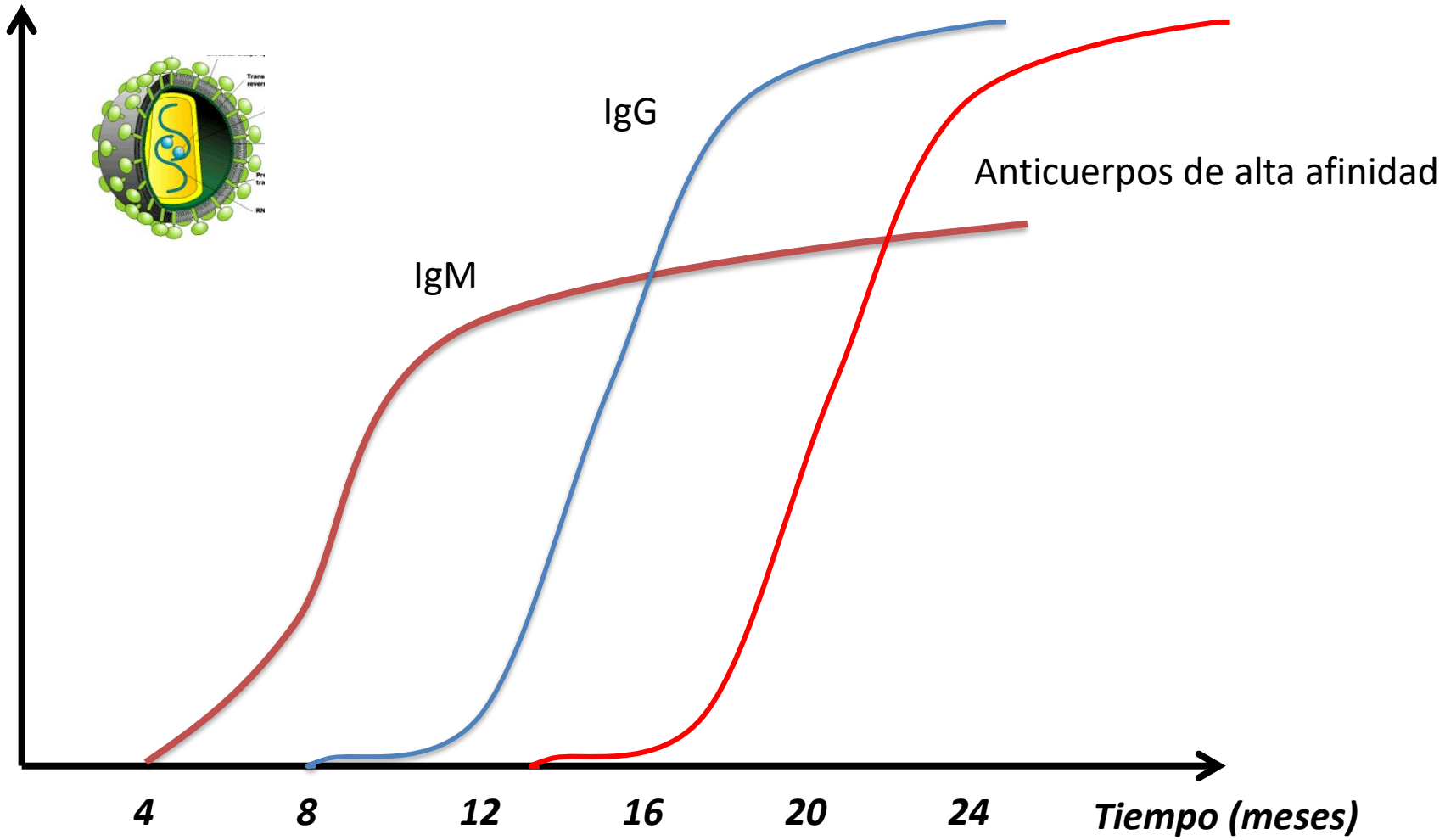
No generamos los anticuerpos apropiados



DINÁMICA DE GENERACIÓN DE ANTICUERPOS EN LAS INFECCIONES VÍRICAS



DINÁMICA DE GENERACIÓN DE ANTICUERPOS EN LA INFECCIÓN POR EL VIH



¿Alguna buena noticia?

1. Identificados Talones de Aquiles en la envuelta

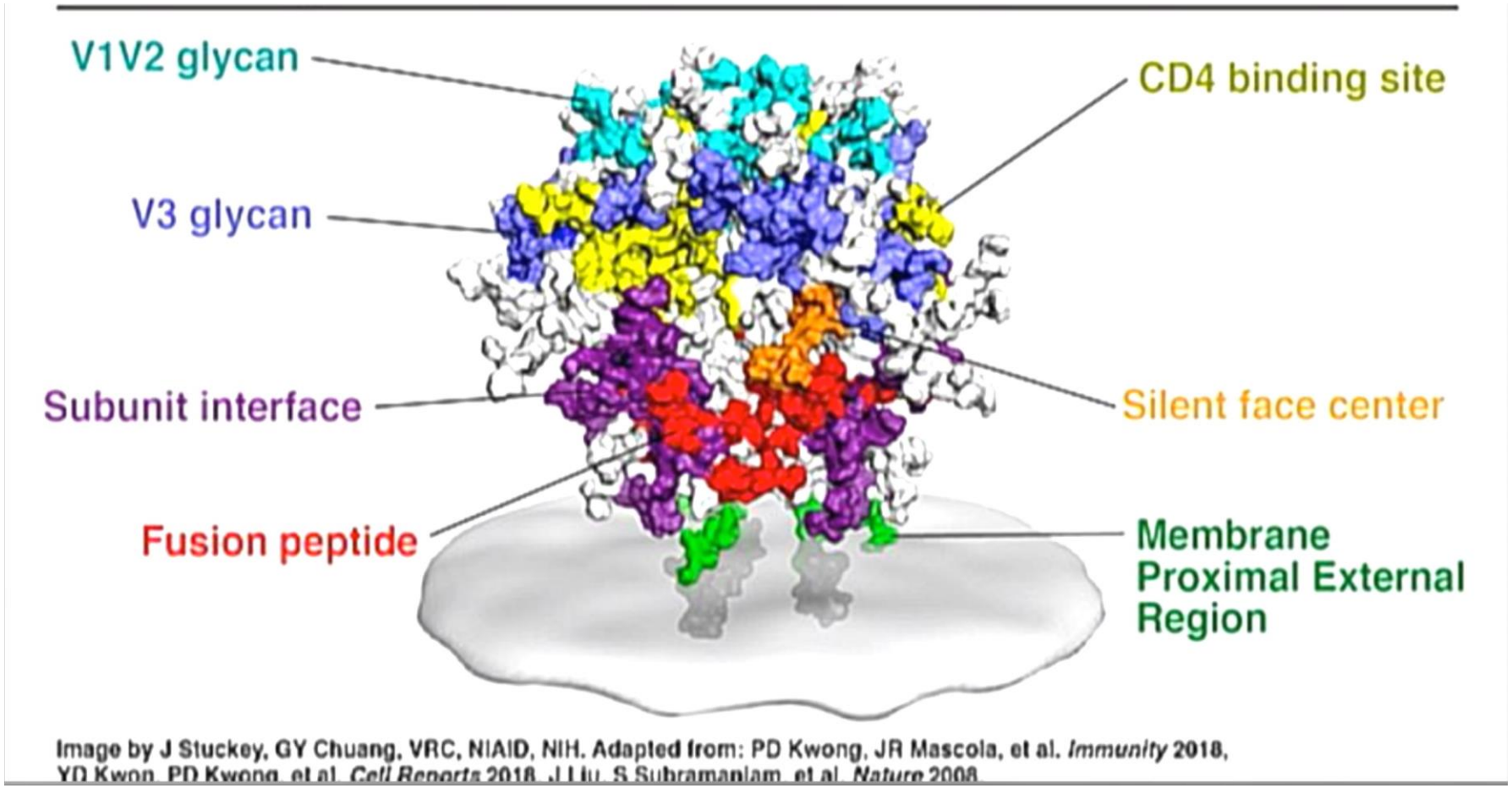
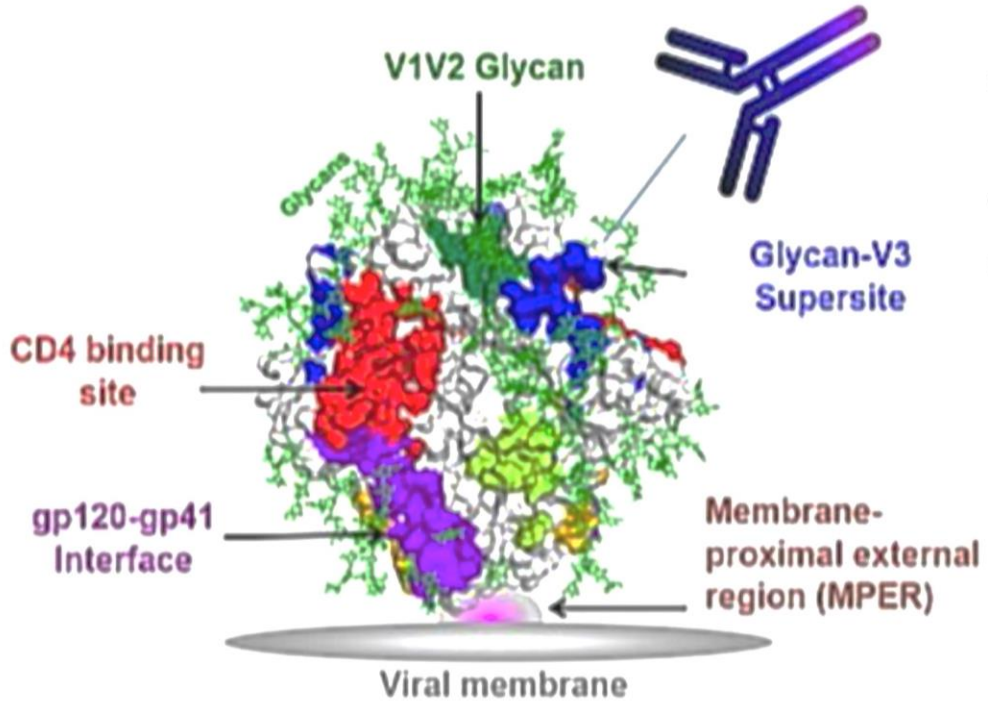


Image by J Stuckey, GY Chuang, VRC, NIAID, NIH. Adapted from: PD Kwong, JR Mascola, et al. *Immunity* 2018,
YD Kwon, PD Kwong, et al. *Cell Reports* 2018, J Liu, S Subramaniam, et al. *Nature* 2008

¿Alguna buena noticia?

2. Algunos pacientes producen Ac de amplio espectro (Neutralizadores de Elite)

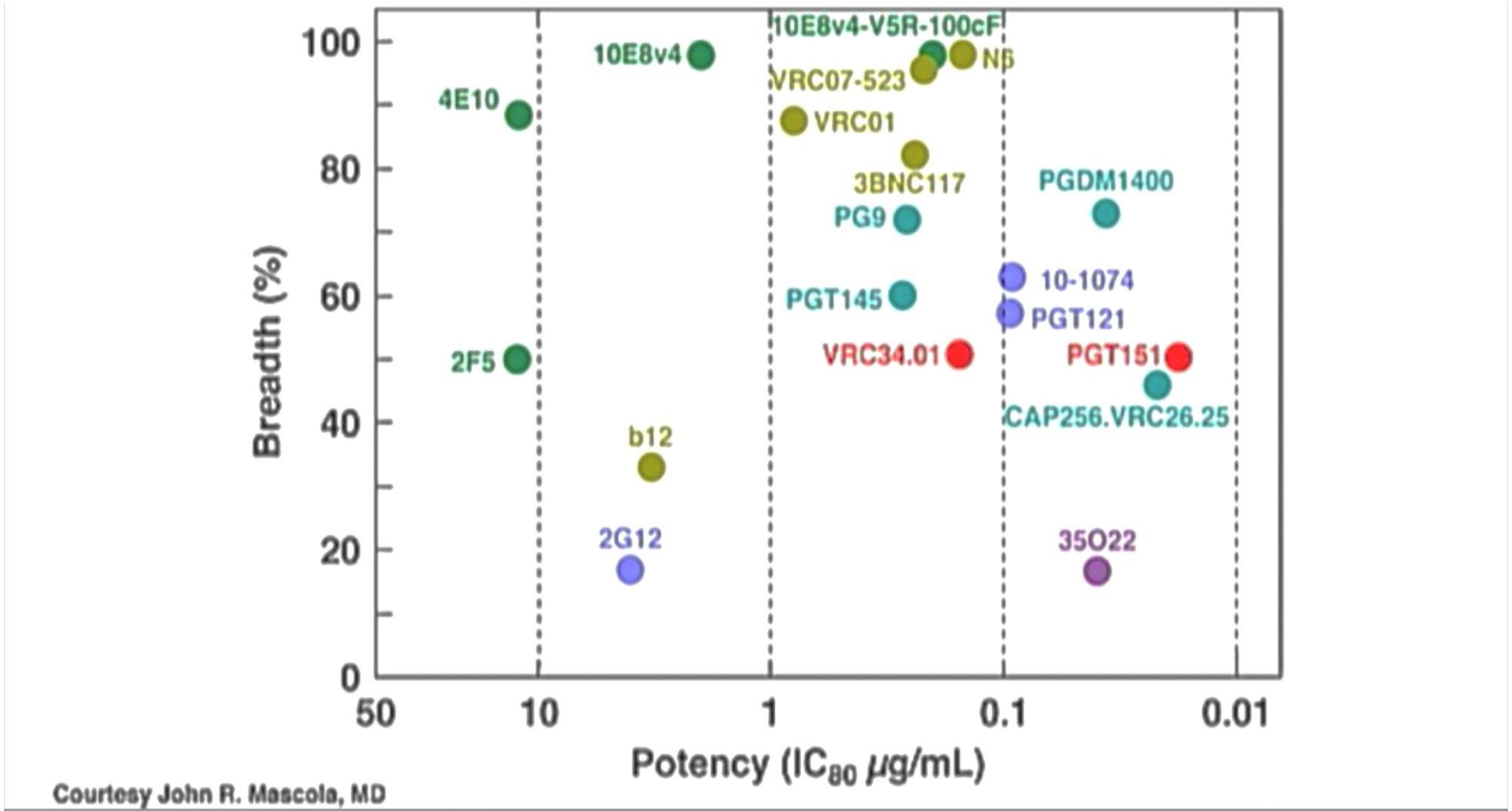


- Isolated from HIV-infected individuals
- Penetrate glycan shield
- Potently neutralize most strains of HIV-1

Image by Stewart-Jones, Doria-Rose, Stuckey
Adapted from Stewart-Jones et al Cell 2016 and Pancera et al Nature 2014

¿Alguna buena noticia?

3. Algunos Ac neutralizantes tienen amplio espectro y potencia

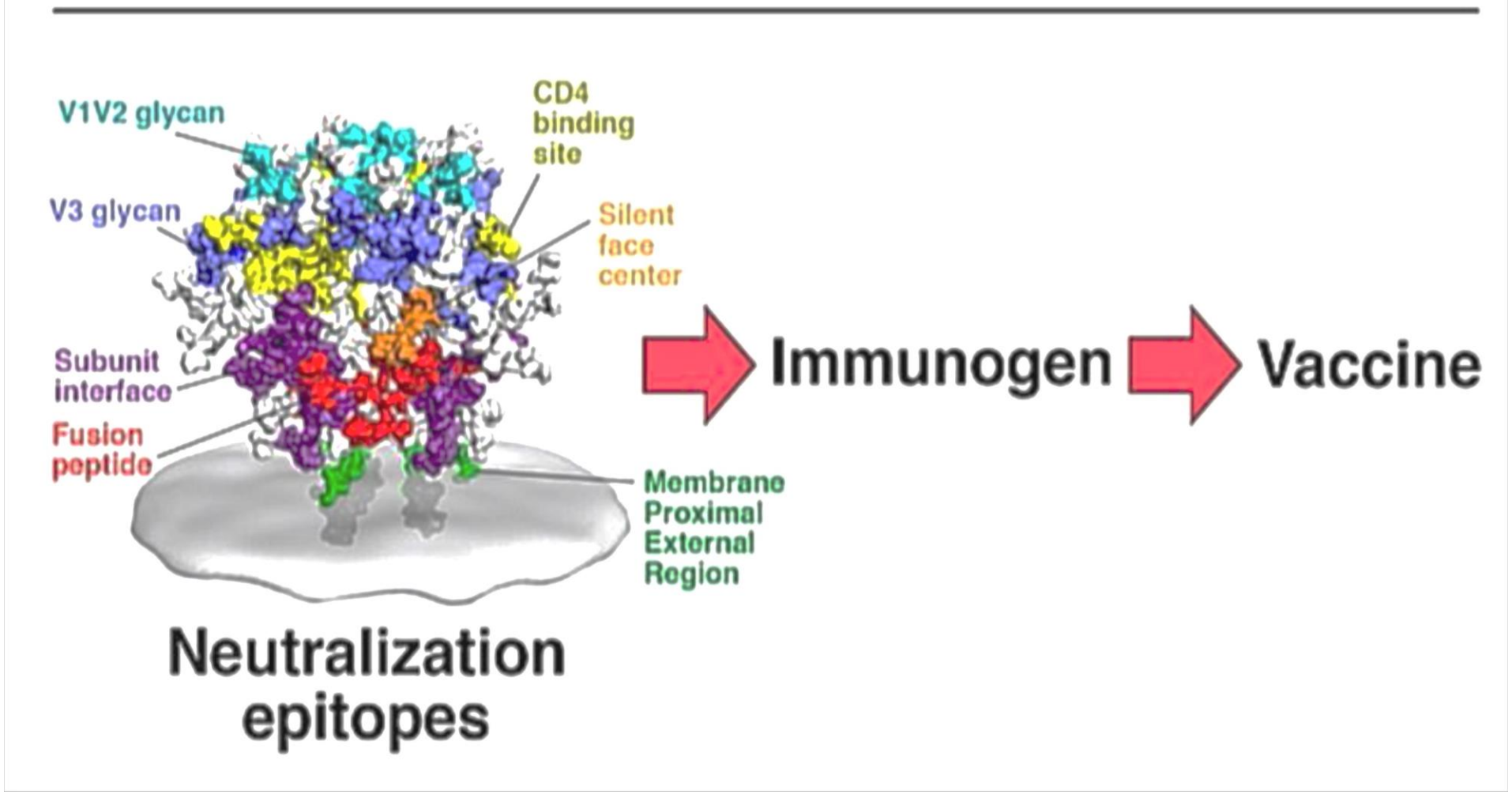


Courtesy John R. Mascola, MD

Una vacuna frente al VIH. Un gran desafío

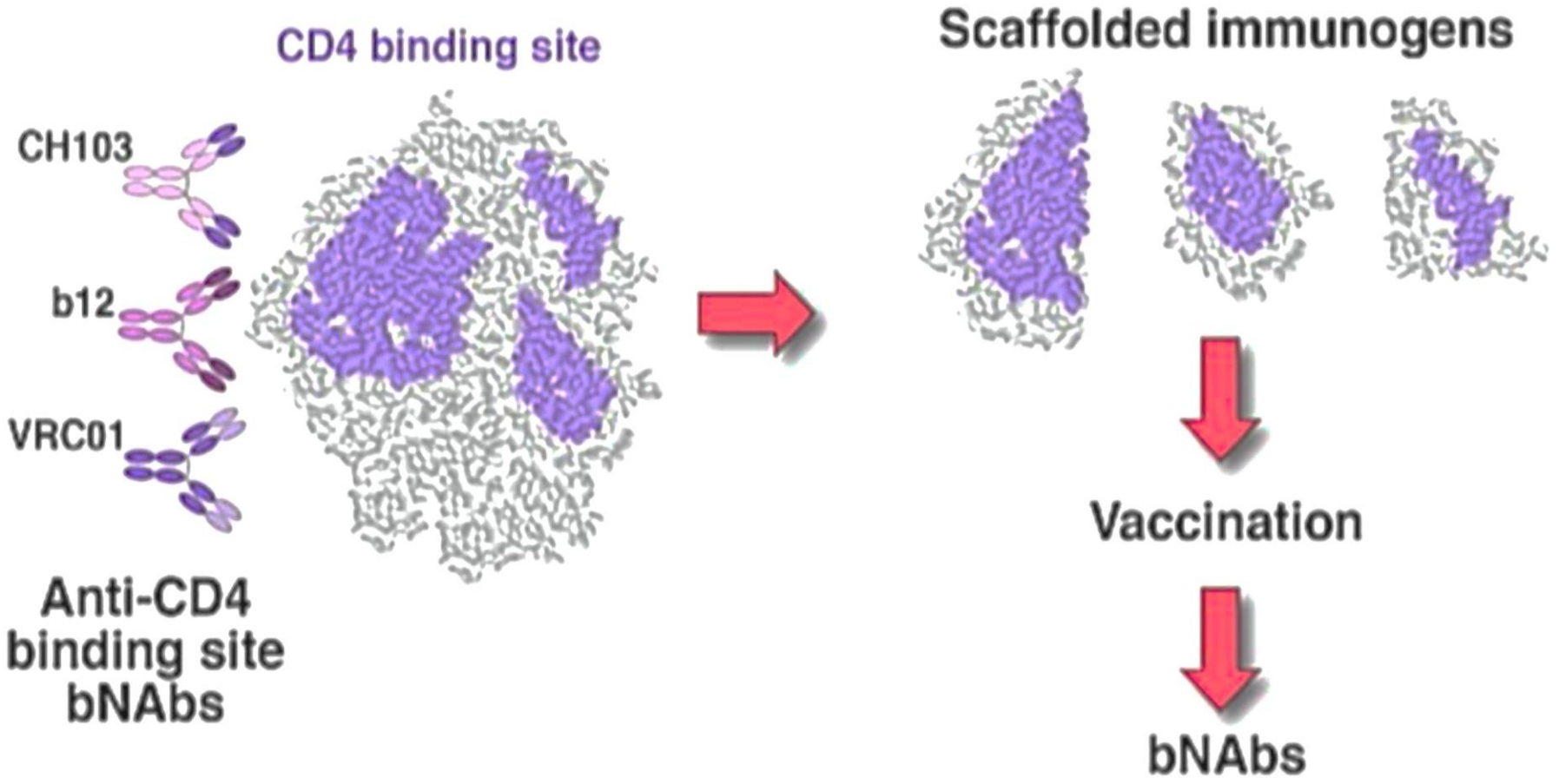
1. Diseñar inmunógenos que induzcan anticuerpos neutralizantes de amplio espectro
2. Los anticuerpos han de tener una estructura que permita alcanzar los dominios de neutralización en la envuelta: conformación cerrada y escudos glicano
3. Es necesario inducir/acelerar la maduración de esos anticuerpos

Gran desafío: Convertir los epítopos de neutralización en vacunas inductoras de Ac neutralizantes de amplio espectro



Fauci AS. HIV R4P 2018

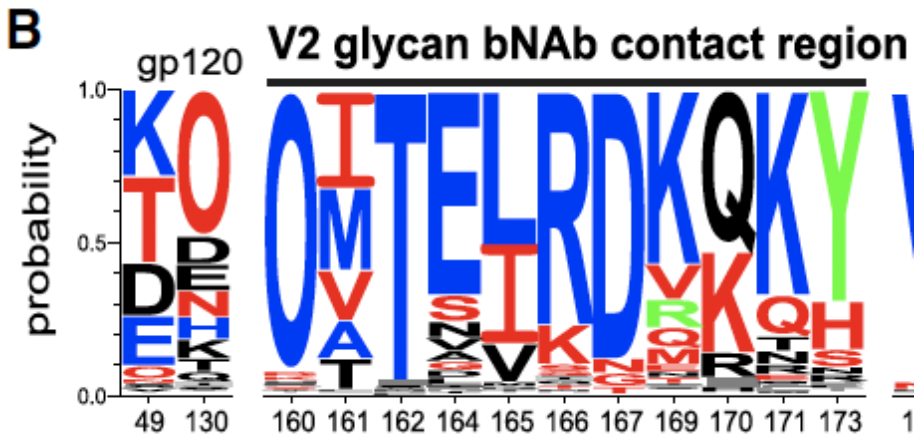
Nueva generación de vacunas preventivas basadas en diseño epitópico

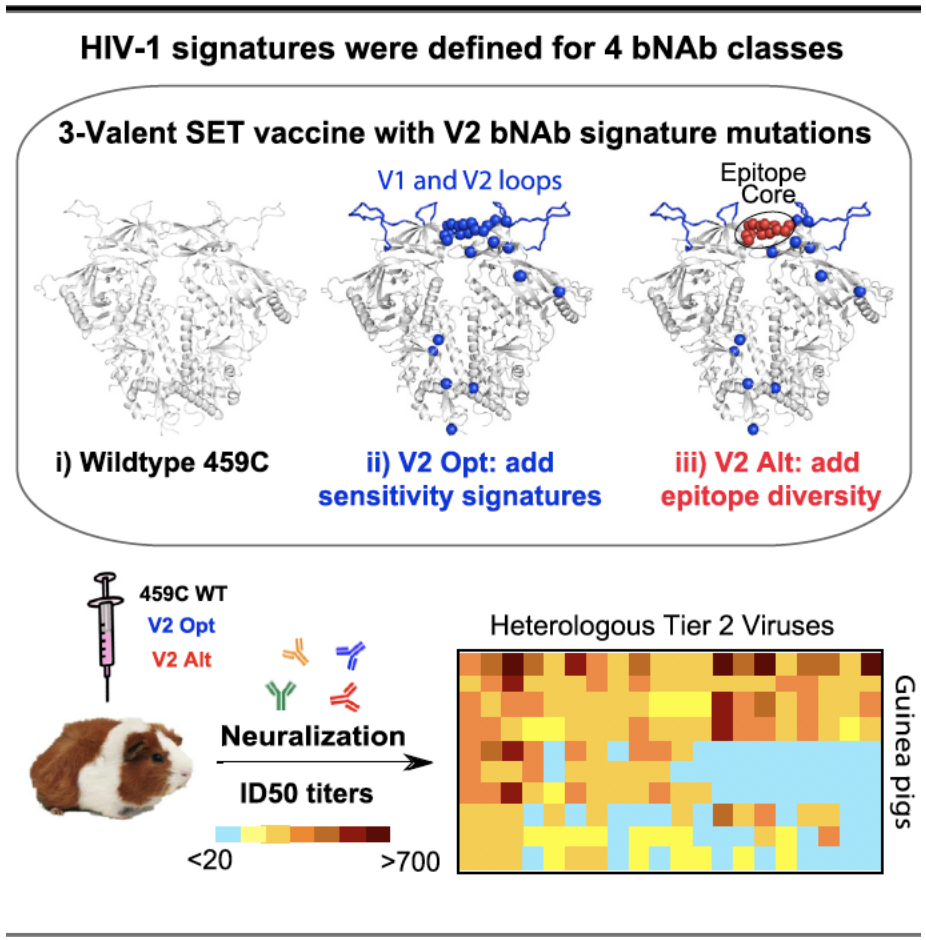


Courtesy: John R. Mascola, MD; PD Kwong and JR Mascola, *Immunity* 2018.

Nuevos abordajes en el desarrollo de vacunas

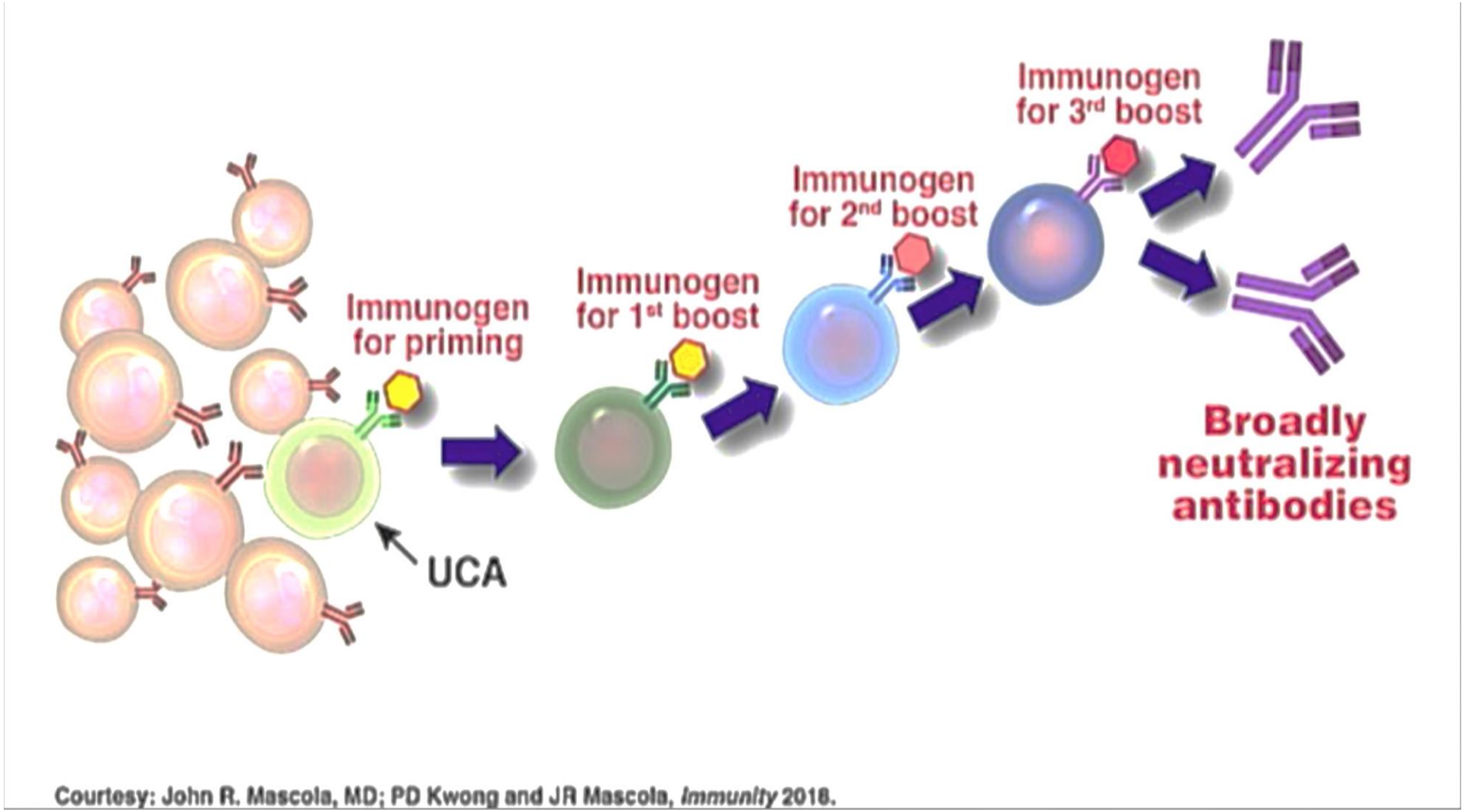
Generar envueltas de diseño utilizando las “firmas” de los anticuerpos neutralizantes de amplio espectro



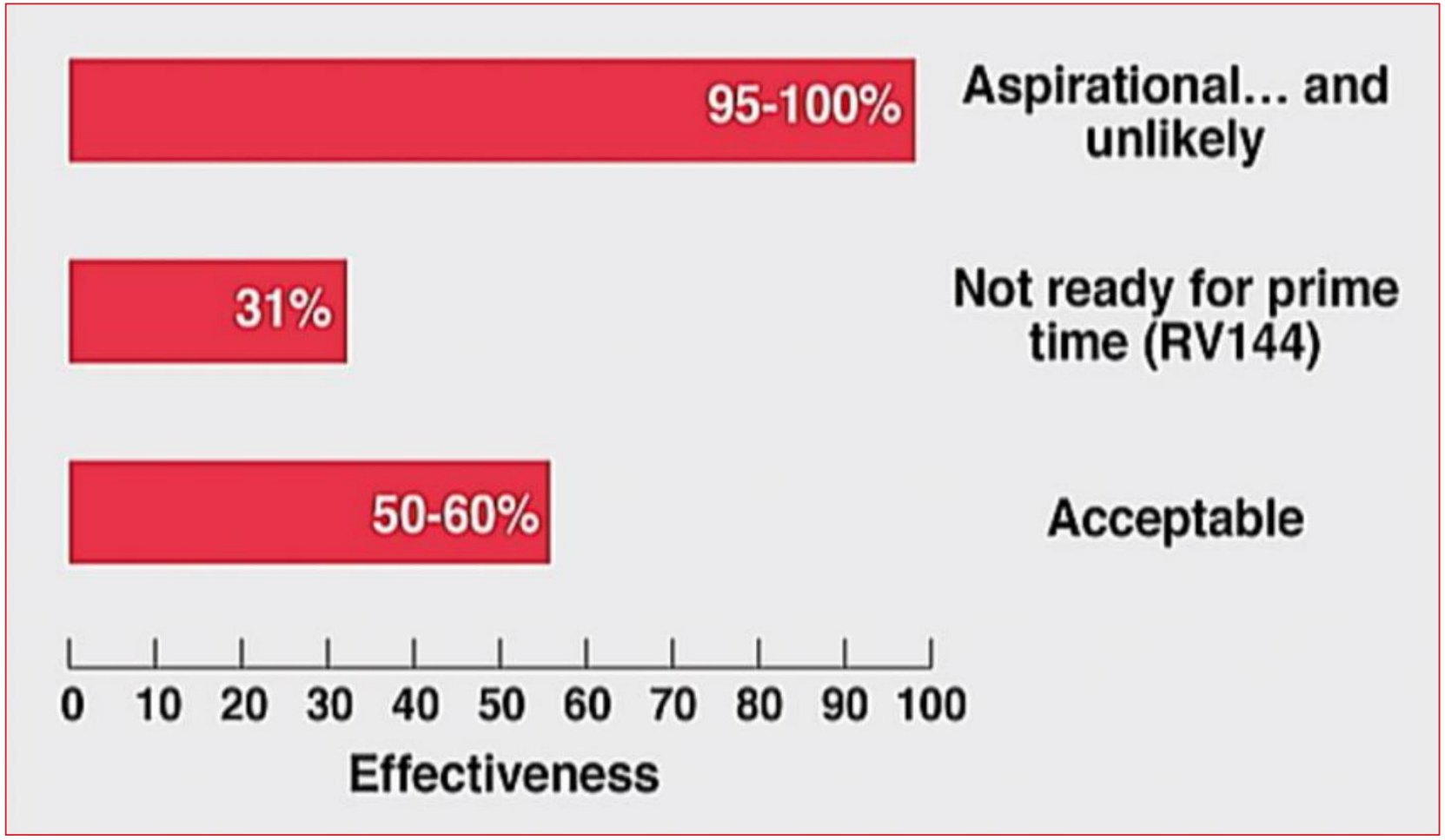


Bricault CA et al. Cell Host & Microbe 2019;25:59-72

Nueva generación de vacunas preventivas basadas en inmunógenos que induzcan un linaje B especifico



Nueva generación de vacunas preventivas ¿Cual es el objetivo realista?



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