COVID-19 que hemos aprendido de inmunología de este virus

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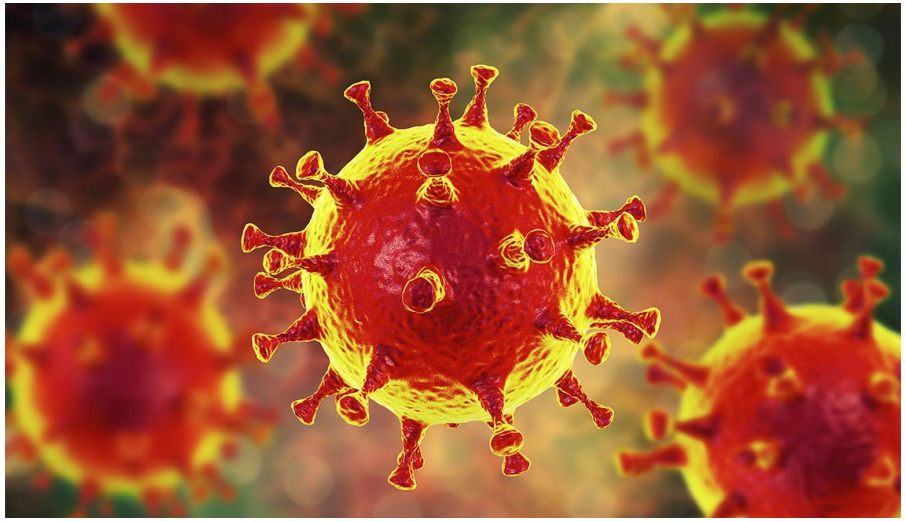
INTRODUCCIÓN



- Escenario: -Virus nuevo

  - Rapidez de la expansión geográfica

  - Elevada capacidad de contagiar

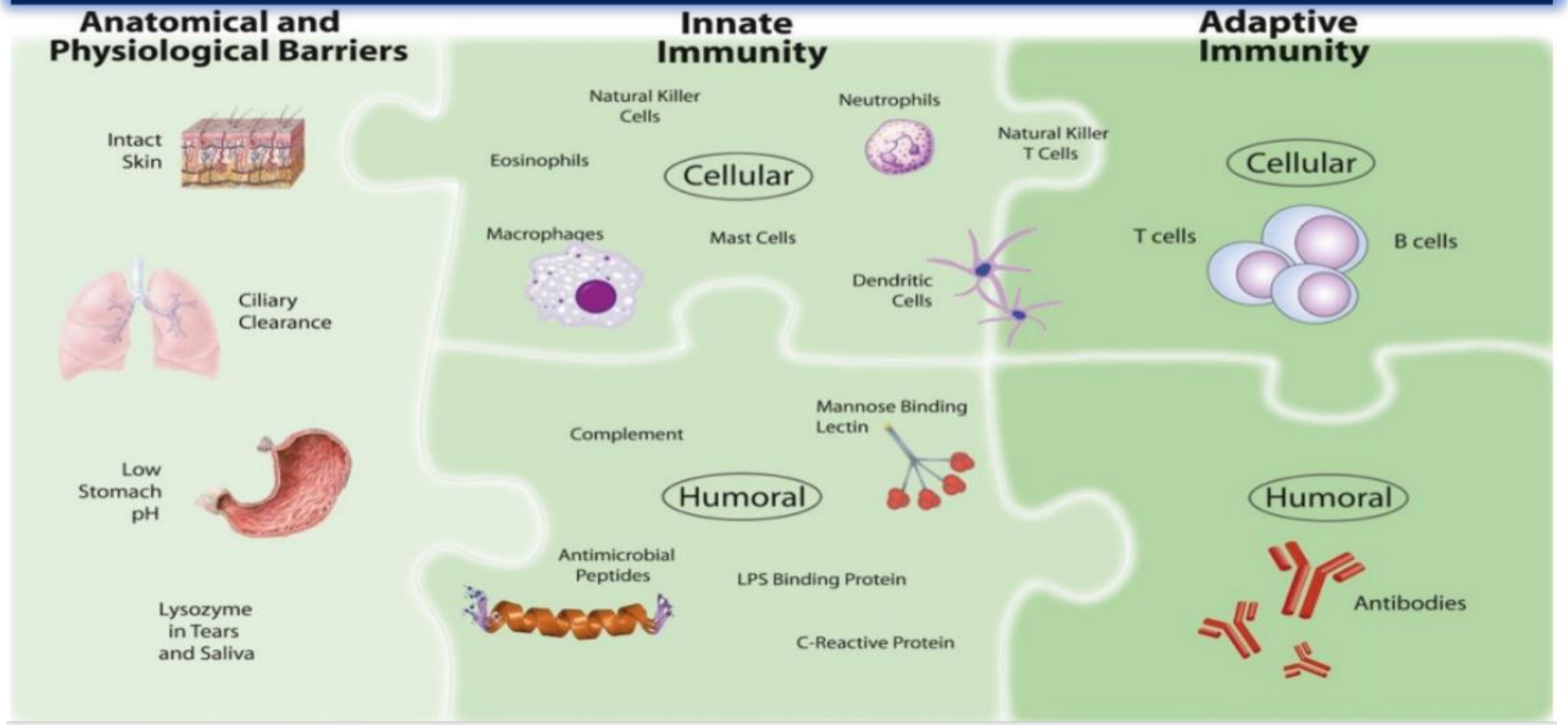
  -Mortalidad

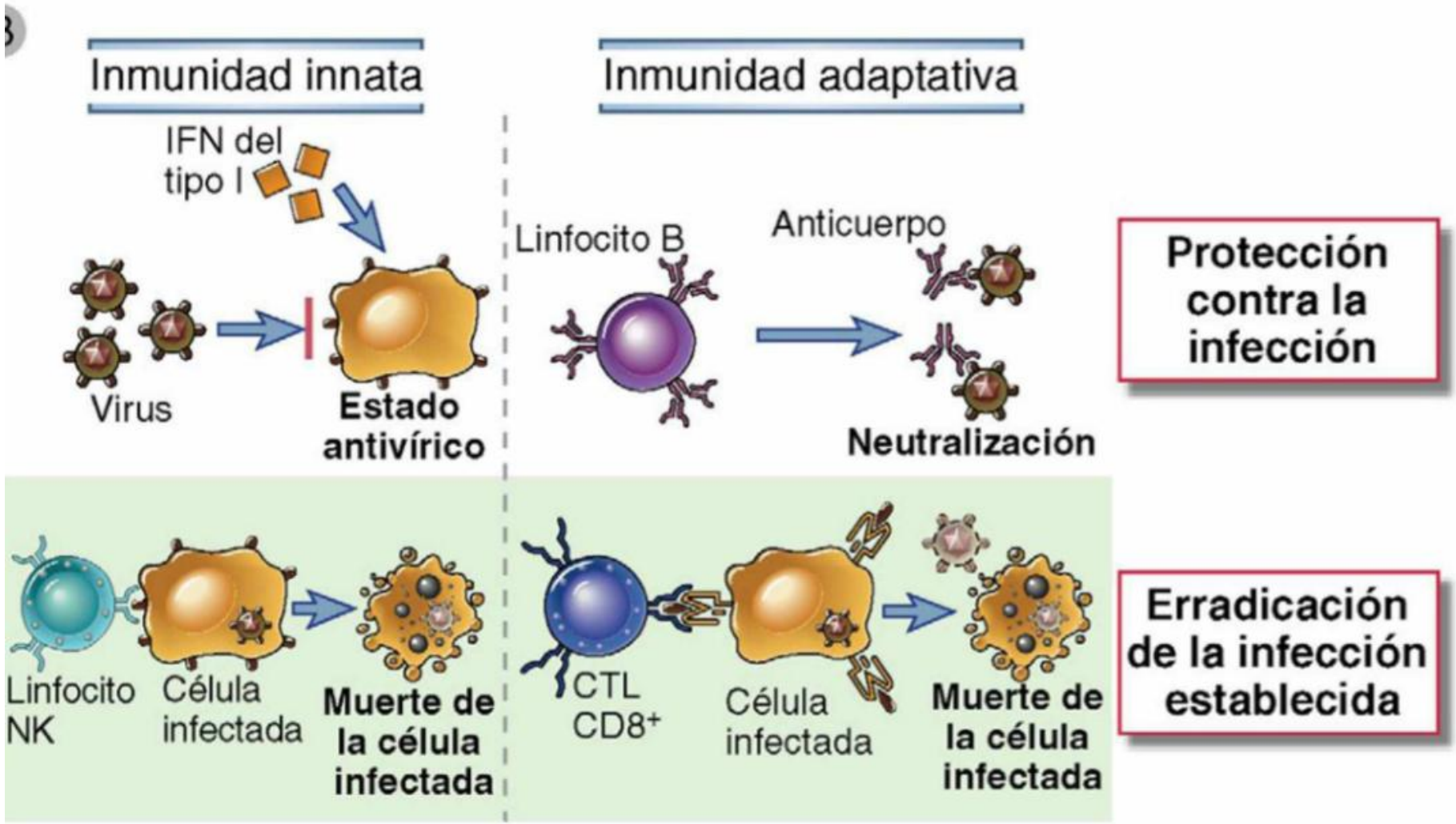
  -Sin tratamiento específico

  -Sin vacuna

- Un coronavirus altamente patogénico frente al que nadie tiene inmunidad…

Componentes del SI




Inmunidad innata
Inmunidad adaptativa
IFN del tipo I
Virus
Estado antivírico
Linfocito B
Anticuerpo
Neutralización
Protección contra la infección
Linfocito NK
Célula infectada
Muerte de la célula infectada
CTL CD8+
Célula infectada
Muerte de la célula infectada
Erradicación de la infección establecida

Cómo se genera la repuesta inmunitaria frente a un virus

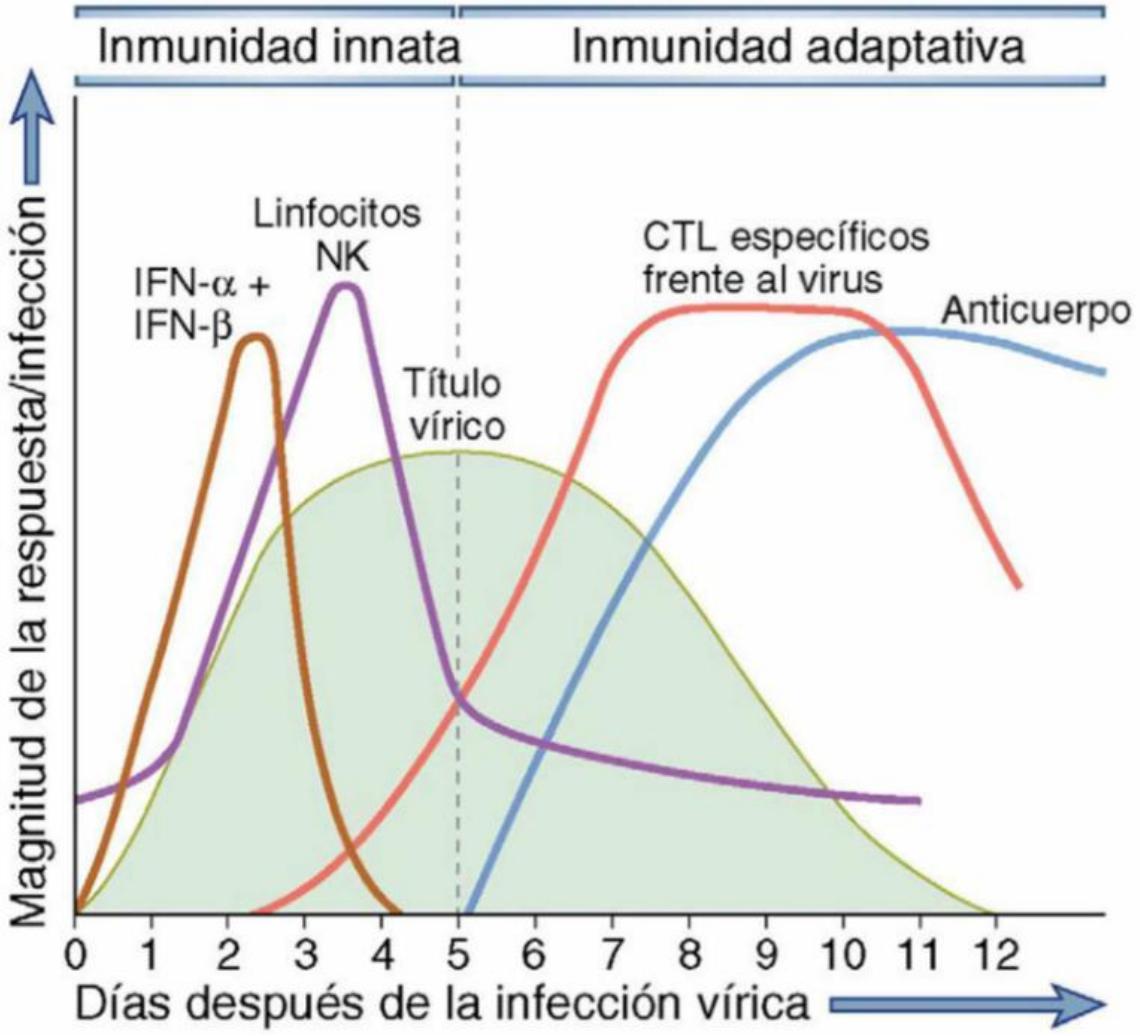
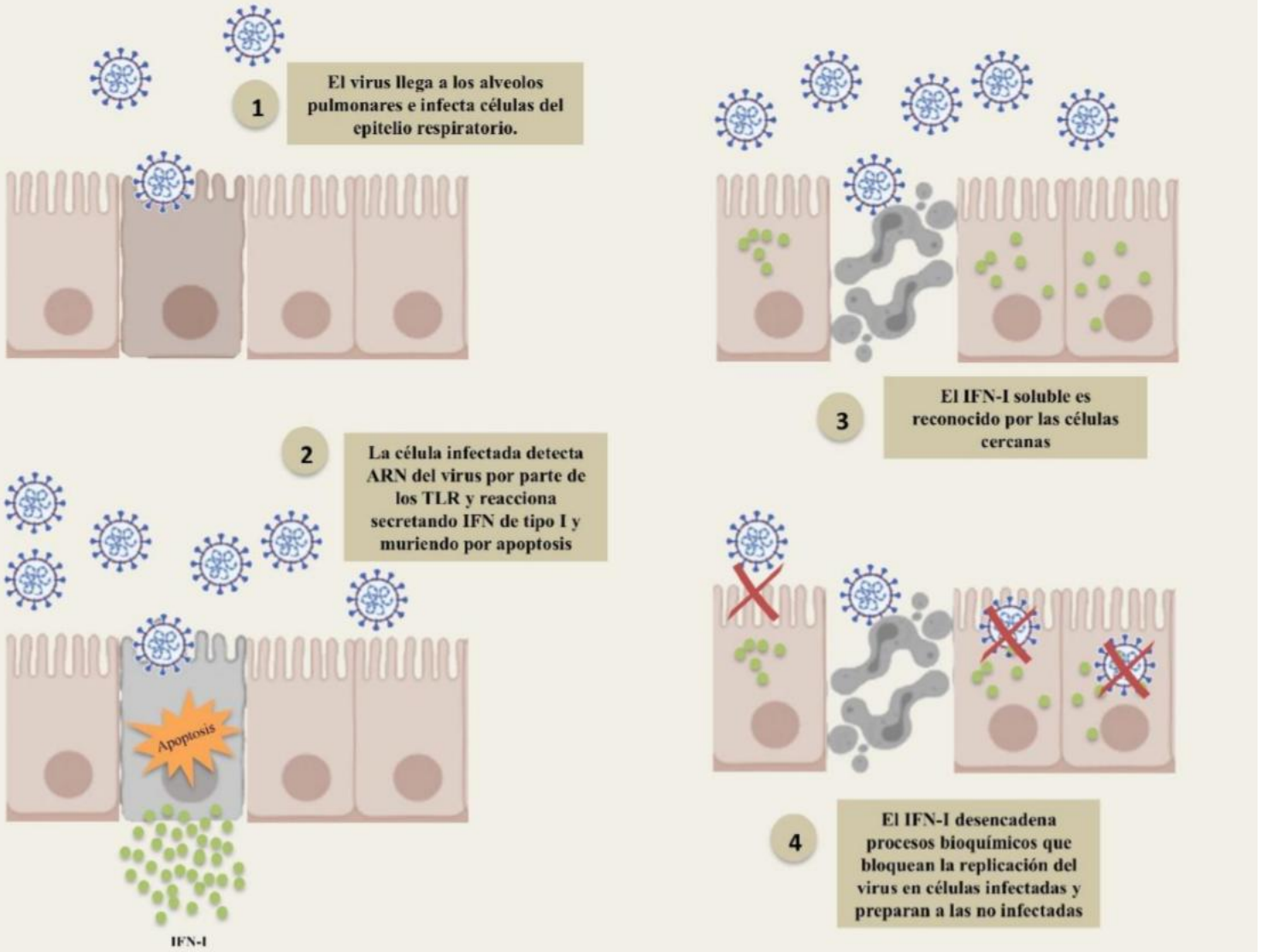
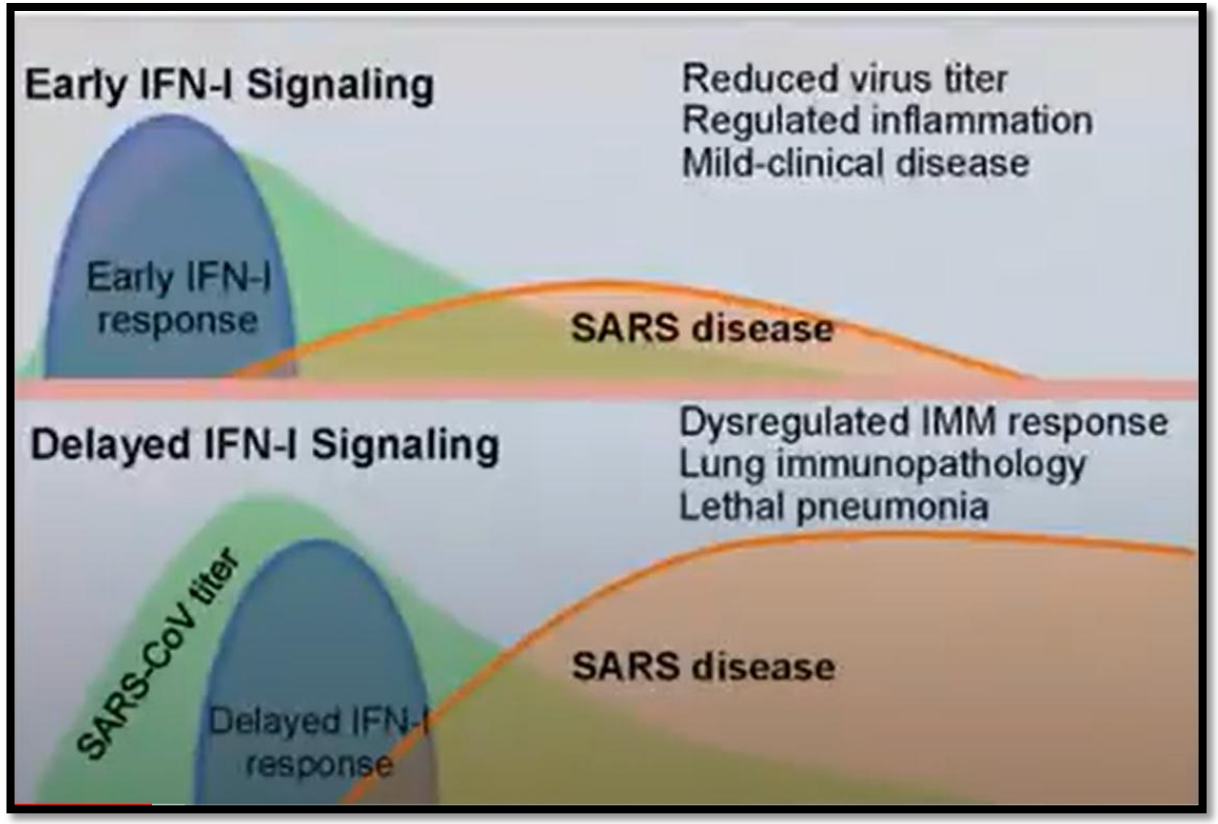


FIGURA 2. EL SISTEMA DEL INTERFERÓN

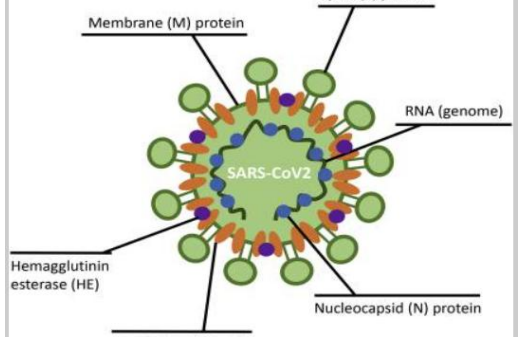


Producción de interferones y citoquinas ayudan a controlar la infección y posteriormente entra en acción la Inmune adaptativa

Respuesta de Interferones: Cuanto antes mejor



Inmuno-evasión



- Los coronavirus, incluido el SARS-CoV2, son "maestros" de la evasión inmune

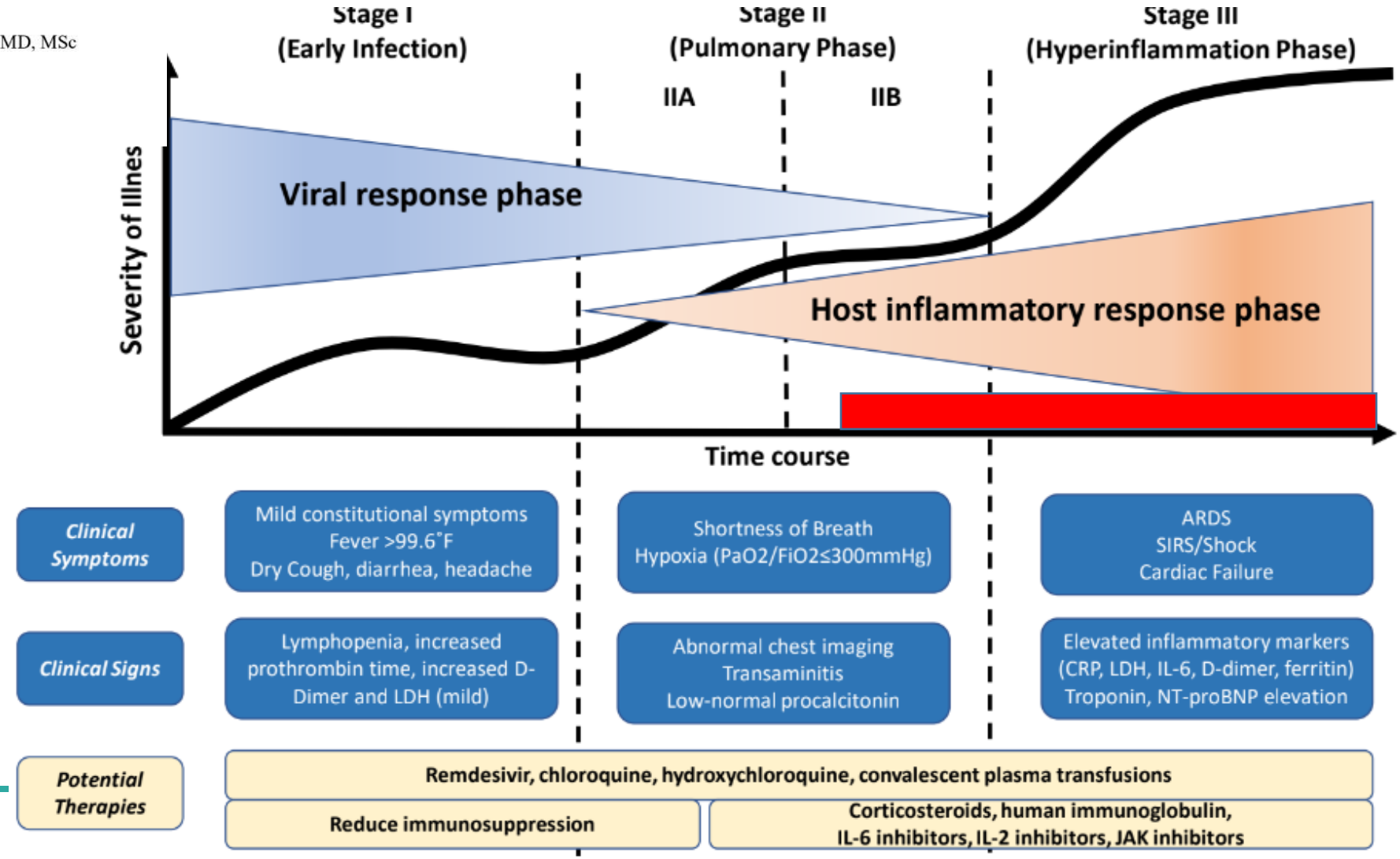
- Lo que contribuye a la replicación incontrolada del virus, destrucción celular masiva y a respuestas proinflamatorias de citoquinas

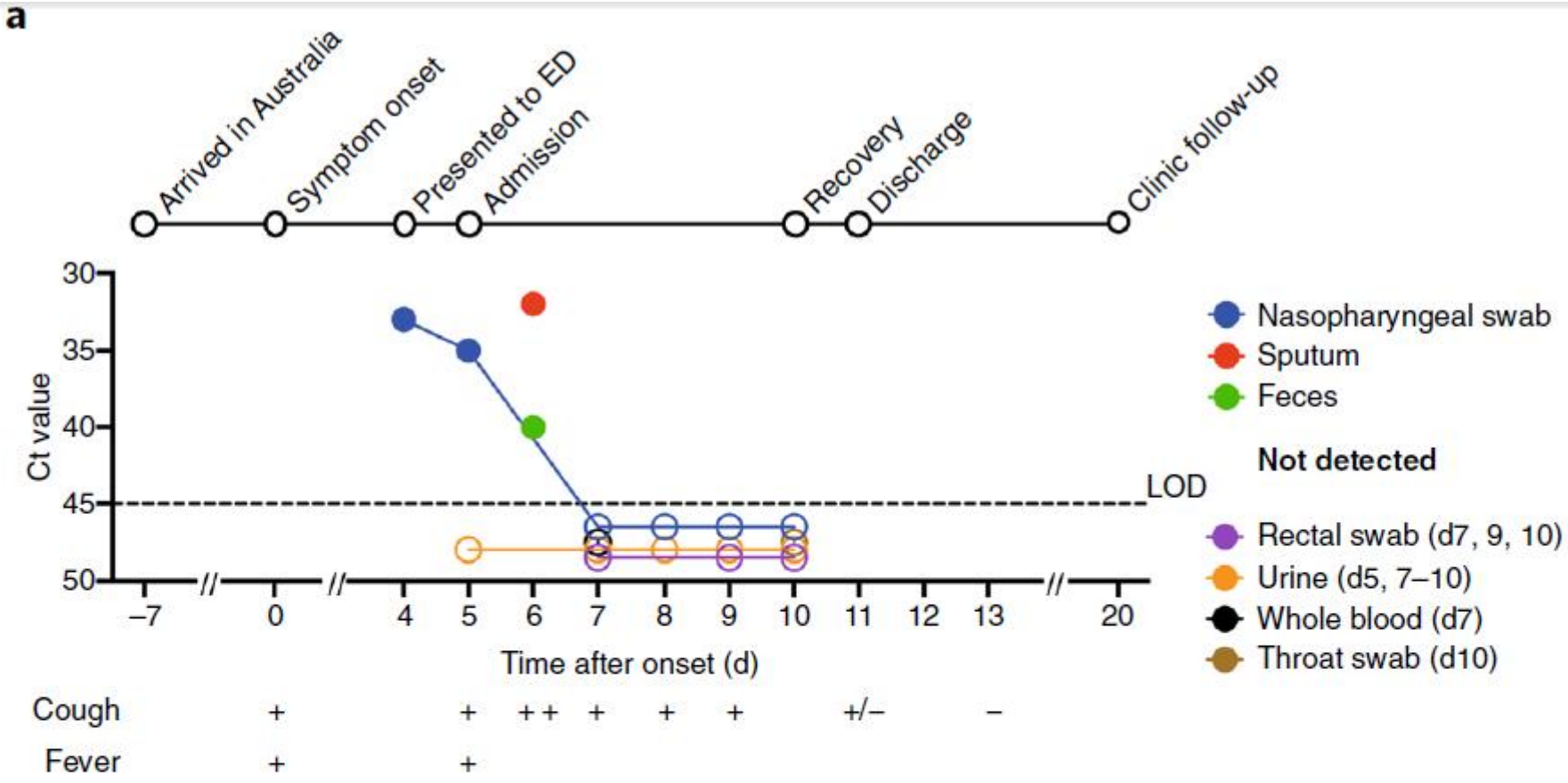
JOURNAL OF HEART AND LUNG TRANSPLANTATION

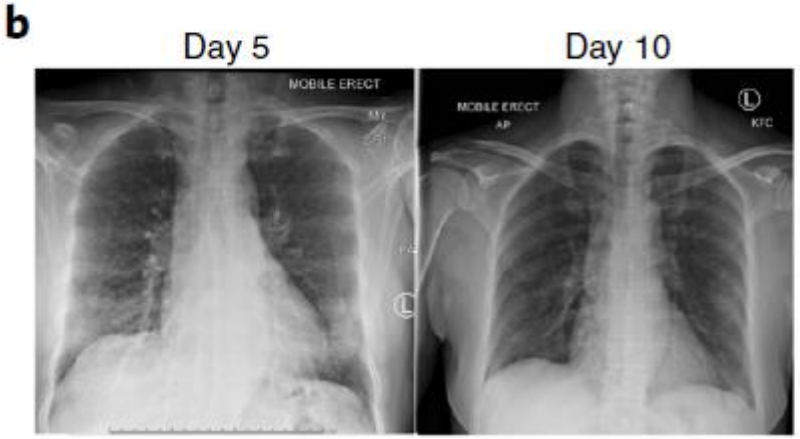
COVID-19 Illness in Native and Immunosuppressed States:

A Clinical-Therapeutic Staging Proposal

Hasan K. Siddiqi, MD, MSCR, and Mandeep R. Mehra, MD, MSc



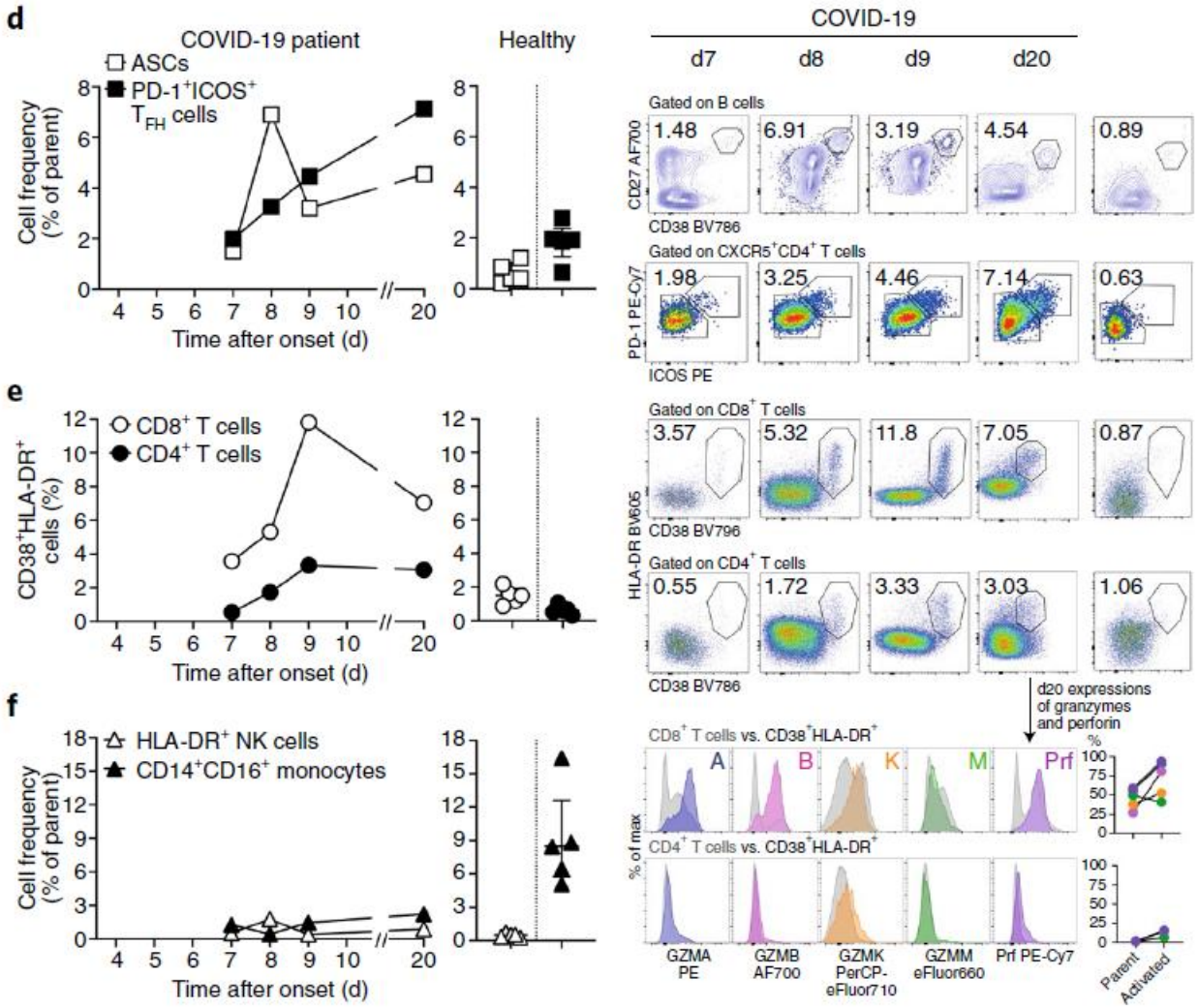




c

	Negative patient	COVID-19 patient d7	d8	d9	d20
Anti-IgG	0	1+	2+	3+	3+
Anti-IgM	0	+/–	+/–	2+	3+

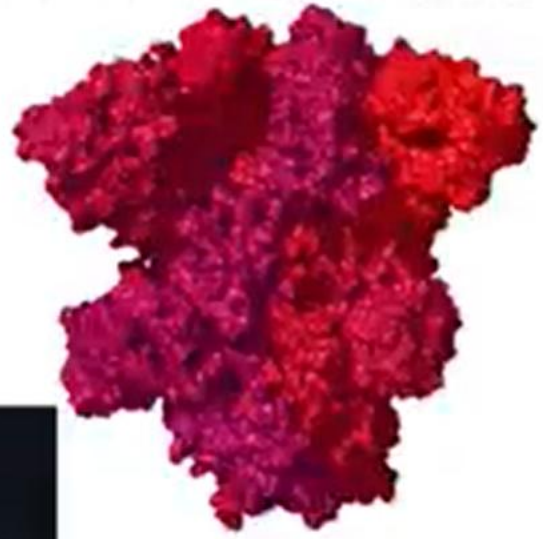
Thevarajan I
Nature Medicine VOL 26
April 2020. 450–455



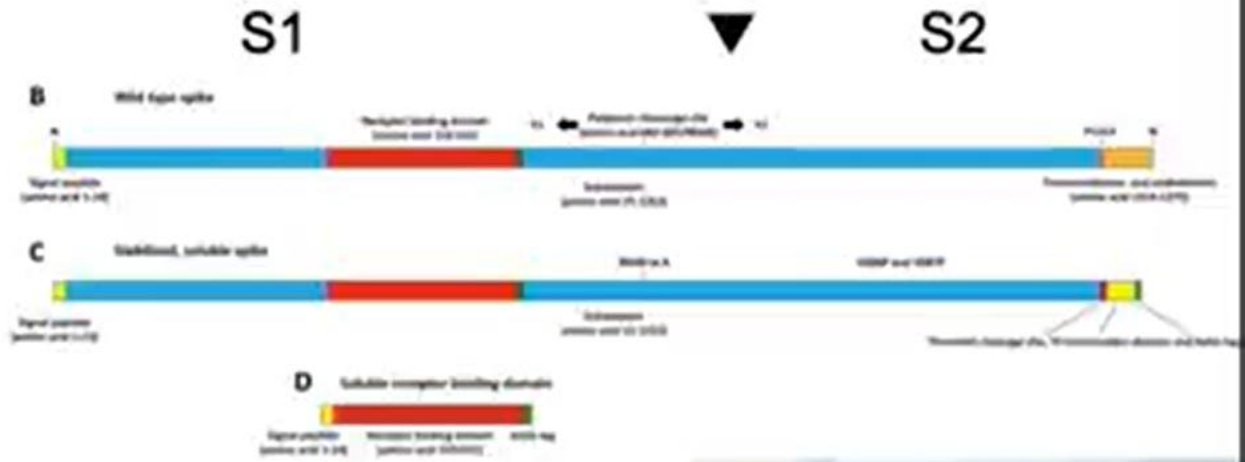
Thevarajan I

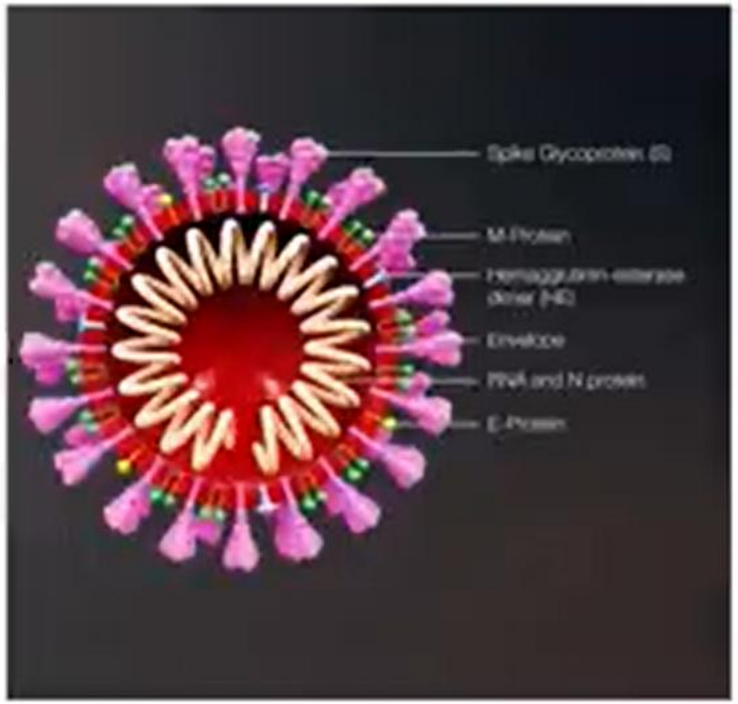
Nature Medicine | VOL 26 | April 2020 | 450–455 |

TARGETS OF IMMUNE RESPONSES



Spike (S). Binds to ACE-2 and other receptors
Requires activation by furin and other proteases





Nucleoprotein (N). Packages viral RNA

Cómo se generan los AcS

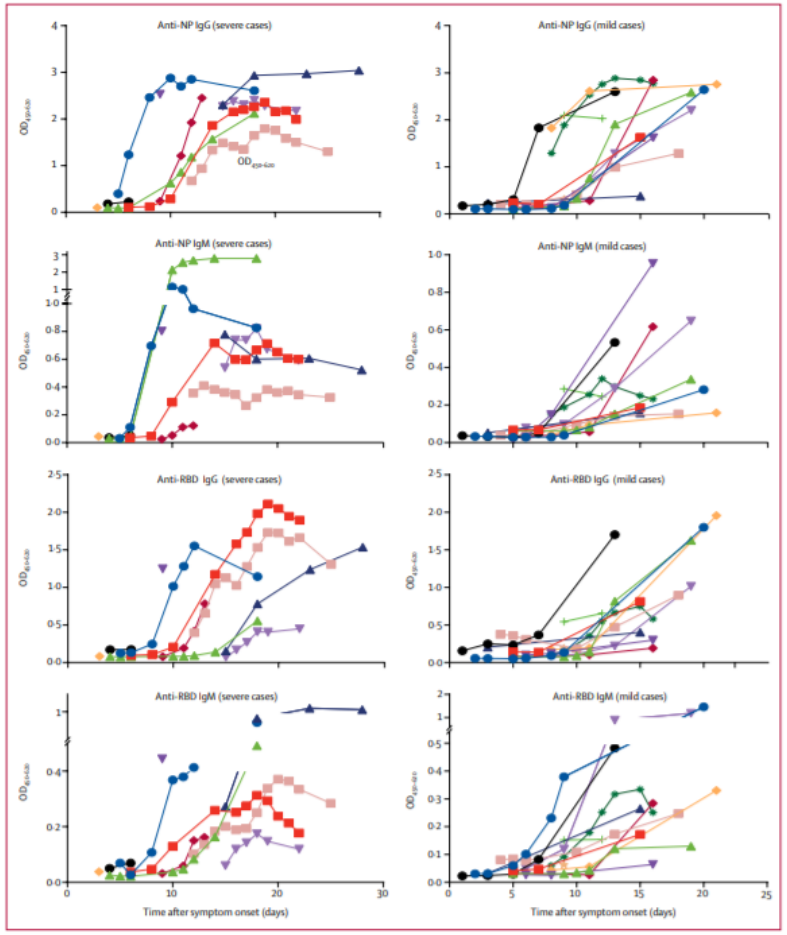


Figure 4: **Temporal profiles of serum IgM and IgG against NP and spike protein RBD, as ascertained by EIA**
Each line represents an individual patient. NP=nucleoprotein. RBD=receptor-binding domain. $OD_{450-620}$=optical density at 450–620 nm.

Temporal profiles of viral load in posterior oropharyngeal saliva samples and serum antibody responses during infection by SARS-CoV-2: an observational cohort study

Kelvin Kai-Wang To, Owen Tak-Yin Tsang*, Wai-Shing Leung, Anthony Raymond Tam, Tak-Chiu Wu, David Christopher Lung, Cyril Chik-Yan Yip, Jian-Piao Cai, Jacky Man-Chun Chan, Thomas Shiu-Hong Chik, Daphne Pui-Ling Lau, Chris Yau-Chung Choi, Lin-Lei Chen, Wan-Mui Chan, Kwok-Hung Chan, Jonathan Daniel Ip, Anthony Chin-Ki Ng, Rosana Wing-Shan Poon, Cui-Ting Luo, Vincent Chi-Chung Cheng, Jasper Fuk-Woo Chan, Ivan Fan-Ngai Hung, Zhiwei Chen, Honglin Chen, Kwok-Yung Yuen*

Lancet Infect Dis 2020; 20: 565–74

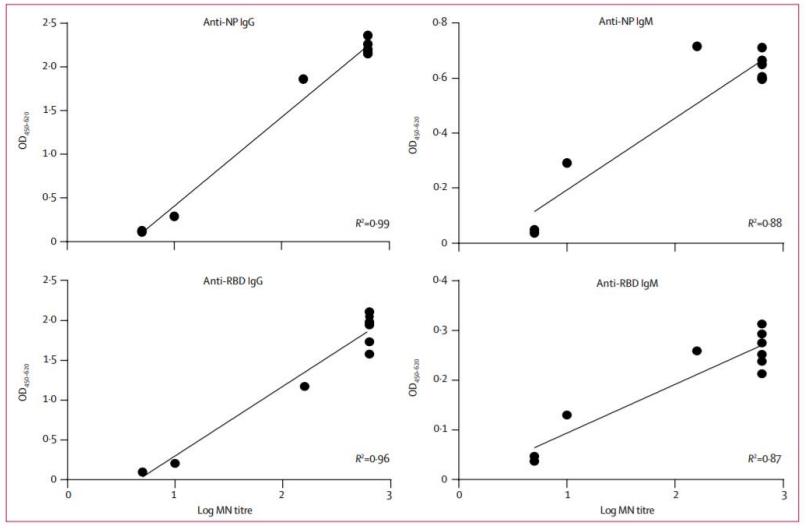
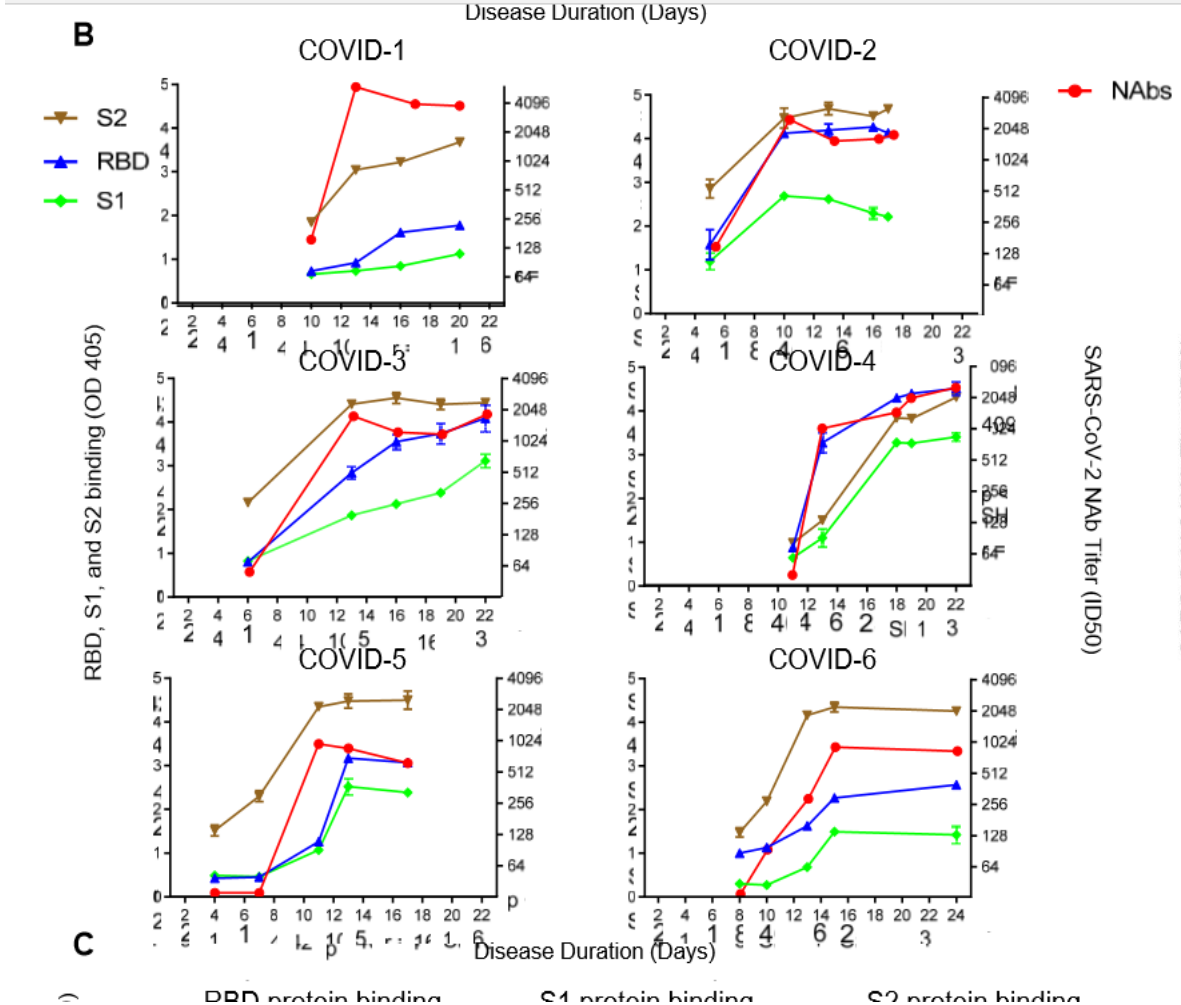


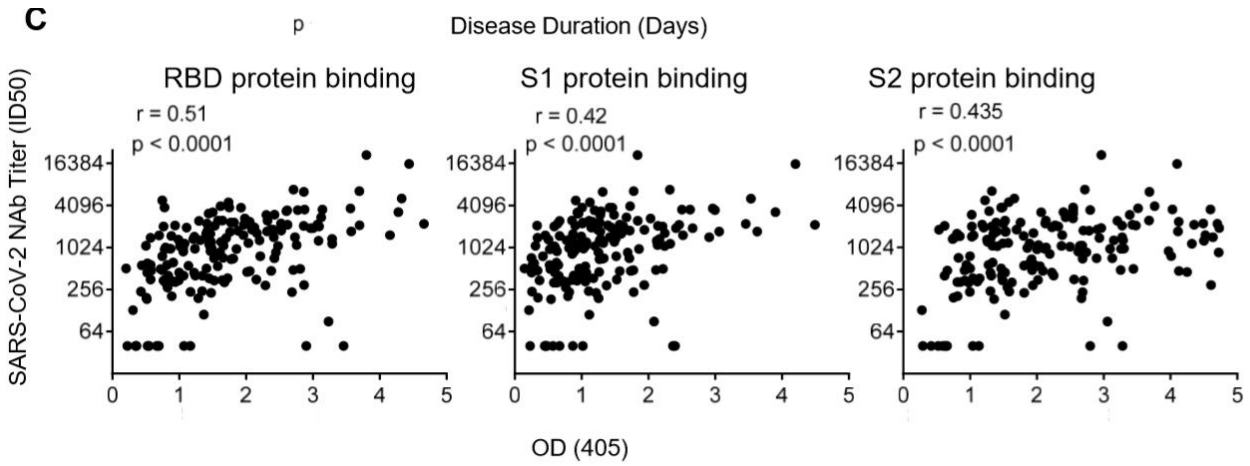
Figure 5: **Correlation between MN antibody titres and anti-NP or anti-RBD IgG or IgM**
$OD_{450-620}$=optical density at 450–620 nm. MN=microneutralisation. NP=nucleoprotein. RBD=receptor-binding domain.

Anticuerpos neutralizantes



Neutralizing antibody responses to SARS-CoV-2 in a COVID-19 recovered patient cohort and their implications

Fan Wu*, Aojie Wang, Mei Liu, Qimin Wang, Jun Chen, Shuai Xia, Yun Ling, Yuling Zhang, Jingna Xun, Lu Lu, Shibo Jiang, Hongzhou Lu, Yumei Wen, Jinghe Huang*



¿Reactividad cruzada?

- Antígenos inmunodominantes: la glicoproteina S y la NP son las que genera la respuesta se ACS.

- Se debe descartar reactividades cruzadas sobre todo a la hora de poder establecer diagnóstico Sars-cov2

- Sabemos que el dominio S1 es específico de la cepa, mientras que la proteína N muestra reactividad cruzada a través de cepas.

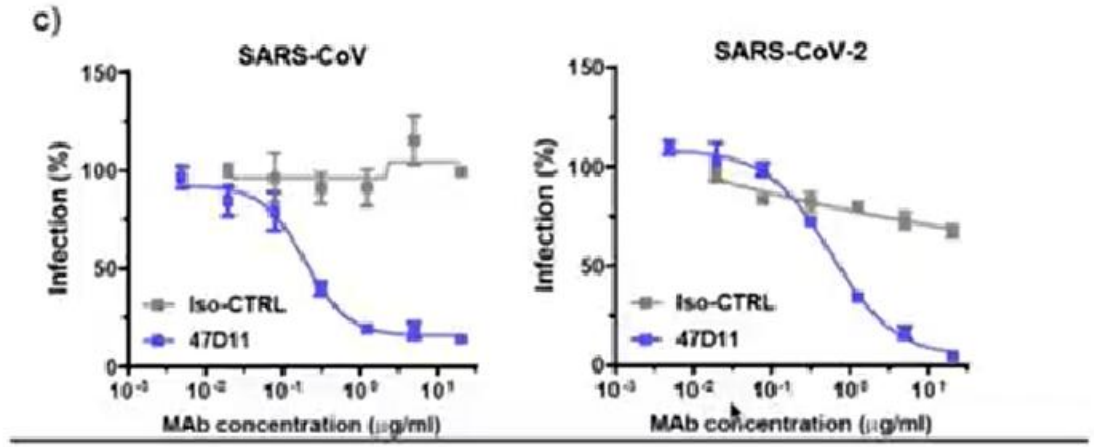
¿Reactividad cruzada?

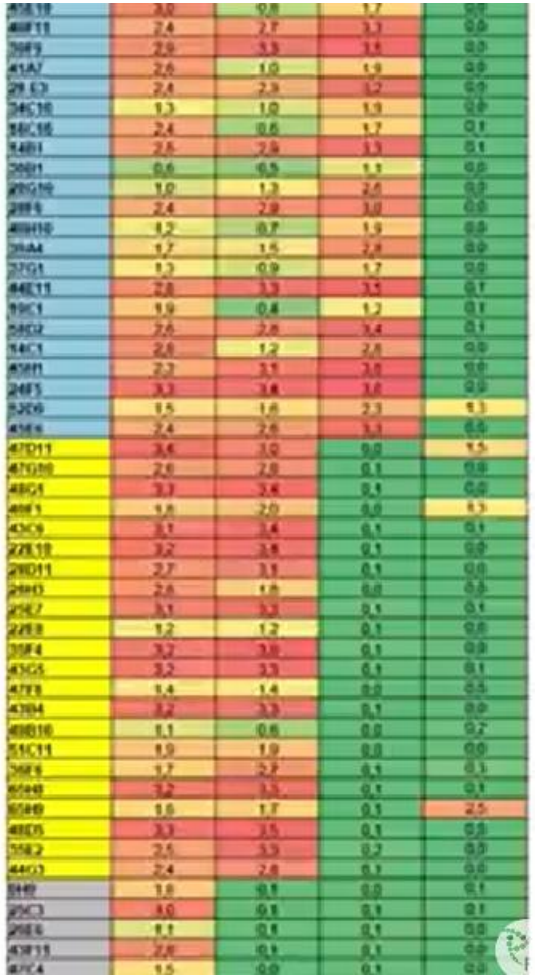
CROSS REACTIVITY

A human monoclonal antibody blocking SARS-CoV-2 infection

Running head: A cross-neutralizing human antibody targeting SARS-CoV and SARS-CoV-2

Chunyan Wang[1,*], Wentao Li[1,*], Dubravka Drabek[2,3,*], Nisreen M.A. Okba[4], Rien van Haperen[2,3], Albert D.M.E. Osterhaus[4], Frank J.M. van Kuppeveld[1], Bart L. Haagmans[4], Frank Grosveld[2,3] and Berend-Jan Bosch[1,5]





Analysis of Serologic Cross-Reactivity Between Common Human Coronaviruses and SARS-CoV-2 Using Coronavirus Antigen Microarray

- 5 sueros de personas *naive* para SARS-CoV2 es realiza técnica de Microarrays
- Se ha construido un microarray de antígenos de coronavirus con antígenos de coronavirus epidémicos que incluyen SARS-CoV-2 y coronavirus humanos comunes, además de otros virus respiratorios comunes.
- Muestra un alto nivel de IgG reactivas a coronavirus humanos comunes
- Baja reactividad de IgG a SARS-CoV2

¿Cuánto duran los Acs ?

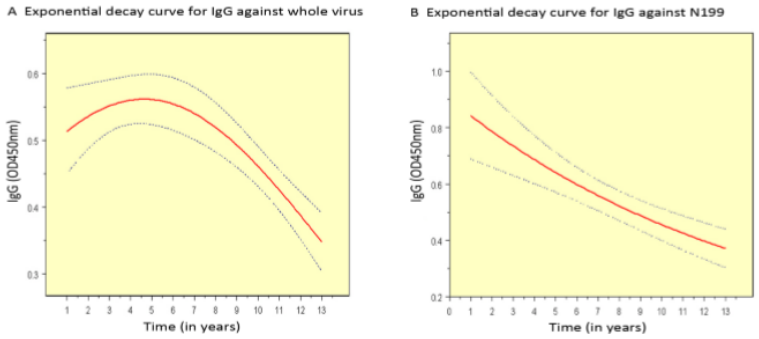
360
361

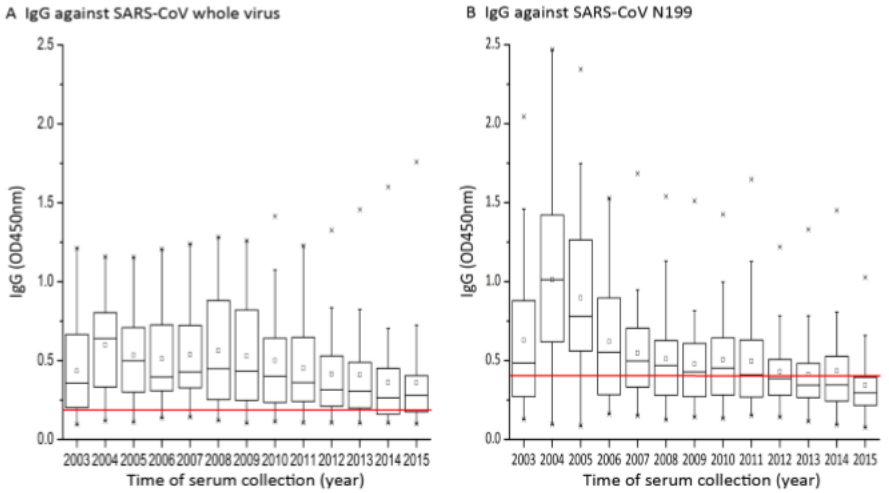
Long-Term Persistence of IgG Antibodies in SARS-CoV Infected Healthcare Workers

Xiaoqin Guo, Zhongmin Guo, Chaohui Duan, Zeliang chen, Guoling Wang, Yi Lu, Mengfeng Li, Jiahai Lu

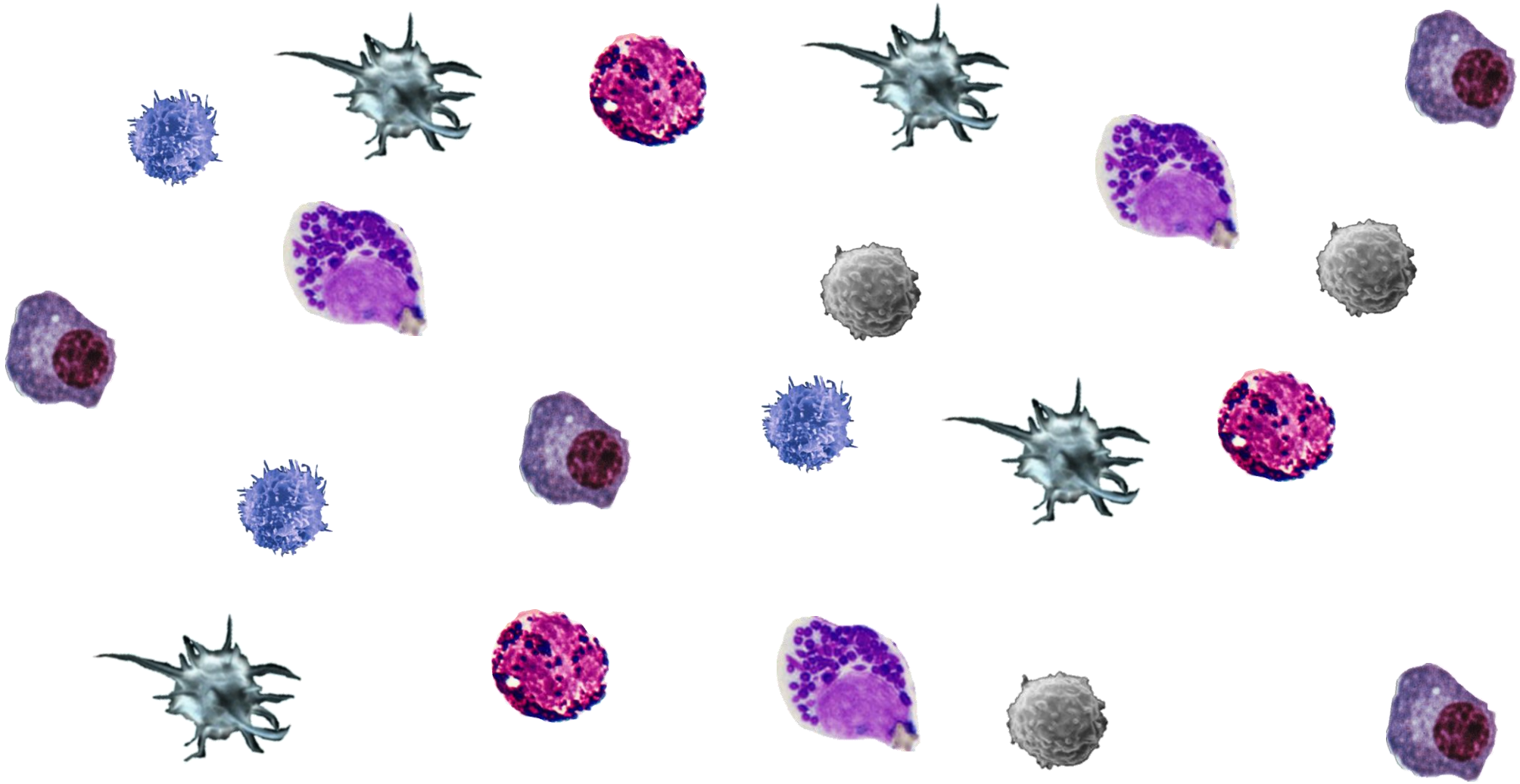
doi: https://doi.org/10.1101/2020.02.12.20021386

This article is a preprint and has not been peer-reviewed [what does this mean?]. It reports new medical research that has yet to be evaluated and so should *not* be used to guide clinical practice.





Y la respuesta celular?



Cell

CellPress

Article

Targets of T Cell Responses to SARS-CoV-2 Coronavirus in Humans with COVID-19 Disease and Unexposed Individuals

Alba Grifoni,[1] Daniela Weiskopf,[1] Sydney I. Ramirez,[1,2] Jose Mateus,[1] Jennifer M. Dan,[1,2] Carolyn Rydyznski Moderbacher,[1] Stephen A. Rawlings,[2] Aaron Sutherland,[1] Lakshmanane Premkumar,[3] Ramesh S. Jadi,[3] Daniel Marrama,[1] Aravinda M. de Silva,[3] April Frazier,[1] Aaron F. Carlin,[2] Jason A. Greenbaum,[1] Bjoern Peters,[1,2] Florian Krammer,[4] Davey M. Smith,[2] Shane Crotty,[1,2,5,*] and Alessandro Sette[1,2,5,6,*]

[1]Center for Infectious Disease and Vaccine Research, La Jolla Institute for Immunology, La Jolla, CA 92037, USA

[2]Department of Medicine, Division of Infectious Diseases and Global Public Health, University of California, San Diego, La Jolla, CA 92037, USA

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[5]These authors contributed equally

[6]Lead Contact

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https://doi.org/10.1016/j.cell.2020.05.015

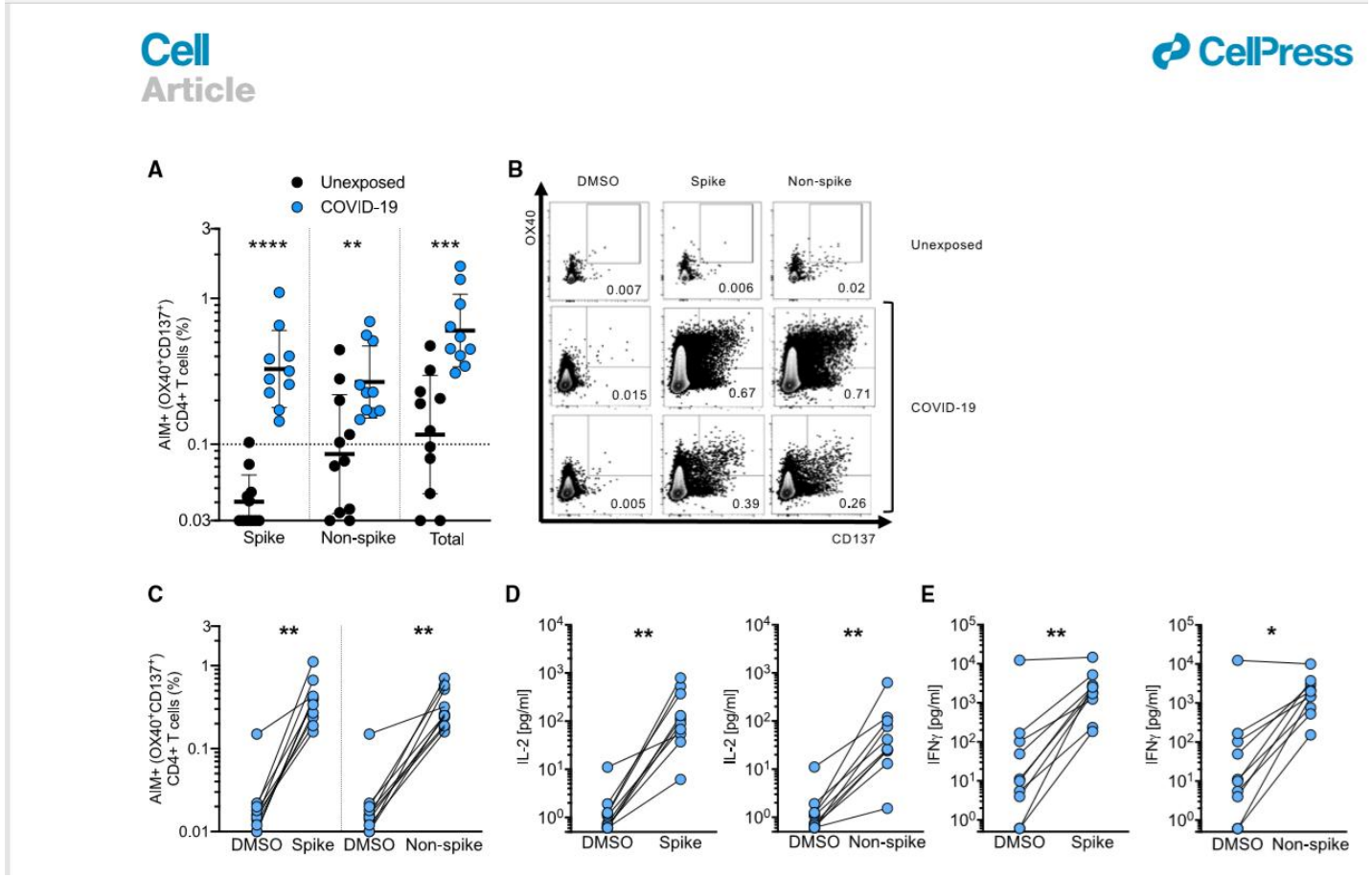
SUMMARY

Understanding adaptive immunity to SARS-CoV-2 is important for vaccine development, interpreting coronavirus disease 2019 (COVID-19) pathogenesis, and calibration of pandemic control measures. Using HLA class I and II predicted peptide "megapools," circulating SARS-CoV-2-specific $CD8^+$ and $CD4^+$ T cells were identified in ~70% and 100% of COVID-19 convalescent patients, respectively. $CD4^+$ T cell responses to spike, the main target of most vaccine efforts, were robust and correlated with the magnitude of the anti-SARS-CoV-2 IgG and IgA titers. The M, spike, and N proteins each accounted for 11%–27% of the total $CD4^+$ response, with additional responses commonly targeting nsp3, nsp4, ORF3a, and ORF8, among others. For $CD8^+$ T cells, spike and M were recognized, with at least eight SARS-CoV-2 ORFs targeted. Importantly, we detected SARS-CoV-2-reactive $CD4^+$ T cells in ~40%–60% of unexposed individuals, suggesting cross-reactive T cell recognition between circulating "common cold" coronaviruses and SARS-CoV-2.

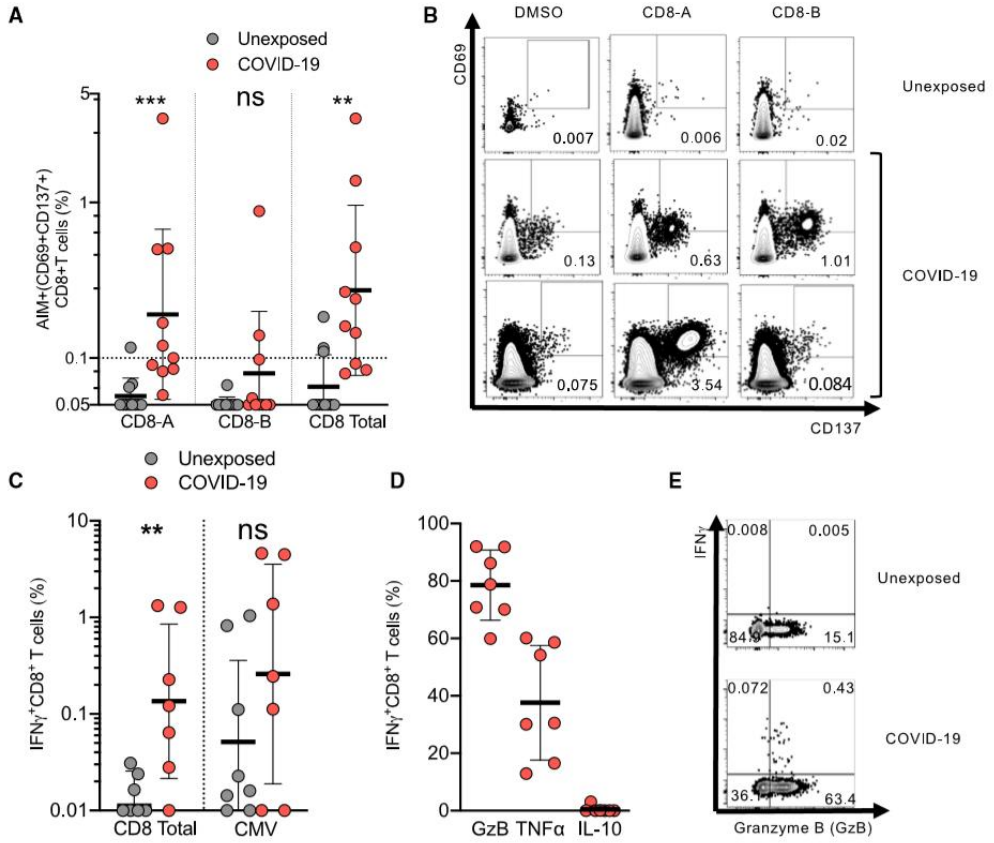
INTRODUCTION

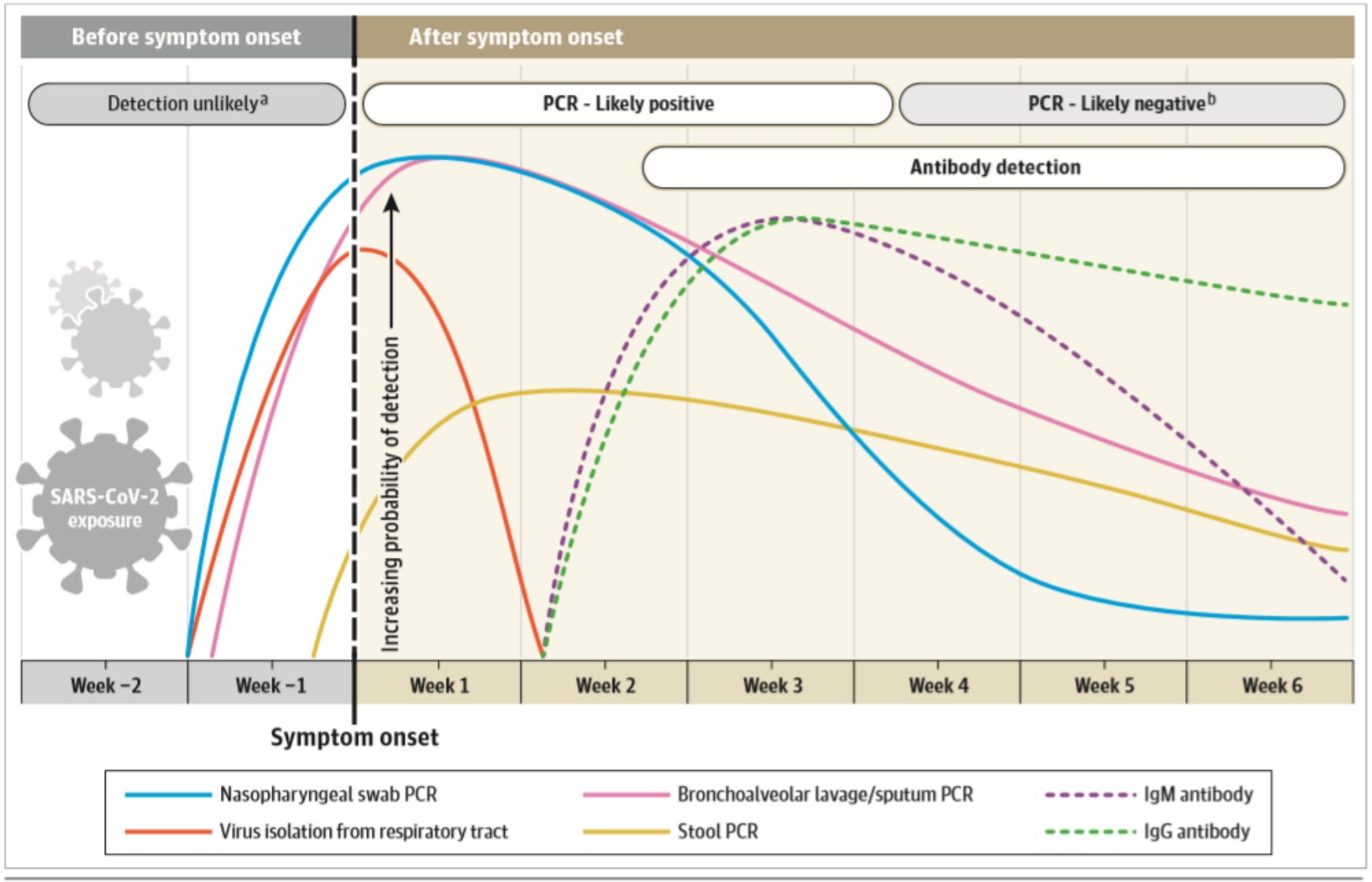
different depending on whether SARS-CoV-2 infection creates

linfocitos T CD4



linfocitos T CD8





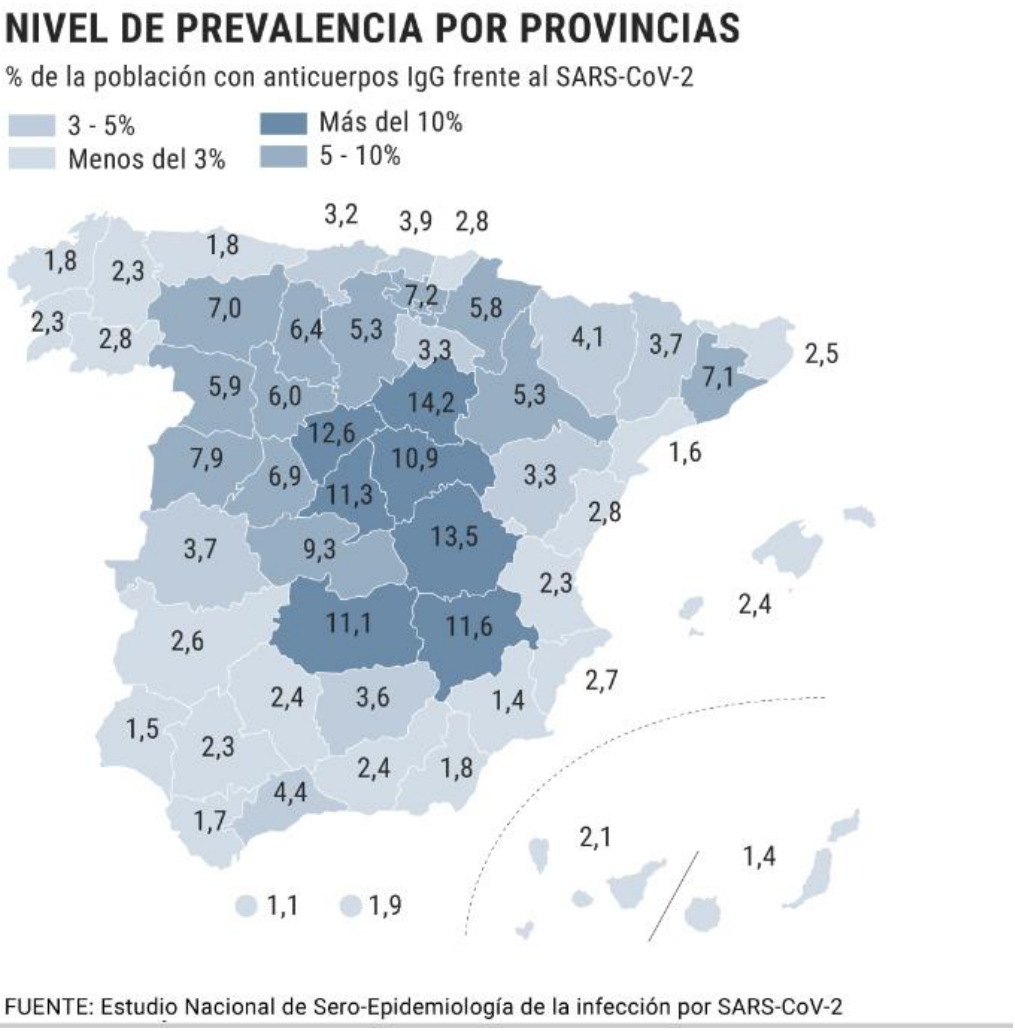
JAMA May 6,2020

Determinar la respuesta inmunitaria muy útil para el diagnóstico

DIAGNÓSTICO DE INFECCIÓN POR SARS-Cov-2

PCR	IgM	IgG	Diagnóstico
-	-	-	Negativo
+	-	-	Fase inicial de infección
+	+	-	Fase temprana de infección
+	+	+	Fase activa de infección
+	-	+	Fase avanzada de infección
-	+	-	Estadio temprano. Falso negativo PCR?
-	+	+	Enfermedad en evolución
-	-	+	Fase de resolución de infección

Seroprevalencia



FUENTE: Estudio Nacional de Sero-Epidemiología de la infección por SARS-CoV-2

No hay inmunidad de grupo

Terapia

Treatment of COVID-19 Patients with Convalescent Plasma

Eric Salazar[a,b], Katherine K. Perez[a,c], Madiha Ashraf[d], Jian Chen[a], Brian Castillo[a], Paul A. Christensen[a], Taryn Eubank[c], David W. Bernard[a,b], Todd N. Eagar[a,b], S. Wesley Long[a,b,e], Sishir Subedi[a], Randall J. Olsen[a,b,e], Christopher Leveque[a], Mary R. Schwartz[a], Monisha Dey[a], Cheryl Chavez-East[a], John Rogers[a], Ahmed Shehabeldin[a], David Joseph[a], Guy Williams[a], Karen Thomas[a], Faisal Masud[d], Christina Talley[g], Katharine G. Dlouhy[g], Bevin Valdez Lopez[g], Curt Hampton[g], Jason Lavinder[h], Jimmy D. Gollihar[i], Andre C. Maranhao[h], Gregory C. Ippolito[h], Matthew Ojeda Saavedra[a], Concepcion C. Cantu[e], Prasanti Yerramilli[e], Layne Pruitt[e], and James M. Musser[a,b,e,#]

Respuesta inmunitaria innata

Cell
Leading Edge

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Perspective

Trained Immunity: a Tool for Reducing Susceptibility to and the Severity of SARS-CoV-2 Infection

Mihai G. Netea,[1,2,*] Evangelos J. Giamarellos-Bourboulis,[3] Jorge Domínguez-Andrés,[1] Nigel Curtis,[4] Reinout van Crevel,[1] Frank L. van de Veerdonk,[1] and Marc Bonten[5]

[1]Department of Internal Medicine and Center for Infectious Diseases, Radboud University, 6500 Nijmegen, the Netherlands
[2]Immunology and Metabolism, Life & Medical Sciences Institute, University of Bonn, 53115 Bonn, Germany
[3]4th Department of Internal Medicine, National and Kapodistrian University of Athens, 12462 Athens, Greece
[4]Department of Paediatrics, The University of Melbourne and Murdoch Children's Research Institute, Royal Children's Hospital Melbourne, Parkville, VIC, Australia
[5]Department of Medical Microbiology, University Medical Center Utrecht, University of Utrecht, the Netherlands
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https://doi.org/10.1016/j.cell.2020.04.042

SARS-CoV-2 infection is mild in the majority of individuals but progresses into severe pneumonia in a small proportion of patients. The increased susceptibility to severe disease in the elderly and individuals with co-morbidities argues for an initial defect in anti-viral host defense mechanisms. Long-term boosting of innate immune responses, also termed "trained immunity," by certain live vaccines (BCG, oral polio vaccine, measles) induces heterologous protection against infections through epigenetic, transcriptional, and functional reprogramming of innate immune cells. We propose that induction of trained immunity by whole-microorganism vaccines may represent an important tool for reducing susceptibility to and severity of SARS-CoV-2.

Pregunta 1

- ¿Los paciente que han recibido tratamiento inmunosupresor esperarías tener la misma respuesta inmune?

1. Si
2. No

Pregunta 1

- ¿Los paciente que han recibido tratamiento inmunosupresor esperarías tener la misma respuesta inmune?

1. Si
2. **No**

JOURNAL OF HEART AND LUNG TRANSPLANTATION

COVID-19 Illness in Native and Immunosuppressed States:

A Clinical-Therapeutic Staging Proposal

Hasan K. Siddiqi, MD, MSCR, and Mandeep R. Mehra, MD, MSc

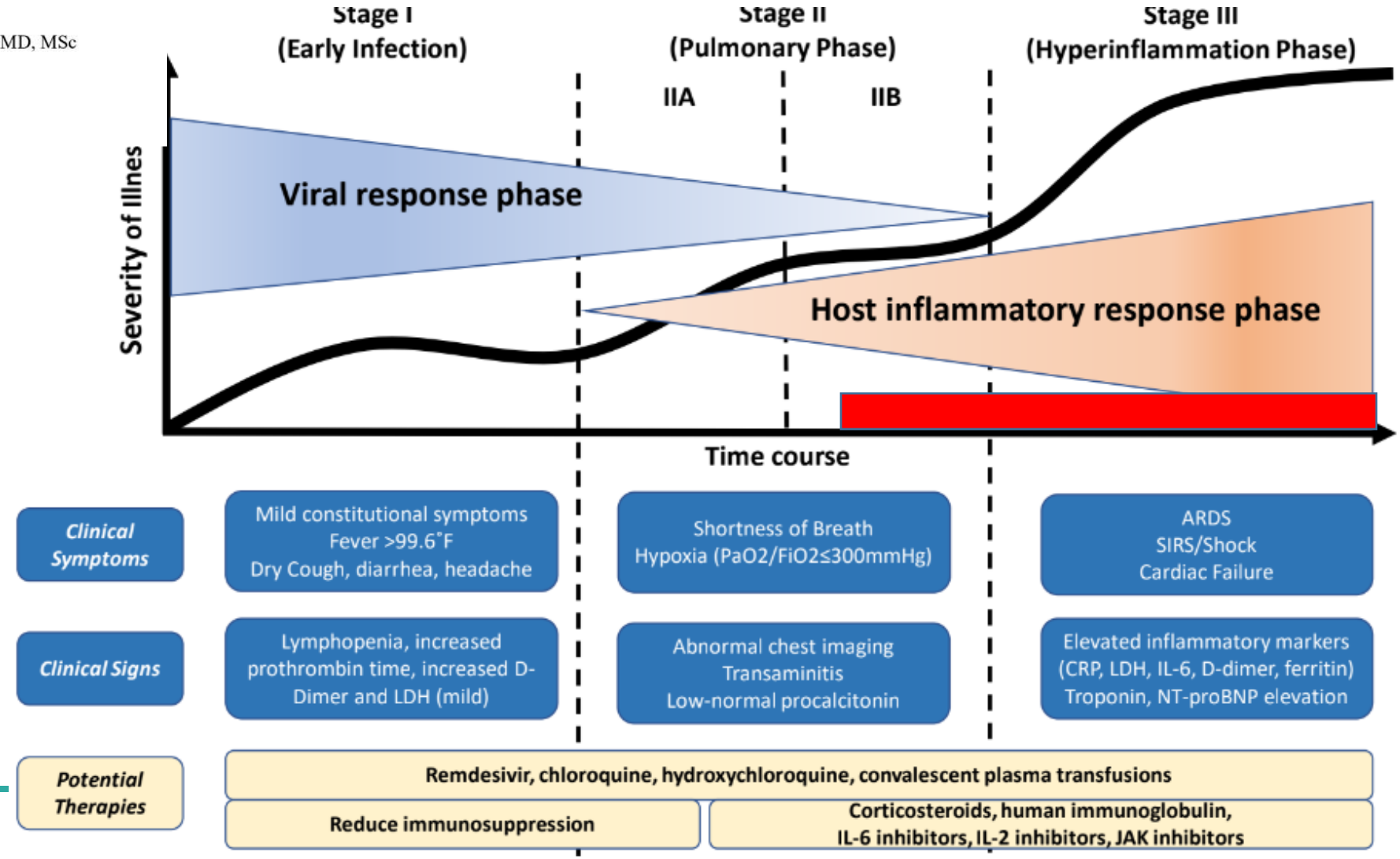
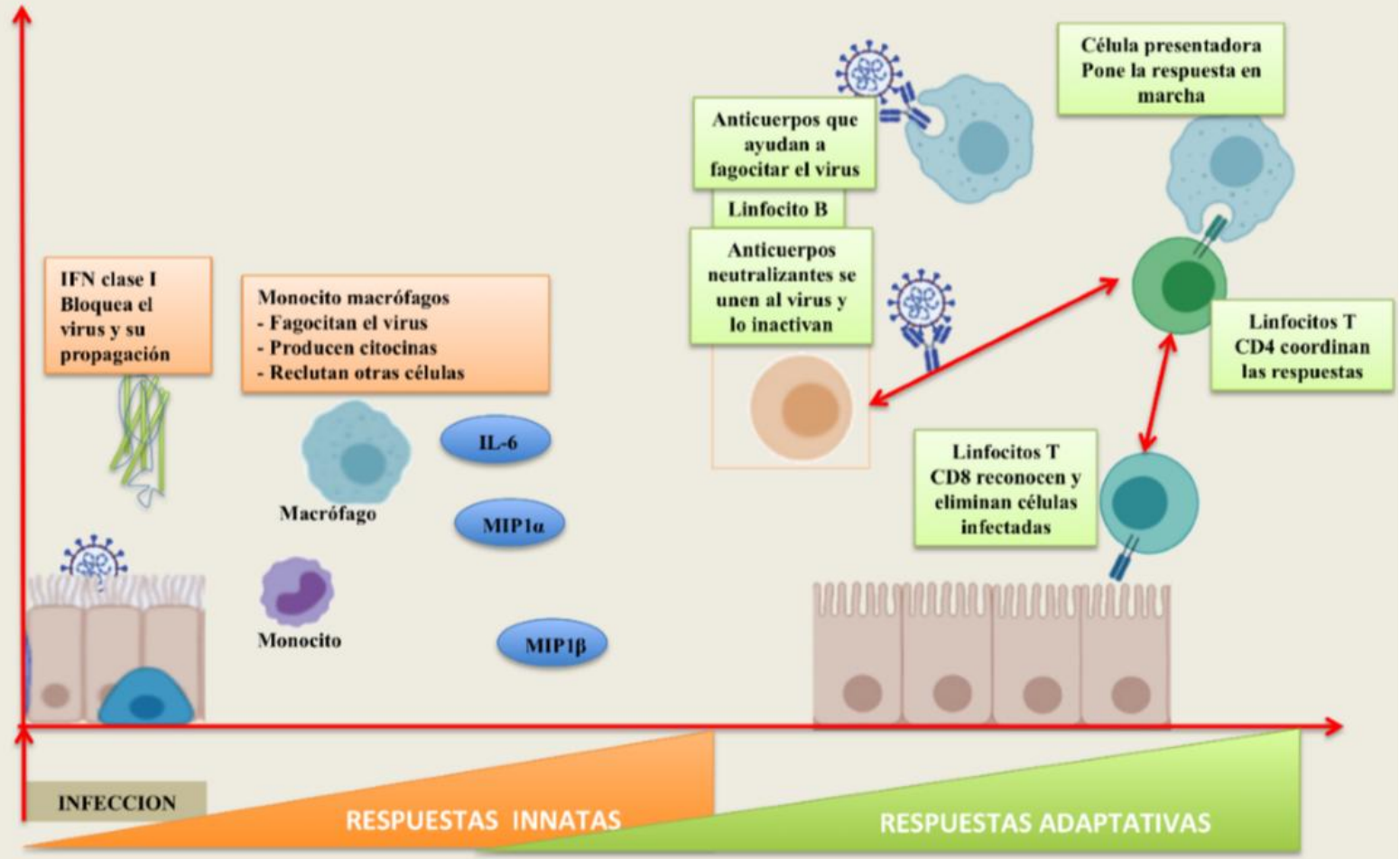
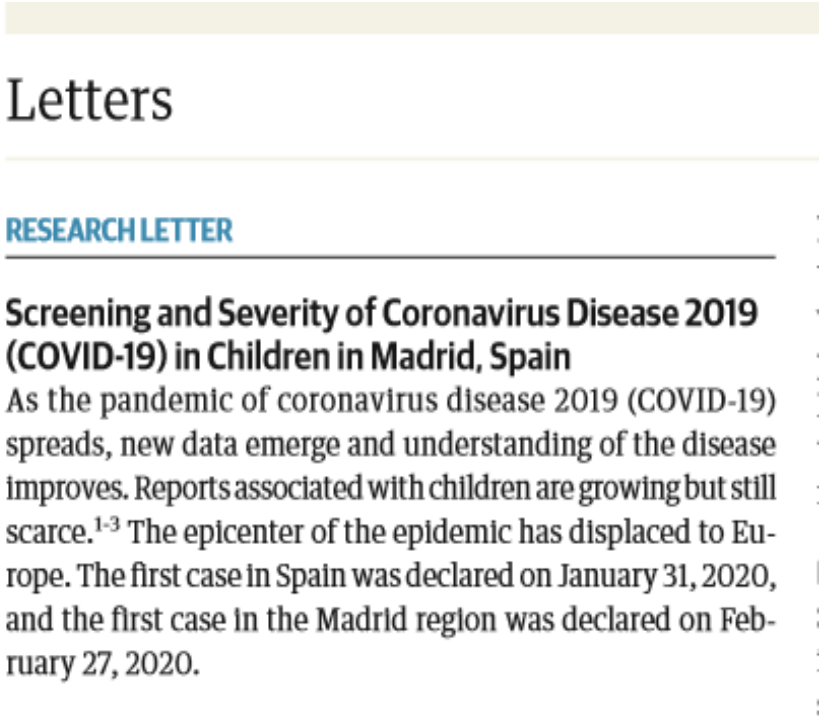


FIGURA 1. ESQUEMA GENERAL DE LA RESPUESTA INMUNE



¿Qué ocurre con los niños?



Letters

RESEARCH LETTER

Screening and Severity of Coronavirus Disease 2019 (COVID-19) in Children in Madrid, Spain

As the pandemic of coronavirus disease 2019 (COVID-19) spreads, new data emerge and understanding of the disease improves. Reports associated with children are growing but still scarce.[1-3] The epicenter of the epidemic has displaced to Europe. The first case in Spain was declared on January 31, 2020, and the first case in the Madrid region was declared on February 27, 2020.

Systematic review of COVID-19 in children shows milder cases and a better prognosis than adults Ludvigsson JF Acta Paediatr. 2020 Apr 14 : 10.

Pregunta 2 ¿Por qué afecta menos a los niños?

1. Los niños tienen menos comorbilidades
2. Respuesta inmunitarias innatas más fuertes que en adultos
3. Infecciones por otros virus y/o coronavirus pueden ayudar a los niños a superar el SARS-CoV2 de manera más eficaz.
4. Diferente expresión de ACE2
5. Factores hormonales
6. Todas pueden contribuir

¿Qué ocurre con los niños?

- No se conoce por que los niños desarrollan una enfermedad leve/moderada que los adultos y rara vez desarrollan síndrome de tormenta de citoquina…SHI

1. Los niños tienen menos comorbilidades.
2. Respuesta inmune fuertes respuestas inmunitarias innatas. Esto puede contribuir a la neutralización eficaz del virus y a la reducción de la inflamación secundaria
3. Otras infecciones (y el co-aclaramiento) con otros virus y/o coronavirus pueden ayudar a los niños a superar el SARS-CoV2 de manera más eficaz.
4. Diferente expresión de ACE2 que es esencial para la infección de células epiteliales
5. Uno de los cofactores requiere estímulo androgénico se relaciona con la adrenarquia.
6. **Todas pueden contribuir y seguro hay más mecanismos que desconocemos aún**

ACE2-2

Research Letter

ONLINE FIRST

May 20, 2020

Nasal Gene Expression of Angiotensin-Converting Enzyme 2 in Children and Adults

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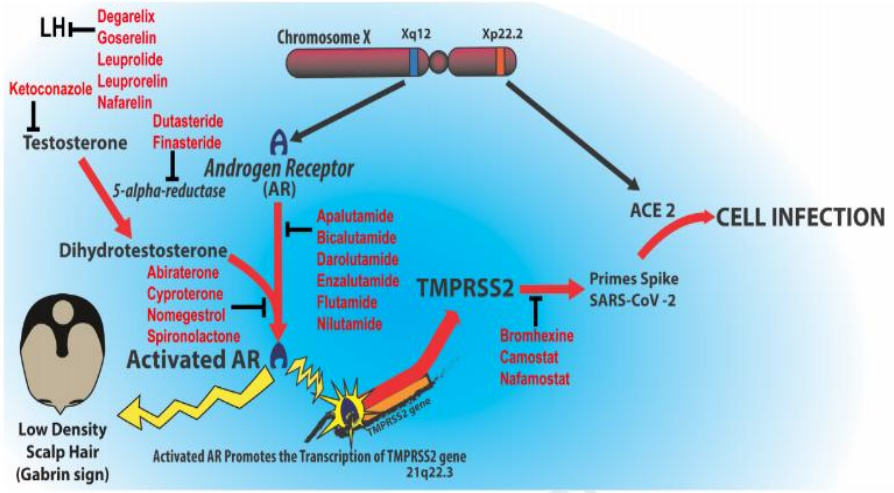
Adrenarquia



Journal Pre-proof

Androgenetic Alopecia Present in the Majority of Hospitalized COVID-19 Patients – the "Gabrin sign"

Carlos Gustavo Wambier, MD, PhD, Sergio Vaño-Galván, MD, PhD, John McCoy, PhD, Alba Gomez-Zubiaur, MD, Sabina Herrera, MD, PhD, Ángela Hermosa-Gelbard, MD, Oscar M. Moreno-Arrones, MD, PhD, Natalia Jiménez-Gómez, MD, Alvaro González-Cantero, MD, PhD, Pablo Fonda Pascual, MD, Gonzalo Segurado-Miravalles, MD, Jerry Shapiro, MD, Bibiana Pérez-García, MD, PhD, Andy Goren, MD

Conclusiones

- Queda mucho que aprender
- No hay inmunidad de grupo
- Una respuesta inmune innata rápida y potente es fundamental para control CV.
- Con un buen control CV hay menos daño tisular y menor respuesta inflamatoria.
- ¿perfiles de susceptibilidad ? ¿disegulación?
- Se genera respuesta de Acs y parece que a mayor título mayor capacidad neutralizante
- Se genera respuesta celular B y linfocitos T CD4 Y CTL.