ASOCIACIÓN HONDUREÑA
DE PARASITOLOGÍA (AHPA)

Tiene el agrado de invitar a la

conferencia

La ivermectina como preventivo ante el COVID-19

Dr. Miguel Sierra Hoffmann
Baylor Scott & White Hospital
Texas, Estados Unidos de América

FECHA: Marzo 13, 2021 | **HORA:** 5:00 pm

¡Les esperamos!

zoom https://us02web.zoom.us/j/82103701932
ID de reunión: **821 0370 1932**

https://fb.me/e/h2WHWp371

Cortesía del Colegio de Microbiólogos y Químicos Clínicos de Honduras, Tegucigalpa, Honduras

Grabación disponible en

https://www.facebook.com/colegiomicrobiologoshn/videos/558352928462919/

Ensayo Catracho : Ivermectina, realidades vs mitos

Miguel Sierra Hoffman MD
&
Fernando Valerio MD

Declaration

- No tengo Conflicto de intereses
- Pero tengo miles de conflictos Interesantes

Casos Clinicos 1

- Paciente indice : Anestesiologo , nucleo Familiar 5
- Toma IVM prophylactica , 6 meses
- Desarolla Pneumonitis 25 % , sigue con asa + Ivm dia y colchina
- No ocupa hospitalizacion
- 4 miembros de familia , en IVM PCR negative x 2, incluyendo abuelo de 89 anos

Caso clinic 2

- Paciente viaja a EEUU
- Hija es Residente de Medicina
- Hija se enferma junto a un gran grupo de residents
- Al visitar a sus padres no sabe tiene Covid 19
- Desarrolla sintomas . + pcr
- Papas no solo no desarrolan enfermendad si no que PCR negative

Prophylaxis : types

- Post exposure prohylaxis
- Pre exposure prophylaxis (PReP)
- Prophylaxis

Basic Principles

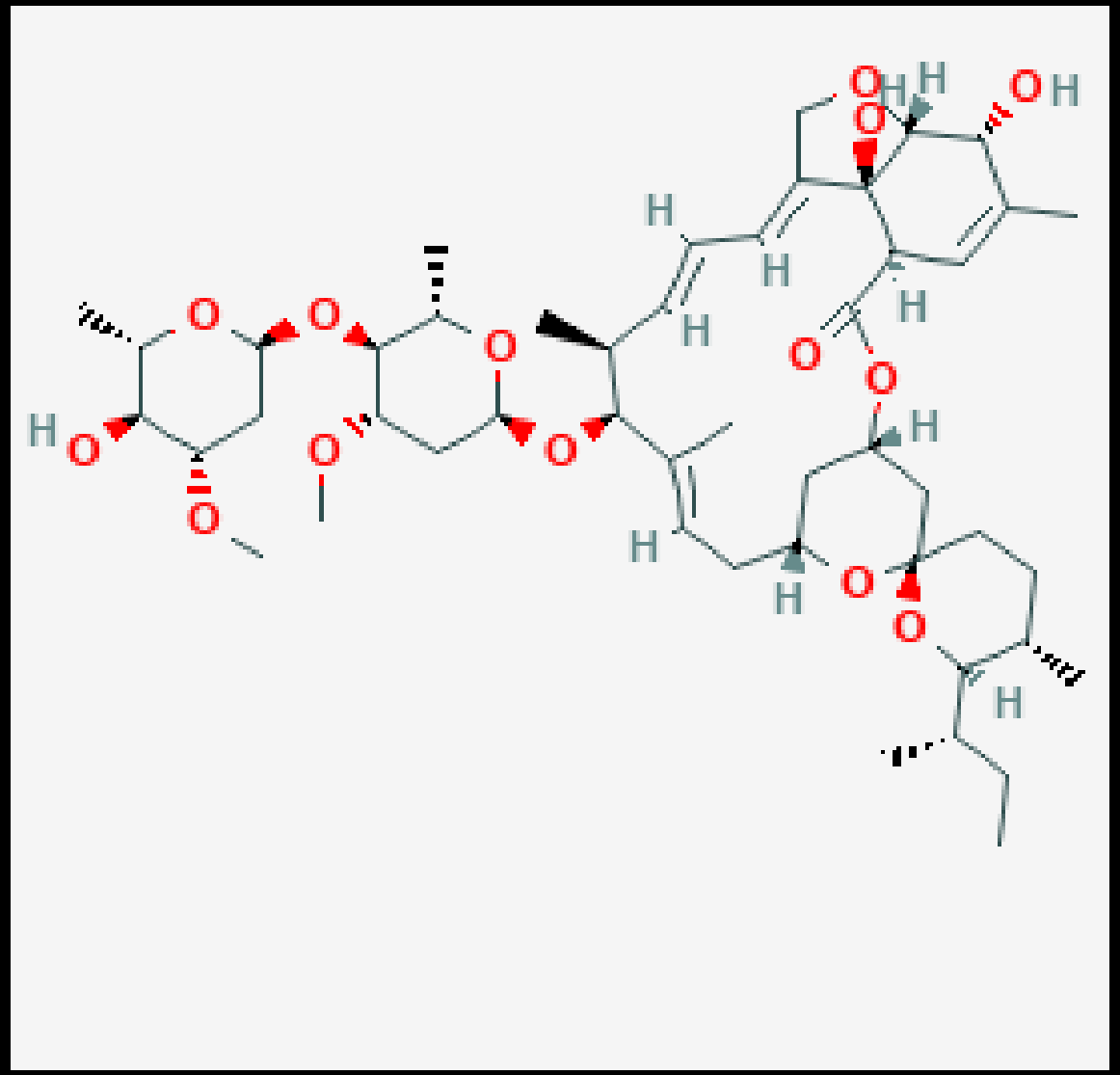
Toxicity

actividad therapeutica deseada

Inefficiency

Ivermectin

- Bioavailibility is increased 100% with post prandial
- Plasma concentrations decrease with orange juice
- Increase with the ingestion of beer
- Distribution is widely throughout the body
- Highest concentration is in adipose tissue and liver
- Highly lipophilic
- Metabolized by cytochrome CYP3A4
- Drug overdose can lead to CNS toxicity that is reversable with withdraw of medication



Lymphatic filariasis

- Caused by parasitic worms of the species, *Wuchereria bancrofti* (90%) & *Brugia malayi* (10%), transmitted by various species of mosquitoes

Infection causes filarial fever, elephantiasis, male genital damage & severe social stigma

• People at risk	> 1.3 billion
• People infected	120 million
• Countries affected	83

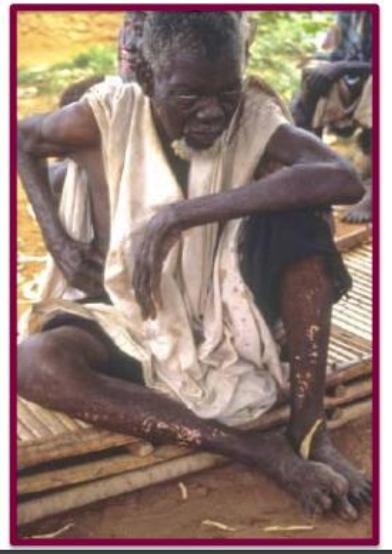
(data ~2000)

(Source: Global Alliance to Eliminate Lymphatic Filariasis (GAELF), 2010)

17

Human health goals : Onchocerciasis (River blindness)

- Caused by filarial worms, transmitted by *Simulium* black flies
- Females release millions of immature worms; migrate to skin & eyes - skin disease, unbearable itching & blindness.



• People at risk	120 million
• People infected 18 million	
• Blinded / disabled	770,000
• Disease burden (DALY)	1.1 million
• Countries affected	36
• No safe drugs available	

(data~1987)

(Source: UNDP/World Bank/WHO Special Programme for Research & Training in Tropical Diseases (TDR))

12

Tratamiento para la Oncocercisis, filariasis linfática(Tomado de S Omura)

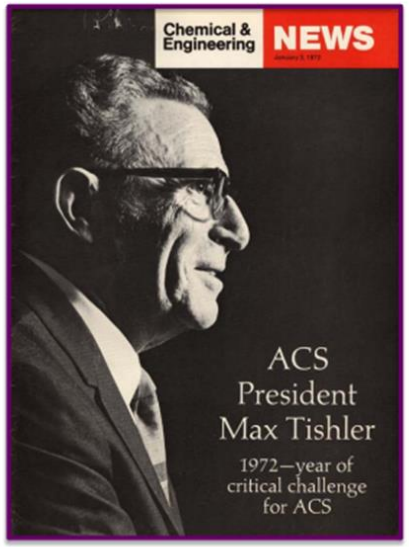
- https://www.nobelprize.org/uploads/2018/06/omura-lecture-sli

Ωra

Ivermectin: the beginning

Satoshi Ōmura | Max Tishler (1906-1989)

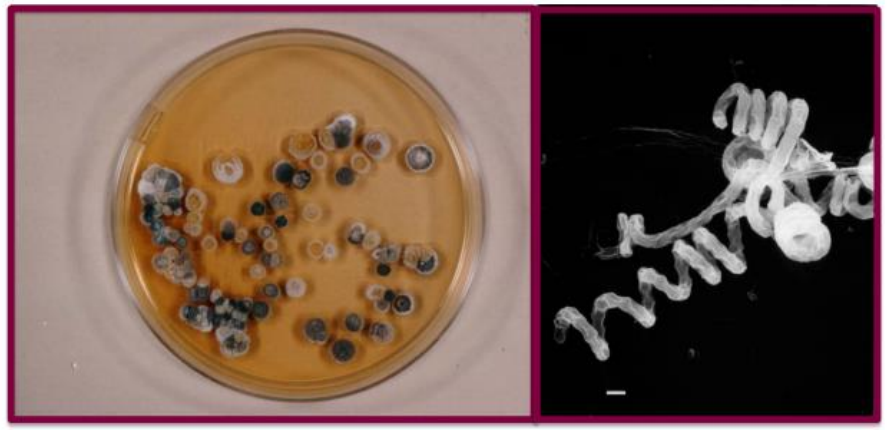
Wesleyan University
USA (1972)



8

Ωra

The avermectin producing strain



Streptomyces avermectinius (S. avermitilis)

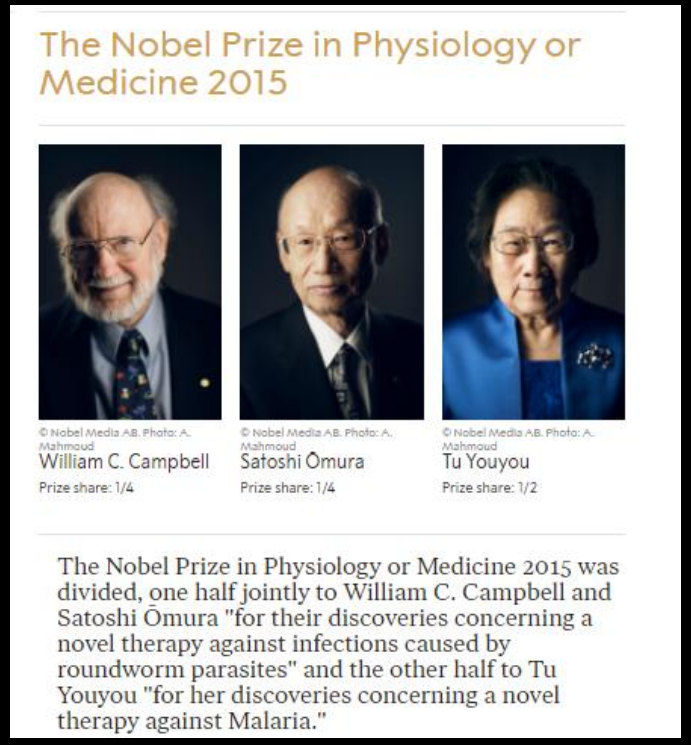
(white bar: 1 ⎰m)

11

Ivermectina (tomado de la conferencia de Premio Nobel del Prof S Omura)

- https://www.nobelprize.org/uploads/2018/06/omura-lecture-sli

- https://www.nobelprize.org/uploads/2018/06/omura-lecture-sli



Premio Nobel de Medicina 2015

- 3 billones de dosis a nivel mundial

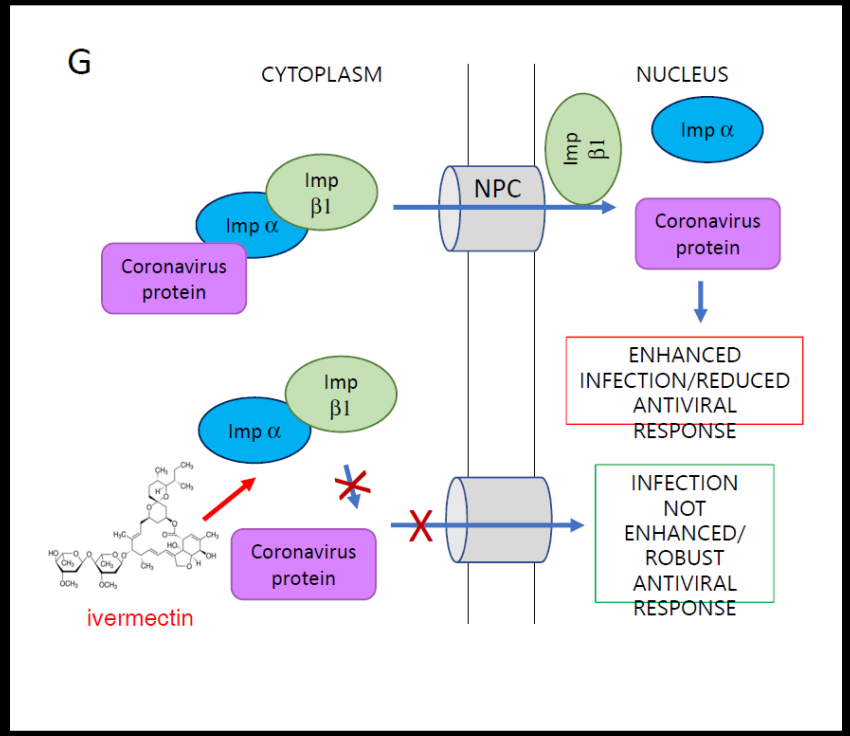
Ivermectina

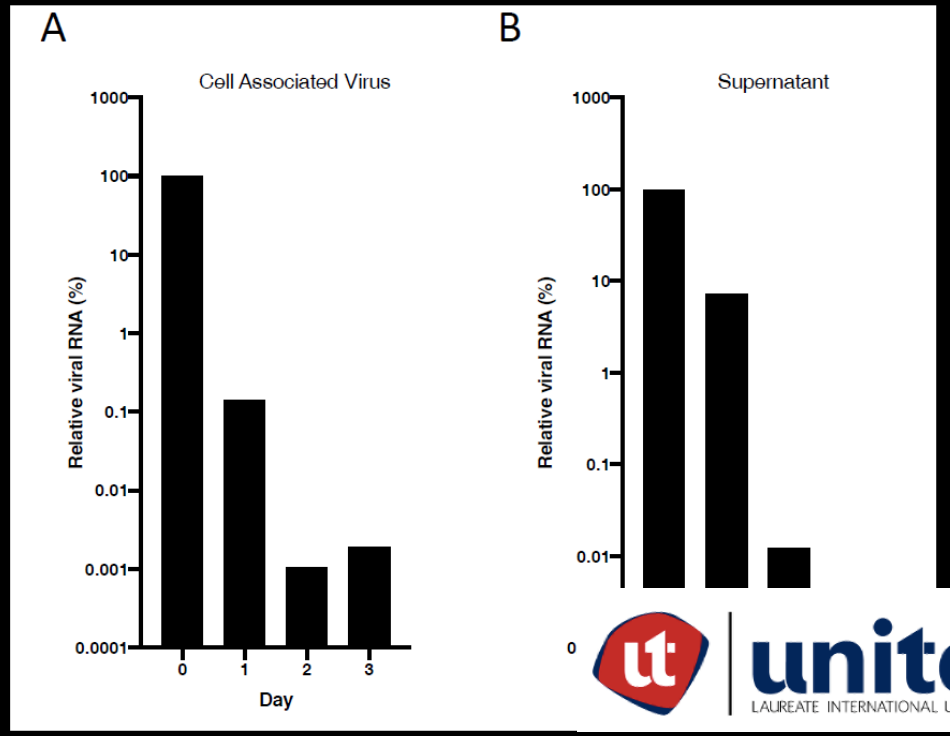
La ivermectina es un medicamento formado por una mezcla 80:20 de avermectina B1a y B1b. Las avermectinas son derivados macrocíclicos de la lactona producidas por la actinobacteria Streptomyces avermitilis.

Ikeda, H; H. Kotaki & S. Omura 1989 "Genetic studies of avermectin biosynthesis in Streptomyces avermitilis"; Journal of Bactriology 169(12): 5615–5621.

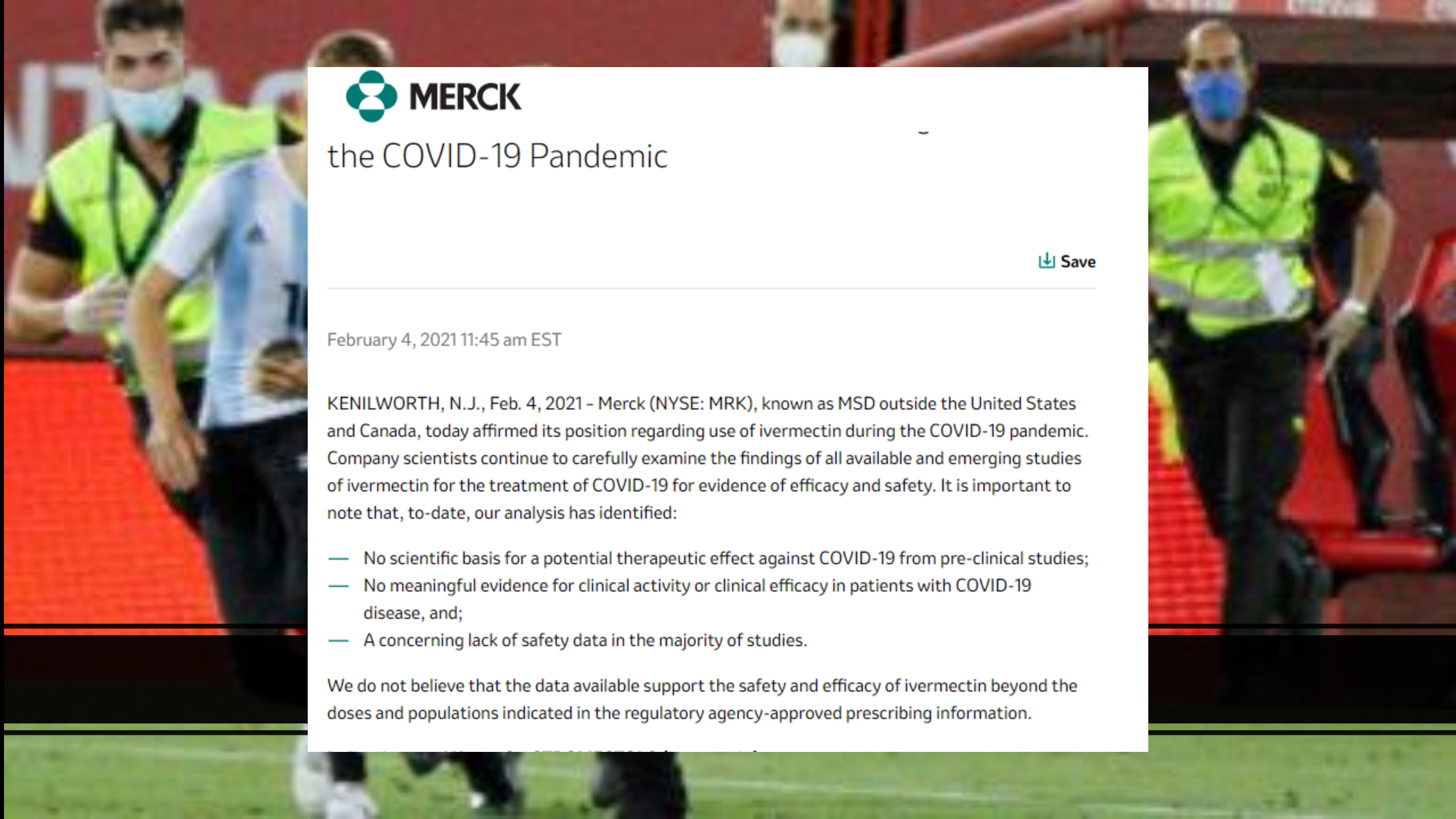
Potential & Science behind Ivermectin

DeTar Healthcare System | TAMU Medicine Texas A&M University





unitec LAUREATE INTERNATIONAL UNIVERSITIES®



MERCK

the COVID-19 Pandemic

Save

February 4, 2021 11:45 am EST

KENILWORTH, N.J., Feb. 4, 2021 – Merck (NYSE: MRK), known as MSD outside the United States and Canada, today affirmed its position regarding use of ivermectin during the COVID-19 pandemic. Company scientists continue to carefully examine the findings of all available and emerging studies of ivermectin for the treatment of COVID-19 for evidence of efficacy and safety. It is important to note that, to-date, our analysis has identified:

- No scientific basis for a potential therapeutic effect against COVID-19 from pre-clinical studies;
- No meaningful evidence for clinical activity or clinical efficacy in patients with COVID-19 disease, and;
- A concerning lack of safety data in the majority of studies.

We do not believe that the data available support the safety and efficacy of ivermectin beyond the doses and populations indicated in the regulatory agency-approved prescribing information.

Coronavirus

New antiviral COVID-19 drug quickly reduces virus, drugmaker Merck reports

Updated Mar 06, 2021; Posted Mar 06, 2021

Clinical trials of a new antiviral COVID treatment were said to be promising, Merck announced on Saturday. AP Photo/Matt Rourke, file

By Ted Sherman | NJ Advance Media for NJ.com

New Jersey-based Merck said Saturday that the experimental antiviral drug molnupiravir it has been developing with Ridgeback Bio showed a quick reduction of the infectious virus in a study among participants with early COVID-19.

"We continue to make progress in our Phase 2/3 clinical programs evaluating molnupiravir in both outpatient and hospital settings," said Roy Baynes, head of global clinical development and chief medical officer at Merck Research Laboratories.

Recomendaciones

Grade Practice Recommendations*

Grade	Descriptor	Qualifying Evidence	Implications for Practice
A	Strong recommendation	Level I evidence or consistent findings from multiple studies of levels II, III, or IV	Clinicians should follow a strong recommendation unless a clear and compelling rationale for an alternative approach is present
B	Recommendation	Levels II, III, or IV evidence and findings are generally consistent	Generally, clinicians should follow a recommendation but should remain alert to new information and sensitive to patient preferences
C	Option	Levels II, III, or IV evidence, but findings are inconsistent	Clinicians should be flexible in their decision-making regarding appropriate practice, although they may set bounds on alternatives; patient preference should have a substantial influencing role
D	Option	Level V evidence: little or no systematic empirical evidence	Clinicians should consider all options in their decision making and be alert to new published evidence that clarifies the balance of benefit versus harm; patient preference should have a substantial influencing role

Medicina Basada en Evidencia RCT; Estudios controlados aleatorios

Table 4

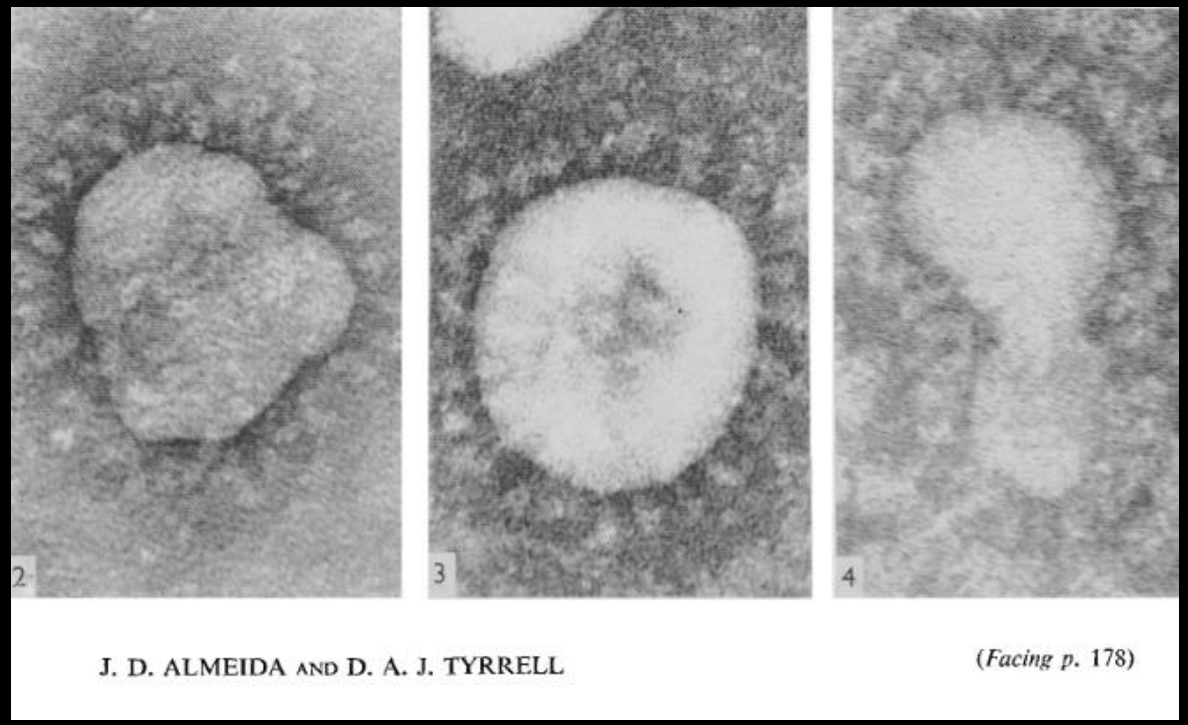
Levels of Evidence for Therapeutic Studies*

Level	Type of evidence
1A	Systematic review (with homogeneity) of RCTs
1B	Individual RCT (with narrow confidence intervals)
1C	All or none study
2A	Systematic review (with homogeneity) of cohort studies
2B	Individual Cohort study (including low quality RCT, e.g. <80% follow-up)
2C	"Outcomes" research; Ecological studies
3A	Systematic review (with homogeneity) of case-control studies
3B	Individual Case-control study
4	Case series (and poor quality cohort and case-control study
5	Expert opinion without explicit critical appraisal or based on physiology bench research or "first principles"

*From the Centre for Evidence-Based Medicine, http://www.cebm.net.

CORONAVIRUS

- J.D.Almeida, D.A.Tyrrell. J.Gen.Virol.1(1967)175–178.



J. gen. Virol. (1967), **1**, 175–178
With 2 plates
Printed in Great Britain

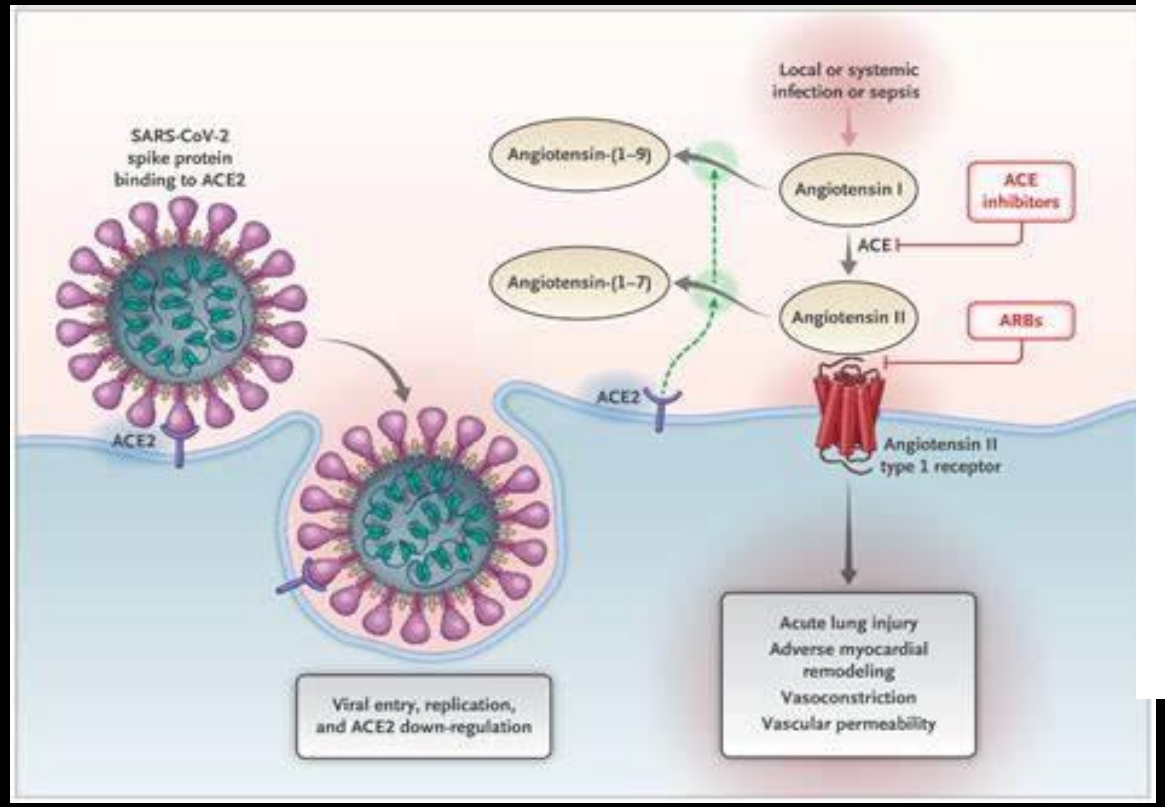
The Morphology of Three Previously Uncharacterized Human Respiratory Viruses that Grow in Organ Culture

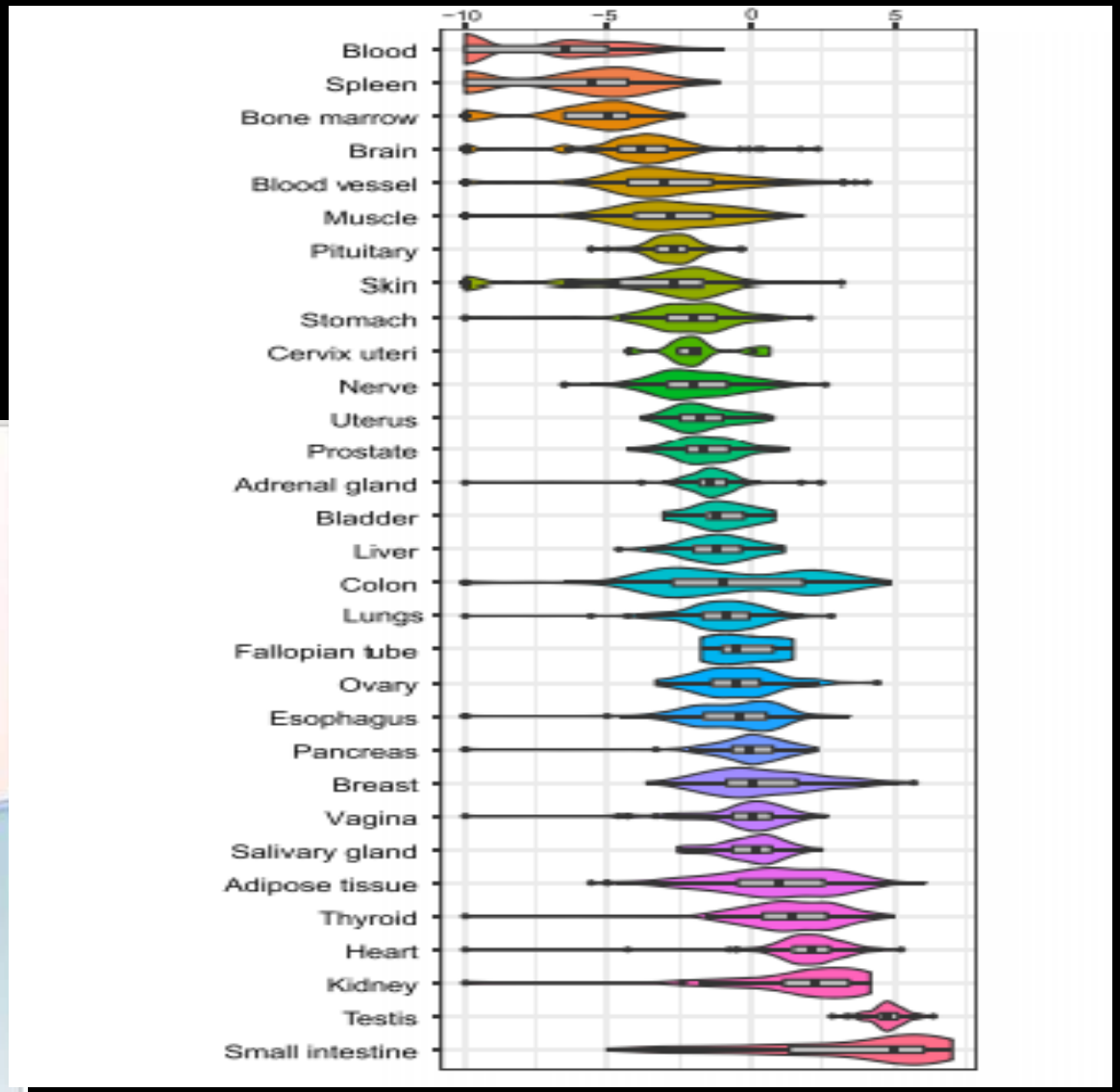
By JUNE D. ALMEIDA
Department of Medical Microbiology, St Thomas's Hospital Medical School, London, S.E.1
AND D. A. J. TYRRELL
Common Cold Research Unit, Medical Research Council, Salisbury, England

(*Accepted* 28 *November* 1966)

Basics

- SARS-CoV-2 (+ssRNA)
  - Coronaviridae Nidovirales betacoronavirus
  - HCoV-OC43, SARS-HCoV, HCoV-HKU1, MERS-CoV





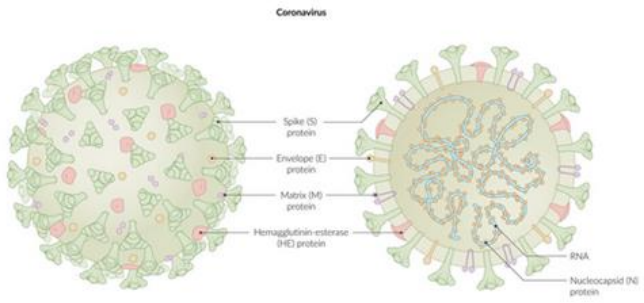
N Engl J Med. 2020 May 21.
N Engl J Med. 2020; 382.1653-1659
J Infect Public Health 2020
Infect Dis Poverty. 2020;9:45

Estructura del SARS-CoV-2

- Spike protein

Structural Protein	Protein Function and Features
Nucleocapsid protein (N)	• Binds with RNA genome to make helical ribonucleoprotein
Membrane protein (M)	• Transmembrane envelope protein • Determines shape of viral envelope
Envelope protein (E)	• Interacts with M protein to form viral envelope • Important for virus infectivity
Spike protein (S)	• Binds to host cell receptors to facilitate entry into host cells • Targeted by host neutralizing antibodies

Structural proteins of coronaviruses and their functions. Summarized from Fields, Knipe, Howley, Fields Virology 6e 2013.



Coronavirus structure. Schematic showing major structural proteins of the coronavirus virion. From AMBOSS.

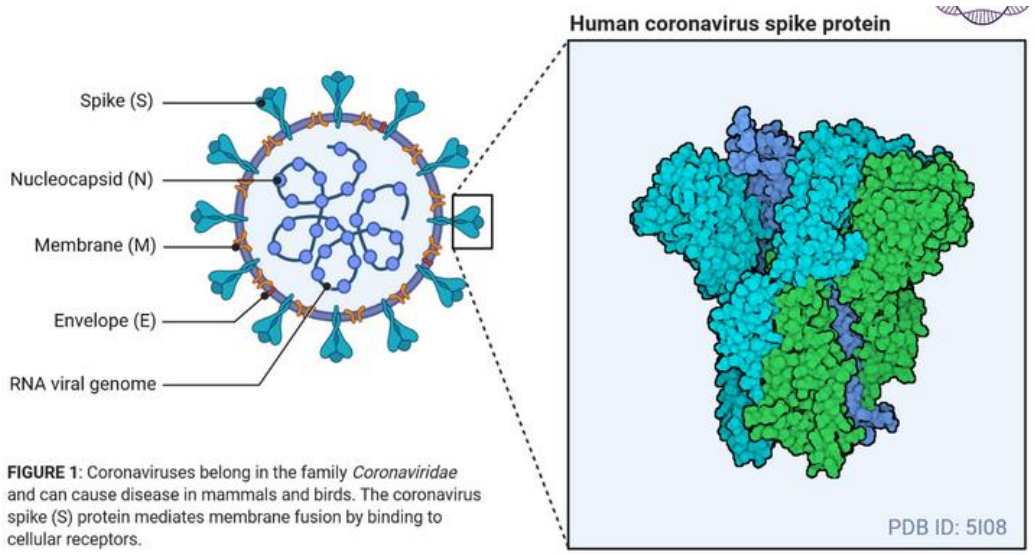
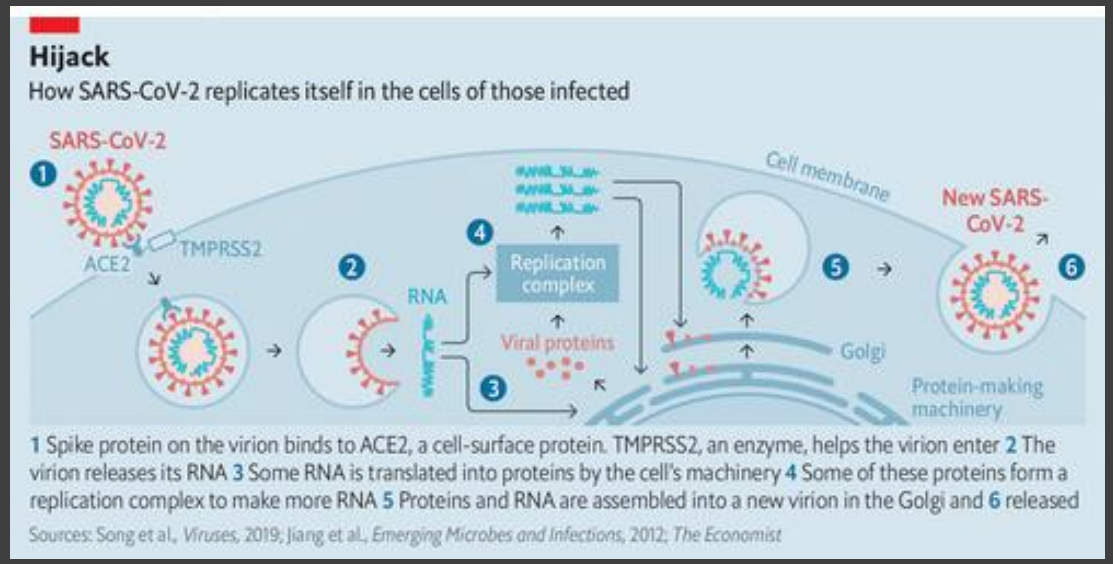
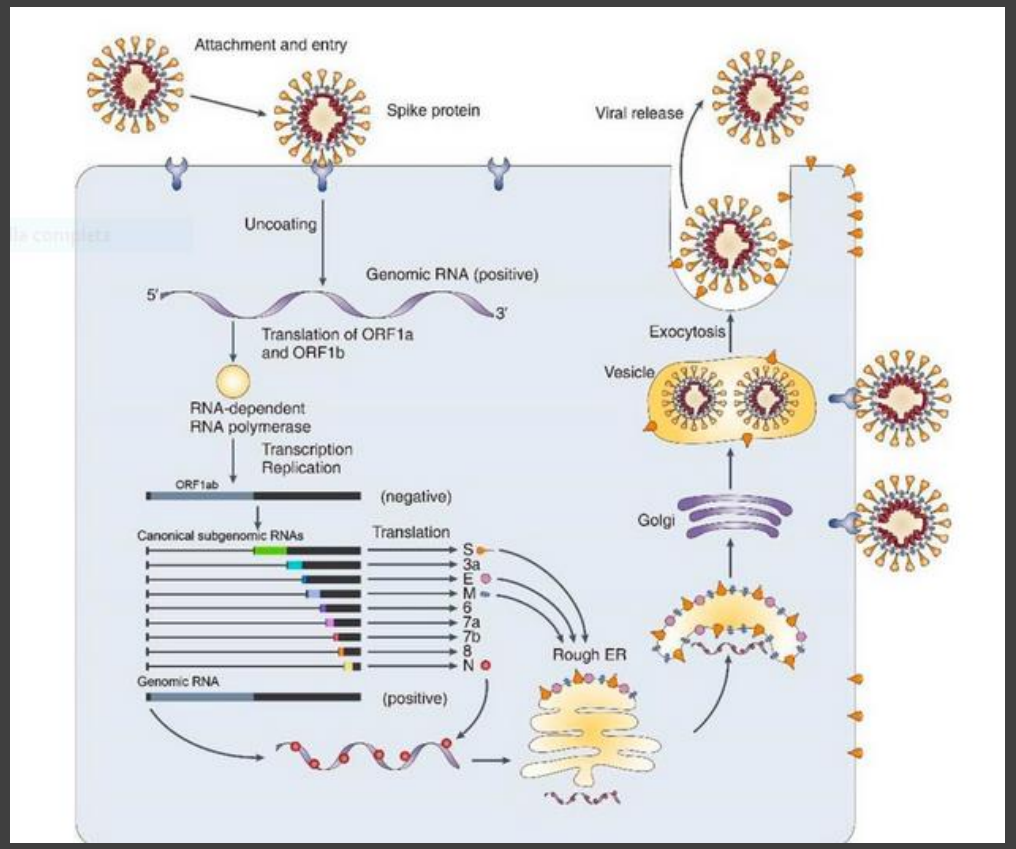


FIGURE 1: Coronaviruses belong in the family *Coronaviridae* and can cause disease in mammals and birds. The coronavirus spike (S) protein mediates membrane fusion by binding to cellular receptors.

Figure: Structure of SARS-CoV-2, created with biorender.com

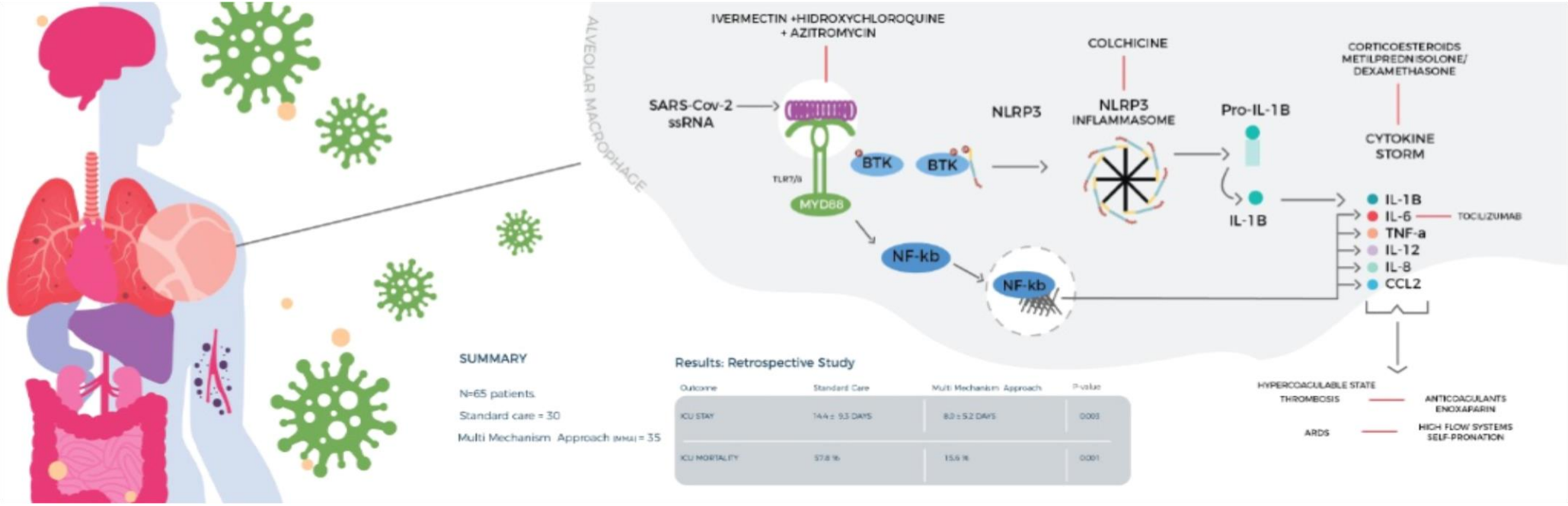




Mecanismo de Replicacion

- Sars CoV 2

Innovation: A Multi Mechanism Approach towards COVID-19 Therapy



Valerio Pascua Oscar Diaz Et al PLoS One Jan 7 2021

Nuevo campo de Batalla 2021

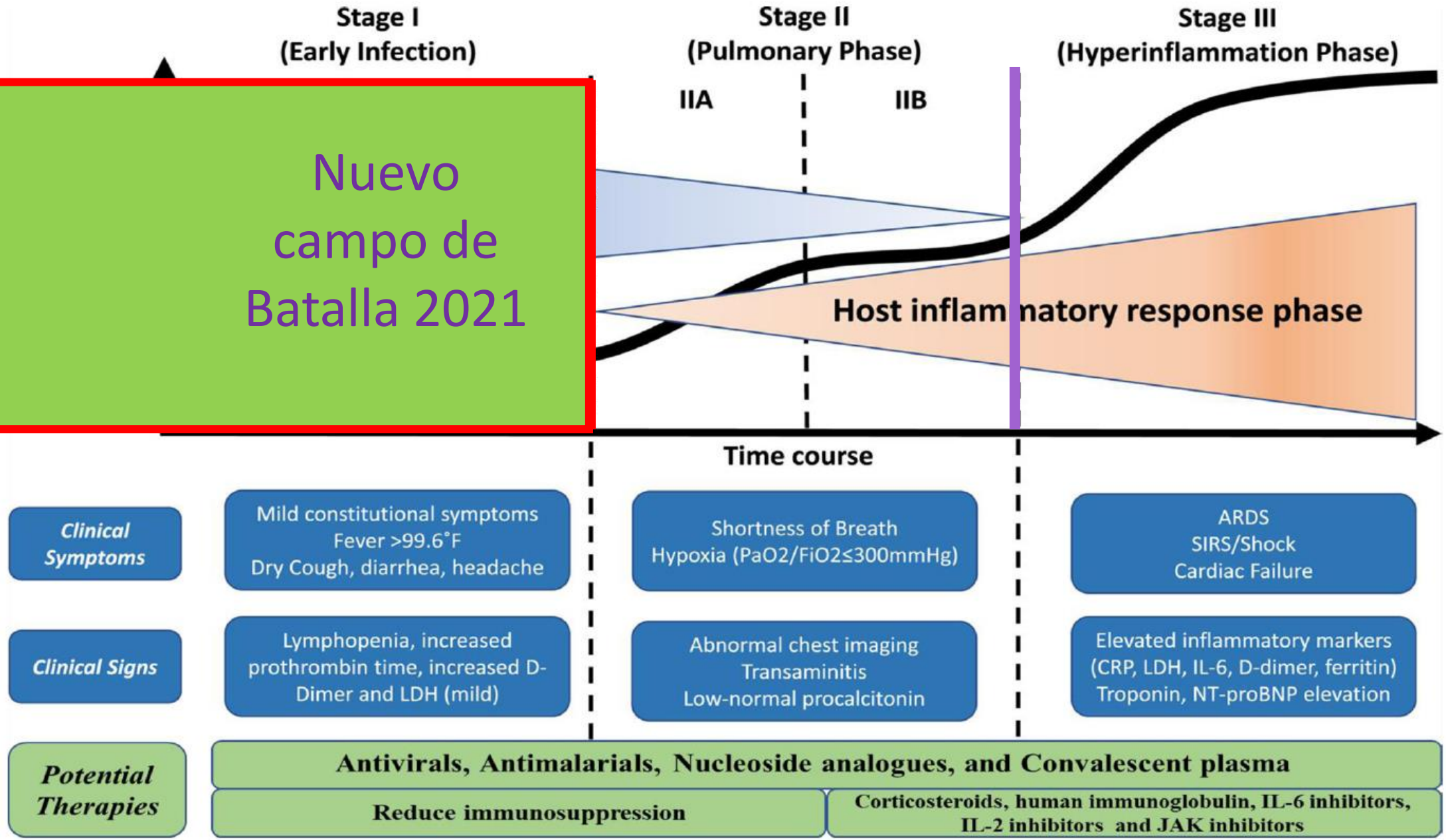
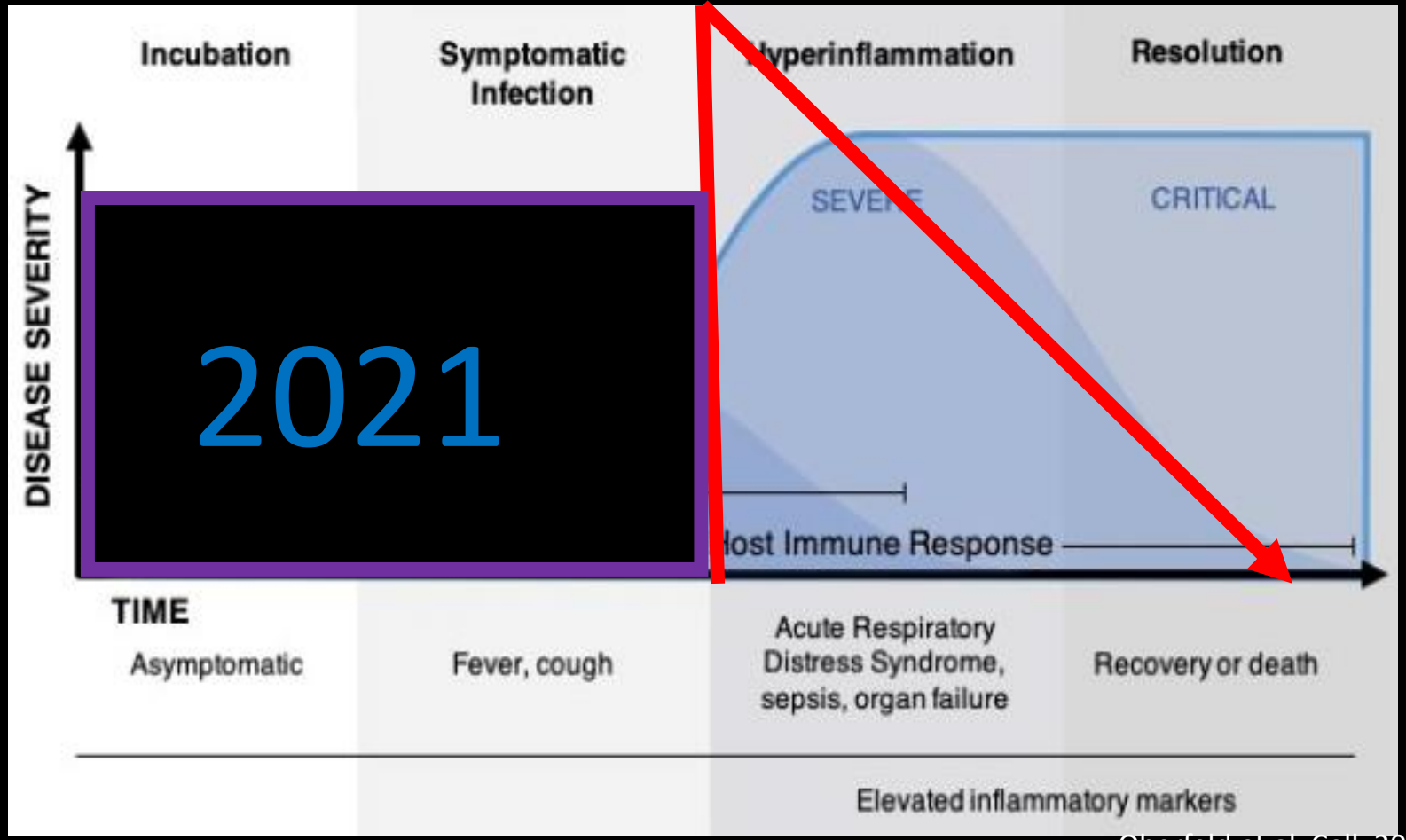


Fig. 1. COVID-19 pathogenic phases and potential therapeutic targets (modified and adopted from Siddiqi and Mehra, 2020 [38]).

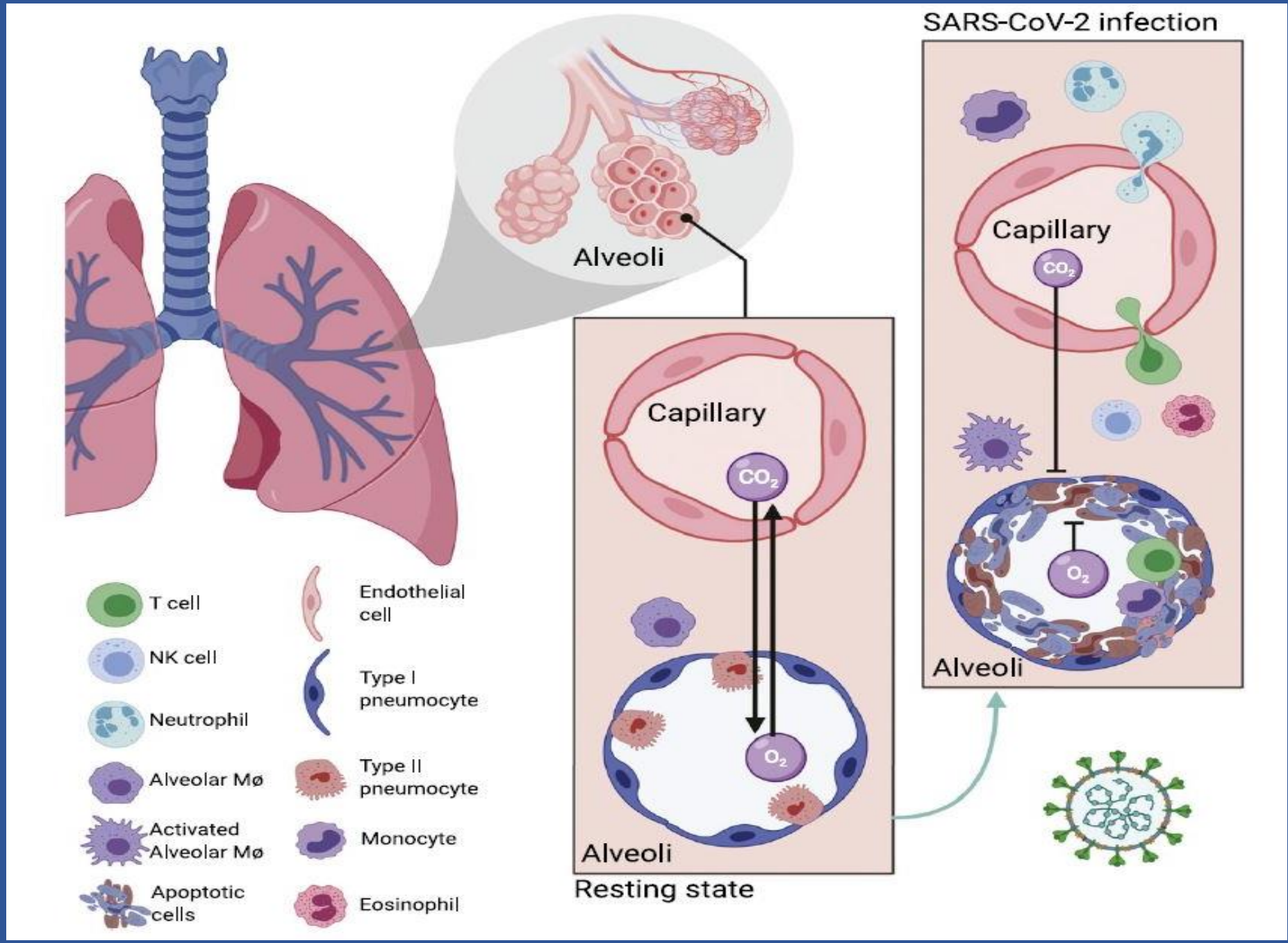
Natural History

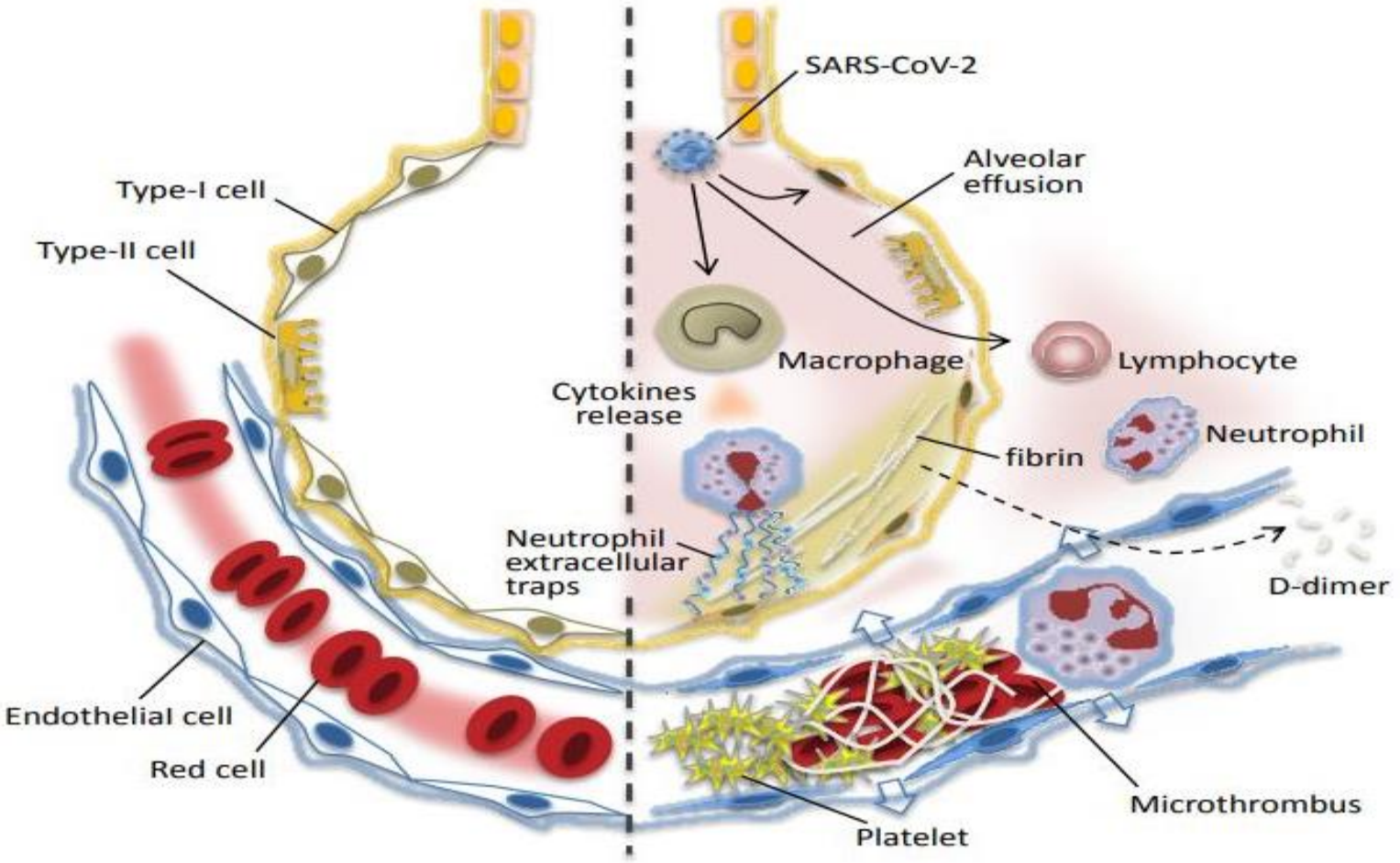


Oberfeld et al. Cell. 2020

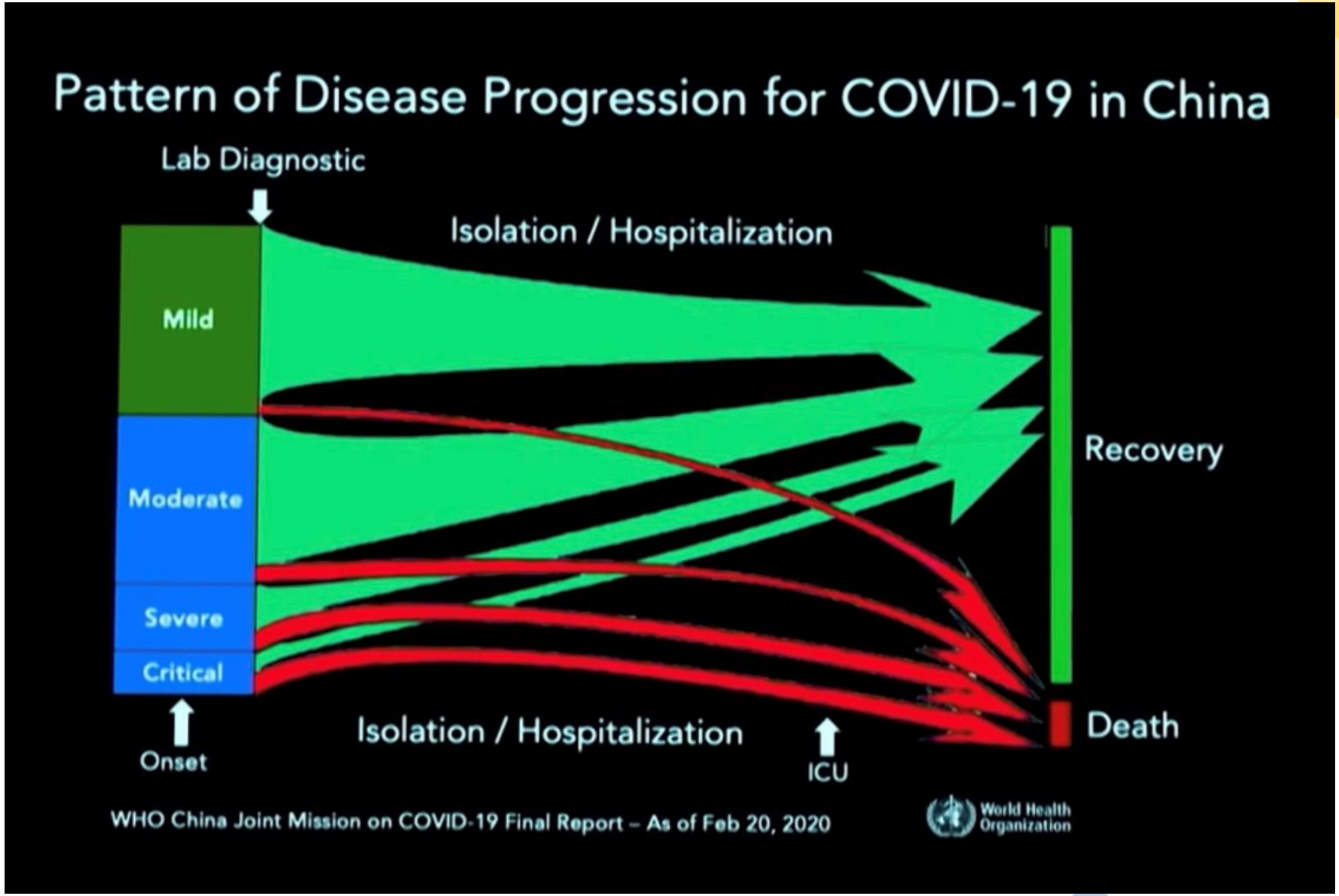
DeTar Healthcare System | MEDICINE Texas A&M University

FIGURE 3. Immune pathology in SARS-CoV-2–infected lung tissue. The lung, the critical organ for gas exchange, is the target of SARS-CoV-2 Infection. In healthy tissue, the alveolae at the ends of terminal bronchi are critical for the flow of oxygen, and few immune cells, such as alveolar macrophages, are located in the tissue but in a resting state. The proximity of capillaries to the alveoli allows the exchange of O2 and CO2 to replenish the O2 supply in the blood. After SARS-COV-2 infection, inflammation is induced in the tissue, involving cellular recruitment of many types of immune cells, including T cells, NK cells, neutrophils, inflammatory monocytes, and potentially others (28, 49). These immune cells have an activated phenotype and can even be found in the BAL (49). Tissue damage results in a hyaloid membrane, a layer of dead and dying cells in the alveoli that may limit gas exchange (48).



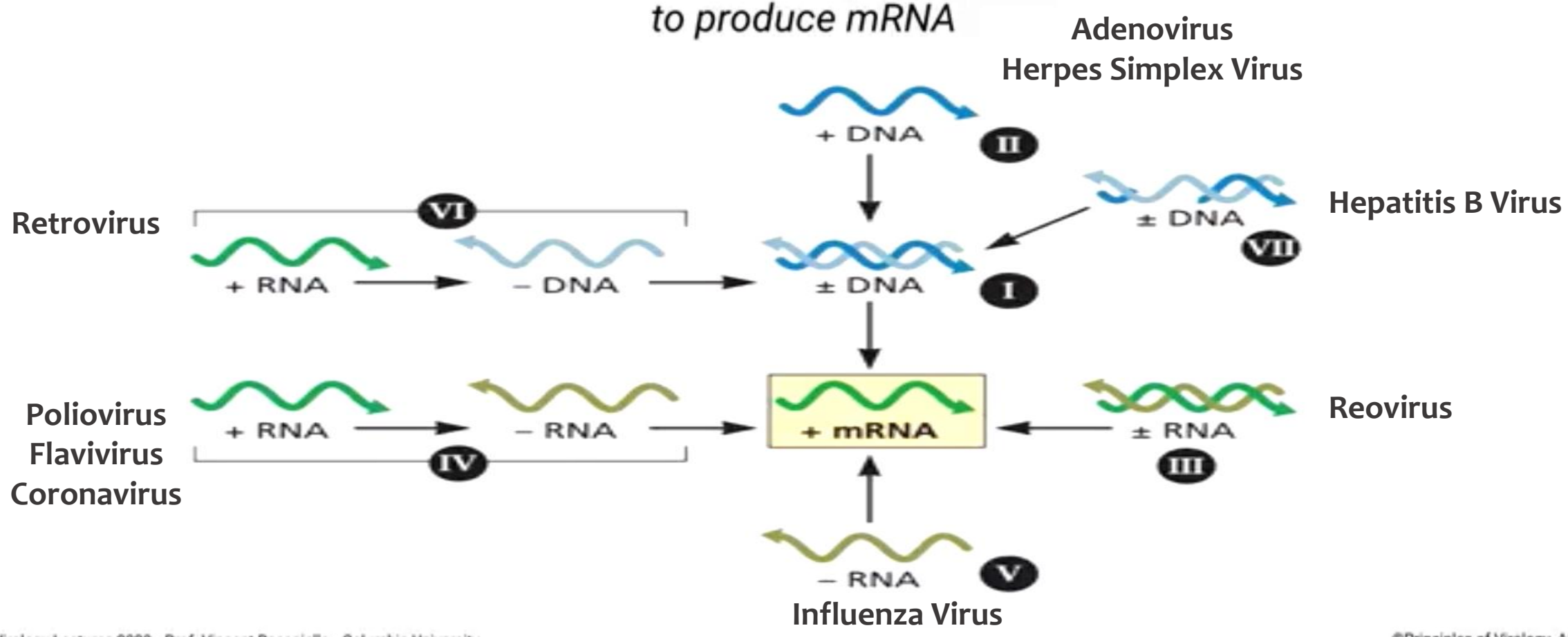


Iba T, et al, 2020


Pattern of Disease Progression for COVID-19 in China
Lab Diagnostic
Isolation / Hospitalization
Mild
Moderate
Severe
Critical
Recovery
Death
Onset
Isolation / Hospitalization
ICU
WHO China Joint Mission on COVID-19 Final Report – As of Feb 20, 2020
World Health Organization

The elegance of the Baltimore system

Knowing only the nature of the viral genome, one can deduce the basic steps that must take place to produce mRNA



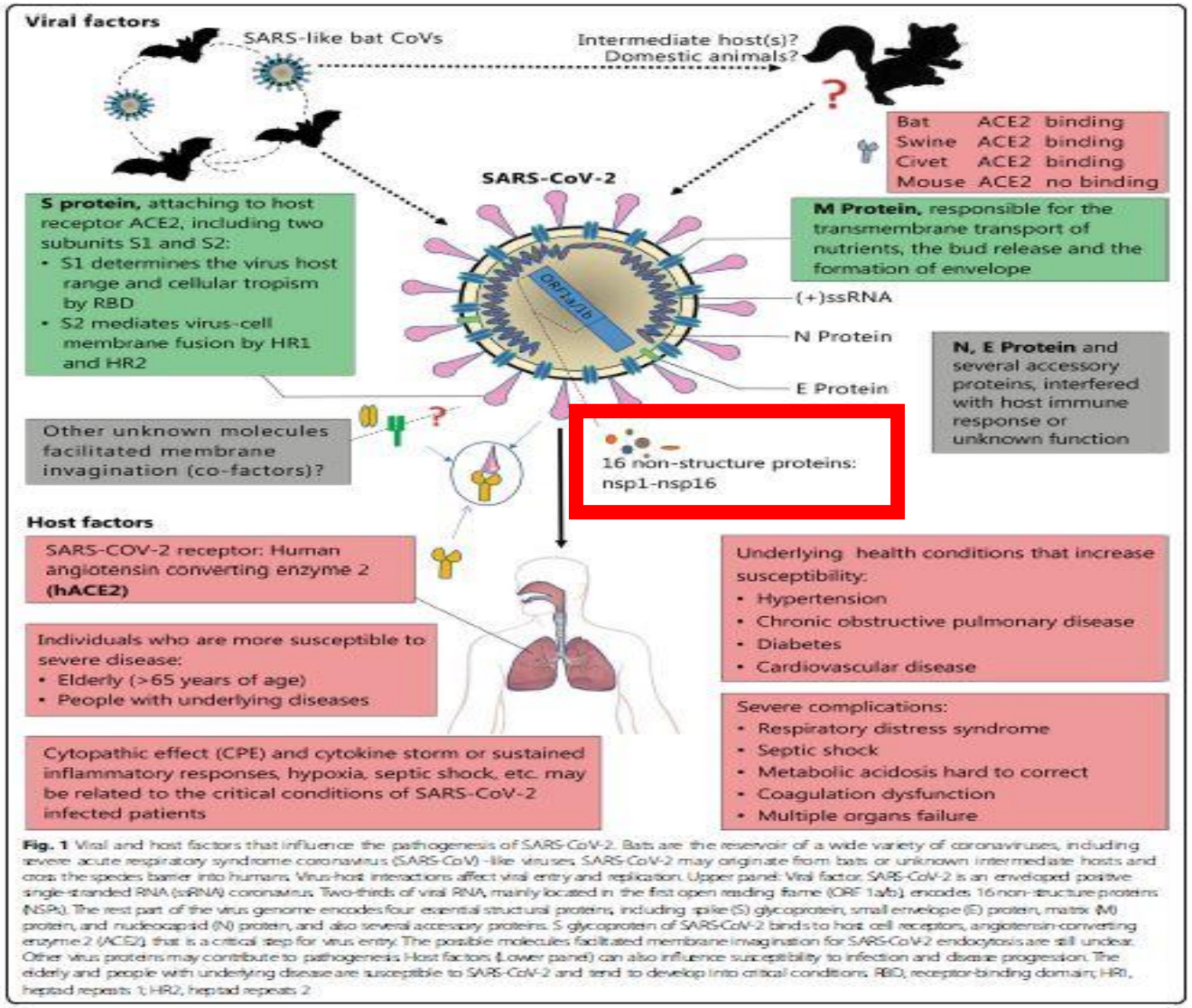


Fig. 1 Viral and host factors that influence the pathogenesis of SARS-CoV-2. Bats are the reservoir of a wide variety of coronaviruses, including severe acute respiratory syndrome coronavirus (SARS-CoV) -like viruses. SARS-CoV-2 may originate from bats or unknown intermediate hosts and cross the species barrier into humans. Virus-host interactions affect viral entry and replication. Upper panel: Viral factor. SARS-CoV-2 is an enveloped positive single-stranded RNA (ssRNA) coronavirus. Two-thirds of viral RNA, mainly located in the first open reading frame (ORF 1a/b), encodes 16 non-structure proteins (NSPs). The rest part of the virus genome encodes four essential structural proteins, including spike (S) glycoprotein, small envelope (E) protein, matrix (M) protein, and nucleocapsid (N) protein, and also several accessory proteins. S glycoprotein of SARS-CoV-2 binds to host cell receptors, angiotensin-converting enzyme 2 (ACE2), that is a critical step for virus entry. The possible molecules facilitated membrane invagination for SARS-CoV-2 endocytosis are still unclear. Other virus proteins may contribute to pathogenesis. Host factors (Lower panel) can also influence susceptibility to infection and disease progression. The elderly and people with underlying disease are susceptible to SARS-CoV-2 and tend to develop into critical conditions. RBD, receptor-binding domain; HR1, heptad repeats 1; HR2, heptad repeats 2.

DeTar Healthcare System | Texas A&M Medicine

unitec Laureate International Universities

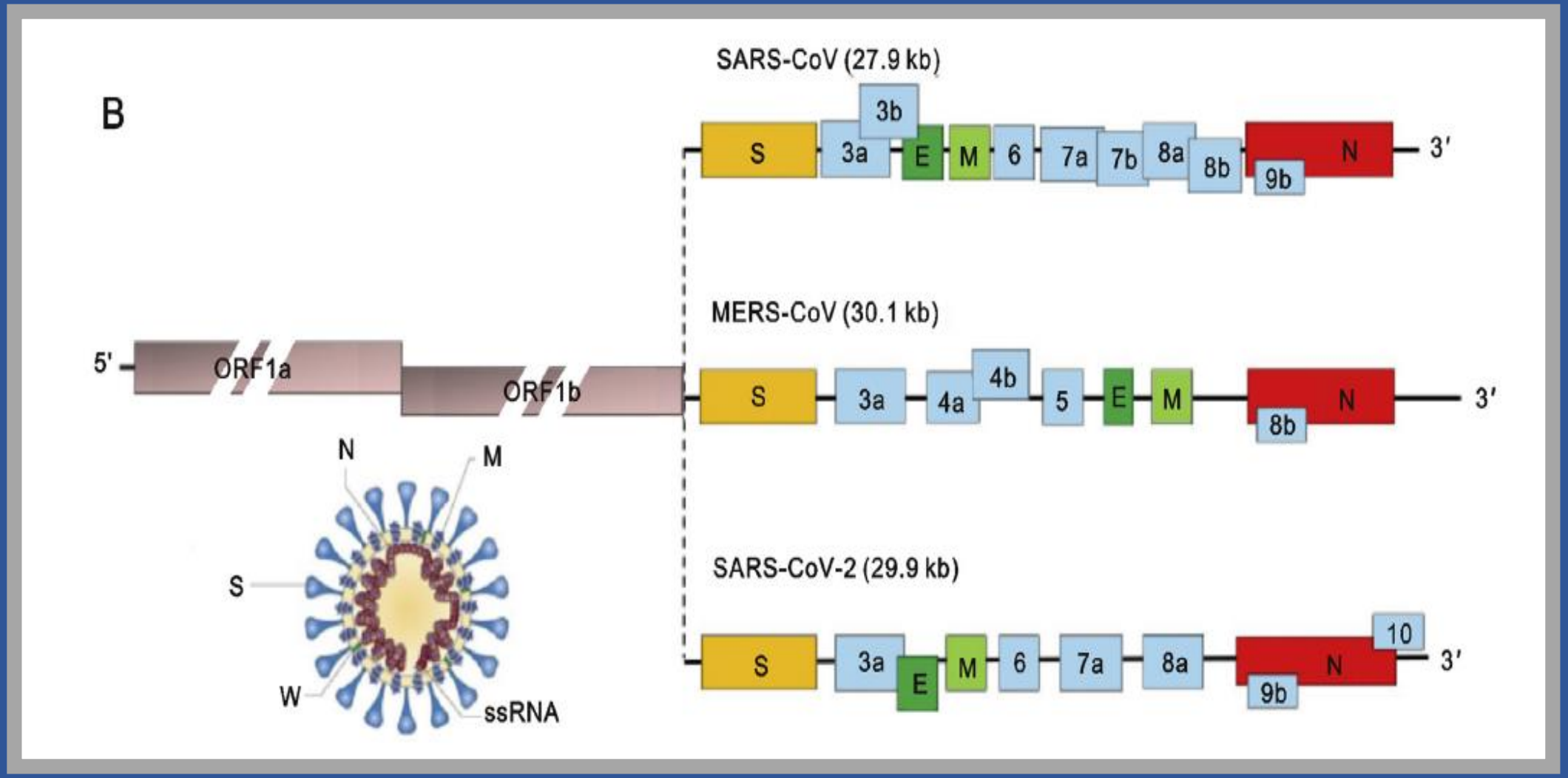
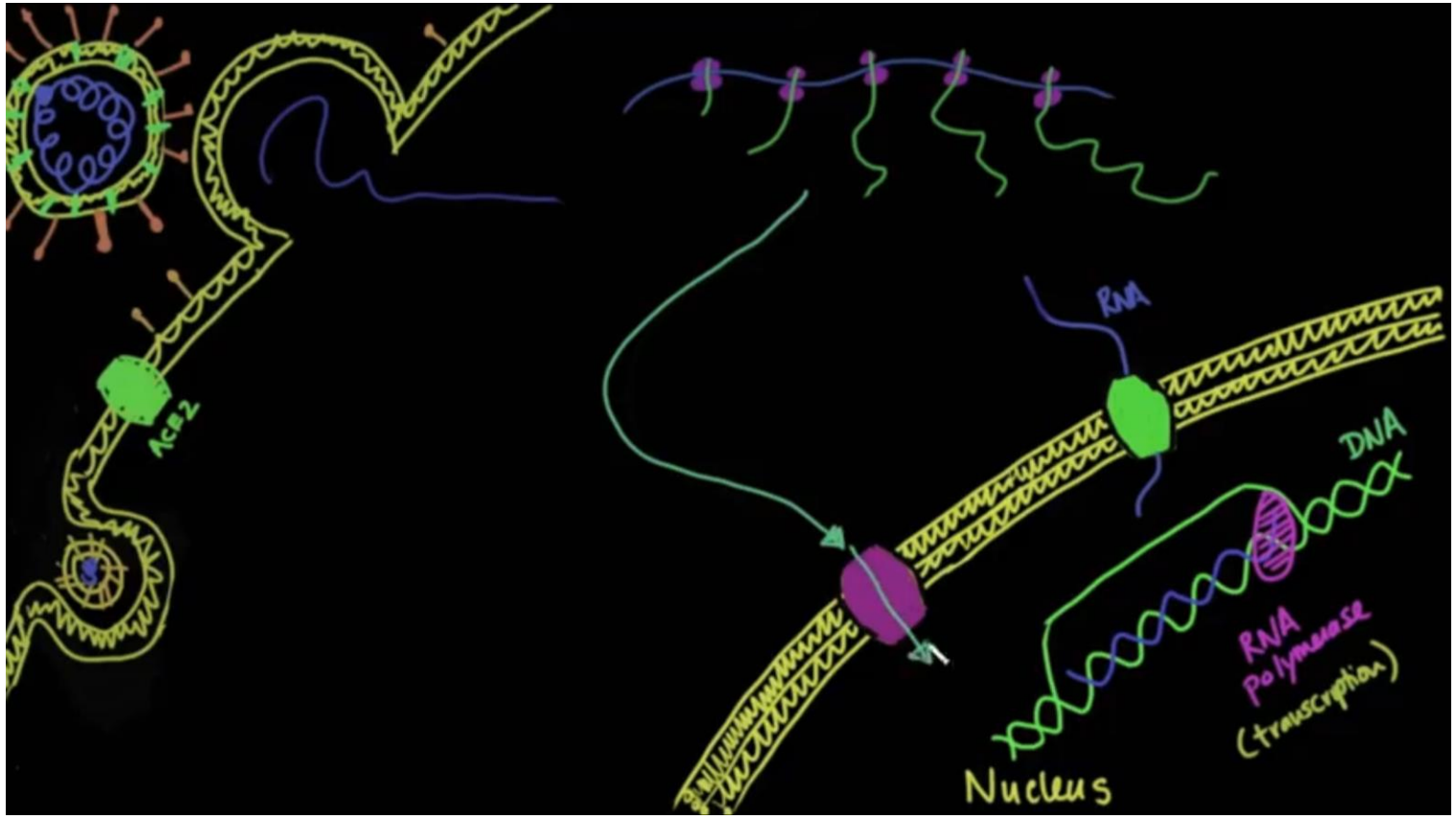


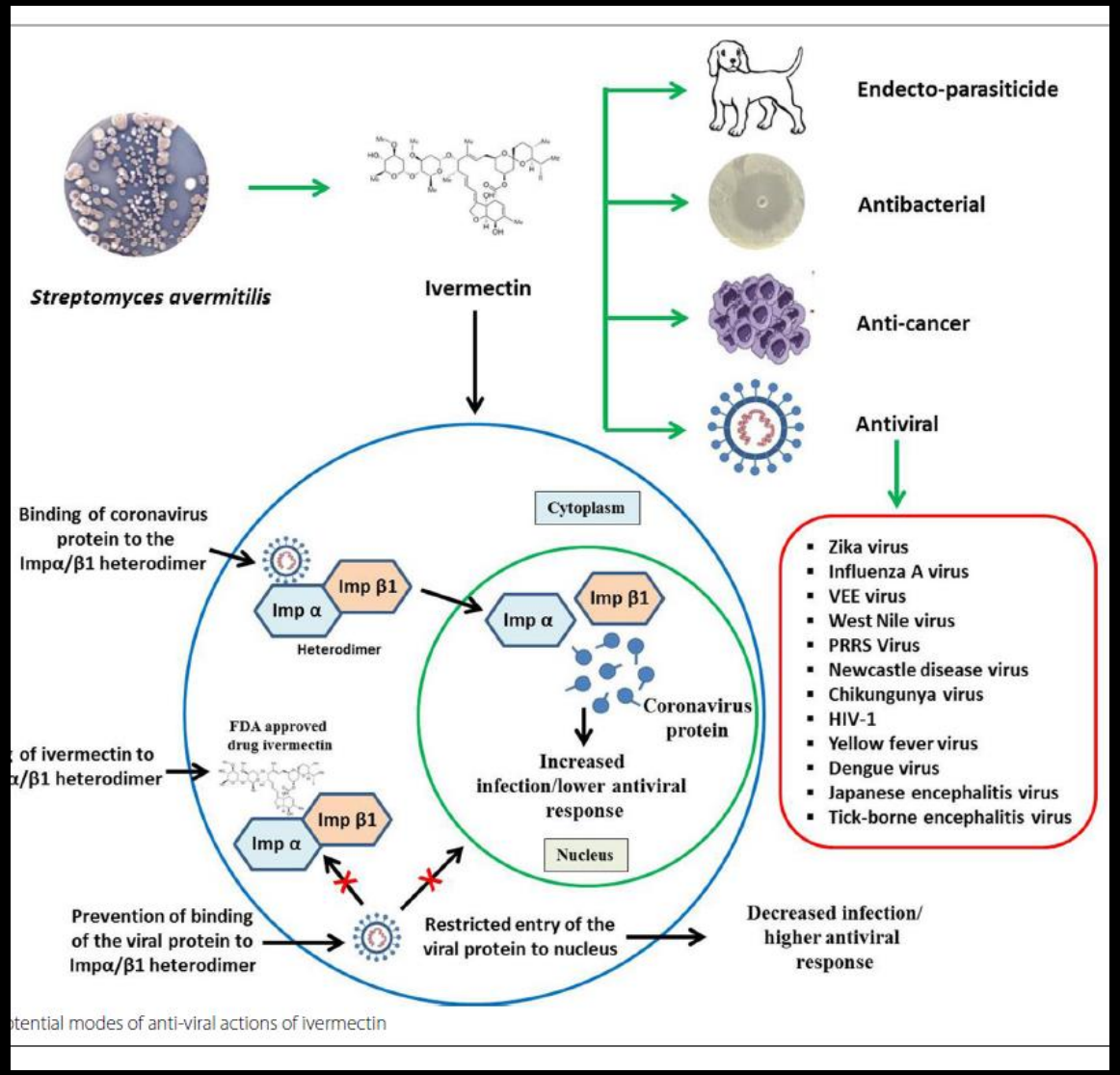
Fig. 1. (B) Coronaviruses form enveloped and spherical
particles of 100e160 nm in diameter. They contain a positivesense single stranded RNA (ssRNA) genome of 26e32 kb in size. In SARS-CoV, MERS-CoV and SARS-CoV-2, the 50-
terminal two-thirds of the genome ORF1a/b encodes polyproteins, which form the viral replicase transcriptase complex. The other ORFs on the one-third of the genome encode four
main structural proteins: spike (S), envelope (E), nucleocapsid (N) and membrane (M) proteins, as well as several accessory proteins.

Li, X., Geng, M., Peng, Y., Meng, L., & Lu, S. (2020). Molecular immune pathogenesis and diagnosis of COVID-19. Journal of pharmaceutical analysis, 10(2), 102–108. https://doi.org/10.1016/j.jpha.2020.03.001

MEDCRAM

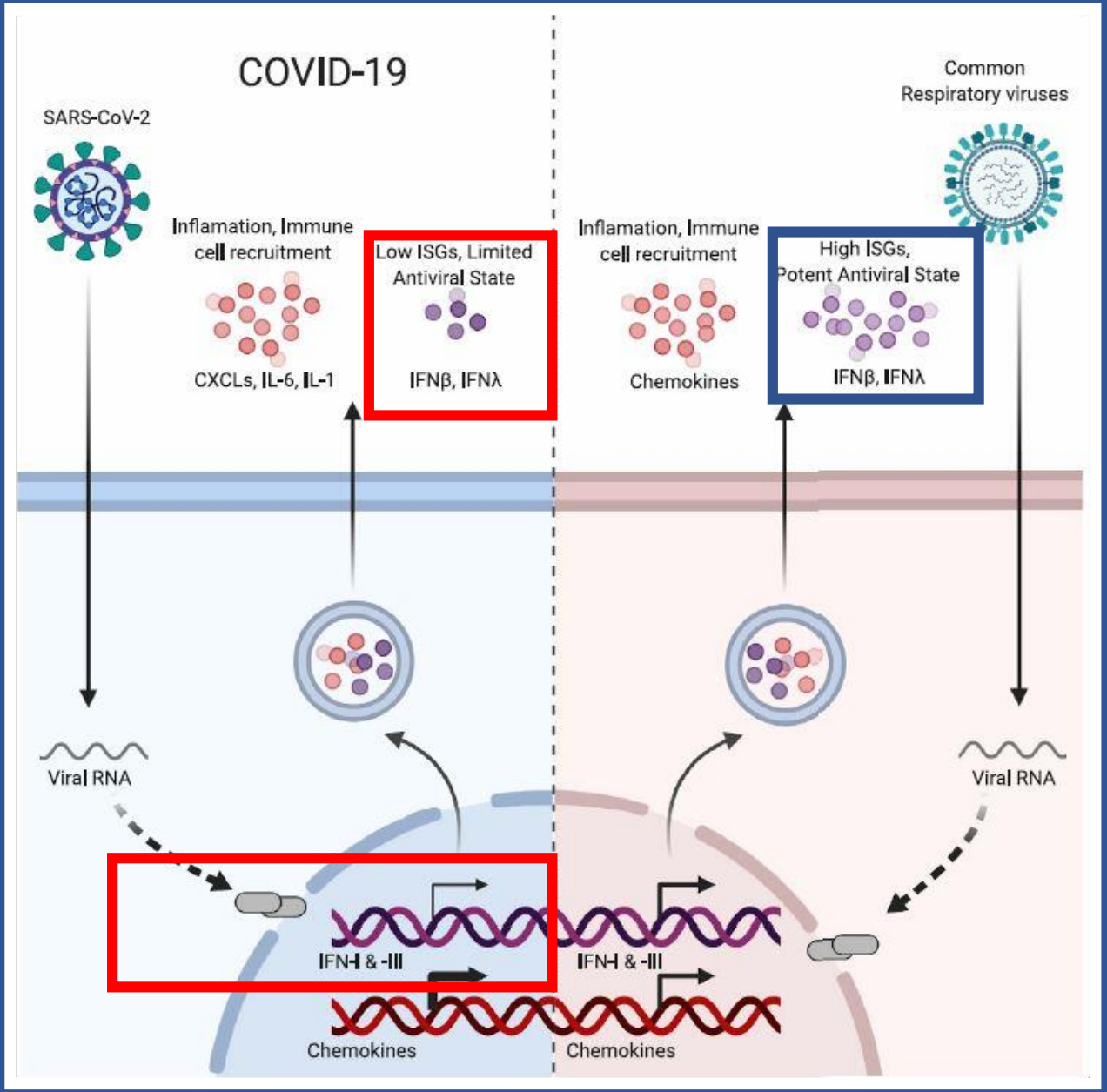


- *Sharun et al. Ann Clin Microbiol Antimicrob 2020 19:23*

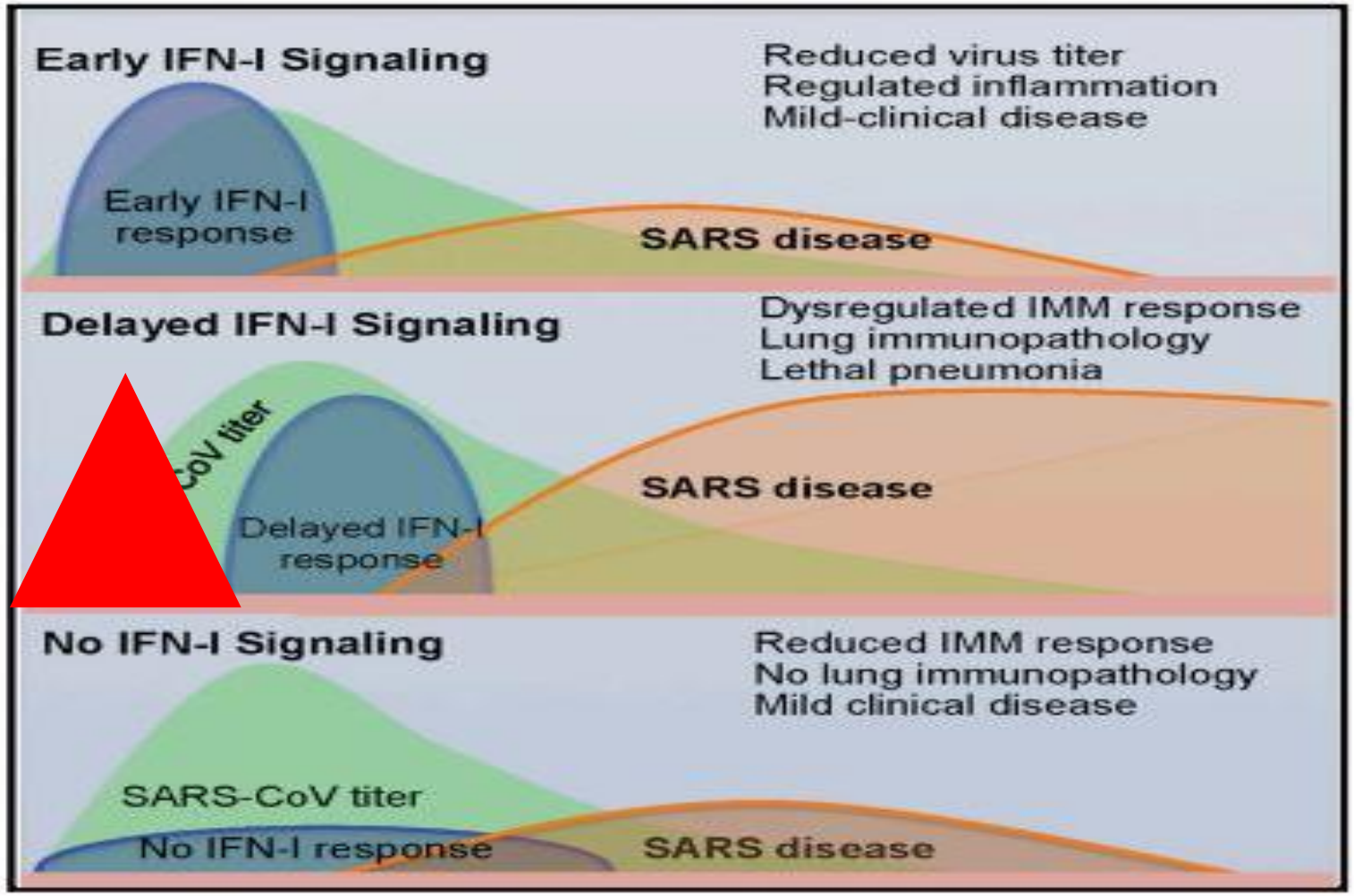


Imbalanced Host Response to SARS-CoV-2 Drives Development of COVID-19

Daniel Blanco-Melo,
Benjamin E. Nilsson-Payant,
Wen-Chun Liu, Jean K. Lim,
Randy A. Albrecht,
Benjamin R. tenOever

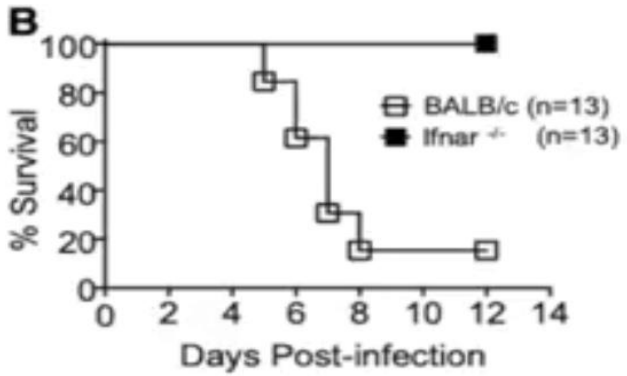


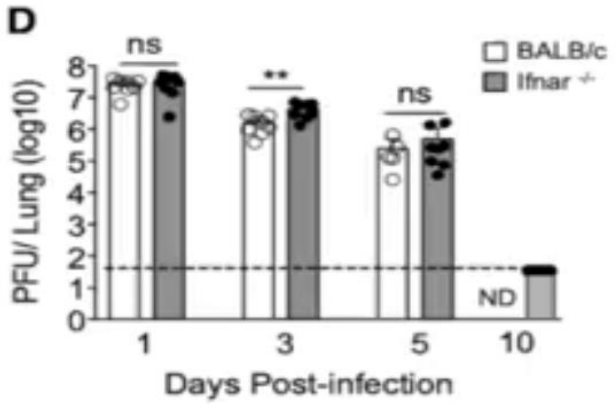
Interferon Rol

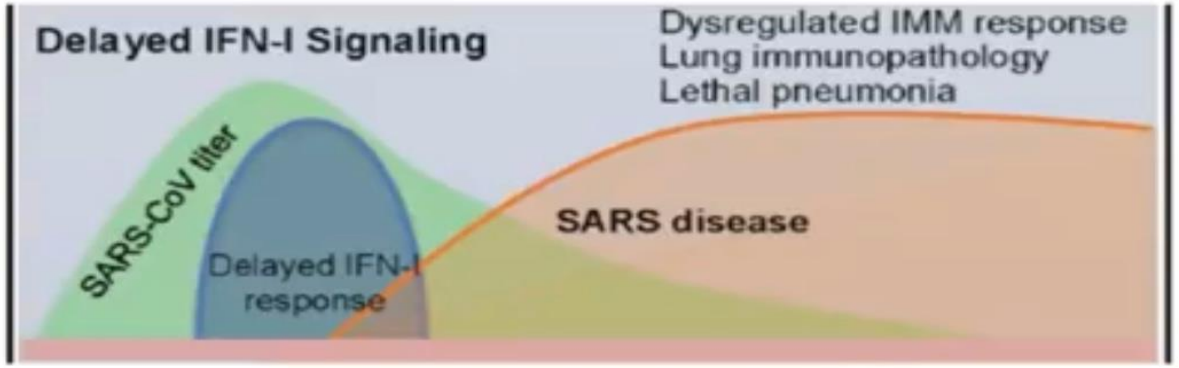


Cell Host & Microbe *19*, 181–193, February 10, 2016 ©2016 Elsevier Inc.

SARS pathogenesis is linked to delayed IFN-I signaling and subsequent immune toxicity





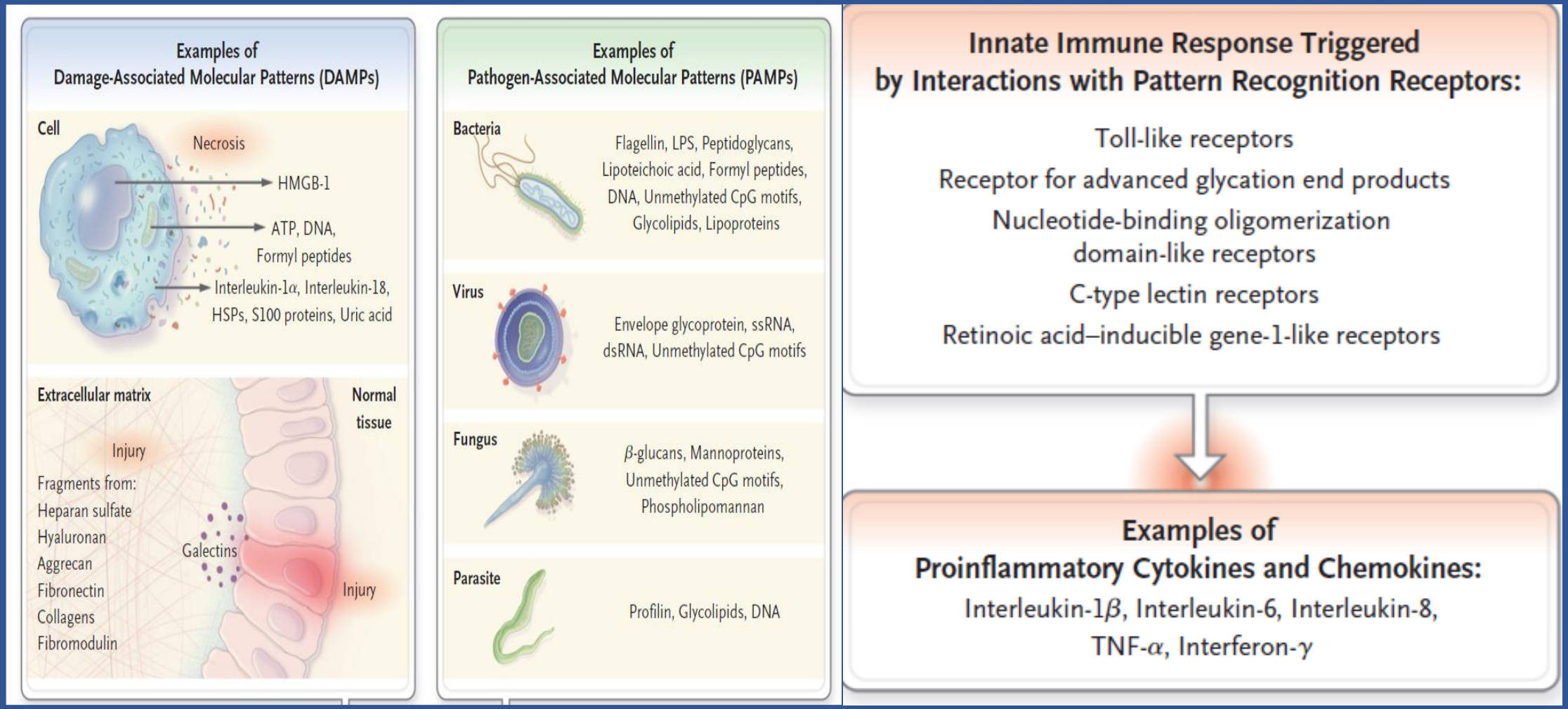


Cell Host & Microbe 19, 181–193, February 10, 2016

High initial virus titers due to a late interferon response
—> drives aberrant recruitment of pathogenic inflammatory monocyte-macrophages (IMMs), activation of innate immune response
—> cytotoxicity

Patter Recognition Receptors: the key to understanding the CRS

Classification : DAMP & PAMP



N ENGL J MED 363;8 NEJM.ORG AUGUST 19, 2010

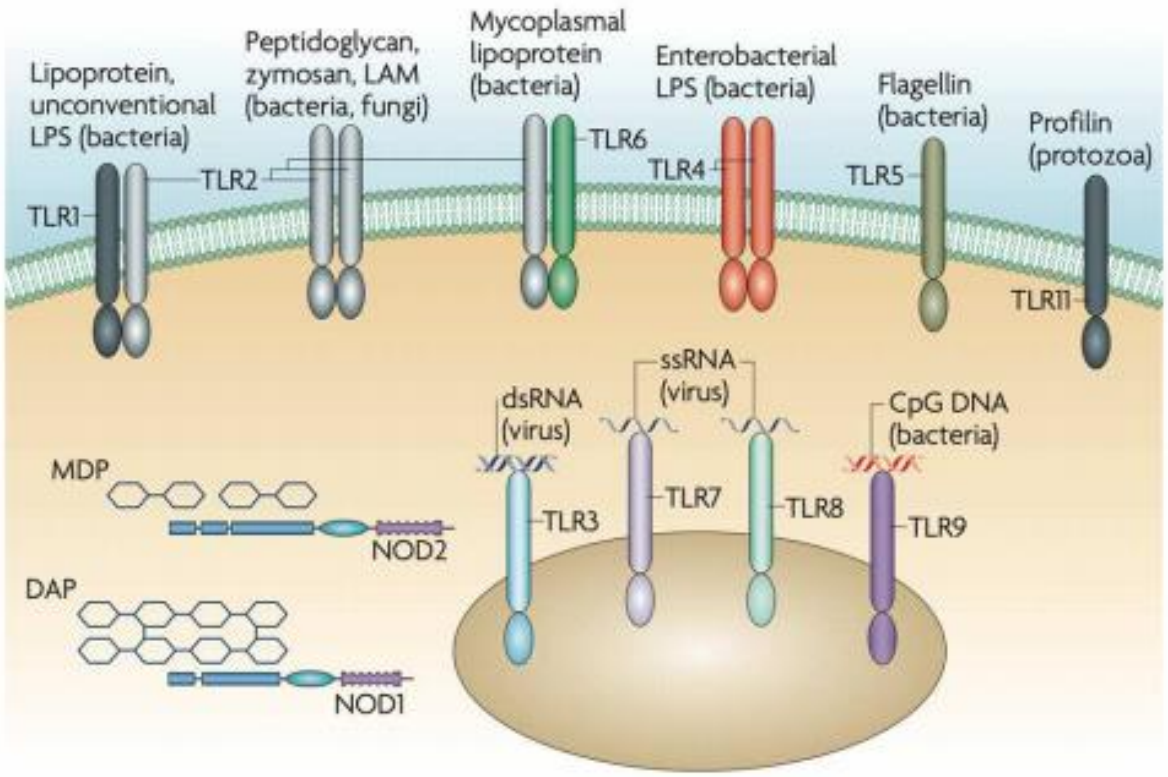
Pathogen Response – innate immunity

Pattern recognition receptors (PRRs) are proteins capable of recognizing:

- Pathogen-associated molecular patterns (PAMPs)
- Damage-associated molecular patterns (DAMPs).

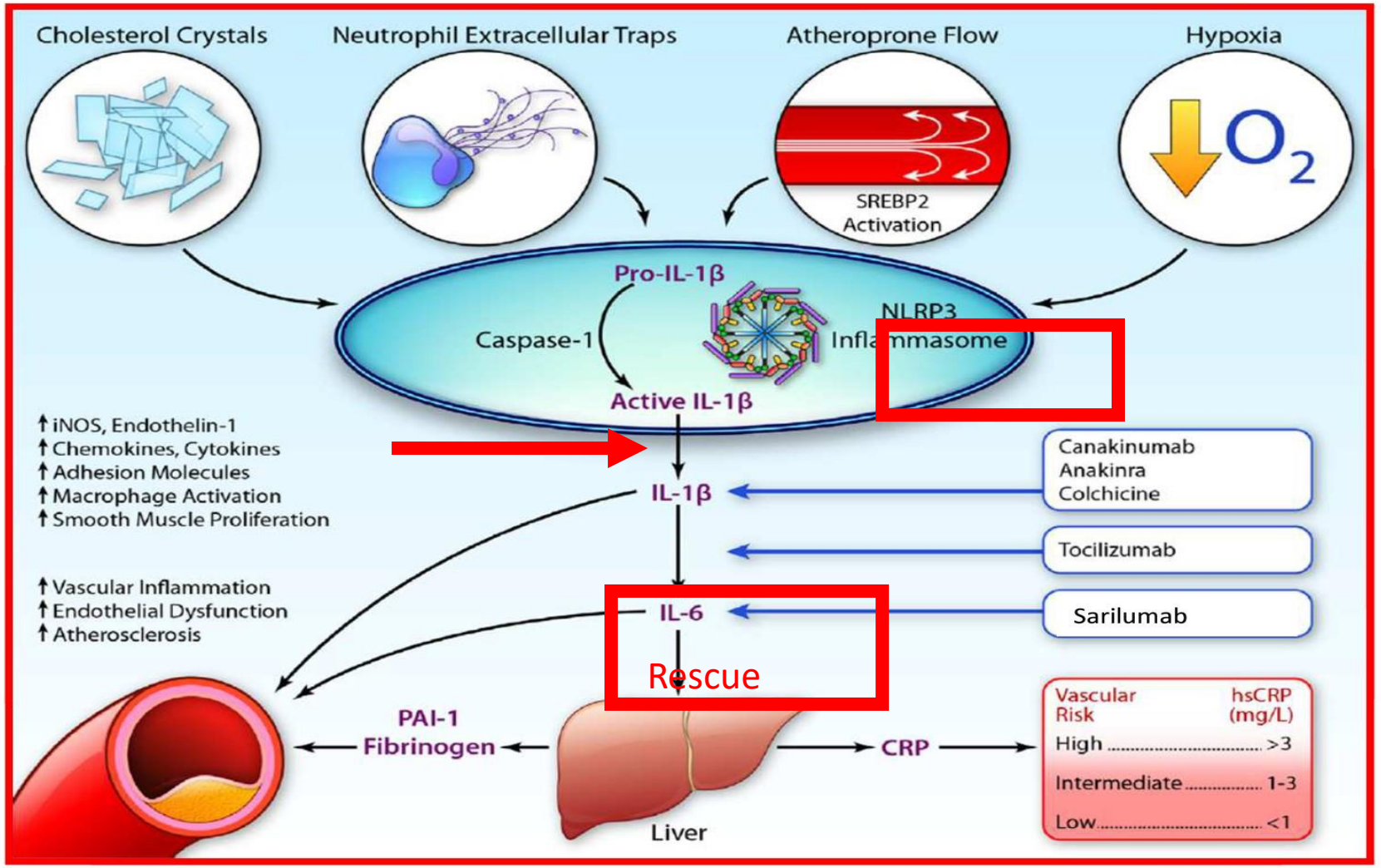
Can be membrane bound or cytoplasmic

Most well known are the Toll-like receptors (TLR)



Downstream signaling initiates the immune response, transcription of pro-inflammatory genes, cytokine release, and recruitment of other inflammatory cells

From CRP to IL-6 to IL-1: Moving Upstream to Identify novel Targets for Atheroprotection



Circ Res 2016;118:145-156.

Cytokine release syndrome

Alexander Shimabukuro-Vornhagen, Philipp Gödel, Marion Subklewe, Hans Joachim Stemmler, Hans Anton Schlößer, Max Schlaak, Matthias Kochanek, Boris Böll and Michael S. von Bergwelt-Baildon

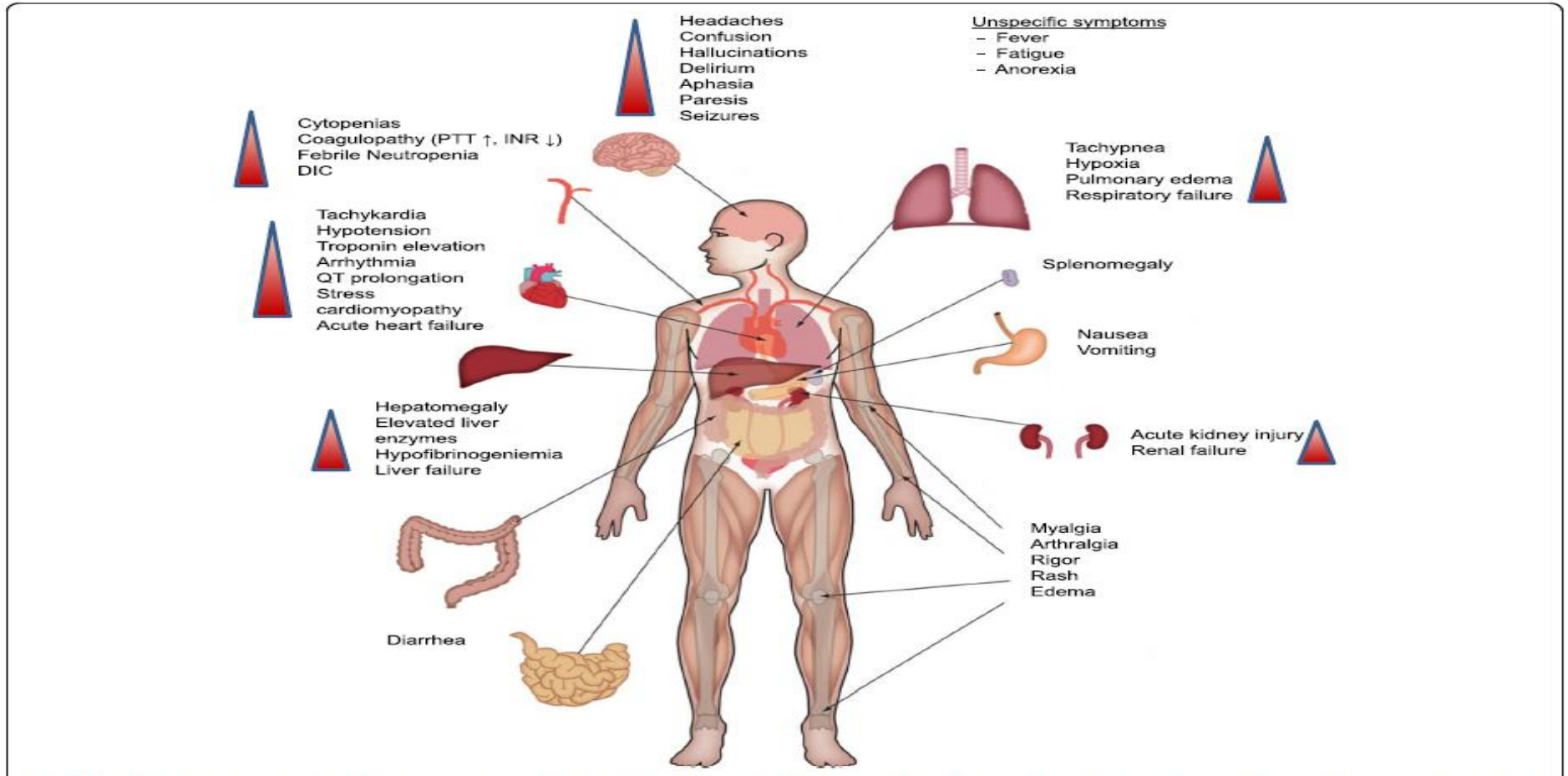


Fig. 1 Clinical presentation of CRS. Beginning with fever and unspecific symptoms CRS might impact most organ systems. Mild cases can present as flu-like illness. Grade °III to IV shows signs of life threatening cardiovascular, pulmonary and renal involvement. Neurotoxicity can occur concurrent or with delay. Abbreviations: DIC: disseminated intravascular coagulation; INR: international normalized ratio; PTT: partial thromboplastin time

Shimabukuro-Vornhagen et al. Journal for ImmunoTherapy of Cancer

Table 1. Clinical studies on the efficacy of ivermectin as a prophylactic agent against COVID-19

Prophylaxis Trials					% Ivermectin vs. % Controls
AUTHOR, COUNTRY, SOURCE	STUDY DESIGN, SIZE	STUDY SUBJECTS	IVERMECTIN DOSE	DOSE FREQUENCY	CLINICAL OUTCOMES REPORTED
Elgazzar A, Egypt ResearchSquare doi.org/10.21203/rs.3.rs-100956/v1	RCT N=200	Health care and Household contacts of pts with +COVID-19 PCR test	0.4mg/kg	Two doses, Day 1 and Day 7	2% vs. 10% tested positive for COVID-19 p<.05
Shouman W, Egypt *www.clinicaltrials.gov* NCT04422561	RCT N=304	Household members of pts with +COVID-19 PCR test	40–60kg: 15mg 60–80kg: 18mg > 80kg: 24mg	Two doses, 72 hours apart	7.4% vs. 58.4% developed COVID-19 symptoms, p<.001
Carvallo H, Argentina *www.clinicaltrials.gov* NCT04425850	RCT N=229	Healthy patients negative for COVID-19 PCR	0.2mg drops	1 drop five times a day x 28 days	0.0% vs. 11.2% contracted COVID-19 p<.001
Behera P, India *medRxiv* doi.org/10.1101/2020.10.29.20222661	OCT N=186 case control pairs	Health Care Workers	0.3 mg/kg	Day 1 and Day 4	2 doses reduced odds of contracting COVID-19 (OR 0.27 95% CI 0.16–0.53)

Table 2. Case count decreases in Brazilian cities with ivermectin distribution programs
(bolded cities distributed ivermectin, neighboring city listed below did not)

Region	Confirmed new cases/month	June	July	August	Population 2020 (1000)	% August vs. June/July
South	**Itajaí**	**2123**	**2854**	**998**	**223**	**40%**
	Chapecó	1760	1754	1405	224	80%
North	**Macapá**	**7966**	**2481**	**2370**	**503**	**45%**
	Ananindeua	1520	1521	1014	535	67%
North East	**Natal**	**9009**	**7554**	**1590**	**890**	**19%**
	João Pessoa	9437	7963	5384	817	62%

Table 3. Clinical studies on the efficacy of ivermectin in mildly ill outpatients with COVID-19

Clinical Trials – Outpatients					
AUTHOR, COUNTRY, SOURCE	STUDY DESIGN, SIZE	STUDY SUBJECTS	IVERMECTIN DOSE	DOSE FREQUENCY	CLINICAL OUTCOMES REPORTED
Carvallo H, Argentina *medRxiv* doi.org/10.1101/2020.09.10.20191619	Case Series N=167	Outpatients and hospitalized	24mg=mild, 36mg=moderate, 48mg=severe	Days 0 and 7	All 135 with mild illness survived, 1/32 (3.1% of hospitalized patients died
Mahmud R, Bangladesh *www.clinicaltrials.gov* NCT0452383	RCT N=363	Outpatients and hospitalized	12mg + doxycycline	Once, within 3 days of PCR+ test	Early improvement 60.7% vs. 44.4%, p<.03, deterioration 8.7% vs 17.8%, p<.02
Podder CS, Bangladesh *IMC J Med Sci 2020;14(2)*	RCT, N=62	Outpatients	0.2 mg/kg	Once	Recovery time 10.1 vs 11.5 days (NS), average time 5.3 vs 6.3 (NS)
Alam A, Bangladesh, *J of Bangladesh College Phys and Surg*, 2020;38:10-15 doi.org/10.3329/jbcps.v38i0.47512	Case series N=100	Outpatients	0.2 mg/kg/kg + doxycycline	Once	All improved within 72 hours
Chowdhury A, Bangladesh *Research Square* doi:10.21203/rs.3.rs-38896/v1	RCT N=116	Outpatients	0.2 mg//kg + doxycycline	Once	Recovery time 5.93 vs 9.33 days (p=.071)
Morgenstern J, Dominican Republic *medRxiv* doi: https://doi.org/10.1101/2020.10.29.20222505	Case Series N=3,099	Outpatients and hospitalized	Outpatients: 0.4mg/kg Hospital Patients: 0.3mg/kg	Outpatients:0.3mg/kg x 1 dose Inpatients: 0.3mg/kg, Days 1,2,6,7	Mortality = 0.03% in 2688 outpatients, 1% in 300 non-ICU hospital patients, 30.6% in 111 ICU patients

Table 4. Clinical studies on the efficacy of ivermectin in hospitalized patients with COVID-19

Clinical Trials – Hospitalized Patients					
AUTHOR, COUNTRY, SOURCE	STUDY DESIGN, SIZE	STUDY SUBJECTS	IVERMECTIN DOSE	DOSE FREQUENCY	CLINICAL OUTCOMES REPORTED
Elgazzar A, Egypt ResearchSquare doi.org/10.21203/rs.3.rs-100956/v1	RCT N=400	Hospitalized Patients	0.4 mg/kg	Once	Moderate Illness worsened (1% vs 22%, p<.001. Severe illness worsened 4% vs 30%, mortality 2% vs 20%, p<.001
Rajter JC, Florida *Chest 2020* doi.org/10.1016/j.chest.2020.10.009	OCT N=280	All hospitalized patients	0.2 mg/kg + azithromycin	Day 1 and Day 7 if needed	Overall mortality 15.0% vs. 25.2%, p=.03, Severe illness mortality 38.8 vs. 80.7%, p=.001)
Khan X, Bangladesh *Arch Bronconeumol. 2020* doi.org/10.1016/j.arbres.2020.08.007	OCT N=248	All hospitalized patients	12 mg	Once on admission	Mortality 0.9% vs. 6.8%, p<.05, LOS 9 vs. 15 days, p<.001
Gorial FI, Iraq *medRxiv* doi.org/10.1101/2020.07.07.20145979	OCT N=87	All Hospitalized patients	0.2 mg/kg + HCQ and azithromycin	Once on admission	LOS 7.6 vs. 13.2, p<.001, 0/15 vs. 2/71 died
Soto-Beccerra P, Peru *medRxiv* doi.org/10.1101/2020.10.06.20208066	OCT N=5683, IVM, N=563	Hospitalized patients, database analysis	Unknown dose <48hrs after admission	Unknown	No benefits found
Hashim H, Iraq *medRxiv* doi.org/10.1101/2020.10.26.20219345	RCT N=140	2/3 outpatients, 1/3 hospital pts	0.2 mg/kg + doxycycline	Daily for 2–3 days	Recovery time 6.3 vs 13.6 days (p<.001), 0% vs 27.3% mortality in severely ill (p=.052)
Portman-Baracco A, Brazil *Arch Bronconeumol. 2020* Doi.org/10.1016/j.arbres.2020.06.011	OCT N=1408	All Hospitalized patients	0.15 mg/kg	Once	Overall mortality 1.4% vs. 8.5%, HR 0.2, 95% CI 0.11-0.37, p<.0001

Figure 1. Meta-analysis of ivermectin clinical studies

Group by RCT-Obs	Study name	Odds ratio	Lower limit	Upper limit	Z-Value	p-Value
OBS	Rajter	0.524	0.287	0.958	-2.099	0.036
OBS	Khan	0.121	0.015	0.969	-1.990	0.047
OBS	Gorial	0.842	0.039	18.393	-0.109	0.913
OBS		0.477	0.270	0.844	-2.546	0.011
RCT	Mahmud	0.138	0.007	2.694	-1.306	0.192
RCT	Hashim	0.314	0.061	1.611	-1.389	0.165
RCT	Elgazzar	0.074	0.017	0.318	-3.502	0.000
RCT		0.140	0.050	0.389	-3.772	0.000
Overall		0.357	0.217	0.587	-4.060	0.000

Statistics for each study

Odds ratio and 95% CI

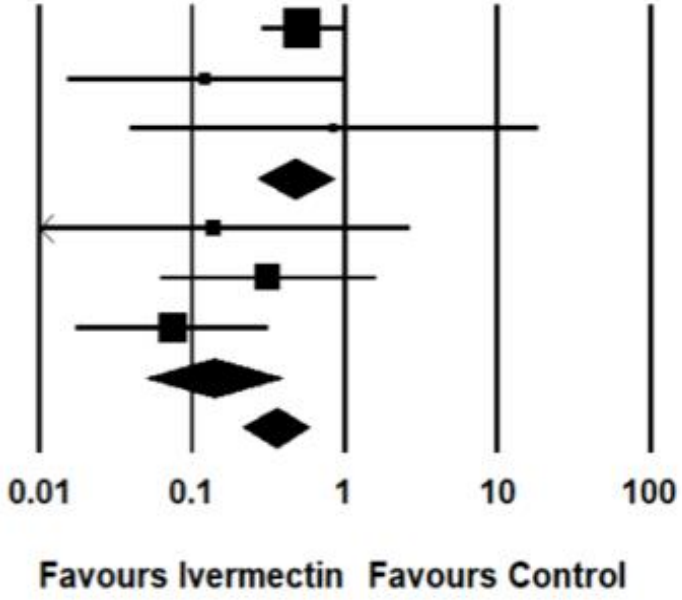


Figure 2. Total deaths/population and case incidence for COVID-19/population in population older than 60 years old for eight Peruvian states deploying mass ivermectin treatment

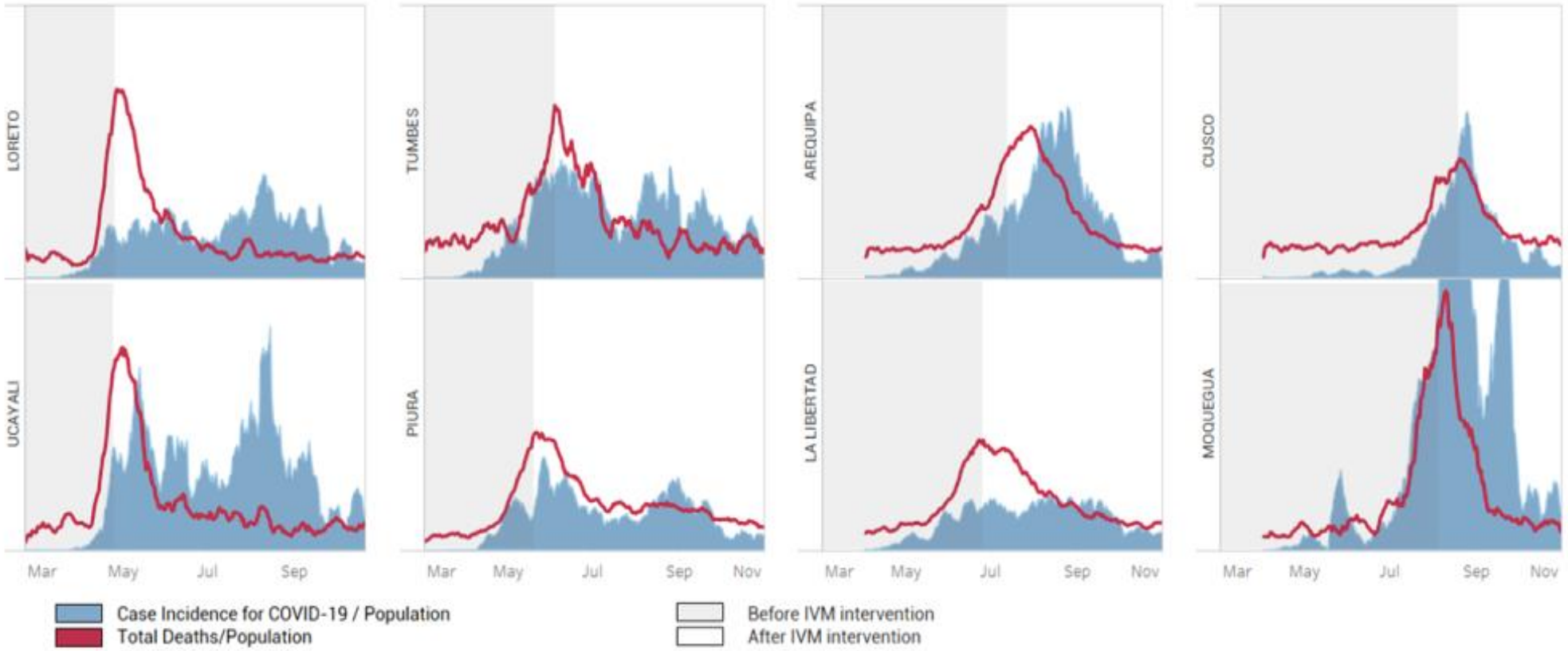
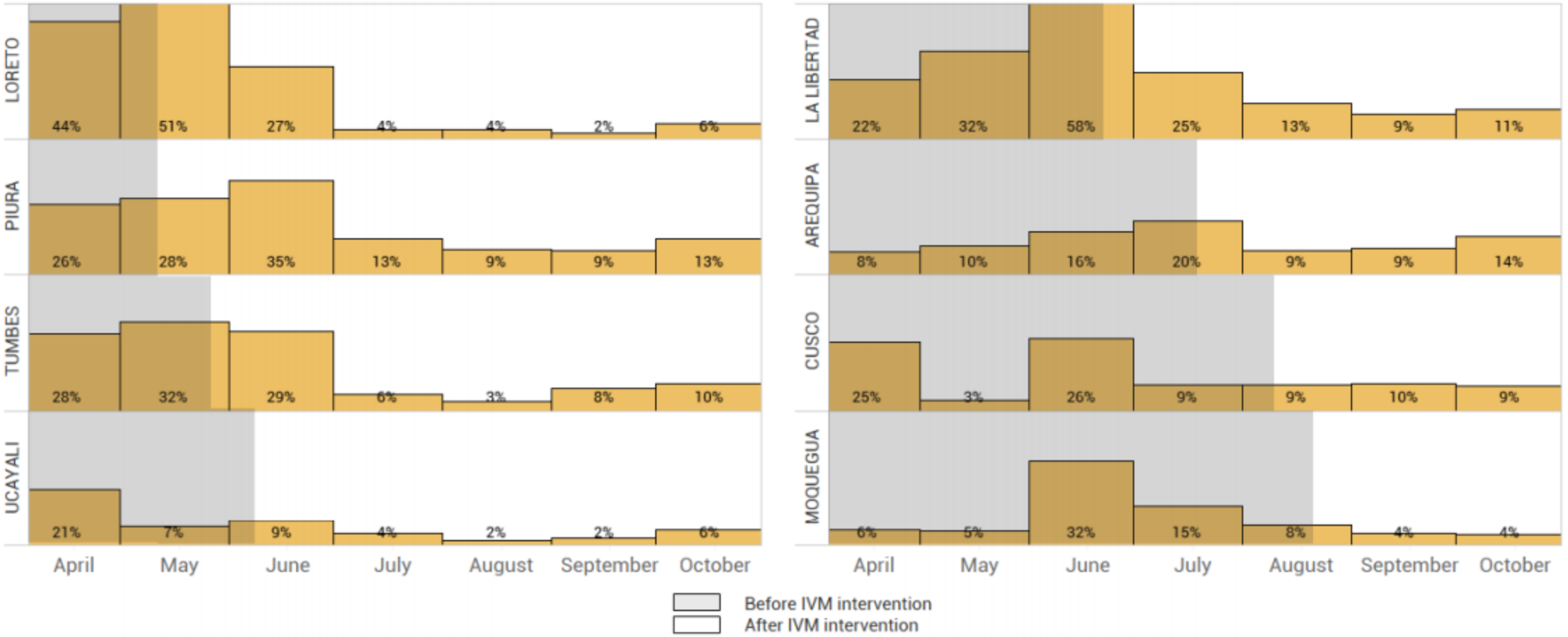


Figure 3. Case fatality rate in population older than 60 years old for eight Peruvian states deploying mass ivermectin treatment



Source: Datos Abiertos Gobierno de Perú SINADEF_DATOS_ABIERTOS_08112020 Data Analyst: Juan Chamie @jjchamie

Table 5. Change in death rates among neighboring regions in Brazil

(bolded regions contained a major city that distributed Ivermectin to its citizens, the other regions did not)

REGION	STATE	% CHANGE IN AVERAGE DEATHS/ WEEK COMPARED TO 2 WEEKS PRIOR	TOTAL COVID-19 RELATED DEATHS	DEATHS/100K
South	**Santa Catarina**	**–36**	**2,529**	**35.6**
	PARANÁ	–3	3,823	35.3
	Rio Grande do Sul	–5	4,055	33.4
North	**Amapá**	**–75**	**678**	**80.2**
	AMAZONAS	–42	3,892	93.9
	Pará	13	6,344	73.7
North East	**Rio Grande do Norte**	**–65**	**2,315**	**66.0**
	CEARÁ	62	8,666	95.1
	Paraíba	–30	2,627	65.4

Figure 4. Paraguay – COVID-19 case counts and deaths in Alto Parana (blue) after Ivermectin distribution began (yellow highlight), compared to other departments[31,48]

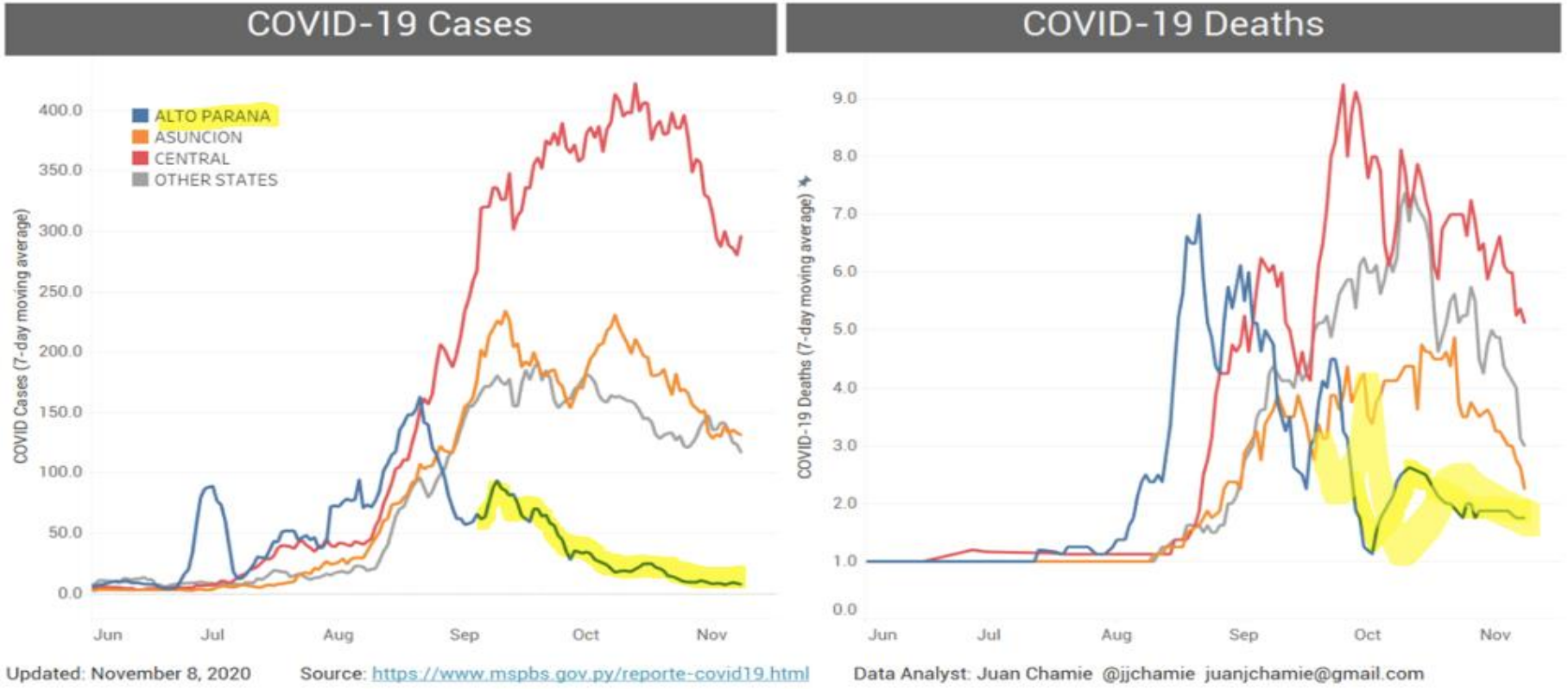


Table 6. I-MASK+ Prophylaxis & Early Outpatient Treatment Protocol for COVID-19

PROPHYLAXIS PROTOCOL	
MEDICATION	RECOMMENDED DOSING
Ivermectin	*Weekly Prophylaxis for high risk individuals*: 0.2 mg/kg* — one dose on day 1 and day 3, then take one more dose every 4 weeks
	*Post COVID-19 exposure prophylaxis***: 0.2 mg/kg* — one dose on day 1 and day 3
Vitamin D3	1,000–3,000 IU/day
Vitamin C	1,000 mg twice daily
Quercetin	250 mg/day
Zinc	50 mg/day elemental zinc
Melatonin	6 mg before bedtime (causes drowsiness)

EARLY OUTPATIENT TREATMENT PROTOCOL***	
MEDICATION	RECOMMENDED DOSING
Ivermectin	0.2 mg/kg* — one dose on day 1 and day 3
Vitamin D3	4,000 IU/day
Vitamin C	2,000 mg 2–3 times daily
Quercetin	250 mg twice a day
Zinc	100 mg/day elemental zinc
Melatonin	10 mg before bedtime
Aspirin	325 mg/day (unless contraindicated)

* ≈ 0.09 mg/lb per dose (take on an empty stomach with water). Example for a person of 50 kg (body weight): 50 kg × 0.15 mg = 7.5 mg (1 kg = 2.2 lbs)= 2.5 tablets (3mg/tablet). See table 6 for weight-based dose calculations

** To use if a household member is COVID-19 positive, or if you have had prolonged exposure to a COVID-19+ patient without wearing a mask

*** For late phase – hospitalized patients – see the FLCCC's "MATH+" protocol on www.flccc.net

Table 7. Suggested ivermectin dose by body weight for prophylaxis and treatment of COVID-19

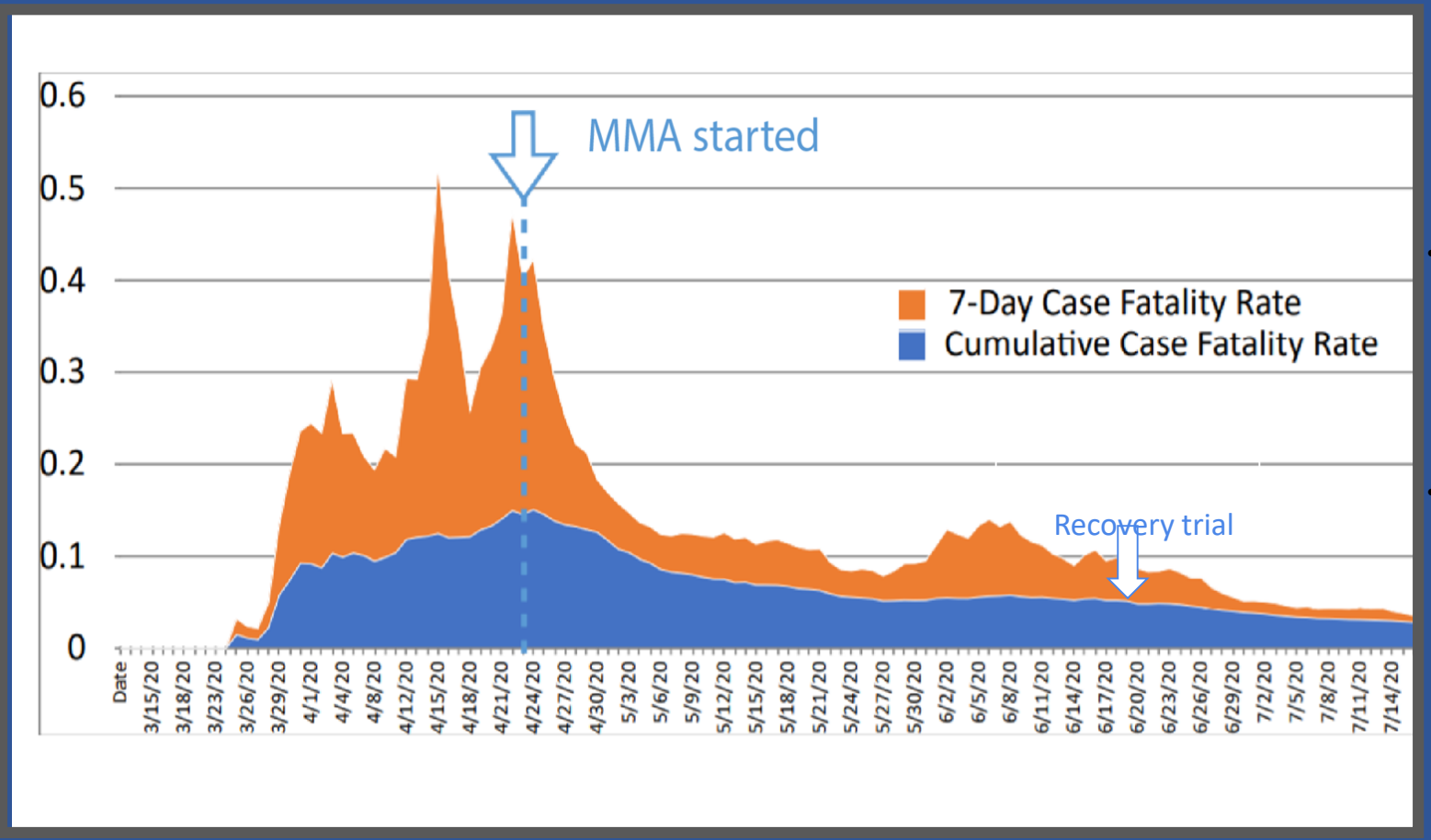
Body weight Conversion (1 kg ≈ 2.2 lbs) (doses calculated per upper end of weight range)		Dose 0.2 mg/kg ≈ 0.09 mg/lb (Each tablet = 3 mg; doses rounded to nearest half tablet above)	
70–90 lb	32–40 kg	8 mg	(3 tablets=9 mg)
91–110 lb	41–50 kg	10 mg	(3.5 tablets)
111–130 lb	51–59 kg	12 mg	(4 tablets)
131–150 lb	60–68 kg	13.5 mg	(4.5 tablets)
151–170 lb	69–77 kg	15 mg	(5 tablets)
171–190 lb	78–86 kg	16 mg	(5.5 tablets)
191–210 lb	87–95 kg	18 mg	(6 tablets)
211–230 lb	96–104 kg	20 mg	(7 tablets=21 mg)
231–250 lb	105–113 kg	22 mg	(7.5 tablets=22.5 mg)
251–270 lb	114–122 kg	24 mg	(8 tablets)
271–290 lb	123–131 kg	26 mg	(9 tablets =27 mg)
291–310 lb	132–140 kg	28 mg	(9.5 tablets=28.5 mg)

Texas A&M University
Health Science Center

Vincent J. VanBuren, PhD, FAHA

Director,
Computational Biology
& Bioinformatics
Laboratory

Resultados



- El 10 de marzo de 2020 se reportó el primer caso de SARS-CoV-2 en Honduras. A principios de abril, la tasa de mortalidad era del 14,5%, una de las más altas de Centroamérica.
- El 23 de abril de 2020 se implementó un protocolo de tratamiento de múltiples mecanismos basado en la fisiopatología de COVID-19.
- Para el 18 de julio de 2020, se había confirmado el SARS-CoV-2 en 31,966 pacientes y la tasa de letalidad había disminuido al 2,66%, lo que representa una disminución del 81,6% con un valor de $p < 2,2x10e-16$.

Texas A&M University
College of Engineering

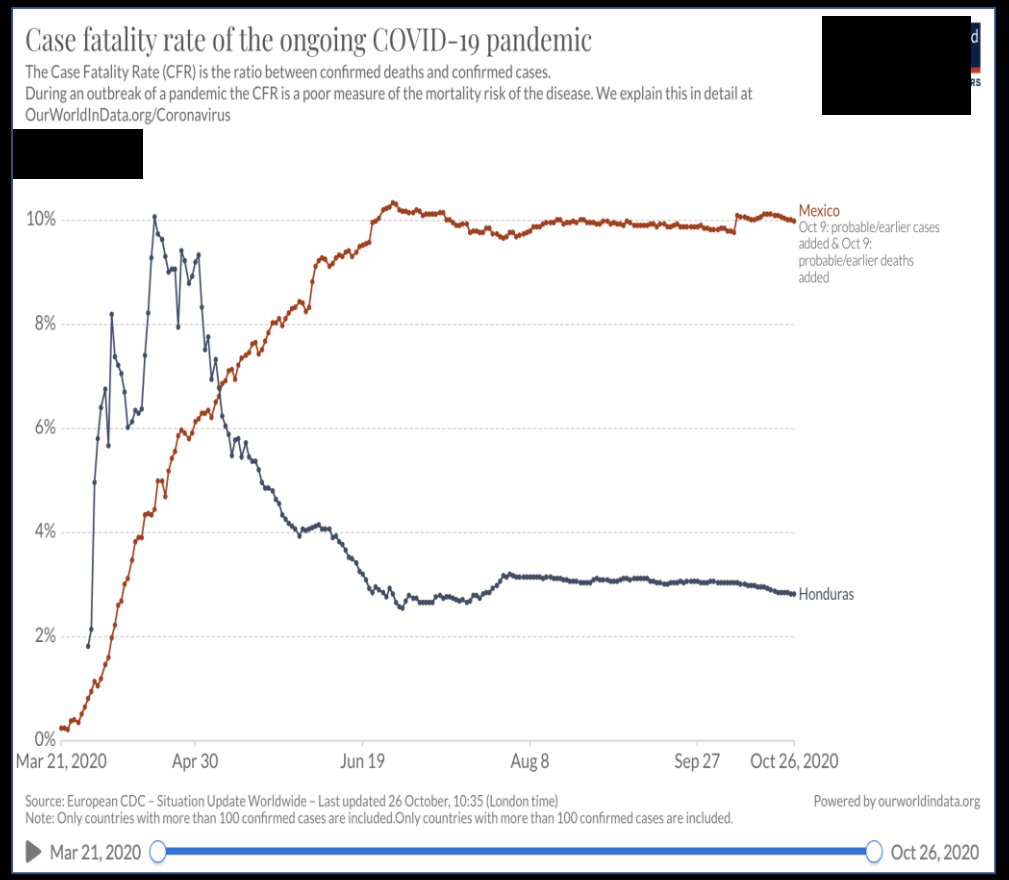
Li Zeng, PhD

Associate Professor
Industrial & Systems Engineering

Epidemiologic Study: Honduras Public Health Initiative

The Honduras Health Department promoted inpatient and outpatient (“MAIZ Pack”)MMA treatment for COVID-19 starting in April 2020.

Mexico’s government issued a “*primum non nocere*” (“above all do no harm”) strategy recommending no medications except optional dexamethasone for hospitalized patients requiring respiratory support.



Statistical Process Control

Pasteur and parachutes: when statistical process control is better than a randomized controlled trial

M Diaz, D Neuhauser

Qual Saf Health Care 2005;14:140–143. doi: 10.1136/qshc.2005.013763

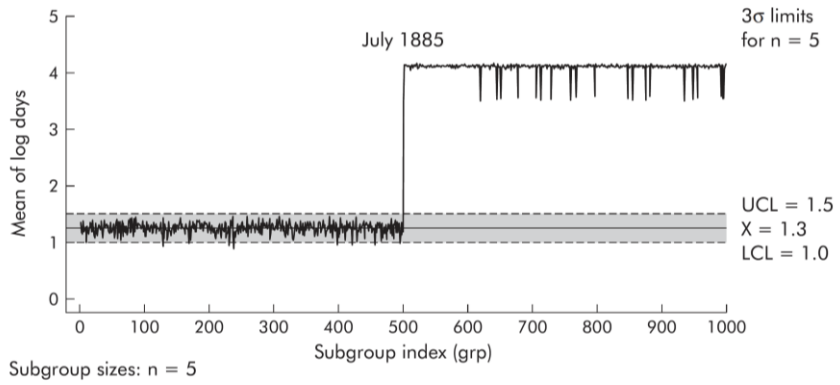
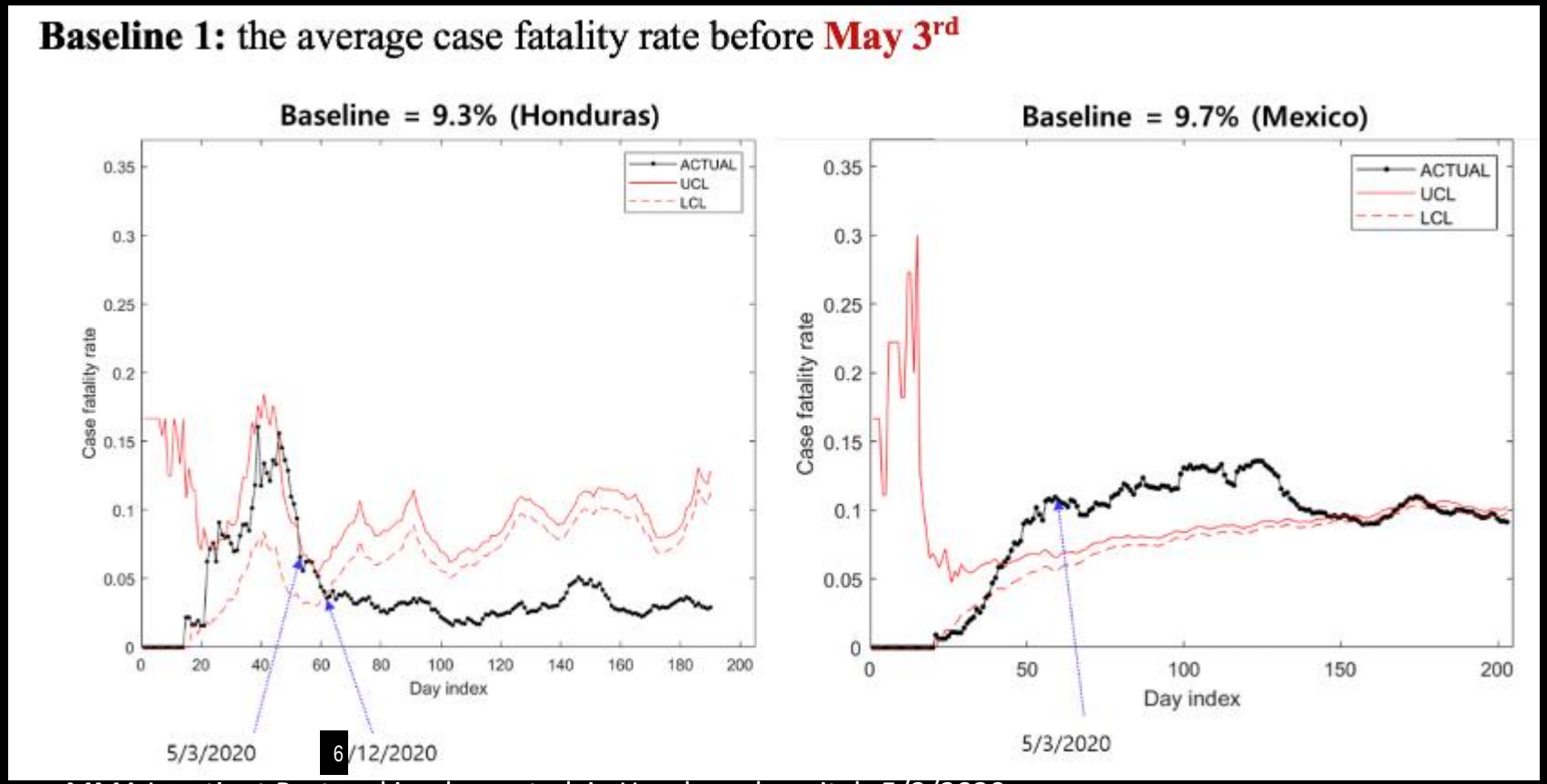


Figure 2 Shewhart control chart for mean log survival days after onset of rabies symptoms. This chart indicates when there is a shift in the mean of the process. In this case the mean of the process was set to 1.3 days in the log scale (the mean survival after onset of rabies symptoms before July 1885). This graph allows us to identify more clearly the control limits of the process (LCL and UCL) which contains all the points for people presenting with symptoms before July 1885.

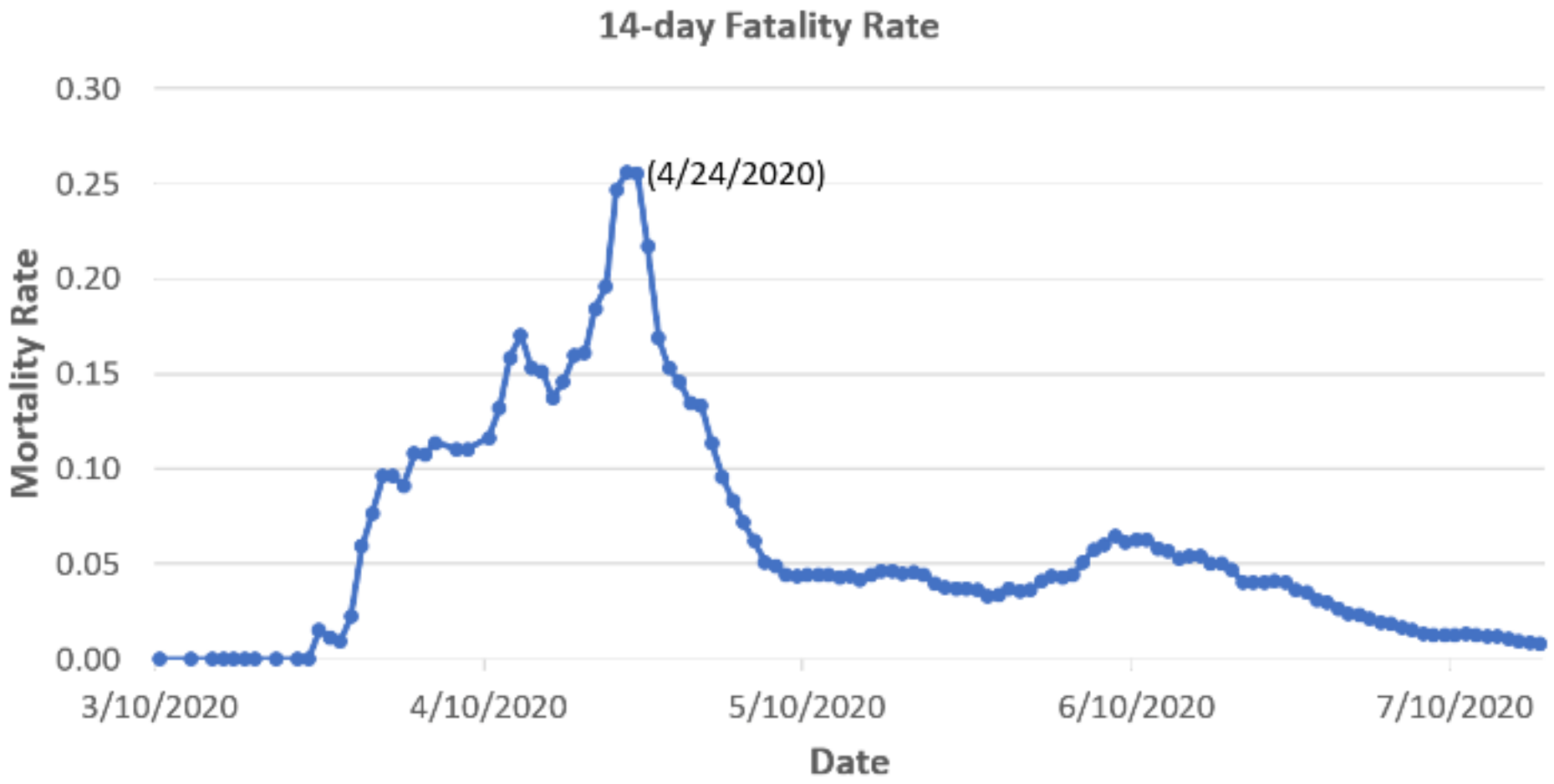
Statistical Process Control Analysis, Honduras v. Mexico Case Fatality Rate

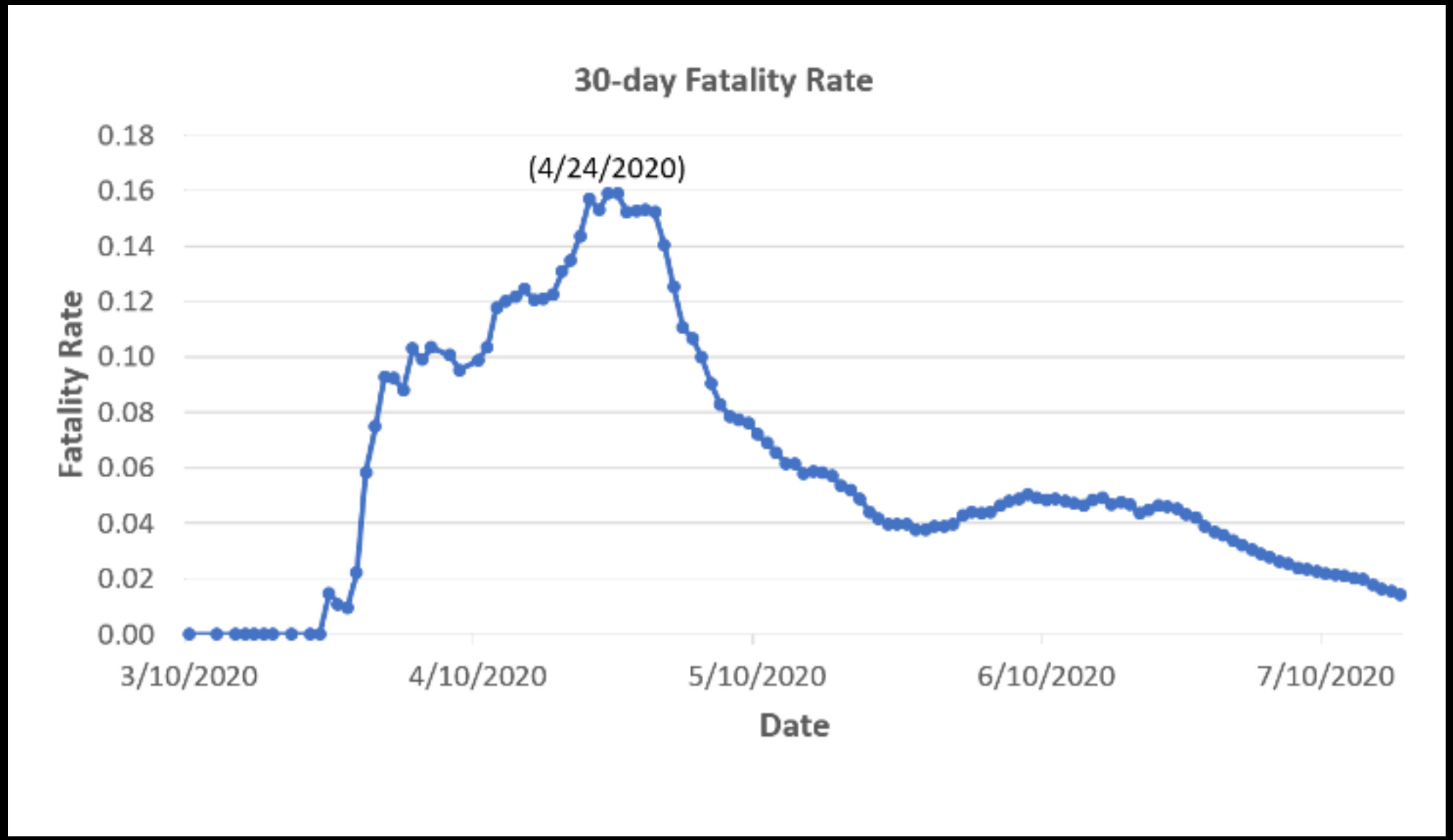


MMA Inpatient Protocol implemented in Honduras hospitals 5/3/2020

MMA Outpatient protocol implemented by government/NGO “health brigades” 6/9/2020

1. Estimation of Fatality Rate



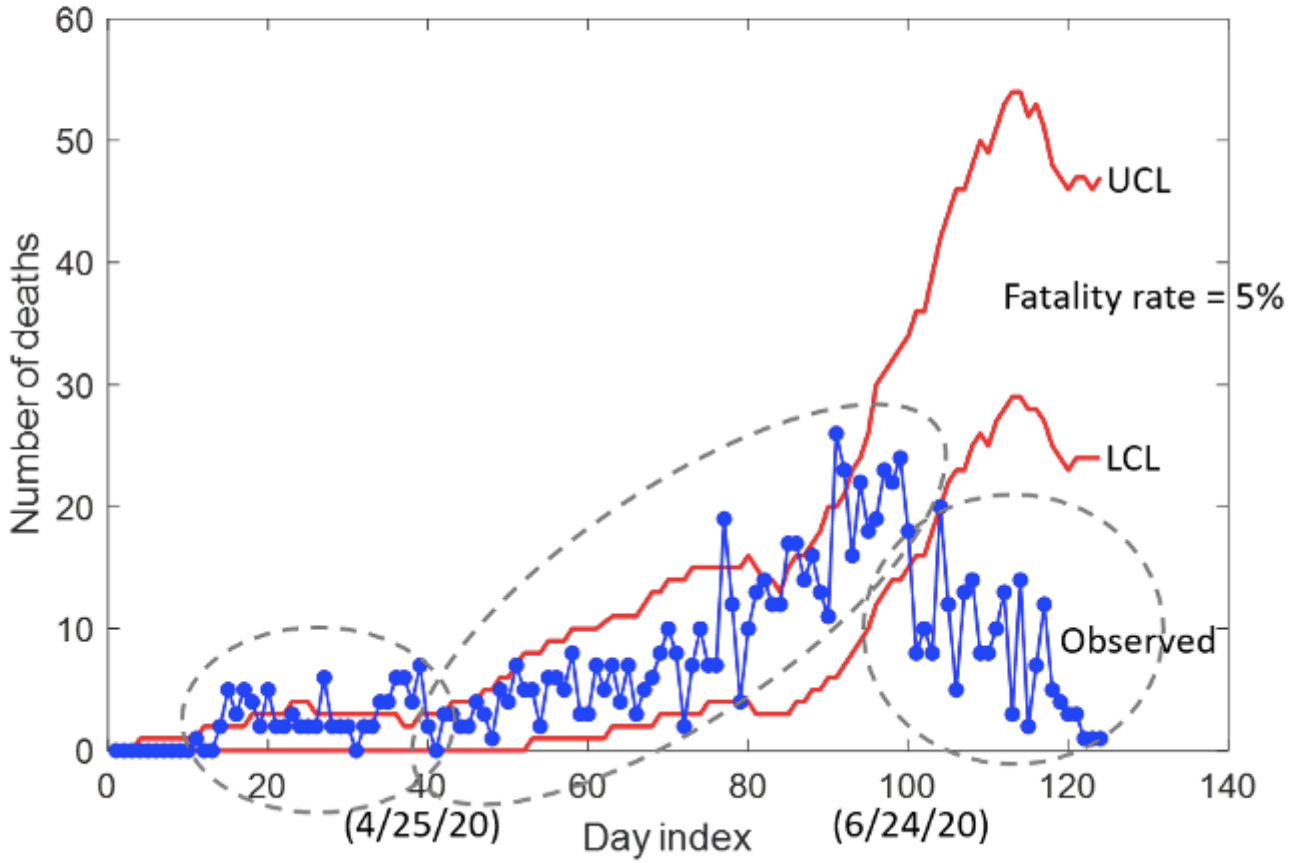

30-day Fatality Rate
(4/24/2020)
Fatality Rate
0.18
0.16
0.14
0.12
0.10
0.08
0.06
0.04
0.02
0.00
3/10/2020
4/10/2020
5/10/2020
6/10/2020
7/10/2020
Date

2. Dealth count data in SPC perspective

Totally 124 days. Day index is used in the fugure.

40th day = 4/25/2020

100th day = 6/24/2020



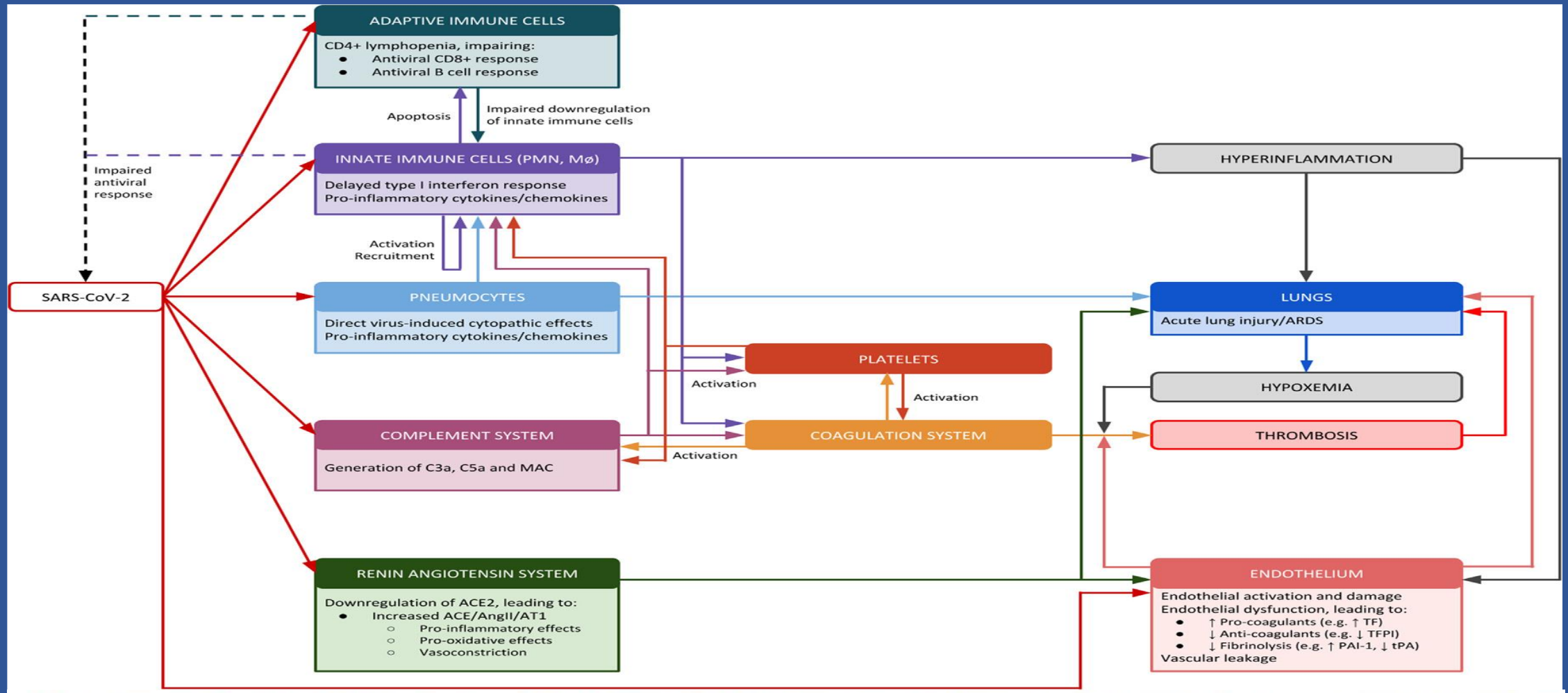


Fig. 1. Pathophysiologic Model of Immunothrombisis in COVID-19. SARS-CoV-2 is associated with an impaired antiviral host response, leading to rapid viral replication and a subsequent hyperinflammatory state. The hyperinflammation and virus-induced dysregulation of the renin angiotensin aldosterone system (RAAS) induces acute lung injury, leading to hypoxemia. Together, hyperinflammation, RAAS and hypoxemia induces endothelial dysfunction and a hypercoagulable state leading to widespread immunothrombosis which further propagates organ damage. ACE = angiotensin converting enzyme, ACE2 = angiotensin converting enzyme 2, AngII = angiotensin II, ARDS = acute respiratory distress syndrome, AT1 = angiotensin II receptor type 1, MAC = membrane attack complex, Mø = monocytes/macrophages, PAI-1 = plasminogen activator inhibitor-1, PMN = polymorphonuclear neutrophils, SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2, TF = tissue factor, TFPI = tissue factor pathway inhibitor, tPA = tissue plasminogen activator.

Henry BM, Vikse J, Benoit S, Favaloro EJ, Lippi G. Hyperinflammation and derangement of renin-angiotensin-aldosterone system in COVID-19: A novel hypothesis for clinically suspected hypercoagulopathy and microvascular immunothrombosis. *Clin Chim Acta*. 2020;507:167-173. doi:10.1016/j.cca.2020.04.027

Tik Tok : el tiempo
es ORO puro:
365 dias despues
es un factor critico