



What has happened two weeks after the
Post-CROI March 17th 2020 Webinar?

Update on COVID19 (SARS-CoV-2)

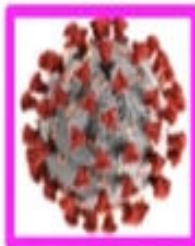
April 2nd 2020

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Hospital Clinic - IDIBAPS
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Barcelona (Spain)



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SARS-CoV-2 pandemic (COVID-19) Update

April 2nd 2020

- **Coronavirus History**
- Current Epidemiology **NEW!**
- The Virus & Pathogenesis **NEW!**
- Clinical Manifestations & Diagnosis **NEW!**
- Prognosis **NEW!**
- Treatment **NEW!**
- Prevention
- Take-home messages

Human Coronaviruses (HCoVs)

▪ Common HCoVs (lower pathogenicity):

- HCoV-229E (alpha)
- HCoV-NL63 (alpha)
- HCoV-OC43 (beta)
- HCoV-HKU1 (beta)

Mild Respiratory
Infections

▪ XXI Century HCoVs (higher pathogenicity):

- SARS-CoV (beta)
- MERS-CoV (beta)



Lai & Holmes, Fundamental Virology, 4th Edition 2001.

Coronavirus are found in Bats all over the world



Journal of Virology 2013, 87(10):1009-1010

DOI: 10.1128/JVI.01507-13

Coronaviruses in bats from Mexico

S. J. Anthony^{1,2*}, R. Gopalakrishnan¹, D. R. S. Silva¹,
J. Hernandez-Munoz¹, C. M. Zamora-Torres¹, W. H. Wang¹,
J. M. Espinoza¹, T. Tzipori¹, R. Liang¹, W. Sanchez-Lopez¹,
J. Sanchez-Balboa¹, A. A. Argente¹, R. A. Pardo¹, R. A. Morales¹,
T. S. Smith¹, S. J. Smith¹, R. J. Smith¹ and W. J. Smith¹

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² Center for Infectious Disease Research, National Institute of Health, Bethesda, Maryland, USA

ABSTRACT

Detection of Novel SARS-like and Other Coronaviruses in Bats from Kenya

Anthony J. Smith, Christine Connors, Joseph Smith,
John J. Smith, William Smith, Mary Smith,
Michael Smith, John Smith,
Bernard Smith, Robert J. Smith,
Liam J. Smith, and Charles J. Smith

Recent outbreaks including SARS, MERS-CoV, and
Ebola virus in addition to SARS-CoV-2 (1,2,3,4).

The Study

Over the past decade of rapid emerging infectious
diseases, bats have been implicated as the source
of the zoonotic pathogen SARS-CoV-2. The
study of bats has been a priority for the
National Institute of Health and the Centers for
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response to the growing threat of zoonotic
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Manuscript received 10 May 2013; accepted 10 May 2013
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VIROLOGY JOURNAL

REPORT

Open Access

Diversity of coronavirus in bats from Eastern Thailand

Anthony J. Smith¹, Christine Connors¹, Joseph Smith¹,
John J. Smith¹, William Smith¹, Mary Smith¹, Michael Smith¹,
John Smith¹, Bernard Smith¹, Robert J. Smith¹, Liam J. Smith¹,
Charles J. Smith¹, and Charles J. Smith¹

Bat Coronaviruses and Experimental Infection of Bats, the Philippines

Anthony J. Smith¹, Christine Connors¹, Joseph Smith¹,
John J. Smith¹, William Smith¹, Mary Smith¹, Michael Smith¹,
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Original Contribution

Coronavirus Infection and Diversity in Bats in the Australasian Region

Anthony J. Smith¹, Christine Connors¹, Joseph Smith¹,
John J. Smith¹, William Smith¹, Mary Smith¹, Michael Smith¹,
John Smith¹, Bernard Smith¹, Robert J. Smith¹, Liam J. Smith¹,
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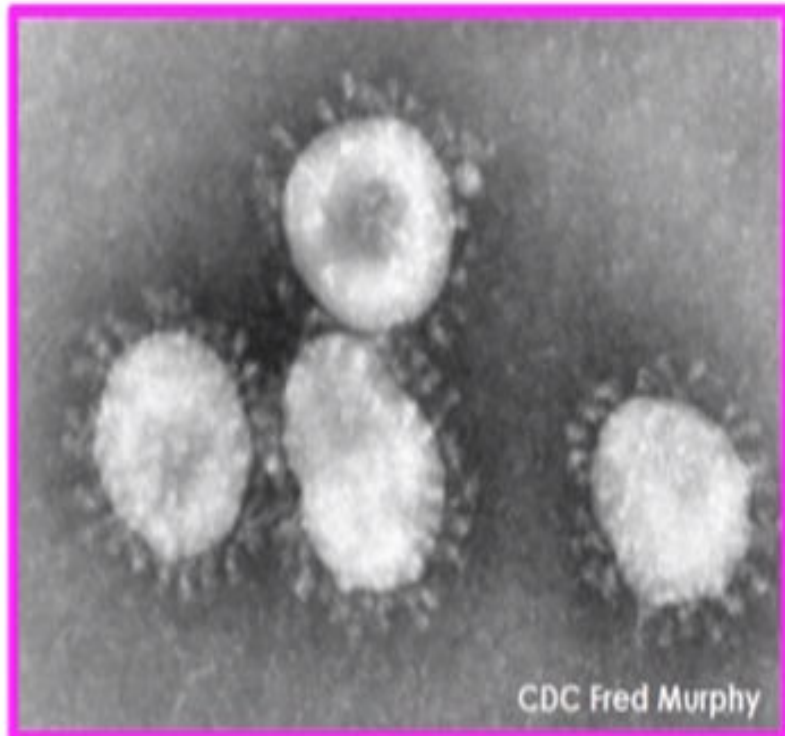
Seven Human Coronaviruses (HCoVs)

■ Common HCoVs (lower pathogenicity):

- HCoV-229E (alpha)
- HCoV-NL63 (alpha)
- HCoV-OC43 (beta)
- HCoV-HKU1 (beta)

■ XXI Century HCoVs (higher pathogenicity):

- SARS-CoV (beta)
- MERS-CoV (beta)
- **SARS-CoV-2*** (beta)



The illness COVID-19 is caused by SARS-CoV-2, which is more like SARS-CoV than MERS-CoV

A seafood market in Wuhan, China the probably source of an outbreak of a novel Coronavirus (COVID-19) in Dec. 2019



Widespread rapid dissemination in our hyper-connected world creates real-time challenges to prediction analyses

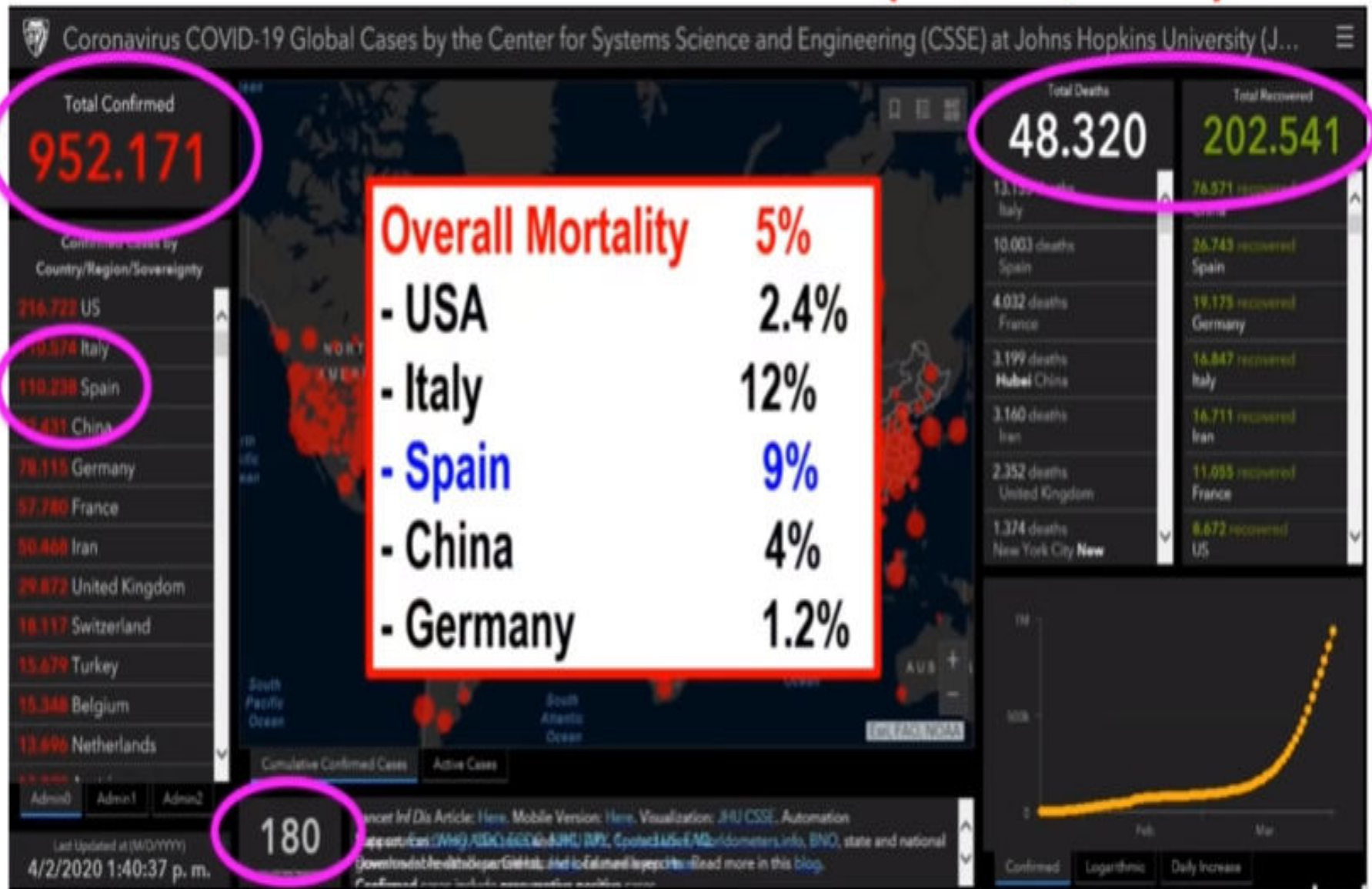


SARS-CoV-2 Global Cases (CSSE, JHU)



<https://www.arcgis.com/apps/opstdashboard/index.html#/bda7594740fd40299423467b48e9ecf6>; accessed on April 2nd 2020

SARS-CoV-2 Global Cases (CSSE, JHU)

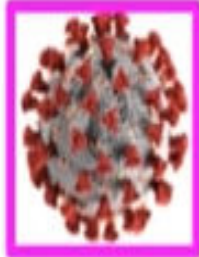


SARS-CoV-2 Transmission – $R_0 \approx 3$ (2.4-3.8)

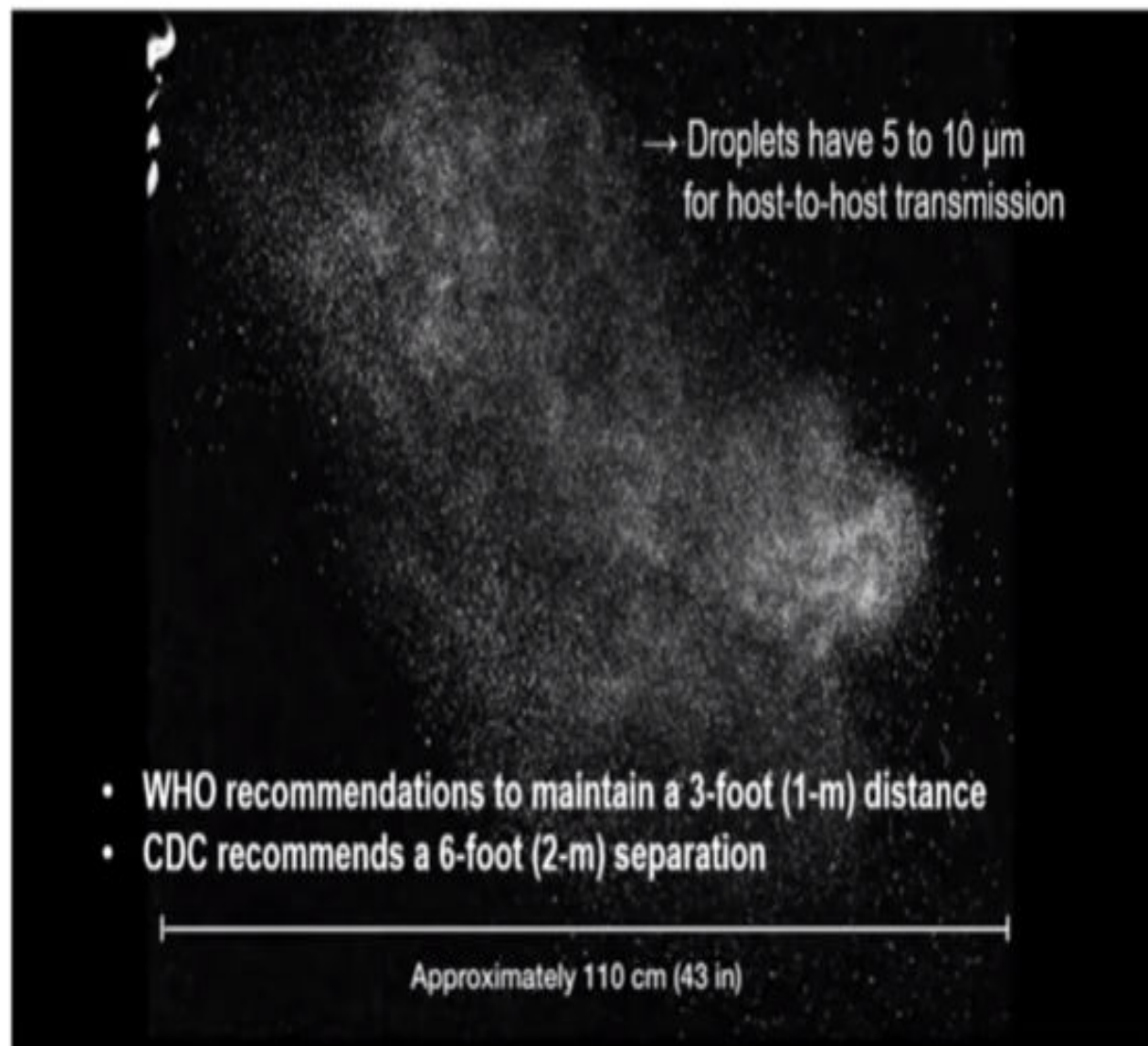
- **Respiratory secretions – Main mode of transmission (person to person spread)**
 - Infection is spread through **respiratory droplets** in the **air** (2 m.) and that land on **surfaces**
 - **Transmission** from persons who are **pre-symptomatic is possible**. Recent studies suggested that the rate is around **50% of cases**
 - **Transmission after curation is also possible**. WHO recommends isolation measures at least two additional weeks
- **Stool – oral-fecal transmission seems possible**
 - Some cases reported
- **Perinatal – few data.**
 - Not detected by RT-PCR in amniotic fluid, cord blood, neonatal throat swab, breast milk

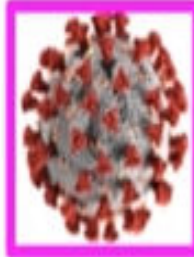


Zou 2020, N Engl J Med; DOI: 10.1056/NEJMc2001737. Pan 2020, Lancet Infect Dis; [https://doi.org/10.1016/S1473-3099\(20\)30113-4](https://doi.org/10.1016/S1473-3099(20)30113-4).
Zhang 2020; China CDC Weekly; <http://weekly.chinacdc.cn/en/article/id/ffa97a96-db2a-4715-9dfb-ef662660e89d>. Chen 2020; Lancet; [https://doi.org/10.1016/S0140-6736\(20\)30360-3](https://doi.org/10.1016/S0140-6736(20)30360-3). Zhu 2020; Transl Pediatr; <http://dx.doi.org/10.21037/tp.2020.02.06>. Bai et al JAMA, 2020, Feb 21; Tapiwa 2020, medRxiv <https://doi.org/10.1101/2020.03.05.20031815> WHO March 16th 2020



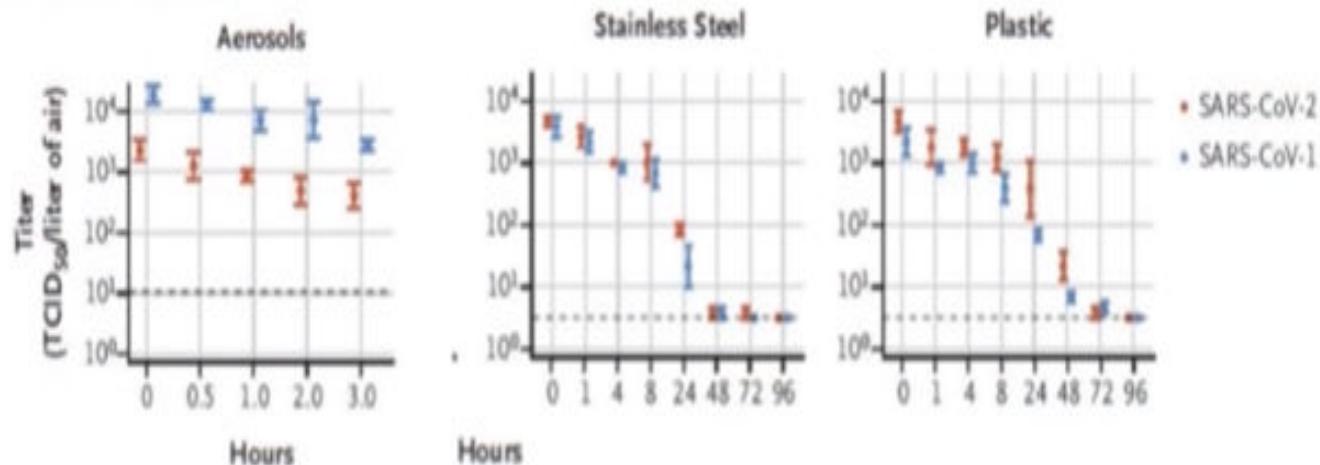
Droplets Demonstrate Their Ability to Travel Great Distances



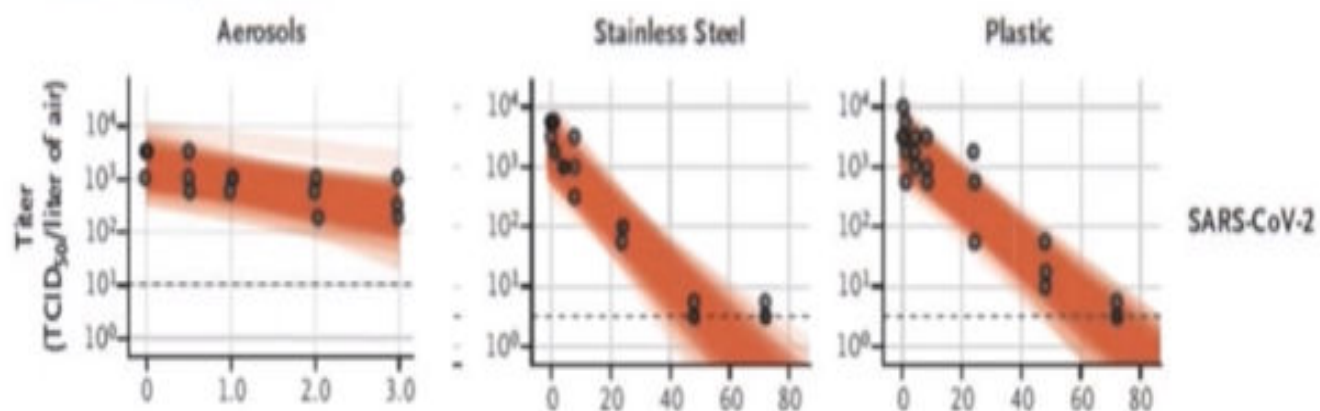


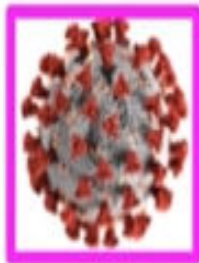
Aerosol (hr.) and Surface (d.) Stability of SARS-CoV-2

A Titers of Viable Virus



B Predicted Decay of Virus Titer





SARS-CoV-2 pandemic (COVID-19) Update

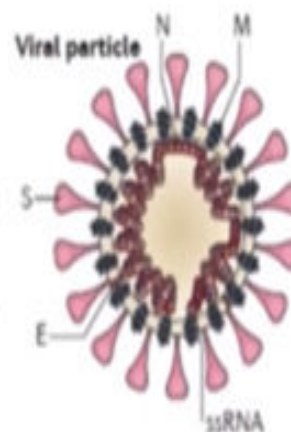
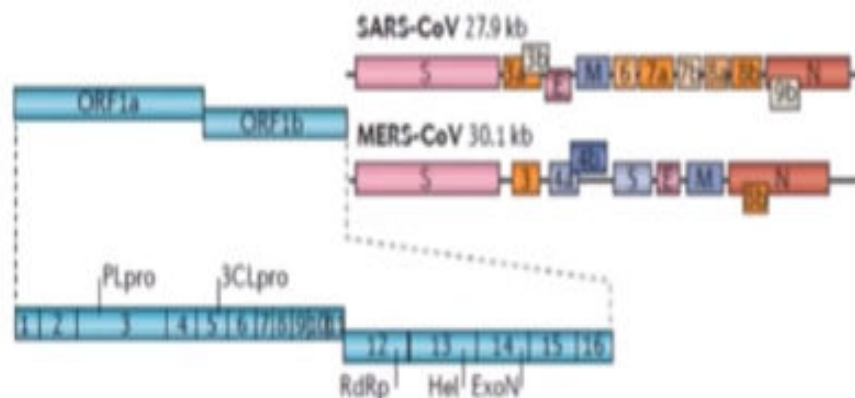
April 2nd 2020

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SARS-CoV-2 (COVID19) Genome

Enveloped single strand RNA virus with a genome size of 32 Kb

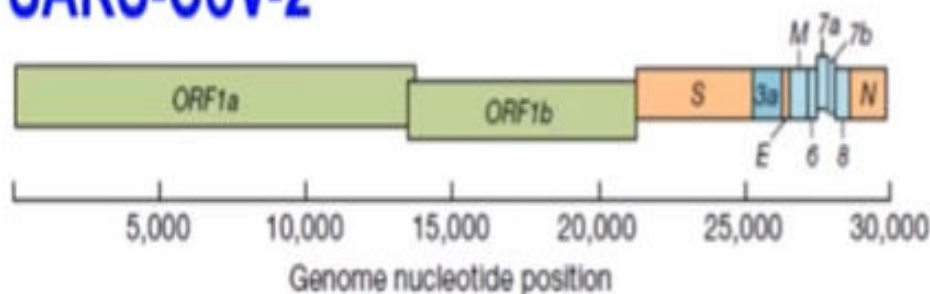
a
Genomes



Spike (S) in
the prefusion
conformation

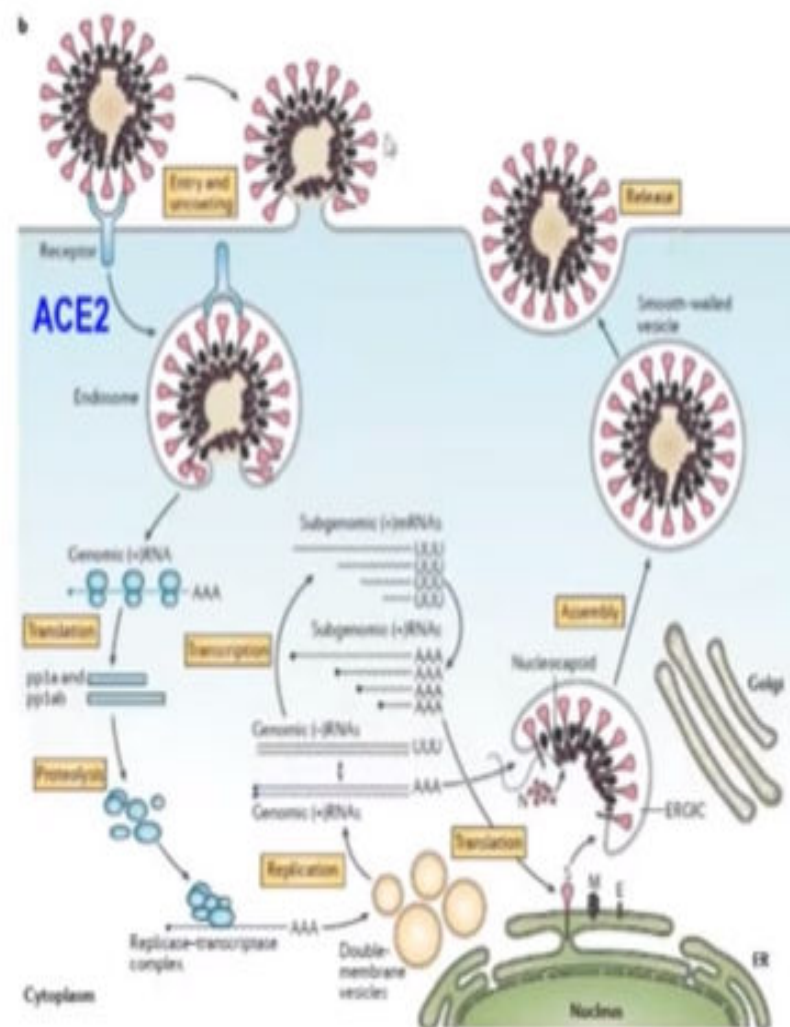
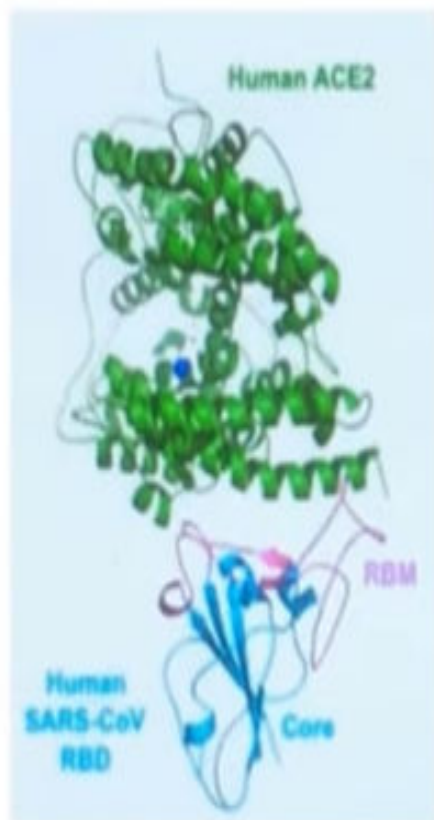


SARS-CoV-2



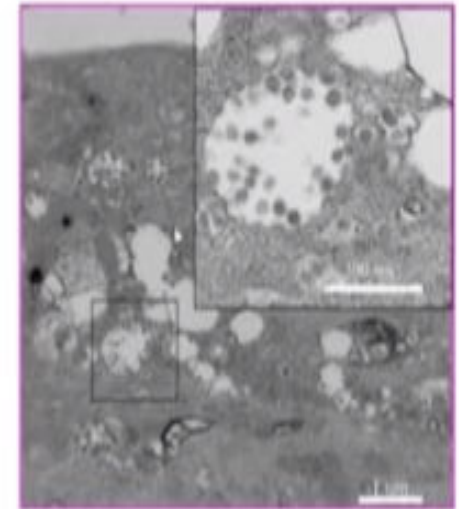
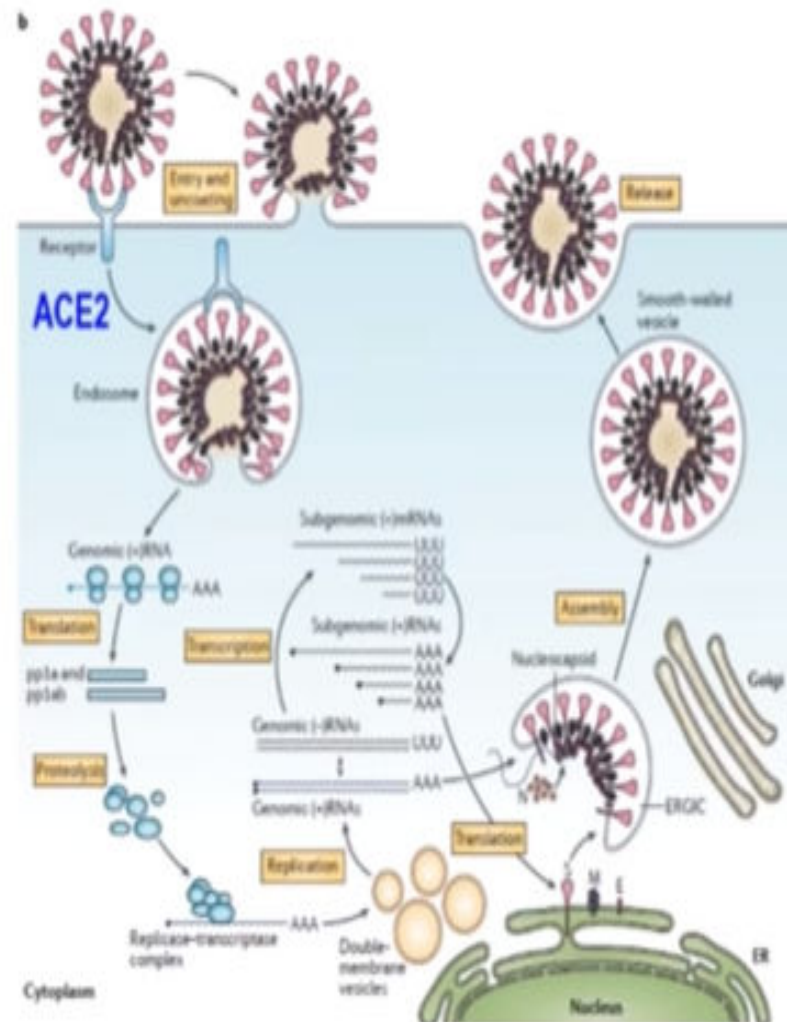
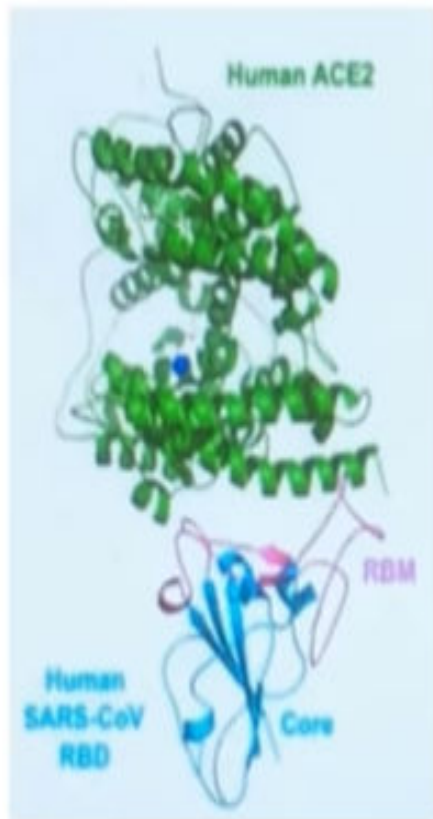
SARS-CoV-2 (COVID19) Life Cycle

It uses **ACE2** for viral entry
(angiotensin-converting enzyme 2)



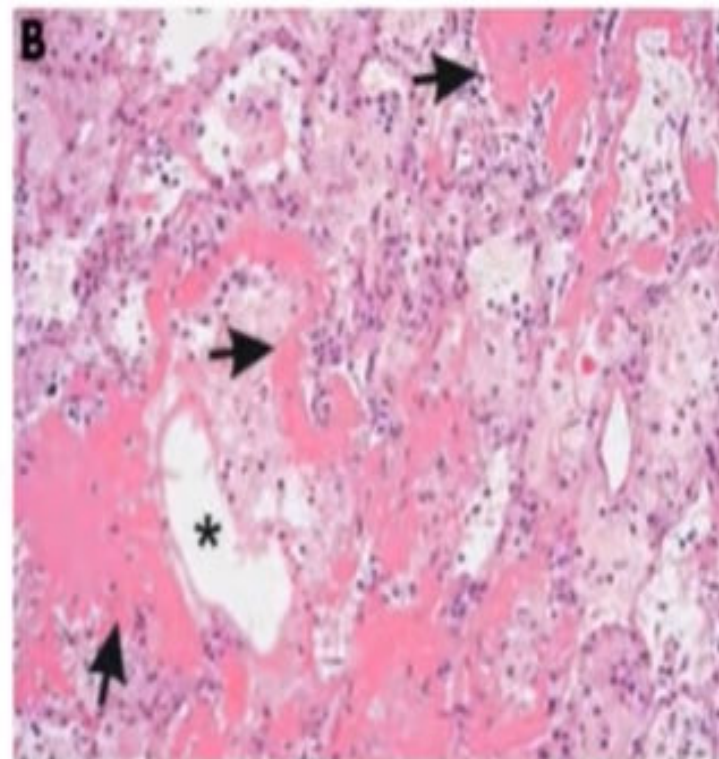
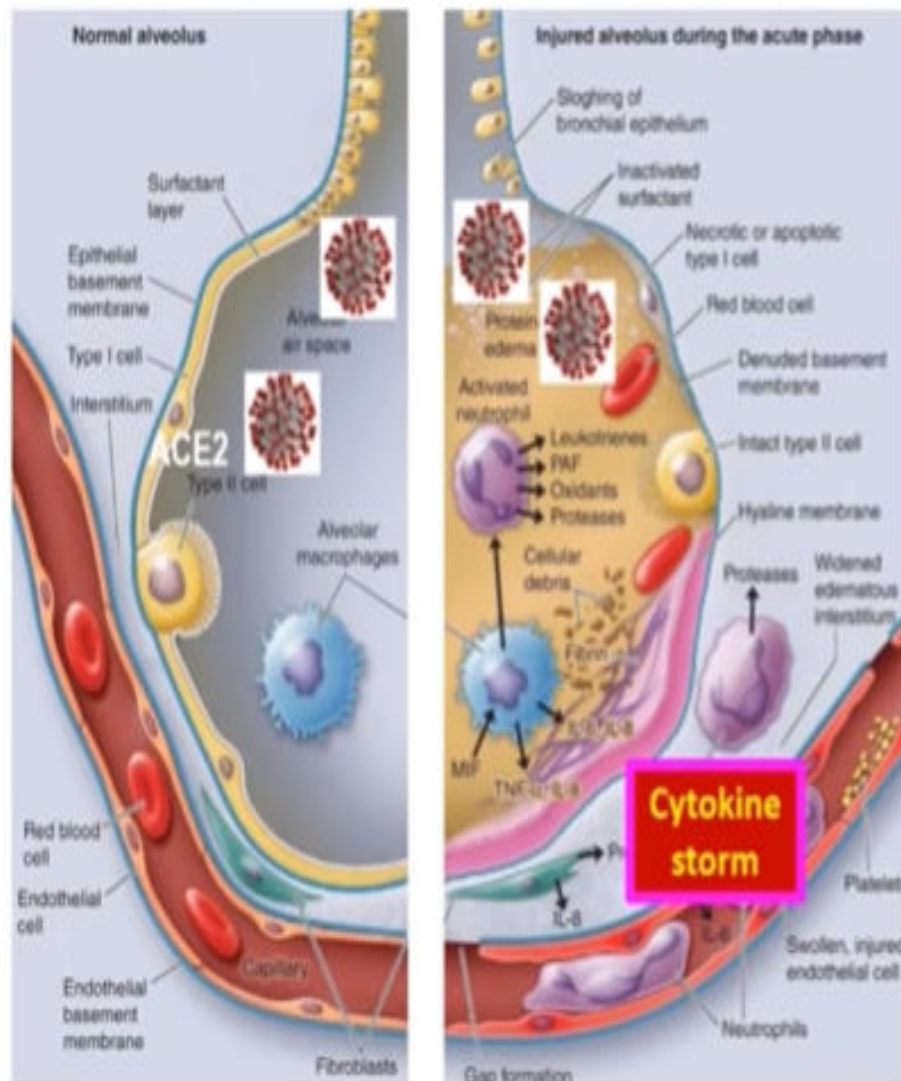
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Viral particles in the ultrathin sections were imaged using electron microscopy at 200 kV. The sample was from virus-infected Vero E6 cells. The inset shows the viral particles in an intra-cytosolic vacuole

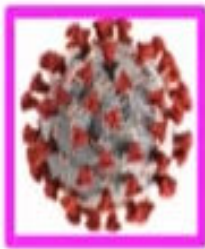
SARS-CoV-2 (COVID19) Pathogenesis: ARDS



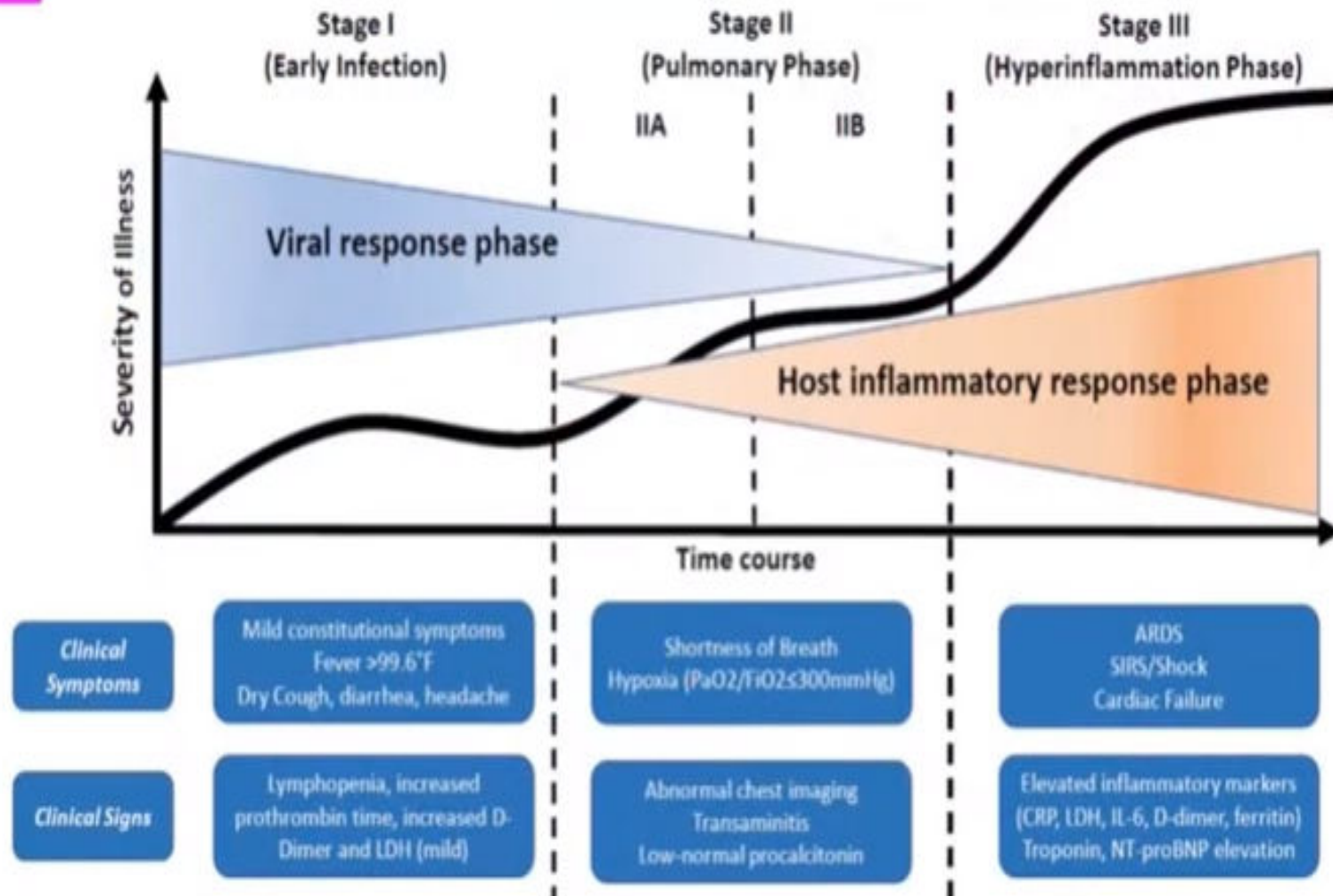
Acute Respiratory Distress Syndrome (ARDS) pathology

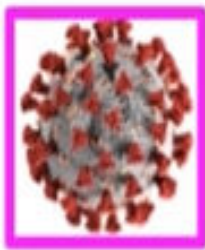
Acute diffuse alveolar damage, with pulmonary edema and formation of a hyaline membrane in a SARS-CoV patient

The airspaces are indicated by asterisks and some of the hyaline membranes lining the alveolar spaces are highlighted by arrows (hematoxylin and eosin stain; original magnification, x100).



Classification of COVID-19 Disease Stages



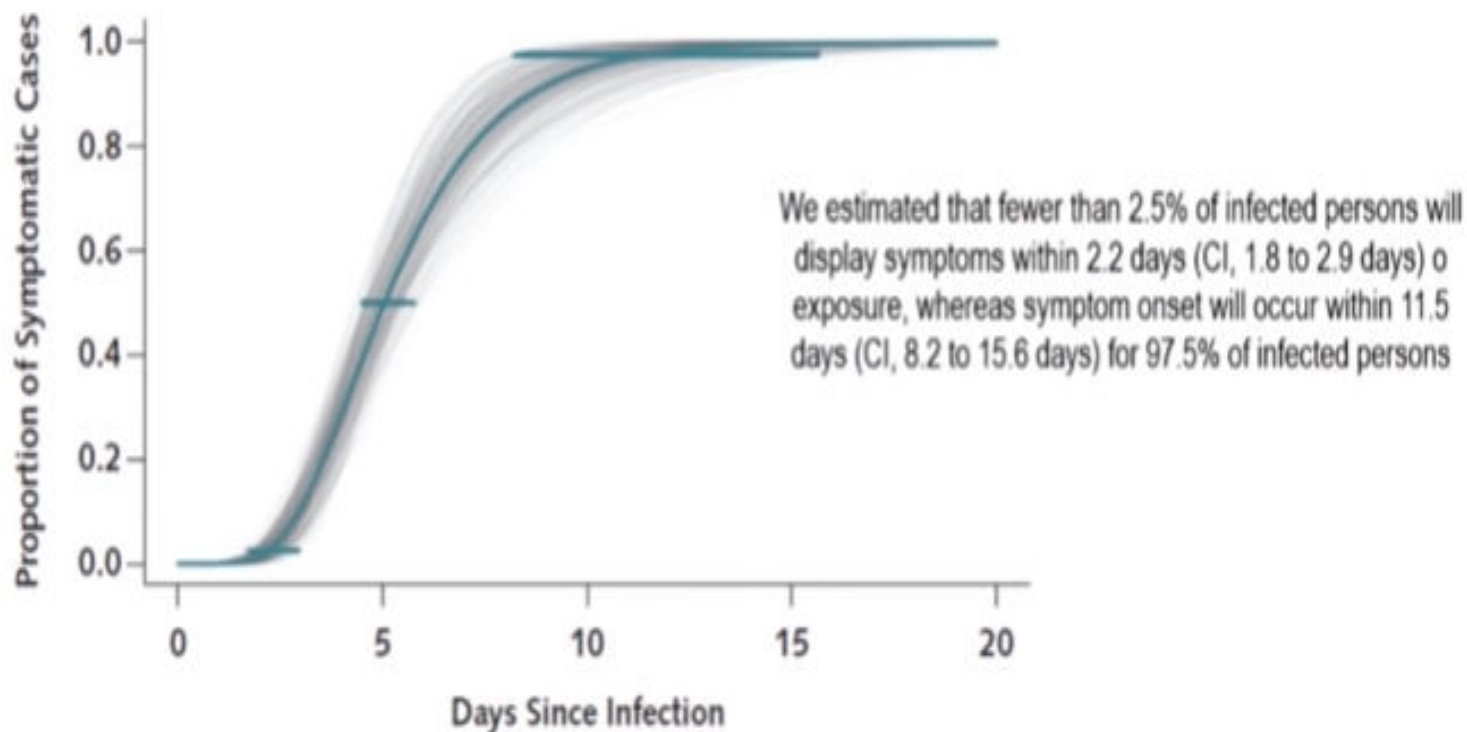


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Incubation period 5 days (range 2-14 days).

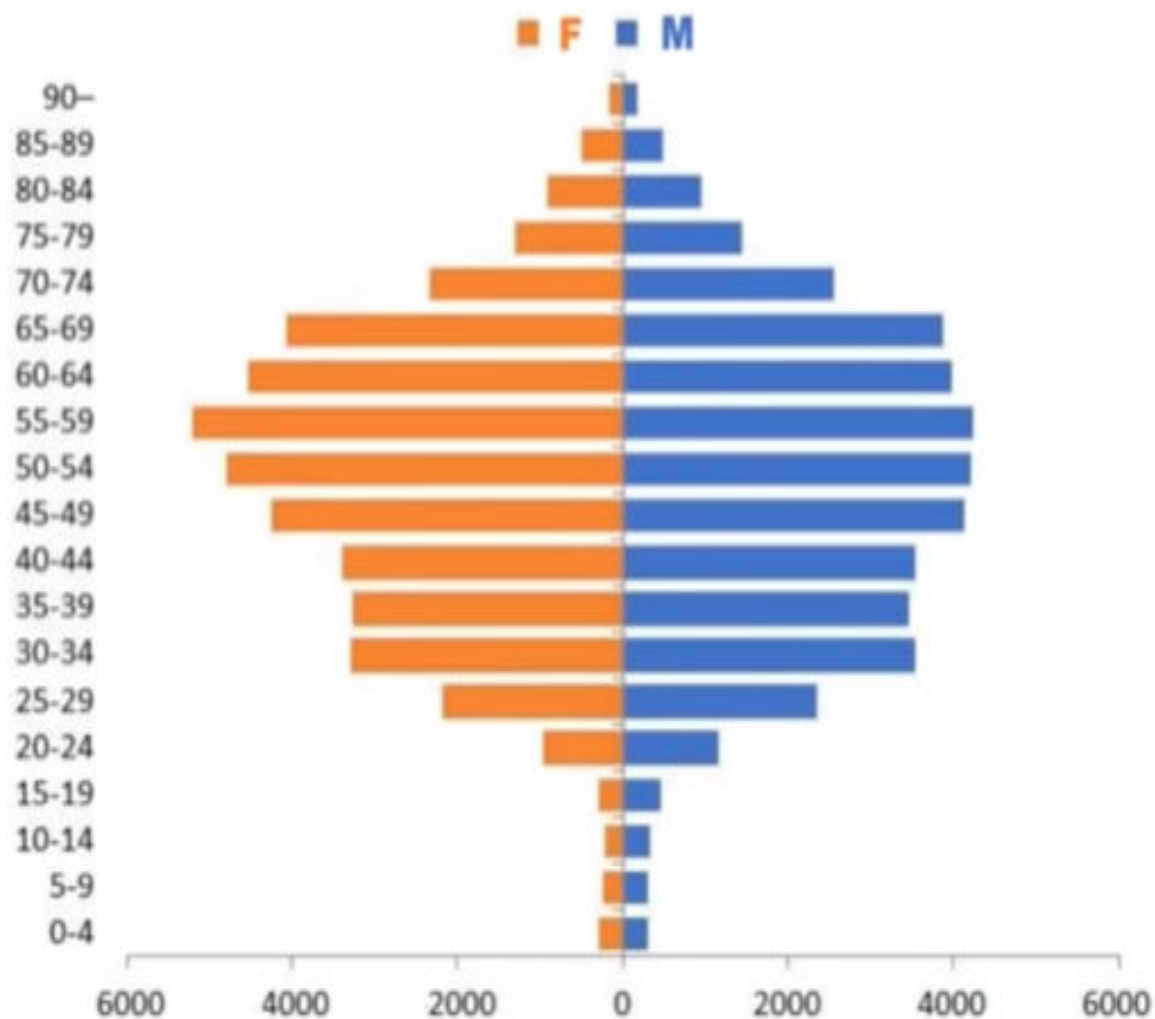


Signs/Symptoms of COVID-19 in China

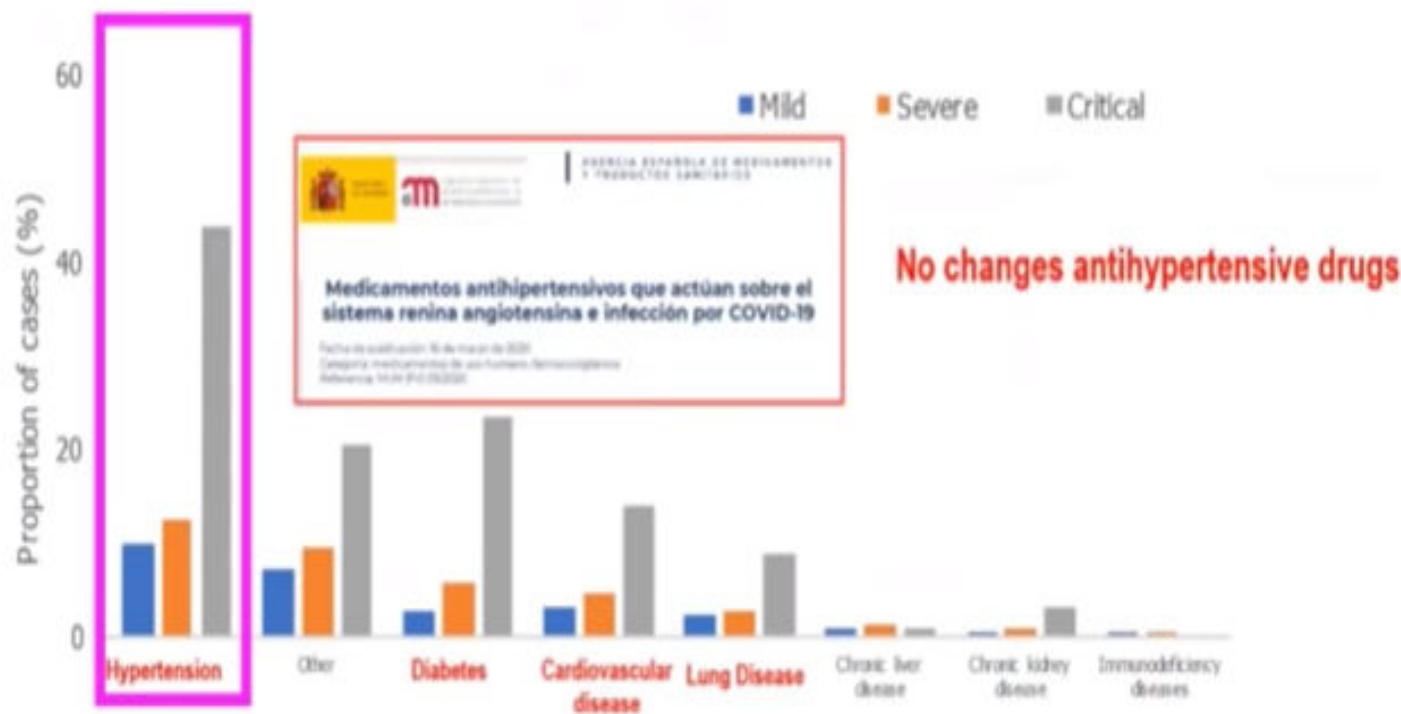
- No particular set of signs or symptoms can reliably discriminate SARS-CoV-2 from other respiratory viral illnesses such as influenza
 - Subacute to acute onset
 - Non-productive cough
 - Fever or “feverish” (often low-grade or not initially measurable)
 - Some reports of **diarrhea** alone preceding cough and fever
- Most people will recover spontaneously with supportive care
- **Complications include pneumonia, respiratory failure, multiorgan system failure**
- **Children** tend to have milder disease than adults.



COVID-19 cases by Sex and Age in China



Underlying Medical Conditions of COVID-19 in China



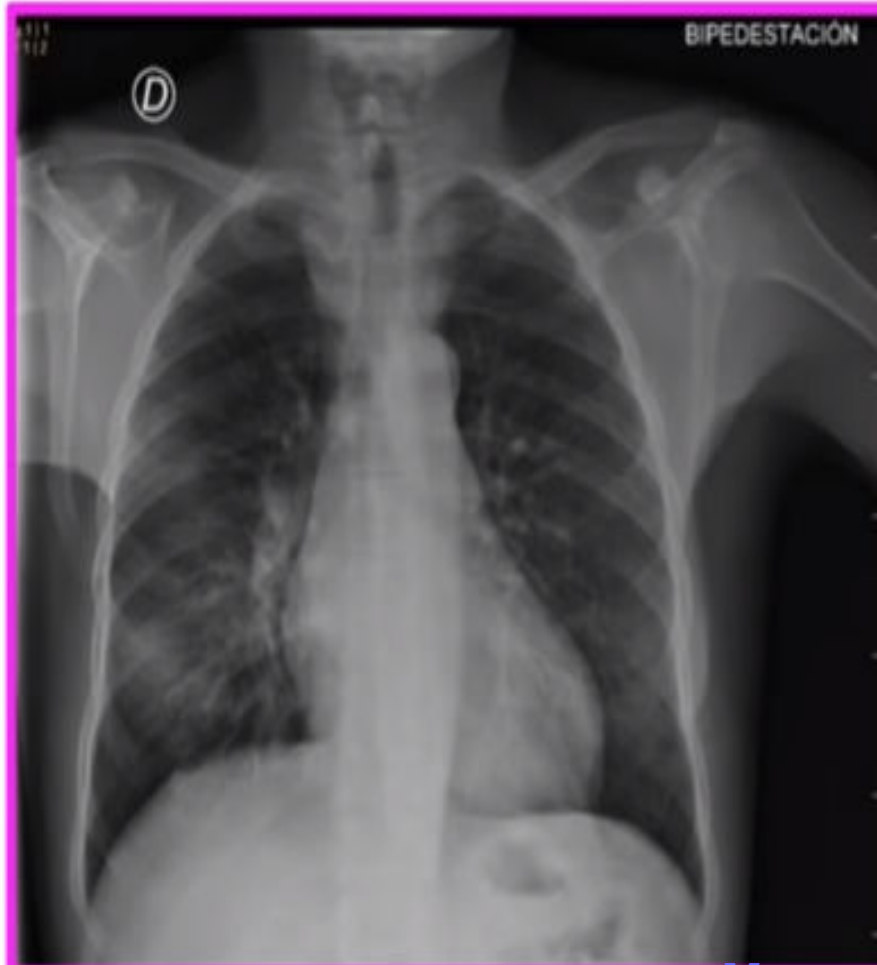
19230 Confirmed cases with detailed epidemiological investigation information

Chest X-ray and CT findings in SARS-CoV-2

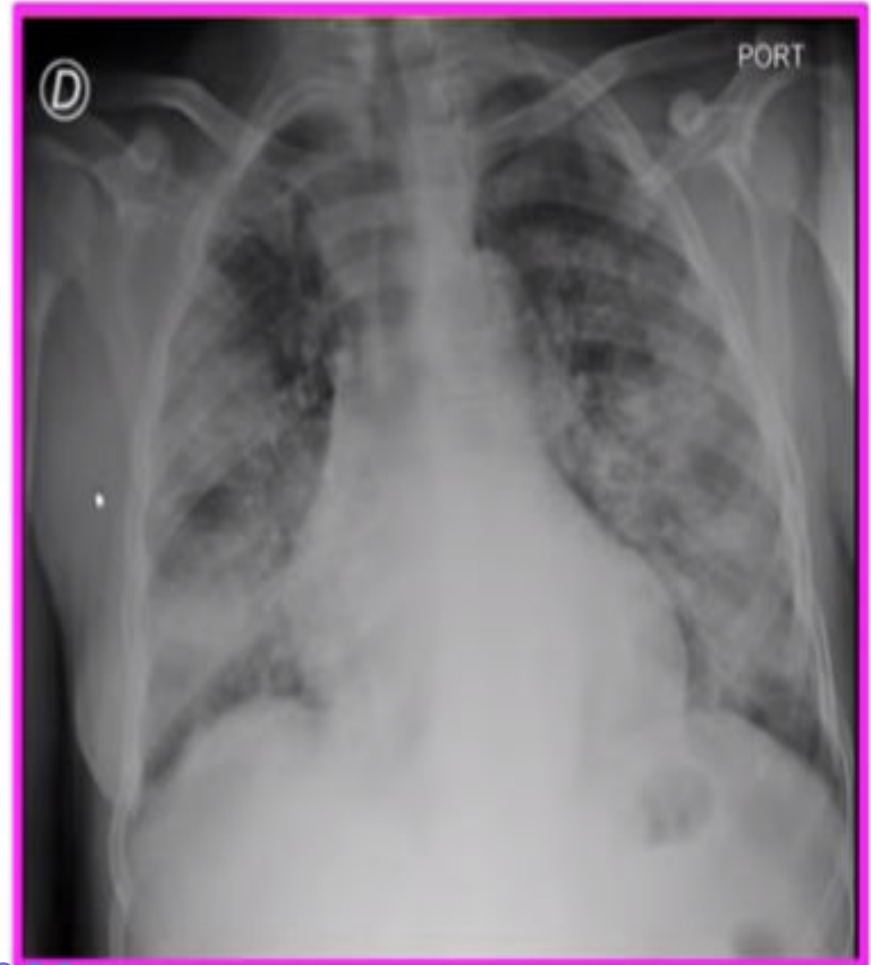
Radiologic findings

Abnormalities on chest radiograph — no./total no. (%)	162/274 (59.1)
Ground-glass opacity	55/274 (20.1)
Local patchy shadowing	77/274 (28.1)
Bilateral patchy shadowing	100/274 (36.5)
Interstitial abnormalities	12/274 (4.4)
Abnormalities on chest CT — no./total no. (%)	840/975 (86.2)
Ground-glass opacity	550/975 (56.4)
Local patchy shadowing	409/975 (41.9)
Bilateral patchy shadowing	505/975 (51.8)
Interstitial abnormalities	143/975 (14.7)

Chest X-ray and CT findings in SARS-CoV-2



May 4th 2020



May 7th 2020

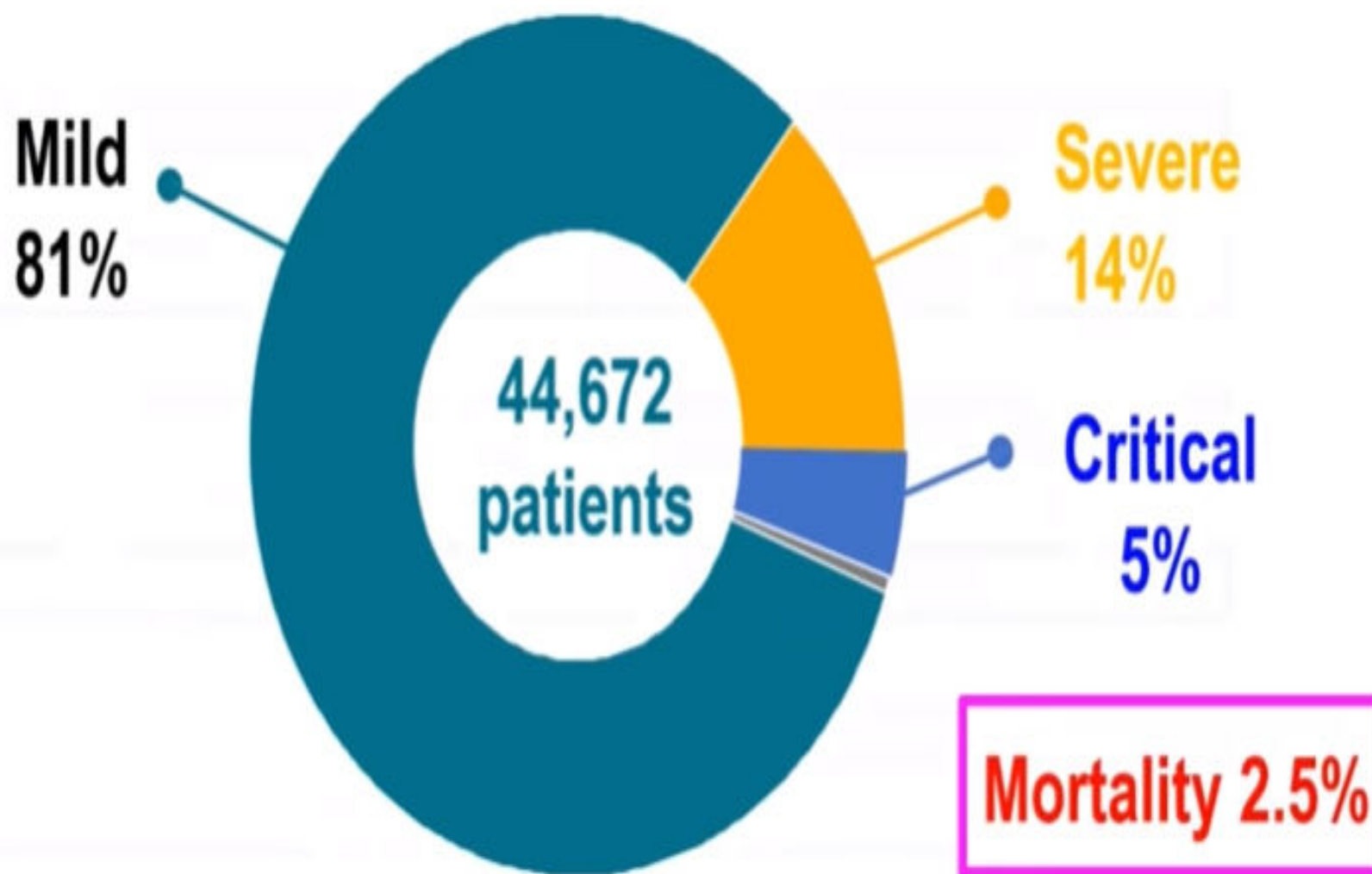
Marzo 2020

Complications of COVID-19 in China

Complications

Septic shock — no. (%)	12 (1.1)
Acute respiratory distress syndrome — no. (%)	37 (3.4)
Acute kidney injury — no. (%)	6 (0.5)
Disseminated intravascular coagulation — no. (%)	1 (0.1)
Rhabdomyolysis — no. (%)	2 (0.2)
Physician-diagnosed pneumonia — no./total no. (%)	972/1067 (91.1)
Median time until development of pneumonia (IQR) — days*	
After initial Covid-19 diagnosis	0.0 (0.0–1.0)
After onset of Covid-19 symptoms	3.0 (1.0–6.0)

Illness Severity COVID-19 in China



Molecular Virology of SARS-CoV-2 - Diagnosis

- Amplification of coronavirus genes by RT-PCR
 - Hospital Clinic of Barcelona assay (3-4 hours)
 - First line screening assay: *E* gene assay (coronavirus)
 - Confirmatory assay: *RdRp* gene assay (SARS-CoV-2)
- Rapid viral antigen* detection tests (POC, 15-20 minutes)
 - Low sensitivity but high PPV.
- Antibody detection (IgG, IgM) by ELISA has little usefulness in early diagnosis (antibodies appear after 7-14 days)

*The test uses mixed recombinant SARS-CoV-2 nucleocapsid protein (*N* protein) and spike protein (*S* protein) both conjugated with colloidal gold and anti-human IgM and IgG antibody coated on different test lines respectively.

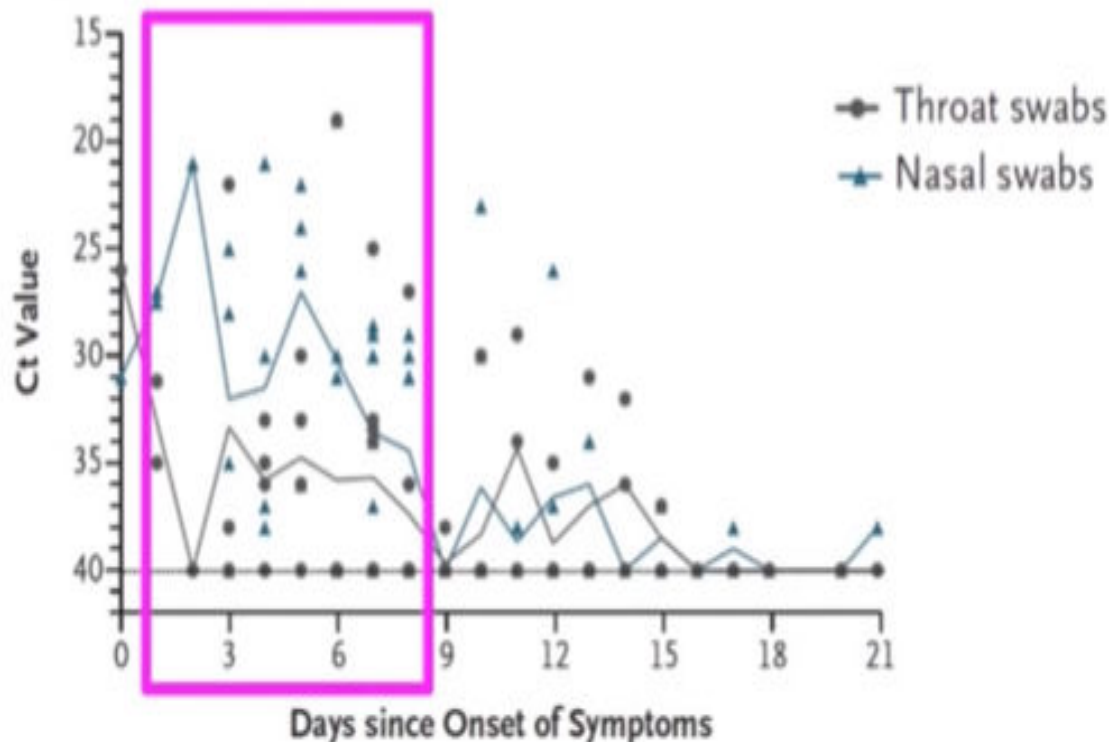
Virology of SARS-CoV-2

- **Virus shedding is highest early in the course of disease**
(vs. SARS shedding, which peaks at least 5 days after onset)
- Virus **shedding** can occur in the **24-48 hours** prior to **symptom onset** (**pre-symptomatic period**)
- Virus can be **isolated from stool** but there is no epidemiologic evidence of fecal-oral transmission
- **Virus shedding** usually continues for **7-12 days in mild/moderate cases**, and for **more than 2 weeks in severe cases**
- Patients who recover can be PCR positive after symptoms resolve

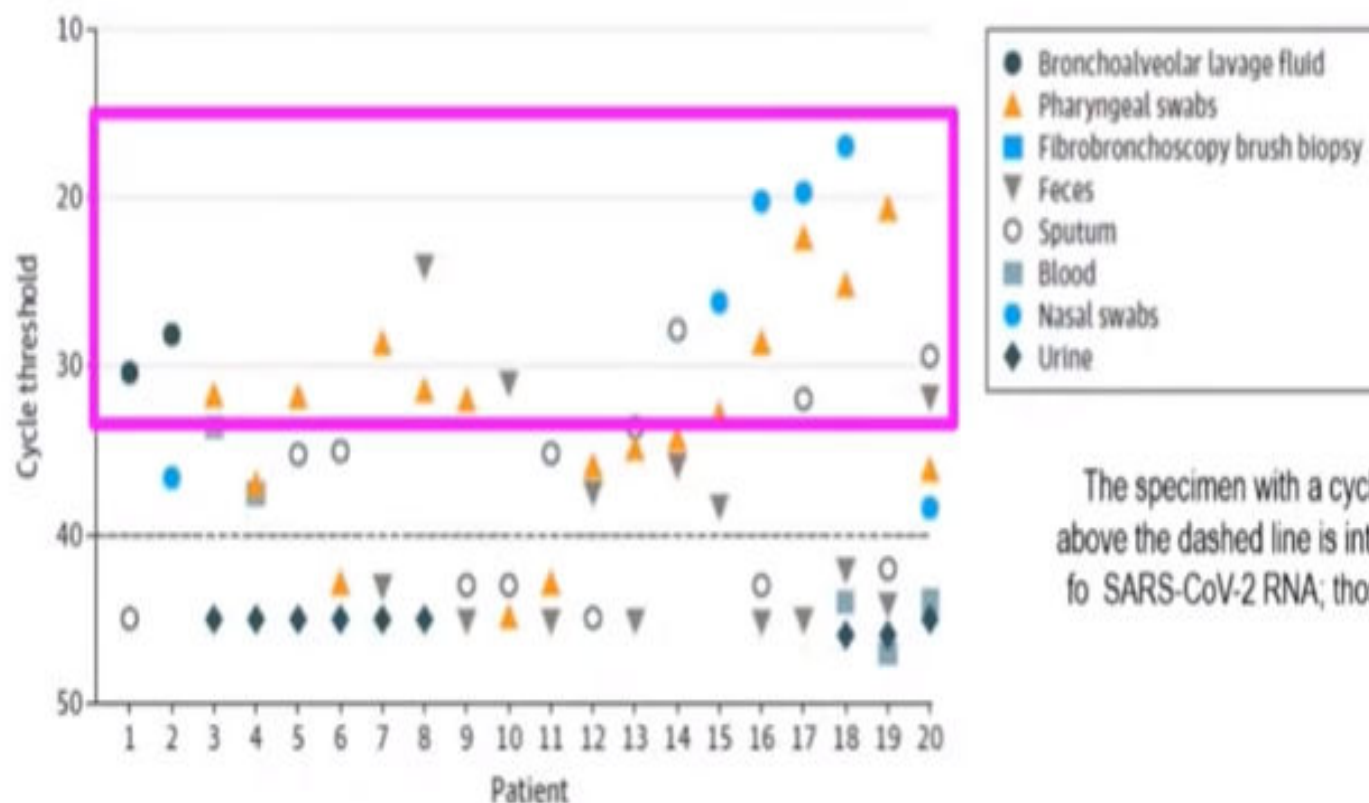
Viral Shedding Greatest At Time Symptoms Start

- SARS-CoV-2 viral loads in 17 symptomatic patients
- No data regarding duration of replication-competent virus shedding (e.g., culture)

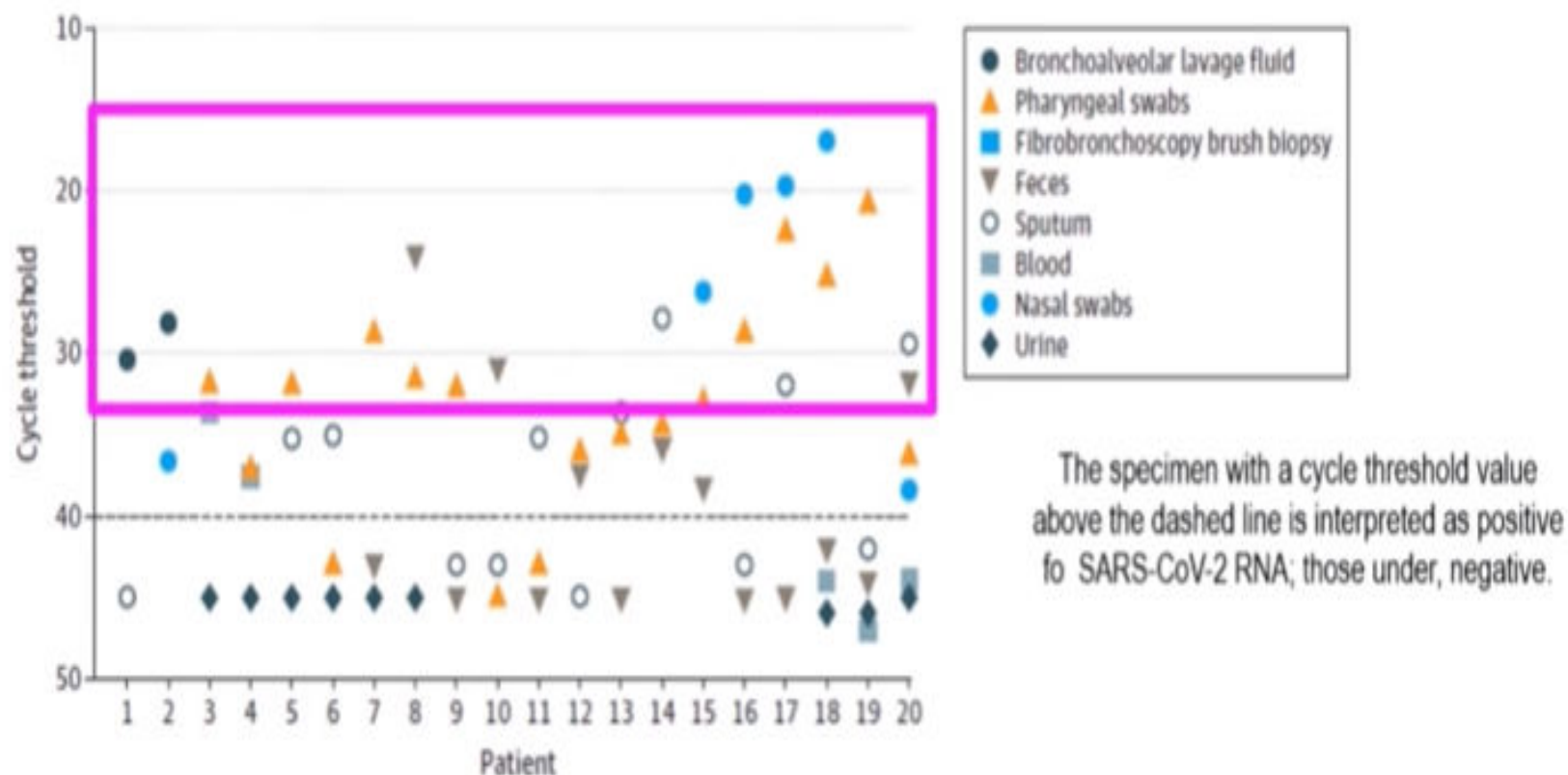
C Aggregated Ct Values

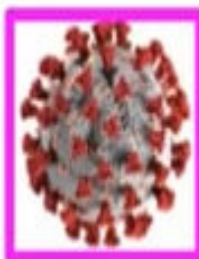


SARS-CoV-2 Distribution and Shedding Patterns Among 20 Hospitalized Patients



SARS-CoV-2 Distribution and Shedding Patterns Among 20 Hospitalized Patients



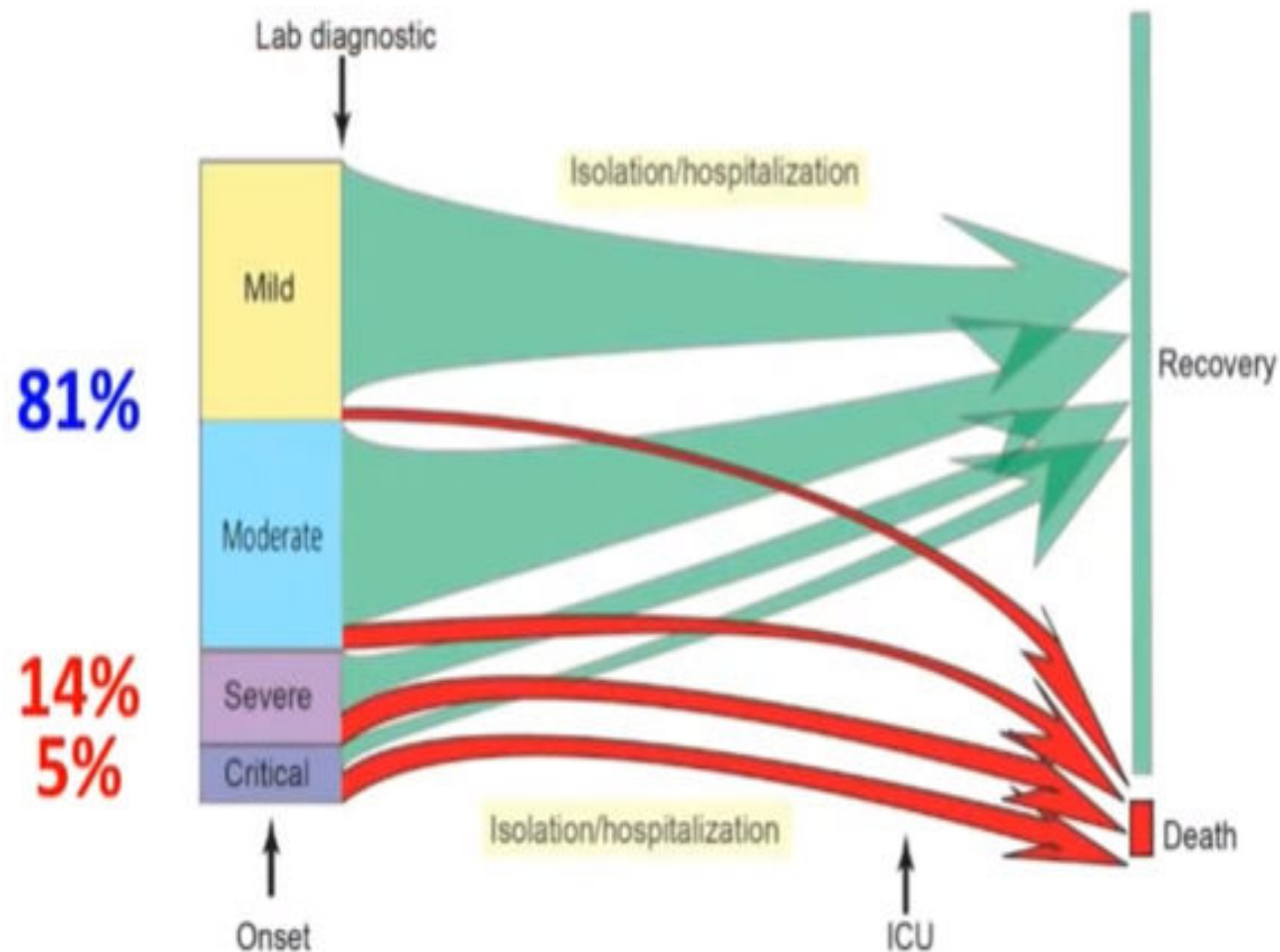


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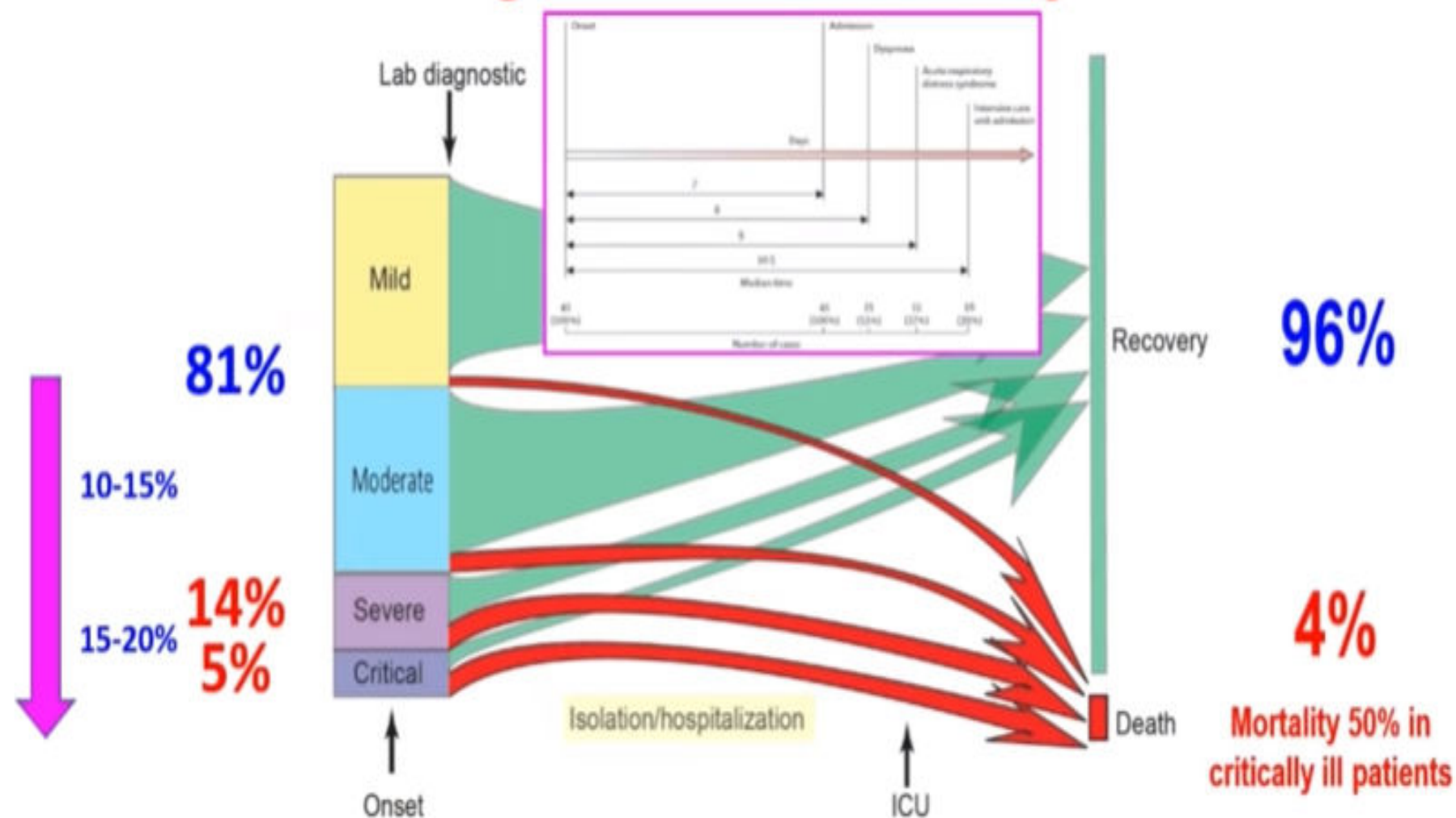
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Clinical Prognosis and Recovery in China

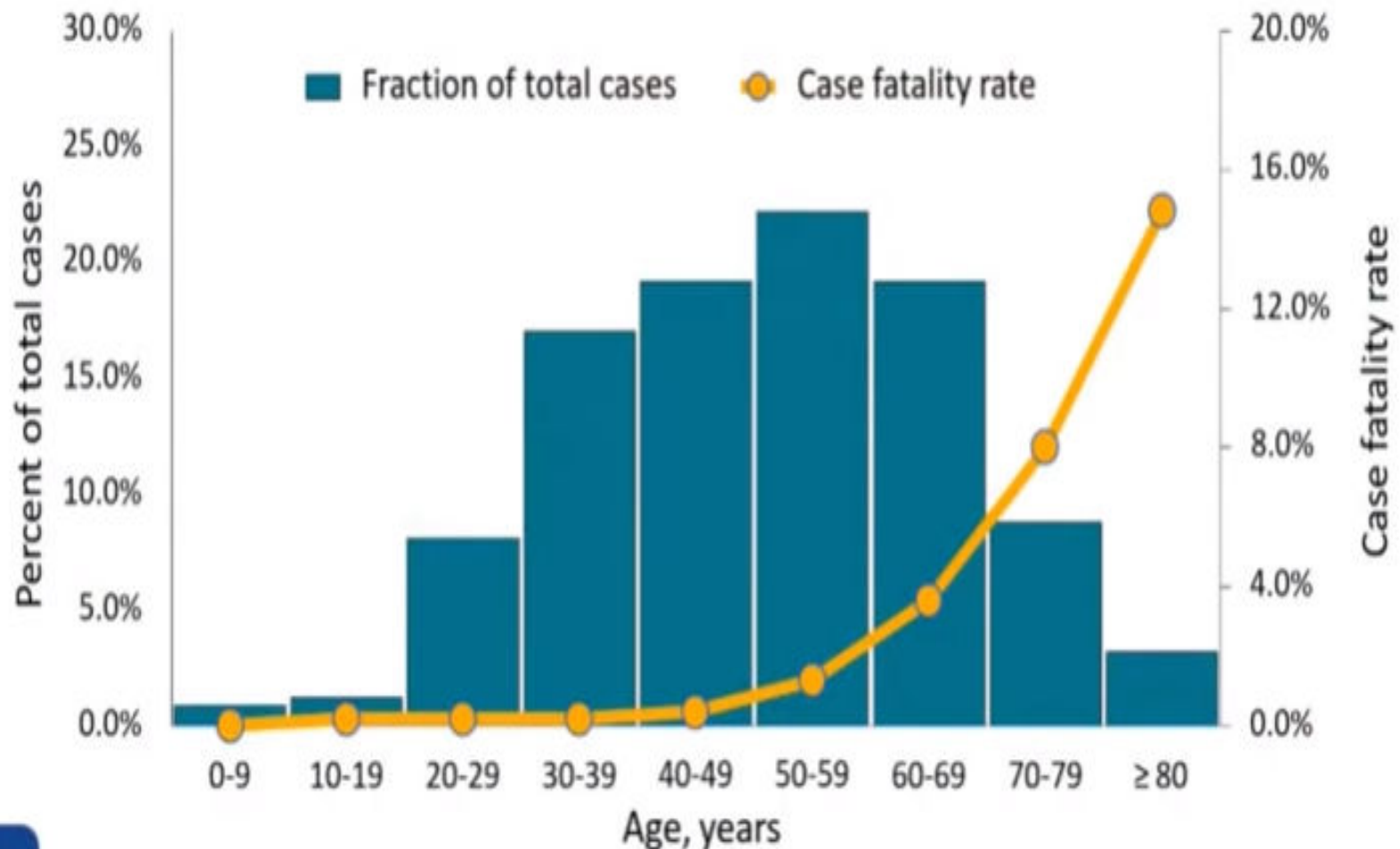


Clinical Prognosis and Recovery in China



Age Distribution and Case Fatality Rate COVID-19

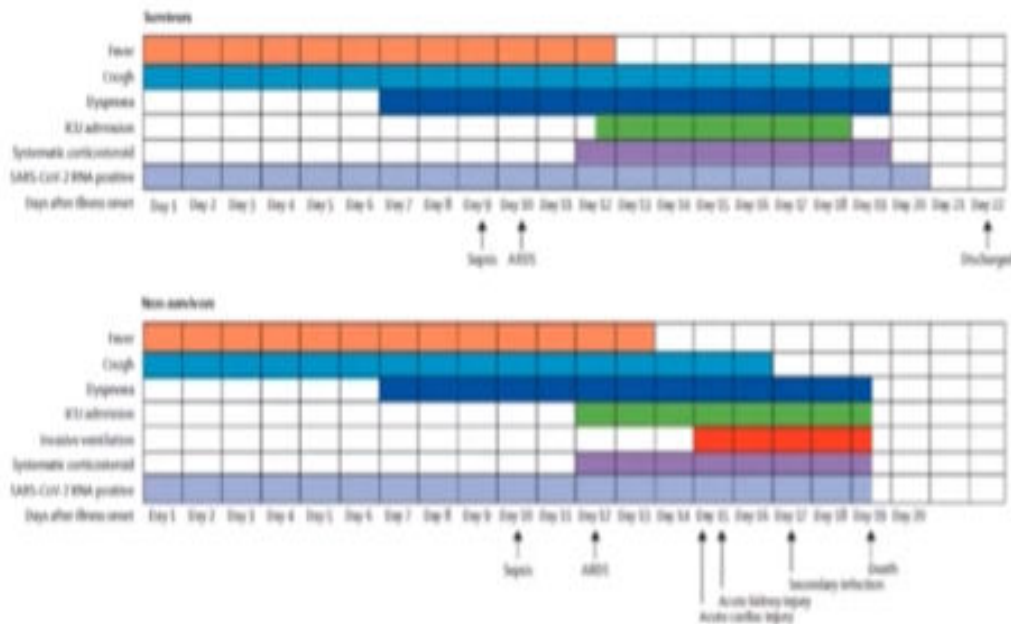
China through 11-Feb-2020 (N = 44,672 confirmed cases)



adapted from Zhang 2020, China CDC Weekly Rep; 2(8):113-122.

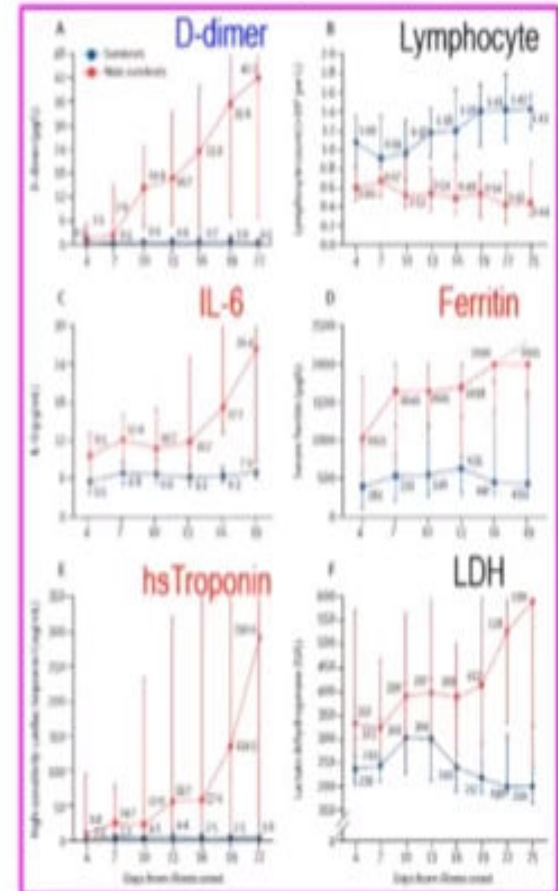


In-hospital Mortality Prognostic factors



- Age (per yr.): 1.10 (1.03-1.17)
- SOFA score: 5.65 (2,61-12,23)
- D-dimer >1 $\mu\text{g/mL}$: 18.42 (2.64-128)

Temporal changes in **laboratory markers** from illness onset in hospitalized patients



In-hospital Mortality Prognostic factors

■ Clinical variables

- Age (above 50 yr.)
- Comorbidities

■ Laboratory variables

- IL-6, CRP, LDH, Ferritin
- D-dimer
- us-Troponin
- Degree of respiratory insufficiency
 - $\text{SpO}_2 \leq 93\%$ (ambient air)
 - $\text{PaO}_2/\text{FiO}_2 < 300$ mmHg

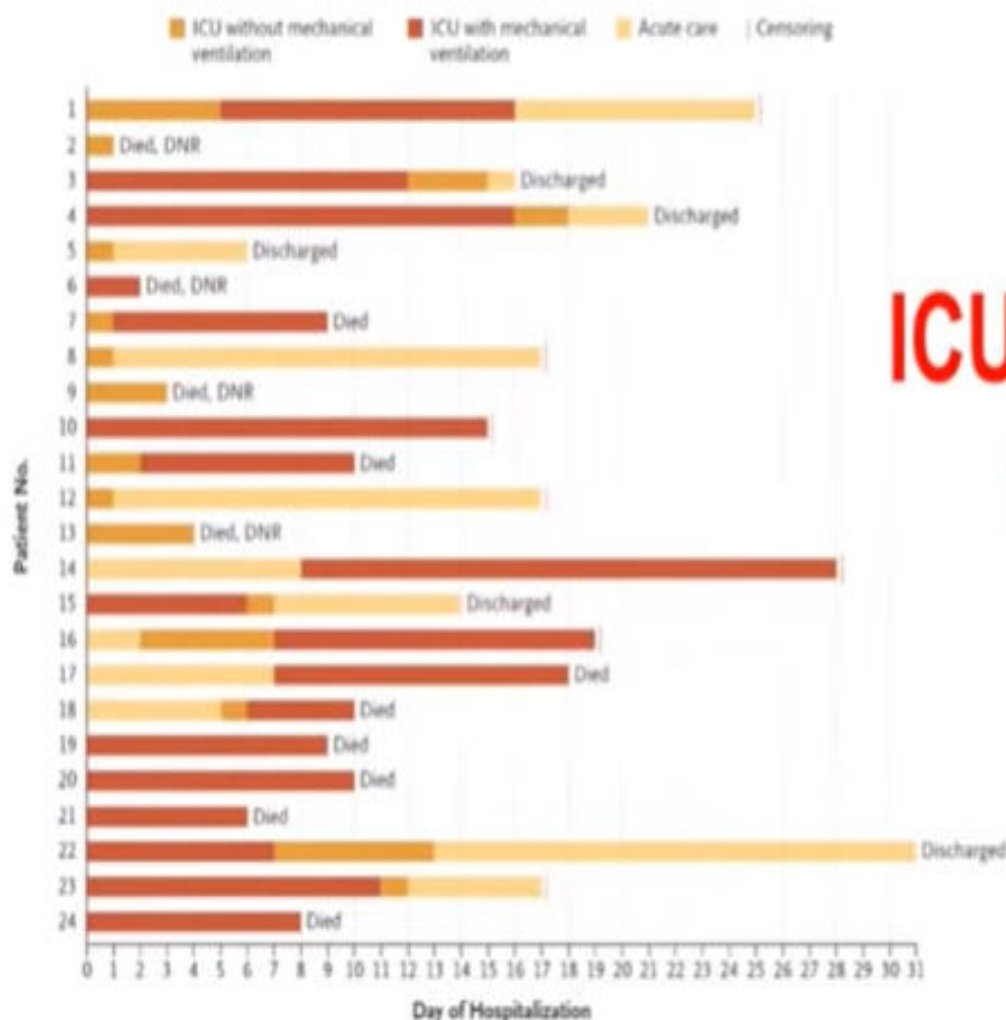
■ Chest-X ray / CT scan

- Bilateral involvement
- Radiological progression ($>50\%$)

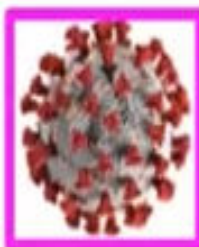
■ Evolutive variables

- SOFA score
- ICU admission
- Mechanical ventilation

Covid-19 in Critically ill Patients in the Seattle Region



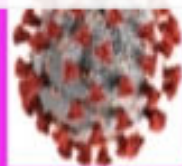
**ICU mortality
is 50%**



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246 studies on going !!!
→ 157 clinical trials

Also see

pic On Map Search Details

Showing: 1-10 of 246 studies

Clear

Row	Saved	Status
1	☐	Not yet recruiting NEW
2	☐	Active, not recruiting NEW
3	☐	Not yet recruiting NEW
4	☐	Not yet recruiting

Only *in vitro* and *in vivo* studies
Few clinical studies in SARS-CoV and MERS-CoV
We are using drugs in off-label indications.
... but in few weeks we have learned:
→ Antivirals must be started in early stages
→ Stop the inflammatory response before ARDS

Subscribe to RSS

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NCT Number

Control	NCT04318418
Respective	
Control	NCT04318301
Respective	
Group	NCT04316728
Label	
Primary Purpose: Diagnostic	
Allocation: Randomized	NCT04323800
Intervention Model: Parallel	

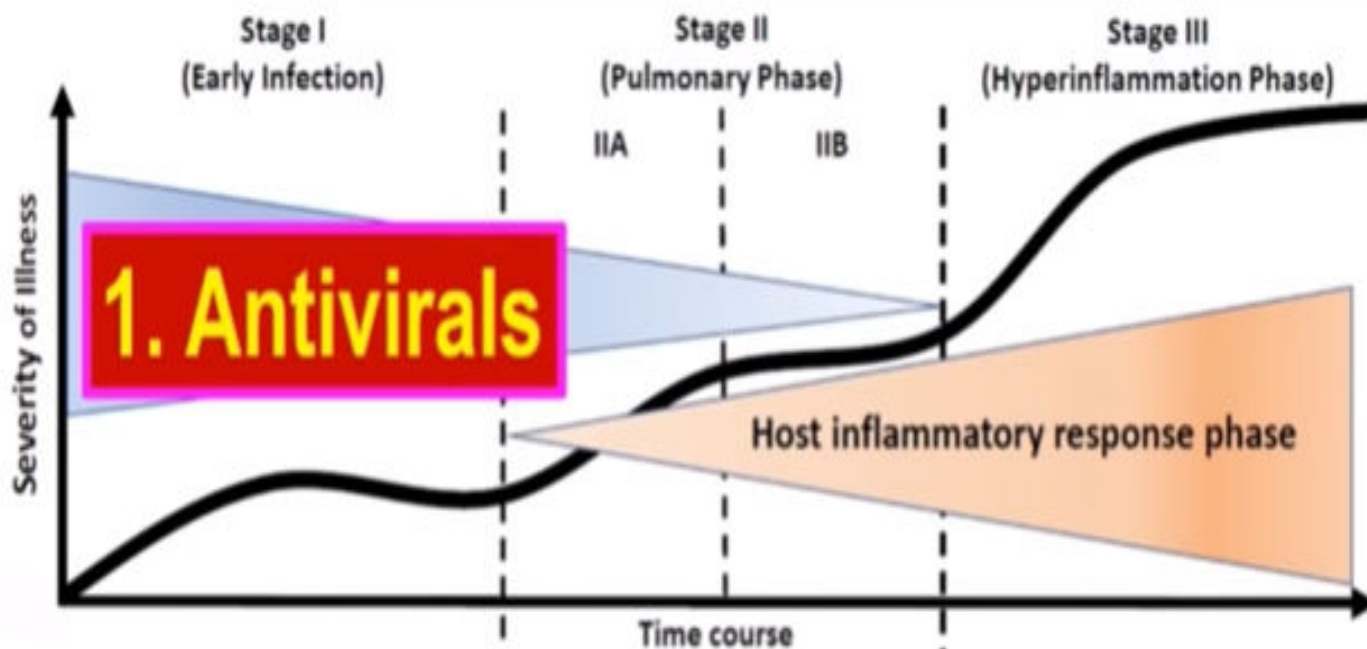
Efficacy and Safety Human Coronavirus Immune Plasma (HICIP) vs. Control (SARS-CoV-2 Non-immune Plasma) Among Adults Exposed to COVID-19

Other

- Allocation: Randomized
- Intervention Model: Parallel



Objectives COVID-19 Treatment: Treat Early & Hard



Clinical Symptoms

Mild constitutional symptoms
Fever $>99.6^{\circ}\text{F}$
Dry Cough, diarrhea, headache

Shortness of Breath
Hypoxia ($\text{PaO}_2/\text{FiO}_2 \leq 300\text{mmHg}$)

ARDS
SIRS/Shock
Cardiac Failure

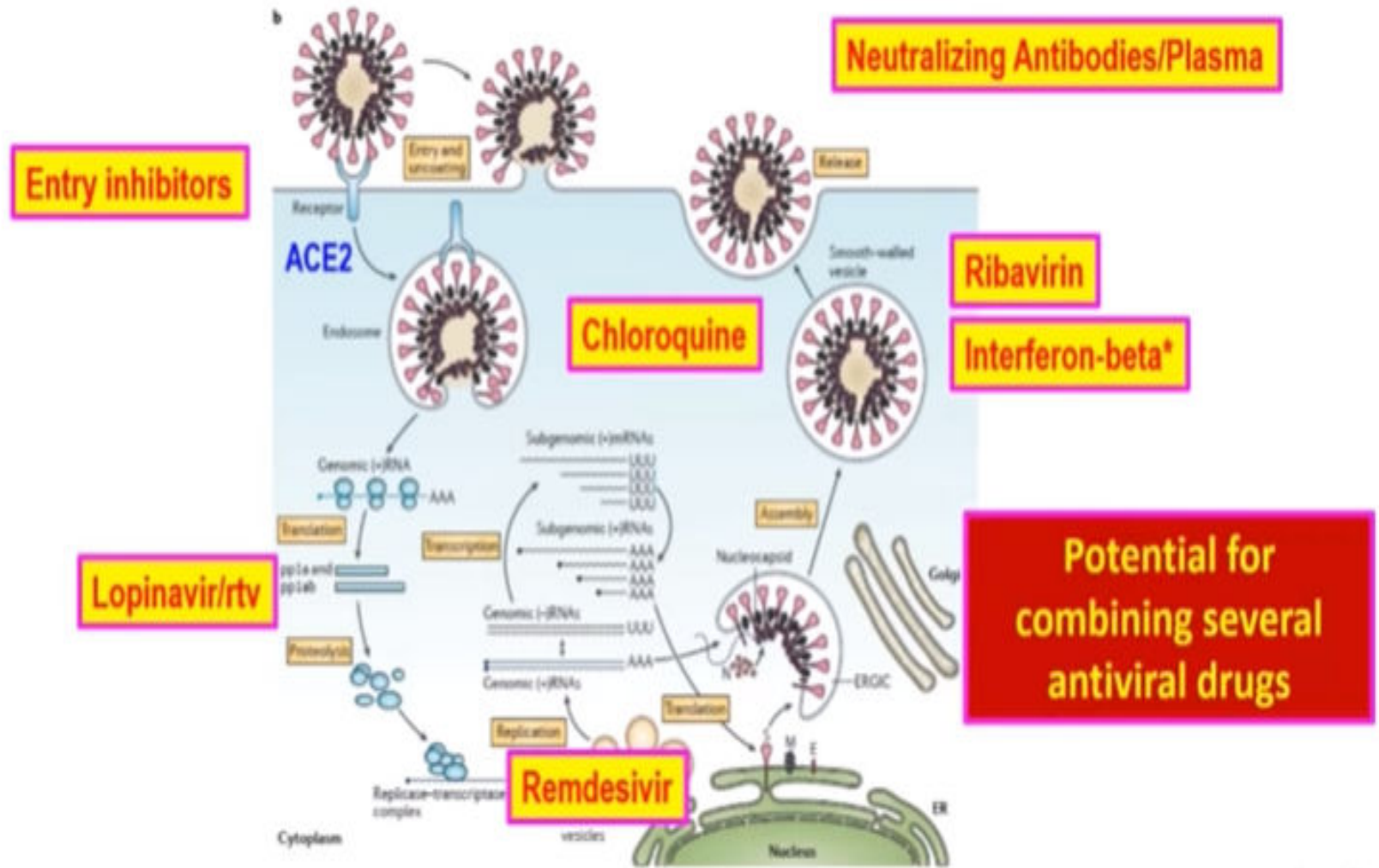
Clinical Signs

Lymphopenia, increased
prothrombin time, increased D-
Dimer and LDH (mild)

Abnormal chest imaging
Transaminitis
Low-normal procalcitonin

Elevated inflammatory markers
(CRP, LDH, IL-6, D-dimer, ferritin)
Troponin, NT-proBNP elevation

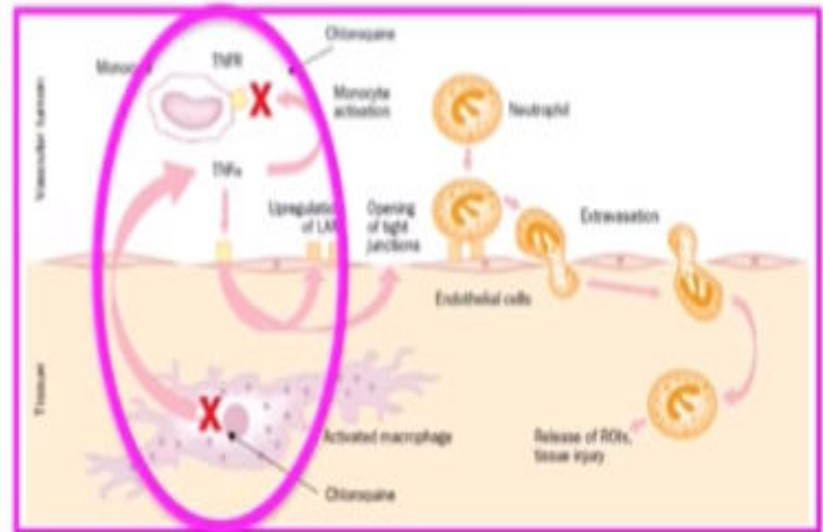
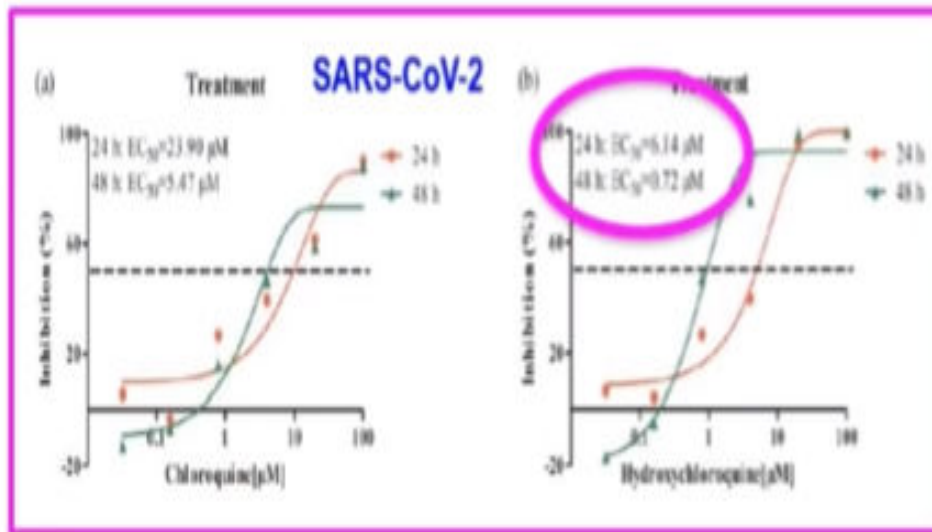
SARS-CoV-2 life cycle: Potential targets for antivirals



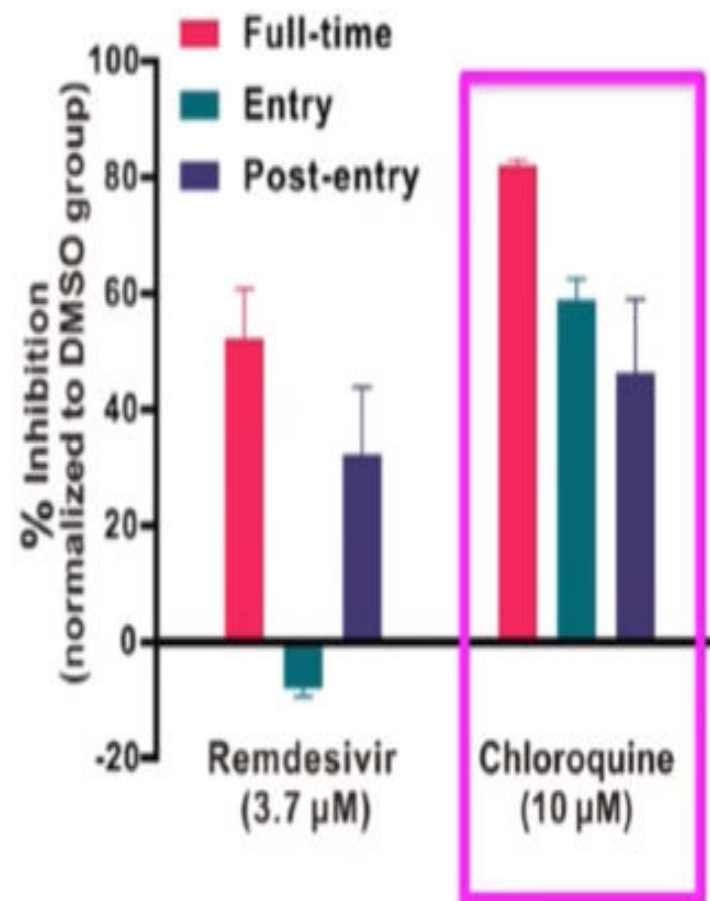
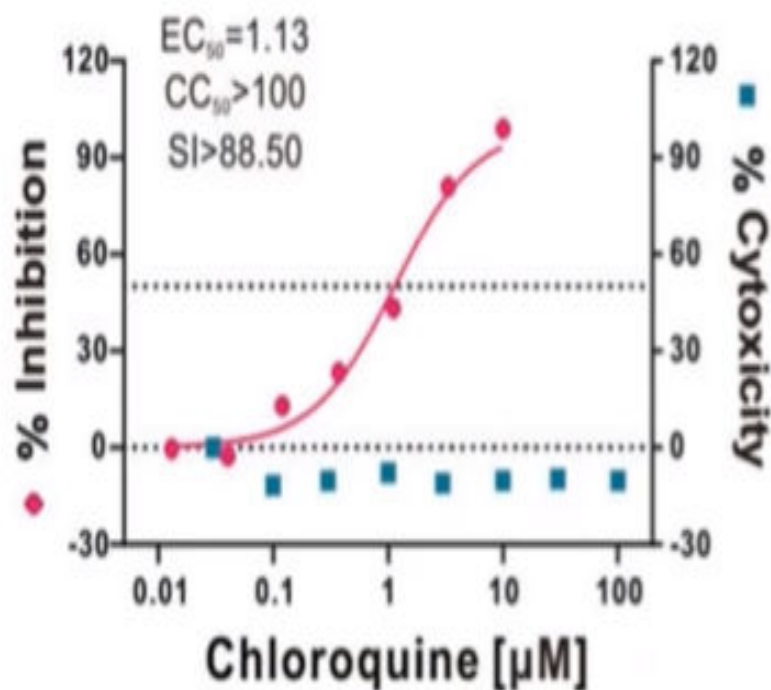
* Interferon induces hundreds of genes which can act on various parts of the lifecycle from potentially degrading viral RNA (OAS, RNASL) to inhibiting virus egress (BST-2)

Hydroxychloroquine

- Endosome-mediated viral entry and replication of enveloped viruses interactions
- Two potential beneficial mechanisms
 - **In vitro:** Hydroxychloroquine (HCQ) is more active than chloroquine (CQ)
 - **Anti-inflammatory properties**, stopping production IFN, TNF, IL6, IL1 (ARDS)
- **Dosage:** 400 mg/12 h first day, then 200 mg/12 h 14 days oral route.



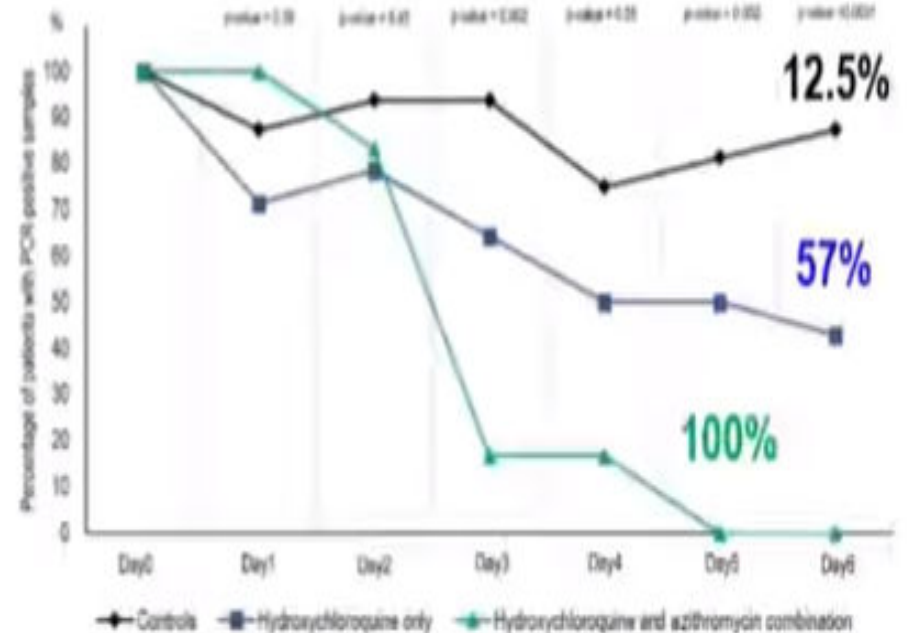
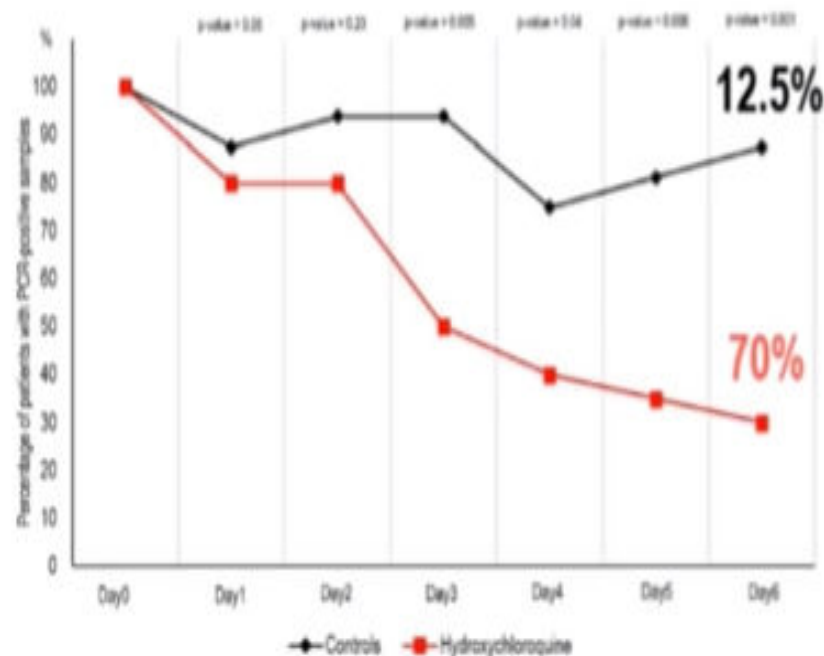
The in vitro activity of chloroquine against SARS-CoV-2



Hydroxychloroquine and azithromycin as a treatment of COVID-19

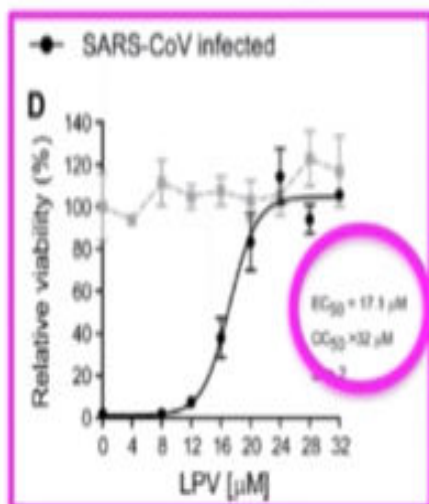
- Small open-label non-randomized multicenter clinical trial performed in France
- 22 patients with upper respiratory tract infection symptoms, 8 with pneumonia and 6 asymptomatic (total 36 patients).
- Hydroxychloroquine 600 mg/d (N=20). Azithromycin (N=6) was added according to clinical presentation. Control group (N=16).
- Daily nasopharyngeal swabs was tested daily in a hospital setting

Percentage of patients with PCR-negative nasopharyngeal samples from baseline to day 6.

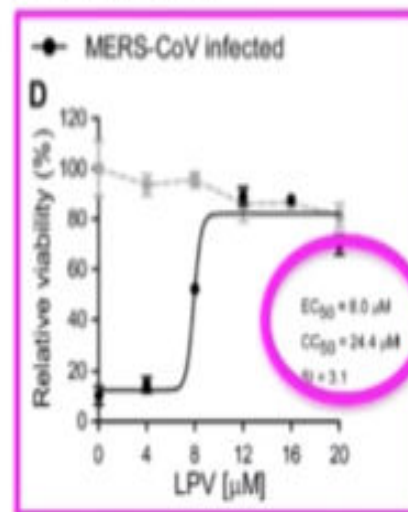


Lopinavir/ritonavir (Kaletra®)

- Protease inhibitor. Coronavirus encodes two cysteine proteases
- Effective *in vitro* and in animal models against SARS-CoV and MERS-CoV.
- Synergy with interferon- β 1b (MIRACLE trial)
- Limited clinical experience. Used as PEP (post-exposure prophylaxis).
- Important drug-drug interactions (DDI).
- Dosage: 400/100 mg 12 h during 14 days by oral route.

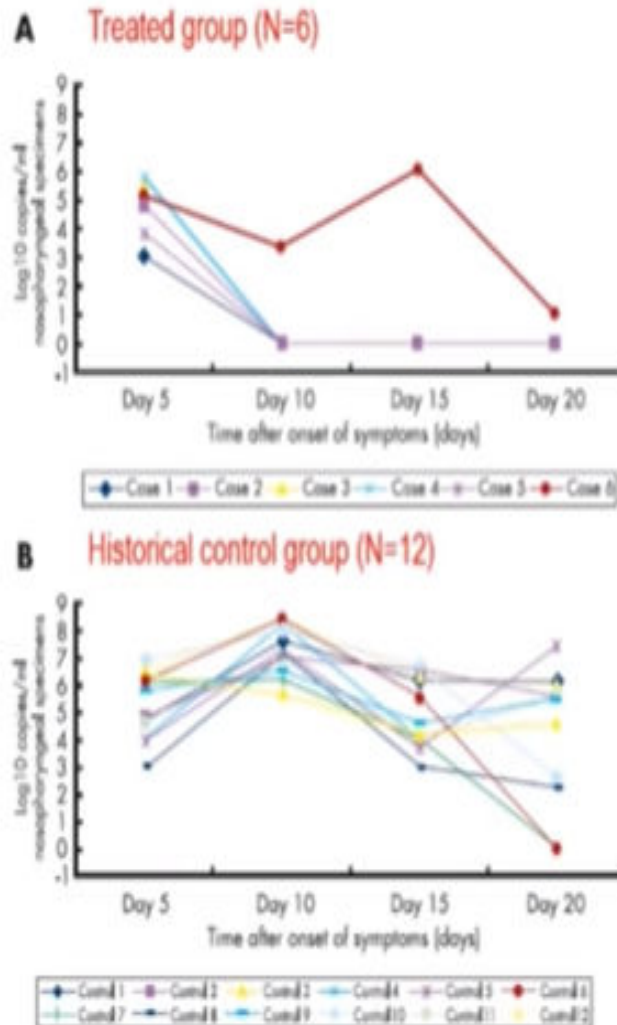


LPV/rtv 400/100 mg
Cmax 157 μ M/L



Lopinavir/ritonavir (Kaletra®)

Change in SARS-CoV viral load in nasopharyngeal swabs



Do all HIV-1 protease inhibitors have cross-activity against SARS-CoV-2?

Darunavir/cobicistat*

- *In vitro* SARS-CoV-2 inhibition at 300 μ M
 - 800/150 Median Cmin 3.4 μ M
- **Different viral proteases:** SARS-CoV-2 has a cysteine protease and HIV-1 a dimeric aspartate protease. **Darunavir has low affinity** with the catalytic center of the SARS-CoV-2 protease active site.

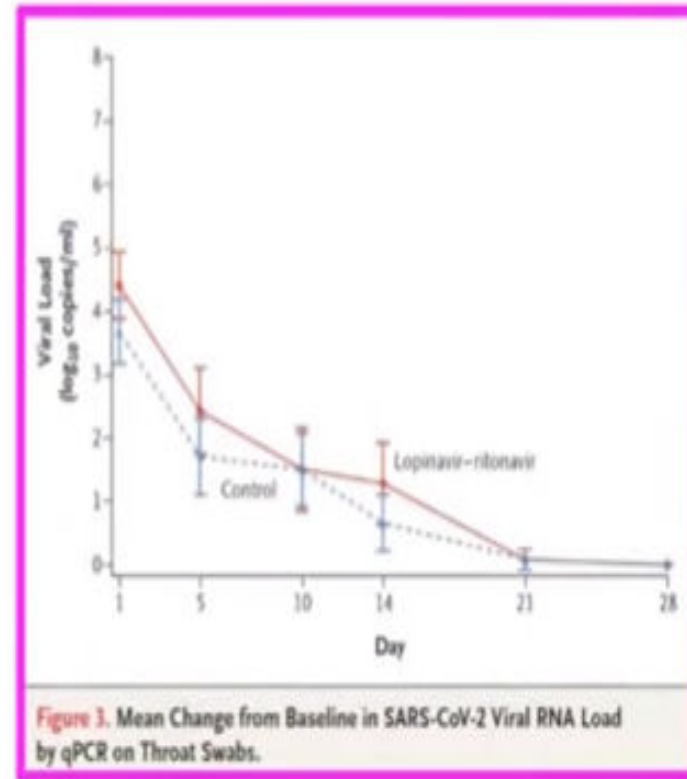
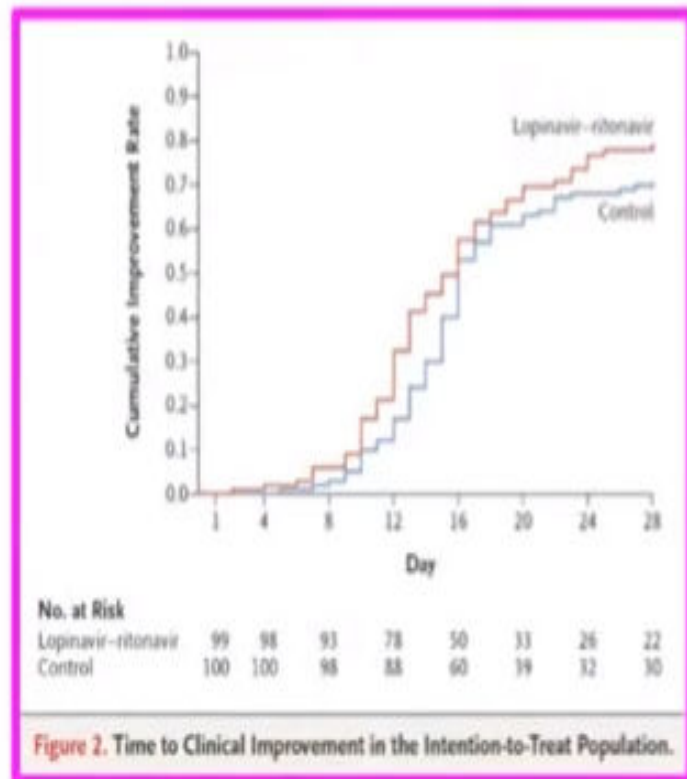
ORIGINAL ARTICLE

A Trial of Lopinavir–Ritonavir in Adults Hospitalized with Severe Covid-19

B. Cao, Y. Wang, D. Wen, W. Liu, Jingli Wang, G. Fan, L. Ruan, B. Song, Y. Cai, M. Wei, X. Li, J. Xia, N. Chen, J. Xiang, T. Yu, T. Bai, X. Xie, L. Zhang, C. Li, Y. Yuan, H. Chen, Huadong Li, H. Huang, S. Tu, F. Gong, Y. Liu, Y. Wei, C. Dong, F. Zhou, X. Gu, J. Xu, Z. Liu, Y. Zhang, Hui Li, L. Shang, K. Wang, K. Li, X. Zhou, X. Dong, Z. Qu, S. Lu, X. Hu, S. Ruan, S. Luo, J. Wu, L. Peng, F. Cheng, L. Pan, J. Zou, C. Jia, Juan Wang, X. Liu, S. Wang, X. Wu, Q. Ge, J. He, H. Zhan, F. Qiu, L. Guo, C. Huang, T. Jaki, F.G. Hayden, P.W. Horby, D. Zhang, and C. Wang

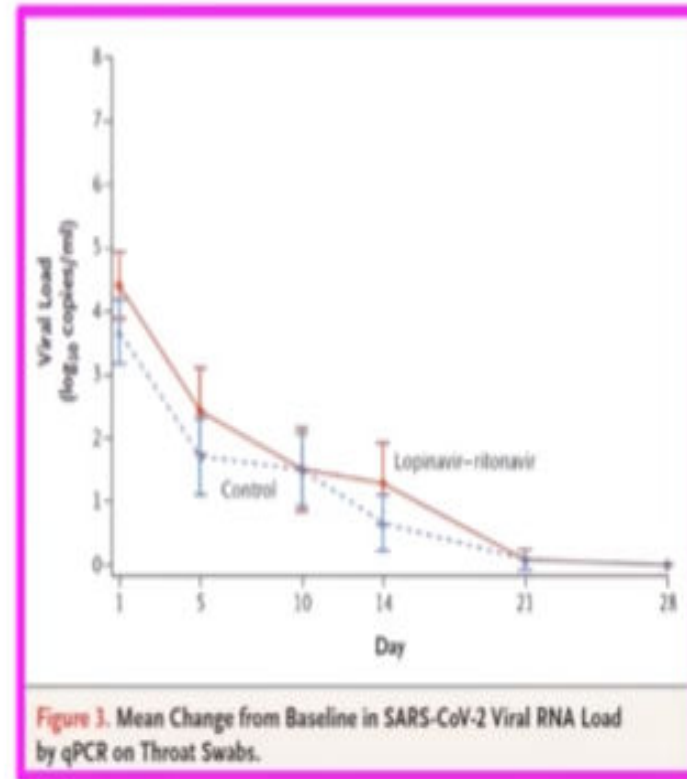
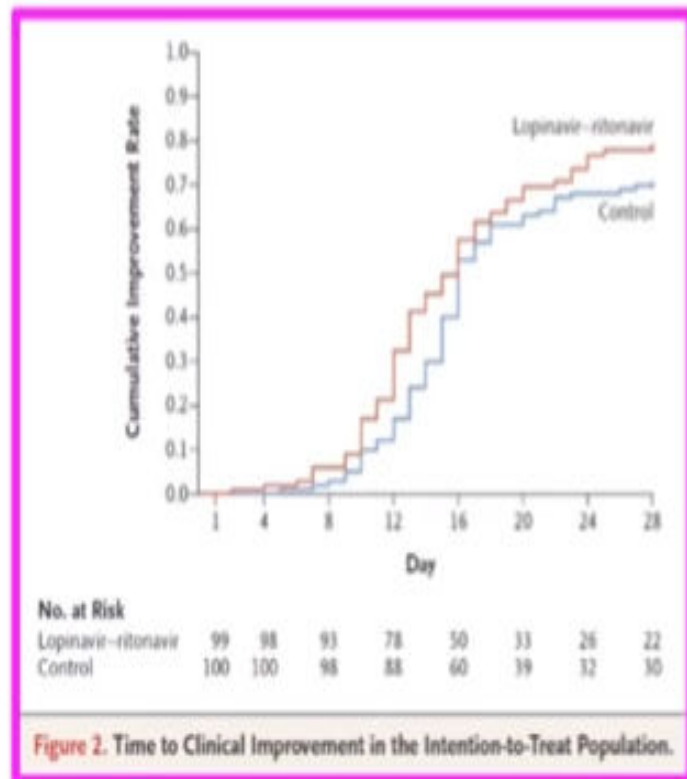
No benefit of Lopinavir–Ritonavir Treatment in Monotherapy vs. Standard of Care (SoC) in Severe COVID-19 Pneumonia

- Randomized, controlled, open-label clinical trial in China: [Lopinavir/ritonavir vs. SoC](#)
- 199 hospitalized adult patients with COVID-19 pneumonia with $\text{Sao}_2 \leq 94\%$ (ambient air) or $\text{PaO}_2/\text{FiO}_2 < 300$ mm Hg.
- Primary endpoint: [clinical improvement](#) (two points on a seven-category ordinal scale or discharge from the hospital).



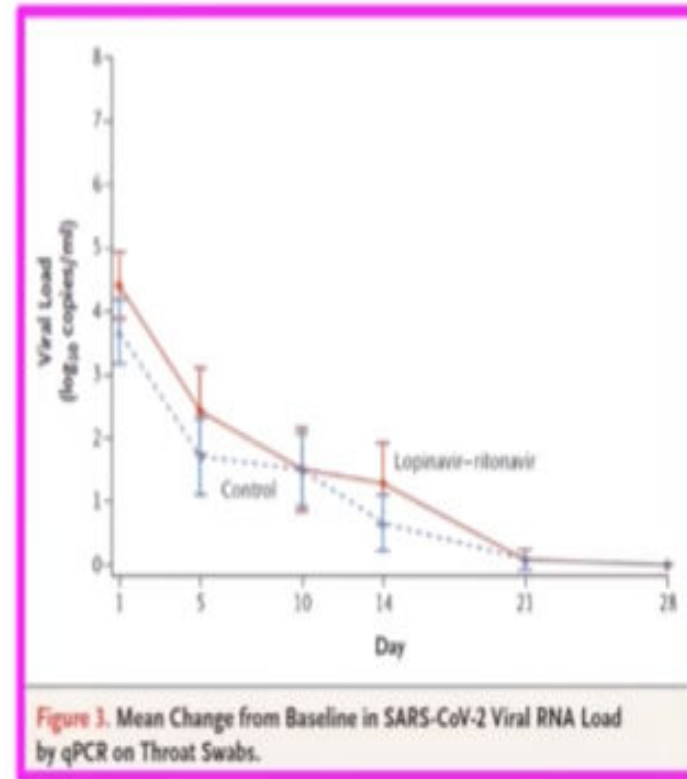
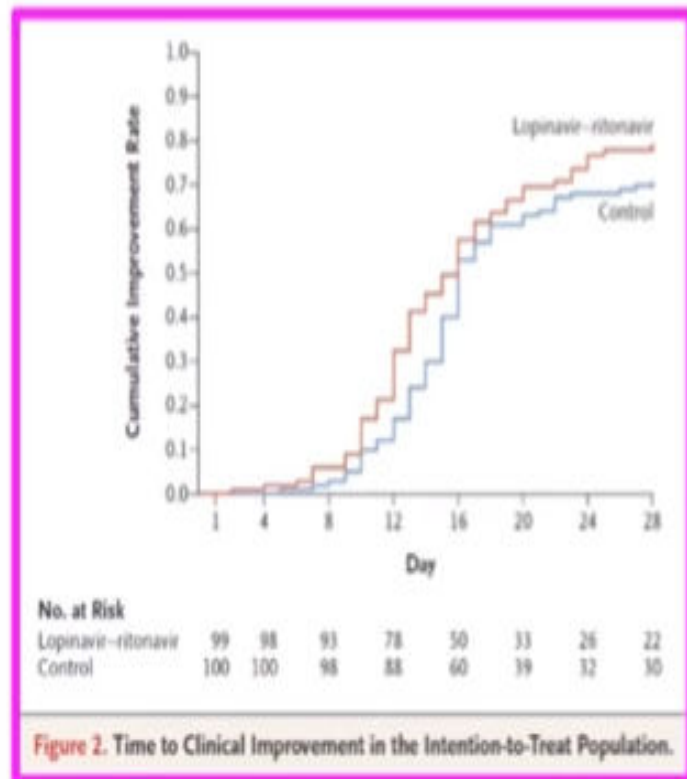
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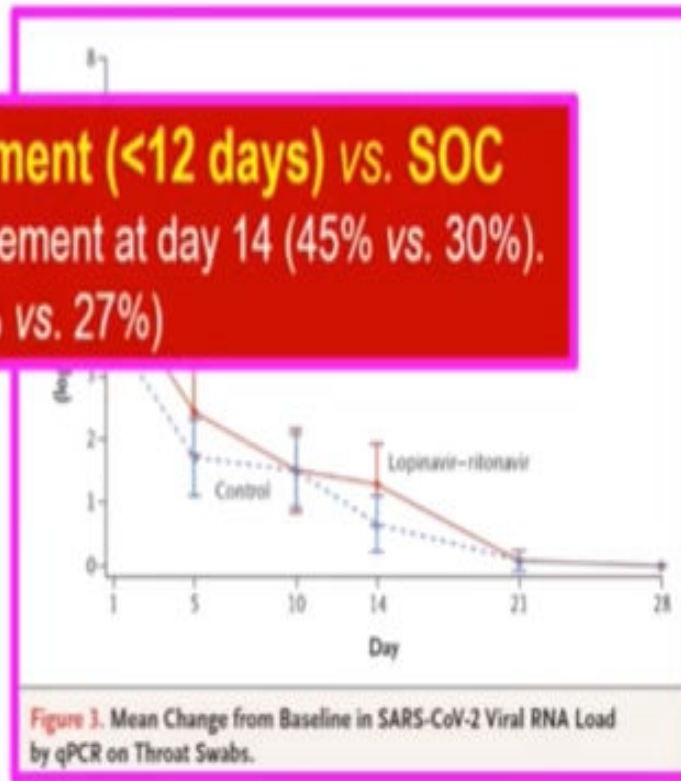
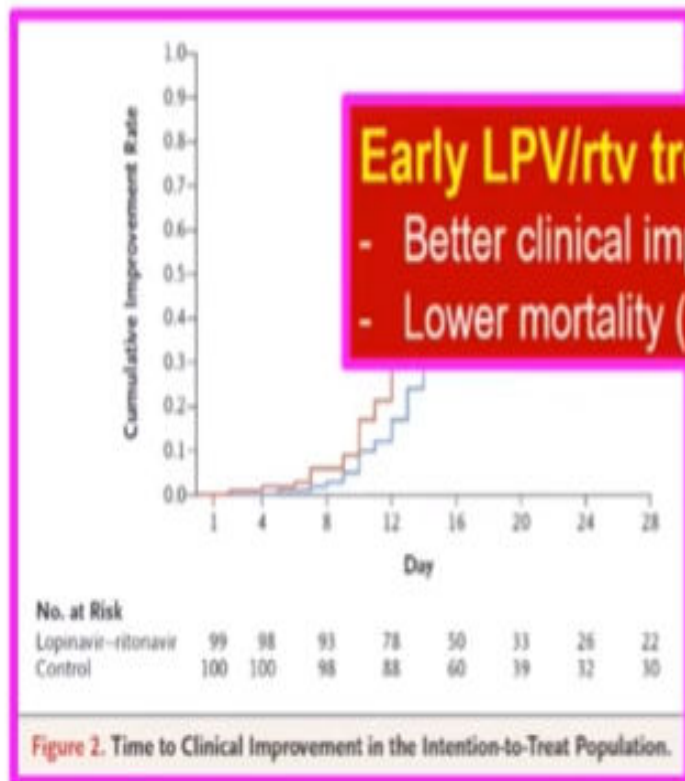
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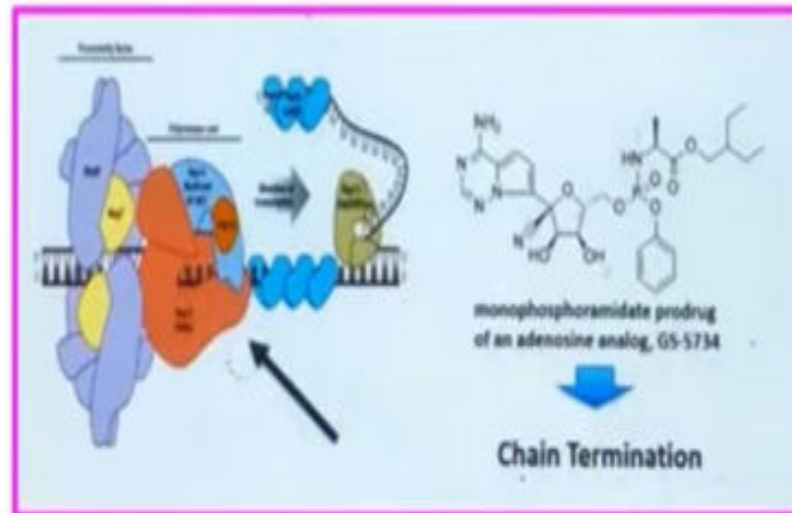
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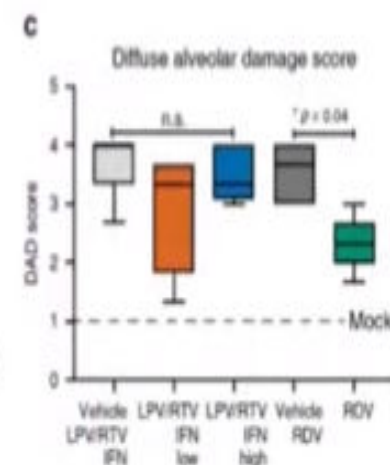
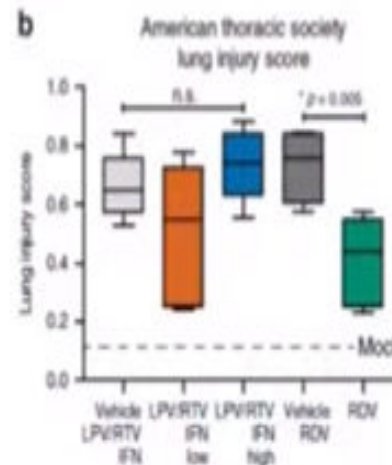
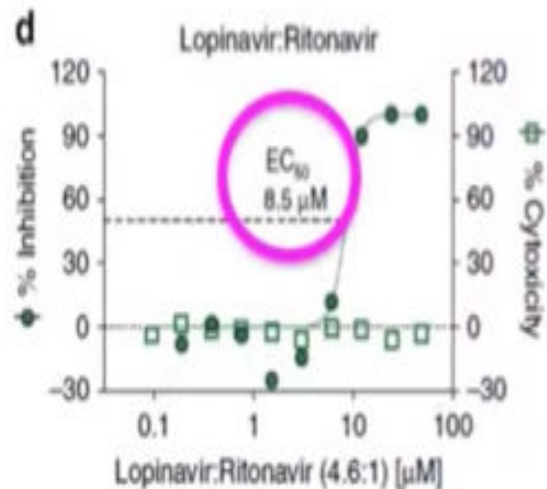
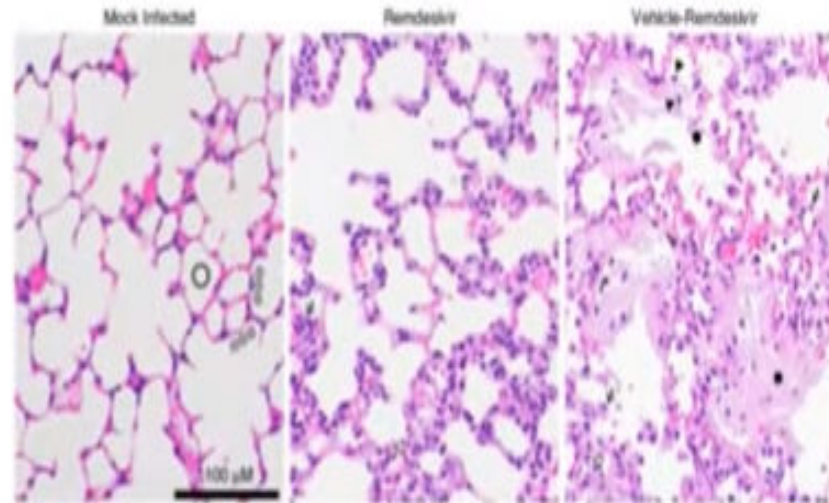
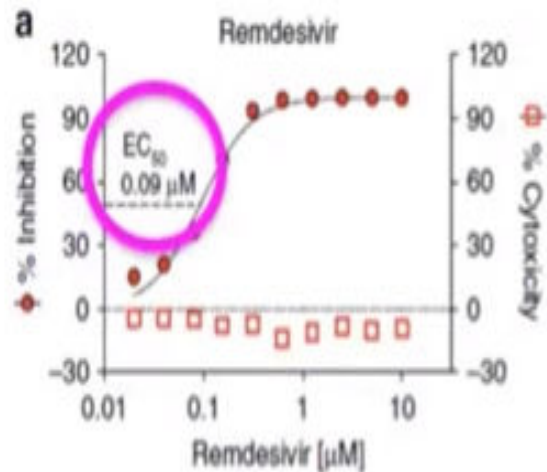
Remdesevir (GS-5734)

- RNA-dependent RNA polymerase inhibitor.
- Effective *in vitro* and in animal models against zoonotic and epidemic SARS-CoV and MERS-CoV as both prophylactic and therapeutic agent.
- Limited clinical experience. Several RCT are underway
- No drug-drug interactions (DDI).
- Dosage: 200 mg IV, then 100 mg/24 h during 5-10 days.



Remdesivir (RDV) is superior to Lopinavir/ritonavir (LPV/RTV)

Therapeutic RDV but not LPV/RTV-IFN β diminishes signs of Acute Lung Injury



Clinical trials with Remdesivir (N=9)

Recruiting NEW	Study to Evaluate the Safety and Antiviral Activity of Remdesivir (GS-5734™) in Participants With Severe Coronavirus Disease (COVID-19)	Industry	NCT04292899
Recruiting NEW	Study to Evaluate the Safety and Antiviral Activity of Remdesivir (GS-5734™) in Participants With Moderate Coronavirus Disease (COVID-19) Compared to Standard of Care Treatment	Industry	NCT04292730
Recruiting	Mild/Moderate 2019-nCoV Remdesivir RCT	Other	NCT04252664
Available NEW	Expanded Access Treatment Protocol: Remdesivir (RDV, GS-5734) for the Treatment of SARS-CoV2 (CoV) Infection	Industry	NCT04323761
Recruiting	Severe 2019-nCoV Remdesivir RCT	Other	NCT04257656
Recruiting	Adaptive COVID-19 Treatment Trial (ACTT)	NIH	NCT04280705
Available NEW	Expanded Access Remdesivir (RDV, GS-5734™)	U.S. Fed	NCT04302766
Not yet recruiting NEW	The Efficacy of Different Anti-viral Drugs in (Severe Acute Respiratory Syndrome-Corona Virus-2) SARS-CoV-2	Other	NCT04321616
Recruiting NEW	Trial of Treatments for COVID-19 in Hospitalized Adults	Other	NCT04315948

Clinical trials with Remdesivir (N=9)

Recruiting NEW	Study to Evaluate the Safety and Antiviral Activity of Remdesivir (GS-5734™) in Participants With Severe Coronavirus Disease (COVID-19)	Industry	NCT04292899
Recruiting NEW	Study to Evaluate the Safety and Efficacy of Remdesivir (GS-5734™) Compared to Standard of Care Treatment in Participants With Severe Coronavirus Disease (COVID-19)	Industry	NCT04292730
Recruiting	Mild/Moderate 2019-nCoV Remdesivir Treatment Study	Other	NCT04252664
Available NEW	Expanded Access Treatment Program for Remdesivir (GS-5734™) in Participants With Severe Coronavirus Disease (COVID-19)	Industry	NCT04323761
Recruiting	Severe 2019-nCoV Remdesivir RCT	Other	NCT04257656
Recruiting	Adaptive COVID-19 Treatment Study	NIH	NCT04280705
Available NEW	Expanded Access Remdesivir Study	U.S. Fed	NCT04302766
Not yet recruiting NEW	The Efficacy of Different Treatments in Patients With Severe Coronavirus Disease (COVID-19)	Other	NCT04321616
Recruiting NEW	Trial of Treatments for COVID-19	Other	NCT04315948

Types of COVID-19 pneumonia

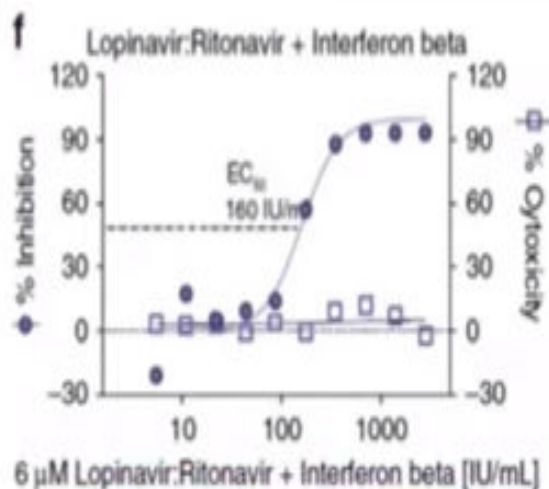
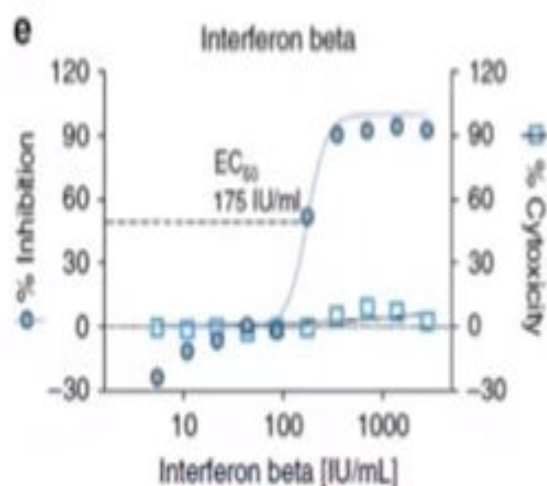
- Mild/Moderate
- Severe (ICU patients)
- Critical (intubated patients)

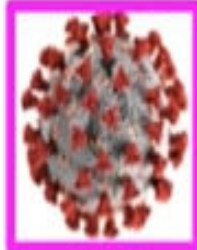
Study arms

- Remdesivir 5 vs. 10 days
- vs. HCQ 10 days
- vs. HCQ vs. LPV/r + INF-β1a 10 days

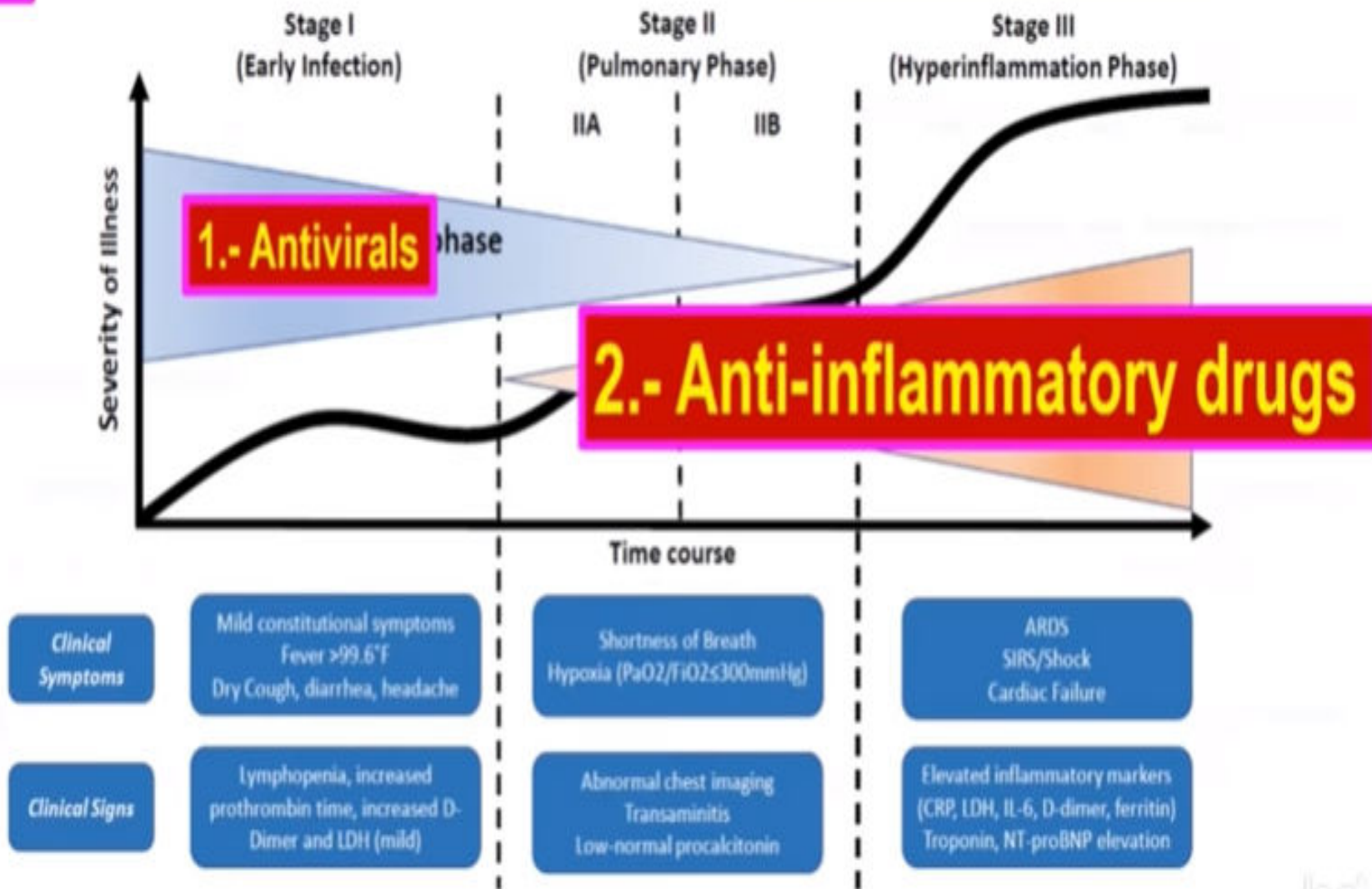
Interferons

- Effective *in vitro* and *in vivo* against SARS-CoV and MERS-CoV.
- Synergy with **ribavirin** and **lopinavir/ritonavir**
- Some clinical experience mainly in MERS-CoV.
- Dosage: **Interferon- β 1b** 250 mcg/48 h **SC** during 14 days
Interferon- α 2b 100,000-400,000 UI/kg **nebulized** BID during 5-7 days



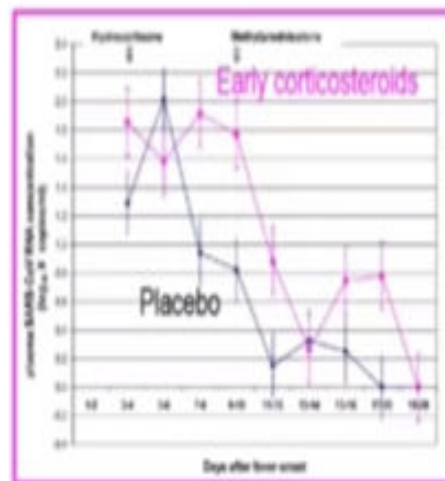
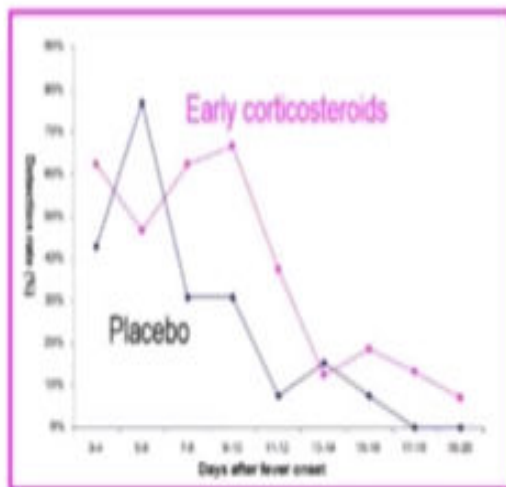


Objectives COVID-19 Treatment: Treat Early & Hard



Corticosteroids

- **Effective for treating ARDS of non-infectious cause** (Meta-Analysis and RCT)
- Increasing mortality in **influenza**-related pneumonia and ARDS.
- **Short pulse-therapy** might be beneficial in some SARS-CoV and MERS-CoV studies but also have important side effects. **No RCT.**
- Increased plasma viremia and delayed clearance in SARS-CoV and MERS-CoV.



Ho JC, AJRCCM, 2003; Sung JJY, Thorax, 2004; Lau ACW, Respiriology, 2004; Lee N, JCV, 2004; Rabaan AA, JMM, 2017; Arabi YM, AJRCCM, 2018, Sun S, ETM 2019; Zhou Y, Sci Rep, 2020; Villar J, Lancet RM, 2020.

Clinical evidence does not support corticosteroid treatment for SARS-CoV-2 induced lung injury

	Outcomes of corticosteroid therapy*	Comment
MERS-CoV	Delayed clearance of viral RNA from respiratory tract ²	Adjusted hazard ratio 0.4 (95% CI 0.2–0.7)
SARS-CoV	Delayed clearance of viral RNA from blood ³	Significant difference but effect size not quantified
SARS-CoV	Complication: psychosis ⁴	Associated with higher cumulative dose, 10 975 mg vs 6780 mg hydrocortisone equivalent
SARS-CoV	Complication: diabetes ²	33 (35%) of 95 patients treated with corticosteroid developed corticosteroid-induced diabetes
SARS-CoV	Complication: avascular necrosis in survivors ⁴	Among 40 patients who survived after corticosteroid treatment, 12 (30%) had avascular necrosis and 30 (75%) had osteoporosis
Influenza	Increased mortality ⁵	Risk ratio for mortality 1.75 (95% CI 1.3–2.4) in a meta-analysis of 6548 patients from ten studies
RSV	No clinical benefit in children ^{10,11}	No effect in largest randomised controlled trial of 600 children, of whom 305 (51%) had been treated with corticosteroids

CoV=coronavirus. MERS=Middle East respiratory syndrome. RSV=respiratory syncytial virus. SARS=severe acute respiratory syndrome. *Hydrocortisone, methylprednisolone, dexamethasone, and prednisolone.

Tocilizumab (RoActemra®)

- Interleukin-6 (IL-6) inhibitor. Tocilizumab binds specifically to both soluble and membrane-bound IL-6 receptors (sIL-6R and mIL-6R).
 - Indications:
 - Rheumatoid arthritis,
 - Systemic juvenile idiopathic arthritis,
 - Juvenile idiopathic polyarthritis,
 - Giant cell arteritis,
 - CAR-T cell induced cytokine release syndrome (CRS).
 - Limited published clinical experience in **COVID-19 pneumonia**. Several clinical trials ongoing.
- Criteria used:
- Confirmed COVID-19 pneumonia (Chest X-ray or CT scan)
 - $\text{SPO}_2 \leq 93\%$ or $\text{PaO}_2/\text{FiO}_2 < 300$ mmHg

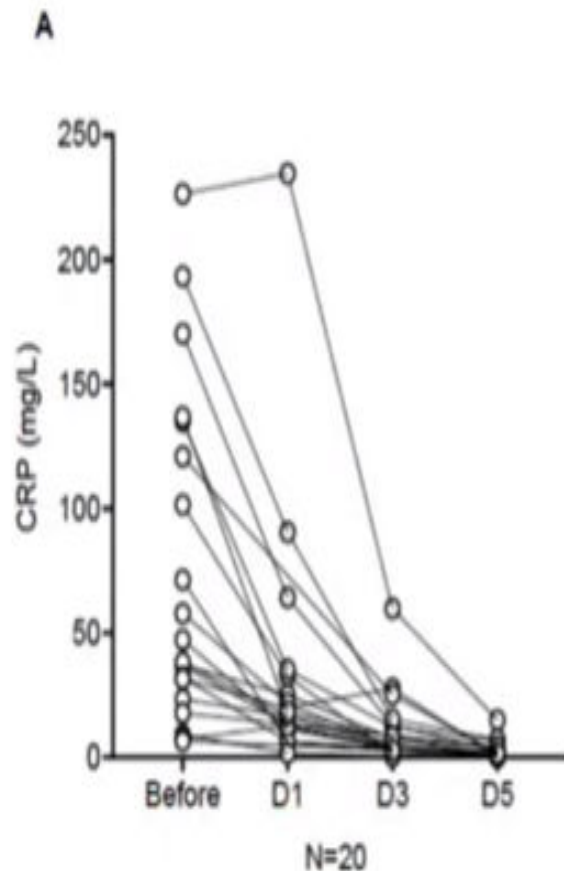
Tocilizumab (RoActemra®)

- **Dosage (8 mg/kg):** **≥80 kg:** Single 600 mg IV dose. Consider second dose 12 h later
<80 kg: Single 400 mg IV dose. Consider second dose 12 h later
- Exceptionally, a third dose could be administered 16-24h later.
- **PK:** Very long $t_{1/2}$: 7-14 days.
- **Drug-drug interactions (DDI):** modest CYP450 inducer. Potential mild interactions with amiodarone, quinidine, some anticoagulants and anti-platelets.
- **Side effects:** upper respiratory tract infections, nasopharyngitis, headache, hypertension and abnormal liver function tests.
 - SAE: severe infections, complications of diverticulitis and hypersensitivity reactions.
- Potential reactivation of latent TB and HBV infection.

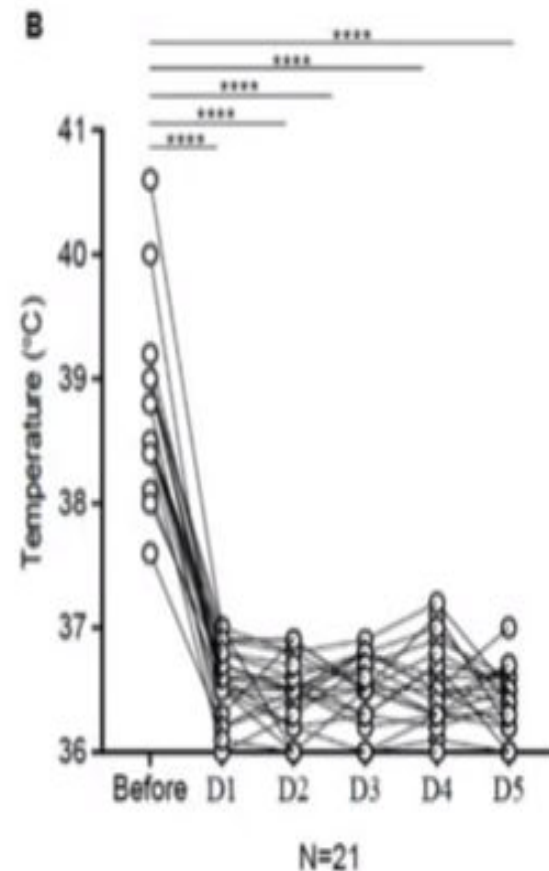
Tocilizumab was an Effective Treatment of 21 patients with Severe COVID-19 in China

- N=21, 17 severe, 4 critical.
- Mean age 57 yr. 85% males. All 21 patients received SoC treatment for a week before deteriorating with sustained fever, hypoxemia, and chest CT image worsening.
- Mean IL-6 level before tocilizumab was 132.38 pg/mL (normal < 7 pg/mL).
- **Efficacy:** fever returned to normal, all other symptoms improved remarkably
- 15/20 patients (75.0%) had lowered their oxygen intake, 1 needed no oxygen therapy
- CT scans showed significant remission of opacities in both lungs in 19/20 patients (90.5%) after treatment.
- No adverse drug reactions and no subsequent pulmonary infections were reported
- All but one patients discharged.
- No deaths

CRP and Temperature Changes Following TCZ Treatment



CRP



Temperature

Treatment Regimens in Moderate/Severe COVID-19 Pneumonia

Antivirals

(ASAP & <10 days)

Hydroxychloroquine

(azithromycin)

+

Lopinavir/ritonavir

+

Remdesivir

Anti-inflammatory drugs

(before ARDS)

IL-6 Inhibitors

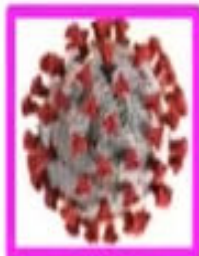
Tocilizumab

Others

(IL1/JAK inhibitors)

ARDS

Corticosteroids



SARS-CoV-2 pandemic (COVID-19) Update

April 2nd 2020

- Coronavirus History
- Current Epidemiology **NEW!**
- The Virus & Pathogenesis **NEW!**
- Clinical Manifestations & Diagnosis **NEW!**
- Prognosis **NEW!**
- Treatment **NEW!**
- **Prevention**
- Take-home messages

Prevention

■ At personal level

- Avoid close contact **sick people** (surgical masks)
- Wash hands with soap & water
- **FPP2 N95** Face Mask (HCW)
- Personal Protective Equipment (**PPE** x HCW)

→ **RCT of PEP in close contacts & PrEP in HCW.**

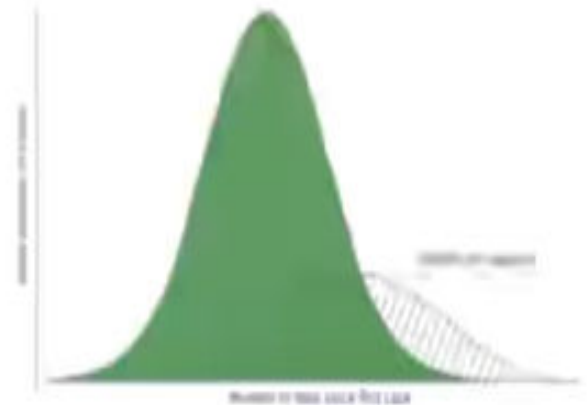
- Hydroxychloroquine $\pm$ azithromycin

■ At population level

- Aggressive approach to delay transmission
- Implementation of public health measures



www.cdc.gov/handwashing

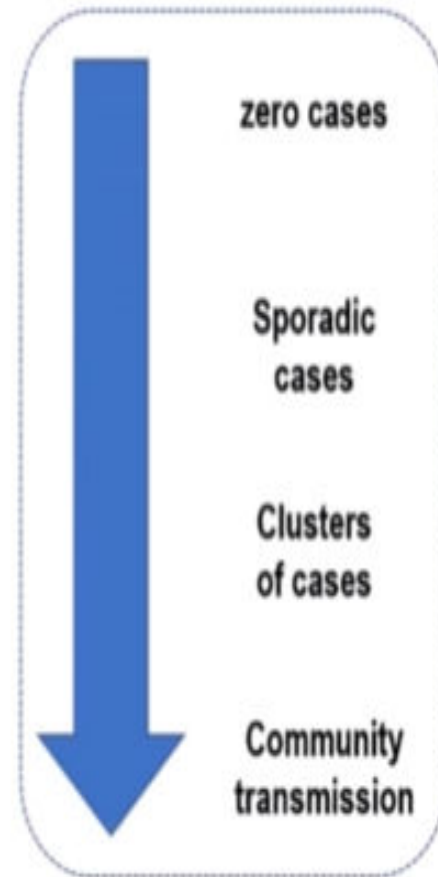


Community mitigation measures

CDC & ECDC, 2020.

China used mitigation public health measures...

- Universal population measures
- Case isolation & management
- Close contact quarantine
- Suspension of public gatherings
- Movement restrictions



CORONAVIRUS

EL PERIÓDICO

Since March 15th 2020

ón sobre la crisis



PUBLICADO YA EN EL BLOG

España, cerrada por decreto para evitar el colapso

Sánchez se otorga casi plenos poderes y centraliza competencias en Sanidad, Interior, Defensa y Transportes

💬 615 Comentarios

EDITORIAL · *Unidad para vencer el virus*

MEDIDAS CONTRA LA ENFERMEDAD



EL DECRETO DE ESTADO DE ALARMA

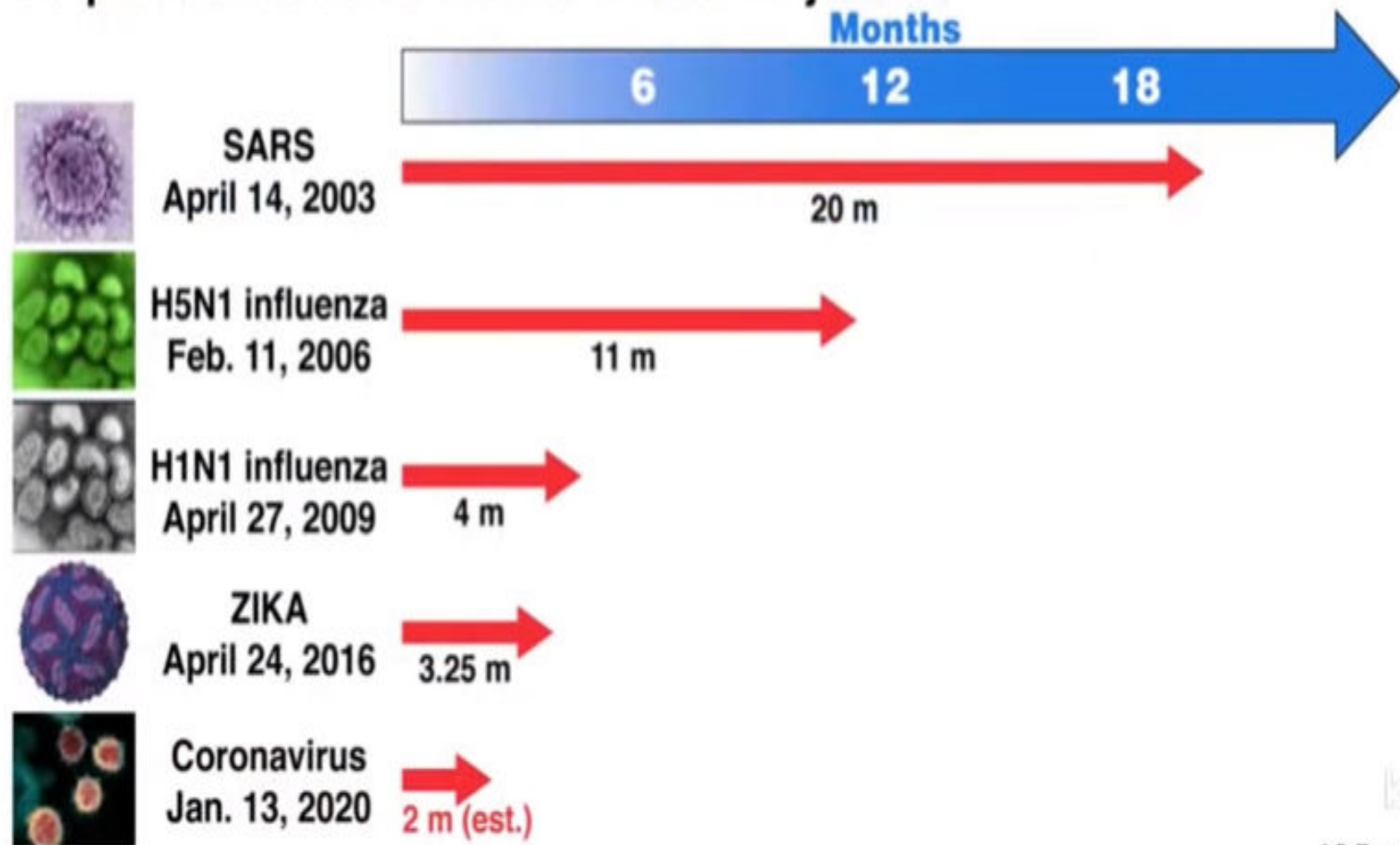


CHOQUE TERRITORIAL



NIH Vaccine Research Center: Vaccines for Emerging Diseases

Sequence Selection to 1st Human Injection



Government official: Coronavirus vaccine trial starts Monday

By ZEKE MILLER March 16, 2020 GMT

March 16th, 2020

WASHINGTON (AP) — The first participant in a clinical trial for a vaccine to protect against the new coronavirus will receive an experimental dose on Monday, according to a government official.

The National Institutes of Health is funding the trial, which is taking place at the Kaiser Permanente Washington Health Research Institute in Seattle. The official who disclosed plans for the first participant spoke on condition of anonymity because the move has not been publicly announced.

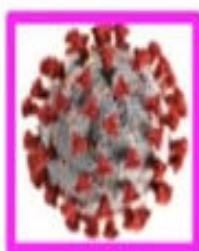
Public health officials say it will take a year to 18 months to fully validate any potential vaccine.

MORE ON THE VIRUS OUTBREAK:

- Lockdowns erupt as world infections surpass those in China
- Virus toll in Iran climbs as lockdowns deepen across Mideast
- The Latest: UK asks Ford, Rolls-Royce to make ventilators

→ Multiple SARS-CoV-2 vaccine candidates being pursued by >30 organizations globally





SARS-CoV-2 pandemic (COVID-19) Update

April 2nd 2020

- Coronavirus History
- Current Epidemiology **NEW!**
- The Virus & Pathogenesis **NEW!**
- Clinical Manifestations & Diagnosis **NEW!**
- Prognosis **NEW!**
- Treatment **NEW!**
- Prevention
- **Take-home messages**



Take-home Messages

- We are facing a pandemic of colossal challenges with millions of people infected.
- SARS-CoV-2 is a new coronavirus with high infectivity ($R_0=3$). Cause severe respiratory infection in 20% of cases, mainly in elderly and in patients with comorbidities. **Overall mortality is high, $\approx 10\%$.**
- Antiviral and anti-inflammatory drugs must be started early in order to avoid the development of ARDS and mechanical ventilation, with 50% mortality.
- **Results of most clinical trials will be available soon (April & May 2020)**
- Case isolation, contact tracing and personal and population prevention measures should contain the epidemic. Vaccine studies are already started.



Acknowledgements



J.T. Brooks
CDC, Atlanta



A.S. Fauci
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T.P. Sheahan
UNC, Chapel Hill

R.S. Baric
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A. Moreno
M. Peck
C. Sierra
M. Tuset
Z. Wu

To all my front-line colleagues
To our patients