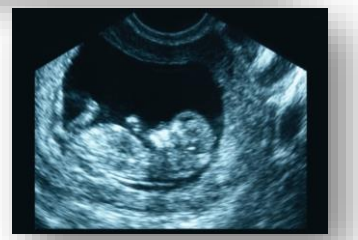
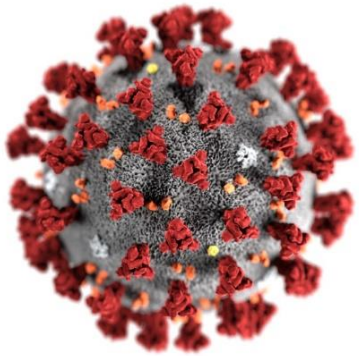




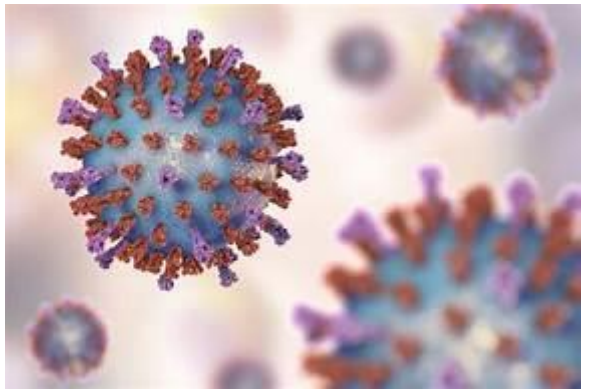
COVID-19: What Pediatric HIV Programs Need to Know

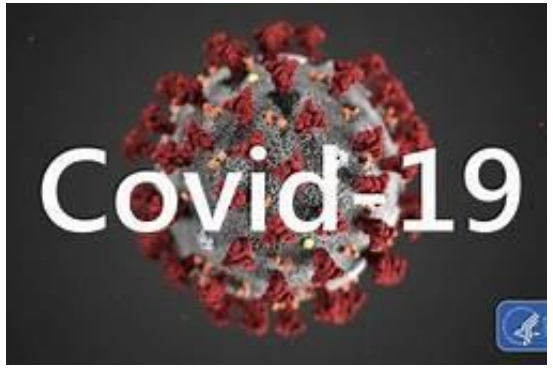
Basics of SARS CoV-2 and Effect on Mothers and Children

Lynne M. Mofenson, M.D.

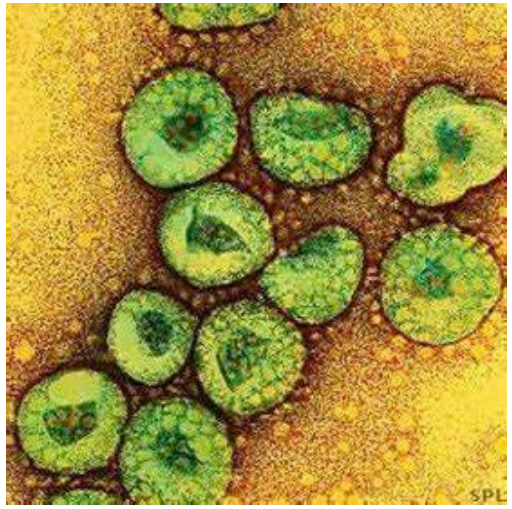
April 23 2020

Please Note that Data are Limited, Preliminary, Some of Poor Quality, and Change Almost Daily



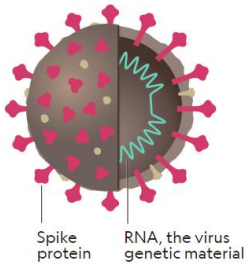


Basic Information on the SARS-CoV-2/ COVID-19

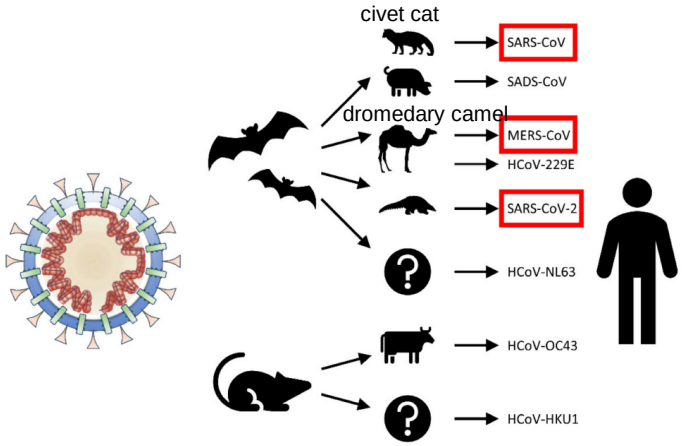


What is a Coronavirus?

- Coronaviruses (CoV) are single-stranded RNA viruses, named because the virus has projections (spike protein) on envelope resembling a crown.



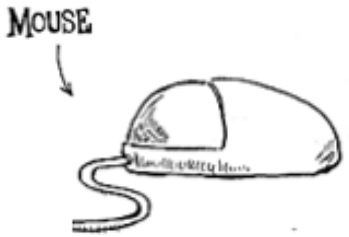
- They are classified in 4 genera based on genomic structure; can infect different hosts and have different tissue tropism:
  - Gamma and delta CoV infect birds, fishes and only a few mammals.
  - **Alpha and beta CoV** infect only mammals, including **humans**, and have repeatedly crossed species barriers; bats and rodents are the primary gene sources.
    - There are 7 human CoV known to date, 4 cause mild and 3 cause severe disease.



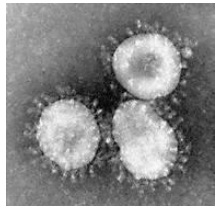
Rabi FA et al. Pathogens. 2020 Mar 20;9 (3).

Virus	Genus	Disease	Discovery
CoV-229E	Alpha	Mild respiratory infection	1967
CoV-NL-63	Alpha	Mild respiratory infection	1965
COV-HKU-1	Beta	Mild respiratory infection; pneumonia	2005
CoV-OC43	Beta	Mild respiratory infection	2004
SARS-CoV	Beta	Severe acute respiratory infection, 10% mortality	2003
MERS-CoV	Beta	Severe acute respiratory infection, 37% mortality	2012
SARS-CoV-2	Beta	Severe acute respiratory infection, ?2% mortality	2019

Loeffelholz MJ et al. Emerg Microb Infect. 2020 Dec;9:747-56

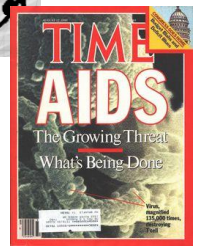


Terminology



- SARS-CoV-2 (serious acute respiratory syndrome coronavirus 2) refers to the virus itself.

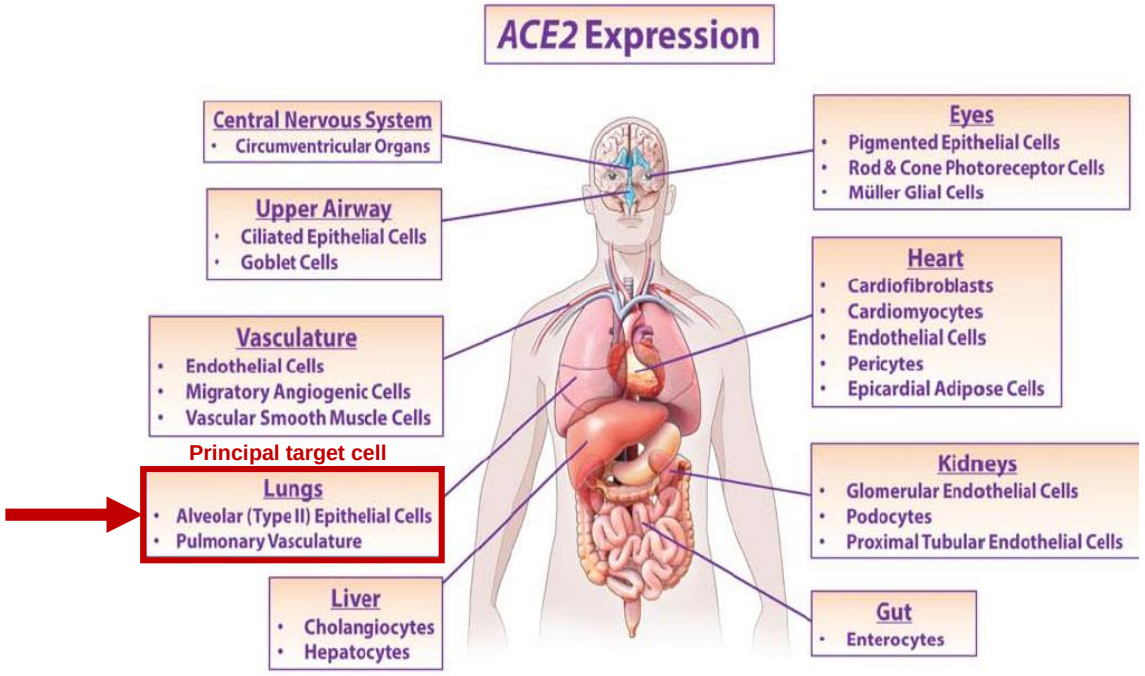
- COVID-19 (**Co**rnona**vi**rus **D**isease 20**19**) is the disease caused by the virus (named by WHO in a press release on Feb 11, 2020).



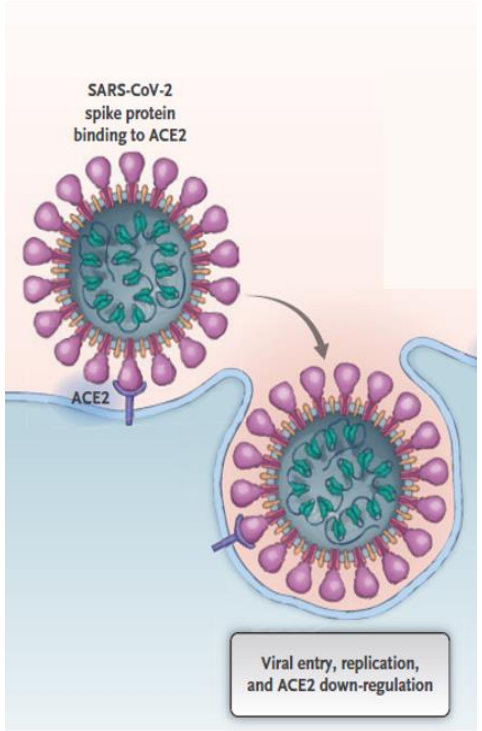
- Terminology similar to HIV (human immunodeficiency virus), which is the virus that can cause the disease called AIDS (Acquired Immune Deficiency Syndrome).

How Does SARS-CoV-2 Cause Infection?

- The human receptor for SARS-CoV-2 is Angiotensin-converting enzyme 2 (ACE2).
- This enzyme is involved in regulation of blood pressure, through catalyzing cleavage of angiotensin II, a vasoconstrictor peptide, into angiotensin, a vasodilator peptide, and is expressed by many cells in the body.
- SARS-CoV-2 binds to ACE2 through the spike proteins and subsequently downregulates ACE2 expression (which could have negative effect clinically).

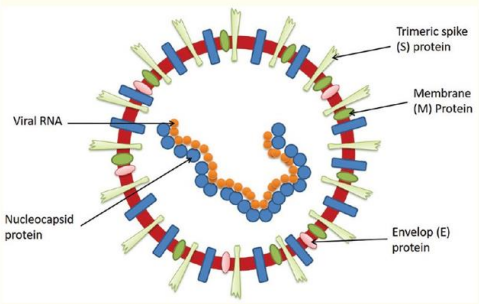


Gheblawi M et al. Circ Res. 2020 Apr 8 epub



Vaduganathan M et al. N Engl J Med. 2020 Mar 30 epub

Simplified Replication Cycle

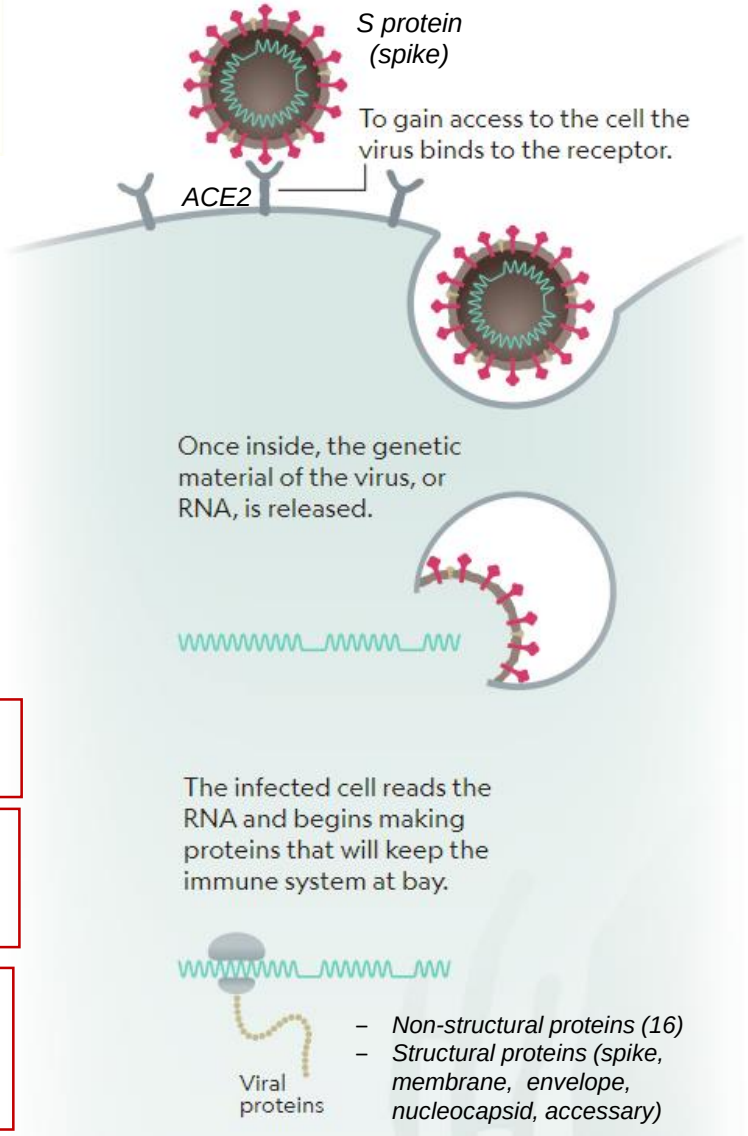


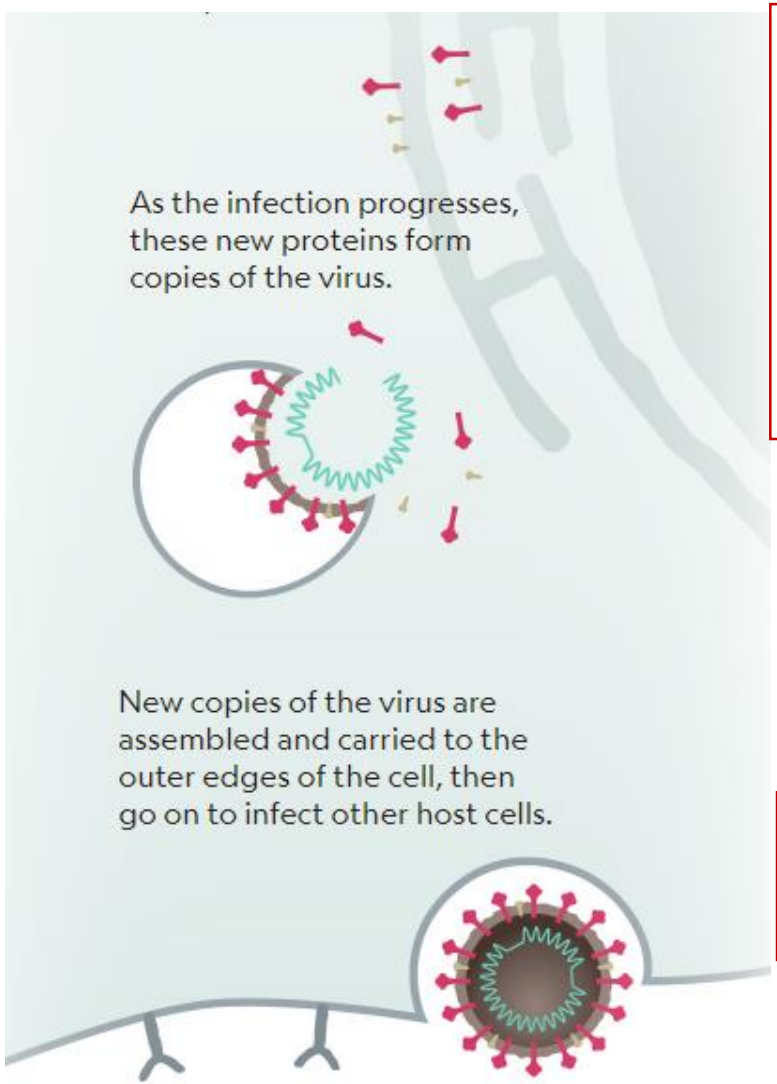
FUSION
Endosomal Pathway

RNA TRANSLATION
by host ribosomes into proteins

PROTEOLYSIS
polyproteins cleaved by viral specific protease

TRANSCRIPTION
replicase-transcription complex: replicates viral RNA with viral RNA-dependent RNA polymerase





PACKAGING

Products enter endoplasmic reticulum Golgi intermediate compartment: assembly viral envelope (M, E, S proteins) and viral RNA binds to N protein to form ribonucleoprotein complex

→mature virion buds out of Golgi to form an intracellular vesicle

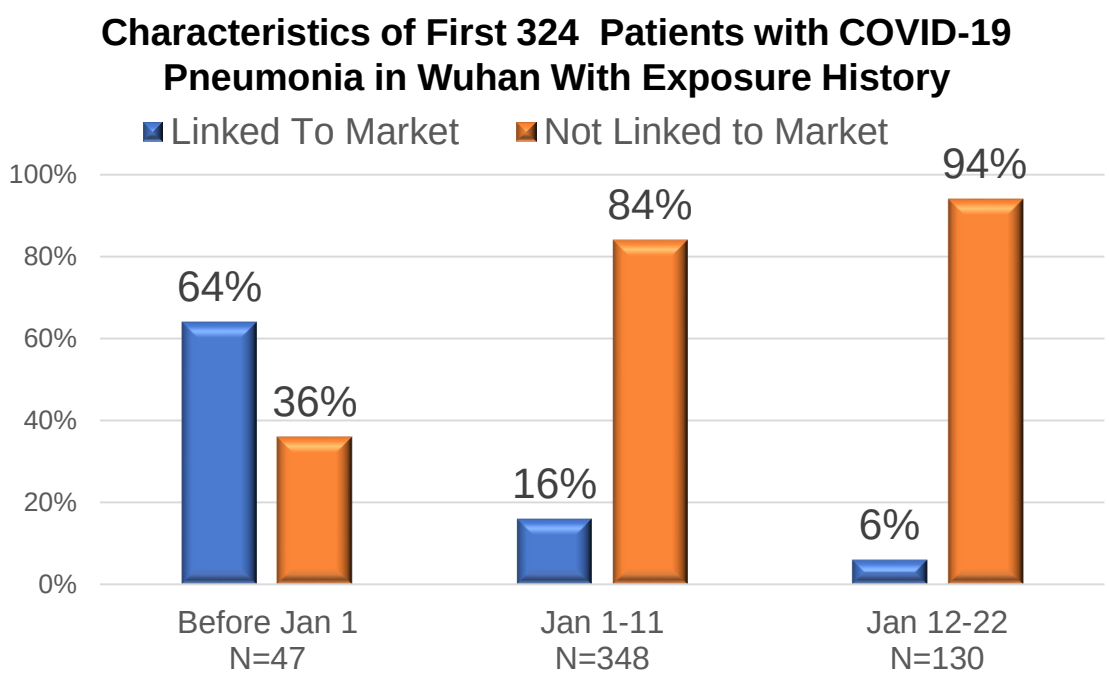
VIRION RELEASE
Exocytosis
fusion of virion vesicle with plasma membrane and release

National Geographic: https://www.nationalgeographic.com/science/2020/03/covid-overview-coronavirus/
Prajapat M et al. Indian J Pharmacol. 2020;52:56-65

Epidemiology: Early COVID-19 Cases Were Linked to Wuhan Seafood Wholesale Market with Rapid Spread Among Close Contacts

→A pneumonia of unknown cause detected in Wuhan, Hubei Province, China was first reported to WHO China Country Office on Dec 31, 2019 and was rapidly linked to exposure to the Wuhan Seafood Wholesale Market.

→Epidemic doubled in size every 7.4 days, with transmission among close contacts rapidly evident.

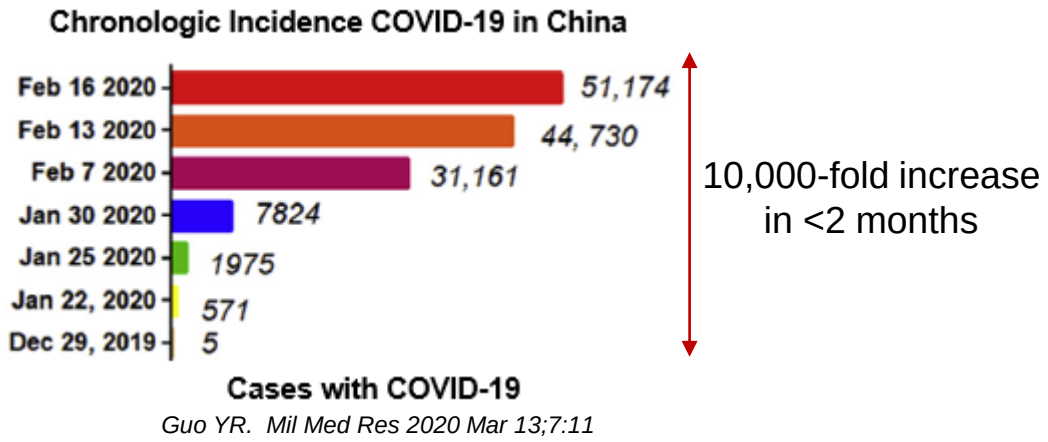


Li Q et al. N Engl J Med 2020 Mar 26;382:1199-207

Wuhan Seafood Wholesale Market closed and disinfected Jan 1, 2020 after identified as potential origin of outbreak

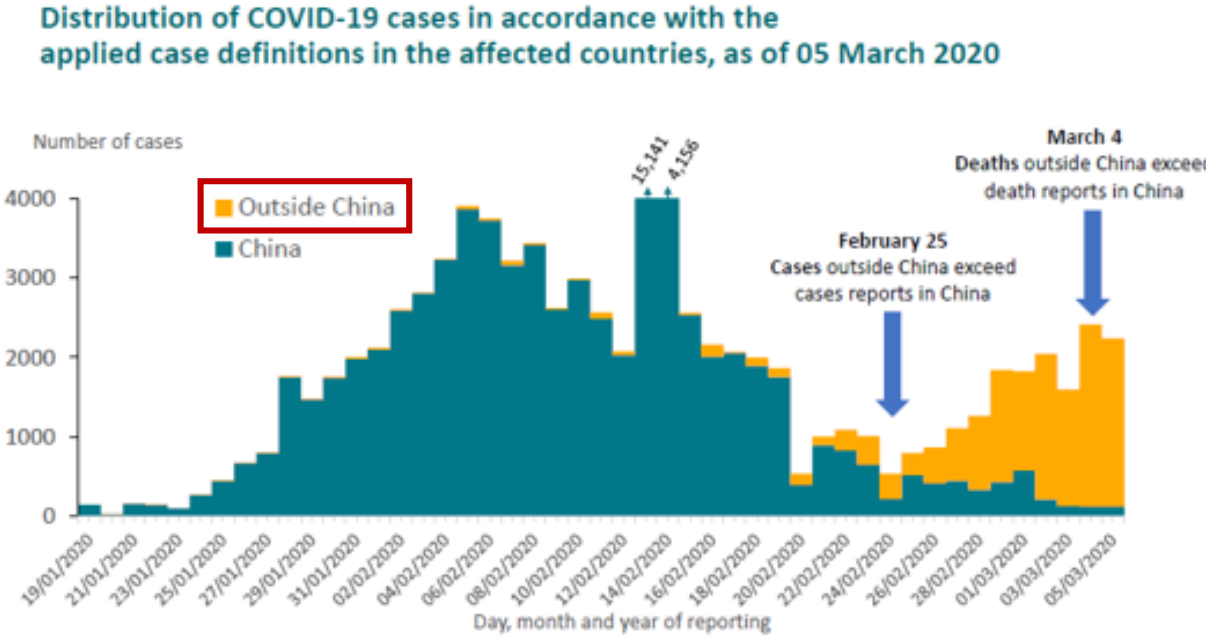
Rapid Spread → Global Pandemic

- Rapid spread outside of Wuhan to rest of China.

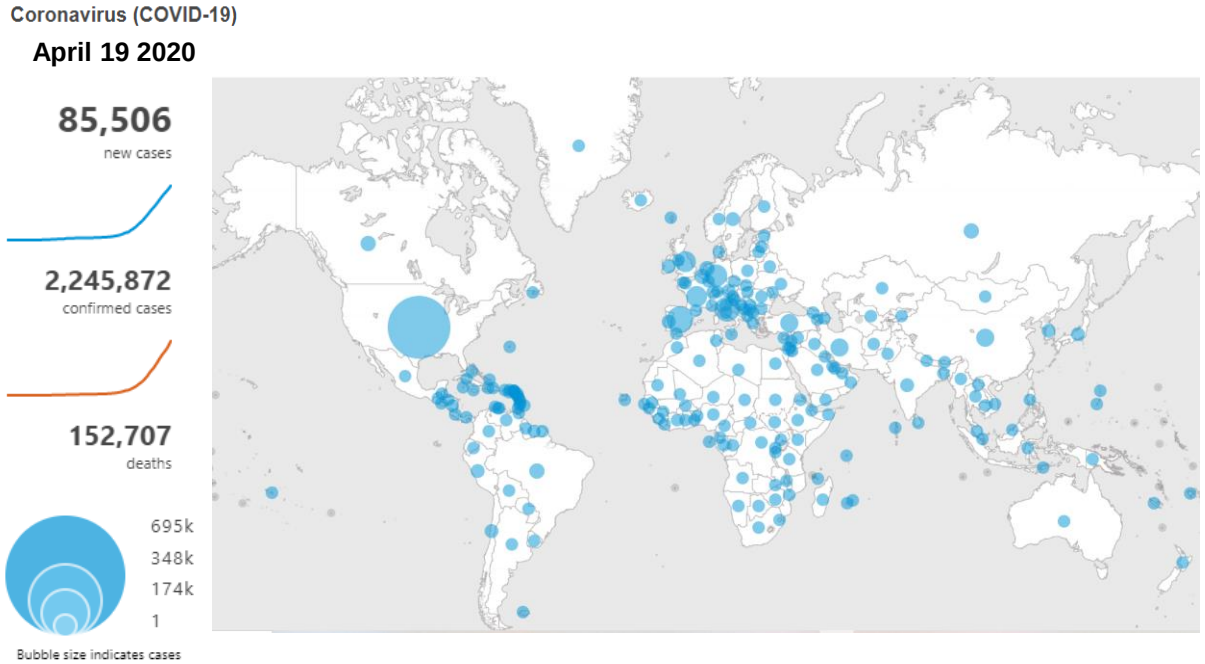


Guo YR. Mil Med Res 2020 Mar 13;7:11

- Then spread outside of China to current global pandemic.



E. Raizes, CDC



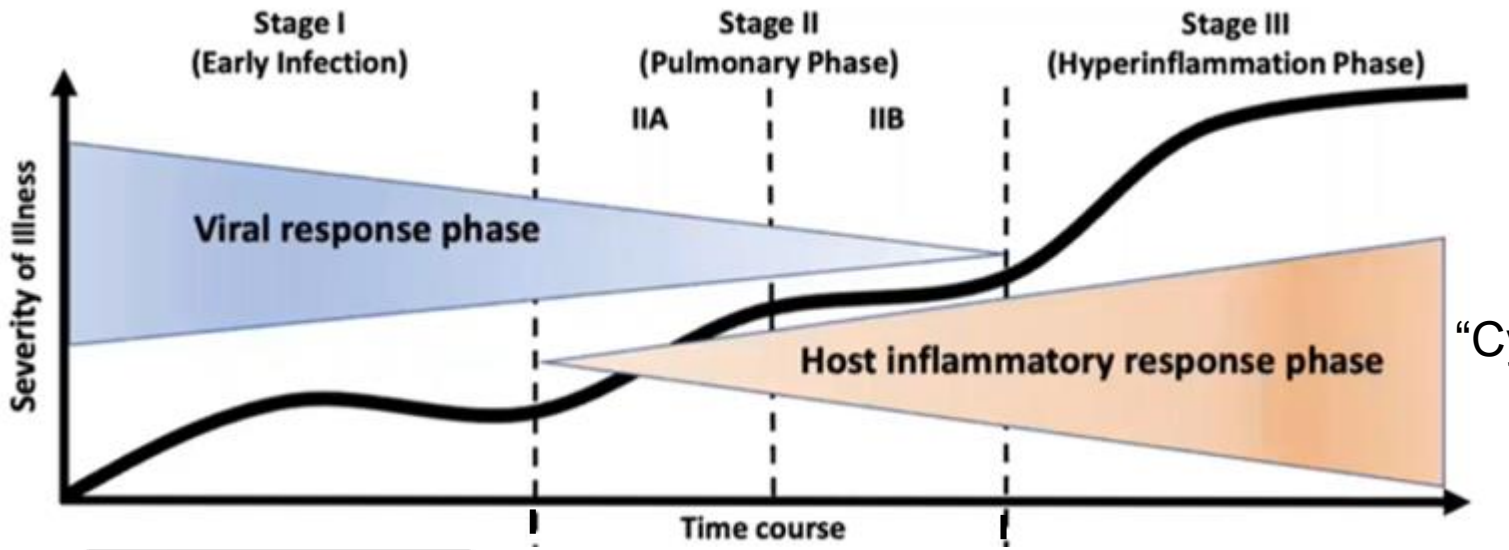
World Health Organization

Why Such Rapid Global Spread?

- Ease of transmission – respiratory droplets, touching contaminated surfaces
- High attack rate because:
  - Infectious before symptoms – viral shedding 1-3 d before symptoms *(Wei WE. MMWR 2020 Apr 10).*
  - Prolonged shedding after symptoms - median duration 17 days; more severe disease = higher viral load, ↑ duration shedding *(Xu K. Clin Infect Dis. 2020 Ap 9; Xu K. Clin Infect Dis 202 Apr 9; Pan Y. Lancet Infect Dis 2020 Feb 24)*
  - Transmission from asymptomatic persons *(Bai Y. JAMA 2020 Feb 21, Rothe C. NEJM 2020 Mar 5).*
- Population level lack of immunity - Novel virus, no “herd immunity” globally.
- Ease of importation of cases – due to widespread global travel

COVID 19 Disease in Adults
Both Virus and Host Immune Response to Virus Play a Part

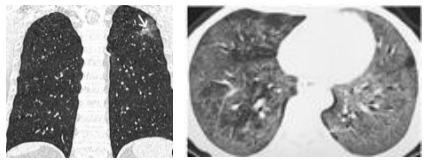
Siddiqi HK. J Heart Lung Trans 2020
doi:10/1016/jhealun.2020.03.012

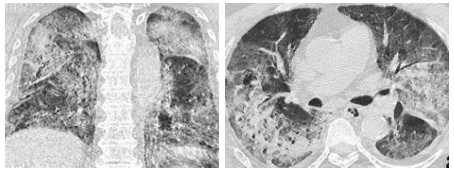


"Cytokine storm"

	No Sx	MILD	MODERATE-SEVERE	CRITICAL
	1%	81%	14%	5%
Clinical symptoms		*Mild constitutional symptoms* *Fever >99.6° F* *Dry cough, headache, diarrhea* *Loss of taste and/or smell*	*Shortness of breath, dyspnea* *hypoxia*	*ARDS* *Systemic inflammatory response syndrome/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*

Zhang W. JAMA 2020
Feb 24 epub
72,314 cases China





Mortality 1%-3.8%?

Risk factors:

- Older age
- Male sex
- Comorbidity

SARS-CoV-2 Can Affect Organs Other than Respiratory Tract

JAMA Neurology | Original Investigation

Neurologic Manifestations of Hospitalized Patients With Coronavirus Disease 2019 in Wuhan, China

Ling Mao; Huijuan Jin; Mengdie Wang; Yu Hu; Shengcai Chen; Quanwei He; Jiang Chang; Candong Hong; Yifan Zhou; David Wang; Xiaoping Miao; Yanan Li, MD, PhD; Bo Hu, MD, PhD

Acute cerebrovascular disease, impaired consciousness, skeletal muscle injury

Chen L, *et al*. *Br J Ophthalmol* 2020;**0**:1–4. doi:10.1136/bjophthalmol-2020-316304

OPEN ACCESS

Ocular manifestations of a hospitalised patient with confirmed 2019 novel coronavirus disease

Lu Chen,[1] Meizhou Liu,[1] Zheng Zhang,[2] Kun Qiao,[2] Ting Huang,[2] Miaohong Chen,[1] Na Xin,[1] Zuliang Huang,[1] Lei Liu,[2] Guoming Zhang,[1] Jiantao Wang[1]

Systemic Disorders

Fever, Cough, Fatigue, Sputum Production, Headache

Respiratory Disorders

Conjunctivitis

Rhinorrhoea, Sneezing, Sore Throat

Smell, taste

JAMA Cardiology | Original Investigation

Association of Cardiac Injury With Mortality in Hospitalized Patients With COVID-19 in Wuhan, China

Shaobo Shi, MD; Mu Qin, MD; Bo Shen, MD; Yuli Cai, MD; Tao Liu, MD; Fan Yang, MD; Wei Gong, MMSC; Xu Liu, MD, PhD; Jinjun Liang, MD, Qinyan Zhao, MD, PhD; He Huang, MD, PhD; Bo Yang, MD, PhD; Congxin Huang, MD, PhD

JAMA Otolaryngology–Head & Neck Surgery Published online April 8, 2020

OBSERVATION

Sudden and Complete Olfactory Loss Function as a Possible Symptom of COVID-19

Michael Eliezer, MD; Charlotte Hautefort, MD; Anne-Laure Hamel, MD; Benjamin Verillaud, MD; Philippe Herman, MD, PhD; Emmanuel Houdart, MD, PhD; Corinne Eloit, MD

Haemoptysis,

Acute Cardiac Injury

Pneumonia

Ground-glass Opacities

Hypoxemia

RNAaemia, Acute Respiratory Distress Syndrome

Dyspnoea, Lymphopenia

Diarrhoea

Kidney

AJOG MFM

Two Cases of COVID-19 Related Cardiomyopathy in Pregnancy.

Alexander Juusela, MD, MPH, Munir Nazir, MD, Martin Gimovsky, MD.

European Archives of Oto-Rhino-Laryngology
https://doi.org/10.1007/s00405-020-05965-1

RHINOLOGY

Olfactory and gustatory dysfunctions as a clinical presentation of mild-to-moderate forms of the coronavirus disease (COVID-19): a multicenter European study

Jerome R. Lechien[1,2,3,4] · Carlos M. Chiesa-Estomba[1,5] · Daniele R. De Siati[1,6] · Mihaela Horoi[4] · Serge D. Le Bon[4] · Alexandra Rodriguez[4] · Didier Dequanter[4] · Serge Blecic[7] · Fahd El Afia[1,3] · Lea Distinguin[1,3] · Younes Chekkoury-Idrissi[1,3] · Stéphane Hans[3] · Irene Lopez Delgado[1,8] · Christian Calvo-Henriquez[1,9] · Philippe Lavigne[1,10] · Chiara Falanga[1,11] · Maria Rosaria Barillari[1,11] · Giovanni Cammaroto[1,12] · Mohamad Khalife[13] · Pierre Leich[14] · Christel Souchay[14] · Camelia Rossi[15] · Fabrice Journe[2] · Julien Hsieh[1,16] · Myriam Edjlali[17,18] · Robert Carlier[19] · Laurence Ris[19] · Andrea Lovato[20] · Cosimo De Filippis[20] · Frederique Coppee[21] · Nicolas Fakhry[1,22] · Tareck Ayad[1,10] · Sven Saussez[1,2,4,13]

Lin L, *et al*. *Gut* 2020;**0**:1–5. doi:10.1136/gutjnl-2020-321013 Gut immunity

ORIGINAL RESEARCH

Gastrointestinal symptoms of 95 cases with SARS-CoV-2 infection

Lu Lin,[1] Xiayang Jiang,[1] Zhenling Zhang,[1] Siwen Huang,[1] Zhenyi Zhang,[1] Zhaoxiong Fang,[1] Zhiqiang Gu,[1] Liangqing Gao,[1] Honggang Shi,[1] Lei Mai,[1] Yuan Liu,[1] Xianqi Lin,[1] Renxu Lai,[1] Zhixiang Yan,[2] Xiaofeng Li,[1] Hong Shan[2,3]

Fanelli *et al*. *Critical Care* (2020) 24:155
https://doi.org/10.1186/s13054-020-02872-z

Critical Care

COMMENTARY Open Access

Acute kidney injury in SARS-CoV-2 infected patients

Vito Fanelli[1], Marco Fiorentino[2], Vincenzo Cantaluppi[3], Loreto Gesualdo[4], Giovanni Stallone[5], Claudio Ronco[6] and Giuseppe Castellano[7]

Modified from: Guo YR. Mil Med Res 2020 Mar 13;7:11

Risk Factors for Severe Disease/Poor Outcome of COVID-19 Disease

Patient Characteristics	Vital Signs	Laboratory
Pre-existing pulmonary disease	Respiratory rate >24/min	D-dimer >1000 ng/mL
Chronic kidney disease	Heart rate >125 beats/min	Elevated CPK
Diabetes	SpO2 <90% on ambient air	Elevated CRP
History of hypertension	SOFA (sequential organ failure assessment) score	Lymphopenia (<0.8)
History cardiovascular disease	Respiratory rate >24/min	Elevated LDH
Use of biologics (presume)		Elevated troponin
History transplant or other immunosuppression (presumed)		Elevated ferritin
HIV, CD4 count <200 or unknown (presumed)		Elevated IL-6

There are only FOUR papers including 8 cases of COVID-19 and HIV in the literature I could find as of April 19, 2020 – so minimal amount is known. No deaths, although 2 admitted to ICU (1 advanced HIV with CD4 13, other with comorbidity). It is hypothesized if on ART and high CD4, COVID-19 disease would not be different than for those without HIV infection.

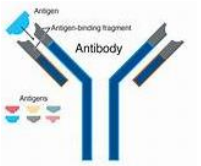
COVID-19 disease has been in low HIV prevalence countries, not (yet) in areas with high HIV prevalence. However, we are now seeing cases in Africa and it s critical to monitor impact.

1. Zhu F, Cao Y, Xu S, Zhou M. Co-infection of SARS-CoV-2 and HIV in a patient in Wuhan city, China. *J Med Virol*. 2020 Mar 11 (epub)
2. Zhao J, Liao X, Wang H, Wei L, Xing M, Liu L, Zhang Z. Early virus clearance and delayed antibody response in a case of COVID019 with a history of coinfection with HIV-1 and HCV *Clin Infect Dis*. 2020 Apr 9 (epub).
3. Blanco JL et al. COVID-19 in patients with HIV: clinical case series. Lancet HIV 2020 Apr 15
4. Chen J Computerizied tomography imaging of an HIV-infected patient with COVID 19.J Med Virol. Apr 13 2020

Testing for SAR-CoV-2/COVID-19 and Potential Uses

Report form American Society for Microbiology COVID-19 International Summit, March 23 202

Patel R et al. mBio. 2020 Mar 26 (epub)



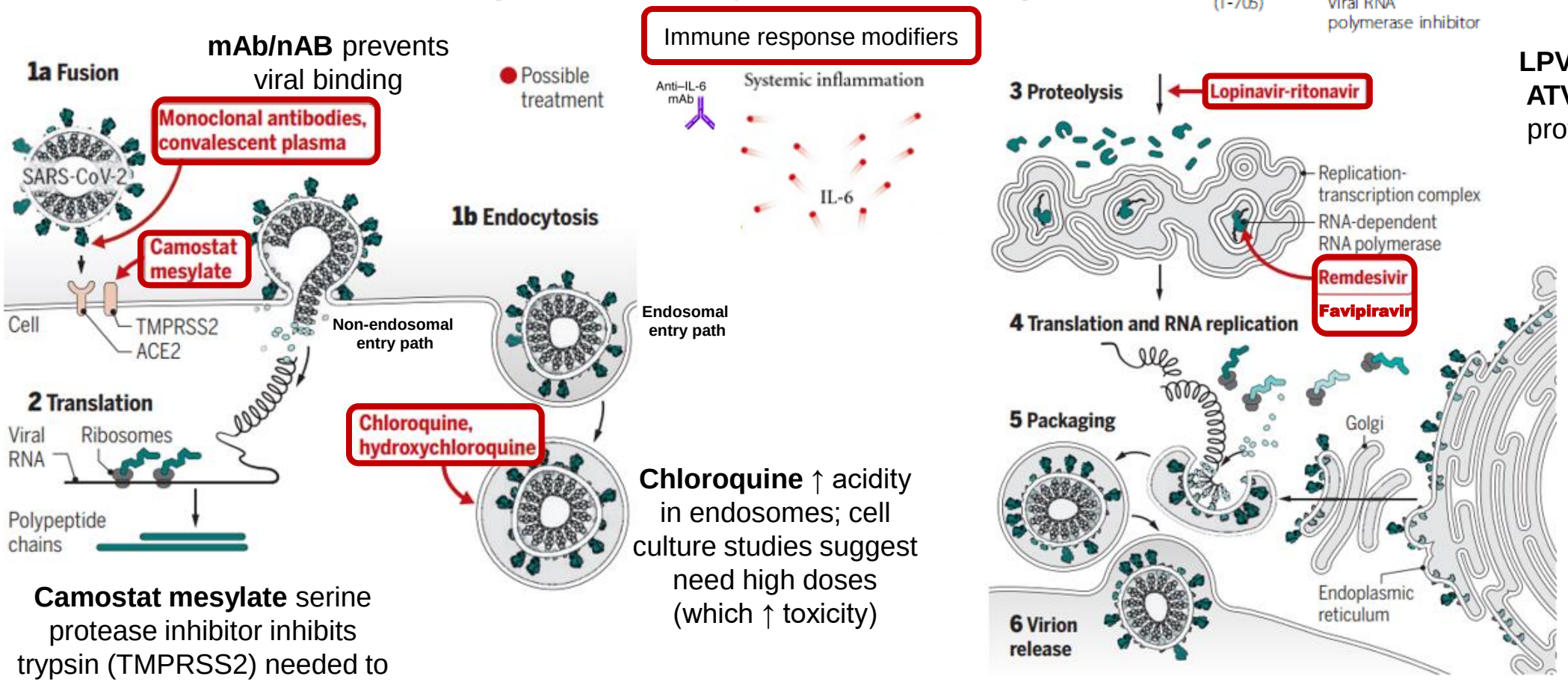
Type of Test	Meaning	Value	Beneficiary
Real-Time Nucleic Acid Amplification Test (NAAT) (rtPCR) for SARS-CoV-2 RNA* *(nasopharyngeal swab, oropharyngeal swab, sputum, bronchoalveolar lavage, other fluids/tissues*	Current infection with SARS-CoV-2	▪ Inform individual of infection status so can anticipate course illness and take action to prevent transmission ▪ Inform patient management and actions needed to prevent transmission ▪ Inform actions needed to prevent transmission	→ Individual → Healthcare or long-term care facility → Public health
SARS-CoV-2 Antibody Dectection *(virus-specific IgG, IgM)*	Past exposure To SARS-CoV-2	▪ Detect susceptible persons (antibody negative) and those previously infected ▪ Identify individuals with neutralizing antibodies ▪ Facilitate contract tracing and surveillance	→ ID those potentially immune and can be returned to work. → Health care facilities, experimental therapy → Public health

*As of April 17, there were 34 commercial diagnostic NAAT tests given emergency use authorization by the FDA (lack rigorous assessment) including 3 point-of-care NAAT tests; antigen immunoassay tests (use antibody to detect viral antigen as opposed to direct viral detection) under development. *(Cheng MP et al. Ann Int Med. 2020 Apr 13; FDA website https://www.fda.gov/media/136702/download)*

There Are No Proven Treatments for SARS-CoV-2 But Many Under Study – 645 Clinical Trials!

April 18, 2020
U.S. National Library of Medicine
ClinicalTrials.gov
645 Studies found for: COVID 19 SARS CoV 2

→ Experimental treatment strategies attempt to interfere at different steps in SARS-CoV-2 replication cycle – examples:



mAb/nAB prevents viral binding

Camostat mesylate serine protease inhibitor inhibits trypsin (TMPRSS2) needed to "prime" spike to enter (non-endosomal path)

Chloroquine ↑ acidity in endosomes; cell culture studies suggest need high doses (which ↑ toxicity)

LPV/r (& other PI, ATV, DRV) inhibit protease enzyme

Remdesivir & **favipiravir** inhibits viral RNA polymerase

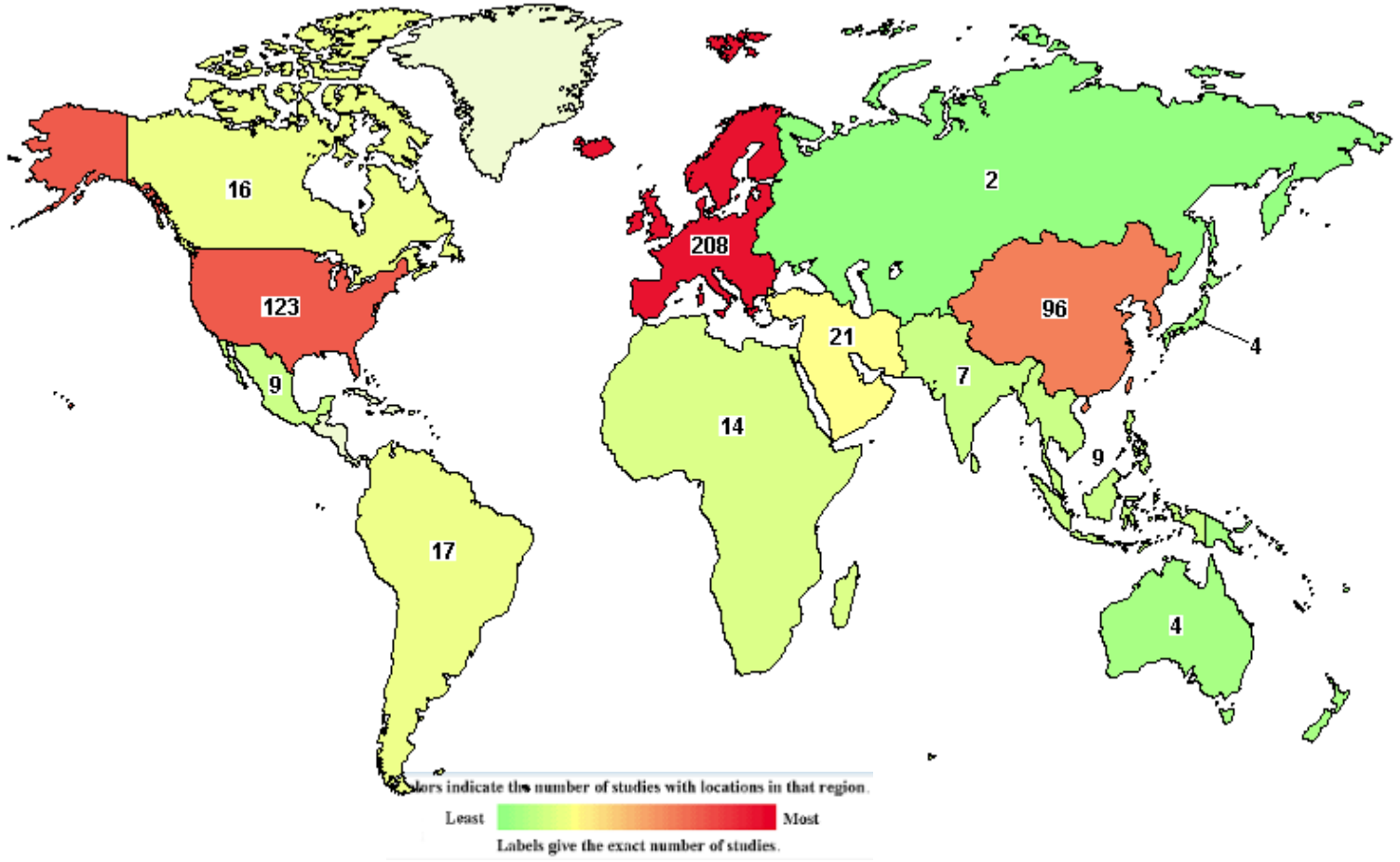
Immune Response Modifiers (modulate "cytokine storm")
Tocilizumab
Sarilumab
Zitivekumab

Science. Kupferschmidt K et al. Mar 26 2020;367:1412-3.

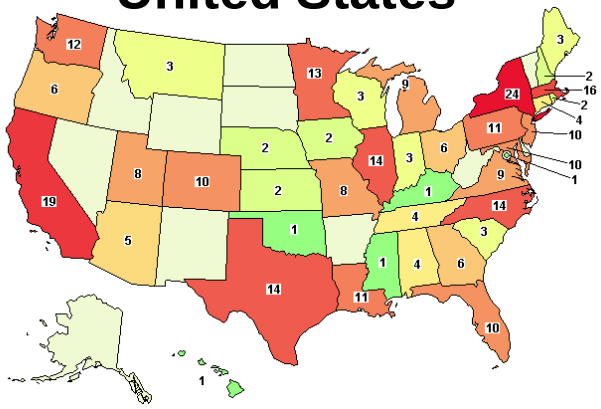
Global Clinical Trials of COVID-19 Therapeutics *(as of April 19, 2020)*
645 Clinical Trials

Region Name	Number of Studies
World	645
Africa [map]	14
East Asia [map]	96
Japan	4 [studies]
Europe [map]	208
Middle East [map]	21
North America	144
Canada [map]	16 [studies]
Mexico	9 [studies]
United States [map]	123 [studies]
North Asia [map]	2
Pacifica [map]	4
South America [map]	17
South Asia [map]	7
Southeast Asia [map]	9

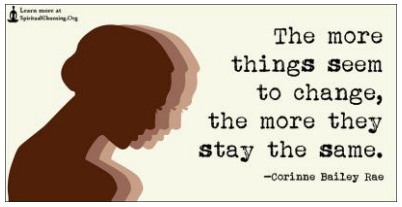
Global



United States



Alabama	4 [studies]	Missouri	8 [studies]
Arizona	5 [studies]	Montana	3 [studies]
California	19 [studies]	Nebraska	2 [studies]
Colorado	10 [studies]	New Hampshire	2 [studies]
Connecticut	4 [studies]	New Jersey	10 [studies]
District of Columbia	1 [studies]	New York	24 [studies]
Florida	10 [studies]	North Carolina	14 [studies]
Georgia	6 [studies]	Ohio	6 [studies]
Hawaii	1 [studies]	Oklahoma	1 [studies]
Illinois	14 [studies]	Oregon	6 [studies]
Indiana	3 [studies]	Pennsylvania	11 [studies]
Iowa	2 [studies]	Rhode Island	2 [studies]
Kansas	2 [studies]	South Carolina	3 [studies]
Kentucky	1 [studies]	Tennessee	4 [studies]
Louisiana	11 [studies]	Texas	14 [studies]
Maine	3 [studies]	Utah	8 [studies]
Maryland	10 [studies]	Virginia	9 [studies]
Massachusetts	16 [studies]	Washington	12 [studies]
Michigan	9 [studies]	Wisconsin	3 [studies]
Minnesota	13 [studies]		
Mississippi	1 [studies]		



***NOTE: trials generally EXCLUDE pregnant & breastfeeding women (and children)**

Randomized Trials Needed To Discern Efficacy & Safety Scientific Data Are Rapidly Changing Every Day

NO BENEFIT

March 18, 2020

The NEW ENGLAND JOURNAL of MEDICINE

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

CONCLUSIONS

In hospitalized adult patients with severe Covid-19, no benefit was observed with lopinavir–ritonavir treatment beyond standard care. Future trials in patients with severe illness may help to confirm or exclude the possibility of a treatment benefit.

NO BENEFIT & POTENTIALLY HARMFUL

April 4, 2020

The NEW ENGLAND JOURNAL of MEDICINE

Clinical Outcomes of Hydroxychloroquine in Hospitalized Patients with COVID-19: A Quasi-Randomized Comparative Study

Article Type:	Rapid Review
Date Submitted by the Author:	04-Apr-2020
Complete List of Authors:	Barbosa, Joshua; Wayne State University School of Medicine; Sinai Grace Hospital Kaitis, Daniel; Henry Ford Hospital Freedman, Ryan; Wayne State University School of Medicine Le, Kim; Henry Ford Hospital Lin, Xihui; Wayne State University School of Medicine,

Conclusion: Hydroxychloroquine administration to the hospitalized SARS-CoV-2 positive population was associated with an increased need for escalation of respiratory support. There were no benefits of hydroxychloroquine on mortality, lymphopenia, or neutrophil-to-lymphocyte ratio improvement.

SUGGESTION OF CLINICAL BENEFIT (NOT RANDOMIZED)

April 10, 2020

The NEW ENGLAND JOURNAL of MEDICINE

Compassionate Use of Remdesivir for Patients with Severe Covid-19

J. Grein, N. Ohmagari, D. Shin, G. Diaz, E. Asperges, A. Castagna, T. Feldt, G. Green, M.L. Green, F.-X. Lescure, E. Nicastri, R. Oda, K. Yo, E. Quiros-Roldan, A. Studemeister, J. Redinski, S. Ahmed, J. Bernett, D. Chelliah, D. Chen, S. Chihara, S.H. Cohen, J. Cunningham, A. D'Arminio Monforte, S. Ismail, H. Kato, G. Lapadula, E. L'Her, T. Maeno, S. Majumder, M. Massari, M. Mora-Rillo, Y. Mutoh, D. Nguyen, E. Verweij, A. Zoufaly, A.O. Osinusi, A. DeZure, Y. Zhao, L. Zhong, A. Chokkalingam, E. Elboudwarej, L. Telep, L. Timbs, I. Henne, S. Sellers, H. Cao, S.K. Tan, L. Winterbourne, P. Desai, R. Mera, A. Gaggar, R.P. Myers, D.M. Brainard, R. Childs, and T. Flanigan

CONCLUSIONS

In this cohort of patients hospitalized for severe Covid-19 who were treated with compassionate-use remdesivir, clinical improvement was observed in 36 of 53 patients (68%). Measurement of efficacy will require ongoing randomized, placebo-controlled trials of remdesivir therapy. (Funded by Gilead Sciences.)

NO BENEFIT & HIGHER DOSE HARMFUL

April 11, 2020

medRxiv CSH Cold Spring Harbor Laboratory BMJ Yale

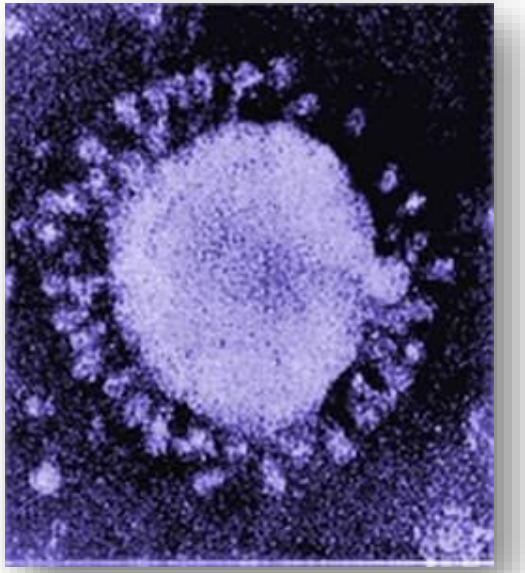
This article is a preprint and has not been certified by peer review

Chloroquine diphosphate in two different dosages as adjunctive therapy of hospitalized patients with severe respiratory syndrome in the context of coronavirus (SARS-CoV-2) infection: Preliminary safety results of a randomized, double-blinded, phase IIb clinical trial (CloroCovid-19 Study)

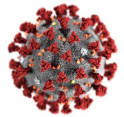
Mayla Borba, Fernando de Almeida Val, Vanderson Sousa Sampaio, Marcia Araujo Alexandre, Gisely Cardoso Melo, Marcelo Brito, Maria Mourao, Jose Diego Brito Sousa, djane Baia-da-Silva, Marcus Vinitius Farias Guerra, Ludhmila Hajjar, Rosemary Costa Pinto, Antonio Balieiro, Felipe Gomes Naveca, Mariana Xavier, Alexandre Salomao, Andre Siqueira, Alexandre Schwarzbolt, Julio Henrique Rosa Croda, Mauricio Lacerda Nogueira, Gustavo Romero, Quique Bassat, Cor Jesus Fontes, Bernardino Albuquerque, Claudio Daniel-Ribeiro, Wuelton Monteiro, Marcus Lacerda, CloroCovid-19 Team

The high dose CQ arm presented more QTc>500ms (25%), and a trend toward higher lethality (17%) than the lower dosage. Fatality rate was 13.5% (95%CI=6.9-23.0%), overlapping with the CI of historical data from similar patients not using CQ (95%CI=14.5-19.2%). In 14 patients with paired samples, respiratory secretion at day 4 was negative in only one patient.

SARS-CoV-2/ COVID-19 in Children



Summary of Available Data on Pediatric COVID-19



- Children appear less likely to be symptomatic with SARS-CoV-2 than adults, although severe disease can occur.
- Asymptomatic disease reported in 1.3% (US) to 16% (China) of children *(MMWR 2020 Apr 6; Zhang NEJM 020 Mar 18; Dong Pediatr 2020 Mar 16).*
- Most common presenting symptoms are cough and fever; upper respiratory symptoms such as rhinorrhea and sore throat also common (30-40%); ~10% may present with diarrhea/vomiting.
- Children appear to have less severe disease and less hospitalization; death can occur but is rare and may be more likely in youngest infants.
- In the absence of widespread community or serologic testing, uncertain what the true proportion of children without symptoms actually is.

Age Distribution COVID-19 Cases in Children in 8 Large Studies

Country/Reference	Total # COVID-19 Cases	# Children 0-19 yr (% of total cases)	Proportional Age Distribution Among Pediatric COVID-19 cases				
			0-10 yr	*<1 yr*	*1-4 yr*	*5-9 yr*	10-19 yr
China *(China CDC)1*	44,672	965 (2%)	416 (43%)	-	-	-	549 (57%)
China *(Dong, Pediatrics)2*	-	2,141	1,393 (65%)	*379*	*493*	*523*	748 (35%)
Italy *(Italy website)3*	42,220	507 (1.2%)	-	-	-	-	-
US *(MMWR)4*	149,760	2,572 (1.7%)	1,077 (42%)	*398*	*291*	*388*	1,495 (58%)
Japan *(Mizumoto. MedRxiv)5*	294	10 (3.4%)	-	-	-	-	-
Korea *(COVID team. MedRxiv)6*	7,755	480 (6.2%)	75 (16%)	-	-	-	405 (84%)
Iceland *(Gudbjartsson.NEJM)7*	9,199 *targeted* *13,080 population*	38 (0.4%) *0/848 tested*	(38)	-		-	-
Madrid *(Taggaro JAMA Ped)8*	4,695	41 (0.8%)	-	-	-	-	-
TOTAL	**258,595***	**4,613 (1.8%) ****	***2961/6158 (48%)***	-	-	-	***3197/6158 (52%)***

* only COVID-19 cases (excluding population screening)
* excluding Dong paper, no denominator overall cases

→ Children account for 1.8% of COVID-19 *cases*

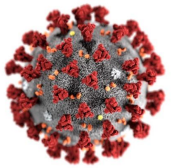
→ In population surveillance (non symptomatic) Iceland, no detected infections in 848 children <10 yr.

→ Of child cases, 48% were 0-10 yr (about 1/3 in each age group <1, 1-4 and 5-9 yr) and 52% were 10-19yr.

1 Chinese CDC. Chinese J Epidemiol. 2020Mar 3
2 Dong Y et al. Pediatrics. 2020 Mar 16
3 https://www.epicentro.iss.it/coronavirus/bollettino/Infografica_20marzo%20ENG.pdf
4 CDC COVID-19 Response Team. MMWR 2020 Apr 6
5 COVID-19 National Emergency Response Center. MedRxiv 2020 Mar 15
6 Mizumoto K et al. MedRxiv 2020 Mar 9
7 Gudbjartsson DF et al. N Engl J Med 2020 Apr 14
8 Taggaro A et al. JAMA 2020 Apr 8

Non-Specific Signs COVID-19 in Infancy

19 Case Reports COVID-19 in Infants from Around the World



- Presentation of COVID-19 in infancy may be non-specific with URI Sx with/without fever, with/without respiratory symptoms; 2/19 cases had no symptoms and 1/19 cases did not have known exposure other than in epidemic situation (NYC).

Country/ Author	Age at admit	Initial symptoms	Exposure	SARS-CoV-2 testing	Outcome
China/Wei	9 pt: 8 wk-11 mo	4/9 fever; 3/9 mild URI, 1/9 **no symptoms**	Yes	NP rtPCR +	Did well, d/c
China/Cui	55 d	URI, cough, **no fever**, CT abnl	Yes	NP rt PCR+ high titer	d7 liver, cardiac injury, supplemental O_2; d/c
Korea/Han	27 d	Fever, vomiting, mild cough, **CXR nl**	Yes	NP, oral, plasma, urine, stool, saliva rtPCR + high titer	Did well, d/c
Iran/Mogharab, Aghdam	2 pt: 15 d, 75 d	2/2 fever, 1/2 Cough, 1 CXR abnl, **1 CXR nl**	Yes	NP rtPCR +	Required O_2, d/c
Italy/Canarutto	32 d	URI sx, fever, **CXR nl**	Yes	NP rt PCR+	Did well, d/c
New York/Robbins, Paret	3 pt: 25, 56, 58 d	Fever (all), **no respiratory sx**, **CXR nl**	2 Yes **1 No**	NP rtPCR+	Did well, d/c
Vietnam/Le	3 mos	URI sx, fever, **CXR nl**	Yes	NP rtPCR+	Did well, d/c
Singapore/Kam	6 mos	**No symptoms**	Yes	NP rtPCR+	Did well, d/c

Wei M et al. JAMA . 2020 Feb 14
Cui Y et al J Infect Dis. 2020 Mar 17
Han MS et al. Clin Infect Dis. 2020 Ap 16
Mogharab V et al. J Formosan Med Assoc. 2020 Apr 13
Aghdam MK et la. Infect Dis. 2020 Apr 1
Canarutto D et al. Ped Pulmon. 2020 Mar 19
Robbins E et al. Pediar Infect Dis J. 2020 Apr 13
Paret M et al. Clin Infect Dis. 2020 Apr 17
Le HT et al. Lancet Child Adoles Health. 2020 Mar 23
Kam K-Q et al. Clin Infect Dis. 2020 Feb 28

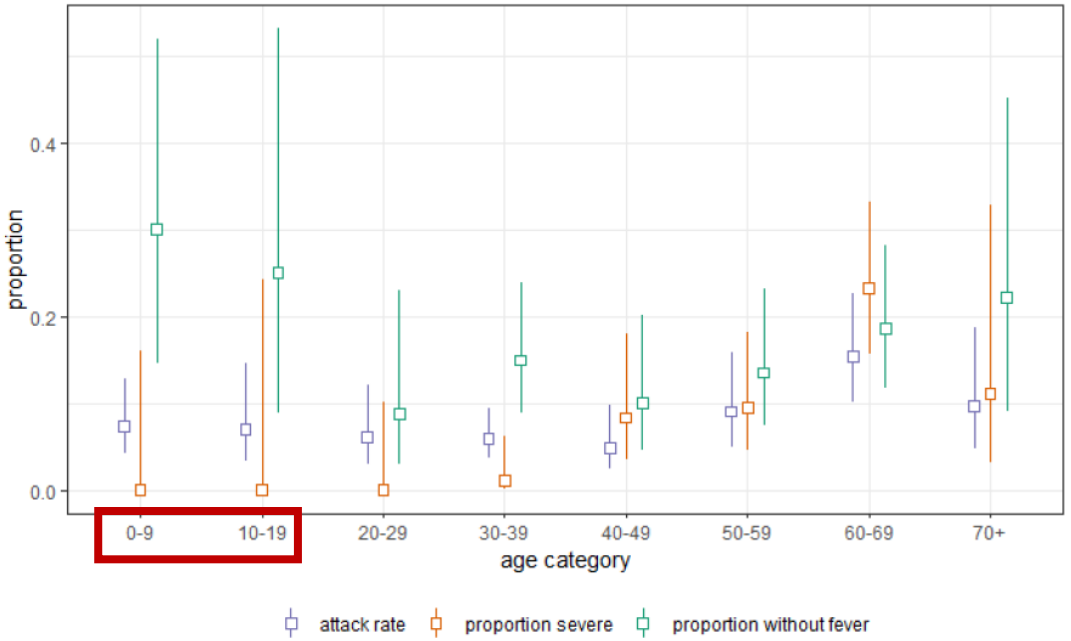
Children Less Likely Infected or Less Likely Symptomatic?

China: Household Contact Screening Suggests Less Symptoms

Bi Q et al. MedRxiv 2020 Mar 3

- Identified 391 COVID-19 cases in China from Jan 14-Feb 12, 2020 and 1,286 close contacts (live together, shared a meal, travel or social interaction with case starting 2 days before symptom onset); 95% followed for ≥12 days; 15% household attack rate.
- Children were as likely to be infected as adults to 50 yr; somewhat more likely to have no fever and have non-severe disease.

Attack Rate Among Close Contacts, % Severe Disease and % Without Fever by Age



Rate of SARS-CoV-2 Positive Test in Contacts by Age

Age (yr)	# tested	# +	%
0-9	148	11	7.4% (4.2-12.8)
10-19	85	6	7.1% (3.3-14.6)
20-29	114	7	6.1%(3.0-12.1)
30-39	268	16	6.0% (3.7-9.5)
40-49	143	7	4.9% (2.4-9.8)
50-59	110	10	9.1% (5.0-15.9)
60-69	*130*	*20*	*15.4% (10.2-22.6)*
70%	*72*	*7*	*9.7% (4.8-18.7)*

Suggestion attack rate may be higher in older adults (>60 yr)

Children Less Likely Infected or Less Likely Symptomatic?

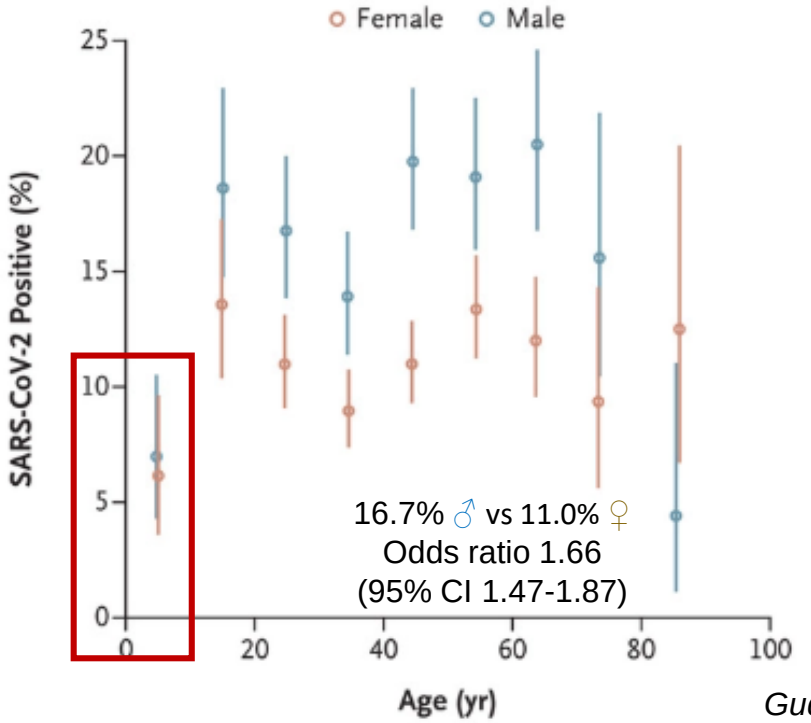
Iceland: Population-Based Screening Suggests Less Infection

- Conducted targeted testing of symptomatic persons coming from high-risk area or in contact with infected persons (Jan 31-Mar 31) & population screening (Mar 13-Ap 4)

→Targeted: 564 children age <10 yr tested, 38 (**6.7%**) were positive (♂ **~=**♀) compared to 1,183 (**13.7%**) of 8,635 >10 yr (♂**>**♀).

→Population-based: **None** of 848 children age <10 yr were positive compared to 100 (**0.8%**) of 12,232 >10 yr

Targeted: SARS-CoV-2 + by Age and Sex

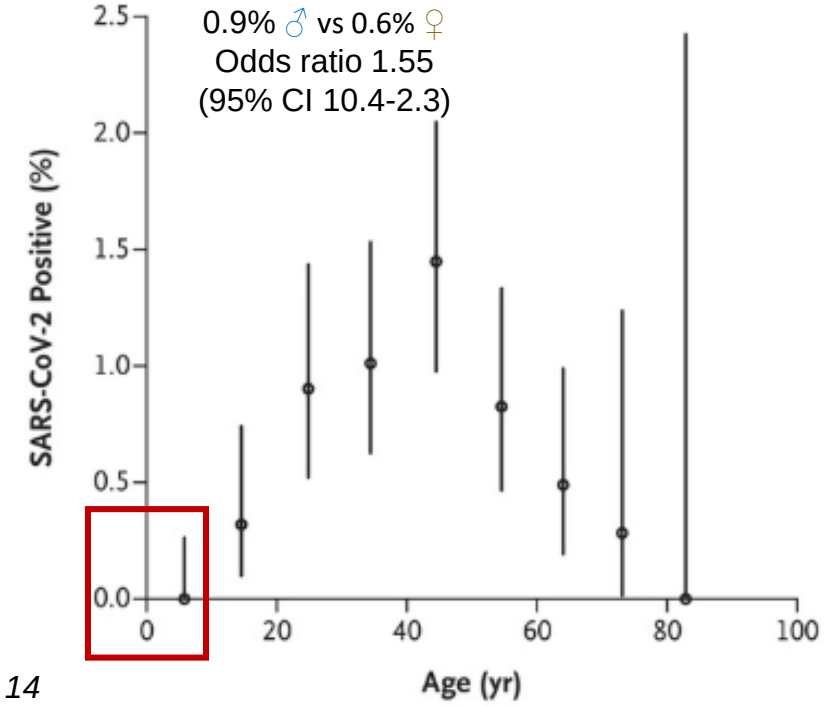


Not Resolved Yet:

Are children less susceptible to SARS-CoV-2?

Or are they less symptomatic with similar rates infection?

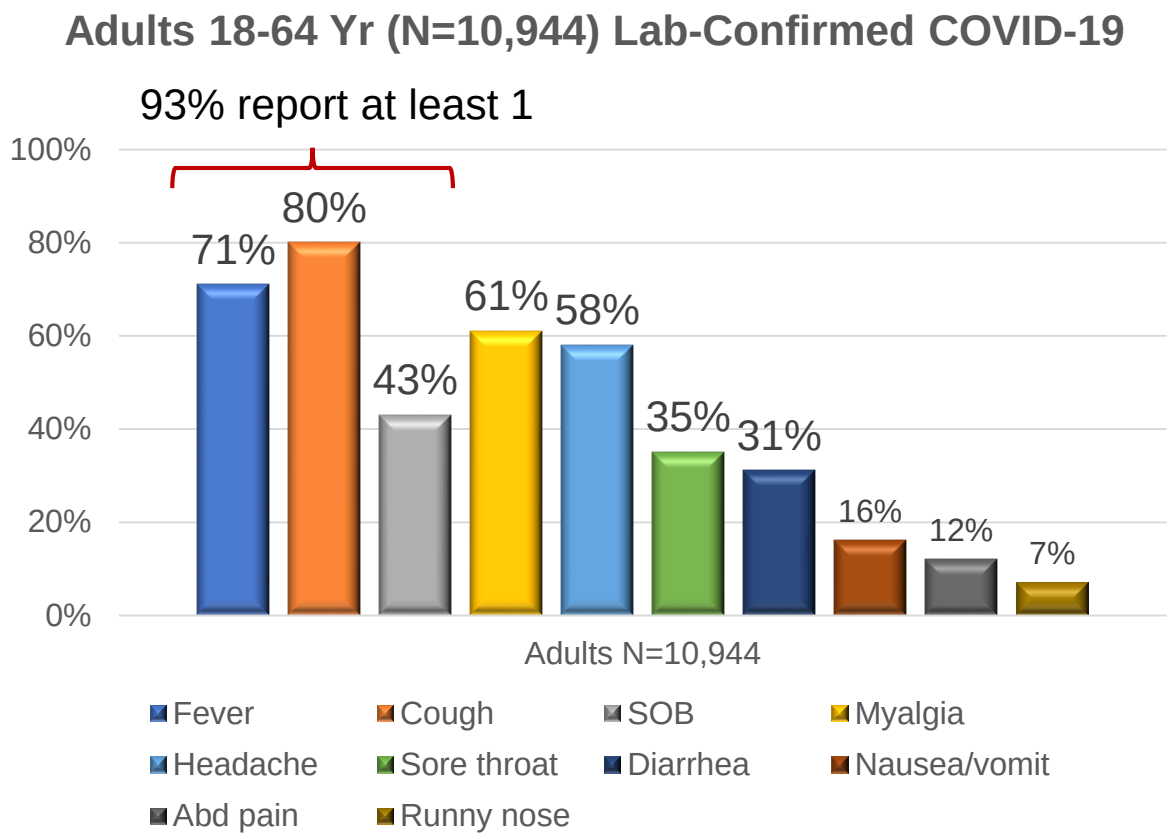
Population: SARS-CoV-2 + by Age

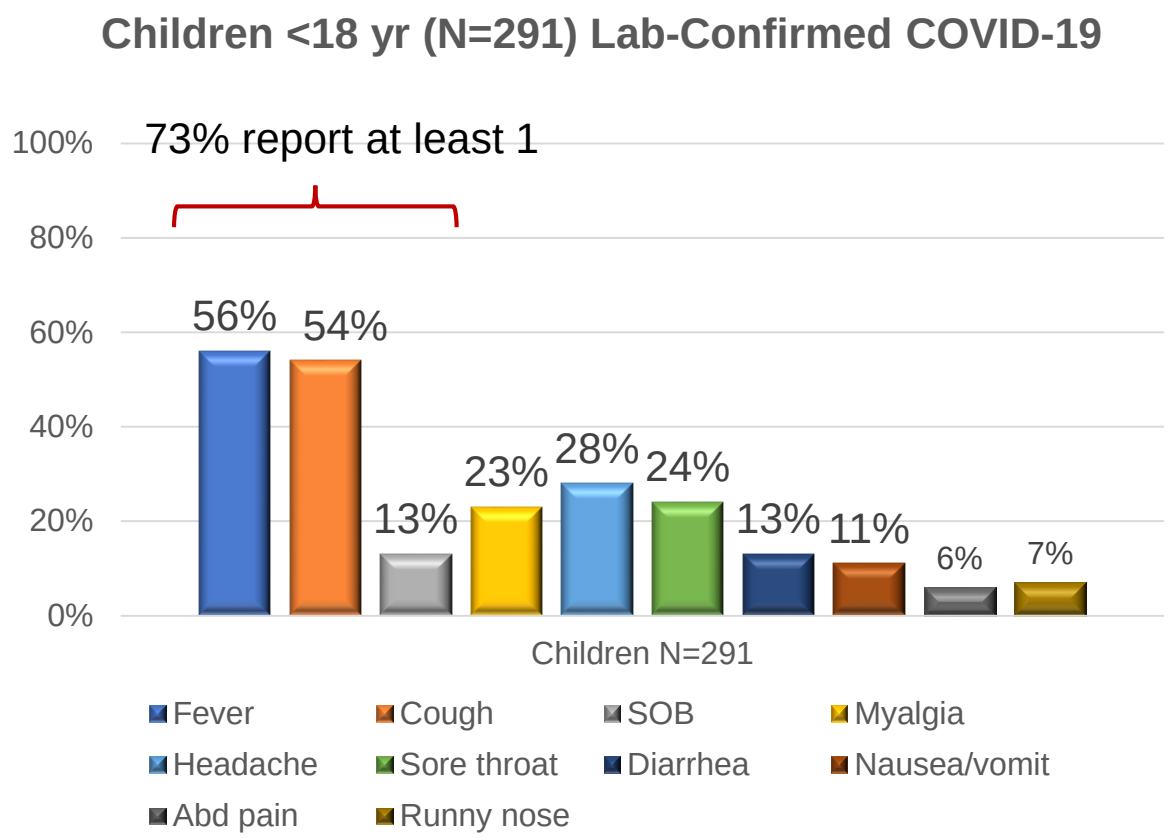


Gudbjartsson DF et al. N Engl J Med. 2020 Apr 14

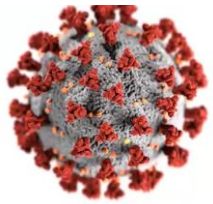
Signs and Symptoms of COVID -19 in Children and Adults, US

CDC COVID-19 Response Team. MMWR 2020 Apr 6;69

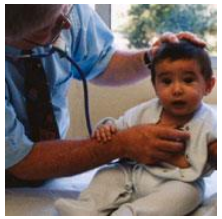




→Fever/cough/SOB less common in children – and symptoms in general less common (93% adults vs 73% children had one or more symptoms of fever, cough, SOB); 1.3% of children reported to be asymptomatic.



Severity of COVID-19 in Children



- *Dong Y et al. Pediatr. 2020 Mar 16*: 2,143 cases (731 confirmed, 1,412 suspected) in children in China.
  - **Majority (90%) have only mild-moderate disease; minority (4%) asymptomatic.**
  - **Infants <1 yr highest risk more severe disease.**

Characteristics of Children with COVID-19 China

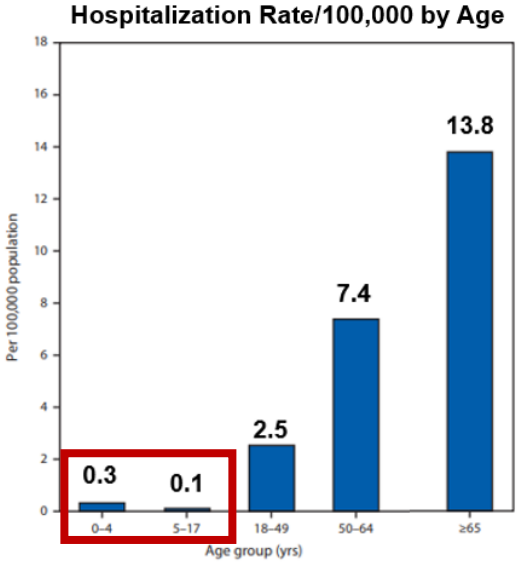
Characteristics	All cases
Median age (Interquartile range)	7.00 (11.0)
Age group	
<1	379(17.7)
1-5	493(23.0)
6-10	523(24.4)
11-15	413(19.3)
>15	335(15.6)
Gender	
Boy	1213(56.6)
Girl	930(43.4)
Severity of illness	
Asymptomatic	94(4.4)
Mild	1091(50.9)
Moderate	831(38.8)
Severe	112(5.2)
Critical	13(0.6)
Missing	2(0.1)
Days from symptom onset to diagnosis	
Median days (Interquartile range)	2(4.0)
Range	0-42
Province	
Hubei	984(45.9)
Surrounding areas*	397(18.5)
Others	762(35.6)
Total	2143

4%
90%

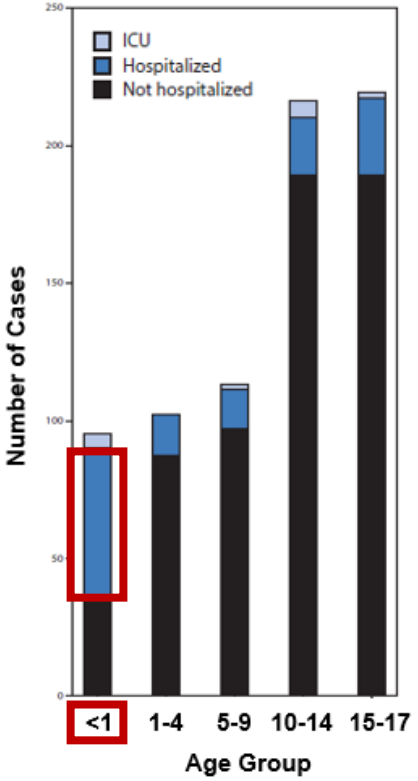
Different Severity of Illness by Age Group

Age	Total	ASx	Mild	Moderate	Severe	Critical
<1	379 (18%)	7 (2%)	205 (54%)	127 (34%)	33 **(9%)**	7 **(2%)**
1-5	493 (23%)	15 (3%)	245 (50%)	197 (40%)	34 (7%)	2 (0.4%)
6-10	521 (24%)	30 (6%)	278 (53%)	191 (37%)	22 (4%)	0 (0%)
11-15	413 (19%)	27 (7%)	199 (48%)	170 (41%)	14 (3%)	3 (0.7%)
15-18	335 (16%)	15 (4%)	164 (49%)	146 (44%)	9 (3%)	1 (0.3%)
Total	2141	94 (4%)	1091 (51%)	831 (39%)	112 (5%)	13 (1%)

- *MMWR 2020 2020 Apr 17*: In US, children less likely hospitalized than adults.



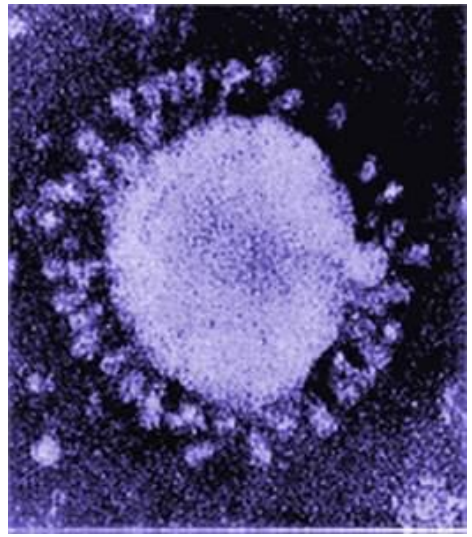
- *MMWR 2020 2020 Apr 6*: Among children <18 yr, those age <1 yr most likely hospitalized (62%) vs 1-17 yr (4.1%-14%)



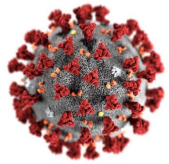
Why Might Children Have Milder Disease or Be Less Susceptible?

- Difference in immune system compared to adults = less likely to have cytokine storm type of response?
- Presence of other coronaviruses in mucosa of lung and airways which could give cross-protective antibodies or limit the growth of SARS-CoV-2 by direct virus-virus interactions and competition?
- Lower levels of ACE2 receptor in lung alveolar cells of their lower respiratory tract so primarily get upper rather than lower respiratory infection? (note - could not find any data to address this hypothesis)
- Less likely to have underlying disease/co-morbidity associated with poor prognosis?

SARS-CoV-2/ COVID-19 in Pregnancy



Summary of Data on COVID-19 in Pregnant Women



- Clinical manifestations of COVID-19 in pregnant women are similar to nonpregnant individuals.
- Pregnancy does not appear to increase susceptibility to infection or worsen clinical course, and most infected mothers have mild disease and recover without undergoing delivery.
- However, severe disease necessitating ICU admission and mechanical ventilation can occur; in review of 118 pregnant women in China with COVID-19, 8% had severe disease (with two-thirds developing severe disease postpartum) *(Chen L et al. N Engl J Med. 2020 Apr 17)*. At least one death reported (0.2%) *(Karami P et al. Travel Med Infect Dis 2020 Apr 13)* (consistent with mortality in non-pregnant adults 20-44, 0.2%).

COVID-19 in Pregnant Women Can Be Asymptomatic

- Although most women present with symptoms while pregnant, in a review of 40 papers including 542 women, **8% did not have symptoms until admitted in labor (2%) or after delivery (6%)**. Additionally, **11% had no symptoms** but screened + for SARS-CoV-2 (tested either because of known exposure or, in New York City, universal screening of women presenting in labor was instituted).
  - *Sutton D et al. N Engl J Med. 2020 Apr 13:* 215 pregnant women delivered at 2 hospitals in NYC, where universal NP rtPCR testing being done in labor.
    - 4/215 (1.9%) had symptoms, all positive.
    - 29/210 (13.7%) of women <u>without</u> symptoms who were tested were positive.
    - Thus, 29/33 (87.9%) positive for SARS-CoV-2 had no symptoms at admission.
    - Fever developed PP in 3/29 (10%) initially without sx.

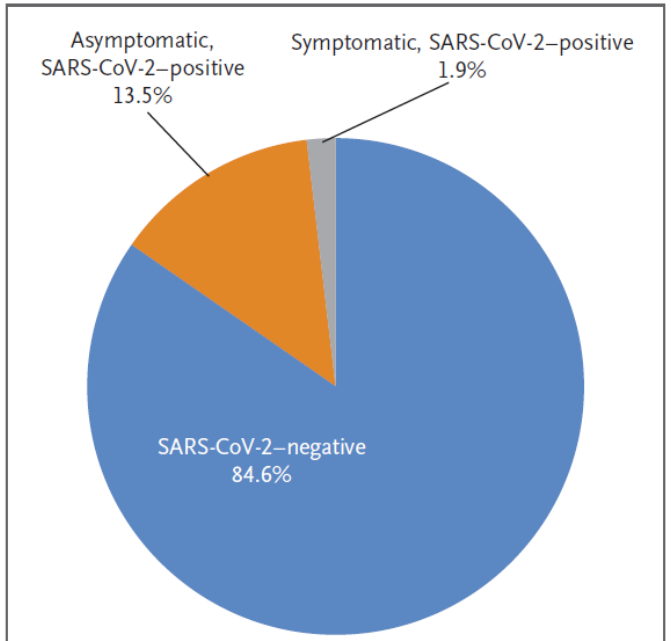
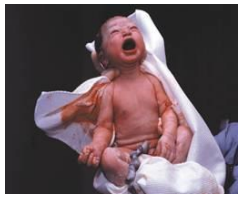
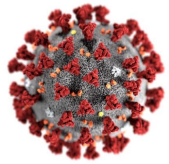


Figure 1. Symptom Status and SARS-CoV-2 Test Results among 215 Obstetrical Patients Presenting for Delivery.

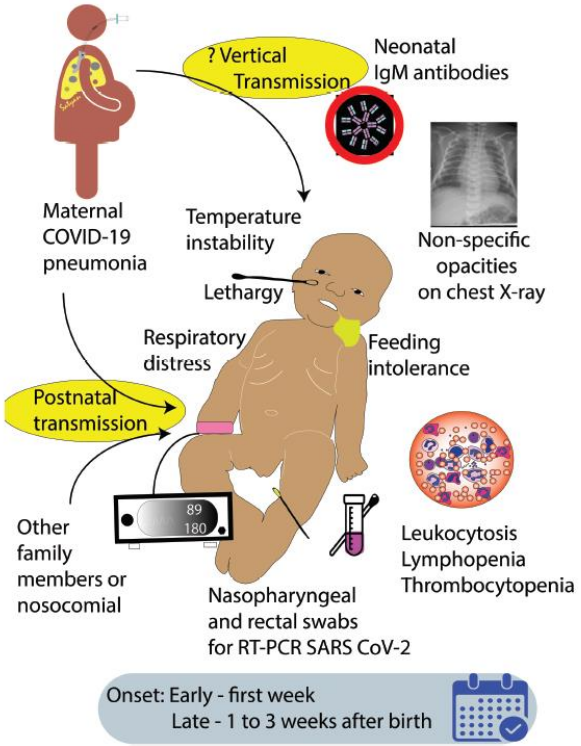


COVID-19 and Pregnancy Outcome



- Infected women, especially those who develop pneumonia, appear to have an increased frequency of pre-eclampsia, cesarean delivery for fetal distress (likely related to severe maternal illness), premature rupture of membranes, and preterm birth – whether directly due to SARS-CoV-2 infection or maternal illness not clear.
- However, severe neonatal outcomes rare, and most not felt associated with maternal COVID-19.
- Cases of neonatal COVID-19 disease have been reported but appear to be rare, and likely associated with infant exposure to virus postpartum.
- It is unknown if SARS-CoV-2 mother to child transmission occurs.

Is There Mother to Child Transmission?



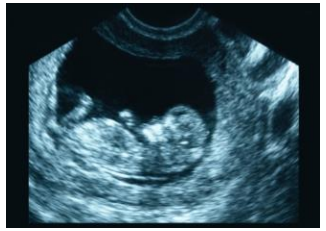
→ *Is MTCT feasible?*

→ *Immunologic evidence*

→ *Virologic evidence*

Chandrasekharan P et al. Am J Perinatol. 2020 Apr 8 (epub ahead of print)

What are Requirements for *In Utero* Transmission?

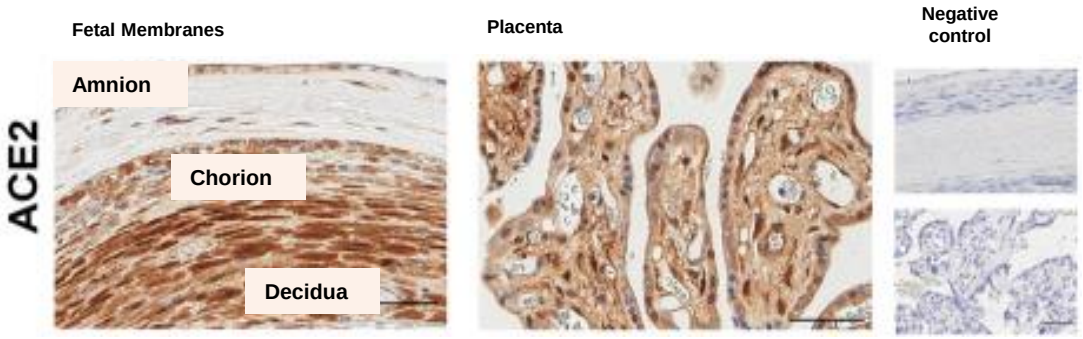


- *In utero* infection requires the pathogen to be able to cross the placenta and to infect the fetus.
  - Is there a receptor for SARS-CoV-2 in the placenta to enable the virus to cross the intact placenta?
  - Is there a receptor for ACE-2 in the fetus – and specifically fetal lung given symptoms reported – to enable the virus to infect the fetus?

ACE2 Enzyme Can Be Found in the Placenta

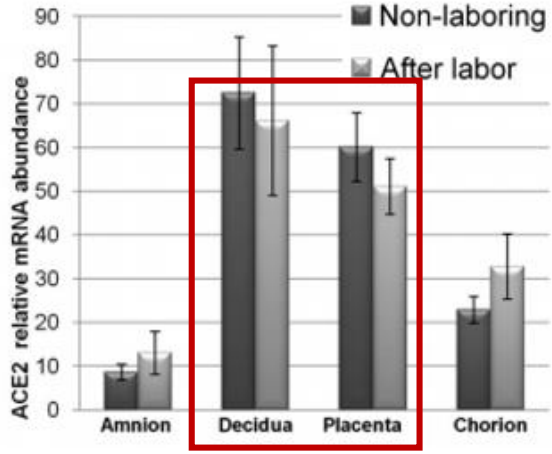
- ACE-2 found in placenta localized to:
  - decidua,
  - syncytiotrophoblast,
  - villous stroma;

Immunohistochemical localization of mRNA for ACE2 (brown = ACE2 mRNA) in fetal membranes and placenta



Marques FX et al. Placenta. 2011;32:214-21

ACE2 mRNA levels (no difference labor/non-labor)



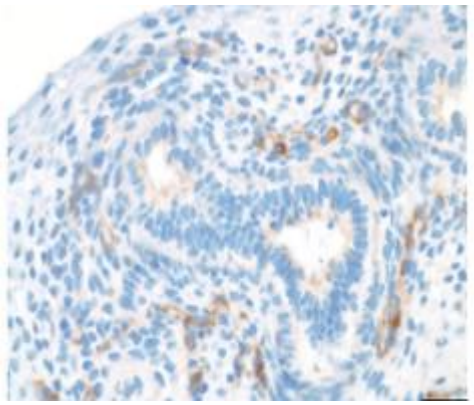
Marques FX et al. Placenta. 2011;32:214-21

- ACE2 is most abundant in placenta in early gestation but is also identified at term.

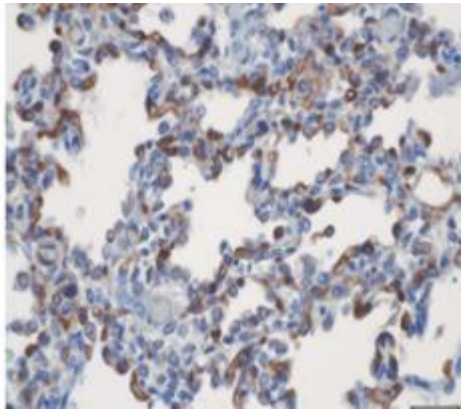
ACE2 Enzyme Can Be Found in the Fetal Lung

- ACE-2 can be found in the fetal lung:
  - Found as early as 12 weeks gestation
  - Age-related increase in ACE2 - peaks mid-gestation, then remaining high throughout gestation and postnatal development.

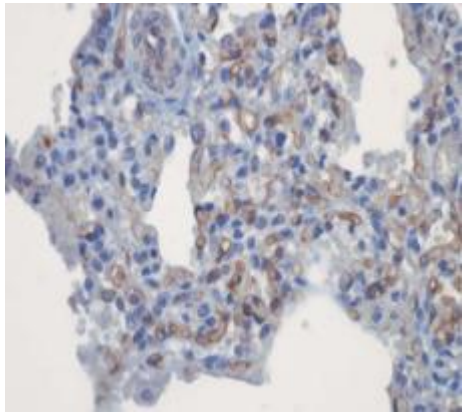
Immunohistochemical localization of ACE2 antibody (brown = ACE2 presence) in fetal lung



12 weeks gestation

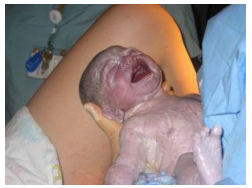


24 weeks gestation



6 weeks infant

Castro E et al. Pediatr Pulmon. 2014;49:985-90

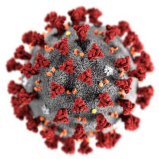


What About Intrapartum Transmission of SARS-CoV-2

- Intrapartum transmission during passage through the birth canal requires fetal exposure to infectious virus. Is SARS-CoV-2 found in vaginal fluids?
- Study of 10 *postmenopausal* women in the ICU with severe COVID-19 (+ PCR, + CT scan), testing for SARS-CoV-2 in vaginal fluid (as well as blood and urine) with RT-PCR assay 17-40 days after diagnosis (while still in ICU):
  - All samples were negative for the virus
- Data to date from *pregnant* women at delivery:
  - 0/6 samples negative for virus
- However, potential exposure to virus after birth in delivery room is possible (but is really postnatal not intrapartum infection)

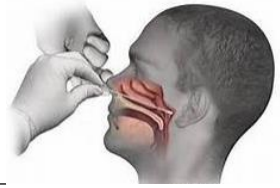
What About Breast Milk Transmission of SARS-CoV-2

- SARS-CoV-2 rt PCR evaluated in 40 breast milk samples.
  - All tested negative for virus
- Postnatally, transmission more likely through close contact of infected mother with infant than through breast milk.

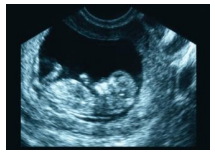


SARS-CoV-2 Virologic rtPCR Testing

(review of 40 papers through April 17, 2020)



Specimens tested by rtPCR	# Papers with data	Number/total sample	Percent
Nasopharyngeal (NP) swab “newborn”	36	**12/337**	**4%**
Amniotic fluid	8	0/24	0%
Placenta	10	0/14	0%
Cord blood	11	0/31	0%
Infant gastric aspirate	2	0/11	0%
Infant stool	9	5/59	8%
Maternal breast milk	11	0/40	0%
Maternal vaginal swab	4	0/6	0%



Proposed Definitions for MTCT (Simplified)

Shah PF et al. Acta Obstet Gynecol Scand. 2020 Apr 11 (epub)

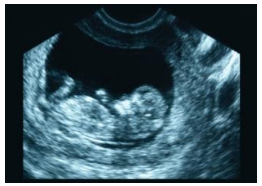
- Accounts for 1) maternal testing; 2) symptoms in infant (more stringent if no symptoms); 2) detection of virus (and type/timing of sample: blood, amniotic fluid > placenta > NP swab); 3) presence of IgM antibody
- In utero: requires testing at birth; *confirmed or probable* infection requires detection of SARS-CoV-2 virus in cord/neonatal blood, amniotic fluid, or placenta (if virus in NP swab, must also be in placenta); *possible* infection if IgM antibodies in cord/neonatal blood even if NP swab negative.
- Intrapartum: *confirmed* requires NP swab positive at birth and 24-48 hours; *possible* is NP swab positive at birth and no test at 24-48 hr.
- Postpartum: *confirmed* requires detection in NP or anal swab $\geq$48 hours and negative at birth; *probable* is detection in NP or anal swab $\geq$48 hours and no test at birth.

How Well Do Described Possible MTCT Cases Fit Definitions?

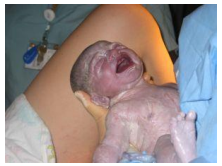
Cases	Mom	Infant Sx	Birth sample	Type sample	Timing +	Later Tests
Virologic test +						
1	+	Yes? resp distress birth	**NO**	NP	8 d	Negative 6 d
2	+	No clinical sx, +CXR	**NO**	NP	3 d	Negative 4, 8 15 d
3	+	No clinical sx, +CXR	**NO**	NP	*36 hr*	Negative 14 d
4	+	No clinical sx, +CXR, lab	**NO**	NP	*36 hr*	Negative 14 d
5	+	No clinical sx, +CXR, lab	**NO**	NP	2 d	Negative 14 d
6	+	No clinical sx, +CXR	**NO**	NP	2 & 4 d	Negative 6 d
7	+	Yes	**NO**	NP	2 & 4 d	Negative 7 d
8-9	+	Unclear, ?+CXR	Maybe?	NP	*Within 24 hr*	No information
10-11	+	1 SOB, 1 no sx, both +CT	**NO** 30 hrs, ?5 d	NP	*30 hr*, ?5 d	Negative ~2 wk
Immunologic test +						
Cases 1-7 **all IgM+ at or ~ birth**	+	**NO**	Few hours	Blood and NP	None +	All samples negative

Meet definition of POSSIBLE IU infection (IgM + cord blood, negative detection virus in blood)

- NONE meet definition confirmed/probable IU as no birth blood or placental sample or antibody test done
- 2 meet definition POSSIBLE INTRAPARTUM (had + test at <24 hr, with no second test in infant without/minimal symptoms)
- 9 may meet definition of PROBABLE POSTNATAL if view 30-36 hr = 48 hr (detection virus NP ≥48 hrs in neonate not tested birth)

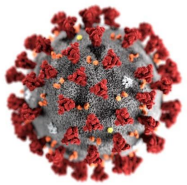


Feasibility of MTCT of SARS-CoV-2?



- Serologic data not definitive but suggestive.
- ACE2 receptors on placenta and in fetal lung suggest it could be possible for SARS-CoV-2 to be transmitted *in utero*.
- Virologic data and IgM serology suggestive but no birth testing and rapid conversion from rtPCR positive to rtPCR negative and rapid decrease IgM within a few days is concerning re: potential false positive tests.
- Thus – is it possible? Yes.
- Do we have definitive proof? Not at this time.

Summary



- Children appear to have mild and less severe disease than adults and may have asymptomatic carriage. Severe disease can rarely occur and is more frequent in infancy (<1 year).
- The exact burden of SARS-CoV-2 in children in the overall population remains to be defined.
- Pregnant women do not appear to have increased risk of infection or severity of disease. However, severe disease and even death can rarely occur.
- Adverse pregnancy outcome (e.g., fetal distress, preterm delivery) may be increased (possibly due to systemic disease in mother).
- Evidence for SARS-CoV-2 mother to child transmission is limited.

Thank You For Your Attention!