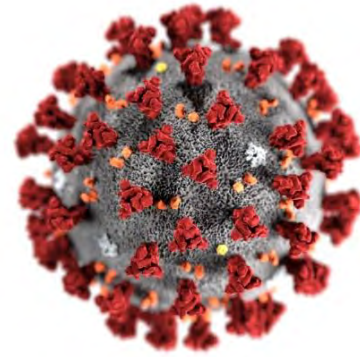


COVID-19: What Pediatric HIV Programs Need to Know

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



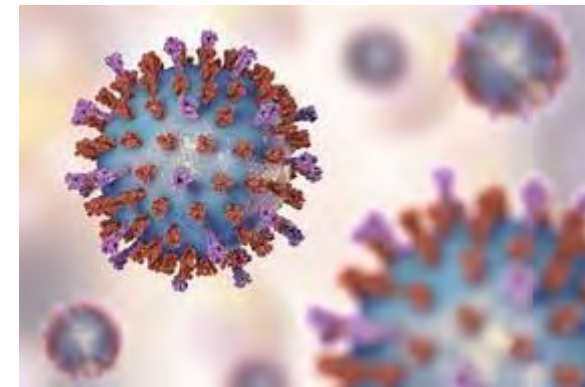
April 23 2020

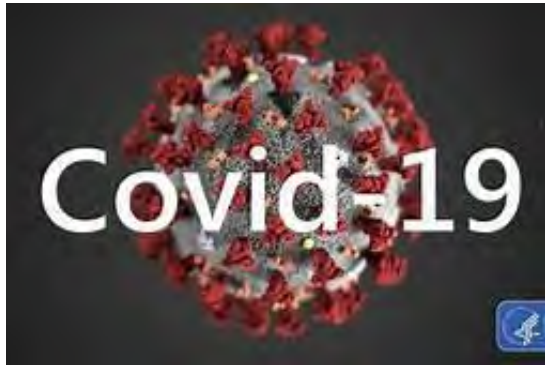
Lynne M. Mofenson, M.D.



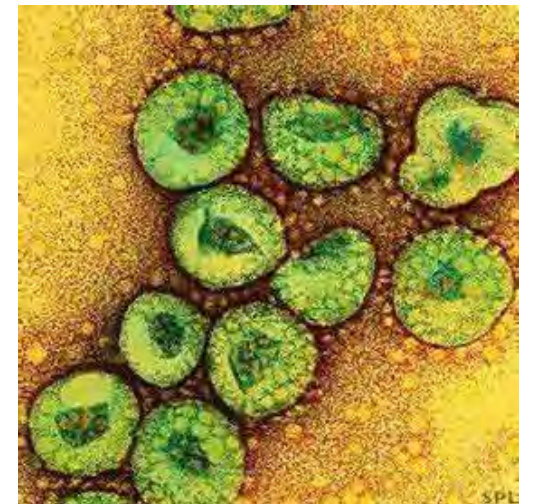


Please Note that Data are
Limited, Preliminary, Some
of Poor Quality, and Change
Almost Daily



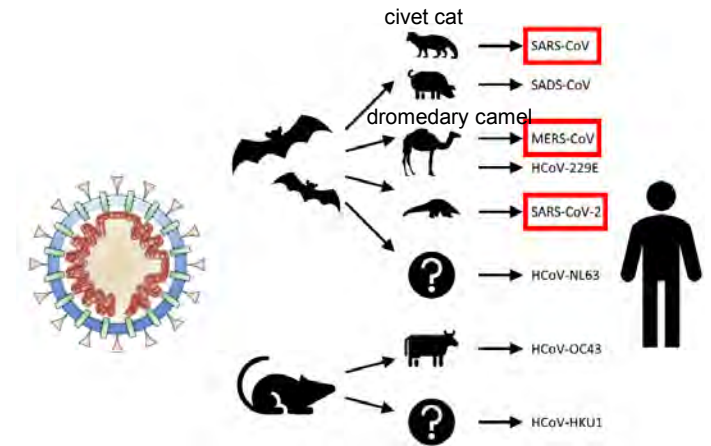
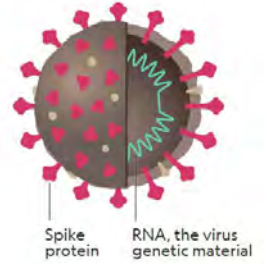


Basic Information on the SARS-CoV-2/ COVID-19



What is a Coronavirus?

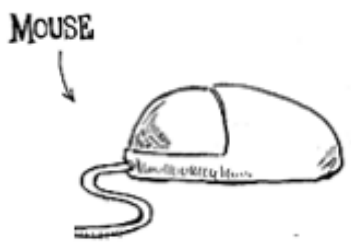
- Coronaviruses (CoV) are single-stranded RNA viruses, named because the virus has projections (spike protein) on envelope resembling a crown.
- They are classified in 4 genera based on genomic structure; can infect different hosts and have different tissue tropism:
 - Gamma and delta CoV infect birds, 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.



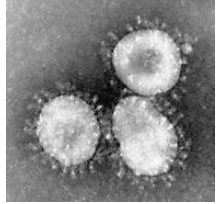
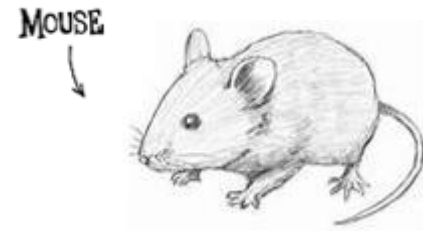
Rabi FA et al. *Pathogens*. 2020 Mar 20;9 (3).

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, 22% 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.



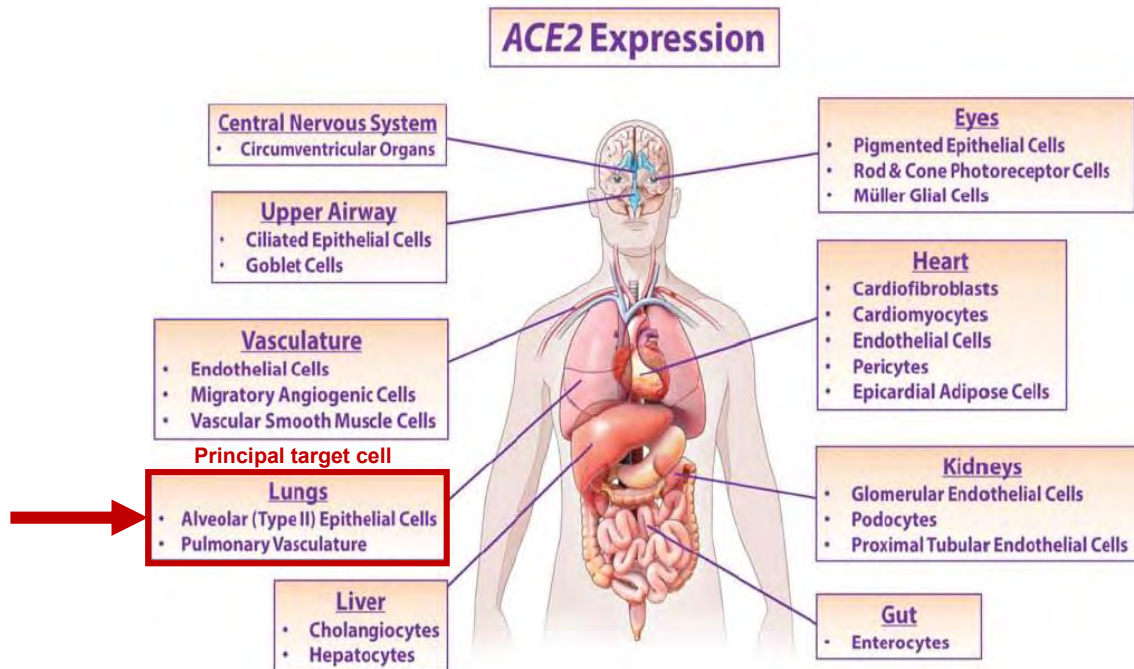
- COVID-19 (**C**orona**v**irus **D**isease 20**19**) is the disease caused by the virus (named by WHO in a press release on Feb 11, 2020).



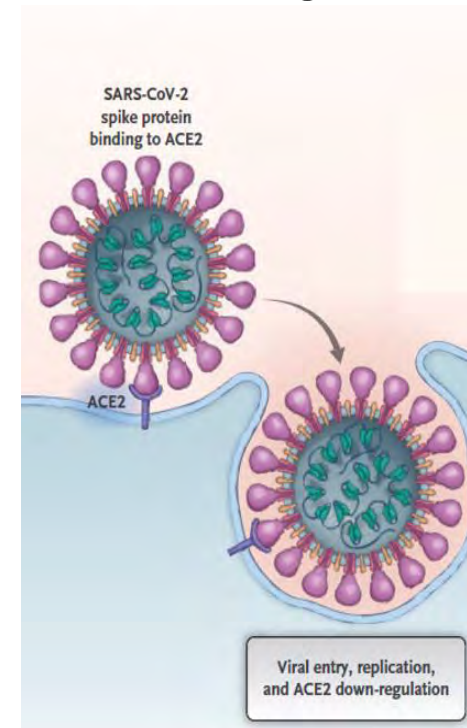
- Terminology similar to HIV (human immunodeficiency virus), which is the virus that can cause the disease called AIDS (Acquired Immune Deficiency Syndrome).

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).

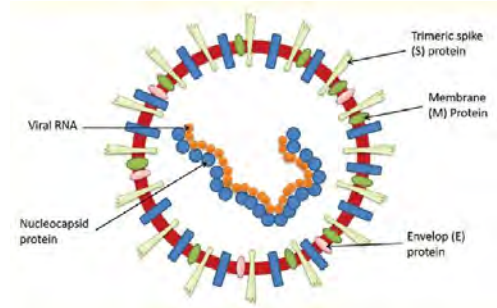


Gheblawi M et al. Circ Res. 2020 Apr 8 epub



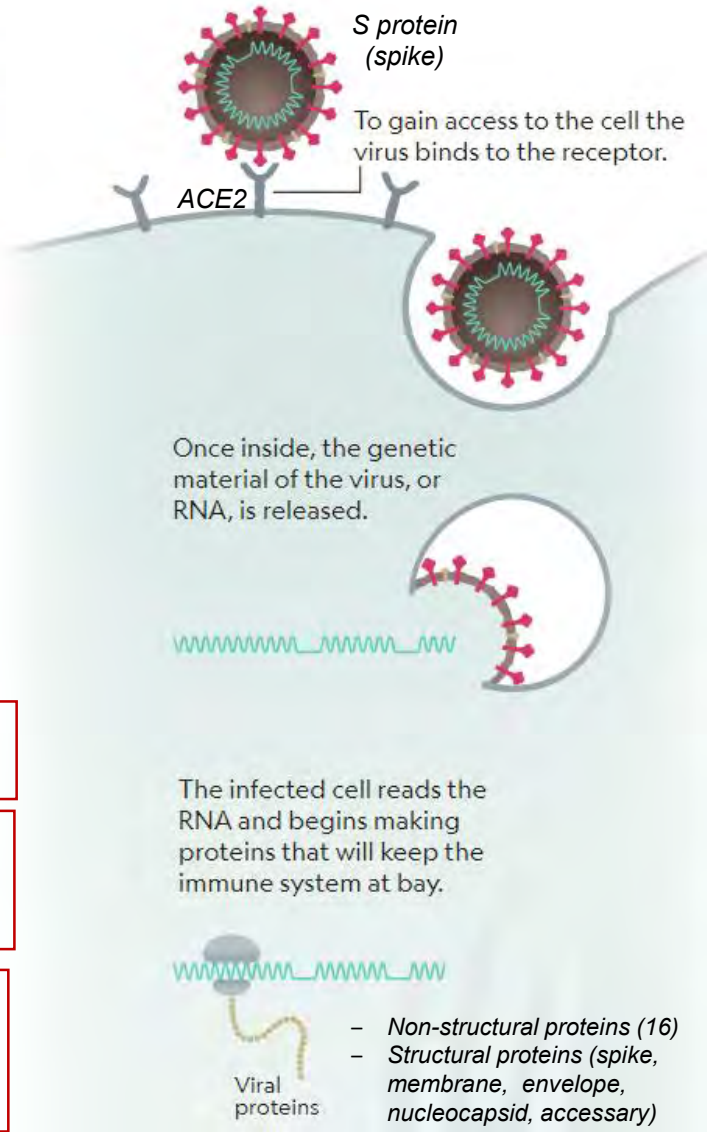
Vaduganathan M et al. N Engl J Med. 2020 Mar 30 epub

Simplified Replication Cycle



FUSION

Endosomal Pathway



RNA TRANSLATION

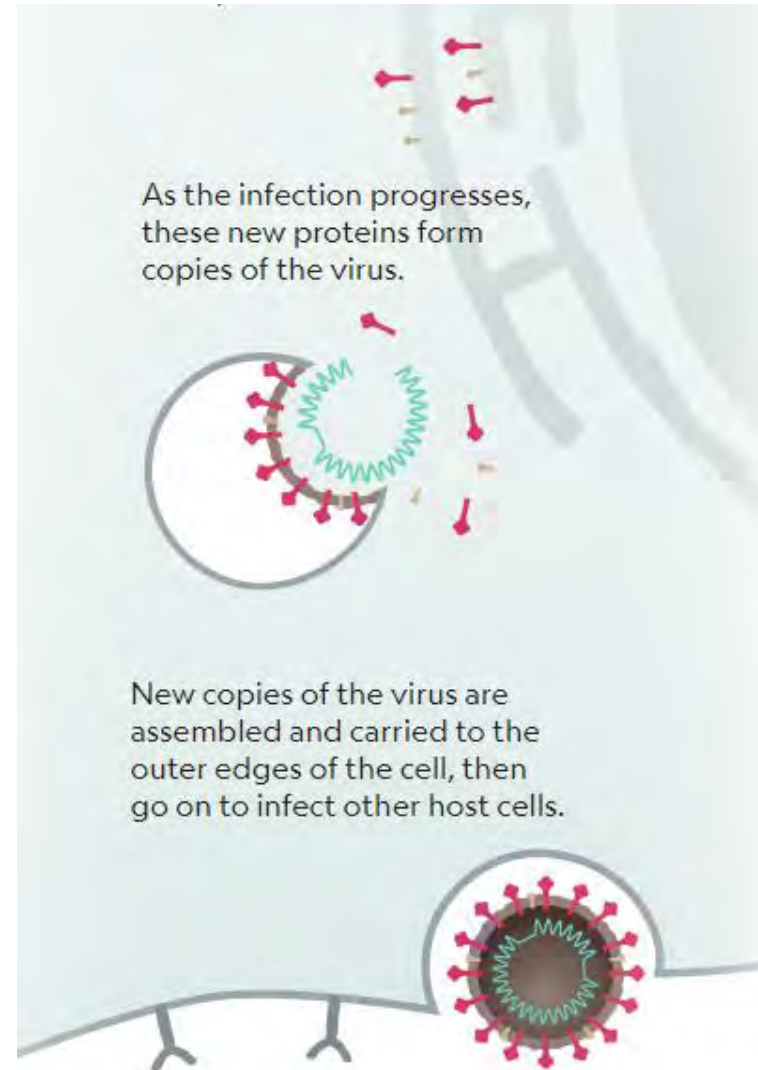
by host ribosomes into proteins

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

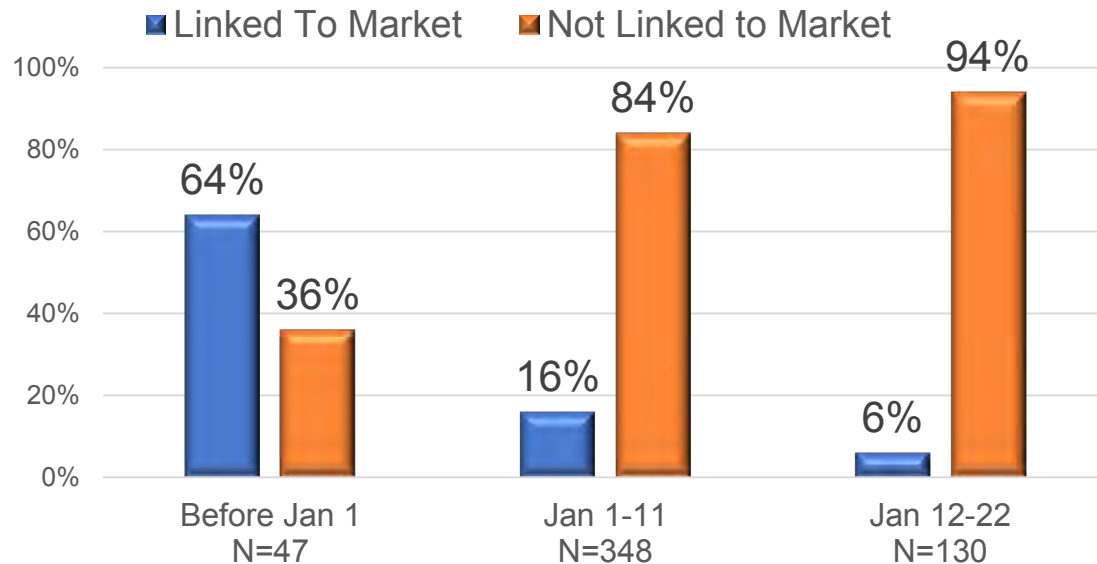
VIRION RELEASE

*Exocytosis
fusion of virion vesicle with plasma membrane and release*

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.

Characteristics of First 324 Patients with COVID-19 Pneumonia in Wuhan With Exposure History



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

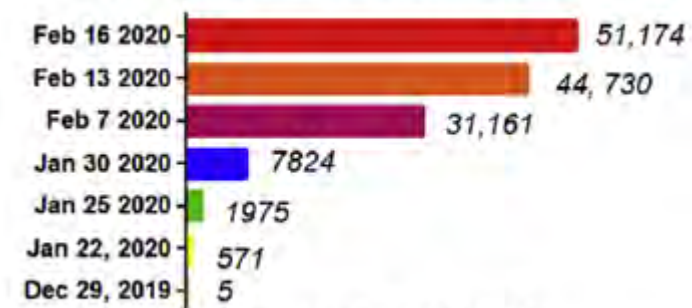


Wuhan Seafood Wholesale Market closed and disinfected Jan 1, 2020 after identified as potential origin of outbreak

Rapid Spread → Global Pandemic

- Rapid spread outside of Wuhan to rest of China.
- Then spread outside of China to current global pandemic.

Chronologic Incidence COVID-19 in China

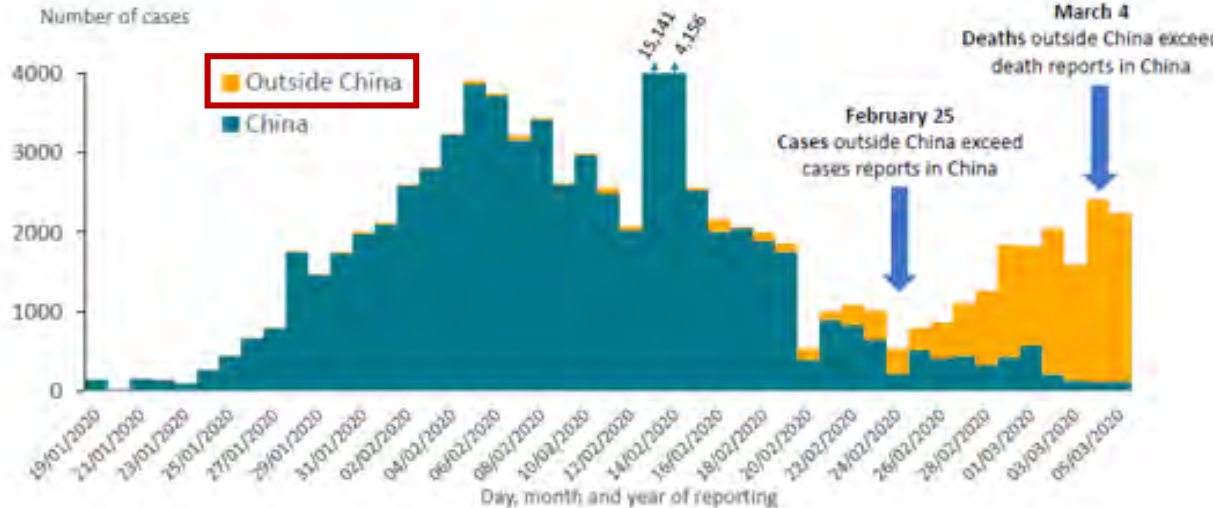


10,000-fold increase
in <2 months

Cases with COVID-19

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

Distribution of COVID-19 cases in accordance with the applied case definitions in the affected countries, as of 05 March 2020



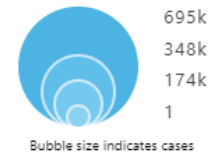
Coronavirus (COVID-19)

April 19 2020

85,506
new cases

2,245,872
confirmed cases

152,707
deaths





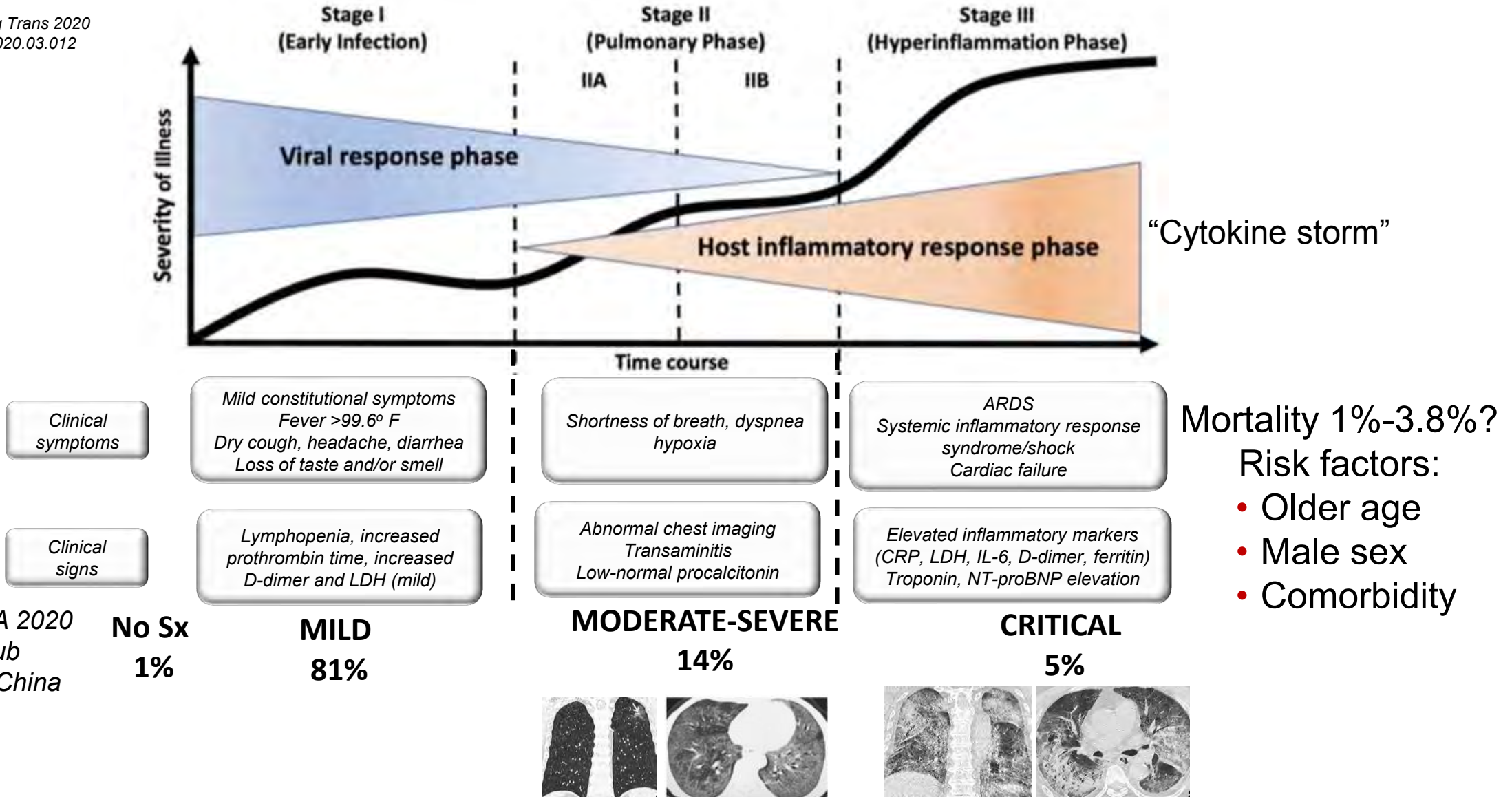
Why Such Rapid Global Spread?

- **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 Apr 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

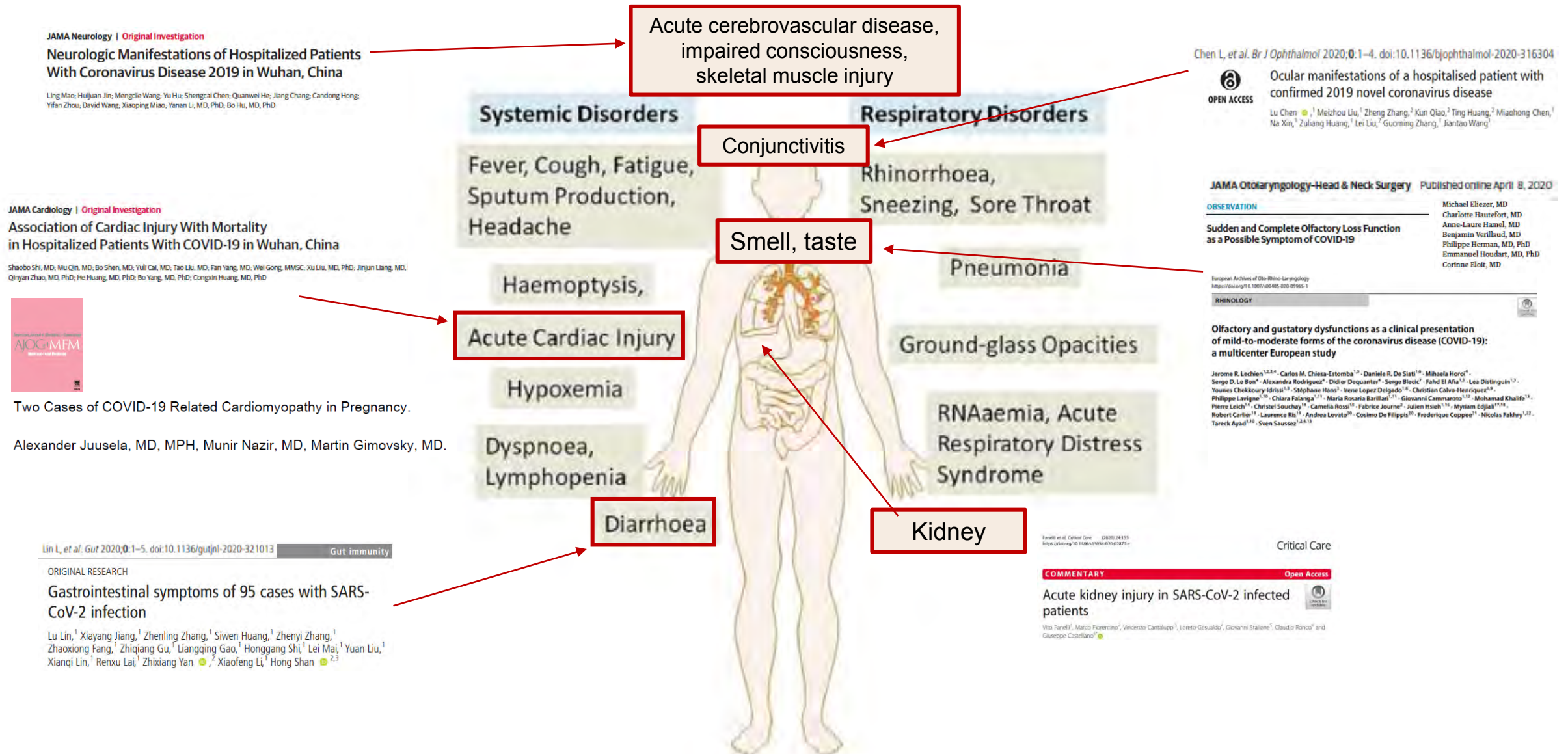
Both Virus and Host Immune Response to Virus Play a Part

Siddiqi HK. J Heart Lung Trans 2020
doi:10.1016/j.healun.2020.03.012



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

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



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 COVID19 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 Computerized 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 Detection
(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!

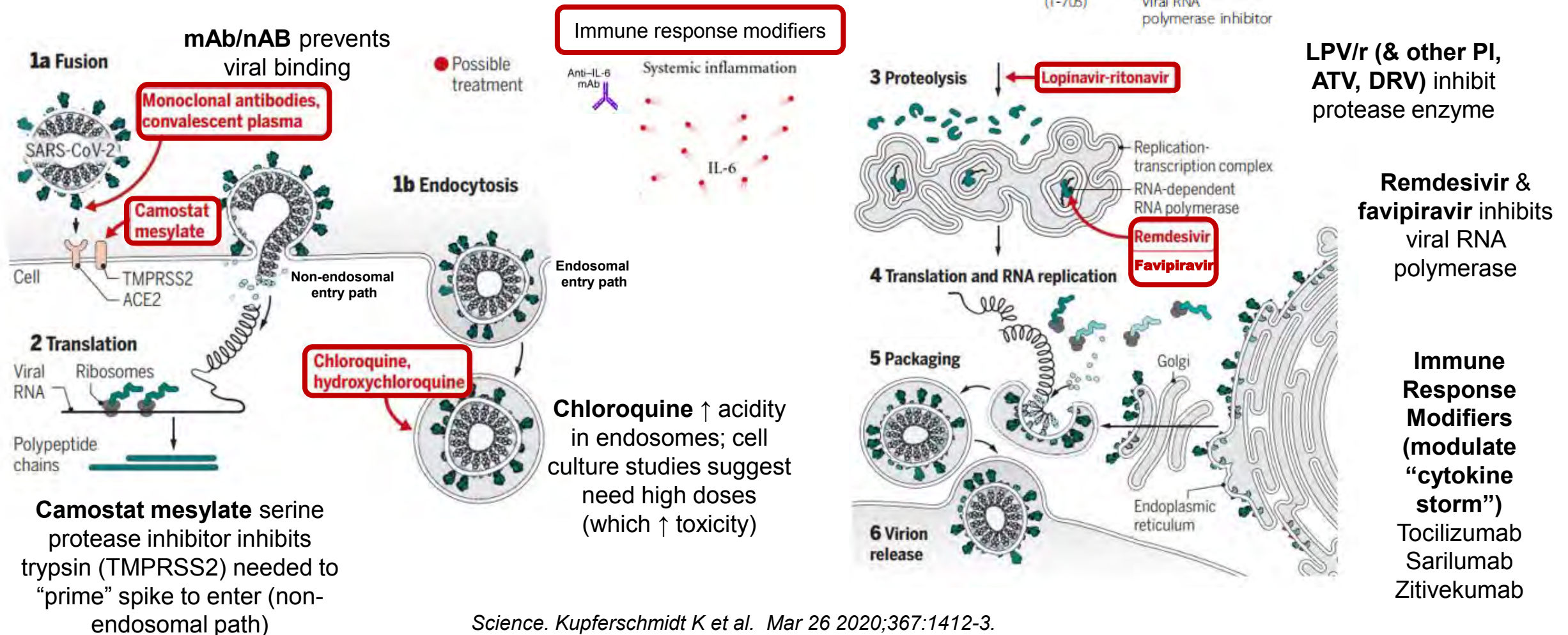
April 18, 2020

NIH U.S. National Library of Medicine

ClinicalTrials.gov

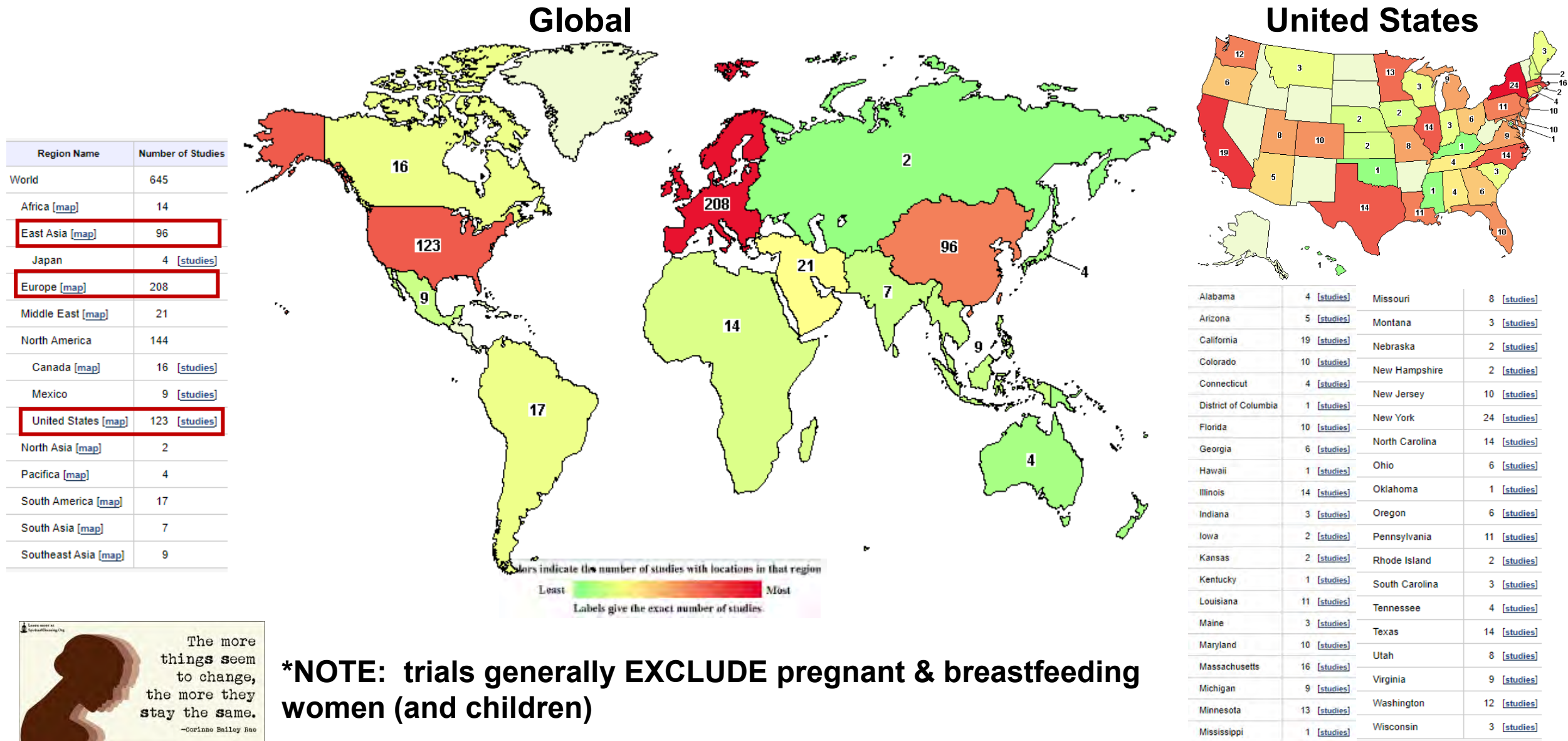
645 Studies found for: COVID 19 SARS CoV 2

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



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

645 Clinical Trials



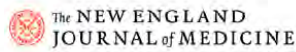


Randomized Trials Needed To Discern Efficacy & Safety Scientific Data Are Rapidly Changing Every Day



NO BENEFIT

March 18, 2020



ORIGINAL ARTICLE

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

Bi Cao, Y. Wang, D. Wen, W. Liu, Jinghui Wang, G. Fan, L. Xuan, 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, Y. Li, X. Zhou, X. Dong, Z. Qu, S. Lu, X. Hu, S. Buan, S. Lun, 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. Zhang, 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



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 Kaltis, 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



Compassionate Use of Remdesivir for Patients with Severe Covid-19

J. Gren, N. Ohmigan, D. Shin, G. Dias, E. Aspranger, A. Castagna, T. Feldt, G. Green, M.L. Green, F.G. Lescure, E. Nicastri, R. Oda, K. Yo, E. Quintos-Roldan, A. Studemeister, J. Redinski, S. Ahmed, J. Berneil, D. Chelliah, D. Chen, S. Chikara, S.H. Cohen, J. Cunningham, A. D'Amico Monforte, S. Ismail, H. Kato, G. Lapadula, E. L'Her, T. Maeno, S. Majumder, M. Massari, M. Mora-Rillo, C. Mutohi, D. Nguyen, E. Verweij, A. Zoufaly, A.O. Osimusi, A. DeZure, Y. Zhao, L. Zhong, A. Chokkalingam, E. Elhousdware, L. Telep, L. Timbs, J. Henno, S. Sellers, H. Cao, S.K. Tan, L. Winterbourne, P. Desai, R. Mera, A. Gaggan, R.P. Myers, D.M. Braunrod, R. Childs, and T. Flanagan

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



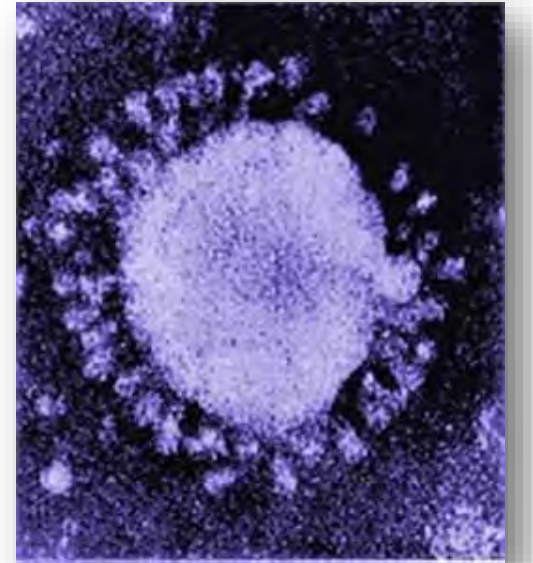
Chloroquine diphosphate in two different dosages as adjunctive therapy of hospitalized patients with severe respiratory syndrome in the context of coronavirus (SARS-CoV-2) infection: Preliminary safety results of a randomized, double-blinded, phase IIb clinical trial (CloroCovid-19 Study)

Mayla Sorbo, Fernando de Almeida Val, Vanderison Sousa Sampaio, Marcos Araujo Alexandre, Gracy Cardoso Nêvo, Marcelo Brito, Maria Mourao, Jose Diego Brito Sousa, Ibane Batista Silva, Marcus Vinicius Farias Goetta, Ludmila Hajec Rosemary Costa Pires, Antonio Balduino, Felipe Gomes Naveca, Marcos Xavier, Alexandre Saloman, Andre Siqueira, Alexandre Schwartz, Julio Henrique Rosa Cruda, Mauricio Lacerda Nogueira, Gustavo Romero, Quisque Bassat, Cor Jesu Foltes, Bernardino Albuquerque, Claudio Daniel Ribeiro, Welfton Moreira, Marcus Lacerda, CloroCovid-19 Team

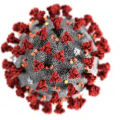
The high dose CQ arm presented more QTc>500ms (25%), and a trend toward higher lethality (1.7%) than the lower dosage. Fatality rate was 13.5% (95%CI=6.9-23.0%), overlapping with the CI of historical data from similar patients not using CQ (95%CI=14.5-19.2%), in 14 patients with paired samples, respiratory 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 (<i>China CDC</i>) ¹	44,672	965 (2%)	416 (43%)	-	-	-	549 (57%)
China (<i>Dong, Pediatrics</i>) ²	-	2,141	1,393 (65%)	379	493	523	748 (35%)
Italy (<i>Italy website</i>) ³	42,220	507 (1.2%)	-	-	-	-	-
US (<i>MMWR</i>) ⁴	149,760	2,572 (1.7%)	1,077 (42%)	398	291	388	1,495 (58%)
Japan (<i>Mizumoto. MedRxiv</i>) ⁵	294	10 (3.4%)	-	-	-	-	-
Korea (<i>COVID team. MedRxiv</i>) ⁶	7,755	480 (6.2%)	75 (16%)	-	-	-	405 (84%)
Iceland (<i>Gudbjartsson.NEJM</i>) ⁷	9,199 targeted	38 (0.4%)	(38)	-		-	-
	13,080 population	0/848 tested					
Madrid (<i>Taggaro JAMA Ped</i>) 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

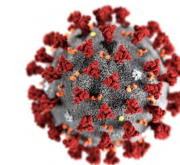
⁷ Gudbjartsson DF et al. *N Engl J Med* 2020 Apr 14

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 <u>no</u> symptoms	Yes	NP rtPCR +	Did well, d/c
China/Cui	55 d	URI, cough, <u>no</u> 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 <u>nl</u>	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 <u>nl</u>	Yes	NP rtPCR +	Required O ₂ , d/c
Italy/Canarutto	32 d	URI sx, fever, CXR <u>nl</u>	Yes	NP rt PCR+	Did well, d/c
New York/Robbins, Paret	3 pt: 25, 56, 58 d	Fever (all), <u>no</u> respiratory sx, CXR <u>nl</u>	2 Yes 1 No	NP rtPCR+	Did well, d/c
Vietnam/Le	3 mos	URI sx, fever, CXR <u>nl</u>	Yes	NP rtPCR+	Did well, d/c
Singapore/Kam	6 mos	<u>No</u> 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 Apr 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. Pediatr 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



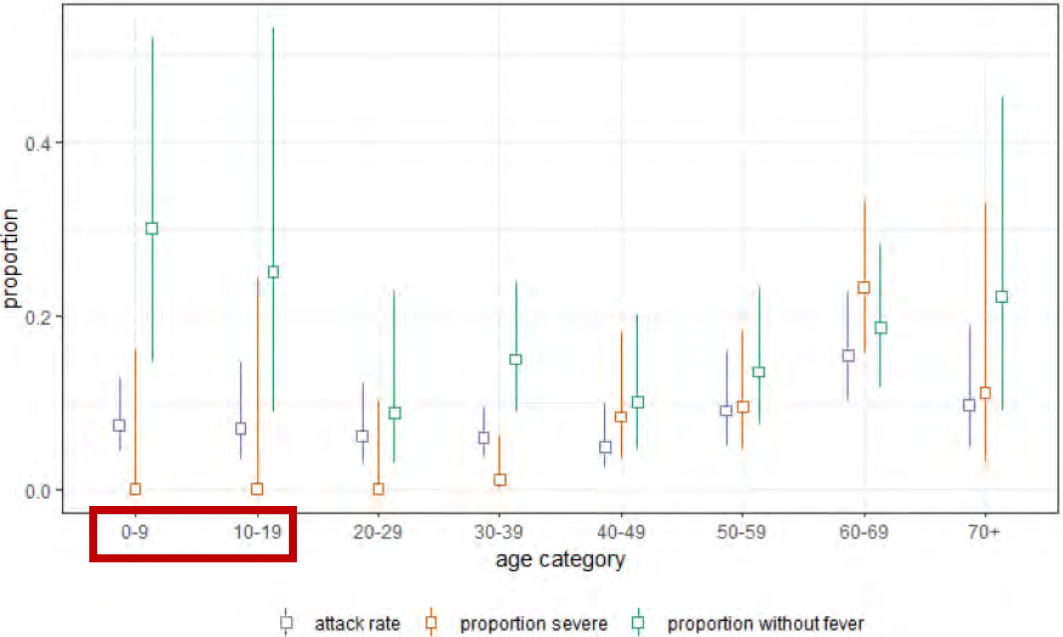
Children Less Likely Infected or Less Likely Symptomatic?

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)

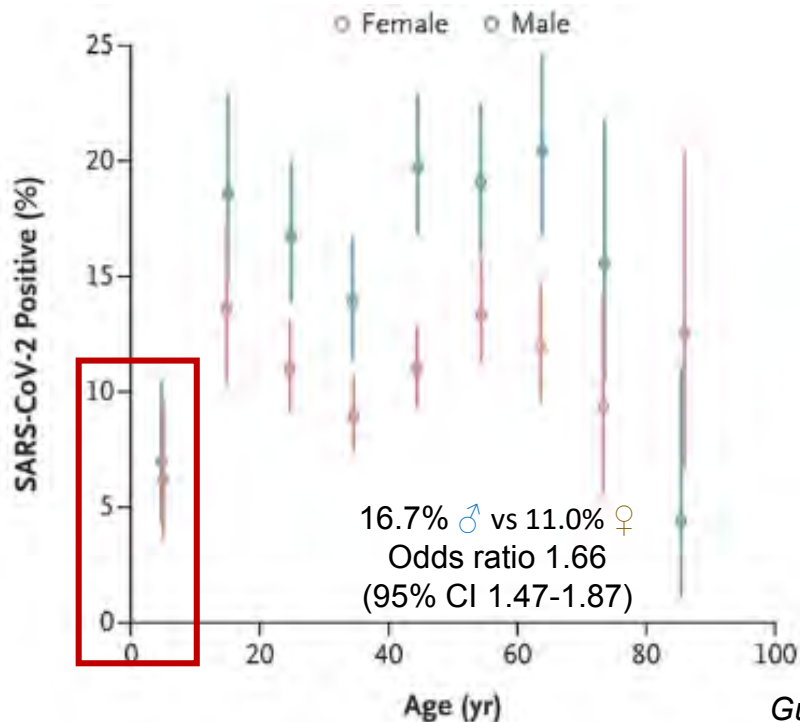


Children Less Likely Infected or Less Likely Symptomatic?

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-Apr 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

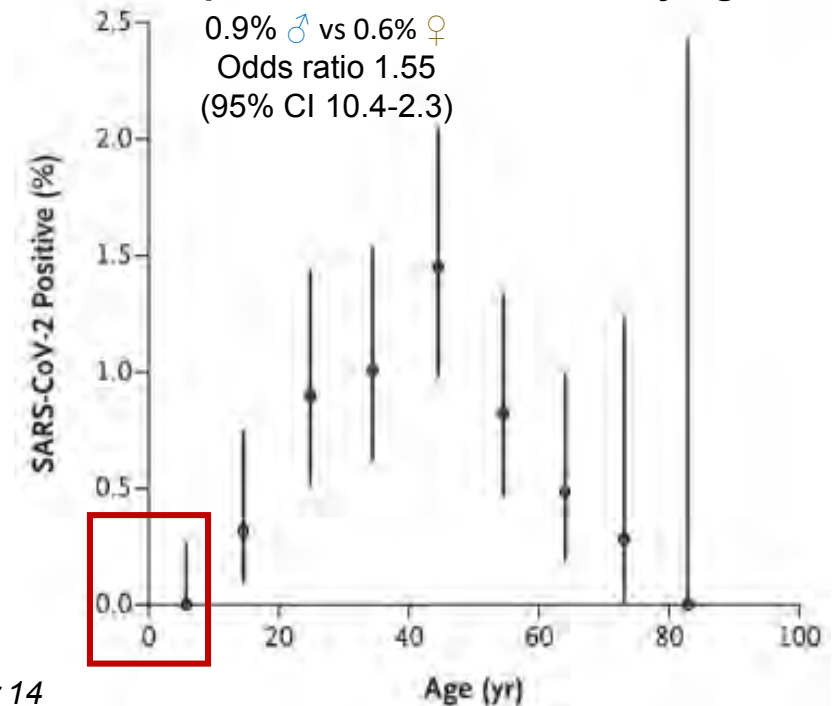


Not Resolved Yet:

Are children less susceptible to SARS-CoV-2?

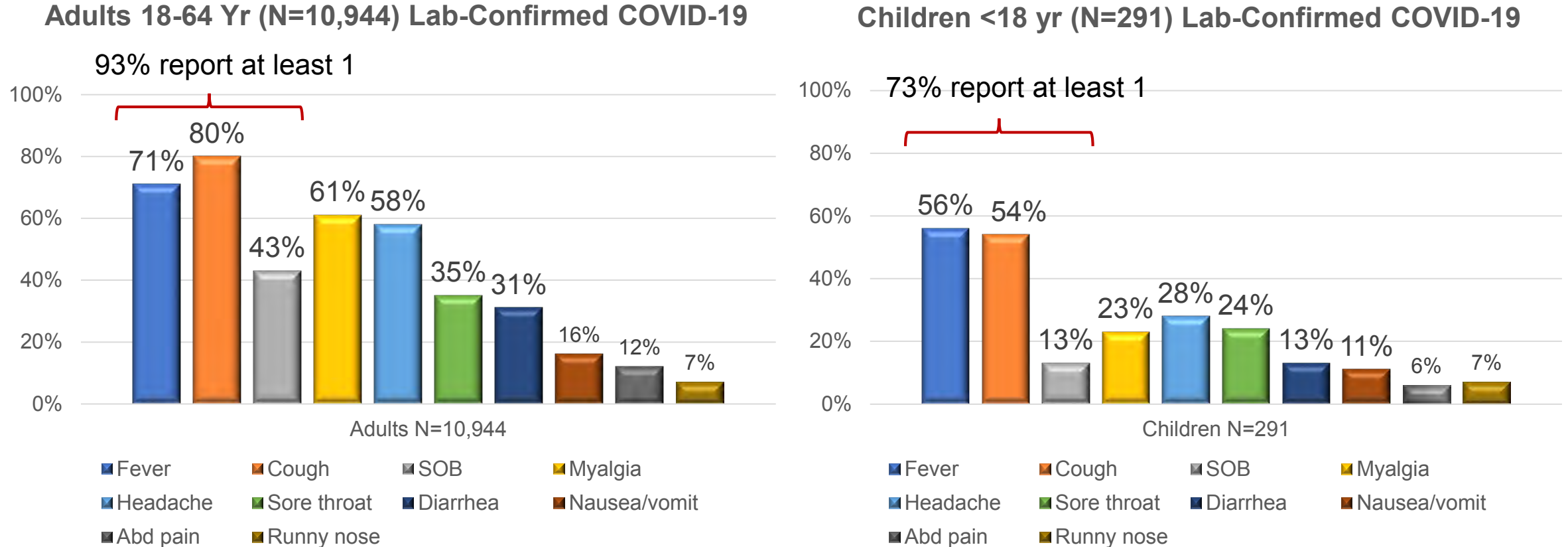
Or are they less symptomatic with similar rates infection?

Population: SARS-CoV-2 + by Age

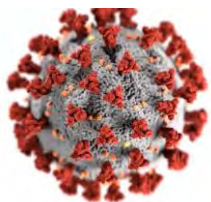


Signs and Symptoms of COVID -19 in Children and Adults, US

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.

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

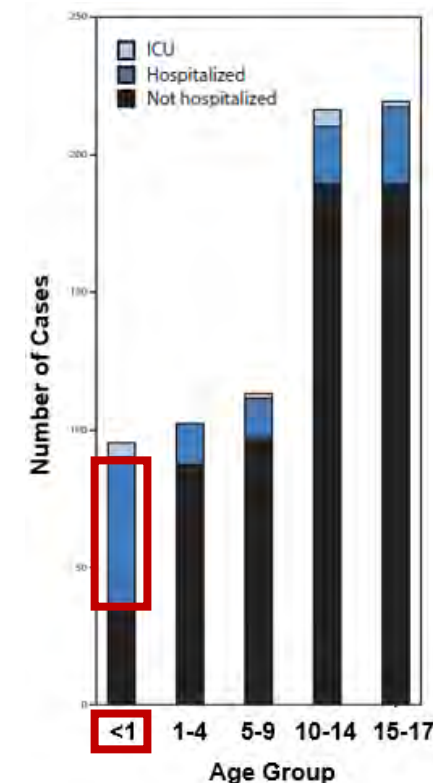
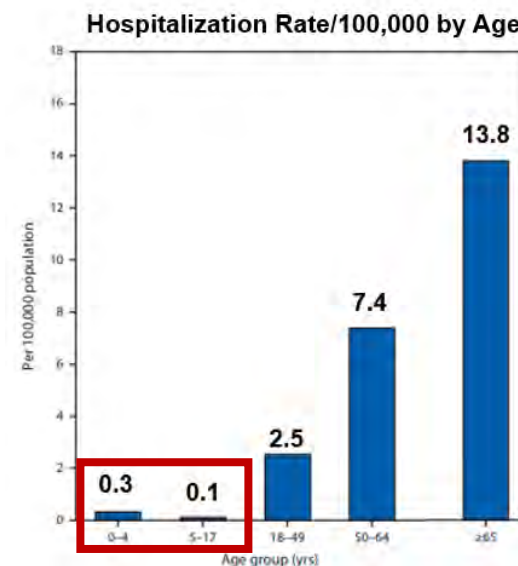
- MMWR 2020 2020 Apr 6: Among children <18 yr, those age <1 yr most likely **hospitalized** (62%) vs 1-17 yr (4.1%-14%)

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	415(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	3(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

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%)

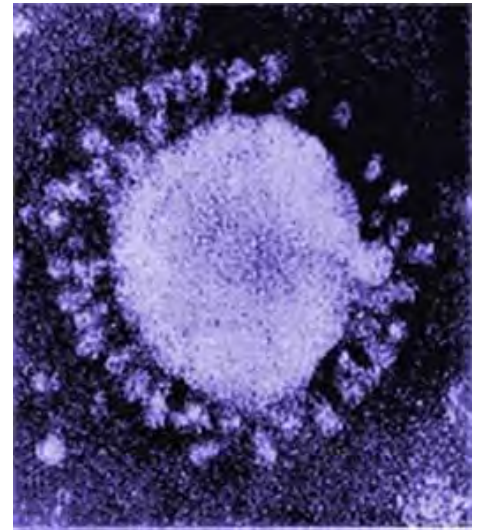


Why Might Children Have Milder Disease or Be Less Susceptible?

- **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?

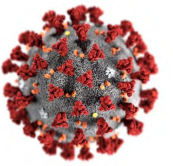


SARS-CoV-2/ COVID-19 in Pregnancy





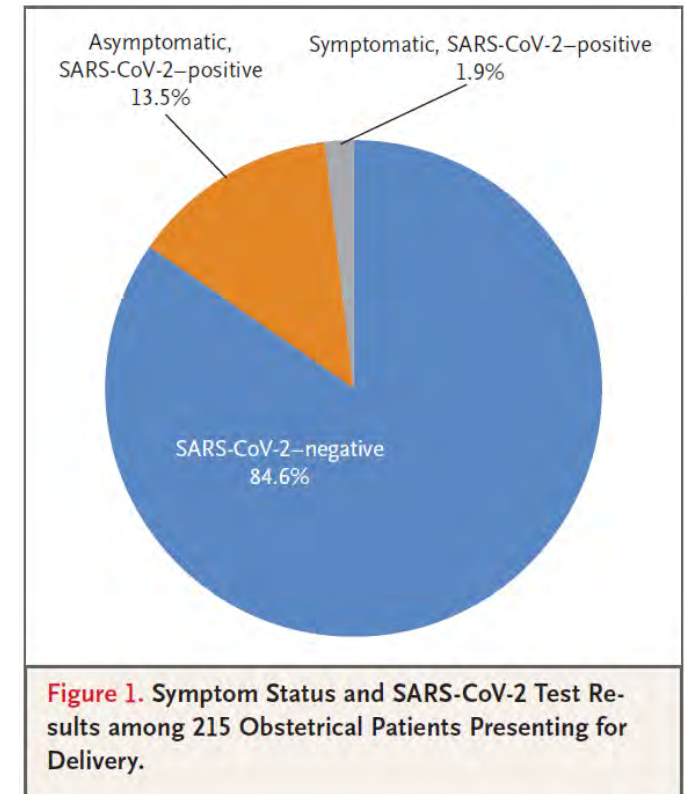
Summary of Data on COVID-19 in Pregnant Women



- 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%).

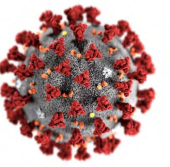
COVID-19 in Pregnant Women Can Be Asymptomatic

- 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 without 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.



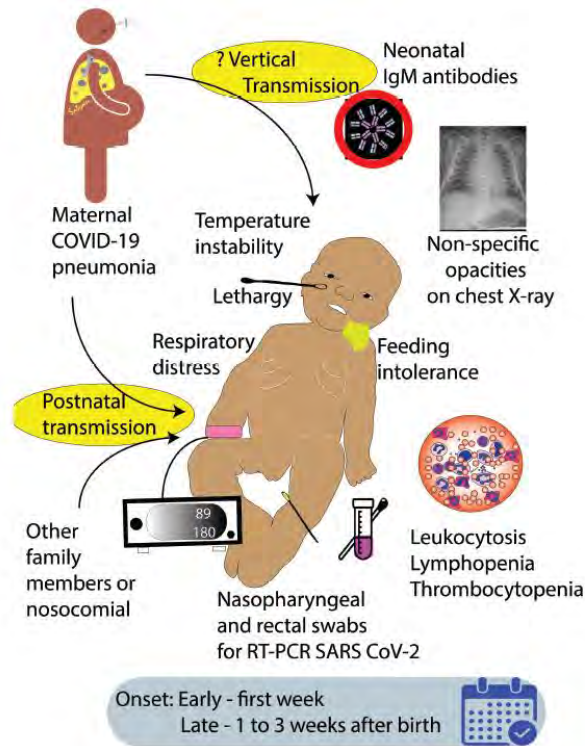


COVID-19 and Pregnancy Outcome



- 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*

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?

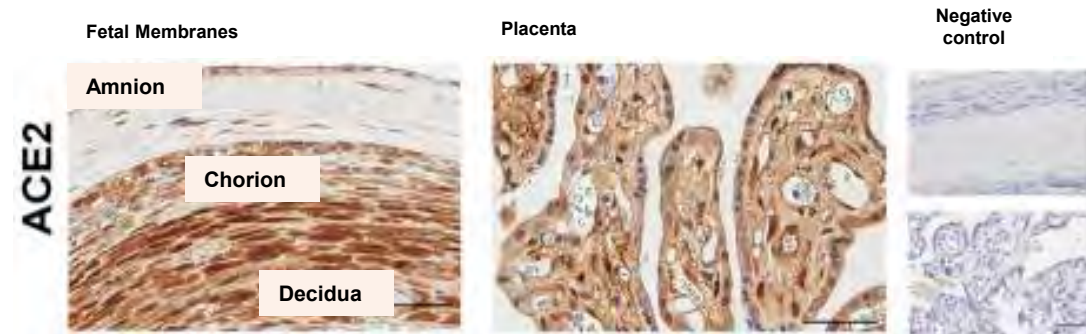
ACE2 Enzyme Can Be Found in the Placenta

- ACE-2 found in placenta localized to:

- decidua,
- syncytiotrophoblast,
- villous stroma;

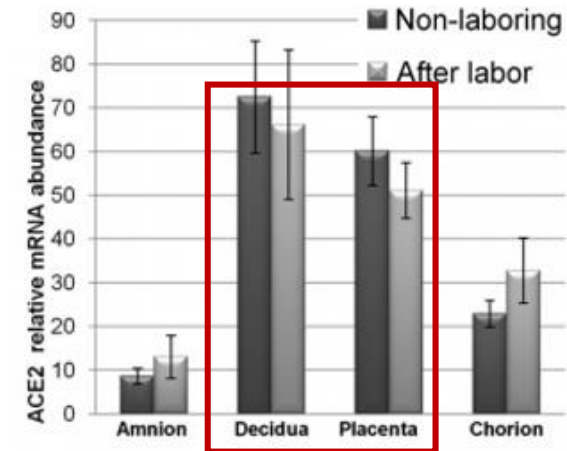
- ACE2 is most abundant in placenta in early gestation but is also identified at term.

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)



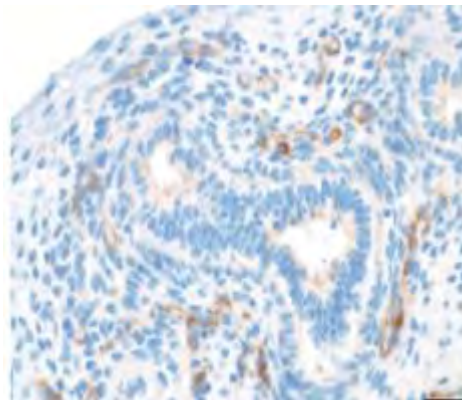
Marques FX et al. *Placenta*. 2011;32:214-21



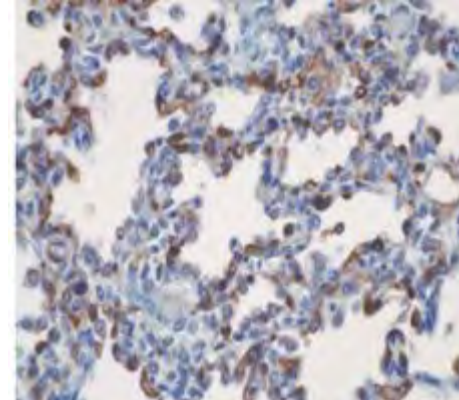
ACE2 Enzyme Can Be Found in the Fetal Lung

- 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.

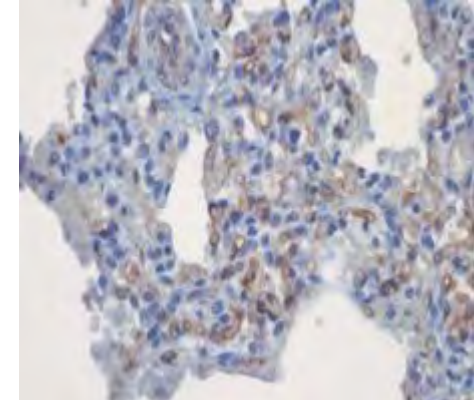
Immunohistochemical localization of ACE2 antibody
(brown = ACE2 presence) in fetal lung



12 weeks gestation



24 weeks gestation



6 weeks infant



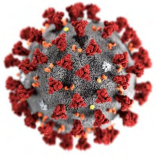
What About Intrapartum Transmission of SARS-CoV-2

- 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 ≥ 48 hours and negative at birth; *probable* is detection in NP or anal swab ≥ 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	<i>Within 24 hr</i>	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 $\geq$ 48 hrs in neonate not tested birth)



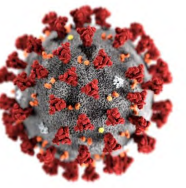
Feasibility of MTCT of SARS-CoV-2?



- 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.

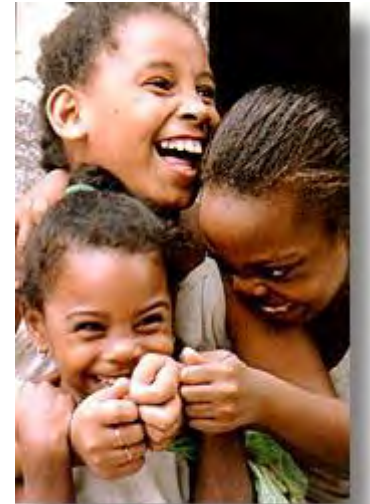
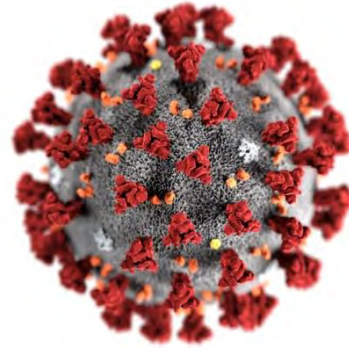


Summary



- 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!





COVID-19 and HIV in ESA region: Impact, implications and early programming experience

Laurie A. Gulaid
HIV/AIDS Advisor
UNICEF ESA Region
20 April 2020

OUTLINE

Context

Programming
priorities and early
implementation

Emerging needs
and asks

Country	# Reported Cases	# Reported Deaths	# Reported Recovered
South Africa	3,158	54	903
Kenya	270	14	67
Tanzania	170	7	11
Somalia	164	7	3
Rwanda	147	0	76
Madagascar	121	0	39
Ethiopia	108	3	16
Zambia	61	3	33
Uganda	55	0	28
Mozambique	39	0	8
Zimbabwe	25	3	2
Angola	24	2	6
Eswatini	22	1	8
Botswana	20	1	0
Malawi	17	2	3
Namibia	16	0	6
South Sudan	4	0	0
Lesotho	0	0	0
Total	4,421	97	1,209

SITUATION IN SELECT ESA COUNTRIES

(20/4/20 8AM)

<https://gisanddata.maps.arcgis.com/apps/opsdashboard/index.html#/bda7594740fd40299423467b48e9ecf6> (JHU)

GOVERNMENT RESPONSE MEASURES IN SELECT ESA COUNTRIES (AFRICA CDC 18/4/20)

Last updated	Country	Closure of educational institutions	Banning of mass gatherings, closure of public spaces	Limitations on prison and hospital visits	Curfew	Partial lockdown	National lockdown
April 13	Angola	yes	yes	yes			yes
April 13	Botswana	yes	yes				yes
April 18	Eswatini	yes	yes	yes			yes
April 13	Ethiopia	yes	yes	yes			
April 13	Kenya	yes	yes		yes	yes	
April 13	Lesotho	yes	yes				yes
April 13	Madagascar	yes	yes		yes		yes
April 18	Malawi	yes	yes		yes		yes
April 18	Mozambique	yes	yes	yes	yes		
April 13	Namibia	yes	yes			yes	
April 13	Rwanda	yes	yes				yes
April 18	Somalia	yes	yes		yes		
April 13	South Africa	yes	yes	yes			yes
April 13	South Sudan	yes	yes		yes		
April 13	Tanzania	yes	yes				
April 18	Uganda	yes	yes		yes		yes
April 13	Zambia	yes	yes				
April 13	Zimbabwe	yes	yes				yes

IMPLEMENTATION CONTEXT IN EASTERN AND SOUTHERN AFRICA

- Epicentre of global HIV epidemic
- Widespread poverty, young populations and areas of high population density
- Ongoing emergencies – drought, conflict, locusts, political unrest and economic distress.
- Weak health infrastructure and limited health workforce
- While the early and strong response measures may be controlling COVID-19, they are also affecting movement, prices and income, food security and availability/access to social services

PROGRAMMING CONSIDERATIONS

- Who and where are the most vulnerable populations and how can they be prioritized?
- What are the COVID-19 response measures in place and how do they affect service delivery and vulnerability?
- What are the short, medium and longer term needs?

OUTLINE

Context

Programming
priorities and early
implementation

Emerging needs
and asks

PRIORITY POPULATIONS

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

We do not know if PLHIV are more likely to acquire COVID-19 and we do not know for certain if there is a different disease progression for PLHIV.

We can infer that PLHIV who are immunosuppressed may be more at risk of complex and severe forms of COVID-19 and mortality.

May include children, adolescents and PBF women LHIV who are undiagnosed, not on ART, in treatment failure or unstable on ART and possibly young children who are exposed and uninfected

Estimated 425,000
children LHIV not on
ART

76% are in seven
countries:
South Africa,
Mozambique,
Kenya, Angola,
Uganda, Malawi
Tanzania

Unknown number of
adolescents LHIV not
on ART; issues with
adherence/VLS

Three countries
have the highest
AIDS-related
adolescent
deaths: Kenya,
South Africa,
Mozambique

Low retention /
seroconversion among
pregnant and
breastfeeding women
LHIV

National and
sub-national
stacked bar
analysis can
help to quantify
and locate these
women

Unknown
considerations for
10.6m children who are
HIV exposed and
uninfected

77% are in six
countries: South
Africa, Uganda,
Mozambique,
Tanzania,
Zimbabwe,
Kenya

UNAIDS July, 2019

PRIORITY POPULATIONS

PRIORITIES FOR HIV PROGRAMMING IN THE CONTEXT OF COVID-19

C

Continuity of HIV services and supplies

P

Prevention and protection for PLHIV and HWs

R

Research and documentation on HIV and COVID-19

CONTINUITY OF HIV SERVICES & SUPPLIES

Context

- Reports of declines in clinic attendance from several countries, even where exempt from lockdown (fear, transport)
- Redeployment of health workers to COVID-19 response
- Looming ARV shortages, possibly test kits too
- Community-based and outreach HIV services curtailed

Implementation

- Governments introducing modified and interim health care guidance around COVID-19 and HIV
- Ramping up MM refills and expanding eligibility criteria (though children, adolescents and pregnant women are often excluded from this guidance)
- Aligning MM refills guidance with the supply of ARVs
- Different models of community delivery of ARVs depending on movement restrictions and PPE availability
- Modifying clinic flow for physical distancing or separate service areas
- Less information on testing, but some promotion of self-testing
- Remote and virtual platforms being expanded for appointment tracking and adherence support (e.g., SMS, WhatsApp, U-report, etc.)

EMERGING NATIONAL GUIDANCE ON COVID-19 AND HIV SERVICE DELIVERY


Rapid Guidance on HIV Service Delivery in COVID-19 Context
Version 2: 26 March, 2020

**INTERIM GUIDANCE ON PROVISION OF HIV PREVENTION AND CARE SERVICES
IN THE CONTEXT OF COVID-19 OUTBREAK IN TANZANIA.**


**Interim Guidance for management of People Living with
HIV (PLHIV) in the context of COVID-19 Outbreak in
Ethiopia**

**UGANDA MINISTRY OF HEALTH COVID-19 INFECTION
PREVENTION AND CONTROL GUIDANCE FOR HIV/TB SERVICES
DELIVERY**

This guidance will continue to be updated as new guidance on COVID-19 evolves globally. The Ministry of Health emphasizes the importance of maintaining critical HIV/TB prevention, care and treatment services during COVID-19 to reduce vulnerability of PLHIV and TB infected people to COVID-19, ensure continuity of ART therapy and accelerated decongestion of health facilities to minimize transmission of COVID-19.


GAUTENG PROVINCE
HEALTH
REPUBLIC OF SOUTH AFRICA
**SBAH Department of Paediatrics and Obstetrics and Gynecology
COVID-19 - guideline for Paediatric Services**



Q&A on COVID-19, HIV and antiretrovirals
WHO Department of Global HIV, Hepatitis and STI Programmes

PREVENTION & PROTECTION FOR PLHIV & HWs

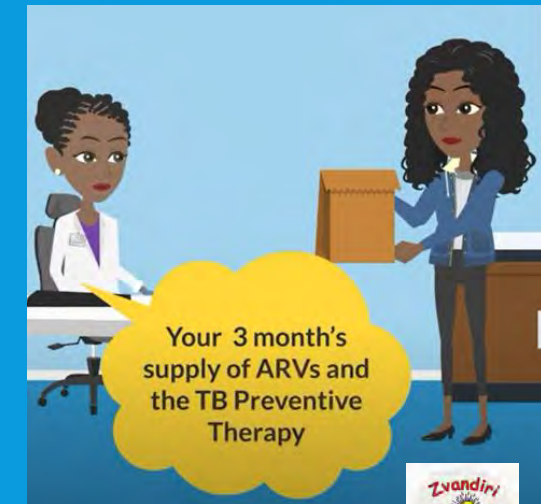
Context

- Limited supply of PPE and limited physical space for IPC at facilities
- Community-based peer support, teen clubs, other face-to-face activities halted in many countries
- Myths and misconceptions highly prevalent and creating fear

Implementation

- Procurement of PPE for HWs; emerging efforts as well for community cadres
- Tailored FAQs and other resources on COVID-19 prevention for PLHIV are being created and adapted to local context and target audience
- Radio, social media, phone-based and digital information and outreach, including tailored and interactive for adolescents
 - Reinforce prevention measures
 - Reduce misconceptions and myths
 - Provide MHPSS
- Engagement of PLHIV/ALHIV in the COVID-19 response

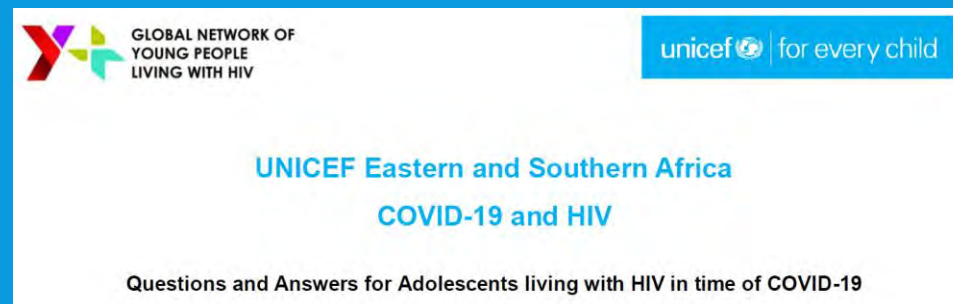
EMERGING INFORMATION FOR COMMUNITIES



COVID-19 and HIV: What you need to know

We realize that the COVID-19 pandemic is causing much uncertainty around the world, including for people living with and affected by HIV. Here you can find the latest HIV and COVID-19 related information and ways that you can [get involved](#).

What people living with HIV need to know about HIV and COVID-19



R ESEARCH & DOCUMENTATION ON HIV & COVID-19

Context

- No standard reporting form/template as yet for COVID-19 and HIV coinfection
- Limited COVID-19 testing coupled with difficulty identifying asymptomatic and mild cases challenges research efforts, especially for statistical analysis

Implementation

- Countries selecting and monitoring indicators to quickly detect lapses in service delivery, for example increases in missed appointments.
- Rapid assessments undertaken and being planned in some countries (KAP, Survey Monkey, etc).
- There is some planning underway for research of COVID-19 and HIV interaction (e.g., South Africa, INGOs).
- However, we have not yet explored this systematically or comprehensively and would welcome information on specific activities.

OUTLINE

Context

Programming
priorities and early
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Emerging needs
and asks

EMERGING NEEDS AND ASKS

Coordination

How can the rapidly emerging information resources, guidance and support be brought together more coherently to leverage greater impact and results?

Supply

With the expansion of MM refills and travel / movement restrictions, what can be done to prevent stockouts of ARVs and other supplies (e.g., test kits, SRH supplies)?

Innovation

What new ways can be found to provide services and support across the continuum while physically distancing? How can new approaches be rapidly evaluated?

Information

What indicators should be tracked on service continuity to rapidly detect declines? How can monitoring and research be promoted and standardized?

ACKNOWLEDGEMENTS

- UNICEF ESARO HIV/AIDS Team
- UNICEF COs in Angola, Botswana, Eswatini, Ethiopia, Kenya, Lesotho, Malawi, Mozambique, Namibia, Rwanda, South Africa, Tanzania, Uganda, Zambia and Zimbabwe and their respective Governments and implementing partners
- UNICEF HQ HIV/AIDS Team



The coronavirus is coming to Africa, and with creative actions, large and small, Africans are aiming to meet it head on.

*Wafaa M. El-Sadr, M.D., M.P.H.,
M.P.A., and Jessica Justman, M.D.*



THIS IS AN IMPORTANT WEEK

10-16 April

If we reach more than 90
new cases per day,
lockdown will continue.

(Average new daily cases
last week was 67)

**STAY
HOME**

SAVE SOUTH AFRICA

TOGETHER WE CAN BEAT THE CORONAVIRUS

LINKS TO SOME PROGRAMMING RESOURCES

For adolescents and young people

- <https://www.voicesofyouth.org/campaign/take-action-and-help-fight-covid-19>
- <http://www.yplusnetwork.org/resource/covid-19-and-hiv/>
- <https://ureport.in/>
- <https://www.internetofgoodthings.org/>
- <https://www.youtube.com/watch?v=-ap1XXyRolo&t=152s>
- [https://www.unfpa.org/sites/default/files/resource-pdf/COVID-19 Preparedness and Response - UNFPA Interim Technical Briefs Adolescents and Young People 23 March 2020.pdf](https://www.unfpa.org/sites/default/files/resource-pdf/COVID-19_Preparedness_and_Response_-_UNFPA_Interim_Technical_Briefs_Adolescents_and_Young_People_23_March_2020.pdf)

Pregnancy and COVID-19 with considerations for HIV

- https://www.unicef.org/southafrica/SAF_resources_COVID-19FAQs_pregnant_patients.pdf

COVID-19: HEALTH PROVIDER REALITIES ON THE FRONTLINE

ARE WE READY AND PREPARED?

Dr Patrick Oyaro
HIK, Kenya
PATA, South Africa

20 April 2020
UNICEF Children and AIDS Learning Collaborative
COVID-19:
What paediatric HIV Programmes need to know!



Health Innovations Kenya



Introduction



- **PATA and frontline health provider network COVID-19 survey**



- **HIK and Kenya: Reality on the ground**

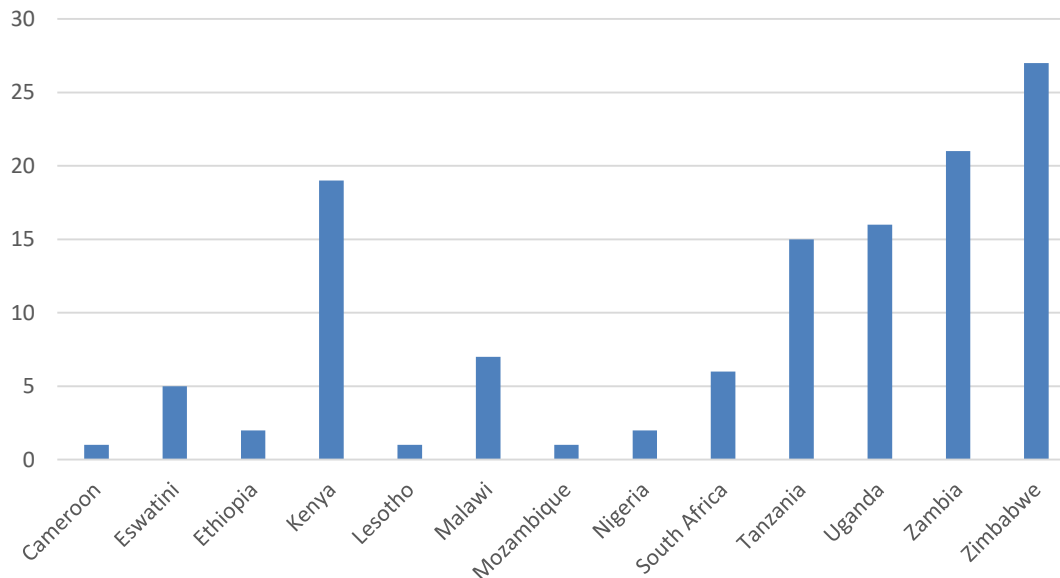
“The importance of frontline health providers, both in the community and the health facility, is greater now than ever. Health providers need to be equipped with information, resources and protection.”

Richard Kilonzo, PATA TA, Uganda

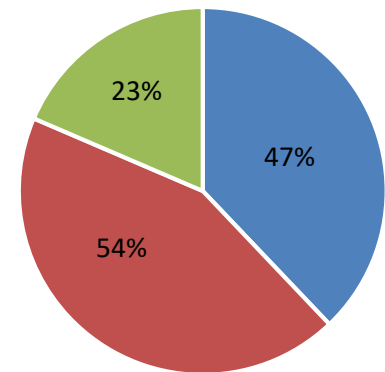
Preliminary Results PATA survey

- 124 respondents from ESA
- 97% provide HIV treatment and care services for children/adolescents

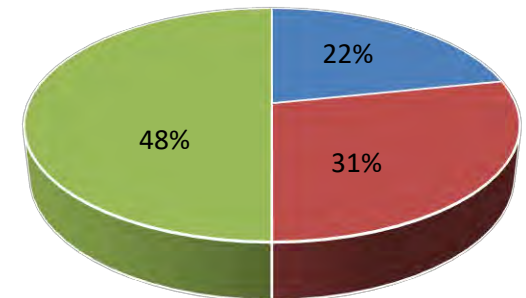
Initial survey results



Health facilities



■ primary ■ secondary ■ tertiary



■ peri-urban ■ rural ■ urban

Emerging themes: PATA survey

- 27% report to have 3+ month ARV supply and can provide MMD
- 13% of respondents say to have a triage systems in place
- 27% have hand wash stations/sanitizers in facility
- 64% report to have no COVID-19 test kits or screening ability
- Less than 4% have sufficient PPE masks/gowns gloves
- 71% clinics have no respirator support equipment

Emerging themes: PATA survey

- 23% do not have an SOP on COVID-19 screening/management in place and 60 % report they need more SOP
- 20% do not have an SOP on infection control, personal safety protocols and use of PPE and 62% report they need more
- 68% report their clinic is unprepared
- 95% + respondents report feeling stressed about COVID-19
- 50% indicate that the community needs sensitization and more information about COVID-19

Key themes: frontline health providers across the region

- Fear of the unknown/anxiety
- Guidance – is it filtering down?
- Information – overlooked or overloaded?
- Safety and lack of PPE
- Managing HIV services – not losing gains
- Mental health
- Multiple vulnerabilities

Frontline health providers – Your voice counts!

Please forward the survey in your networks! We have extended the survey to the 25th of April.

Complete one of the following:

- [English survey](#)
- [Portuguese survey](#)
- [French survey](#)
- [Swahili survey](#)



Thank You!

- Survey respondents
- Frontline health providers and peer supporters
- UNICEF and the Children and AIDS Learning Collaborative
- HIK, Kenya
- PATA, South Africa
- PATA Technical Assistants (TAs)

