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.
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.

<table>
<thead>
<tr>
<th>Virus</th>
<th>Genus</th>
<th>Disease</th>
<th>Discovery</th>
</tr>
</thead>
<tbody>
<tr>
<td>CoV-229E</td>
<td>Alpha</td>
<td>Mild respiratory infection</td>
<td>1967</td>
</tr>
<tr>
<td>CoV-NL-63</td>
<td>Alpha</td>
<td>Mild respiratory infection</td>
<td>1965</td>
</tr>
<tr>
<td>COV-HKU-1</td>
<td>Beta</td>
<td>Mild respiratory infection; pneumonia</td>
<td>2005</td>
</tr>
<tr>
<td>CoV-OC43</td>
<td>Beta</td>
<td>Mild respiratory infection</td>
<td>2004</td>
</tr>
<tr>
<td>SARS-CoV</td>
<td>Beta</td>
<td>Severe acute respiratory infection, 10% mortality</td>
<td>2003</td>
</tr>
<tr>
<td>MERS-CoV</td>
<td>Beta</td>
<td>Severe acute respiratory infection, 37% mortality</td>
<td>2012</td>
</tr>
<tr>
<td>SARS-CoV-2</td>
<td>Beta</td>
<td>Severe acute respiratory infection, 72% mortality</td>
<td>2019</td>
</tr>
</tbody>
</table>


Terminology

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

- COVID-19 (Coronavirus Disease 2019) 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).

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**Gheblawi M et al.** Circ Res. 2020 Apr 8
**PACKAGING**

Products enter endoplasmic reticulum Golgi intermediate compartment: assemble 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

**FUSION**

Endosomal Pathway

**RNA TRANSLATION**

by host ribosomes into proteins

**PROTEOLYSIS**

polypeptides cleaved by viral specific protease

**TRANSCRIPTION**

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

- Non-structural proteins (16)
- Structural proteins (spike, membrane, envelope, nucleocapsid, accessory)

**VIRION RELEASE**

Exocytosis fusion of virion vesicle with plasma membrane and release

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National Geographic: https://www.nationalgeographic.com/science/2020/03/covid-overview-coronavirus/

Prajapat M et al. Indian J Pharmacol. 2020;52:56-65
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.
Rapid spread outside of Wuhan to rest of China.

Then spread outside of China to current global pandemic.
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

Mortality 1%-3.8%?

Risk factors:
- Older age
- Male sex
- Comorbidity

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

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

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**Stage I (Early Infection)**
- Viral response phase
- Severity of illness

**Stage II (Pulmonary Phase)**
- Host inflammatory response phase
- Time course

**Stage III (Hyperinflammation Phase)**
- "Cytokine storm"

**Clinical symptoms**
- Mild constitutional symptoms
  - Fever >99.6°F
  - Dry cough, headache, diarrhea
  - Loss of taste and/or smell

**Clinical signs**
- Lymphopenia, increased prothrombin time, increased D-dimer and LDH (mild)

**Mild constitutional symptoms**
- Fever >99.6°F
- Dry cough, headache, diarrhea
- Loss of taste and/or smell

**Moderate constitutional symptoms**
- Shortness of breath, dyspnea, hypoxia

**Severe constitutional symptoms**
- ARDS
- Systemic inflammatory response syndrome/shock
- Cardiac failure

**No Sx**
- 1%

**Mild**
- 81%

**Moderate-Severe**
- 14%

**Critical**
- 5%

**Zhang W. JAMA 2020**
Feb 24 epub
72,314 cases China
SARS-CoV-2 Can Affect Organs Other than Respiratory Tract

- Acute cerebrovascular disease, impaired consciousness, skeletal muscle injury
- Constrictive pericarditis
- Acute Cardiac Injury
- Hypoxemia
- Dyspnoea, Lymphopenia
- Diarrhoea
- Conjunctivitis
- Smell, taste
- Respiratory Disorders
  - Rhinorrhea, Sneezing, Sore Throat
  - Pneumonia
  - Ground-glass Opacities
  - RNAemia, Acute Respiratory Distress Syndrome
  - Kidney

Modified from: Guo YR. Mil Med Res 2020 Mar 13;7:11
## Risk Factors for Severe Disease/Poor Outcome of COVID-19 Disease

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

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.

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

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

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

<table>
<thead>
<tr>
<th>Type of Test</th>
<th>Meaning</th>
<th>Value</th>
<th>Beneficiary</th>
</tr>
</thead>
</table>
| 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.*  

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

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)
- **Immune response modifiers**
- **Remdesivir** & **favipiravir** inhibits viral RNA polymerase
- **LPV/r** (& other PI, ATV, DRV) inhibit protease enzyme
- **Immune Response Modifiers** (modulate “cytokine storm”)
  - Tocilizumab
  - Sarilumab
  - Zitievikumab

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

*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

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

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

CONCLUSIONS

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 or 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

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 51 patients (70%). 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

This article is a preprint and has not been peer reviewed or certified by a review process. It is intended to present preliminary findings.

Chloroquine diphosphate in two different dosages as adjuvant 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 (Cova-Covid19 Study)

The high dose (550 mg/day) presented more QTc +50ms (7.5%), and a trend toward higher lethality (1.7%) than the lower dose. Mortality rate was 14.3% (5/35) vs 6.23% (3/48), overlapping with the CI of historical data from similar patients not using diphosphate. In 3/14 patients with paired samples, respiratory secretion at day 4 was negative in only one patient.
SARS-CoV-2/ COVID-19 in Children
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

<table>
<thead>
<tr>
<th>Country/Reference</th>
<th>Total # COVID-19 Cases</th>
<th># Children 0-19 yr (% of total cases)</th>
<th>Proportional Age Distribution Among Pediatric COVID-19 cases</th>
</tr>
</thead>
<tbody>
<tr>
<td>China (China CDC)1</td>
<td>44,672</td>
<td>965 (2% )</td>
<td>416 (43%)</td>
</tr>
<tr>
<td>China (Dong, Pediatrics)2</td>
<td>-</td>
<td>2,141</td>
<td>1,393 (65%)</td>
</tr>
<tr>
<td>Italy (Italy website)3</td>
<td>42,220</td>
<td>507 (1.2%)</td>
<td>-</td>
</tr>
<tr>
<td>US (MMWR)4</td>
<td>149,760</td>
<td>2,572 (1.7%)</td>
<td>1,077 (42%)</td>
</tr>
<tr>
<td>Japan (Mizumoto. MedRxiv)5</td>
<td>294</td>
<td>10 (3.4%)</td>
<td>-</td>
</tr>
<tr>
<td>Korea (COVID team. MedRxiv)6</td>
<td>7,755</td>
<td>480 (6.2%)</td>
<td>75 (16%)</td>
</tr>
<tr>
<td>Iceland (Gudbjartsson.NEJM)7</td>
<td>9,199 targeted</td>
<td>38 (0.4%)</td>
<td>(38)</td>
</tr>
<tr>
<td>Madrid (Taggaro JAMA Ped)8</td>
<td>4,695</td>
<td>41 (0.8%)</td>
<td>-</td>
</tr>
<tr>
<td><strong>TOTAL</strong></td>
<td><strong>258,595</strong></td>
<td><strong>4,613 (1.8%)</strong></td>
<td><strong>2961/6158 (48%)</strong></td>
</tr>
</tbody>
</table>

* 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 10-19 yr.

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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  
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).

<table>
<thead>
<tr>
<th>Country/ Author</th>
<th>Age at admit</th>
<th>Initial symptoms</th>
<th>Exposure</th>
<th>SARS-CoV-2 testing</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>China/Wei</td>
<td>9 pt: 8 wk-11 mo</td>
<td>4/9 fever; 3/9 mild URI, 1/9 no symptoms</td>
<td>Yes</td>
<td>NP rtPCR +</td>
<td>Did well, d/c</td>
</tr>
<tr>
<td>China/Cui</td>
<td>55 d</td>
<td>URI, cough, no fever, CT abnl</td>
<td>Yes</td>
<td>NP rt PCR+ high titer</td>
<td>d7 liver, cardiac injury, supplemental O₂, d/c</td>
</tr>
<tr>
<td>Korea/Han</td>
<td>27 d</td>
<td>Fever, vomiting, mild cough, CXR nl</td>
<td>Yes</td>
<td>NP, oral, plasma, urine, stool, saliva rtPCR + high titer</td>
<td>Did well, d/c</td>
</tr>
<tr>
<td>Iran/Mogharab, Aghdam</td>
<td>2 pt: 15 d, 75 d</td>
<td>2/2 fever, 1/2 Cough, 1 CXR abnl, 1 CXR nl</td>
<td>Yes</td>
<td>NP rtPCR +</td>
<td>Required O₂, d/c</td>
</tr>
<tr>
<td>Italy/Canarutto</td>
<td>32 d</td>
<td>URI sx, fever, CXR nl</td>
<td>Yes</td>
<td>NP rt PCR+</td>
<td>Did well, d/c</td>
</tr>
<tr>
<td>New York/Robbins, Paret</td>
<td>3 pt: 25, 56, 58 d</td>
<td>Fever (all), no respiratory sx, CXR nl</td>
<td>2 Yes 1 No</td>
<td>NP rtPCR+</td>
<td>Did well, d/c</td>
</tr>
<tr>
<td>Vietnam/Le</td>
<td>3 mos</td>
<td>URI sx, fever, CXR nl</td>
<td>Yes</td>
<td>NP rtPCR+</td>
<td>Did well, d/c</td>
</tr>
<tr>
<td>Singapore/Kam</td>
<td>6 mos</td>
<td>No symptoms</td>
<td>Yes</td>
<td>NP rtPCR+</td>
<td>Did well, d/c</td>
</tr>
</tbody>
</table>

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  
Aghdam MK et la. Infect Dis. 2020 Apr 1

Canarutto D et al. Ped Pulmon. 2020 Mar 19  
Paret M et al. Clin Infect Dis. 2020 Apr 17  
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 $\geq 12$ 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

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

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

Not Resolved Yet:
Are children less susceptible to SARS-CoV-2?
Or are they less symptomatic with similar rates infection?

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%)
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).

    - 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.
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](image)

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)
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)

<table>
<thead>
<tr>
<th>Specimens tested by rtPCR</th>
<th># Papers with data</th>
<th>Number/total sample</th>
<th>Percent</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nasopharyngeal (NP) swab “newborn”</td>
<td>36</td>
<td>12/337</td>
<td>4%</td>
</tr>
<tr>
<td>Amniotic fluid</td>
<td>8</td>
<td>0/24</td>
<td>0%</td>
</tr>
<tr>
<td>Placenta</td>
<td>10</td>
<td>0/14</td>
<td>0%</td>
</tr>
<tr>
<td>Cord blood</td>
<td>11</td>
<td>0/31</td>
<td>0%</td>
</tr>
<tr>
<td>Infant gastric aspirate</td>
<td>2</td>
<td>0/11</td>
<td>0%</td>
</tr>
<tr>
<td>Infant stool</td>
<td>9</td>
<td>5/59</td>
<td>8%</td>
</tr>
<tr>
<td>Maternal breast milk</td>
<td>11</td>
<td>0/40</td>
<td>0%</td>
</tr>
<tr>
<td>Maternal vaginal swab</td>
<td>4</td>
<td>0/6</td>
<td>0%</td>
</tr>
</tbody>
</table>
Proposed Definitions for MTCT (Simplified)

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?

<table>
<thead>
<tr>
<th>Cases</th>
<th>Mom</th>
<th>Infant Sx</th>
<th>Birth sample</th>
<th>Type sample</th>
<th>Timing +</th>
<th>Later Tests</th>
</tr>
</thead>
<tbody>
<tr>
<td>Virologic test +</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>+</td>
<td>Yes? resp distress birth</td>
<td>NO</td>
<td>NP</td>
<td>8 d</td>
<td>Negative 6 d</td>
</tr>
<tr>
<td>2</td>
<td>+</td>
<td>No clinical sx, +CXR</td>
<td>NO</td>
<td>NP</td>
<td>3 d</td>
<td>Negative 4, 8, 15 d</td>
</tr>
<tr>
<td>3</td>
<td>+</td>
<td>No clinical sx, +CXR</td>
<td>NO</td>
<td>NP</td>
<td>36 hr</td>
<td>Negative 14 d</td>
</tr>
<tr>
<td>4</td>
<td>+</td>
<td>No clinical sx, +CXR, lab</td>
<td>NO</td>
<td>NP</td>
<td>36 hr</td>
<td>Negative 14 d</td>
</tr>
<tr>
<td>5</td>
<td>+</td>
<td>No clinical sx, +CXR, lab</td>
<td>NO</td>
<td>NP</td>
<td>2 d</td>
<td>Negative 14 d</td>
</tr>
<tr>
<td>6</td>
<td>+</td>
<td>No clinical sx, +CXR</td>
<td>NO</td>
<td>NP</td>
<td>2 &amp; 4 d</td>
<td>Negative 6 d</td>
</tr>
<tr>
<td>7</td>
<td>+</td>
<td>Yes</td>
<td>NO</td>
<td>NP</td>
<td>2 &amp; 4 d</td>
<td>Negative 7 d</td>
</tr>
<tr>
<td>8-9</td>
<td>+</td>
<td>Unclear, ?+CXR</td>
<td>Maybe?</td>
<td>NP</td>
<td><strong>Within 24 hr</strong></td>
<td>No information</td>
</tr>
<tr>
<td>10-11</td>
<td>+</td>
<td>1 SOB, 1 no sx, both +CT</td>
<td>NO 30 hrs, ?5 d</td>
<td>NP</td>
<td><strong>30 hr, ?5 d</strong></td>
<td>Negative ~2 wk</td>
</tr>
</tbody>
</table>

### Immunologic test +

<table>
<thead>
<tr>
<th>Cases 1-7</th>
<th>all IgM+ at or ~ birth</th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>+</td>
<td>NO</td>
<td>Few hours</td>
<td>Blood and NP</td>
<td>None +</td>
<td>All samples negative</td>
<td></td>
</tr>
</tbody>
</table>

- 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)

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