COVID-19: What Paediatric HIV Programmes Need to Know

Webinar 3
Planning for Reopening

The webinar will begin shortly. Visit us on: childrenandaids.org/covid19

Adjust your speaker volume
Keep your microphones muted
Type questions for panelists in the Q&A box
Type comments in the chat box
COVID-19: What Pediatric HIV Programs Need to Know

Epidemiologic and Scientific Updates on SARS CoV-2 and Children

Lynne M. Mofenson, M.D.
Please Note that Data Still Continue to be Preliminary, Some of Poor Quality, and Change Almost Daily

HOW TO INTERPRET THE DELUGE OF DATA?
What is New:

SARS-CoV-2/COVID-19 and HIV
17 studies; 146 HIV/COVID-19 coinfected adults from 9 countries: China, Italy, Germany, Spain, Turkey, Singapore, US; 2 case reports from Africa (S Africa, Uganda).

Pooled prevalence (3 studies) of HIV in SARS-CoV-2 cases was 1% (comparable to the 0.6-0.8% prevalence in general population).

65% had at least one comorbidity, most common hypertension (26%), hyperlipidemia (15%), diabetes, HBV/HBC, respiratory disease (10% each).

Symptoms similar to overall population: fever 74%, cough 57%, dyspnea 13%, diarrhea 10%; abnormal chest radiology 54%.

Disease severity: mild 56%; moderate 16%; severe 24%; critical 4%.
**Systematic Review COVID-19 and HIV**


Pooled mortality among HIV/SARS-CoV-2 coinfection cases: 9% (95% CI 3-15%)

Pooled mortality general population COVID-19: 5.6% (95% CI 2.5-12.5%)

*Pormohammad A. Rev Med Virol 2000 June 5 - 20 studies 52,251 pt*
COVID-19 in HIV+ vs HIV-Negative Adults, New York City
Karmen-Tuohy S et al. JAIDS. 2020 June 12 (epub)

- EMR data for hospitalized patients admitted to NYU between Mar 2-Apr 23.
- Matched 21 HIV+ with 42 non-HIV patients (by admission date, age, BMI, gender, smoking, history chronic renal/heart disease, COPD, hypertension or asthma).
- All HIV patients were on ART and 15/17 had HIV RNA <50.
- More HIV patients had consolidation on CXR and a non-statistically significant higher proportion of HIV patients required ICU care, mechanical ventilation or died/hospice compared to non-HIV cohort.

<table>
<thead>
<tr>
<th></th>
<th>HIV-positive N=27</th>
<th>HIV-negative N=42</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abnormal CXR</td>
<td>19 (91%)</td>
<td>27 (64%)</td>
<td>0.027</td>
</tr>
<tr>
<td>Needed ICU</td>
<td>6 (29%)</td>
<td>7 (17%)</td>
<td>0.271</td>
</tr>
<tr>
<td>Mechanical ventilation</td>
<td>5 (24%)</td>
<td>5 (12%)</td>
<td>0.223</td>
</tr>
<tr>
<td>Died/transfer hospice</td>
<td>6 (29%)</td>
<td>10 (24%)</td>
<td>0.682</td>
</tr>
</tbody>
</table>

- Overall findings suggest HIV status did not significantly impact clinical outcomes but further study needed.
HIV, TB and COVID-19 in Adults, South Africa

- Used Western Cape routine public sector data (unique identifier across systems) to look at factors for risk of COVID-19 death in 342 adults age >20 years with confirmed COVID-19 who had died.

→ How much more likely are you to die from COVID-19 if you have vs don’t have a risk factor?

<table>
<thead>
<tr>
<th>Patient characteristics</th>
<th>Adjusted Hazard ratio</th>
<th>95% Confidence Interval</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex</td>
<td></td>
<td></td>
</tr>
<tr>
<td>female</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>male</td>
<td>1.40</td>
<td>1.16; 1.70</td>
</tr>
<tr>
<td>Age</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;40 years</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>40-49 years</td>
<td>3.12</td>
<td>1.88; 5.17</td>
</tr>
<tr>
<td>50-59 years</td>
<td>9.92</td>
<td>6.34; 15.54</td>
</tr>
<tr>
<td>60-69 years</td>
<td>13.55</td>
<td>8.55; 21.48</td>
</tr>
<tr>
<td>≥70 years</td>
<td>19.53</td>
<td>12.20; 31.26</td>
</tr>
<tr>
<td>Non-communicable diseases</td>
<td></td>
<td></td>
</tr>
<tr>
<td>none</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>diabetes well controlled (HbA1c &lt;7%)</td>
<td>4.65</td>
<td>3.19; 6.79</td>
</tr>
<tr>
<td>diabetes poorly controlled (HbA1c 7-9%)</td>
<td>8.99</td>
<td>6.65; 12.14</td>
</tr>
<tr>
<td>diabetes uncontrolled (HbA1c ≥10%)</td>
<td>13.02</td>
<td>10.06; 16.87</td>
</tr>
<tr>
<td>diabetes – no measure of control</td>
<td>3.34</td>
<td>2.25; 4.88</td>
</tr>
<tr>
<td>hypertension</td>
<td>1.40</td>
<td>1.18; 1.71</td>
</tr>
<tr>
<td>chronic kidney disease</td>
<td>2.02</td>
<td>1.55; 2.62</td>
</tr>
<tr>
<td>chronic pulmonary disease</td>
<td>0.98</td>
<td>0.75; 1.30</td>
</tr>
<tr>
<td>Tuberculosis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>never tuberculosis</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>previous tuberculosis</td>
<td>1.41</td>
<td>1.05; 1.90</td>
</tr>
<tr>
<td>current tuberculosis</td>
<td>2.58</td>
<td>1.53; 4.37</td>
</tr>
<tr>
<td>HIV</td>
<td></td>
<td></td>
</tr>
<tr>
<td>negative</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>positive</td>
<td>2.75</td>
<td>2.09; 3.61</td>
</tr>
</tbody>
</table>

Adjusted Hazard Ratio

No difference in risk by viral suppression
HIV, TB and COVID-19 in Adults, South Africa


- Older age and comorbidities increase risk of COVID-19 death – particularly uncontrolled diabetes, hypertension and renal disease.

- Modest 2-2.5 times increased risk of COVID 19 death associated with HIV and TB compared to those without HIV or TB.
  - May be over-estimated as haven’t fully disentangle all comorbidities and risks (e.g., overweight, socioeconomic status)

- Effect HIV or TB smaller than effect of other comorbidities; those with HIV and TB tend to be younger, where overall risk of COVID-19 death is lower.

- Overall, <10% of COVID-19 deaths are due to HIV.
No Data on Children or Adolescents with HIV and SARS-CoV-2/COVID-19 Coinfection To Date
What is New: Treatment of SARS-CoV-2/COVID-19
Chloroquine/Hydroxychloroquine

Doesn't work in animal models
...do not support the use of HCQ in prophylaxis/treatment COVID-19

Doesn't work in severe disease
...do not support its use in patients...who require oxygen...

Doesn't work in mild disease
...do not support its use...
...adverse events higher...

A Randomized Trial of Hydroxychloroquine as Postexposure Prophylaxis for Covid-19

Doesn't works as PEP
...did not prevent illness...

Adverse cardiac effects are observed
...raises safety concerns...high risk QTc prolongation
**Chloroquine/Hydroxychloroquine**

NIH Halts Hydroxychloroquine Study; Says 'unlikely' to Help COVID-19 Patients

June 20, 2020 - 4:52 PM ET

**FDA Withdraws Emergency Use Authorization For Hydroxychloroquine**

June 15, 2020 - 2:30 PM ET

Doesn’t work as PEP…did not prevent illness…

Conclusions:
After high-risk or moderate-risk exposure to Covid-19, hydroxychloroquine did not prevent illness compatible with Covid-19 or confirmed infection when used as postexposure prophylaxis within 4 days after exposure. (Funded by David Bazzucki and Jan Ellison Bazzucki and others; ClinicalTrials.gov number, NCT04308668.)
Remdesivir is a nucleotide analogue given intravenously for 10 days (200 mg loading dose, then 100 mg/day) with moderate efficacy shown in RCT.
Remdesivir is a nucleotide analogue given intravenously for 10 days (200 mg loading dose, then 100 mg/day) with moderate efficacy shown in RCT.

- Viral shedding URT not reduced
- Viral load in lungs lowered
- Reduction in damage to lungs

...remdesivir initiated early during infection had a clinical benefit in SARS-CoV-2 infected rhesus macaques...

Severe-critical illness
(57% ventilated, 8% ECMO)

Clinical improvement in 36/53 (68%) with treatment (no control group)

Severe disease hospitalized with pneumonia (25% ventilated or ECMO)

Superior to placebo in shortening time to recovery (11 vs 15 d) and trend for reduced mortality (21 vs 27%)

Severe disease hospitalized with pneumonia

Did not show difference between 5- and 10-day course in time to clinical recovery or death
Remdesivir

→ Safe use in pregnancy

Compassionate use remdesivir for treatment of severe COVID-19 in pregnant women at a United States academic center

Jennifer A. McCoy, MD, William R. Short, MD, MPH, Sindhu K. Srinivas, MD MSCE, Lisa D. Levine, MD MSCE, Adi Hirshberg, MD

→ Clinical trial in children to begin

Gilead to enroll pediatric patients for late-stage remdesivir study

→ New formulation – inhaled via nebulizer is under study
Dexamethasone

- UK RECOVERY Trial: Large RCT of possible treatments for hospitalized patients with COVID-19
  - Started March 2020; >11,500 participants have been randomized to SOC vs HCQ (stopped), low dose dexamethasone (6 mg), LPV/r, azithromycin, tocilizumab, convalescent plasma
  - DSMB stopped dexamethasone arm for efficacy (including survival) (still enrolling children)

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Effect of Dexamethasone in Hospitalized Patients with COVID-19 – Preliminary Report

**RECOVERY Collaborative Group**

**All participants (n=6425)**

- RR 0.83 (95% CI 0.74–0.92), p<0.001
  - 17% reduction mortality

**Oxygen only (n=3883)**

- RR 0.80 (95% CI 0.70–0.92), p=0.002
  - 20% reduction mortality

**Invasive mechanical ventilation (n=1007)**

- RR 0.65 (95% CI 0.51–0.82), p=0.001
  - 35% reduction mortality

**No oxygen received (n=1535)**

- RR 1.22 (95% CI 0.93–1.61), p=0.14
  - Not severely ill - NO reduction mortality
Key U.S. medical group adds steroids to COVID-19 treatment guidelines

Infectious Diseases Society of America Guidelines on the Treatment and Management of Patients with COVID-19

updated 6/25/20

Recommendation 4. Among hospitalized patients with severe* COVID-19, the IDSA guideline panel suggests glucocorticoids rather than no glucocorticoids. (Conditional recommendation, Moderate certainty of evidence)

- **Remark:** Dexamethasone 6 mg IV or PO for 10 days (or until discharge if earlier) or equivalent glucocorticoid dose may be substituted if dexamethasone unavailable. Equivalent total daily doses of alternative glucocorticoids to dexamethasone 6 mg daily are methylprednisolone 32 mg and prednisone 40 mg.

Recommendation 5. Among hospitalized patients with COVID-19 without hypoxemia requiring supplemental oxygen, the IDSA guideline panel suggests against the use of glucocorticoids. (Conditional recommendation, Low certainty of evidence)

*Severe illness is defined as patients with SpO₂ ≤94% on room air, and those who require supplemental oxygen, mechanical ventilation, or ECMO.
What Are Children With COVID-19 Being Treated With?

- Weekly survey of 87 participating pediatric ICUs in 21 countries to understand clinical practices related to COVID-19 in children

- >50% anticoagulation prophylaxis (primarily low molecular weight heparin or aspirin)
- >50% remdesivir (compassionate use)
- >20% intravenous steroids
- >10% azithromycin, IVIG
Update: SARS-CoV-2/COVID-19 in Children

Demographics/Epidemiology
COVID-19 Incidence in Children Remains Low but Significant Variation

- Country online databases indicate broad range COVID-19 burden in those <20 years as a share of national caseloads (1%-23%).
  - Higher in low/middle-income compared to high-income countries (~11% vs 7%).
  - Note rates in Africa and Brazil, where epidemic just accelerating.

- There may be differing policies in countries related to SARS-CoV-2 diagnostic testing (children less likely tested if testing is confined to individuals with severe disease).

- Accurate, age-disaggregated data are critical to better understand the geographic variations & age distribution in children.
Global Lack of Age-Disaggregated Data

- Difficult to determine proportional age breakdown within age 0-19 years.
- Data limited and existing reports often use different age categories.
- National data on lab-confirmed cases in US and China have been published.
- Cases diagnosed across all age categories – neonates to adolescents, with ~55% in adolescent (age >10 years) age group.

<table>
<thead>
<tr>
<th>Country</th>
<th>Total Pediatric Cases</th>
<th>&lt;1</th>
<th>1-5</th>
<th>6-9</th>
<th>10-14</th>
<th>15-17</th>
</tr>
</thead>
<tbody>
<tr>
<td>USA ¹</td>
<td>2,572</td>
<td>398 (15%)</td>
<td>291 (11%)</td>
<td>388 (15%)</td>
<td>682 (27%)</td>
<td>813 (32%)</td>
</tr>
<tr>
<td>China ²</td>
<td>731</td>
<td>86 (12%)</td>
<td>137 (19%)</td>
<td>171 (23%)</td>
<td>180 (25%)</td>
<td>157 (21%)</td>
</tr>
<tr>
<td>Total</td>
<td>3,303</td>
<td>484 (15%)</td>
<td>428 (13%)</td>
<td>559 (17%)</td>
<td>862 (26%)</td>
<td>970 (29%)</td>
</tr>
</tbody>
</table>

¹ CDC COVID-19 Response Team. MMWR 2020 Apr 6
² Dong Y et al. Pediatrics. 2020 Mar 16
Race/Ethnicity and SARS-CoV-2 Infection

- In US and UK, COVID-19 disease more common among black and ethnic minority adults \((\text{Price-Haywood EG. NEJM. 2020 May 27, de Lusignan S. Lancet Infect Dis. 2020 May 15}).\)
- Limited data in children (most pediatric studies do not report race/ethnicity).

→ Chicago: 474 children tested for SARS-CoV-2 Rush University March-April 2020

- 25/474 (5.3%) positive; 6.8% black, 6.6% Hispanic vs 1.7% white children
- On logistic regression, black race (OR 3.1, 95% CI 1.2-5.3) and older age (OR 1.09, 95% CI 1.1-1.8) were risk factors for SARS-CoV-2 positivity
Race/Ethnicity and SARS-CoV-2 Infection

- Racial disparity in COVID-19 disease may reflect
  - Socioeconomic, demographic, and contact patterns/environmental factors (e.g., household size and composition) increasing exposure risk
  - higher prevalence chronic comorbidities (e.g., hypertension) in minority populations
  - undefined biologic factors

- Disproportionate representation of children of color is concerning given the extension of the pandemic from high-income to low- and middle-income countries.

- At a minimum, studies of SARS-CoV-2 in children (and adults) should report on race/ethnicity, and further studies need to evaluate reasons for this disparity in infection/disease.
Importance of Sociodemographic Factors in SARS-CoV-2 Infection: Evaluation of Factors for Infection in Pregnant Women, New York City

Emeruwa UN et al. JAMA. 20-20 Jun 18:e2011370

- Cross-sectional evaluation of 434 NYC pregnant women delivering at 2 NYC hospitals doing universal SARS-CoV-2 viral screening; 71 (18%) tested positive.

- Able to link 396 of those tested (91%) to SES and demographic data; probability of infection associated with:

  - Neighborhood Median Household Income
  - Neighborhood Unemployment Rate
  - Neighborhood # Residents/Unit
  - Neighborhood % with >1 resident/room
SARS-CoV-2/COVID-19 in Children

Clinical Manifestations of Disease
Aspects of SARS-CoV-2 in Large Pediatric Health Care Network, US


- Children’s Hospital of Philadelphia Care Network, CHOP pediatric hospital plus large ambulatory care network with >1 million pt/yr encounters.
- Electronic records extracted for 7,256 children/youth <21 years with valid SARS-CoV-2 test result from Mar 9-Jun 1 2020.

→ 39% tests came from drive-through test sites; 32% ER; 15% OPD; 11% in-patient; 3% urgent care.

→ 424 (5.8%) rtPCR positive

→ 54/424 (13%) had no symptoms

→ 242 (57%) comorbidity; most common asthma (21%), obesity (13%), mental health (9%), neurologic disease (6%)
**Characteristics of 424 Children with SARS-CoV-2, US**


- Infected children were older
  - Median age 10 yr vs 5.9 yr all tested
  - Highest positivity age 18-21 yr, followed by 12-17 yr.
- African American children more likely to test positive than children of other race/ethnicity
- Children screened due to symptoms or known exposure more likely test positive, 21%.
- 3.8% of children undergoing universal screening regardless of symptoms were infected

### Table: Characteristics of 424 Children with SARS-CoV-2, US

<table>
<thead>
<tr>
<th>Number, n</th>
<th>Total Tests</th>
<th>Positive Tests</th>
<th>Percent Positive (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age in years, median (IQR)</td>
<td>7256</td>
<td>424</td>
<td>5.8%</td>
</tr>
<tr>
<td>Age Group</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0-12 months, n (%)</td>
<td>1193 (16.4%)</td>
<td>70 (16.5%)</td>
<td>5.9%</td>
</tr>
<tr>
<td>1-5 years, n (%)</td>
<td>2456 (33.8%)</td>
<td>96 (22.6%)</td>
<td>3.9%</td>
</tr>
<tr>
<td>6-11 years, n (%)</td>
<td>1535 (21.2%)</td>
<td>77 (18.2%)</td>
<td>5.0%</td>
</tr>
<tr>
<td>12-17 years, n (%)</td>
<td>1651 (22.8%)</td>
<td>134 (31.6%)</td>
<td>8.1%</td>
</tr>
<tr>
<td>18-21 years, n (%)</td>
<td>421 (5.8%)</td>
<td>47 (11.1%)</td>
<td>11.2%</td>
</tr>
<tr>
<td>Male sex, n (%)</td>
<td>3929 (54.3%)</td>
<td>215 (50.7%)</td>
<td>5.5%</td>
</tr>
<tr>
<td>Race</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>White, n (%)</td>
<td>3592 (49.8%)</td>
<td>117 (27.6%)</td>
<td>3.3%</td>
</tr>
<tr>
<td>Black or African-American, n (%)</td>
<td>2132 (29.6%)</td>
<td>226 (53.3%)</td>
<td>10.6%</td>
</tr>
<tr>
<td>Asian or Asian Indian, n (%)</td>
<td>230 (3.2%)</td>
<td>9 (2.1%)</td>
<td>3.9%</td>
</tr>
<tr>
<td>Multi-racial, n (%)</td>
<td>260 (3.6%)</td>
<td>10 (2.4%)</td>
<td>3.8%</td>
</tr>
<tr>
<td>Other Race or Unknown, n (%)</td>
<td>997 (13.8%)</td>
<td>62 (14.6%)</td>
<td>6.2%</td>
</tr>
<tr>
<td>Ethnicity</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Not Hispanic or Latino, n (%)</td>
<td>6373 (87.8%)</td>
<td>364 (85.8%)</td>
<td>5.7%</td>
</tr>
<tr>
<td>Hispanic or Latino, n (%)</td>
<td>739 (10.2%)</td>
<td>55 (13.0%)</td>
<td>7.4%</td>
</tr>
<tr>
<td>Not specified, n (%)</td>
<td>144 (2.0%)</td>
<td>5 (1.2%)</td>
<td>3.5%</td>
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<tr>
<td>Insurance status</td>
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</tr>
<tr>
<td>Commercial Insurance, n (%)</td>
<td>3903 (53.8%)</td>
<td>132 (31.1%)</td>
<td>3.4%</td>
</tr>
<tr>
<td>Government or Public Insurance, n (%)</td>
<td>2847 (39.2%)</td>
<td>265 (62.5%)</td>
<td>9.3%</td>
</tr>
<tr>
<td>Self-pay, n (%)</td>
<td>88 (1.2%)</td>
<td>10 (2.4%)</td>
<td>11.4%</td>
</tr>
<tr>
<td>Other or Unknown, n (%)</td>
<td>418 (5.8%)</td>
<td>17 (4.0%)</td>
<td>4.1%</td>
</tr>
<tr>
<td>Primary Care Network Patient, n (%)</td>
<td>3749 (51.7%)</td>
<td>272 (64.2%)</td>
<td>7.3%</td>
</tr>
<tr>
<td>Reason for Testing</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Indication Not Specified, n (%)</td>
<td>4099 (56.4%)</td>
<td>0 (0.0%)</td>
<td>0.0%</td>
</tr>
<tr>
<td>Prior Exposure or Symptomatic Patient, n (%)</td>
<td>1756 (24.2%)</td>
<td>371 (87.5%)</td>
<td>21.1%</td>
</tr>
<tr>
<td>Pre-procedure or Pre-admission testing, n (%)</td>
<td>1410 (19.4%)</td>
<td>53 (12.5%)</td>
<td>3.8%</td>
</tr>
</tbody>
</table>
Hospitalization, Severe Illness and Mortality was Low But Did Occur


<table>
<thead>
<tr>
<th>Patients (n=77)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Documented comorbidities, n (%)</td>
</tr>
<tr>
<td>Age in years, median (IQR)</td>
</tr>
<tr>
<td>Race</td>
</tr>
<tr>
<td>White, n (%)</td>
</tr>
<tr>
<td>Black or African-American, n (%)</td>
</tr>
<tr>
<td>Asian or Asian Indian, n (%)</td>
</tr>
<tr>
<td>Multi-racial, n (%)</td>
</tr>
<tr>
<td>Other Race or Unknown, n (%)</td>
</tr>
<tr>
<td>Length of stay in days, median (IQR)</td>
</tr>
<tr>
<td>Need for intensive care, n (%)</td>
</tr>
<tr>
<td>Need for respiratory support</td>
</tr>
<tr>
<td>None, n (%)</td>
</tr>
<tr>
<td>Supplemental oxygen, n (%)</td>
</tr>
<tr>
<td>High flow nasal cannula, n (%)</td>
</tr>
<tr>
<td>Non-invasive ventilation, n (%)</td>
</tr>
<tr>
<td>Mechanical ventilation, n (%)</td>
</tr>
<tr>
<td>Extracorporeal membrane oxygenation (ECMO), n (%)</td>
</tr>
<tr>
<td>Vasopressor support, n (%)</td>
</tr>
</tbody>
</table>

Received SARS-CoV-2 directed therapy

| Remdesivir, n (%) | 5 (7.3%) |
| Hydroxychloroquine, n (%) | 3 (3.9%) |
| Azithromycin, n (%) | 1 (1.3%) |
| Lopinavir/ritonavir, n (%) | 0 (0.0%) |

Received immunomodulatory therapy

| Steroids | 15 (19.5%) |
| Convalescent serum, n (%) | 4 (5.2%) |
| Tocilizumab, n (%) | 3 (3.9%) |

Other Immunomodulators, n (%) | 8 (10.4%) |

Death, n (%) | 2 (2.6%) |

→ 77/424 (18%) required hospitalization (COVID was primary reason in 51).
→ 25/77 (33%) required ICU (6% of all)
→ 12/77 (16%) required mechanical ventilation (3% of all), 2 requiring ECMO
→ 13/77 (17%) required vasopressor support
→ Anti-SARS therapy given to 9 (12%)
→ Steroid given to 20%; 8 children (10%) had MIS-C (2% of all), received IVIG
→ 2/77 (3%) died (0.5% of all positive)
Mortality by Age Group, United States
Low Mortality in Children, But May be Higher in Youngest Children

Data from 95,363 Deaths With Age Group Available (99% Deaths)

Overall mortality age 0-17 years 1.8% - with most in the 0-4 years age group

Young adults also low mortality

https://www.cdc.gov/covid-data-tracker/#demographics
Severe and Fatal Forms of COVID-19 in Children

- While mortality in children may be rare, it can occur.
- Mortality high in children admitted to PICU:
  - *Shekerdemian LS et al JAMA 2020 May 11*  US/Canada 48 PICU admissions, 2 deaths (4%), 3 still on ventilator and 1 on ECMO at time of paper (12.5% for all).
- High rates of underlying conditions in children admitted to PICU.
- However, of the 7 deaths, 3 (43%) had no underlying comorbidity.

<table>
<thead>
<tr>
<th>US/Canada N=48 (Shekerdemian)</th>
<th>France N=27 (Oualha)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Underlying condition: 40 (38%)</td>
<td>Underlying condition: 19 (70%)</td>
</tr>
<tr>
<td><strong>Medically complex</strong></td>
<td>19 (40%)</td>
</tr>
<tr>
<td>Malignancy/immune suppression</td>
<td>11 (23%)</td>
</tr>
<tr>
<td>Obesity</td>
<td>7 (15%)</td>
</tr>
<tr>
<td>Diabetes</td>
<td>4 (8%)</td>
</tr>
<tr>
<td>Seizures</td>
<td>3 (6%)</td>
</tr>
<tr>
<td>Congenital heart disease</td>
<td>3 (6%)</td>
</tr>
<tr>
<td><strong>Sickle cell disease</strong></td>
<td>2 (4%)</td>
</tr>
<tr>
<td>Chronic lung disease</td>
<td>2 (4%)</td>
</tr>
<tr>
<td>Other (genetic, etc)</td>
<td>2 (4%)</td>
</tr>
</tbody>
</table>
Underlying Medical Conditions and COVID-19 in Children

- **Asthma:** While one of the common comorbidities in infected children, does not appear to predispose children to infection or increase hospitalization risk in those infected; nasal epithelium of children and adults with asthma has decreased ACE2 gene expression compared to those without asthma (Bandi S et al. Pediatr Allergy Immunol. 2020 May 29; DeBasi et al. J Pediatr May 13; Jackson DJ et al. J Allergy Clin Immunol. 2020 Apr 22).

- **Cancer:** Memorial Sloan Kettering, NYC – screened 178 children with cancer for SARS-CoV-2; 20 (11%) infected, only 5% required hospitalization for symptoms. (Boulad F et al. JAMA. 2020 May 13)

- **Nutritional status, malnutrition:** No data on SARS-CoV-2 in malnourished pts.

Update: Multi-System Inflammatory Syndrome Temporally Associated with COVID-19 in Children

SARS-COV-2 related multisystem inflammation

- Bulbar conjunctivitis 89%
- Red and cracked lips 54%
- Cervical and mesenteric lymphadenopathies 60%
- Skin rash 57%
- Fever >4 days and asthenia 100%
- Median age 10 years

Neurological sign 31%
Respiratory signs 34%
Left ventricle dysfunction 100%
- Shock 66%
- VA ECMO 28.6%
- Coronary dilatation 17%
- Pericarditis 8%
Digestive involvement 83%
- Nausea, diarrhoea 83%
- Exploratory laparoscopy 5.7% (2 patients)
Multi-System Inflammatory Syndrome

- Child/adolescent presenting with:
  - Persistent fever
  - Laboratory signs of inflammation (e.g., neutrophilia, lymphopenia, elevated CRP, D-dimer, ferritin)
  - Evidence of single- or multi-organ dysfunction - shock, cardiac, respiratory, renal, GI (including abdominal pain, diarrhea), dermatologic, and/or neurologic signs/symptoms
  - May meet full or partial criteria for Kawasaki Disease

- SARS-CoV-2 rtPCR testing may be positive or negative; often SARS-CoV-2 antibody (IgM, IgG) positive or history of recent positive contact.
Multi-System Inflammatory Syndrome

- As of June 23, 36 reports including over 500 children from the United States, Italy, United Kingdom, France and more recently South America, India and Pakistan, have been published regarding this syndrome and potential association with SARS-CoV-2.

- Because of frequent myocardial dysfunction and potential for coronary artery aneurysms, continued F/U (particularly cardiac echos) of these children needed following recovery to evaluate any long-term effects.
Treatment of MIS-C

Mike Levin, Imperial College London

Best Available Treatment Study (BATS)

- Unlikely to have data from RCT.
- >1000 children already treated with clinician “best guess” IVIG, steroids, aspirin, anti-coagulation, anti-IL1, anti-TNF, other – but don’t know what works.
- Many countries have shortage or lack of availability of IVIG or biologicals like anti-IL1/TNF.
- BATS will use data on already treated/newly presenting children; compare response (inflammatory markers) and outcome (need for inotropes, PICU support, coronary artery aneurysm) by what treatment they are receiving.
- International study – currently 60 sites/24 countries – on-line enrollment and no individual patient identifiers. https://bestavailabletreatmentstudy.co.uk
WHO Global COVID-19 Clinical Platform and MIS-C Reporting

Case Report Form for suspected cases of multisystem inflammatory syndrome (MIS) in children and adolescents temporally related to COVID-19

Global COVID-19 Clinical Platform
1 June 2020 | COVID-19: Clinical care

Global COVID-19 Clinical Platform: Case Report Form for suspected cases of Multisystem Inflammatory Syndrome (MIS-C) in children and adolescents temporally related to COVID-19

PARTICIPANT ID

Global COVID-19 Clinical Platform: Case Report Form for suspected cases of Multisystem Inflammatory Syndrome (MIS-C) in children and adolescents temporally related to COVID-19

Preliminary case definition

Children and adolescents 0-19 years of age with fever ≥3 days

AND one of the following:

a) Rash or blister-like non-pruritic papules or truncal urticarial inflammation signs (oral, hoarseness or fever)
b) Hypertension or shock
c) Features of impaired inflammation, pericarditis, valvulitis, or coronary abnormalities (including ECHO findings or echocardiography)
d) Evidence of capillaritis (by PT, PTT, dermoid fever)
e) Acute gastrointestinal problems (diarrhea, vomiting or abdominal pain)

AND

1. Elevated markers of inflammation such as ESR, CRP, acute-phase proteins or procalcitonin
2. Other evidence included causes of inflammation, such as infection, toxins, immune-mediated diseases, or neoplastic or neoplastic causes or rises in angiotensin-converting enzyme 2 activity

Evidence of COVID-19 PCR, antigen test or serological positive test should confirm contact with SARS-CoV-2

MODULE 1. Complete this form for all children aged 0-19 suspected to have multisystem inflammatory disorder (even if all criteria in the case definition are not met - to capture full spectrum of the condition). Initiate the form at the time the disorder is suspected. Submit Module 1 when initial investigations included in case definition are available.

Facility name:

Date of completing form:

Date of admission to hospital:

1. Clinical features of current illness (complete unless still is not suspected)

General:

- Cough
- Shortness of breath
- Fatigue
- Myalgia or arthralgia
- Headache
- Diaphoresis
- Nausea
- Vomiting
- Diarrhea
- Numbness or tingling

Cardiovascular:

- Chest pain
- Tachycardia
- Hypertension
- Hypotension
- Arrhythmia

Respiratory:

- Shortness of breath
- Hypoxia
- Pleuritic pain

Gastrointestinal:

- Abdominal pain
- Vomiting
- Diarrhea

Neurological:

- Headache
- Nuchal rigidity
- Seizures

Cutaneous:

- Rash
- Petechiae

https://apps.who.int/iris/handle/10665/332095

SARS-CoV-2/COVID-19 in Children

Susceptibility
Susceptibility to SARS-CoV-2 in Children and Adolescents: Systematic Review and Meta-Analysis

Viner RM et al. MedRxiv 2020 May 24 (https://www.medrxiv.org/content/10.1101/2020.05.20.20108126v1)

- Systematic review:
  - Contact-tracing studies (secondary infection)
  - Population prevalence studies (virologic testing or serologic testing)

- 18 studies were identified
  - 9 contact-tracing; 1 review of household contact-tracing; 8 population-screening
  - 6 China; 1 each from Taiwan, Japan, Iceland, Italy, Netherlands, Sweden, Germany, Spain, Switzerland, Australia and UK, and one multiple countries
8 Contact/Household Contact Tracing Studies
Preliminary Data Suggest Lower Odds Infection in Children vs Adults
Viner RM et al. MedRxiv 2020 May 24 (https://doi.org/10.1101/2020.05.20.108126)

- Child contacts (age <18-20 yrs) had **56% lower odds of becoming infected after contact with an infected individual** (OR 0.44) than adult contacts.
- Little difference when include only better-quality studies with lower bias (OR 0.51).
- Data insufficient to explore differences between younger children vs adolescents.
8 Population-Based Surveillance Studies
Heterogeneous Data, Mixed Results – Insufficient to Draw Conclusions
Viner RM et al. MedRxiv 2020 May 24 (https://doi.org/10.1101/2020.05/20108126

### Ratios of Prevalence SARS-CoV-2 Infection in Children Compared to Adults

<table>
<thead>
<tr>
<th>Study</th>
<th>Child</th>
<th>Adult</th>
<th>Prevalence Ratio with 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Virus prevalence studies</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gudbjartsson, Iceland, PCR, non-random/volunteer</td>
<td>984</td>
<td>100</td>
<td>12,132</td>
</tr>
<tr>
<td>Lavezzo, Italy, city Vo, viral PCR</td>
<td>464</td>
<td>70</td>
<td>2,275</td>
</tr>
<tr>
<td>Stockholm, Viral PCR screening</td>
<td>143</td>
<td>13</td>
<td>547</td>
</tr>
</tbody>
</table>

| Late virus prevalence study during lockdown |       |       |                              |
| UK ONS, Home self-nasal PCR              | 1,510 | 17    | 5,555                       | 1.08 (0.40, 2.93) |

| National sero-prevalence studies         |       |       |                              |
| Netherlands Pienter, Random sero-epi     | 410   | 71    | 1,611                       | 0.23 (0.08, 0.62) |
| ENE-COVID-19, Spain, Random sero-epi     | 11,062| 2,724 | 46,700                      | 0.60 (0.54, 0.67) |

| Municipal sero-prevalence studies        |       |       |                              |
| Stræik, Germany, Ganglet, seroepi,      | 50    | 132   | 725                         | 0.59 (0.25, 1.38) |
| Stringini, Switzerland, Geneva canton, seroepi | 201   | 70    | 1,051                       | 0.97 (0.56, 1.73) |

- Data more heterogeneous and not suitable for meta-analysis; mixed results.
- Two viral-detection studies and two national sero-prevalence surveys (Netherlands, Spain) show **lower prevalence in children than adults**.
- Two viral-detection studies (Stockholm, UK) and two municipal sero-prevalence studies (Germany, Switzerland) show prevalence of infection was **similar in children and adults**.
- Significant uncertainty of estimates; issues including timing of survey and timing of COVID-19 interventions.
Two cellular proteins on the cell surface are involved in viral entry: angiotensin-converting enzyme 2 (ACE-2) and type II transmembrane serine protease (TMPRSS2); TMPRSS2 expression increases cellular uptake of coronavirus.

→ Spike protein on virus binds to ACE-2 on surface target cell
→ Cellular protease TMPRSS2 binds to and cleaves ACE2 receptor and cleaves the spike protein, activating/priming the virus for cell entry
→ Cleaved ACE-2 and activated spike protein enables cell fusion
Young Children Have Lower Nasal ACE-2 Levels than Adolescents, Young Adults, and Older Adults

Bunyavanich S et al. JAMA. 2020 May 20 (epub)

- Retrospective exam stored nasal epithelium from 305 persons age 4-60 years from a study evaluating nasal markers of asthma 2015-2018 (50% of sample had asthma and 50% did not).

- Evaluated ACE-2 enzyme gene expression in stored samples.
  - ACE-2 enzyme gene expression was age-dependent, being lowest in children <10 years, then ↑ with age.
  - ACE-2 was significantly lower in children <10 year than adolescents 10-17 years (p=0.01) and young adults 18-24 years (p<.001) as well as those >25 years (p=0.001), independent of sex and asthma.
Children Have Lower Levels of Nasal and Bronchial ACE-2 and TMPRSS2 than Adults

Sharif-Askari NS et al. Molec Ther Methods Clin Develop. 2020 Sept; Vol 18

- Used public gene expression datasets.
- Differential expression of both ACE2 and TMPRSS2 in nasal and bronchial airways relative to age and in certain diseases.
- **Children had significantly lower expression of both ACE2 and TMPRSS2 in the upper and lower airways** (nasal and bronchial) compared to adults.
- Expression of both ACE 2 and TMPRSS2 in lung biopsy tissues was significantly upregulated in smokers and persons with COPD, both associated with more severe COVID-19 disease.
What About Transmission of SARS-CoV-2 from Children to Others?

The role that children and young people play in transmission of SARS-CoV-2 depends on multiple factors:

- **Risk of exposure to infected individual**: children less likely to be exposed during mitigation interventions
- **Probability of being infected upon exposure**: children may have lower susceptibility
- **Extent develops symptoms**: children more likely asymptomatic
- **Propensity to make potentially infectious contact with others** (number of social contacts across age groups): school re-openings increase possibility
- **Extent develops viral load sufficiently high to transmit and duration of infectiousness**: mixed data on viral load in children vs adults
Asymptomatic vs Symptomatic SARS-CoV-2 Infection: Similar SARS-CoV-2 Viral Load but Longer Duration/Lower IgG in Asymptomatic Persons


- Compared viral load (cycle threshold) and immune response in 37 asymptomatic adults (rtPCR+ but no clinical sx prior to/during central isolation) to 37 sex-, age-, and comorbidity-matched mildly symptomatic patients.

Viral Load Similar Regardless of Symptoms RT-PCR Cycle Threshold Values 1st NP swab

More Prolonged Viral Shedding in Asymptomatic vs Mildly Symptomatic

Lower Acute and Convalescent SARS-CoV-2-Specific IgG and IgM

→ No significant difference in NP swab cycle threshold PCR response to viral genes between aSx and Sx adults.

→ Viral shedding (time from 1st positive to 1st negative RT-PCRtest) longer in aSx than Sx individuals

→ Virus-specific IgG and IgM levels significantly lower in aSx than Sx persons; in convalescent phase 40% aSx and 13% Sx persons became IgG negative.
Issue of Susceptibility and Transmissibility of Children is Particularly Important in Relation to School Closing/Re-Opening

School Closures


https://www.cdc.gov/covid-data-tracker/#school-closures
COVID-19 Investigation, Schools, New South Wales, Australia
Low Rate Infection in Students, None in Teachers/Staff


- 9 students/9 staff from 5 primary and 10 high schools had COVID-19 dx
  - 735 students and 128 staff viewed as close contacts of cases.
- 288 students/staff agreeing to participate had SARS-CoV-2 rtPCR swab taken 5-10 days after last contact with case and 96 had blood sample taken to detect antibodies to virus.
  → Of those evaluated for infection:
    • 1/288 (0.3%) students had positive rtPCR viral test
    • 1/96 (1%) students with negative rtPCR had SARS-CoV-2 antibody
  → Overall:
    • 2/735 (0.3%) students and 0/128 staff had possible secondary infection from exposure to case
In Norway, as globally, proportion of children with COVID-19 low.

Of 8,135 cases, 7% have been in children:
- 72 (0.9%) age 0-5 yrs (preschool)
- 162 (2.0%) age 6-13 yrs (primary school)
- 341 (4.2%) age 14-19 yrs

No ↑ school-age or overall infections over 4-week period
Organisation of cohorts for physical distancing in primary schools during COVID-19 pandemic, Norway, 2020

<table>
<thead>
<tr>
<th>Grade (age)</th>
<th>Organisation</th>
</tr>
</thead>
</table>
| 1 to 4 (6–10 years) | - As a general rule, one staff member should accompany the cohort  
- The cohort should minimise changing classrooms  
- Within a cohort, pupils and staff can socialise and play together  
- Separate desks 1 m apart recommended  
- Cohorts should also be maintained in after-school programmes  
- Cohorts 1 and 2 can work together for practical reasons during the day, preferably outdoors  
- Staff from cohort 1 can provide relief in cohort 2, vice versa  
- Cohorts 3 and 4, and so on, should be organised in a similar way  
- Cohorts 1 and 2 should generally not mix with cohorts 3 and 4, and so on  
- Cohorts that are not working together have separate areas or different time points for outdoor activities  
- Cohorts that are not working together can mind each other and be in the same area for short periods of time (up to 15 min)  
- Cohorts that are not working together can remain in the same room, provided that a distance of at least 2 m can be maintained between the cohorts over a long period of time  
- The composition of cohorts can be altered weekly after a weekend |
| 5 to 7 (11–13 years) | - Teachers can teach in different classes, but cohorts should remain in the same classroom  
- Cohorts should move between classrooms as little as possible  
- Pupils and staff within a cohort must strive to stay 1 m apart wherever possible  
- Consider in-school teaching combined with digital education at home |

Checklist for school administrators to ensure infection prevention and control in primary schools during COVID-19 pandemic, Norway, 2020

<table>
<thead>
<tr>
<th>The school owner’s overarching responsibility</th>
</tr>
</thead>
<tbody>
<tr>
<td>Train staff regarding infection control measures</td>
</tr>
<tr>
<td>Information for parents/guardians concerning new routines at schools/after-school programmes</td>
</tr>
<tr>
<td>Prepare plan for hand washing procedures for pupils and staff</td>
</tr>
<tr>
<td>Prepare written procedure for cleaning of premises</td>
</tr>
<tr>
<td>Prepare plan for establishment and organisation of cohorts</td>
</tr>
<tr>
<td>Establish dialogue with any staff who are in a risk group and children who require special provision</td>
</tr>
</tbody>
</table>

Hygiene measures

- Ensure sufficient soap and paper towels are available at all handwashing stations and toilets  
- Training of pupils in handwashing procedures and respiratory hygiene  
- Put up posters about handwashing procedures and respiratory hygiene  
- Provide alcohol-based disinfectants where no handwashing facilities are available  
- Plan hand hygiene measures to be applied outside or on excursions (wet wipes and alcohol-based disinfectants)  

Physical distancing measures

- Consider the use of rooms relative to the number of pupils in the cohorts  
- Plan for outdoor activities, including staggered times for different cohorts  
- Divide outdoor areas so that pupils from different cohorts do not mix unless it is possible  
- Avoid large gatherings of pupils  
- Ensure that sufficient stationary and other equipment/materials is available to limit sharing  
- Provide a separate desk/chair per pupil with a safe distance between pupils  
- Provide a separate seat for each pupil during meals and activities, with a safe distance between pupils  
- Ensure distance between pupils at meals and serving food in the cafeteria while children are seated  
- Plan to reduce crowding in changing rooms, toilets and premises entries and exits  
- If appropriate, apply markings/stripes to ensure safe distances are maintained in areas where crowding may occur  
- Plan for alternating times for breaks to limit the number of pupils who are outside at the same time  
- Plan for additional adults to be out at break times in order to help pupils maintain a safe distance from each other  
- Plan for dispersed places where people can assemble before the start of the school day in order to avoid crowding  
- Plan school transport (school buses, need for additional capacity)  
- Avoid using public transport for school trips  

Cleaning

- Draw up a cleaning plan, which describes the frequency and methods to be used for the various points; the plan must cover toilets, washbasins and frequently touched objects (door handles, stair balustrades, light switches, etc)  
- Draw up a plan for cleaning toys, tablets, etc; toys and items that cannot be cleaned must be tidied away  

Recommendations for staff

- Limit physical meetings, arrange video conferencing where appropriate  
- Maintain social distancing during breaks  
- Establish procedures for cleaning shared tablets, computers/keyboards  
- Limit use of public transport
However, We Are in the Midst of a “Grand Experiment”

May 18 2020
CORONAVIRUS | News
70 cases of COVID-19 at French schools days after reopening

June 3 2020
France closes 120 schools as Morbihan becomes third Covid-19 hotspot

PARIS — Just one week after a third of French schoolchildren went back to school in an easing of the coronavirus lockdown, there has been a worrying flareup of about 70 COVID-19 cases linked to schools, the government said Monday.

France has closed some 120 schools in areas with the largest numbers of coronavirus infection, with more likely to follow in the coming days. As a fourth Covid-19 death was reported on Tuesday, the northwestern department of Morbihan became the third epidemic hotspot, with parts placed under confinement.

June 3 2020
After Reopening Schools, Israel Orders Them To Shut If COVID-19 Cases Are Discovered

Two weeks after Israel fully reopened schools, a COVID-19 outbreak sweeping through classrooms — including at least 150 cases at a single school — has led officials to close dozens of schools where students and staff were infected. A new policy orders any school where a virus case emerges to close.

The government decision, announced Wednesday evening, comes after more than 200 cases have been confirmed among students and staff at various schools. At least 244 students and school employees have tested positive for the coronavirus, according to the education ministry. At least 42 kindergartens and schools have been shuttered indefinitely. More than 6,800 students and teachers are in home quarantine by government order.

June 1 2020
PEOPLE.COM | HEALTH
Spike in Coronavirus Cases Causes Hundreds of Schools in South Korea to Close After Reopening

South Korea began relaxing social distancing guidelines in May.

By Maria Pasquini | June 01, 2020 12:33 PM
On investigation of 3 U. Texas students diagnosed with symptomatic SARS-CoV-2 infection on return from spring break in Mexico, of 231 other spring break youth or contacts tested, 64 (28%) had positive SARS-CoV-2 rtPCR results, including one-third of travelers; approximately one-fifth (14/64) were asymptomatic when tested.
Changing Epidemiology of SARS-CoV-2 to Younger Age Group, Germany
Goldstein E et al. Eurosurveillance. 2020;25:2000596

- Evaluated the relative increase in SARS-CoV-2 prevalence after physical distancing measures over time in those age 15-34 years (particularly 20-24 years) compared with 35-49 and 10-14 years.

→ The relative risk of being a COVID-19 case, comparing early period wks 10-11 to later period wks 13-14 was increased in those 15-34 yrs (particularly 20-24 yrs), while it decreased in those age >35 yrs or 10-14 yrs.

→ Growing role of adolescents and young adults – while may have milder illness may be highest risk contracting and spreading infection.
Data from weekly WA State DOH confirmed COVID-19 cases to evaluate trends in age distribution over time from Mar 1 to May 3

Over this 9-week period:
- Increase in cases age 0-19 yrs from 1% to 11%
- Increase in cases 20-39 yrs from 19% to 39%
- No change 40-59 yrs
- Decline in cases among those >50, and particularly those 50-79 yrs (36% to 14%)
COVID-19 Disease in Children

- Children continue to represent low proportion of cases, but disparities between countries, and issues of race/ethnicity, needs to be explored with global and country-specific age-disaggregated data.

- Children with comorbidities are over-represented in those with more severe disease/mortality (especially obesity, neurologic disease, sickle cell).

- Continuing evidence of multi-system inflammatory syndrome in older children and adolescents with SARS-CoV-2 infection (either current infection or infection in recent past) continues to demonstrate how disease due to SARS-CoV-2 in children and youth remains yet to be defined.

- Better data are needed on susceptibility of young children to infection and transmission, particularly related to potential role (or lack of role) of schools in the pandemic.

- Adolescents/young adults represent emerging proportion of infections as pandemic evolves over time and may represent an asymptomatic reservoir of spread.
Thank You For Your Attention!