BCM Infectious Disease COVID19 Literature Review Newsletter: WEEK 2
April 6th-10th, 2020

The number of COVID-19 confirmed cases, related deaths, and total tests reported for State and County

<table>
<thead>
<tr>
<th>Data Source</th>
<th>Last Updated</th>
<th>COVID-19 cases in Texas</th>
<th>COVID-19 cases in Harris County</th>
<th>COVID-19 related deaths in Texas</th>
<th>COVID-19 related deaths in Harris County</th>
<th>Total tests performed in Texas</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Texas DHSH a</td>
<td>April 10, 2020, 12:00 PM</td>
<td>11,671</td>
<td>3,047</td>
<td>226</td>
<td>34</td>
<td>115,918</td>
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<tr>
<td>2. Johns Hopkins b</td>
<td>April 10, 2020, 12:02 PM</td>
<td>11,484</td>
<td>3,047</td>
<td>223</td>
<td>34</td>
<td>N/A</td>
</tr>
</tbody>
</table>

a DHSHS updated the method of reporting COVID-19 cases in Texas on March 24, 2020 to provide the public with more timely information. The DHSHS daily case count now includes all cases reported publicly by local health departments around the state.
b Data sources from WHO, CDC, ECDC, NHC, DXY, 1point2acres, Worldometers.info, BNO, state and national government health departments, and local media reports.

Data represents total tests from private and public labs unless otherwise stated. N/A = not available

(Source: https://txdshs.maps.arcgis.com/apps/opsdashboard/index.html#/ed483ecd702b4298ab01e8b9cacf8b83)

**Background:** The epidemiological and clinical patterns of the COVID-19 remain unclear, particularly among children.

**Methods:**
- Retrospective study of 2143 pediatric patients (<18) with suspected and confirmed COVID-19 diagnosed based on clinical manifestation and exposure from 1/16-2/8/2020 in mainland China.
- Severity classified as asymptomatic (+ normal imaging), mild (URI symptoms), moderate (with pneumonia but without respiratory distress or hypoxemia), severe (with respiratory failure needing support), and critical (ARDS and multiorgan failure).

**Results**
- 731 (34.1%) laboratory-confirmed cases, 1412 (65.9%) suspected cases
- 94 (4.45%) asymptomatic, 1091 (50.9%) mild, 831 (38.8%) moderate, and 127 (5.9%) severe.
- Children < 1 yo were more vulnerable to severe disease. Severe and critical cases was 10.6 %, 7.3%, 4.2%, 4.1% and 3.0% for the age group of <1, 1-5, 6-10, 11-15 and ≥16 years. 1 death was reported.
- Median time from illness onset to diagnoses was 2 days (range: 0 to 42 days).

**Conclusion:**
- Children at all ages are susceptible.
- Young children, particularly infants < 1 year are vulnerable to severe infection.

**Strength/limitations:**
- Nationwide, large scale study with clinical and epidemiological data. First evaluation of severity of infection in children.
- Suspected cases may include other pathogens (like RSV that can cause bronchiolitis)
- Assessment of clinical outcome limited since many children affected were still in the hospital
- See commentary by Dr. Andrea Cruz (TCH Pedi ID Faculty) [https://pediatrics.aappublications.org/content/pediatrics/early/2020/03/16/peds.2020-0834.full.pdf](https://pediatrics.aappublications.org/content/pediatrics/early/2020/03/16/peds.2020-0834.full.pdf)

2. **Miller et al.** Correlation between universal BCG vaccination policy and reduced morbidity and mortality for COVID-19: an epidemiological study. doi: [https://doi.org/10.1101/2020.03.24.20042937](https://doi.org/10.1101/2020.03.24.20042937) [https://www.medrxiv.org/content/10.1101/2020.03.24.20042937v1.full.pdf](https://www.medrxiv.org/content/10.1101/2020.03.24.20042937v1.full.pdf)(pre-print)

**Background:** While COVID-19 has spread to most countries around the world, the impact of disease is varied. BCG childhood vaccination has been shown to offer broad protection to respiratory infections due to “trained immunity” through increased secretion of proinflammatory cytokines (IL-1B).

**Methods:**
Collected BCG vaccination policies from the BCG World Atlas and obtained data of COVID-19 cases and death per country from [https://google.org/crisisresponse/covid19-map](https://google.org/crisisresponse/covid19-map)

- Classified country’s GNI per capita in 2018 using World Bank Data and grouped as follows: low, lower middle, middle high and high income (excluded low-income countries due to potential underreporting/lack of testing)
- Evaluated number of deaths per million inhabitants per country due to COVID-19 between groups that did and did not have universal BCG vaccination policies.

**Results:**

- Middle high and high-income countries with universal BCG policies had 0.78 deaths per million people compared to countries without universal BCG policy with 16.39 deaths per million people.
- Countries that have had long-standing universal BCG vaccination policies (indicating a larger fraction of the elderly population would have had received BCG in childhood) had reduced mortality due to COVID-19 compared to countries with more recent use of universal BCG vaccination policies

**Conclusion:**

- Some of the difference in COVID-19 morbidity and mortality globally could be partially explained by BCG vaccination policies
- The earlier a country established BCG vaccination policies correlated with reduced deaths potentially by protecting the elderly

**Strength/weakness:**

- Pathophysiology has been demonstrated with other viruses in children
- Epidemiologic modeling study, no RCT, associated with several confounding variables (differences in testing capabilities, reporting, different BCG policies and strains, public health efforts)
  - Current clinical trial in Australia: [https://clinicaltrials.gov/ct2/show/NCT04327206](https://clinicaltrials.gov/ct2/show/NCT04327206)
  - Current US clinical trial (Andrew Dinardo at BCM)

**Additional Resources:**

**Background:**
- Solid organ transplant (SOT) population provides a unique sub-group of patients to evaluate during the COVID19 pandemic. Current data however is limited.
- SOT societies are adjusting their guidelines and clinical practice in response to the COVID-19 pandemic.
Please see the following additional SOT related resources:

b. Organ Procurement and Transplantation Network / United Network for Organ Sharing (Updated on April 7, 2020) which is provides data on COVID-19 testing in deceased donors. https://unos.org/covid/

Articles:


Methods: Heart transplant recipients during December 20, 2019 to February 25, 2020 were studied in a single center, retrospective study. A web-based questionnaire and hospital database was used.

Results:

- 87 heart transplant (HTx) recipients - 72.4% were men and average age was 51 years
- No obvious contact with confirmed or suspected COVID-19 patients within cohort
- 96.6% of the HTx recipients undertook precautionary measures after the January 2020 Wuhan lockdown and 92.9% self-quarantined at home for 22-28 days
- 4 patients reported URI, 3 tested negative for SARS-CoV-2 and the 4th recovered and was not tested
- 21.3% had pre-existing lymphopenia and 87.2% had therapeutic tacrolimus concentration.

Discussion:

- Recipients who used enhanced protection measures and self-quarantine during the SARS-CoV-2 outbreak did not have a higher rate of infection among the population.
- Unclear if immunosuppression from SOT makes patients more susceptible or more resistant to severe disease. Further evaluation of the role of immunosuppression is required.


Background: There are two distinct but overlapping pathological subsets occurring in COVID19: Virus-related injury and host response. Developing a classification system for SOT patients may allow for determinants of treatment protocols and potential prognostication as information is gathered.

Proposed Three Stage Classification System for COVID19:
**Stage I (Mild) – Early Infection:** Time of inoculation and early establishment of disease through SARS-CoV-2 binding to angiotensin-converting enzyme 2 (ACE2) receptor on human cells, mild and non-specific symptoms

- **Treatment:** Symptomatic relief and supportive measures, Anti-viral therapy (Remdesivir)

**Stage II (Moderate) – Pulmonary Involvement (IIa) without and with hypoxia (IIb):** Viral multiplication and localized inflammation with chest imaging showing bilateral infiltrates or ground glass opacifications and lab abnormalities (lymphopenia, transaminitis, elevated systemic inflammatory markers)

- **Treatment:** Symptomatic relief and supportive measures, Anti-viral therapy (Remdesivir)
  - IIb (in presence of hypoxia)- Start anti-inflammatory therapy like steroids

**Stage III (Severe) – Systemic Hyperinflammation:** Extra-pulmonary systemic hyperinflammation syndrome with shock, vasoplegia and respiratory failure, decreased cellular immunity, increased pro-inflammatory cytokines

- **Treatment:** Immunomodulatory agents to reduce systemic inflammation such as Tocilizumab (IL-6 inhibitor), Anakinra (IL-1 receptor antagonist), IVIg

**Conclusions:** Rapid recognition of these stages may help deploy interventions early to improve outcomes. More information is needed to determine if interventions are beneficial at these stages

**Additional Resources:**

4. NotifyLibrary on COVID-19 and Transplant (Compendium of Guidelines from different institutions) - [https://www.notifylibrary.org/background-documents#SARS-CoV-2](https://www.notifylibrary.org/background-documents#SARS-CoV-2)

**COVID19 Literature Review Newsletter Volume #6**
Infectious Diseases Fellow: Dierdre Axell-House, MD
Faculty: Jill Weatherhead, MD
April 10th, 2020

**Article:** CBF Vogels *et al.* Analytical sensitivity and efficiency comparisons of SARS-CoV-2 and qRT-PCR assays. medRxiv; doi:[https://doi.org/10.1101/2020.03.30.20048108](https://doi.org/10.1101/2020.03.30.20048108)
Background:
- There are many "COVID-19 PCR tests" in use; they detect pieces of SARS-CoV-2 genetic material using primers
- It is unknown if the various tests are comparable in their ability to detect SARS-CoV-2
- Each PCR test uses 2-3 primer sets to detect the following genes/genetic sections:
  *N (Nucleocapsid)
  *E (Envelope)
  *S (Spike)
  *RdRp (RNA-dependent RNA polymerase)
  *ORF-1ab/nsp10 (Open Reading Frame/non-structural protein)
  *ORF-1b/nsp14 (Open Reading Frame/non-structural protein)

This study evaluates the 4 most common PCR tests: US CDC, China CDC, Charité Germany, Hong Kong University

<table>
<thead>
<tr>
<th>Institute</th>
<th>Primers in the test target:</th>
<th>Primers in the test target:</th>
</tr>
</thead>
<tbody>
<tr>
<td>US CDC</td>
<td>Gene section #1: N1</td>
<td>Gene section #2: N2</td>
</tr>
<tr>
<td>China CDC</td>
<td>N</td>
<td>ORF-1ab/nsp10</td>
</tr>
<tr>
<td>Charité Germany</td>
<td>E</td>
<td>RdRp</td>
</tr>
<tr>
<td>Hong Kong U</td>
<td>N</td>
<td>ORF-1b/nsp14</td>
</tr>
</tbody>
</table>

Methods:
- SARS-CoV-2 RNA was obtained from a virus isolated from an early Seattle pt
- The primer sets were tested on:
  1. SARS-CoV-2 RNA (in 10-fold dilutions, simulating “high” and “low” viral loads)
  2. Negative controls: viral RNA from pts w/respiratory viruses in 2017
  3. Mock Samples: Negative controls from #2 spiked with SARS-CoV2 RNA

Conclusions:
- The SARS-CoV-2 PCRs developed by US CDC, China CDC, Charité Germany/WHO, and Hong Kong University all have similar analytical sensitivity and specificity.
- The China CDC primer sets, and US CDC primer sets N2 and N3 result in higher background amplification. This could give a result as “inconclusive.”
- The Charite E and the HKU-ORF1 were the most sensitive, detecting RNA at $10^1$ virus genome equivalents/μL in 75% of samples.
- All primer/probe sets could detect $10^2$ virus genome equivalents/μL except RdRp which had the lowest analytical sensitivity of the group. This could give a result as a “false negative.”
- Commercial tests in the US use different combinations of primers on different platforms, and further testing is needed to determine which tests are optimal.

Additional Resources:
- As of 2/26/20, the US CDC test only tests N1 and N2 – N3 has been removed due to cross reactivity.
- The “WHO test” is a version of the Charité Germany assay.
- The SARS-CoV-2 tests that have received Emergency Use Authorizations (EUAs) from the FDA.

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