BCM Infectious Disease COVID19 Literature Review Newsletter: WEEK 3
April 13th-17th, 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>
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</thead>
<tbody>
<tr>
<td>1. Texas DSHS *</td>
<td>April 17, 2020, 11:45 AM</td>
<td>17,371</td>
<td>4,306</td>
<td>428</td>
<td>63</td>
<td>169,536</td>
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<td>161,006 Private Labs</td>
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<td>8,530 Public Labs</td>
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<td>2. Johns Hopkins b</td>
<td>April 17, 2020, 1:38 PM</td>
<td>17,423</td>
<td>4,306</td>
<td>436</td>
<td>63</td>
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</tbody>
</table>

*DSHS updated the method of reporting COVID-19 cases in Texas on March 24, 2020 to provide the public with more timely information. The DSHS daily case count now includes all cases reported publicly by local health departments around the state.

b Data sources from WHO, CDC, ECDC, NHL, DXY, 1point1acres, 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

COVID-19 in the greater Houston area

Source: County health authorities, Houston Chronicle reporting


Background:
- Remdesivir is a prodrug that when metabolized, inhibits RNA polymerase
- Activity against Ebola, SARS, and MERS; *in-vitro* activity against SARS CoV-2
- No current therapeutic for COVID-19

Methods:
- Inclusion criteria for compassionate use:
  - Hospitalized patients, + SARS-CoV-2 by RT-PCR
  - O2 saturation of less than or equal to 94% on room air, or a need for oxygen support
  - CrCl >30mL/min
  - AST and ALT are < 5 times the upper limit
- Treatment: 10-day course
  - For children > 40kg and adults: 200mg IV on day 1, then 100mg IV days 2-10
  - For children < 40kg: 5mg/kg IV on day 1, then 2.5mg/kg IV days 2-10
- Followed for 28 days or until discharge or death
- No pre-specified end points
- Monitoring data: oxygen support, adverse events and labs
- No sample-size calculations were performed

Results:
- 61 patients received at least one dose of Remdesivir, 53 patients were included in analysis with 75% receiving the full 10-day course of Remdesivir
  - Enrolled in US, Japan, Italy, Austria, France, Germany, the Netherlands, Spain, and Canada
  - Age range: 23-82y/o with median of 64 years
  - 30 patients (57%) required mechanical ventilation with 4 (8%) required ECMO
  - Median duration of symptoms prior to Remdesivir 12 days
- 18 days after first dose of Remdesivir:
  - 36/53 (68%) of patients had overall improvement in oxygen support, 15% had worsening
  - 17/30 (57%) of patients receiving mechanical ventilation were extubated and 75% receiving ECMO were removed from ECMO
- 28 days after first dose of Remdesivir: cumulative clinical improvement: 84%
  - 25/53 (47%) of patients were discharged
- 13% died after Remdesivir completion, median interval between Remdesivir initiation and death was 15 day
- Safety: 32 patients (60%) reported adverse events: elevated liver enzymes, diarrhea, rash, renal impairment, and hypotension
- 23% reported “severe” adverse events
- 8% discontinued treatment early

**Discussion/Conclusion:** Remdesivir may be a promising treatment for hospitalized patients needing oxygen support due to COVID-19. Limitations: no control group, study was not randomized, power not calculated, not all patients received full 10-day course of Remdesivir. Additionally, no information on viral load data. RCT is needed.

2. **Article #2:** MMWR. Coronavirus Disease 2019 in Children – United States, February 12-April 2, 2020. [https://www.cdc.gov/mmwr/volumes/69/wr/mm6914e4.htm](https://www.cdc.gov/mmwr/volumes/69/wr/mm6914e4.htm)

**Background:** Data from China proposes less severe and different symptoms in children infected with SARS-CoV-2; however, no U.S. pediatric data has been available to compare

**Methods:**
- 149,760 total U.S. cases of lab-confirmed COVID-19 were analyzed, 2572 (1.7%) were children <18y/o, however limited data was available (% similar to comparison data in Adults from data set)
  - 11% of the pediatric cases had information regarding signs symptoms
  - 13% of the pediatric cases had information regarding underlying conditions
  - 33% of the pediatric cases had information regarding hospital status

**Results:**
- Among 2572 U.S. pediatric cases:
  - 850 (22%) in New York City
  - 584 (23%) in New York State (other than New York City)
  - 393 (15%) in New Jersey
  - 745 (29%) elsewhere in the U.S.
- Positive Covid-19 in pediatric cases, median age: 11y/o:
  - <1y/o: 398 (15%)
  - 1-4y/o: 291 (11%)
  - 5-9y/o: 388 (15%)
  - 10-14y/o: 682 (27%)
  - 15-17y/o: 813 (32%)
- In pediatric patients with signs AND symptoms of Covid-19:
  - Fever: 56% (vs 71% in adults)
  - Cough: 54% (vs 80% in adults)
  - Shortness of breath: 13% (vs 43% in adults)

- In known pediatric hospital status (29% of known pediatric cases): 147 (5.7-20%) children hospitalized (vs 10-33% in 18-64y/o adult patients)
  - Children < 1 year accounted for the highest percentage of hospitalized children with COVID-19
- In known pediatric underlying conditions (345 patients): chronic lung disease (including asthma), cardiovascular disease, and immunosuppression
  - 3 pediatric deaths currently under investigation

**Discussion:**
- Relatively few pediatric COVID-19 cases were hospitalized, hospitalization was most common in children < 1 yo and with underlying conditions
- U.S. children with COVID-19 might not have reported fever or cough as often as adult, may have more asymptomatic cases
- Limitations: study is a preliminary analysis with significant missing data on asymptomatic status,
presentation, hospitalizations, underlying conditions and outcomes. Results must be interpreted with caution

Additional Resources:

COVID19 Literature Review Newsletter Volume #8
Faculty: Jill Weatherhead, MD
April 15th, 2020

Please see https://covid.idea.medicine.uw.edu/ to find “up-to-date information and teaching slide decks focused on clinical trials and published data related to potential high-impact treatments of persons with COVID-19” maintained by the University of Washington.

Articles:

Background: SARS-CoV-2 can be detect on different surfaces in a contaminated site leading to risk of transmission.

Methods:
- Stability of SARS-CoV-2 was evaluated at different temperature ranges, on different surfaces (paper, glass, stainless steel, plastic and surgical masks) and in contact with different disinfectants
- SARS-CoV-2 virus was incubated in virus transport media, virus titres were titrated using Vero-E6 cells at defined time periods

Results (see supplement for data):
- Differences in temperature: SARS-CoV-2 is more stable at cool temperatures
  - at 4°C: minimal reduction of viral titre on day 14 of incubation
  - at 22°C: ~50% reduction of viral titre on day 7 of incubation, undetectable on Day 14
  - at 37°C: ~50% reduction of viral titre on day 1 of incubation, undetectable on Day 2
  - at 56°C: undetectable virus titre at 30 minutes incubation
  - at 70°C: undetectable virus titre at 5 minutes incubation
- Differences in surfaces (virus was eluted from surface):
  - Printing/tissue paper: no detectable virus at 3 hours
  - Wood/cloth: no detectable virus at 2 days
  - Glass/banknote: no detectable virus at 4 days
  - Stainless steel/plastic: no detectable virus at 7 days
  - Outer layer surgical mask: detectable virus at 7 days
- Differences in disinfectants:
  - No detectable virus after 5-min incubation with household disinfectants (20% bleach, 1% bleach, 70% ethanol, povidone-iodine, chloroxylenol, chlorhexidine, benzalkonium chloride)
  - No detectable virus after 15-minutes incubation with hand soap solution (no water was added)
Conclusions:
- SARS-CoV-2 can be highly stable in favorable environments (at 4°C and on smooth surfaces) but is susceptible to standard disinfection methods and high temperatures
- The environmental conditions on surfaces do not represent casual contact transmission due to eluting of the virus from the material


Background: Obstetrics patients have multiple interactions with health care system including admittance into hospital for delivery. Universal screening for SARS-CoV-2 has been implemented in some health care settings for pregnant women.

Methods:
- Between March 22nd and April 4th, 2020, a total of 215 pregnant women delivered infants at New York Presbyterian Allen Hospital and Columbia University Irving Medical Center, New York City
- All pregnant women presenting to labor and delivery were screened for SARS-CoV-2

Results:
- 4 patients had symptoms (fever +/- other symptoms) at admission, all tested positive for SARS-CoV2
- Of the 211 asymptomatic patients at admission, 29 (13.7%) tested positive for SARS-CoV2
  - 10% of SARS-CoV2 positive patients developed fever prior to post-partum discharge
  - 1 patient was SARS-CoV2 negative on admission, developed post-partum fever and repeat testing was positive for SARS-CoV2

Conclusions:
- Majority of SARS-CoV-2 positive obstetric patients presenting for delivery in New York City in late March-early April 2020 were asymptomatic highlighting risk of asymptomatic infection in the community
- Universal screening obstetric programs can be used for infection control practices in the hospital as well as to inform neonatal care.
- Limitations: potentially low external validity due to geographic differences (rates of community spread, community based stay at home orders, hospital practices and testing) as well as evaluation of a specific population with high exposure to health care settings.

3. MMWR. Characteristics of Health Care Personnel with COVID-19 – United States February 12-April 9,2020. https://www.cdc.gov/mmwr/volumes/69/wr/mm6915e6.htm?s_cid=mm6915e6_e&deliveryName=USCDC_921-DM25829&fbclid=IwAR2titK6ORf-VCThDBjrITxTeaThYHIW1E_2I74Qffix7VVvuEa9Gr-d5DgM

Background: Health care personnel (HCP) are essential workers with potential direct or indirect exposure to patients with COVID-19 or infectious materials

Methods: February 12- April 9, out 315,531 reported COVID-19 cases to CDC using a standard form, 49,370 (16%) included data on if the patient was a health care worker in the US
  - reported from 50 states, 4 US territories and DC
  - 19% were identified as HCP
  - all analysis are descriptive

Results:
Of the patients with COVID-19 who identified as HCP to the CDC:
- median age 42 years, 73% female, 38% reported at least one underlying health condition
- HCP with known COVID-19 positive contact, 55% reported this occurred in health care setting
- 8% of HCP with COVID-19 did not have fever, cough or shortness of breath
- 16% had loss of smell or taste
- 27 deaths occurred in HCP with COVID-19, deaths more frequently occurred in HCP > 65 yo

Discussion:
- Preliminary findings suggest majority of HCP with COVID-19 have exposure to COVID-19 contact within the hospital setting
- Strategies to limit exposure of HCP by providing appropriate personal protective equipment (PPE), screening all HCP at beginning of their shifts, prioritizing HCP testing and discouraging working while ill.
- Limitation: incomplete data set (likely underreporting), more details will be required to fully reflect impact of COVID-19 on HCP

Additional Resources:

COVID19 Literature Review Newsletter Volume #9
Infectious Diseases Fellow: Alison Robins, MD
Faculty: Jill Weatherhead, MD
April 17th, 2020

Please see https://jamanetwork.com/journals/jama/fullarticle/2764727 for a Review on Pharmacologic Treatment for Coronavirus Disease 2019 (JAMA April 13th, 2020)


Background:
- Known main routes of transmission for SARS-CoV-2 include droplet and close contact
- Ongoing controversy of aerosol transmission
- SARS-CoV2 has been found on toilets and other surfaces in an infected patient’s room

Methods:
- Swab samples collected from ICU and general COVID19 ward (GW) from potentially contaminated surfaces from February 19 through March 2, 2020 in Wuhan, China
- Samples additionally taken from air and air outlets for aerosol detection
- SARS-CoV-2 detection through quantitative real-time PCR

Results:
- Higher rates of positivity in ICU (43.5%) compared to GW (7.9%)
- Pharmacy floor (where there is no patient exposure) had 100% rate of positivity
  - Suggests contamination of workers shoes (which also tested positive)
- Other surfaces with high rates of positivity:
  - Computer mice: 75% in ICU and 20% in GW
  - Trash cans: 60% in ICU and 0% in GW
  - Bed handrails: 42.9% in ICU and 0% in GW
  - Doorknobs: 8.3% in GW
- Air samples: 35% positive results in ICU and 12.5% in GW
  - Highest rates at patient site and air outlet in ICU, but also found around doctor’s office
  - Distribution suggests 4m (13 feet) transmission distance

**Conclusions/Limitations:**
- Contamination rates were greater in the ICU than GW but there was still virus present throughout air and surfaces in both areas implying a potentially high infection risk for medical staff and close contacts
- Appropriate precautions could effectively prevent infection
- Limitations: unclear if PCR positive tests results indicate viability of virus for infection, unknown minimal infectious dose

**Article #2:** Xu et al. Factors associated with prolonged viral RNA shedding in patients with COVID-19, *Clinical Infectious Diseases*, 2020 [accepted manuscript].
https://doi.org/10.1093/cid/ciaa351

**Background:**
- Some hospitals have discharge criteria of two negative swabs for COVID-19
- Suggested viral shedding similar to influenza and different from SARS-CoV-1, but limited data is currently available

**Methods:**
- Retrospective study to evaluate SARS-CoV-2 RNA shedding in patients admitted to 2 hospitals outside of Wuhan, China
- Used electronic medical record (EMR) to obtain clinical, treatment, and outcome data
- Daily collection of respiratory tract specimen for real-time reverse transcription polymerase chain reaction (RT-PCR) with preference for lower respiratory specimen

**Results:**
- 113 symptomatic patients with median age of 52, 58.4% male, median time from illness onset to hospitalization was 5 days
- Treatment varied between patients and included lopinavir/ritonavir and interferon-a most commonly (additional treatment included Umifenovir, Ribavirin)
- 56.5% of patients received steroids
- 74.3% of patients had viral RNA clearance within 21 days (after symptom onset) with median duration of shedding of 15 days
• Median duration from onset of symptoms to RNA clearance for the entire cohort was 17 days
• 20.4% of patients had severe disease, 15.9% of patients underwent mechanical ventilation, and 2 patients died
• Factors associated with prolonged viral RNA shedding (³15 days): * denotes independent risk factors
  o Male sex* (OR 3.24)
  o Old age
  o Hypertension
  o Use of corticosteroids
  o Severe illness at admission or during hospitalization
  o Use of mechanical ventilation* (OR 9.88)
  o Duration of illness prior to hospitalization* (5 days or less with higher probability of quick viral clearance)
• Higher proportion of patients with severe disease had prolonged shedding compared to those with mild disease
• Patients with prolonged shedding also had longer clinical course, including delayed radiographic change, recovery of body temperature, and prolonged hospital stays

Conclusion/Limitations:
• Male sex, mechanical ventilation, and longer duration of symptoms prior to hospitalization were all independently associated with prolonged viral shedding
• Limitation: Small cohort, mixed treatment regimen within the cohort

Additional Resources:

Week 3 Newsletter Prepared by:
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