**BCM Infectious Disease COVID19 Literature Review Newsletter: WEEK 4**
April 20th-24th, 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>
<th>Private Labs</th>
<th>Public Labs</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Texas DSHS *</td>
<td>April 24, 2020, 11:30 AM</td>
<td>22,806</td>
<td>5,330</td>
<td>593</td>
<td>82</td>
<td>242,547</td>
<td>132,124</td>
<td>10,423</td>
</tr>
<tr>
<td>2. Johns Hopkins h</td>
<td>April 24, 2020, 12:31 PM</td>
<td>22,842</td>
<td>5,330</td>
<td>608</td>
<td>82</td>
<td>225,078</td>
<td>132,124</td>
<td>10,423</td>
</tr>
</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.

* Data sources from WHO, CDC, ECDC, NHG, DXY, 1point3acres, 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

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**COVID-19 in the greater Houston area**

![Graph showing COVID-19 cases in the greater Houston area]

Source: County health authorities, Houston Chronicle reporting
Please see https://rt.live/ for state-by-state live COVID-19 reproduction number calculator

Background:
- Current COVID-19 diagnosis relies on PCR-based methods, which have great analytical sensitivity, but are dependent on the viral load and adequate sample collection risking false negative results
- Serology has advantage of faster turnaround time and high-throughput testing, however, humoral response against SARS-CoV-2 remains largely unknown
- Serology when combined with PCR has the potential to improve sensitivity and accuracy


Methods
- 208 blood samples were collected from 82 confirmed cases (+ SARS-CoV-2 deep sequencing or qPCR) and 58 probable cases (- SARS-CoV-2 testing but epidemiology, clinical presentation, and chest radiography consistent with COVID-19)
  - inpatients in Wuhan and Beijing hospitals
- Controls: 135 adult patient in 2018 with acute lower respiratory tract infection (ALRTI) and 150 plasma samples in 2018-2019 from healthy adults from Wuhan
- ELISA: IgM, IgA, IgG antibodies against SARS-CoV-2 purified rNPS as coating antigens

Results
- Overall positive detection rate was 98.6% when IgM ELISA assay was combined with PCR compared to positive rate of 51.9% with single PCR alone
- IgM for SARS-CoV-2 was positive in 75.2% (62/82) confirmed cases and 93.1% (54/58) probable cases
  - 22% patients with confirmed + qPCR, negative by IgM of which majority were enrolled <7 days after symptom onset
- IgM was detected in 85.4% (35/41) cases collected within 7 days post symptom onset (PSO)
- Detection of SARS-CoV-2 by PCR was higher than IgM ELISA assay prior to 5.5 days PSO but detection of IgM ELISA assay was higher than SARS-CoV-2 by PCR after 5.5 days PSO
- Median time to detection of IgM and IgA antibodies was 5 days (IQR 3-6) and median time to detection of IgG antibody was 14 days (IQR 10-18)
- Western blot and ELISA analyses demonstrated strong cross-reactivity with SARS-CoV-1 but no cross-reactivity with other common human coronavirus types including NL63, 229E, OC43, HKU1
- No anti-SARS-CoV-2 IgM, IgA, or IgG was detected in the plasma of the 135 with ALRTI in 2018 nor the 150 healthy adults from Wuhan during 2018-2019

Conclusion
- SARSV-CoV-2 IgM ELISA testing may improve sensitivity when combined with PCR
- Negative serological testing in confirmed cases (by PCR) could be due to testing within 7-day PSO or by lack of a host response in severely ill patients
- SARS-CoV-2 positive plasma did not cross react with other common types of coronaviruses (there was cross-reactivity with SARS-CoV)
- Limitation: cross-sectional analysis of patient population, longitudinal evaluation of samples needed


Methods
- 173 patients with SARS-CoV-2 RNA detected by rRT-PCR with symptoms and/or chest CT findings were enrolled. Patients were classified as non-severe or severe (O2 sats <93% requiring mechanical ventilation).
- Shenzhen Third People’s Hospital between Jan 11th -Feb 9th, 2020
- Antibody measurement:
  - Total Ab: double antigen sandwich ELISA (Beijing Wantai Biological Pharmacy Enterprise), receptor binding domain (RBD) of the spike protein used as the immobilized antigen
  - IgM: IgM μ-chain capture ELISA, RBD antigen
  - IgG: indirect ELISA, recombinant nucleoprotein
  - Specificity total Ab 99.1%, IgM 98.6%, IgG 99.0% based on pre-outbreak healthy controls

Results
- Seroconversion rate for total Ab, IgM, and IgG were 93.1%, 82.7%, and 64.7%, respectively
- Median time for seroconversion for total Ab, IgM, and IgG were 11, 12, and 14 days post symptom onset
- Less than 7 days post-system onset, sensitivity was higher by PCR vs total Ab testing (66.7% vs 38.3%). The inverse was true for days 8-14 (54.0% vs. 89.6%) and days 15-39 (45.5% vs 100%)
- Total sensitivity of RNA PCR + total Ab was 99.4% (67.1% for PCR alone, 93.1% for total Ab)
- Quantitative antibody titers are higher in critical vs non-critical patients

Conclusion
- Serological testing could be used as a supplement to increase RNA PCR sensitivity during acute illness
- Serological conversion can be confirmed in the second week after disease onset
- There may be a correlation of severity of illness and antibody titers (small sample size)
- Limitations: low clinical sensitivity of rRT-PCR (potential sampling errors of upper respiratory tract), cross-reactivity of ELISA to other coronaviruses was not tested (SARS-CoV1)

Additional Articles
New GUIDELINES/Websites


Please see AIDSinfo Interim Guidance for COVID-19 and Persons with HIV.

Please see NIH COVID-19 Treatment Guidelines regarding critical care and therapeutic options under investigation https://www.covid19treatmentguidelines.nih.gov/introduction/

Please see Journal of the Pediatric Infectious Diseases Society Multicenter initial guidance on use of antivirals for children with COVID-19/SARS-CoV-2.

Please see University of Washington IHME COVID-19 Model Updates on “when states may be able to consider easing currently implemented social distancing policies”
http://www.healthdata.org/covid/updates

New Articles

1. E. Chow, et al. Symptom Screening at Illness Onset of Health Care Personnel With SARS-CoV-2 Infection in King County, Washington, JAMA. Published online April 17, 2020.

Background:
- Screening practices and testing criteria for health care workers have been variable across facilities and health systems, and focused on fever and URI symptoms

Results:
- Investigators compiled data on all lab-confirmed COVID+ health care workers (HCW) in King County, WA from February 28 to March 13
- Conducted phone interviews, obtaining data on: demographics, medical Hx, exposure Hx and disease course
- Evaluated current screening criteria for identifying COVID-19 cases early in illness course among HCW

Results
- N = 48. Median age 43 (range 22-79). 77% female. 77% performed direct patient care. 48% had chronic medical conditions. 50% worked at LTACs, 27% in clinics, and 13% in hospitals.
- Most common presenting symptoms: cough (50%), fever (42%), myalgias (35%)
  - 8 (16.7%) did not have fever, cough, shortness of breath, or sore throat at symptom onset
- Less common presenting symptoms: headache (17%), chills (15%), sore throat (15%), coryza (13%), dyspnea (10%), malaise (10%), diarrhea (6%)
- Adding myalgias and chills to fever/cough/SOB/sore throat as criteria for screening would increase case detection rate from 83% to 90%
- Symptomatic HCW worked a median of 2 days while symptomatic

Conclusion
- Expanding symptoms-based screening criteria to include myalgias and chills to standard HCW screening (cough, fever, shortness of breath, sore throat) could allow earlier detection prevent further transmission of SARS-CoV-2 amongst HCW
- Limitations: small sample size, short study time frame, retrospective/recall bias, limited and variable testing availability, did not address risk of asymptomatic carriers within HCW

2. Li et al. The characteristics of household transmission of COVID-19, Clinical Infectious Diseases, Published online April 17, 2020, ciaa450, https://doi.org/10.1093/cid/ciaa450

Background: Data on transmission probability and infectivity in households is limited

Methods:
- Retrospective cohort study
- Enrolled 105 index patients or infected contacts, positive RT-PCR, from hospitals near Wuhan from January 1 to February 20
- Enrolled 392 household contacts, without alternative exposures, no symptoms, negative RT-PCR twice, family members were quarantined immediately after index case was confirmed
- Reviewed medical records, conducted phone interviews
- Evaluated secondary attack rate (proportion of infected household contacts/total number of household contacts)

Results
- Index patients: median age 51 (IQR 39-60), 57% male
- Overall secondary attack rate was 16.3% (64 of 392 contacts tested positive)
- Broken down by generation: 4% among children and 17% among adults
- 9 (14.1%) of positive cases were asymptomatic carriers
- Median time to symptomatic onset of infected household contact was 6 days into quarantine
- Secondary attack rate for spouses was 28%, compared to 17% among non-spouse household contacts (p=0.01)
- When index case self-quarantined within the household at first sign of disease, the secondary attack rate was 0%, compared to 18% in situations where the index case did not self-quarantine

Conclusion
- Older age and spouse status appear to confer higher risk for disease transmission in household contacts
- Isolation of infected individual within the home may reduce secondary attack rate
- Limitations: small sample size/low power, retrospective, unclear if household asymptomatic carriers could have contributed to secondary attack rate (prior to testing)

Additional Articles
Articles

Background:
• New York has the highest rate of infection compared to other states, making up >30% of US cases
• Most publications on clinical features have come from other countries, with different patient demographics compared to the US population

Methods:
• Inclusion criteria: hospitalized patients with positive nasopharyngeal PCR for SARS-CoV-2 at Northwell Health system (12 hospitals) between March 1 and April 4, 2020
• Data collection from EMR including patient demographics, medications (home and inpatient), medical comorbidities, initial vitals, labs, and ECG, diagnoses, treatment, and clinical outcome

Results:
Total 5700 patients included
• Demographics: median age of 63, 60.3% male, 22.6% African American, 8.7% Asian, 39.8% white, and 28.9% other/multiracial, and 84.4% were never smokers
• Comorbidities: highest rates of comorbidities included hypertension (56.6%), obesity (41.7%), and diabetes (33.8%), followed by coronary artery disease (11.1%). All other comorbidities had rates of <10%.
  o 88% of patients had more than 1 comorbidity, with a median Charlson Comorbidity Index score of 4 (53% estimated 10-year survival)
• Triage vitals: 30.7% febrile, 17.3% with respiratory rate > 24 breaths/min, 20.4% with oxygen saturation of <90%, 27.8% received supplemental oxygen
• Labs:
  o 60% of patients with a lymphocyte count <1000
  o 2.1% of patients had another respiratory virus isolated on a respiratory panel
• Clinical outcomes: 2634/5700 (46.2%) patients were discharged or had died at the study endpoint
  o 14.2% required treatment in ICU
  o 12.2% receiving mechanical ventilation
  o 3.2% receiving renal replacement therapy
  o 21% of patients died, no deaths in younger than 18 age group
  o 88.1% of patients who required mechanical ventilation died
  o Mortality rates were slightly higher for patients taking an ACEi at 32.7% or ARB at 30.6% compared to patients not taking either drug at 26.7% (no statistical analysis)
  o Approximately 18.9% of patients were on either an ACEi or ARB at home
• At all age ranges, mortality was higher in males

Conclusions:
• Only 1/3 of patients were febrile on presentation
• 88% of patients had more than 1 comorbidity, 84.4% were never smokers
• Patient requiring mechanical ventilation have a high mortality rate, males have higher mortality rate at all ages
Limitations: As more than 50% of patients in this study were still hospitalized by the study endpoint, we can draw limited data from some clinical outcomes, such as mortality.


Background: Hydroxychloroquine (HC) +/- azithromycin (AZ) is being widely used to treat COVID-19 based on conflicting data.

Methods:
- National retrospective cohort study
- Inclusion: patients hospitalized with confirmed SARS-CoV-2 infection in all US VA centers
- Three cohorts: HC-treated, HC+AZ-treated, and HC-untreated
- Outcomes: death and need for mechanical ventilation

Results:
- N= 368 males (97 HC-treated, 113 HC + AZ-treated, 158 no HC)
- HC +/- AZ was more likely to be prescribed to patients with severe disease
- Deaths: 27.8% in HC group, 22.1% in HC+AZ, 11.4% in no HC
- Mechanical ventilation based on pre-ventilation treatment: 12/90 (13.3%) in HC group, 7/101 (6.9%) in HC+AZ, 25/177 (14.1%) in no HC
- Propensity score models (adjusting for baseline covariates), compared to no HC group:
  - Higher risk of death from any cause in HC group (adjusted HR 2.61; 95% CI, 1.10 to 6.17; P=0.03) but not in HC+AZ group (adjusted HR, 1.14; 95% CI, 0.56 to 2.32; P=0.72)
  - No difference in risk of ventilation in HC group (adjusted HR, 1.43; 95% CI, 0.53 to 3.79; P=0.48) or HC+AZ group (adjusted HR, 0.43; 95% CI, 0.16 to 1.12; P=0.09)
  - Among patients who required mechanical ventilation, no difference in risk of death in HC group (P=0.10) or HC+AZ group (P=0.82)

Conclusion: In this large cohort, HC +/- AZ did not improve mortality or decrease risk of ventilation. HC use alone was associated with increased risk of mortality. Exercise caution with off-label HC. Additional data is needed from randomized trials.

- Limitations
  - Non-randomized; cannot exclude residual confounding
  - Results from this older male cohort may not be generalizable
  - Preprint, not peer-reviewed

Additional Resources:

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