BCM Infectious Disease COVID19 Literature Review Newsletter: WEEK 8
May 18th-May 22nd, 2020

Week 8 Newsletter Prepared by:

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

| Data Source | Last Updated | COVID-19 cases in Texas | COVID-19 cases in Harris County | COVID-19 related deaths in Texas | COVID-19 related deaths in Harris County | Total tests performed  
|-------------|--------------|-------------------------|--------------------------------|---------------------------------|------------------------------------------|--------------------------|
| 1. Texas DHS  
  May 21, 2020, 4:55 PM | 52,268 | 10,095 | 1,440 | 210 | 800,413 Texas |
| 2. Johns Hopkins  
  May 22, 2020, 2:04 PM | 53,070 | 10,283 | 1,461 | N/A | 770,241 Texas |

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

Data sources from WHO, CDC, ECDC, NHC, DXY, Jpoint3reces, Worldometers.info, BNO, state and national government health departments, and local media reports.

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

COVID-19 in the greater Houston area

Source: County health authorities, Houston Chronicle reporting
COVID-19 Literature Review Newsletter Volume #22
Faculty: Marion Hemmersbach-Miller, MD, PhD and Jill Weatherhead, MD
May 18th, 2020

Please see SARS-CoV-2 Vaccine Development Tracker: https://milkeninstitute.org/covid-19-tracker
- Currently 216 treatments in consideration and 133 vaccines in development

Articles

https://science.sciencemag.org/content/early/2020/05/12/science.abc5312/tab-pdf

Background: Urgent need to manufacture and distribute a safe and effective vaccine for SARS-CoV-2.

Questions:
A. Clinical and Immunological endpoints:
   a. Protection from infection defined by seroconversion
   b. Prevention of clinically symptomatic disease, especially amelioration of disease severity
   c. Challenges:
      i. Requirement of a greater number or enrollees into trials given that asymptomatic infection is 20-40%
      ii. Need for serological and clinical endpoints
      iii. Longer term evaluation due to potential of re-exposure
      iv. Durability of serological and clinical endpoints (re: waning immunity is common in human Coronavirus infections)
      v. High variation / mutation rate, although spike protein seems less affected
      vi. Need for immunization studies with post-vaccine SARS-CoV-2 challenge (not exempt of risks)

B. Vaccine platforms:
   a. Variety of platforms used: recombinant protein, replicating and nonreplicating viral vectors, nucleic acid DNA and mRNA
   b. Likely no single platform will meet the global need, so a strategic approach is critical
   c. Current components are not temperature stable
   d. Pre-existing immunity to certain viral vectors could attenuate immunogenicity of a SARS-CoV-2 vaccine

C. Strategic collaborations:
   a. Under the ACTIV (Accelerating COVID-19 Therapeutic Interventions and Vaccines) public-private partnership, NIH has partnered with its sister agencies in the Department of Health and Human Services, including the Food and Drug Administration, Centers for Disease Control and Prevention, and Biomedical Advanced Research and Development Authority; along with other entities
   b. Emerging consensus that vaccine trials need to use common independent laboratories or contribute samples and data for the purpose of generating surrogate markers that ultimately speed licensure and an overall comparison of efficacy
   c. Common IRB and DSMB should be used

D. Scale Up
a. The ability to manufacture hundreds of millions to billions of doses of vaccine requires the vaccine-manufacturing capacity of the entire world.


**Background:** Urgency in the development of vaccines to curb pandemic and prevent new outbreaks
- Purified inactivated viruses have been traditionally used for vaccine development, safe and effective
- There are reports of antibody-dependent enhancement secondary to SARS and MERS vaccine candidates leading to pulmonary immunopathology
- There is no current gold standard animal model for studying SARS-CoV-2 infections

**Methods:**
- Isolated SARS-CoV-2 strains from 11 hospitalized patients, strains were widely scattered on phylogenetic tree representing circulating SARS-CoV-2 populations
- Strain CN2 was used for purified inactivated vaccine development (PiCoVacc), 10 other strains used as preclinical challenge strains. After inactivation, purification, Cryo-EM showed intact particles
- Antibody response: ELISA, Microneutralization assay
- Animal models: BALB/c mice, Winstar rats, Rhesus macaques

**Results:**
- Developed viral stock:
  - Adapted for efficient growth: growth kinetics evaluated at P5 – 5th passage through Vero cells demonstrated efficient replication
  - Evaluated for genetic stability: whole genome sequencing at P1, P3, P5 and P10 without noted spike protein (S) mutations
- Mouse/rat studies: injected with PiCoVacc + alum adjuvant (at varying doses)
  - S- and RBD-specific IgG developed at week 1 and peaked at week 6 post-vaccination, RBD-specific IgG accounting for half of the S-induced antibody responses
  - SARS-CoV-2 specific neutralizing antibodies (NAb) titer against CN1 strain emerged at week 1 and maximized at week 7 post-vaccination, Nab neutralized 10 additional SARS-CoV-2 strains
- Rhesus macaques studies: received PiCoVacc IM route with medium and high doses at day 0, 7 and 14
  - S-specific IgG and NAb were elevated at week 2
  - Viral challenge with direct inoculation of CN1 via intratracheal route 1 week post-vaccination
    - Controls developed severe interstitial pneumonia, vaccinated macaques had mild and focal histopathologic change in a few lobes of lung
    - Controls developed excessive viral copies, vaccinated macaques that received the high dose vaccine had no detectable viral loads in pharynx and lung at day 7 after infection.
    - No antibody-dependent enhancement of infection was observed
    - No notable changes in T cell subsets or key cytokines (TNF-a, IFNy, IL2, IL-4, IL-5, IL-6)

**Conclusions:**
- PiCoVacc might be capable of eliciting an effective NAb response against circulating strains of SARS-CoV-2 without evidence of inducing immunopathology
- rhesus macaques mimic COVID-19-like symptoms after SARS-CoV-2 infection, and appear promising as potential models for determining vaccine efficacy and safety
- Limitations: small numbers and short follow up time-period, will need long-term safety data and large clinical studies to determine safety and efficacy
Background:
- ChAdOx1 (chimpanzee adeno-vectored vaccine platform), previously used for the MERS spike protein, protected non-human primates against MERS

Methods:
- ChAdOx-1 vectored vaccine encoding a codon optimized full-length spike protein of SARS-CoV-2
- Animal model: BALB/c and outbred CD1 mice vaccinated IM with ChAdOx1 nCoV-19 or ChAdOx1 GFP
  - Humoral and cellular immunity was studied 9-14 days post-vaccination
- Animal model: 6 rhesus macaques received IM vaccination with ChAdOx1 nCoV-19 (single dose) and 3 rhesus macaques received IM vaccination with ChAdOx1 GFP

Results:
- Mouse studies:
  - Total Spike (S1 and S2) protein-specific IgG detected in all ChAdOx1 nCoV-19 vaccinated mice
  - Virus-specific neutralizing antibodies (NAb) were detected in all ChAdOx1 nCoV-19 vaccinated mice
  - High levels of IFNy, TNFa and low levels of IL-4, IL-10 in all ChAdOx1 nCoV-19 vaccinated mice
- Rhesus macaque studies:
  - Spike-specific antibodies were detected as early as 14 days post vaccination and virus-specific NAb were detected in all ChAdOx1 nCoV-19 vaccinated animal before viral challenge
  - Viral challenge study: administration of SARS-CoV-2 to the upper and lower respiratory tract
    - No ChAdOx1 nCoV-19 vaccinated animals developed pulmonary pathology at 7 days post-inoculation and no evidence of immune-enhanced inflammatory disease
    - Virus was detected in all control animals and reduced in bronchoalveolar lavage fluid and respiratory tract tissue of ChAdOx1 nCoV-19 vaccinated animals

Conclusions:
- ChAdOx1 nCoV-19 vaccination may prevent viral replication in the lower respiratory tract without evidence of immune-enhanced disease
- Limitations: small numbers and short follow up time-period, will need long-term safety data and large clinical studies to determine safety and efficacy

Articles with infographics/tables:
NUCLEIC-ACID VACCINES
At least 20 teams are aiming to use genetic instructions (in the form of DNA or RNA) for a coronavirus protein that prompts an immune response. The nucleic acid is inserted into human cells, which then churn out copies of the virus protein, most of those vaccines encode the virus’s spike protein.
RNA- and DNA-based vaccines are safe and easy to develop, to produce them involves making genetic material only, not the virus. But they are unproven no licensed vaccines use this technology.

VIRAL-VECTORS VACCINES
Around 25 groups say they are working on viral-vector vaccines. A virus such as measles or adenovirus is genetically engineered so that it can produce coronavirus proteins in the body. These viruses are weakened so they cannot cause disease. There are two types: those that can still replicate within cells and those that cannot because key genes have been disabled.

Replicating viral vector (such as weakened measles)
The newly approved Ebola vaccine is an example of a viral-vector vaccine that replicates within cells. Such vaccines tend to be safe and provoke a strong immune response. Existing immunity to the vector could blunt the vaccine’s effectiveness, however.

Non-replicating viral vector (such as adenovirus)
No licensed vaccines use this method, but they have a long history in gene therapy. Booster shots can be needed to induce long-lasting immunity. US-based drug giant Johnson & Johnson is working on this approach.

PROTEIN-BASED VACCINES
Many researchers want to inject coronavirus proteins directly into the body. Fragments of proteins or protein shells that mimic the coronavirus’s outer coat can also be used.

Protein subunits
Twenty-eight teams are working on vaccines with viral protein subunits — most of them are focusing on the virus’s spike protein or a key part of it called the receptor binding domain. Similar vaccines against the SARS virus protected monkeys against infection but haven’t been tested in people. To work, these vaccines might require adjuvants — immune-stimulating molecules delivered alongside the vaccine — as well as multiple doses.

Virus-like particles
Empty virus shells mimic the coronavirus structure, but aren’t infectious because they lack genetic material. Five teams are working on ‘virus-like particle’ (VLP) vaccines, which can trigger a strong immune response, but can be difficult to manufacture.

Additional Resources:

COVID-19 Literature Review Newsletter Volume #23
Infectious Disease Fellows: Amy Spallone, MD and Teena Xu, MD
Faculty: Jill Weatherhead, MD
May 20th, 2020

Resources for pet owners:

Brief summary: Sporadic reports have been published on the emergence of SARS-CoV-2 being detected in household pets, raising the concern for human-to-pet transmission. Available data do not indicate that domestic animals play a major role in the spread of COVID-19. Pets do not appear to be easily infected with SARS-CoV-2, but studies are ongoing.

<table>
<thead>
<tr>
<th>Date</th>
<th>Country</th>
<th>Species (#)</th>
<th>RT-PCR</th>
<th>Virus Isolation</th>
<th>Neutralizing Antibody</th>
</tr>
</thead>
<tbody>
<tr>
<td>May 13, 2020</td>
<td>Germany</td>
<td>Cat (1)</td>
<td>Positive</td>
<td>Not reported</td>
<td>Not reported</td>
</tr>
<tr>
<td>May 12, 2020</td>
<td>France</td>
<td>Cat (1)</td>
<td>Positive</td>
<td>Not reported</td>
<td>Not reported</td>
</tr>
<tr>
<td>May 8, 2020</td>
<td>The Netherlands</td>
<td>Mink (multiple)</td>
<td>Positive</td>
<td>Not reported</td>
<td>Not reported</td>
</tr>
<tr>
<td>May 8, 2020</td>
<td>Spain</td>
<td>Cat (1)</td>
<td>Positive</td>
<td>Not reported</td>
<td>Not reported</td>
</tr>
<tr>
<td>May 1, 2020</td>
<td>France</td>
<td>Cat (1)</td>
<td>Positive</td>
<td>Not reported</td>
<td>Not reported</td>
</tr>
<tr>
<td>Apr 28, 2020</td>
<td>USA (North Carolina)</td>
<td>Dog (1)</td>
<td>Positive</td>
<td>Not done</td>
<td>Not done</td>
</tr>
<tr>
<td>Apr 26, 2020</td>
<td>The Netherlands</td>
<td>Mink (multiple)</td>
<td>Positive</td>
<td>Not reported</td>
<td>Not reported</td>
</tr>
<tr>
<td>Apr 1 &amp; 6, 2020</td>
<td>USA (New York)</td>
<td>Cats (2)</td>
<td>Positive</td>
<td>Not reported</td>
<td>Positive</td>
</tr>
<tr>
<td>Mar 30, 2020</td>
<td>Hong Kong</td>
<td>Cat (1)</td>
<td>Positive</td>
<td>Negative</td>
<td>Positive</td>
</tr>
<tr>
<td>Mar 27, 2020</td>
<td>USA (New York/Bronx Zoo)</td>
<td>Tigers and Lions (7)</td>
<td>Positive</td>
<td>Not done</td>
<td>Not done</td>
</tr>
<tr>
<td>Mar 27, 2020</td>
<td>USA (New York/Bronx Zoo)</td>
<td>Lion (1)</td>
<td>Positive</td>
<td>Not reported</td>
<td>Not reported</td>
</tr>
<tr>
<td>Mar 27, 2020</td>
<td>USA (New York/Bronx Zoo)</td>
<td>Tiger (1)</td>
<td>Positive</td>
<td>Not reported</td>
<td>Not reported</td>
</tr>
<tr>
<td>Mar 18, 2020</td>
<td>Belgium</td>
<td>Cat (1)</td>
<td>Positive</td>
<td>Not reported</td>
<td>Not reported</td>
</tr>
<tr>
<td>Mar 18, 2020</td>
<td>Hong Kong</td>
<td>Dog (1)</td>
<td>Positive</td>
<td>Positive</td>
<td>Positive</td>
</tr>
<tr>
<td>Feb 27, 2020</td>
<td>Hong Kong</td>
<td>Dog (1)</td>
<td>Positive</td>
<td>Negative</td>
<td>Positive</td>
</tr>
</tbody>
</table>

Background:
• Reports of human-to-feline transmission of SARS-CoV-2 and reports of limited airborne transmission among cats prompted evaluation of nasal shedding of SARS-CoV-2 inoculated cats

Methods:
• Three domestic cats (with no prior infection with SARS-CoV-2) were inoculated with SARS-CoV-2
• Non-inoculated cats with no previous infection with SARS-CoV-2 were cohoused one day later with the 3 inoculated cats in pairs (1 each)
• Nasal and rectal swab specimens were obtained daily and immediately assessed for infectious virus on VeroE6/TMPRSS2 cells

Results:
• From Day 3-5 post-inoculum (p.i.) virus was detected in all 3 inoculated cats
• For the non-inoculated cats paired with the inoculated cats:
  o On day 3, one of the non-inoculated cats had detectable, infectious virus
  o On day 6, virus was detectable in all 3 non-inoculated cats housed with inoculated cats
  o Viral shedding lasted 4-5 days

Articles:
• No virus was detected in the rectal swabs tested
• None of the cats showed any symptoms, including elevated body temperatures, weight loss, or conjunctivitis
• All cats had IgG Ab titer between 1:5120 – 1:20,480 by day 24 post-inoculation

Conclusions/Limitations:
• Cats may not show any appreciable symptoms when infected with SARS-CoV-2
• Reported data shows an ease of transmission between domestic cats
• This data cannot be used to answer whether or not SARS-CoV-2 can be transmitted from cats to humans
• This study is limited by very small numbers
• There is a public health need to recognize if domestic cats may be a silent intermediate host of SARS-CoV-2

Background:

- SARS-CoV-2 uses ACE-2 receptors for cell entry. Canine ACE-2 is similar to that of humans.
- In Hong Kong, pet owners with COVID-19 can voluntarily quarantine their dogs and cats at the Hong Kong Agriculture, Fisheries, and Conservation Department (AFCD)

Methods:

- Animals were tested on arrival and periodically throughout quarantine at AFCD
- Specimens sites: nasal, oral, rectal, stool and blood
- SARS-CoV-2 testing:
  - Quantitative RT-PCR (positives confirmed by reference lab)
  - Isolation by culture (Vero E6 cells)
  - Serum antibody response by plaque reduction neutralization assays (PRNT90)
  - Correlation with human index case (owner) by viral genome sequencing

Results:

- 2 of 15 dogs were positive (as of 3/2/20). 7 cats were negative.
- Viral load and duration of detection was higher in nasal compared to oral swabs.

<table>
<thead>
<tr>
<th>Positive canine cases</th>
<th>PCR</th>
<th>Viral Culture</th>
<th>Neutralizing antibody</th>
<th>Gene sequence</th>
</tr>
</thead>
<tbody>
<tr>
<td>17yo male Pomeranian, (+) comorbidities</td>
<td>Nasal/oral:</td>
<td>(-)</td>
<td>3/3/20: 1:80</td>
<td>93% genome sequenced, identical to owner and 2 household contacts</td>
</tr>
<tr>
<td>Exposed: 2/12-26</td>
<td>(+) 2/26-3/9/20</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Quarantined: 2/26-3/13</td>
<td>(-) 3/12-13/20</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Symptoms: none</td>
<td>Rectal/stool: (-)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Died: 3/15, reasons unknown</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2.5yo male German Shepherd, healthy*</td>
<td>Nasal/oral:</td>
<td>(+)</td>
<td>3/19/20: &lt;1:10</td>
<td>100% genome sequenced, identical to owner</td>
</tr>
<tr>
<td>Exposed: 3/10-17</td>
<td>(+) 3/18-19/20</td>
<td></td>
<td>3/23/20: 1:40</td>
<td></td>
</tr>
<tr>
<td>Symptoms: none</td>
<td>Rectal: (+) 3/18</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*A second dog in this household was not quarantined and tested negative suggesting transmission between two dogs within the household had not occurred

Conclusions/Limitations:

- Very limited case series showing acquisition of SARS-CoV-2 in asymptomatic dogs residing with COVID-19 positive humans supporting potential human-to-animal transmission of SARS-CoV-2
- Unclear if infected dogs can transmit SARS-CoV-2 back to humans or to other animals.

Additional Resources:


COVID-19 Literature Review Newsletter Volume #24
Infectious Disease Fellows: Denise Francisco, MD
Faculty: Jill Weatherhead, MD
May 22nd, 2020

Find information on Convalescent Plasma:


Background:
- Chloroquine and its hydroxyl analogue hydroxychloroquine (HCQ) has been used for many decades as anti-malarial treatment and for rheumatological diseases like Lupus. Due to its noted *in-vitro* activity against the SARS-COV-2 virus, it may be potential prophylactic or treatment option against COVID 19.
- While generally well tolerated, there are also adverse reactions to the drug, including gastrointestinal, retinal and cardiac side effects.

Methods:
- A multicenter, open label, parallel, randomized controlled trial was held in 16 government designated COVID-19 hospitals in China from February 11 to 29, 2020
  - No placebo was used, and HCQ was not blinded.
  - Stratified random sampling was used (mild/moderate versus severe) followed by random assignment (1:1) to HCQ with standard of care vs standard of care only. Diagnosis by RT-PCR
    - Mild/Moderate COVID-19
      - Mild Disease: Mild symptoms but no manifestation of pneumonia on imaging
      - Moderate Disease: Patients with fever, cough, sputum production, and other respiratory tract or non-specific symptoms along with manifestation of pneumonia on imaging without hypoxemia
    - Severe COVID-19: Evidence of hypoxemia SaO2/SpO2 below 94% on room air or a PaO2 to FiO2 ratio of 300 or lower
  - HCQ was given within 24 hours of randomization with a loading dose of 1200 mg daily for 3 days then a maintenance dose of 800 mg daily for 2 weeks (mild to moderate disease) and 3 weeks for severe disease with an option of decreasing the dose if adverse events developed
Patients, investigators, and statisticians were not blinded.

Sample size calculation: 360 patients (180 per group)
- Interim analysis was done on March 14, 2020 and due to the decline of new COVID-19 cases in China, the trial was unable to reach its target enrollment and stopped early.

Primary Outcome:
- Negative conversion of SARS-CoV-2 by 28 days (2 negative results at least 24 hours apart)
- Severe COVID-19: Clinical improvement by 28 days
  - Trial was stopped early and only 2 patients with severe disease were enrolled

Secondary Outcome:
- Probability of a negative conversion at day 4, 7, 10, 14, 21
- Adverse events
- Alleviation of clinical symptoms within 28 days (resolution of fever, normalization of oxygenation n room air and disappearance of respiratory symptoms)

Results:
- 150 patients were randomized (75 patients to standard of care and 75 to HCQ and standard of care)
  - Mean age of the patients was 46 years, and 55% were male
  - 60% patients received concomitant drug treatment before randomization
  - Almost all (99%) patients had mild to moderate COVID-19
- Primary Outcome: Negative conversion within 28 days
  - A total of 109 (73%) patients (56 standard of care; 53 standard of care plus hydroxychloroquine) had negative conversion before 28 days

Figure 1: Kaplan-Meier curves of time to negative conversion of SARS-CoV-2
- Probability of negative conversion by 28 days in the HCQ group was 85.4% (95% CI 73.8% to 93.8%) versus 81.3% (95% CI 71.2% to 89.6%) in the standard of care group with a hazard ratio 0.85, 95% confidence interval 0.58 to 1.23; P=0.34 by log rank test

Secondary Outcome: Safety
- 21 (30%) patients in the HCQ group reported adverse events, compared with 7 (9%) patients in the standard of care group with the most common adverse event in the HCQ group being diarrhea
- Two hydroxychloroquine recipients reported serious adverse events
Conclusions/Limitations:
- HCQ did not result in increased probability of negative conversion of RT-PCR vs standard or care alone in patients with mild to moderate COVID-19.
- There were a higher number of adverse events in HCQ patients than in standard of care alone
- Trial was stopped early due to decreased cases in China, did not meet power criteria


Background:
- Convalescent plasma and hyperimmune immunoglobulin have been used before in other viral diseases and may reduce mortality in patients. These modalities are currently being investigated as potential therapy for COVID-19 since they contain virus-specific neutralizing antibodies.

Methods:
- A review was done via Cochrane Rapid Reviews. Studies evaluating convalescent plasma or hyperimmune immunoglobulin for people with COVID-19, irrespective of disease severity, age, gender or ethnicity
- Assessed certainty of evidence using GRADE criteria: all-cause mortality at hospital discharge, improvement of clinical symptoms, adverse events

Results:
- Eight studies were included (7 case-series, and 1 prospectively planned, single-arm intervention study) with 32 participants.
  - Due to the study design and small number of participants, the overall risk of bias was high and outcomes rated as very low certainty
  - The reviewers were unable to summarize numerical data, hence they just reported narratively
- Effectiveness of convalescent plasma:
  - All-cause mortality at hospital discharge (very low-certainty evidence)
    - All participants were alive at the end of the reporting period, but not all participants had been discharged from hospital by the end of the study
  - Improvement of clinical symptoms (very low-certainty evidence)
    - Six studies, including 28 participants, reported the level of respiratory support required
    - Most participants required respiratory support at baseline. All studies reported improvement in clinical symptoms in at least some participants.
- Safety of convalescent plasma (very low-certainty evidence):
  - The studies did not report the grade of adverse events after convalescent plasma transfusion.
  - One case study reported a participant who had moderate fever (38.9 °C). Another study (3 participants) reported a case of severe anaphylactic shock.
  - Four studies reported the absence of adverse events.
Conclusions/Limitations:

- Unfortunately, due to the small number of participants in these smaller studies, it was difficult to compare results and draw conclusions leading to very-low certainty evidence on the effectiveness and safety of convalescent plasma therapy for patients with COVID-19.
- Need for randomized controlled trials to evaluate the risks and benefits of convalescent plasma.
- There are currently 47 ongoing studies evaluating convalescent plasma, of which 22 are RCTs, and one trial evaluating hyperimmune immunoglobulin. The Cochrane group has said that they will update this review as more information is published.

Additional Resources:
