2019-nCoV Literature Situation Report (Lit Rep)
February 5, 2020

Key Takeaways

➢ **Researchers continue to conclude that bats are the most likely evolutionary predecessor to 2019-nCoV, though there remains no agreement on precisely how the jump may have occurred.**

➢ **Ongoing reports support that older age and co-morbid conditions (e.g., cardiovascular disease, diabetes) are risks for 2019-nCoV mortality.**

➢ **The term "pandemic" is not being used by CDC, and is being specifically not-used by WHO.**

Modelling and Prediction

- Boldog, et al. model the risk for 2019-nCoV outbreaks outside China by developing local reproduction numbers (R_{loc}) that incorporate factors affecting epidemiology in China and new locations, and their connectivity.

- Countries should balance controlling spread after introduction with preventing introduction. Countries with a low ability to control spread should focus on travel restrictions and traveler screening; whereas those better able, should focus on internal control activities. (Those in between should balance both.)

  Boldog P, et al. (Feb 5, 2020). Risk assessment of novel coronavirus 2019-nCoV outbreaks outside China. Pre-Print downloaded on 5 Feb, 2020 from, https://www.medrxiv.org/content/10.1101/2020.02.04.20020503v1

- DeSalazar, *et al.* use air travel volume estimates out of Wuhan to identify countries that may have undetected cases. Their primary findings indicate the Indonesia likely has undetected cases; and that Cambodia and Thailand may have an undercount of cases. Improved public health surveillance is recommended for these countries.

  DeSalazar, et al. (Feb 5, 2020). Using predicted imports of 2019-nCoV cases to determine locations that may not be identifying all imported cases. Pre-Print downloaded on 5 Feb, 2020 from, https://www.medrxiv.org/content/10.1101/2020.02.04.20020495v1

Virology

- Using previously described similarities between 2019-nCoV and SARS-CoV, Ahmed, et al. used SARS-CoV-derived experimentally-determined B- and T-cell epitope data to find epitopes in the S and N structural proteins of 2019-nCoV that were identical between the two viruses.

- Epitopes are parts of the virus "seen" by the immune system. By finding comparable sites across the two viruses, the researchers were hoping to leverage what is known about SARS-CoV immunogenicity to identify potential vaccine antigen candidates

- They found several sites where SARS-CoV epitopes mapped to 2019-nCoV proteins. The areas of the genes for the 2019-nCoV epitopes appeared stable (i.e., no reported mutations to date), making them good vaccine antigen candidates.

- Also, based on population coverage criteria for the T-cell epitopes (i.e., considering MHC allele distribution in populations to assess the percentage of individuals within a population likely to elicit an immune response to at least one T cell epitope from the set), use of these epitopes as a vaccine target could provide population coverage of 84% (China) or 94% (global) coverage.

  Ahmed SF, et al. (Feb 4, 2020). Preliminary identification of potential vaccine targets for 2019-nCoV based on SARS-CoV immunological studies. Pre-Print downloaded on 5 Feb, 2020 from, https://www.biorxiv.org/content/10.1101/2020.02.03.933226v1

- Ceraolo and Giorgi construct an expansive phylogenetic tree of representative *coronaviridae*. They confirm a >99% match among sequenced 2019-nCov isolates; and a 96.2% match between 2019-nCoV and the most closely-related bat coronavirus. While 2019-nCoV sequences were fairly homogenous, at least two hyper-variable genomic areas were identified (ORF 1ab, silent; ORF8, serine/leucine variation).
- They also assessed protein homology, finding again considerable similarity between 2019-nCoV and one of the bat CoVs. Envelope, membrane, and nucleocapsid proteins were generally highly conserved.

  Ceraolo C and Giorgi FM (Feb 4, 2020). Genomic variance of the 2019-nCoV coronavirus. Pre-Print downloaded on 5 Feb, 2020 from, https://www.biorxiv.org/content/10.1101/2020.02.02.931162v2

- A phylogenetic analysis including 2019-nCoV, SARS-CoV and bat CoVs found evidence of the evolutionary link between bat and bat/SARS-CoV-like viruses and 2019-nCoV, with bat/Yunnan/RaTG13/2013 as a potential most-recent ancestor. Additional epitope identification is also presented.

  Ramaiah A and Arumugaswami V (Jan 30, 2020). Genomic variance of the 2019-nCoV coronavirus. Pre-Print downloaded on 5 Feb, 2020 from, https://www.biorxiv.org/content/10.1101/2020.01.29.925867v2

- Randhawa, *et al.* use a machine-learning approach to confirm classification of 2019-nCoV as a *Betacoronavirus*, subgenus *Sarbecovirus*, of bat origin

  Randhawa, et al. (Feb 4, 2020). Machine learning-based analysis of genomes suggests associations between Wuhan 2019-nCoV and bat Betacoronaviruses. Pre-Print downloaded on 5 Feb, 2020 from, https://www.biorxiv.org/content/10.1101/2020.02.03.932350v1

Clinical Characteristics and Care Seeking

- Liver function abnormalities have been observed in some 2019-nCoV patients. Chai, et al. assess potential pathways for this damage given the presumed role ACE2 expression in 2019-nCoV infection.
- They found liver abnormalities of 2019-nCoV patients could involve cholangiocyte dysfunction more than hepatocyte damage. Drug induced and systemic inflammatory response may also have a role.

  Chai X, et al. (Feb 4, 2020). Specific ACE2 Expression in Cholangiocytes May Cause Liver Damage After 2019-nCoV Infection. Pre-Print downloaded on 5 Feb, 2020 from, https://www.biorxiv.org/content/10.1101/2020.02.03.931766v1

Testing and Treatment

- Gao, *et al.* apply a generative network complex (GNC) machine intelligence approach to identify candidate protease inhibitors for treating 2019-nCoV, including an assessment of two HIV protease inhibitors.
- The GNC identifies 3-dimentional (3-D) drug candidates based on elements that include structure generation and property prediction algorithms. Molecule generation includes assessment of properties like binding affinity for known antigenic sites, solubility, similarity to know protease inhibitors, etc. Information on sequence identity and structural similarity between 2019-nCoV and SARS-CoV proteases was the basis of identifying candidates for an initial protease inhibitor dataset for the training set.
- 15 anti-2019-nCov molecules were generated through the GNC process. A related assessment of the HIV protease inhibitors lopinavir (Aluvia) and ritonavir (Norvir) found them to have some potential (e.g., fit with target protease), but generally scored lower than other protease inhibitors identified.
    - *Gao, et al. (Feb 4, 2020). Machine intelligence design of 2019-nCoV drugs. Pre-Print downloaded on 5 Feb, 2020 from,* https://www.biorxiv.org/content/10.1101/2020.01.30.927889v1

- Using BenevolentAI, knowledge of coronavirus receptors, and assumptions about vulnerable cell types, Richardson, *et al.* assess AP2-associated protein kinase 1 (AAK1) inhibitors for potential 2019-nCoV therapeutic use. They identify baricitinib as a candidate for trials based on its plasma concentration at therapeutic doses.
    - *Richardson, et al. (Feb 3, 2020). Baricitinib as potential treatment for 2019-nCoV acute respiratory disease. The Lancet.* https://doi.org/10.1016/S0140-6736(20)30304-4

Other Resources
Need to get caught up? Today's MMWR and the Infectious Disease Society of America can help:

- In today's MMWR Early Release, Patel, *et al.* summarize the epidemiology, response, clinical features, and clinical guidance for the US 2019-nCoV outbreak, from Dec 31 through Feb 4, 2020.
- After a brief review of current countermeasures, they describe the overall US public health response goals as slowing spread to provide time to better:
    - Prepare health care systems and the general public [in the case of] widespread transmission
    - Characterize 2019-nCoV infection to guide public health recommendations and medical countermeasures
- *General epidemiology of 2019-nCoV:* No commitment regarding "exact origin." Person-to-person transmission "evident," but lack understanding of ease. Primary mode of transmission, respiratory droplet. Primary signs and symptoms, fever, cough, and shortness of breath. Incubation period of 2-14 days. Older adults and persons with underlying health conditions identified as high-risk for severe illness, though overall implications "remain unclear."
- A brief summary of the 11 US cases to date is provided (noting the nine travelers from Wuhan and the 2 household contacts)
- CDC and US Public Health Service activation is described, including coordination with WHO and a review of the US Quarantine Station locations and authorities. Entry screening in coordination with US Customs and Boarder Protection is on-going. Enhanced screening was added.

- As of February 1, 2020, a total of 3,099 persons on 437 flights were screened; five symptomatic travelers were referred by CDC to local health care providers for further medical evaluation, and one of these persons tested positive for 2019-nCoV.
- Sharing of genomic information and the high-level overview of RT-PCR use is described, including permissions to use at CDC-qualified labs
- Current CDC guidance based on management and prevention of other respiratory illnesses including influenza, MERS, and SARS (pending further 2019-nCoV) is provided, with reference to the third Health Advisory with interim guidance for clinicians and public health practitioners. The travel history period cited is 14 days. Social distancing recommendation are also provided.

  Patel A, et al. Initial Public Health Response and Interim Clinical Guidance for the 2019 Novel Coronavirus Outbreak — United States, December 31, 2019–February 4, 2020. MMWR 2020;69(Early release). Available from:
  https://www.cdc.gov/mmwr/volumes/69/wr/mm6905e1.htm

From official sources summarized in ProMED Mail (IDSA), 1.) China reports that, among their fatal cases, 80% are over 60 years old and >75% of have a co-morbid condition; 2.) WHO is not considering the 2019-nCoV epidemic a pandemic at this time, citing intensive global control activities.

Dashboards with updated maps and information on global case counts are available at,
- WHO:http://who.maps.arcgis.com/apps/opsdashboard/index.html#/c88e37cfc43b4ed3baf977d77e4a0667
- JHU:https://gisanddata.maps.arcgis.com/apps/opsdashboard/index.html#/bda7594740fd40299423467b48e9ecf6
- Harvard and Boston Children's Hospital: https://www.healthmap.org/ncov2019/

In addition to the articles described here, there are several editorials, commentaries, and technical (e.g., drug trial) papers available to view via the 2019-nCoV SharePoint site along with previous Lit Reps.