2019-nCoV Literature Situation Report (Lit Rep)
February 4, 2020

Key Takeaways

- **Despite a flawed earlier report, asymptomatic transmission has not been confirmed in peer-reviewed literature.**
- **Incubation period estimates are coalescing around 5 days, with the vast majority of persons developing symptoms within 11 days and a small number (<1%) extending beyond 14 days .**
- **Modeling assumptions continue to change with increasing information on the epidemic.**
- **Review articles are beginning to surface. Wang and Zhang's review in *The Lancet*, published on-line today, is a great read (reference below, under "Other Resources").**

Transmission and Geographic Spread

- Science news reports that the NEJM article on asymptomatic transmission erred in describing the infected traveler from China as asymptomatic. Follow-up by regional authorities in Germany found that the traveler did have respiratory and other symptoms while in Germany.
- An update in the NEJM is expected soon.

  Kupferschmidt K (Feb 3, 2020, 5:30 PM) Study claiming new coronavirus can be transmitted by people without symptoms was flawed. ScienceMag.org (American Association for the Advancement of Science). Accessed 3 Feb, 2020 from, https://www.sciencemag.org/news/2020/02/paper-non-symptomatic-patient-transmitting-coronavirus-wrong

- Incubation periods were assessed by Lauer, *et al.* based on 101 confirmed cases with identifiable exposure windows from outside Hubei province (other parts of China plus globally). Case were 62% male with a mean age of 52 years.
  - Mean incubation period: 5.2 days (95% CI, 4.4, 6.0 days)
  - 95% of persons developed symptoms within 10.5 days (95% CI, 7.3, 15.3 days)
  - 64/10,000 cases may develop symptoms after 14 days (<1%)
  - Median incubation time assessing fever only: 5.7 days, with 97.5% of persons experiencing fever within 11.4 days (95% CI: 6.1, 17.8 days)
- A subset of patients with symptom onset outside a facility had a mean time of 2.7 days from symptoms to hospitalization. [*Note:* Consistent with Sun, *et al.*, below]
- Incubation periods appear on average almost a day shorter in China than elsewhere, possibly due to a bias that persons able to travel out of China tended to have longer incubation periods.
- These estimates are generally consistent with earlier estimates and those for SARS and MERS, though longer than the roughly 3-day period seen for other non-SARS human coronaviruses.

  Lauer SA, et al. (Feb 4, 2020). The incubation period of 2019-nCoV from publicly reported confirmed cases: estimation and application. Pre-Print downloaded on 4 Feb, 2020 from, https://www.medrxiv.org/content/10.1101/2020.02.02.20020016v1

- Tang, et al. provide a brief synopsis of two Thai cases and a case from Japan, noting that these did not enter the specific "wet market" at the epicenter of the current epidemic and were not epi-linked to each other
- They go on to cite the non-specific symptoms identified among the early cases; the lack of pediatric cases; and the need for seroprevalence surveys.

  Tang JW, et al. (2020) Emergence of a novel coronavirus causing respiratory illness from Wuhan, China, Journal of Infection. doi: https://doi.org/10.1016/j.jinf.2020.01.014

Modelling and Prediction

Several recent articles have discussed transport links and spread of disease.

- In locations with "similar transmission potential as Wuhan," three or more introduced cases will lead to a more than 50% chance of the infection becoming established in that locale

  Kucharski, et al. Pre-print downloaded 2 Feb, 2020 at, https://www.medrxiv.org/content/10.1101/2020.01.31.20019901v1

- Chances of sustained transmission from an introduced case are about 37% without surveillance and 0.5% with "intense surveillance."

  Thompson RN (2020) Pre-print downloaded 3 Feb, 2020 at, https://www.biorxiv.org/content/10.1101/2020.01.24.919159v1

- Using information from an International Air Transport Data database, SIR modeling techniques, and R_0 estimates ranging from 1.4-2.9, critical timeframes for outbreak emergence (establishing transmission in a new locale) range from about 18-30 days. To gain 30 days in these scenarios, control measures must reduce connections between locales by 87-95%.

  Yuan HY, et al. Pre-print downloaded 4 Feb, 2020 at, https://www.medrxiv.org/content/10.1101/2020.02.01.20019984v1

- Airport screening will likely miss about 46% of infected travelers (in line with prior estimates)

  Quilty, et al. Pre-print downloaded 2 Feb, 2020 at, https://www.medrxiv.org/content/10.1101/2020.01.31.20019265v1

- Train travel was correlated with the spread of 2019-nCoV through mainland China.

  Zhao S, et al. (in press) DOI: https://doi.org/10.1016/j.tmaid.2020.101568

Virology

- Huang and Herrman perform large-scale protein-protein docking experiments to quantify the interactions of 2019-nCoV S-protein receptor-binding domain (S-RBD) with human receptor ACE2
- Sampling a large number of thermodynamically probable binding conformations with Monte Carlo algorithm, they established an experiment-based strength reference for evaluating the receptor-binding affinity of 2019-nCoV via comparison with SARS-CoV.
- The binding affinity of 2019-nCoV S-RBD was about 73% of that of SARS-CoV
- This method might also be applied for rapidly assessing human transmission capability of other newly emerging CoV; and shows the utility of protein-protein interaction analyses

Huang Q and Herrman A (Feb 4, 2020). Fast assessment of human receptor-binding capability of 2019 novel coronavirus (2019-nCoV). Pre-Print downloaded on 4 Feb, 2020 from, https://www.biorxiv.org/content/10.1101/2020.02.01.930537v2

- Jiang, et al. provide a review of sequence homologies among SARS, MERS, and bat-SL-CoV's related to 2019-nCoV strains in order to predict the potential utility of viral replication inhibitors found effective for SARS and MERS in animal models
- They align 2019-nCoV S protein sequence with those of SARS-CoV and several bat-SL-CoVs to predict the cleavage site for generating S1 and S2 subunits; likely functioning of those subunits; and specific candidate molecules to interfere with viral replication
    - Two functional domains of the S1 subunit: binding of the virion to the host cell receptor
    - Three functional domains of the S2 subunit: fusion between viral and cellular membranes

Jiang S, et al. (2020) An emerging coronavirus causing pneumonia outbreak in Wuhan, China: calling for developing therapeutic and prophylactic strategies, Emerging Microbes & Infections. 9:1, 275-277, DOI: 10.1080/22221751.2020.1723441

Clinical Characteristics and Care Seeking

***Context**: Based on current reports from China,[1] the case fatality (%) among confirmed cases since the start of the epidemic is 2.1% (15% among "severe" cases; 1% among all confirmed and suspected cases).*

- Sun, *et al.* used crowdsourced data from a Chinese healthcare professional community network site and other publicly available data to provide information on demographics, hospitalization, and reporting lag during the period of Dec 2019 - Jan 2020. Case definitions are not specified.
- They identified 288 apparently-hospitalized cases (200 in 5 provinces of mainland China; 88 international), including 39 fatalities (13.5%).
    - Cases were 63% male
    - Median age: 44 years of age, with a majority of case over 30 years.
      Seven (2.4%) cases were under 15 years (est. adjusted relative risk for age <15 yrs was 0.3).
    - Median age among those who died: 70 years. Two deaths (5%) occurred in persons <50 yrs.
    - Average lag in symptom onset to seeking care in China was 3 days, declining from 5 to 2 days before compared to after 18 January. In Hubei, the ~6 day average was probably affected by delays in the early Wuhan cases. Outside Hubei, the average was about 2 days; outside China, the average was same-day.
    - Average lag in hospitalization to report in China was 3 days, declining from 9 to 2 days before compared to after 18 January. In Hubei, the ~9 day average was probably affected by delays in the early Wuhan cases. Outside Hubei and internationally, the average was about 2 days.
    - Average lag in symptom onset to reporting was 5 days, ranging from 0-43 days.
    - Rapid growth of cases in China outside Hubei is reported as consistent with sustained transmission in those other areas.
- Crowdsourced data appeared to capture more cases in China before the 18 Jan, when compared to national reporting; and slowed compared to national reporting after that.

[1] National Health Commission of the People's Republic of China. Feb 4: Daily briefing on novel coronavirus cases in China. Accessed 3 Feb, 2020 at, http://en.nhc.gov.cn/2020-02/04/c_76131.htm

Sun K, et al. (Feb 4, 2020). Early epidemiological analysis of the 2019-nCoV outbreak based on a crowdsourced data. Pre-Print downloaded on 4 Feb, 2020 from, https://www.medrxiv.org/content/10.1101/2020.01.31.20019935v1

Other Resources

Need to get caught up? These review articles do a good job describing the overall 2019-nCoV situation…

- A succinct review of 2019-nCoV epidemiology, virology, and clinical findings. What to do next for 2019-nCoV includes:
    - Assess the full spectrum of person-to-person transmission – including potential transmission before symptom onset and during convalescence, and spread through feces
    - Identify best practices for patient treatment
    - Define clinical stages and pathogenesis, including understanding the lung microenvironment and immune responses
    - Improve diagnostic testing
    - Develop a vaccine; and assess prevention approaches for control through social distancing, quarantine, and isolation

  Wang F and Zhang C. (4 February, 2020) What to do next to control the 2019-nCoV epidemic? The Lancet. https://doi.org/10.1016/S0140-6736(20)30300-7

- While the case counts are out of date, this review includes useful context with comparisons to SARS, MERS, and other human coronaviruses.

  Bassetti M, et al. (31 January, 2020) The Novel Chinese Coronavirus (2019-nCoV) Infections: challenges for fighting the storm. European Journal of Clinical Investigation. https://doi.org/10.1111/eci.13209

Dashboards with updated maps and information on global case counts are available at,

- WHO:https://gisanddata.maps.arcgis.com/apps/opsdashboard/index.html#/bda7594740fd40299423467b48e9ecf6
- JHU:http://who.maps.arcgis.com/apps/opsdashboard/index.html#/c88e37cfc43b4ed3baf977d77e4a0667
- 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.