Urgent research agenda for the novel coronavirus epidemic: transmission and non-pharmaceutical mitigation strategies

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Background

On December 29, 2019, a cluster of cases of severe pneumonia of unknown etiology was identified by hospital clinicians in Wuhan and reported to health authorities who in turn reported the cluster to the World Health Organization (WHO) [1]. On January 8, 2020, the cause of the pneumonia was determined to be a novel coronavirus, 2019-nCoV, and its genetic sequence was provided to WHO. The illness likely to have been caused by this Cov was named “novel coronavirus-infected pneumonia” (NCIP). On January 30, WHO declared the epidemic started by the novel coronavirus to be a Public Health Emergency of International Concern [2]. In the first month since identification of the coronavirus, many scientists have described important research questions that can help understand, predict, and mitigate the epidemic [1,3-7]. Considerable new knowledge about this coronavirus has been generated, but evidence is lacking or not sufficiently precise to address some research questions.

We report a limited research agenda of questions in four domains: transmission, clinical features, prediction on epidemic trajectory and health care capacity needed, and monitoring and evaluation of strategies. The scope of the agenda is short- to medium-term and aims to support epidemic control decision making processes. It does not include research on the origin of the coronavirus, development of new tools such as rapid point-of-care diagnostics, or the use of vaccines and other pharmaceutical strategies. We believe that answers to questions in the four domains can help refine strategies to contain or mitigate the 2019-nCoV epidemic.

Methods

This agenda was developed through review of scientific literature on 2019-nCoV, SARS, MERS, and influenza and discussion with experts at academic and public health institutions. For each of the four domains, we describe briefly what is known, priority research questions, and suggestions of methods to address the questions.

Results

Each of the domains is described in this section, with reference to the lists of research questions for each domain in the boxes.

Box 1. The first domain concerns transmission of the novel coronavirus – who is transmitting the virus, who is getting infected, and how is transmission occurring. This information will help inform efforts to screen for the virus, model the epidemic, refine isolation and quarantine, and inform vaccination strategies. The coronavirus is known to be transmitted primarily through respiratory droplets, but other sources may be significant [8]; the degree to which asymptomatic and mild infections can transmit is not fully understood, nor is the potential role of "super-spreaders" in sustaining the epidemic; and the breadth of infection in Wuhan, Hubei and other provinces is not known but can be informed by serological studies. Serological testing of residual blood from routine clinical laboratory testing obtained in December 2019 and earlier may help determine the extent, if any, of earlier community spread. Methods of study for this domain include epidemiological studies, contact tracing, virological monitoring of close contacts, serological surveys using population-based sampling or residual blood from laboratory testing, and virus detection with RT-PCR of samples from the influenza sentinel surveillance network.

Box 2. The second domain concerns the clinical features associated with 2019-nCoV infection. As described by Munster and colleagues [4], knowledge of the full spectrum of disease and the relation between the surveillance pyramid and outbreak containment is of critical importance for responding to the epidemic and predicting its trajectory. Knowledge of the association of clinical and sociodemographic factors with illness severity and mortality

can help predict health care needs, improve screening strategies, and provide evidence for future vaccine deployment. Methods for this domain include epidemiological investigation of cases, serological testing, virological monitoring of quarantined close contacts of cases, and studies of clinical management and illness outcomes.

Box 3. The third domain concerns prediction of epidemic trajectories and health care capacity needs. Several mathematical models of this epidemic have been developed that provide insight to the epidemic [3,9-13]. It is important to have multiple models and multiple forecasts to evaluate consensus and divergence of models, perform additional sensitivity analyses, and determine which ones appear to be useful for various predictions. High quality data are also important for modeling, necessitating continuous evaluation of data quality. Important model outputs, including the basic and effective reproduction numbers, generation time, epidemic curve shape, burden of isolation, quarantine, healthcare use and economic impact will vary in their sensitivity to model assumptions and parameters. This knowledge can help inform research studies to narrow the range of uncertainty in important model outputs. Modelling has great utility in evaluating the potential impact of countermeasures, such as screening, isolation and quarantine, social distancing strategies, and population movement restrictions. Monitoring model predictions during the epidemic response may be able to help evaluate the validity of models and their ability to predict outcomes of importance to policy makers.

Box 4. The fourth domain concerns establishing or strengthening epidemic response strategies through monitoring and evaluation. The novel coronavirus is a Category B infectious disease that is being managed as a Category A (most severe) infectious disease [14]. To date, several strategies to reduce transmission and risk of infection, and mitigate epidemic impact have been implemented. Evaluation platforms will need to be established to monitor the virus and its spread and evolution, and to monitoring compliance and effectiveness of containment and mitigation strategies under different scenarios. In addition to contact tracing of cases, new platforms to consider include serological monitoring of key population groups, linking 2019-nCoV surveillance into influenza-like illness (ILI), acute respiratory infections (ARI) and hospitalized severe acute respiratory infections (SARI) surveillance, searching for the virus in wet markets, and routine sequencing of isolated viruses to determine the evolution of the coronavirus and update diagnostic tests. Monitoring compliance with containment and mitigation strategies and public engagement for determining the societal acceptability of strategies will be important for effective and sustained response.

Discussion

The 2019-nCoV epidemic is in an early stage following its detection in Wuhan, and many strategies are being implemented to contain this virus and mitigate epidemic impact. Given

limitations in the available data on the transmission dynamics and spectrum of disease of 2019-nCoV, new evidence is urgently needed to guide the response effort and minimize the health and economic costs of the epidemic. New knowledge regarding transmission, the spectrum of disease caused by the virus, modeling key outcomes, and evaluating implementation and potential impact of containment and mitigation strategies will help improve the response to the epidemic.

The research agenda described in this brief article describes questions considered by China CDC to fill priority knowledge gaps in the short- and medium-term. The agenda is limited to the four domains. One assumption that we make is the impending availability of serology tests of evidence of infection. Other research domains – for example, development of treatments, vaccines and other preventive measures, development of new diagnostic tools, and searching for the origin and animal reservoir of the virus – are critically important, but not in the scope of this agenda.

We anticipate that academic institutions, centers for disease control and prevention at all levels, and other research organizations in China and the global public health community will conduct or participate in these research efforts. We also anticipate that research organizations and international partners will help refine and improve this research agenda and update it as new knowledge is generated, and new evidence emerges [15]. As the national level CDC, China CDC is in a position to track research progress and facilitate sharing of results with the domestic and international scientific community, government, and key stakeholders in the 2019-nCoV response.

At this point, hospitals have first-hand patient data and samples, CDCs have disease reporting data and case and contact investigation data, and many academic institutions, NGOs, and other institutions have strong research capabilities and resources. Sincere, open, coordinated, and efficient collaboration among all parties is essential to rapid and orderly advancement of research. The Chinese Center for Disease Control and Prevention is willing to promote the establishment of an urgent research consortium for nCoV epidemic response, to formulate and release high-quality, timely unified research protocols and research tools and promote opening to research partners materials and patient specimens that do not compromise privacy or data sensitivity. Collaboratively, we can join forces to conduct rapid investigations and research and provide strong support for optimizing epidemic response strategies and patient management.

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Box 1. Transmission

Q1 Breadth of virus spread

- How far has the virus spread in human populations, including spread prior to the start of epidemic monitoring?

Q2 Transmissibility

- What is the basic reproductive number (R0), effective reproductive ratio (Re), serial interval, generation time (Tg), and doubling time?
- Have superspreaders been identified and what are the characteristics of superspreading events? Is it possible to identify those at high risk of being superspreaders?
- Do temperature and humidity affect transmissibility? In what way?

Q3 Duration of infection and infectivity

- How long does virus shedding last? Does shedding precede onset of symptoms? If yes, how long before? Does shedding continue after recovery? If yes, for how long?
- Are there differences in the duration of virus shedding in those with mild disease versus those with severe disease? How does clinical presentation (respiratory vs non-respiratory) relate to contagiousness?
- Can infected person transmit virus during the incubation period transmit? How efficiently?
- Can persons with mild (afebrile) infection transmit virus? How efficiently?
- Can persons with asymptomatic infection transmit virus? How efficiently?

Q4 Routes of transmission

- What are the types of respiratory, gastrointestinal, other body fluid secretions/excretions that are infectious? How infectious are they?
- Where in the body and in what body fluids can infectious virus be found in infected people?
- Is virus in blood? This would have implications for the safety of the blood supply. Is virus in blood inactivated by standard methods for blood preparation?
- How does viral RNA detected by PCR correlate with infectious virus?
- Does virus persist on surfaces? If yes, how long?

Q5 High risk occupations and behaviors

- What occupations place people at higher risk of becoming infected?
- What behaviors place people at higher risk of becoming infected?

Q6 Immunity

- Does novel coronavirus infection lead to immunity and prevention of future infection?
- Do some groups of individuals (e.g. children) have pre-existing immunity to infection, or protection against disease if infected?

Box 2. Clinical features

Q1 Clinical spectrum and course of disease

- What proportion of infected individuals remain asymptomatic, have mild illness, have no fever, have serious illness, or die?
- How does the spectrum of disease vary by population characteristics (for example, among children, adult, elderly, individuals with comorbid conditions, and pregnant women)?
- What are the time intervals between symptom onset and testing, symptom onset and hospitalization, and symptom onset and death? Does this vary by disease severity and geography?
- Are there differences in clinical disease and outcomes in people with 2019-nCoV monoinfections versus coinfections with 2019-nCoV and another respiratory pathogen?
- What are the causes of death among those with 2019-nCoV infections?

Q2 Severity and prognostic factors

- How does risk of serious illness and death vary by clinical and sociodemographic characteristics of infected individuals?
- How does the level of required medical support (e.g., hospitalization, respiratory support, intensive care) vary by syndrome and clinical condition?
- What proportion of severe and critically ill patients have recovered? What proportion of patients requiring mechanical ventilation have recovered?
- What proportion of deaths have occurred in previously healthy individuals?
- Have any children or pregnant women developed severe disease? If yes, what were the pregnancy outcomes of infected pregnant women?
- Have any cases occurred in people living with HIV? If yes, did they develop severe disease?

Q3 Case identification

- What clinical features associated with infection lead to seeking testing for infection?
- What proportion of infected individuals seek medical care?
- Are there ways to identify some infected individuals who do not seek medical care?

Box 3. Prediction of epidemic trajectories and health care capacity needs

Q1 Model assumptions and parameters

- What are model assumptions and parameters to which important model predictions (when will the epidemic peak, when will it be over, impact on healthcare system, and economic impact) are most sensitive?
- Which model assumptions and parameters are high priorities for measuring with epidemiological and other studies?

Model parameters and assumptions may include:

- ✓ Immunity resulting from infection
- ✓ Duration of illness
- ✓ Zoonotic source and reservoir that ongoing spillover to humans
- ✓ Human population susceptibility
- ✓ Transmissibility in various clinical states
- ✓ Transmission leading to infections, clinical cases, hospitalizations, deaths

Q2 Model prediction

- **What are counterfactual (no intervention) predictions for this epidemic?**
  - ✓ What is the total number of infections, cases, quarantine need, isolation need, hospital admissions, patients need respiratory support, patients need intensive care, and deaths?
  - ✓ How high will the peak of the epidemic be in different locations?
  - ✓ How much time will it take to reach the peak in different locations?
  - ✓ What are the impacts on healthcare capacity?
- **What are the impacts of combinations of countermeasures (isolation, quarantine, social distancing strategies, population movement restriction strategies, personal protection, and screening)?**
  - ✓ How high will the peak of the epidemic be in different locations?
  - ✓ How much time will it take to reach the peak in different locations?
  - ✓ What is the effectiveness of various public health control measures? Are certain control measures more suitable in some locations than others, for example urban areas versus rural areas?
  - ✓ What is the best timing (start time, stop time) of public health measures?

Q3 Model evaluation

- How should mathematical models be evaluated for accuracy while they are being used?
- What are reliable and timely signs that a mathematical model can provide valid predictions?

Box4. Monitoring and evaluation of strategies

Q1 What monitoring should be established or strengthened for this epidemic, and at what jurisdiction level?

- Infection
  - ✓ Contact tracing of cases (including assessing how effectively contacts are being monitored and determine how many contacts become cases)
  - ✓ Serological monitoring of residual blood from routine laboratory testing to identify evidence of infection in the population, followed by investigation of positives to determine source
  - ✓ ILI, ARI and SARI surveillance for novel coronavirus infection monitoring

- ✓ Routine, periodic sequencing of isolated viruses to determine evolution of virus, update PCR and other diagnostics

- Compliance with strategies
  - ✓ Compliance with quarantine
  - ✓ Compliance with exit screening
  - ✓ Compliance with personal protection
- Societal acceptability of interventions – degree of fatigue from mitigation strategies including quarantine, screening, person protection, social distancing interventions

Q2 Effectiveness evaluation

- Is the containment strategy effective? When should we shift to mitigation strategy?
- Is the mitigation strategy effective? When can mitigation strategies be de-escalated?
- Which countermeasure is most effective and with minimum economic cost?