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Subject: DOM Covid Communication
Date: Sunday, March 29, 2020 10:12:46 AM
Attachments: Clinical Characteristics of Coronavirus Disease 2019 in China.pdf
Early Transmission Dynamics in Wuhan, China, of Novel Coronavirus–Infected Pneumonia.pdf
Covid-19 — Navigating the Uncharted.pdf
image003.png

Dear Friends and Colleagues.

I hope you, your family, and your friends are doing well. I have several important developments I want to share with you (sorry for the length of this email).

Clinical:

Inpatient - Currently Hospital Medicine has 5 Covid teams, MICU has 3 surge-ICU teams that are led by pulmonary, anesthesiology, and surgery, and ID has 5 inpatient services; everyone is pitching in to address the needs of our patients. On a daily basis, I plan to provide you with an up-to-date census of Covid patients that are PUI (patient under investigation) and Covid-19+ (confirmed positive by testing). The Covid census will be updated at midnight and has been prepared by Angela Keniston from Hospital Medicine. You can see that over the past 2 days, testing results have picked up and have move many patients from PUI to confirmed cases.

	Inpatient Total PUI	HM PUI	ICU PUI	ICU PUI: Vent	ICU PUI: Vent/ECMO		Inpatient Total Covid-19+	HM Covid-19+	ICU Covid-19+	ICU Covid-19+: Vent	ICU Covid-19+: Vent/ECMO
3/28/2020	5	4	1	0	0		66	37	29	27	1
3/27/2020	24	20	4	3	0		51	28	23	20	1

Ambulatory - Our Infectious Disease colleagues have established a program for all Covid+ patients discharged from the hospital, regardless of whether ID has consulted on the patient. This program is led by Dr. Molly Eaton and both provides care and follows the population systematically. To enroll a patient in the monitoring program, send the patient MRN prior to discharge to Kristine Erlandson (kristine.erlandson@cuanschutz.edu) or Molly Eaton (molly.2.eaton@cuanschutz.edu).

Clinical Research - Three Covid-19 NEJM articles were published this week (attached). The highlights include:

- Higher morbidity and mortality among the elderly, and those with existing comorbidities (diabetes, HTN, COPD, and CAD) and bilateral infiltrates on initial CXR.
- High transmission rate (each infected person spreads to 2 other people) with high viral titers early in the course of minimally symptomatic disease. This underscores the need for social distancing, hand washing, PPE, and wiping down surfaces.
- Case-fatality of 1.4% for Covid-19 appears to be more consistent with severe season/pandemic influenza than SARS or MERS which was much higher.
- The need for scientific trials, including vaccine, medications, and hyperimmune globulin/monoclonal Ab was also emphasized.

Research:

There is too much use of the RC1 and RC2. **If you are not on the 'critical access list" you should not be using RC1 or RC2. Only emergency and critical access personnel should be using these facilities. Contribute to stopping the pandemic by staying home.**

DOM Deficit Reduction Plan:

As a consequence of changes we've had to make in our clinical operation, we are estimating a $6.7M shortfall in clinical revenue through the end of June of this year. Although we'll be able to reduce some of our expenses, rather than projecting a $2.8M profit, we are now estimating a $2.6M deficit. Divisions that are particularly hard hit will require over $4M to cover their deficits. The division heads and I have decided to cover these deficits from the following sources: 50% from CU Medicine reserves from divisions with losses (all of these divisions will be able maintain at least a 50% of their required by-law reserves at CU Medicine), 14% from divisions with year-end positive balances, and 36% from DOM CU Foundation endowment. In an effort to maintain the current salaries of our staff, faculty, and trainees, we've also decided on the following:

- No salary increases for July 1st
- No incentives, including academic incentives (pending approval from CU Medicine)
- Moving ahead only with critical hires

I know this may disappoint some of you, especially those of you who have been promoted this year. While I sympathize with your concerns, my priority is to make sure we have the same outstanding staff, faculty, and trainees at the end of this crisis that we had before we even knew about Covid-19. Once we emerge from this crisis, I will do everything possible to address these unrealized expectations. I also know that we have more financial planning to do for the next fiscal year (July 1, 2020 – June 30, 2021). I plan to project a conservative clinical revenue stream through the end of October, and will get back to you with additional plans to address these anticipated shortfalls. However, rest assured that all of you will remain my priority, and I will do what I can to maintain the support for our staff, faculty, and trainees.

Housing for our Housestaff:

As Covid-19 becomes ever more present, residents are concerned about what they might bring home to roommates and family during their inpatient service months. We are planning for the possibility of residents needing to isolate should they become exposed to Covid-19. We are asking if any faculty/staff have access to sites where residents can recuperate in isolation that the faculty are willing to volunteer to the residents free of charge. For example, this might be a "carriage house", AirBnB site with separate entrance/kitchenette/fridge that is not being used right now, etc. If you have a space like this that you would be willing to volunteer should the need arise, please contact Mary Meadows (mary.meadows@cuanschutz.edu) in the Residency Training Program.

Reflecting back on this past week, it's hard for me to imagine my life pre-coronavirus. I, like you, have become a germaphobe focused almost exclusively on trying to address the unique clinical, scientific, educational, financial, and social/cultural challenges posed by this incredibly small virus. While this has been challenging for all of us, I think we've grown from this experience. I know I've become more nimble, more collaborative, more appreciative, and more humble. I'm also rapidly transitioning from a Boomer to Zoomer - ☺☺☺.

We have a long road ahead of us, so take care of yourselves. Let me know if there's anything I can do for you. Stay well and stay connected.

David

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ORIGINAL ARTICLE

Clinical Characteristics of Coronavirus Disease 2019 in China

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ABSTRACT

BACKGROUND

Since December 2019, when coronavirus disease 2019 (Covid-19) emerged in Wuhan city and rapidly spread throughout China, data have been needed on the clinical characteristics of the affected patients.

METHODS

We extracted data regarding 1099 patients with laboratory-confirmed Covid-19 from 552 hospitals in 30 provinces, autonomous regions, and municipalities in mainland China through January 29, 2020. The primary composite end point was admission to an intensive care unit (ICU), the use of mechanical ventilation, or death.

RESULTS

The median age of the patients was 47 years; 41.9% of the patients were female. The primary composite end point occurred in 67 patients (6.1%), including 5.0% who were admitted to the ICU, 2.3% who underwent invasive mechanical ventilation, and 1.4% who died. Only 1.9% of the patients had a history of direct contact with wildlife. Among nonresidents of Wuhan, 72.3% had contact with residents of Wuhan, including 31.3% who had visited the city. The most common symptoms were fever (43.8% on admission and 88.7% during hospitalization) and cough (67.8%). Diarrhea was uncommon (3.8%). The median incubation period was 4 days (interquartile range, 2 to 7). On admission, ground-glass opacity was the most common radiologic finding on chest computed tomography (CT) (56.4%). No radiographic or CT abnormality was found in 157 of 877 patients (17.9%) with nonsevere disease and in 5 of 173 patients (2.9%) with severe disease. Lymphocytopenia was present in 83.2% of the patients on admission.

CONCLUSIONS

During the first 2 months of the current outbreak, Covid-19 spread rapidly throughout China and caused varying degrees of illness. Patients often presented without fever, and many did not have abnormal radiologic findings. (Funded by the National Health Commission of China and others.)

The authors' full names, academic degrees, and affiliations are listed in the Appendix. Address reprint requests to Dr. Zhong at the State Key Laboratory of Respiratory Disease, National Clinical Research Center for Respiratory Disease, Guangzhou Institute of Respiratory Health, First Affiliated Hospital of Guangzhou Medical University, 151 Yanjiang Rd., Guangzhou, Guangdong, China, or at nanshan@vip.163.com.

*A list of investigators in the China Medical Treatment Expert Group for Covid-19 study is provided in the Supplementary Appendix, available at NEJM.org.

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In early December 2019, the first pneumonia cases of unknown origin were identified in Wuhan, the capital city of Hubei province.[1] The pathogen has been identified as a novel enveloped RNA betacoronavirus[2] that has currently been named severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), which has a phylogenetic similarity to SARS-CoV.[3] Patients with the infection have been documented both in hospitals and in family settings.[4-8]

The World Health Organization (WHO) has recently declared coronavirus disease 2019 (Covid-19) a public health emergency of international concern.[9] As of February 25, 2020, a total of 81,109 laboratory-confirmed cases had been documented globally.[5,6,9-11] In recent studies, the severity of some cases of Covid-19 mimicked that of SARS-CoV.[1,12,13] Given the rapid spread of Covid-19, we determined that an updated analysis of cases throughout mainland China might help identify the defining clinical characteristics and severity of the disease. Here, we describe the results of our analysis of the clinical characteristics of Covid-19 in a selected cohort of patients throughout China.

Methods

Study Oversight

The study was supported by National Health Commission of China and designed by the investigators. The study was approved by the institutional review board of the National Health Commission. Written informed consent was waived in light of the urgent need to collect data. Data were analyzed and interpreted by the authors. All the authors reviewed the manuscript and vouch for the accuracy and completeness of the data and for the adherence of the study to the protocol, available with the full text of this article at NEJM.org.

Data Sources

We obtained the medical records and compiled data for hospitalized patients and outpatients with laboratory-confirmed Covid-19, as reported to the National Health Commission between December 11, 2019, and January 29, 2020; the data cutoff for the study was January 31, 2020. Covid-19 was diagnosed on the basis of the WHO interim guidance.[14] A confirmed case of Covid-19 was defined as a positive result on high-throughput sequencing or real-time reverse-transcriptase–polymerase-chain-reaction (RT-PCR) assay of nasal and pharyngeal swab specimens.[1] Only laboratory-confirmed cases were included in the analysis.

We obtained data regarding cases outside Hubei province from the National Health Commission. Because of the high workload of clinicians, three outside experts from Guangzhou performed raw data extraction at Wuhan Jinyintan Hospital, where many of the patients with Covid-19 in Wuhan were being treated.

We extracted the recent exposure history, clinical symptoms or signs, and laboratory findings on admission from electronic medical records. Radiologic assessments included chest radiography or computed tomography (CT), and all laboratory testing was performed according to the clinical care needs of the patient. We determined the presence of a radiologic abnormality on the basis of the documentation or description in medical charts; if imaging scans were available, they were reviewed by attending physicians in respiratory medicine who extracted the data. Major disagreement between two reviewers was resolved by consultation with a third reviewer. Laboratory assessments consisted of a complete blood count, blood chemical analysis, coagulation testing, assessment of liver and renal function, and measures of electrolytes, C-reactive protein, procalcitonin, lactate dehydrogenase, and creatine kinase. We defined the degree of severity of Covid-19 (severe vs. nonsevere) at the time of admission using the American Thoracic Society guidelines for community-acquired pneumonia.[15]

All medical records were copied and sent to the data-processing center in Guangzhou, under the coordination of the National Health Commission. A team of experienced respiratory clinicians reviewed and abstracted the data. Data were entered into a computerized database and cross-checked. If the core data were missing, requests for clarification were sent to the coordinators, who subsequently contacted the attending clinicians.

Study Outcomes

The primary composite end point was admission to an intensive care unit (ICU), the use of mechanical ventilation, or death. These outcomes were used in a previous study to assess the severity of other serious infectious diseases, such as H7N9 infection.[16] Secondary end points were the rate of death and the time from symptom onset until the composite end point and until each component of the composite end point.

STUDY DEFINITIONS

The incubation period was defined as the interval between the potential earliest date of contact of the transmission source (wildlife or person with suspected or confirmed case) and the potential earliest date of symptom onset (i.e., cough, fever, fatigue, or myalgia). We excluded incubation periods of less than 1 day because some patients had continuous exposure to contamination sources; in these cases, the latest date of exposure was recorded. The summary statistics of incubation periods were calculated on the basis of 291 patients who had clear information regarding the specific date of exposure.

Fever was defined as an axillary temperature of 37.5°C or higher. Lymphocytopenia was defined as a lymphocyte count of less than 1500 cells per cubic millimeter. Thrombocytopenia was defined as a platelet count of less than 150,000 per cubic millimeter. Additional definitions — including exposure to wildlife, acute respiratory distress syndrome (ARDS), pneumonia, acute kidney failure, acute heart failure, and rhabdomyolysis — are provided in the Supplementary Appendix, available at NEJM.org.

LABORATORY CONFIRMATION

Laboratory confirmation of SARS-CoV-2 was performed at the Chinese Center for Disease Prevention and Control before January 23, 2020, and subsequently in certified tertiary care hospitals. RT-PCR assays were performed in accordance with the protocol established by the WHO.[17] Details regarding laboratory confirmation processes are provided in the Supplementary Appendix.

STATISTICAL ANALYSIS

Continuous variables were expressed as medians and interquartile ranges or simple ranges, as appropriate. Categorical variables were summarized as counts and percentages. No imputation was made for missing data. Because the cohort of patients in our study was not derived from random selection, all statistics are deemed to be descriptive only. We used ArcGIS, version 10.2.2, to plot the numbers of patients with reportedly confirmed cases on a map. All the analyses were performed with the use of R software, version 3.6.2 (R Foundation for Statistical Computing).

RESULTS

DEMOGRAPHIC AND CLINICAL CHARACTERISTICS

Of the 7736 patients with Covid-19 who had been hospitalized at 552 sites as of January 29, 2020, we obtained data regarding clinical symptoms and outcomes for 1099 patients (14.2%). The largest number of patients (132) had been admitted to Wuhan Jinyintan Hospital. The hospitals that were included in this study accounted for 29.7% of the 1856 designated hospitals where patients with Covid-19 could be admitted in 30 provinces, autonomous regions, or municipalities across China (Fig. 1).

The demographic and clinical characteristics of the patients are shown in Table 1. A total of 3.5% were health care workers, and a history of contact with wildlife was documented in 1.9%; 483 patients (43.9%) were residents of Wuhan. Among the patients who lived outside Wuhan, 72.3% had contact with residents of Wuhan, including 31.3% who had visited the city; 25.9% of nonresidents had neither visited the city nor had contact with Wuhan residents.

The median incubation period was 4 days (interquartile range, 2 to 7). The median age of the patients was 47 years (interquartile range, 35 to 58); 0.9% of the patients were younger than 15 years of age. A total of 41.9% were female. Fever was present in 43.8% of the patients on admission but developed in 88.7% during hospitalization. The second most common symptom was cough (67.8%); nausea or vomiting (5.0%) and diarrhea (3.8%) were uncommon. Among the overall population, 23.7% had at least one coexisting illness (e.g., hypertension and chronic obstructive pulmonary disease).

On admission, the degree of severity of Covid-19 was categorized as nonsevere in 926 patients and severe in 173 patients. Patients with severe disease were older than those with nonsevere disease by a median of 7 years. Moreover, the presence of any coexisting illness was more common among patients with severe disease than among those with nonsevere disease (38.7% vs.

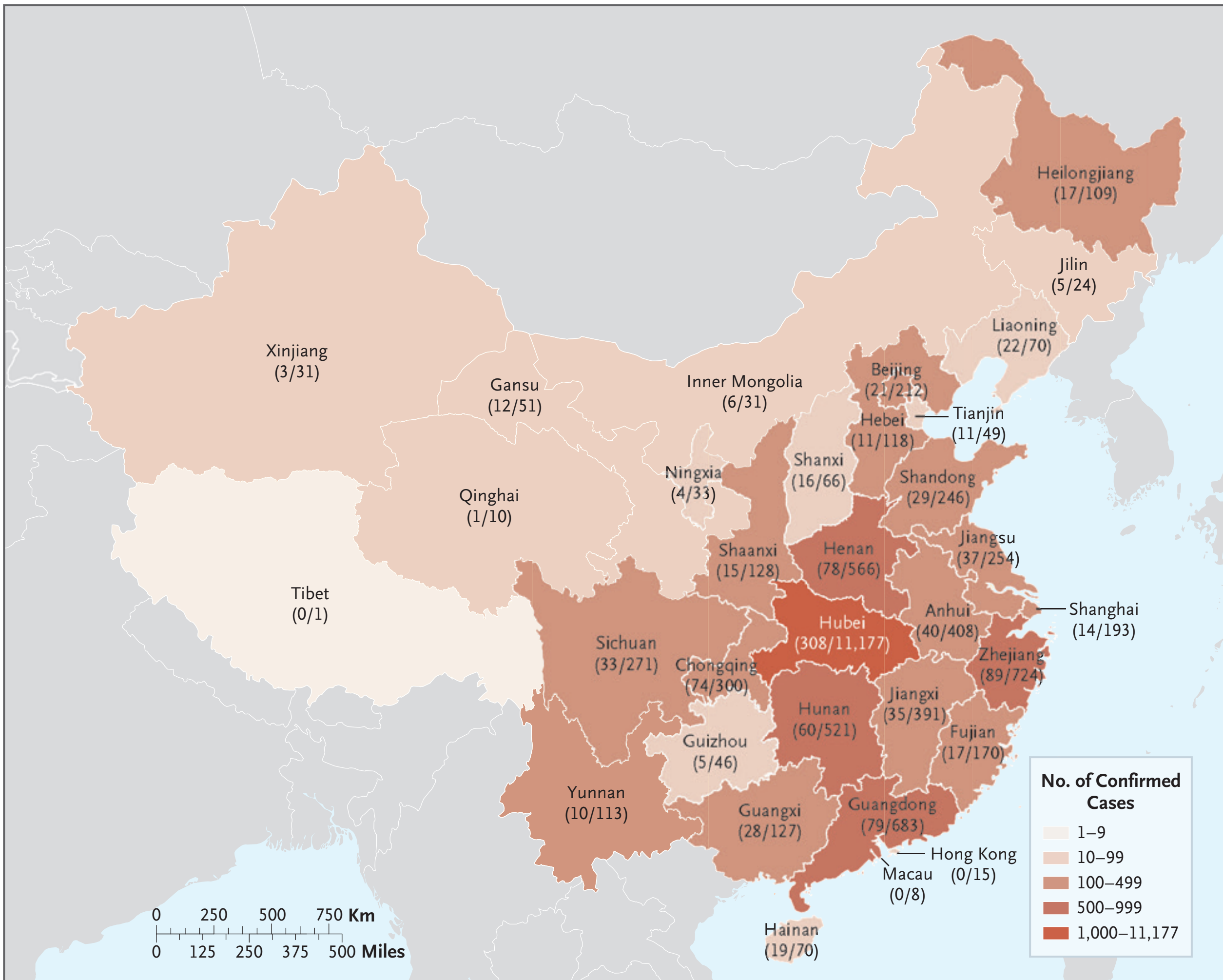

Figure 1. Distribution of Patients with Covid-19 across Mainland China.

Shown are the official statistics of all documented, laboratory-confirmed cases of coronavirus disease 2019 (Covid-19) throughout China, according to the National Health Commission as of February 4, 2020. The numerator denotes the number of patients who were included in the study cohort and the denominator denotes the number of laboratory-confirmed cases for each province, autonomous region, or provincial municipality, as reported by the National Health Commission.

21.0%). However, the exposure history between the two groups of disease severity was similar.

RADIOLOGIC AND LABORATORY FINDINGS

Table 2 shows the radiologic and laboratory findings on admission. Of 975 CT scans that were performed at the time of admission, 86.2% revealed abnormal results. The most common patterns on chest CT were ground-glass opacity (56.4%) and bilateral patchy shadowing (51.8%). Representative radiologic findings in two patients with nonsevere Covid-19 and in another two patients with severe Covid-19 are provided in Figure S1 in the Supplementary Appendix. No radiographic or CT abnormality was found in 157 of 877 patients (17.9%) with nonsevere disease and in 5 of 173 patients (2.9%) with severe disease.

On admission, lymphocytopenia was present in 83.2% of the patients, thrombocytopenia in 36.2%, and leukopenia in 33.7%. Most of the patients had elevated levels of C-reactive protein; less common were elevated levels of alanine aminotransferase, aspartate aminotransferase, creatine kinase, and D-dimer. Patients with severe disease had more prominent laboratory abnormalities (including lymphocytopenia and leukopenia) than those with nonsevere disease.

CLINICAL OUTCOMES

None of the 1099 patients were lost to follow-up during the study. A primary composite end-point event occurred in 67 patients (6.1%), including 5.0% who were admitted to the ICU, 2.3% who underwent invasive mechanical ventilation, and 1.4% who died (Table 3). Among the 173 patients with severe disease, a primary composite end-point event occurred in 43 patients (24.9%). Among all the patients, the cumulative risk of the composite end point was 3.6%; among those with severe disease, the cumulative risk was 20.6%.

TREATMENT AND COMPLICATIONS

A majority of the patients (58.0%) received intravenous antibiotic therapy, and 35.8% received oseltamivir therapy; oxygen therapy was administered in 41.3% and mechanical ventilation in 6.1%; higher percentages of patients with severe disease received these therapies (Table 3). Mechanical ventilation was initiated in more patients with severe disease than in those with nonsevere disease (noninvasive ventilation, 32.4% vs. 0%; invasive ventilation, 14.5% vs. 0%). Systemic glucocorticoids were given to 204 patients (18.6%), with a higher percentage among those with severe disease than nonsevere disease (44.5% vs. 13.7%). Of these 204 patients, 33 (16.2%) were admitted to the ICU, 17 (8.3%) underwent invasive ventilation, and 5 (2.5%) died. Extracorporeal membrane oxygenation was performed in 5 patients (0.5%) with severe disease.

The median duration of hospitalization was 12.0 days (mean, 12.8). During hospital admission, most of the patients received a diagnosis of pneumonia from a physician (91.1%), followed by ARDS (3.4%) and shock (1.1%). Patients with severe disease had a higher incidence of physician-diagnosed pneumonia than those with nonsevere disease (99.4% vs. 89.5%).

DISCUSSION

During the initial phase of the Covid-19 outbreak, the diagnosis of the disease was complicated by the diversity in symptoms and imaging findings and in the severity of disease at the time of presentation. Fever was identified in 43.8% of the patients on presentation but developed in 88.7% after hospitalization. Severe illness occurred in 15.7% of the patients after admission to a hospital. No radiologic abnormalities were noted on initial presentation in 2.9% of the patients with severe disease and in 17.9% of those with nonsevere disease. Despite the number of deaths associated with Covid-19, SARS-CoV-2 appears to have a lower case fatality rate than either SARS-CoV or Middle East respiratory syndrome–related coronavirus (MERS-CoV). Compromised respiratory status on admission (the primary driver of disease severity) was associated with worse outcomes.

Approximately 2% of the patients had a history of direct contact with wildlife, whereas more than three quarters were either residents of Wuhan, had visited the city, or had contact with city residents. These findings echo the latest reports, including the outbreak of a family cluster,[4] transmission from an asymptomatic patient,[6] and the three-phase outbreak patterns.[8] Our study cannot preclude the presence of patients who have been termed "super-spreaders."

Conventional routes of transmission of SARS-CoV, MERS-CoV, and highly pathogenic influenza consist of respiratory droplets and direct contact,[18-20] mechanisms that probably occur with SARS-CoV-2 as well. Because SARS-CoV-2 can be detected in the gastrointestinal tract, saliva, and urine, these routes of potential transmission need to be investigated[21] (Tables S1 and S2).

The term Covid-19 has been applied to patients who have laboratory-confirmed symptomatic cases without apparent radiologic manifestations. A better understanding of the spectrum of the disease is needed, since in 8.9% of the patients, SARS-CoV-2 infection was detected before the development of viral pneumonia or viral pneumonia did not develop.

In concert with recent studies,[1,8,12] we found that the clinical characteristics of Covid-19 mimic those of SARS-CoV. Fever and cough were the dominant symptoms and gastrointestinal symptoms were uncommon, which suggests a difference in viral tropism as compared with SARS-CoV, MERS-CoV, and seasonal influenza.[22,23] The absence of fever in Covid-19 is more frequent than in SARS-CoV (1%) and MERS-CoV infection

Table 1. Clinical Characteristics of the Study Patients, According to Disease Severity and the Presence or Absence of the Primary Composite End Point.*

Characteristic	All Patients (N=1099)	Disease Severity		Presence of Primary Composite End Point†	
		Nonsevere (N=926)	Severe (N=173)	Yes (N=67)	No (N=1032)
Age					
Median (IQR) — yr	47.0 (35.0–58.0)	45.0 (34.0–57.0)	52.0 (40.0–65.0)	63.0 (53.0–71.0)	46.0 (35.0–57.0)
Distribution — no./total no. (%)					
0–14 yr	9/1011 (0.9)	8/848 (0.9)	1/163 (0.6)	0	9/946 (1.0)
15–49 yr	557/1011 (55.1)	490/848 (57.8)	67/163 (41.1)	12/65 (18.5)	545/946 (57.6)
50–64 yr	292/1011 (28.9)	241/848 (28.4)	51/163 (31.3)	21/65 (32.3)	271/946 (28.6)
≥65 yr	153/1011 (15.1)	109/848 (12.9)	44/163 (27.0)	32/65 (49.2)	121/946 (12.8)
Female sex — no./total no. (%)	459/1096 (41.9)	386/923 (41.8)	73/173 (42.2)	22/67 (32.8)	437/1029 (42.5)
Smoking history — no./total no. (%)					
Never smoked	927/1085 (85.4)	793/913 (86.9)	134/172 (77.9)	44/66 (66.7)	883/1019 (86.7)
Former smoker	21/1085 (1.9)	12/913 (1.3)	9/172 (5.2)	5/66 (7.6)	16/1019 (1.6)
Current smoker	137/1085 (12.6)	108/913 (11.8)	29/172 (16.9)	17/66 (25.8)	120/1019 (11.8)
Exposure to source of transmission within past 14 days — no./total no.					
Living in Wuhan	483/1099 (43.9)	400/926 (43.2)	83/173 (48.0)	39/67 (58.2)	444/1032 (43.0)
Contact with wildlife	13/687 (1.9)	10/559 (1.8)	3/128 (2.3)	1/41 (2.4)	12/646 (1.9)
Recently visited Wuhan‡	193/616 (31.3)	166/526 (31.6)	27/90 (30.0)	10/28 (35.7)	183/588 (31.1)
Had contact with Wuhan residents‡	442/611 (72.3)	376/522 (72.0)	66/89 (74.2)	19/28 (67.9)	423/583 (72.6)
Median incubation period (IQR) — days§	4.0 (2.0–7.0)	4.0 (2.8–7.0)	4.0 (2.0–7.0)	4.0 (1.0–7.5)	4.0 (2.0–7.0)
Fever on admission					
Patients — no./total no. (%)	473/1081 (43.8)	391/910 (43.0)	82/171 (48.0)	24/66 (36.4)	449/1015 (44.2)
Median temperature (IQR) — °C	37.3 (36.7–38.0)	37.3 (36.7–38.0)	37.4 (36.7–38.1)	36.8 (36.3–37.8)	37.3 (36.7–38.0)
Distribution of temperature — no./total no. (%)					
<37.5°C	608/1081 (56.2)	519/910 (57.0)	89/171 (52.0)	42/66 (63.6)	566/1015 (55.8)
37.5–38.0°C	238/1081 (22.0)	201/910 (22.1)	37/171 (21.6)	10/66 (15.2)	228/1015 (22.5)
38.1–39.0°C	197/1081 (18.2)	160/910 (17.6)	37/171 (21.6)	11/66 (16.7)	186/1015 (18.3)
>39.0°C	38/1081 (3.5)	30/910 (3.3)	8/171 (4.7)	3/66 (4.5)	35/1015 (3.4)
Fever during hospitalization					
Patients — no./total no. (%)	975/1099 (88.7)	816/926 (88.1)	159/173 (91.9)	59/67 (88.1)	916/1032 (88.8)
Median highest temperature (IQR) — °C	38.3 (37.8–38.9)	38.3 (37.8–38.9)	38.5 (38.0–39.0)	38.5 (38.0–39.0)	38.3 (37.8–38.9)
<37.5°C	92/926 (9.9)	79/774 (10.2)	13/152 (8.6)	3/54 (5.6)	89/872 (10.2)
37.5–38.0°C	286/926 (30.9)	251/774 (32.4)	35/152 (23.0)	20/54 (37.0)	266/872 (30.5)
38.1–39.0°C	434/926 (46.9)	356/774 (46.0)	78/152 (51.3)	21/54 (38.9)	413/872 (47.4)
>39.0°C	114/926 (12.3)	88/774 (11.4)	26/152 (17.1)	10/54 (18.5)	104/872 (11.9)

Symptoms — no. (%)					
Conjunctival congestion	9 (0.8)	5 (0.5)	4 (2.3)	0	9 (0.9)
Nasal congestion	53 (4.8)	47 (5.1)	6 (3.5)	2 (3.0)	51 (4.9)
Headache	150 (13.6)	124 (13.4)	26 (15.0)	8 (11.9)	142 (13.8)
Cough	745 (67.8)	623 (67.3)	122 (70.5)	46 (68.7)	699 (67.7)
Sore throat	153 (13.9)	130 (14.0)	23 (13.3)	6 (9.0)	147 (14.2)
Sputum production	370 (33.7)	309 (33.4)	61 (35.3)	20 (29.9)	350 (33.9)
Fatigue	419 (38.1)	350 (37.8)	69 (39.9)	22 (32.8)	397 (38.5)
Hemoptysis	10 (0.9)	6 (0.6)	4 (2.3)	2 (3.0)	8 (0.8)
Shortness of breath	205 (18.7)	140 (15.1)	65 (37.6)	36 (53.7)	169 (16.4)
Nausea or vomiting	55 (5.0)	43 (4.6)	12 (6.9)	3 (4.5)	52 (5.0)
Diarrhea	42 (3.8)	32 (3.5)	10 (5.8)	4 (6.0)	38 (3.7)
Myalgia or arthralgia	164 (14.9)	134 (14.5)	30 (17.3)	6 (9.0)	158 (15.3)
Chills	126 (11.5)	100 (10.8)	26 (15.0)	8 (11.9)	118 (11.4)
Signs of infection — no. (%)					
Throat congestion	19 (1.7)	17 (1.8)	2 (1.2)	0	19 (1.8)
Tonsil swelling	23 (2.1)	17 (1.8)	6 (3.5)	1 (1.5)	22 (2.1)
Enlargement of lymph nodes	2 (0.2)	1 (0.1)	1 (0.6)	1 (1.5)	1 (0.1)
Rash	2 (0.2)	0	2 (1.2)	0	2 (0.2)
Coexisting disorder — no. (%)					
Any	261 (23.7)	194 (21.0)	67 (38.7)	39 (58.2)	222 (21.5)
Chronic obstructive pulmonary disease	12 (1.1)	6 (0.6)	6 (3.5)	7 (10.4)	5 (0.5)
Diabetes	81 (7.4)	53 (5.7)	28 (16.2)	18 (26.9)	63 (6.1)
Hypertension	165 (15.0)	124 (13.4)	41 (23.7)	24 (35.8)	141 (13.7)
Coronary heart disease	27 (2.5)	17 (1.8)	10 (5.8)	6 (9.0)	21 (2.0)
Cerebrovascular disease	15 (1.4)	11 (1.2)	4 (2.3)	4 (6.0)	11 (1.1)
Hepatitis B infection¶	23 (2.1)	22 (2.4)	1 (0.6)	1 (1.5)	22 (2.1)
Cancer‖	10 (0.9)	7 (0.8)	3 (1.7)	1 (1.5)	9 (0.9)
Chronic renal disease	8 (0.7)	5 (0.5)	3 (1.7)	2 (3.0)	6 (0.6)
Immunodeficiency	2 (0.2)	2 (0.2)	0	0	2 (0.2)

* The denominators of patients who were included in the analysis are provided if they differed from the overall numbers in the group. Percentages may not total 100 because of rounding. Covid-19 denotes coronavirus disease 2019, and IQR interquartile range.
† The primary composite end point was admission to an intensive care unit, the use of mechanical ventilation, or death.
‡ These patients were not residents of Wuhan.
§ Data regarding the incubation period were missing for 808 patients (73.5%).
¶ The presence of hepatitis B infection was defined as a positive result on testing for hepatitis B surface antigen with or without elevated levels of alanine or aspartate aminotransferase.
‖ Included in this category is any type of cancer.

Table 2. Radiographic and Laboratory Findings.*

Variable	All Patients (N=1099)	Disease Severity		Presence of Composite Primary End Point	
		Nonsevere (N=926)	Severe (N=173)	Yes (N=67)	No (N=1032)
Radiologic findings					
Abnormalities on chest radiograph — no./total no. (%)	162/274 (59.1)	116/214 (54.2)	46/60 (76.7)	30/39 (76.9)	132/235 (56.2)
Ground-glass opacity	55/274 (20.1)	37/214 (17.3)	18/60 (30.0)	9/39 (23.1)	46/235 (19.6)
Local patchy shadowing	77/274 (28.1)	56/214 (26.2)	21/60 (35.0)	13/39 (33.3)	64/235 (27.2)
Bilateral patchy shadowing	100/274 (36.5)	65/214 (30.4)	35/60 (58.3)	27/39 (69.2)	73/235 (31.1)
Interstitial abnormalities	12/274 (4.4)	7/214 (3.3)	5/60 (8.3)	6/39 (15.4)	6/235 (2.6)
Abnormalities on chest CT — no./total no. (%)	840/975 (86.2)	682/808 (84.4)	158/167 (94.6)	50/57 (87.7)	790/918 (86.1)
Ground-glass opacity	550/975 (56.4)	449/808 (55.6)	101/167 (60.5)	30/57 (52.6)	520/918 (56.6)
Local patchy shadowing	409/975 (41.9)	317/808 (39.2)	92/167 (55.1)	22/57 (38.6)	387/918 (42.2)
Bilateral patchy shadowing	505/975 (51.8)	368/808 (45.5)	137/167 (82.0)	40/57 (70.2)	465/918 (50.7)
Interstitial abnormalities	143/975 (14.7)	99/808 (12.3)	44/167 (26.3)	15/57 (26.3)	128/918 (13.9)
Laboratory findings					
Median Pa_{O_2}:FI_{O_2} ratio (IQR)†	3.9 (2.9–4.7)	3.9 (2.9–4.5)	4.0 (2.8–5.2)	2.9 (2.2–5.4)	4.0 (3.1–4.6)
White-cell count					
Median (IQR) — per mm^3	4700 (3500–6000)	4900 (3800–6000)	3700 (3000–6200)	6100 (4900–11,100)	4700 (3500–5900)
Distribution — no./total no. (%)					
>10,000 per mm^3	58/978 (5.9)	39/811 (4.8)	19/167 (11.4)	15/58 (25.9)	43/920 (4.7)
<4000 per mm^3	330/978 (33.7)	228/811 (28.1)	102/167 (61.1)	8/58 (13.8)	322/920 (35.0)
Lymphocyte count					
Median (IQR) — per mm^3	1000 (700–1300)	1000 (800–1400)	800 (600–1000)	700 (600–900)	1000 (700–1300)
Distribution — no./total no. (%)					
<1500 per mm^3	731/879 (83.2)	584/726 (80.4)	147/153 (96.1)	50/54 (92.6)	681/825 (82.5)

Platelet count					
Median (IQR) — per mm^3	168,000 (132,000–207,000)	172,000 (139,000–212,000)	137,500 (99,000–179,500)	156,500 (114,200–195,000)	169,000 (133,000–207,000)
Distribution — no./total no. (%)					
<150,000 per mm^3	315/869 (36.2)	225/713 (31.6)	90/156 (57.7)	27/58 (46.6)	288/811 (35.5)
Median hemoglobin (IQR) — g/dl‡	13.4. (11.9–14.8)	13.5 (12.0–14.8)	12.8 (11.2–14.1)	12.5 (10.5–14.0)	13.4 (12.0–14.8)
Distribution of other findings — no./total no. (%)					
C-reactive protein ≥10 mg/liter	481/793 (60.7)	371/658 (56.4)	110/135 (81.5)	41/45 (91.1)	440/748 (58.8)
Procalcitonin ≥0.5 ng/ml	35/633 (5.5)	19/516 (3.7)	16/117 (13.7)	12/50 (24.0)	23/583 (3.9)
Lactate dehydrogenase ≥250 U/liter	277/675 (41.0)	205/551 (37.2)	72/124 (58.1)	31/44 (70.5)	246/631 (39.0)
Aspartate aminotransferase >40 U/liter	168/757 (22.2)	112/615 (18.2)	56/142 (39.4)	26/52 (50.0)	142/705 (20.1)
Alanine aminotransferase >40 U/liter	158/741 (21.3)	120/606 (19.8)	38/135 (28.1)	20/49 (40.8)	138/692 (19.9)
Total bilirubin >17.1 μmol/liter	76/722 (10.5)	59/594 (9.9)	17/128 (13.3)	10/48 (20.8)	66/674 (9.8)
Creatine kinase ≥200 U/liter	90/657 (13.7)	67/536 (12.5)	23/121 (19.0)	12/46 (26.1)	78/611 (12.8)
Creatinine ≥133 μmol/liter	12/752 (1.6)	6/614 (1.0)	6/138 (4.3)	5/52 (9.6)	7/700 (1.0)
D-dimer ≥0.5 mg/liter	260/560 (46.4)	195/451 (43.2)	65/109 (59.6)	34/49 (69.4)	226/511 (44.2)
Minerals§					
Median sodium (IQR) — mmol/liter	138.2 (136.1–140.3)	138.4 (136.6–140.4)	138.0 (136.0–140.0)	138.3 (135.0–141.2)	138.2 (136.1–140.2)
Median potassium (IQR) — mmol/liter	3.8 (3.5–4.2)	3.9 (3.6–4.2)	3.8 (3.5–4.1)	3.9 (3.6–4.1)	3.8 (3.5–4.2)
Median chloride (IQR) — mmol/liter	102.9 (99.7–105.6)	102.7 (99.7–105.3)	103.1 (99.8–106.0)	103.8 (100.8–107.0)	102.8 (99.6–105.3)

* Lymphocytopenia was defined as a lymphocyte count of less than 1500 per cubic millimeter. Thrombocytopenia was defined as a platelet count of less than 150,000 per cubic millimeter. To convert the values for creatinine to milligrams per deciliter, divide by 88.4.
† Data regarding the ratio of the partial pressure of arterial oxygen to the fraction of inspired oxygen (Pa_{O_2}:F_{IO_2}) were missing for 894 patients (81.3%).
‡ Data regarding hemoglobin were missing for 226 patients (20.6%).
§ Data were missing for the measurement of sodium in 363 patients (33.0%), for potassium in 349 patients (31.8%), and for chloride in 392 patients (35.7%).

Table 3. Complications, Treatments, and Clinical Outcomes.

Variable	All Patients (N=1099)	Disease Severity		Presence of Composite Primary End Point	
		Nonsevere (N=926)	Severe (N=173)	Yes (N=67)	No (N=1032)
Complications					
Septic shock — no. (%)	12 (1.1)	1 (0.1)	11 (6.4)	9 (13.4)	3 (0.3)
Acute respiratory distress syndrome — no. (%)	37 (3.4)	10 (1.1)	27 (15.6)	27 (40.3)	10 (1.0)
Acute kidney injury — no. (%)	6 (0.5)	1 (0.1)	5 (2.9)	4 (6.0)	2 (0.2)
Disseminated intravascular coagulation — no. (%)	1 (0.1)	0	1 (0.6)	1 (1.5)	0
Rhabdomyolysis — no. (%)	2 (0.2)	2 (0.2)	0	0	2 (0.2)
Physician-diagnosed pneumonia — no./total no. (%)	972/1067 (91.1)	800/894 (89.5)	172/173 (99.4)	63/66 (95.5)	909/1001 (90.8)
Median time until development of pneumonia (IQR) — days*					
After initial Covid-19 diagnosis	0.0 (0.0–1.0)	0.0 (0.0–1.0)	0.0 (0.0–2.0)	0.0 (0.0–3.5)	0.0 (0.0–1.0)
After onset of Covid-19 symptoms	3.0 (1.0–6.0)	3.0 (1.0–6.0)	5.0 (2.0–7.0)	4.0 (0.0–7.0)	3.0 (1.0–6.0)
Treatments					
Intravenous antibiotics — no. (%)	637 (58.0)	498 (53.8)	139 (80.3)	60 (89.6)	577 (55.9)
Oseltamivir — no. (%)	393 (35.8)	313 (33.8)	80 (46.2)	36 (53.7)	357 (34.6)
Antifungal medication — no. (%)	31 (2.8)	18 (1.9)	13 (7.5)	8 (11.9)	23 (2.2)
Systemic glucocorticoids — no. (%)	204 (18.6)	127 (13.7)	77 (44.5)	35 (52.2)	169 (16.4)
Oxygen therapy — no. (%)	454 (41.3)	331 (35.7)	123 (71.1)	59 (88.1)	395 (38.3)
Mechanical ventilation — no. (%)	67 (6.1)	0	67 (38.7)	40 (59.7)	27 (2.6)
Invasive	25 (2.3)	0	25 (14.5)	25 (37.3)	0
Noninvasive	56 (5.1)	0	56 (32.4)	29 (43.3)	27 (2.6)
Use of extracorporeal membrane oxygenation — no. (%)	5 (0.5)	0	5 (2.9)	5 (7.5)	0
Use of continuous renal-replacement therapy — no. (%)	9 (0.8)	0	9 (5.2)	8 (11.9)	1 (0.1)
Use of intravenous immune globulin — no. (%)	144 (13.1)	86 (9.3)	58 (33.5)	27 (40.3)	117 (11.3)
Admission to intensive care unit — no. (%)	55 (5.0)	22 (2.4)	33 (19.1)	55 (82.1)	0
Median length of hospital stay (IQR) — days†	12.0 (10.0–14.0)	11.0 10.0–13.0)	13.0 (11.5–17.0)	14.5 (11.0–19.0)	12.0 (10.0–13.0)

Clinical outcomes at data cutoff — no. (%)					
Discharge from hospital	55 (5.0)	50 (5.4)	5 (2.9)	1 (1.5)	54 (5.2)
Death	15 (1.4)	1 (0.1)	14 (8.1)	15 (22.4)	0
Recovery	9 (0.8)	7 (0.8)	2 (1.2)	0	9 (0.9)
Hospitalization	1029 (93.6)	875 (94.5)	154 (89.0)	51 (76.1)	978 (94.8)

* For the development of pneumonia, data were missing for 347 patients (31.6%) regarding the time since the initial diagnosis and for 161 patients (14.6%) regarding the time since symptom onset.

† Data regarding the median length of hospital stay were missing for 136 patients (12.4%).

(2%),[20] so afebrile patients may be missed if the surveillance case definition focuses on fever detection.[14] Lymphocytopenia was common and, in some cases, severe, a finding that was consistent with the results of two recent reports.[1,12] We found a lower case fatality rate (1.4%) than the rate that was recently reportedly,[1,12] probably because of the difference in sample sizes and case inclusion criteria. Our findings were more similar to the national official statistics, which showed a rate of death of 3.2% among 51,857 cases of Covid-19 as of February 16, 2020.[11,24] Since patients who were mildly ill and who did not seek medical attention were not included in our study, the case fatality rate in a real-world scenario might be even lower. Early isolation, early diagnosis, and early management might have collectively contributed to the reduction in mortality in Guangdong.

Despite the phylogenetic homogeneity between SARS-CoV-2 and SARS-CoV, there are some clinical characteristics that differentiate Covid-19 from SARS-CoV, MERS-CoV, and seasonal influenza infections. (For example, seasonal influenza has been more common in respiratory outpatient clinics and wards.) Some additional characteristics that are unique to Covid-19 are detailed in Table S3.

Our study has some notable limitations. First, some cases had incomplete documentation of the exposure history and laboratory testing, given the variation in the structure of electronic databases among different participating sites and the urgent timeline for data extraction. Some cases were diagnosed in outpatient settings where medical information was briefly documented and incomplete laboratory testing was performed, along with a shortage of infrastructure and training of medical staff in nonspecialty hospitals. Second, we could estimate the incubation period in only 291 of the study patients who had documented information. The uncertainty of the exact dates (recall bias) might have inevitably affected our assessment. Third, because many patients remained in the hospital and the outcomes were unknown at the time of data cutoff, we censored the data regarding their clinical outcomes as of the time of our analysis. Fourth, we no doubt missed patients who were asymptomatic or had mild cases and who were treated at home, so our study cohort may represent the more severe end of Covid-19. Fifth, many patients did not undergo sputum bacteriologic or fungal assessment on admission because, in some hospitals, medical resources were overwhelmed. Sixth, data generation was clinically driven and not systematic.

Covid-19 has spread rapidly since it was first identified in Wuhan and has been shown to have a wide spectrum of severity. Some patients with Covid-19 do not have fever or radiologic abnormalities on initial presentation, which has complicated the diagnosis.

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APPENDIX

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EDITORIAL

Covid-19 — Navigating the Uncharted

Anthony S. Fauci, M.D., H. Clifford Lane, M.D., and Robert R. Redfield, M.D.

The latest threat to global health is the ongoing outbreak of the respiratory disease that was recently given the name Coronavirus Disease 2019 (Covid-19). Covid-19 was recognized in December 2019.[1] It was rapidly shown to be caused by a novel coronavirus that is structurally related to the virus that causes severe acute respiratory syndrome (SARS). As in two preceding instances of emergence of coronavirus disease in the past 18 years[2] — SARS (2002 and 2003) and Middle East respiratory syndrome (MERS) (2012 to the present) — the Covid-19 outbreak has posed critical challenges for the public health, research, and medical communities.

In their *Journal* article, Li and colleagues[3] provide a detailed clinical and epidemiologic description of the first 425 cases reported in the epicenter of the outbreak: the city of Wuhan in Hubei province, China. Although this information is critical in informing the appropriate response to this outbreak, as the authors point out, the study faces the limitation associated with reporting in real time the evolution of an emerging pathogen in its earliest stages. Nonetheless, a degree of clarity is emerging from this report. The median age of the patients was 59 years, with higher morbidity and mortality among the elderly and among those with coexisting conditions (similar to the situation with influenza); 56% of the patients were male. Of note, there were no cases in children younger than 15 years of age. Either children are less likely to become infected, which would have important epidemiologic implications, or their symptoms were so mild that their infection escaped detection, which has implications for the size of the denominator of total community infections.

On the basis of a case definition requiring a diagnosis of pneumonia, the currently reported case fatality rate is approximately 2%.[4] In another article in the *Journal*, Guan et al.[5] report mortality of 1.4% among 1099 patients with laboratory-confirmed Covid-19; these patients had a wide spectrum of disease severity. If one assumes that the number of asymptomatic or minimally symptomatic cases is several times as high as the number of reported cases, the case fatality rate may be considerably less than 1%. This suggests that the overall clinical consequences of Covid-19 may ultimately be more akin to those of a severe seasonal influenza (which has a case fatality rate of approximately 0.1%) or a pandemic influenza (similar to those in 1957 and 1968) rather than a disease similar to SARS or MERS, which have had case fatality rates of 9 to 10% and 36%, respectively.[2]

The efficiency of transmission for any respiratory virus has important implications for containment and mitigation strategies. The current study indicates an estimated basic reproduction number (R_0) of 2.2, which means that, on average, each infected person spreads the infection to an additional two persons. As the authors note, until this number falls below 1.0, it is likely that the outbreak will continue to spread. Recent reports of high titers of virus in the oropharynx early in the course of disease arouse concern about increased infectivity during the period of minimal symptoms.[6,7]

China, the United States, and several other countries have instituted temporary restrictions on travel with an eye toward slowing the spread of this new disease within China and throughout the rest of the world. The United States has seen a dramatic reduction in the number of travelers from China, especially from Hubei province.

At least on a temporary basis, such restrictions may have helped slow the spread of the virus: whereas 78,191 laboratory-confirmed cases had been identified in China as of February 26, 2020, a total of 2918 cases had been confirmed in 37 other countries or territories.[4] As of February 26, 2020, there had been 14 cases detected in the United States involving travel to China or close contacts with travelers, 3 cases among U.S. citizens repatriated from China, and 42 cases among U.S. passengers repatriated from a cruise ship where the infection had spread.[8] However, given the efficiency of transmission as indicated in the current report, we should be prepared for Covid-19 to gain a foothold throughout the world, including in the United States. Community spread in the United States could require a shift from containment to mitigation strategies such as social distancing in order to reduce transmission. Such strategies could include isolating ill persons (including voluntary isolation at home), school closures, and telecommuting where possible.[9]

A robust research effort is currently under way to develop a vaccine against Covid-19.[10] We anticipate that the first candidates will enter phase 1 trials by early spring. Therapy currently consists of supportive care while a variety of investigational approaches are being explored.[11] Among these are the antiviral medication lopinavir–ritonavir, interferon-1β, the RNA polymerase inhibitor remdesivir, chloroquine, and a variety of traditional Chinese medicine products.[11] Once available, intravenous hyperimmune globulin from recovered persons and monoclonal antibodies may be attractive candidates to study in early intervention. Critical to moving the field forward, even in the context of an outbreak, is ensuring that investigational products are evaluated in scientifically and ethically sound studies.[12]

Every outbreak provides an opportunity to gain important information, some of which is associated with a limited window of opportunity. For example, Li et al. report a mean interval of 9.1 to 12.5 days between the onset of illness and hospitalization. This finding of a delay in the progression to serious disease may be telling us something important about the pathogenesis of this new virus and may provide a unique window of opportunity for intervention. Achieving a better understanding of the pathogenesis of this disease will be invaluable in navigating our responses in this uncharted arena. Furthermore, genomic studies could delineate host factors that predispose persons to acquisition of infection and disease progression.

The Covid-19 outbreak is a stark reminder of the ongoing challenge of emerging and reemerging infectious pathogens and the need for constant surveillance, prompt diagnosis, and robust research to understand the basic biology of new organisms and our susceptibilities to them, as well as to develop effective countermeasures.

Disclosure forms provided by the authors are available with the full text of this editorial at NEJM.org.

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Early Transmission Dynamics in Wuhan, China, of Novel Coronavirus–Infected Pneumonia

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ABSTRACT

BACKGROUND

The initial cases of novel coronavirus (2019-nCoV)–infected pneumonia (NCIP) occurred in Wuhan, Hubei Province, China, in December 2019 and January 2020. We analyzed data on the first 425 confirmed cases in Wuhan to determine the epidemiologic characteristics of NCIP.

METHODS

We collected information on demographic characteristics, exposure history, and illness timelines of laboratory-confirmed cases of NCIP that had been reported by January 22, 2020. We described characteristics of the cases and estimated the key epidemiologic time-delay distributions. In the early period of exponential growth, we estimated the epidemic doubling time and the basic reproductive number.

RESULTS

Among the first 425 patients with confirmed NCIP, the median age was 59 years and 56% were male. The majority of cases (55%) with onset before January 1, 2020, were linked to the Huanan Seafood Wholesale Market, as compared with 8.6% of the subsequent cases. The mean incubation period was 5.2 days (95% confidence interval [CI], 4.1 to 7.0), with the 95th percentile of the distribution at 12.5 days. In its early stages, the epidemic doubled in size every 7.4 days. With a mean serial interval of 7.5 days (95% CI, 5.3 to 19), the basic reproductive number was estimated to be 2.2 (95% CI, 1.4 to 3.9).

CONCLUSIONS

On the basis of this information, there is evidence that human-to-human transmission has occurred among close contacts since the middle of December 2019. Considerable efforts to reduce transmission will be required to control outbreaks if similar dynamics apply elsewhere. Measures to prevent or reduce transmission should be implemented in populations at risk. (Funded by the Ministry of Science and Technology of China and others.)

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Since December 2019, an increasing number of cases of novel coronavirus (2019-nCoV)–infected pneumonia (NCIP) have been identified in Wuhan, a large city of 11 million people in central China.[1-3] On December 29, 2019, the first 4 cases reported, all linked to the Huanan (Southern China) Seafood Wholesale Market, were identified by local hospitals using a surveillance mechanism for "pneumonia of unknown etiology" that was established in the wake of the 2003 severe acute respiratory syndrome (SARS) outbreak with the aim of allowing timely identification of novel pathogens such as 2019-nCoV.[4] In recent days, infections have been identified in other Chinese cities and in more than a dozen countries around the world.[5] Here, we provide an analysis of data on the first 425 laboratory-confirmed cases in Wuhan to describe the epidemiologic characteristics and transmission dynamics of NCIP.

Methods

Sources of Data

The earliest cases were identified through the "pneumonia of unknown etiology" surveillance mechanism.[4] Pneumonia of unknown etiology is defined as an illness without a causative pathogen identified that fulfills the following criteria: fever (≥38°C), radiographic evidence of pneumonia, low or normal white-cell count or low lymphocyte count, and no symptomatic improvement after antimicrobial treatment for 3 to 5 days following standard clinical guidelines. In response to the identification of pneumonia cases and in an effort to increase the sensitivity for early detection, we developed a tailored surveillance protocol to identify potential cases on January 3, 2020, using the case definitions described below.[1] Once a suspected case was identified, the joint field epidemiology team comprising members from the Chinese Center for Disease Control and Prevention (China CDC) together with provincial, local municipal CDCs and prefecture CDCs would be informed to initiate detailed field investigations and collect respiratory specimens for centralized testing at the National Institute for Viral Disease Control and Prevention, China CDC, in Beijing. A joint team comprising staff from China CDC and local CDCs conducted detailed field investigations for all suspected and confirmed 2019-nCoV cases.

Data were collected onto standardized forms through interviews of infected persons, relatives, close contacts, and health care workers. We collected information on the dates of illness onset, visits to clinical facilities, hospitalization, and clinical outcomes. Epidemiologic data were collected through interviews and field reports. Investigators interviewed each patient with infection and their relatives, where necessary, to determine exposure histories during the 2 weeks before the illness onset, including the dates, times, frequency, and patterns of exposures to any wild animals, especially those purportedly available in the Huanan Seafood Wholesale Market in Wuhan, or exposures to any relevant environments such as that specific market or other wet markets. Information about contact with others with similar symptoms was also included. All epidemiologic information collected during field investigations, including exposure history, timelines of events, and close contact identification, was cross-checked with information from multiple sources. Households and places known to have been visited by the patients in the 2 weeks before the onset of illness were also investigated to assess for possible animal and environmental exposures. Data were entered into a central database, in duplicate, and were verified with EpiData software (EpiData Association).

Case Definitions

The initial working case definitions for suspected NCIP were based on the SARS and Middle East respiratory syndrome (MERS) case definitions, as recommended by the World Health Organization (WHO) in 2003 and 2012.[6-8] A suspected NCIP case was defined as a pneumonia that either fulfilled all the following four criteria — fever, with or without recorded temperature; radiographic evidence of pneumonia; low or normal white-cell count or low lymphocyte count; and no reduction in symptoms after antimicrobial treatment for 3 days, following standard clinical guidelines — or fulfilled the abovementioned first three criteria and had an epidemiologic link to the Huanan Seafood Wholesale Market or contact with other patients with similar symptoms. The epidemiologic criteria to define a suspected case were updated on January 18, 2020, once new information on identified cases became available. The criteria were the following: a travel history to Wuhan or direct contact with patients from Wuhan who had fever or respiratory symptoms, within 14 days before illness onset.[9] A confirmed case was defined as a case with respiratory specimens that tested positive for the 2019-nCoV by at least one of the following three methods: isolation of 2019-nCoV or at least two positive results by real-time reverse-transcription–polymerase-chain-reaction (RT-PCR) assay for 2019-nCoV or a genetic sequence that matches 2019-nCoV.

LABORATORY TESTING

The 2019-nCoV laboratory test assays were based on the previous WHO recommendation.[10] Upper and lower respiratory tract specimens were obtained from patients. RNA was extracted and tested by real-time RT-PCR with 2019-nCoV–specific primers and probes. Tests were carried out in biosafety level 2 facilities at the Hubei (provincial) CDC and then at the National Institute for Viral Disease Control at China CDC. If two targets (open reading frame 1a or 1b, nucleocapsid protein) tested positive by specific real-time RT-PCR, the case would be considered to be laboratory-confirmed. A cycle threshold value (Ct-value) less than 37 was defined as a positive test, and a Ct-value of 40 or more was defined as a negative test. A medium load, defined as a Ct-value of 37 to less than 40, required confirmation by retesting. If the repeated Ct-value was less than 40 and an obvious peak was observed, or if the repeated Ct-value was less than 37, the retest was deemed positive. The genome was identified in samples of bronchoalveolar-lavage fluid from the patient by one of three methods: Sanger sequencing, Illumina sequencing, or nanopore sequencing. Respiratory specimens were inoculated in cells for viral isolation in enhanced biosafety laboratory 3 facilities at the China CDC.[3]

STATISTICAL ANALYSIS

The epidemic curve was constructed by date of illness onset, and key dates relating to epidemic identification and control measures were overlaid to aid interpretation. Case characteristics were described, including demographic characteristics, exposures, and health care worker status. The incubation period distribution (i.e., the time delay from infection to illness onset) was estimated by fitting a log-normal distribution to data on exposure histories and onset dates in a subset of cases with detailed information available. Onset-to-first-medical-visit and onset-to-admission distributions were estimated by fitting a Weibull distribution on the dates of illness onset, first medical visit, and hospital admission in a subset of cases with detailed information available. We fitted a gamma distribution to data from cluster investigations to estimate the serial interval distribution, defined as the delay between illness onset dates in successive cases in chains of transmission.

We estimated the epidemic growth rate by analyzing data on the cases with illness onset between December 10 and January 4, because we expected the proportion of infections identified would increase soon after the formal announcement of the outbreak in Wuhan on December 31. We fitted a transmission model (formulated with the use of renewal equations) with zoonotic infections to onset dates that were not linked to the Huanan Seafood Wholesale Market, and we used this model to derive the epidemic growth rate, the epidemic doubling time, and the basic reproductive number (R_0), which is defined as the expected number of additional cases that one case will generate, on average, over the course of its infectious period in an otherwise uninfected population. We used an informative prior distribution for the serial interval based on the serial interval of SARS with a mean of 8.4 and a standard deviation of 3.8.[11]

Analyses of the incubation period, serial interval, growth rate, and R_0 were performed with the use of MATLAB software (MathWorks). Other analyses were performed with the use of SAS software (SAS Institute) and R software (R Foundation for Statistical Computing).

ETHICS APPROVAL

Data collection and analysis of cases and close contacts were determined by the National Health Commission of the People's Republic of China to be part of a continuing public health outbreak investigation and were thus considered exempt from institutional review board approval.

RESULTS

The development of the epidemic follows an exponential growth in cases, and a decline in the most recent days is likely to be due to underascertainment of cases with recent onset and delayed identification and reporting rather than

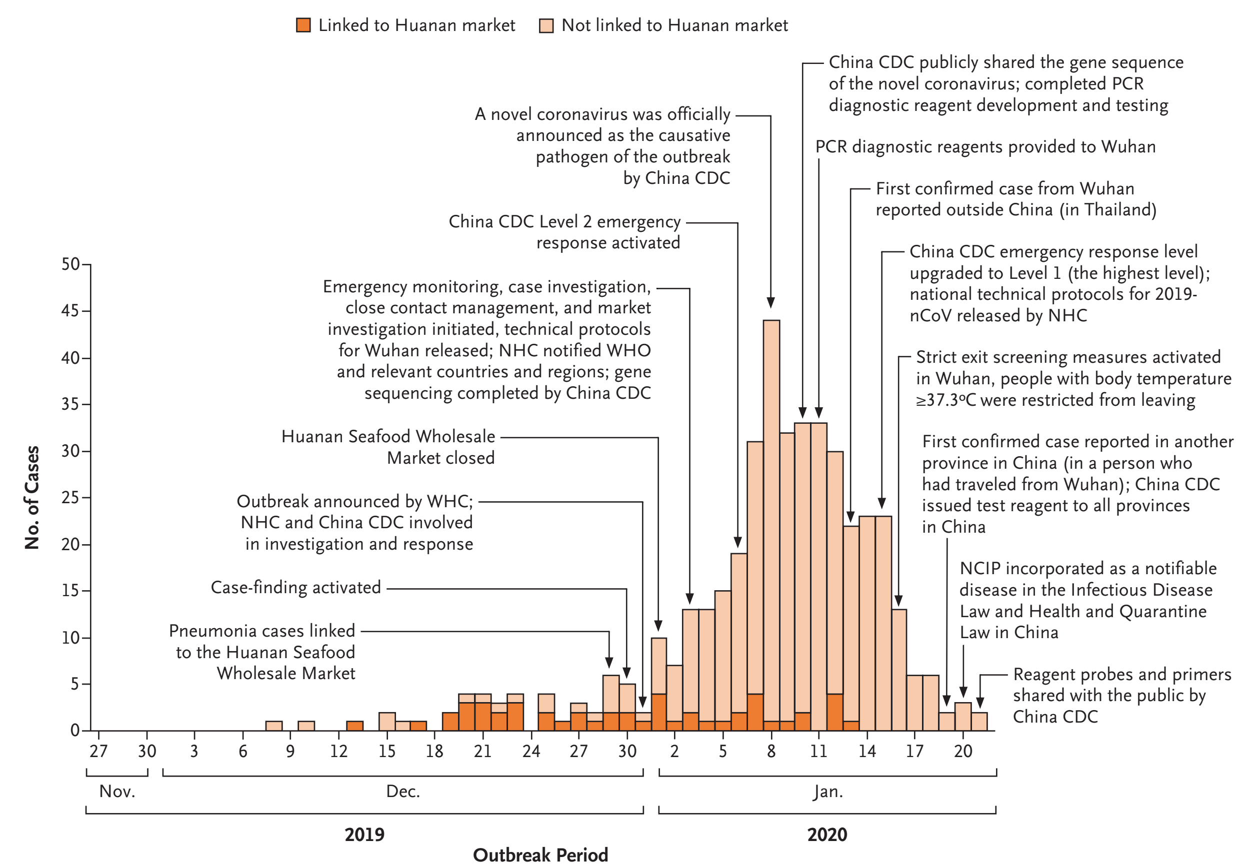


Figure 1. Onset of Illness among the First 425 Confirmed Cases of Novel Coronavirus (2019-nCoV)–Infected Pneumonia (NCIP) in Wuhan, China.

The decline in incidence after January 8 is likely to be due to delays in diagnosis and laboratory confirmation. China CDC denotes Chinese Center for Disease Control and Prevention, NHC National Health Commission of the People's Republic of China, PCR polymerase chain reaction, WHC Wuhan Health Commission, and WHO World Health Organization.

a true turning point in incidence (Fig. 1). Specifically, the latter part of the curve does not indicate a decrease in the number of incident cases but is due to delayed case ascertainment at the cutoff date. Care should be taken in interpreting the speed of growth in cases in January, given an increase in the availability and use of testing kits as time has progressed. The majority of the earliest cases included reported exposure to the Huanan Seafood Wholesale Market, but there was an exponential increase in the number of nonlinked cases beginning in late December.

The median age of the patients was 59 years (range, 15 to 89), and 240 of the 425 patients (56%) were male. There were no cases in children below 15 years of age. We examined characteristics of cases in three time periods: the first period was for patients with illness onset before January 1, which was the date the Huanan Seafood Wholesale Market was closed; the second period was for those with onset between January 1 and January 11, which was the date when RT-PCR reagents were provided to Wuhan; and the third period was those with illness onset on or after January 12 (Table 1). The patients with earlier onset were slightly younger, more likely to be male, and much more likely to report exposure to the Huanan Seafood Wholesale Market. The proportion of cases in health care workers gradually increased across the three periods (Table 1).

We examined data on exposures among 10 confirmed cases, and we estimated the mean

Table 1. Characteristics of Patients with Novel Coronavirus–Infected Pneumonia in Wuhan as of January 22, 2020.*

Characteristic	Before January 1 (N=47)	January 1–January 11 (N=248)	January 12–January 22 (N=130)
Median age (range) — yr	56 (26–82)	60 (21–89)	61 (15–89)
Age group — no./total no. (%)			
<15 yr	0/47	0/248	0/130
15–44 yr	12/47 (26)	39/248 (16)	33/130 (25)
45–64 yr	24/47 (51)	106/248 (43)	49/130 (38)
≥65 yr	11/47 (23)	103/248 (42)	48/130 (37)
Male sex — no./total no. (%)	31/47 (66)	147/248 (59)	62/130 (48)
Exposure history — no./total no. (%)			
Wet market exposure	30/47 (64)	32/196 (16)	5/81 (6)
Huanan Seafood Wholesale Market	26/47 (55)	19/196 (10)	5/81 (6)
Other wet market but not Huanan Seafood Wholesale Market	4/47 (9)	13/196 (7)	0/81
Contact with another person with respiratory symptoms	14/47 (30)	30/196 (15)	21/83 (25)
No exposure to either market or person with respiratory symptoms	12/47 (26)	141/196 (72)	59/81 (73)
Health care worker — no./total no. (%)	0/47	7/248 (3)	8/122 (7)

* Reduced denominators indicate missing data. Percentages may not total 100 because of rounding.

incubation period to be 5.2 days (95% confidence interval [CI], 4.1 to 7.0); the 95th percentile of the distribution was 12.5 days (95% CI, 9.2 to 18) (Fig. 2A). We obtained information on 5 clusters of cases, shown in Figure 3. On the basis of the dates of illness onset of 6 pairs of cases in these clusters, we estimated that the serial interval distribution had a mean (±SD) of 7.5±3.4 days (95% CI, 5.3 to 19) (Fig. 2B).

In the epidemic curve up to January 4, 2020, the epidemic growth rate was 0.10 per day (95% CI, 0.050 to 0.16) and the doubling time was 7.4 days (95% CI, 4.2 to 14). Using the serial interval distribution above, we estimated that R_0 was 2.2 (95% CI, 1.4 to 3.9).

The duration from illness onset to first medical visit for 45 patients with illness onset before January 1 was estimated to have a mean of 5.8 days (95% CI, 4.3 to 7.5), which was similar to that for 207 patients with illness onset between January 1 and January 11, with a mean of 4.6 days (95% CI, 4.1 to 5.1) (Fig. 2C). The mean duration from onset to hospital admission was estimated to be 12.5 days (95% CI, 10.3 to 14.8) among 44 cases with illness onset before January 1, which was longer than that among 189 patients with illness onset between January 1 and 11 (mean, 9.1 days; 95% CI, 8.6 to 9.7) (Fig. 2D). We did not plot these distributions for patients with onset on or after January 12, because those with recent onset and longer durations to presentation would not yet have been detected.

DISCUSSION

Here we provide an initial assessment of the transmission dynamics and epidemiologic characteristics of NCIP. Although the majority of the earliest cases were linked to the Huanan Seafood Wholesale Market and the patients could have been infected through zoonotic or environmental exposures, it is now clear that human-to-human transmission has been occurring and that the epidemic has been gradually growing in recent weeks. Our findings provide important parameters for further analyses, including evaluations of the impact of control measures and predictions of the future spread of infection.

We estimated an R_0 of approximately 2.2, meaning that on average each patient has been spreading infection to 2.2 other people. In general, an epidemic will increase as long as R_0 is greater than 1, and control measures aim to reduce the reproductive number to less than 1. The

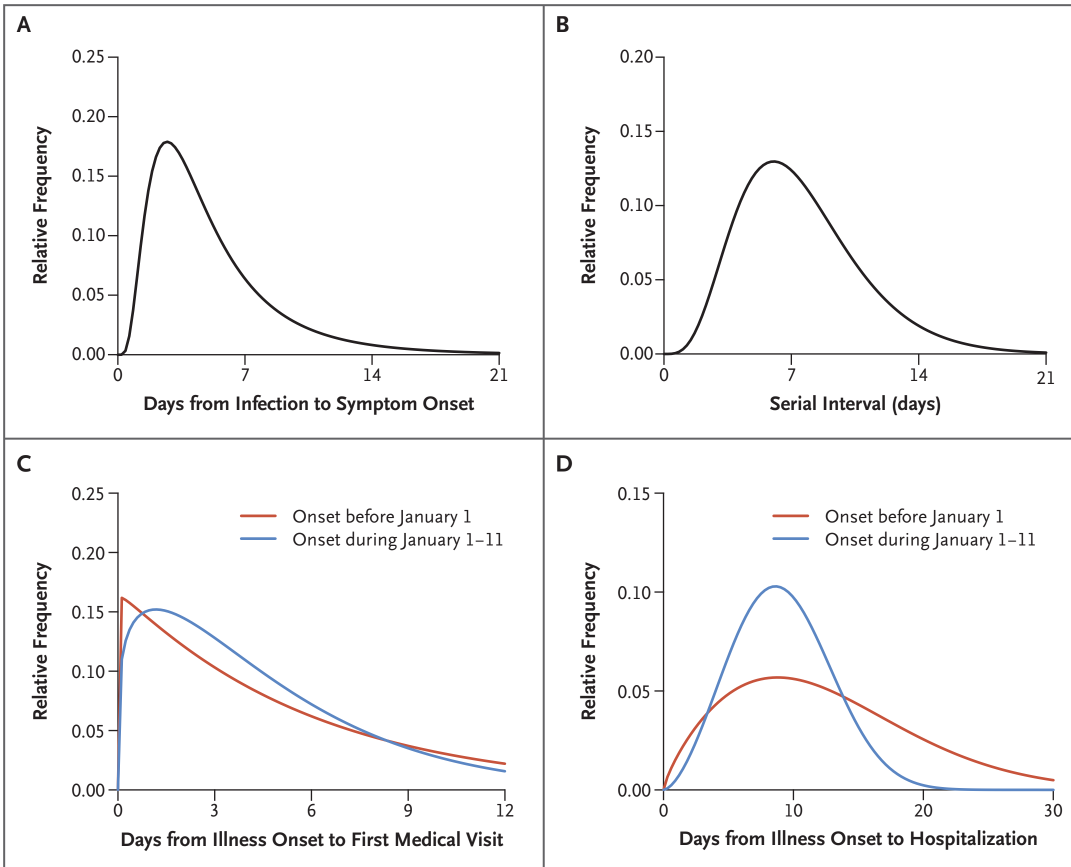
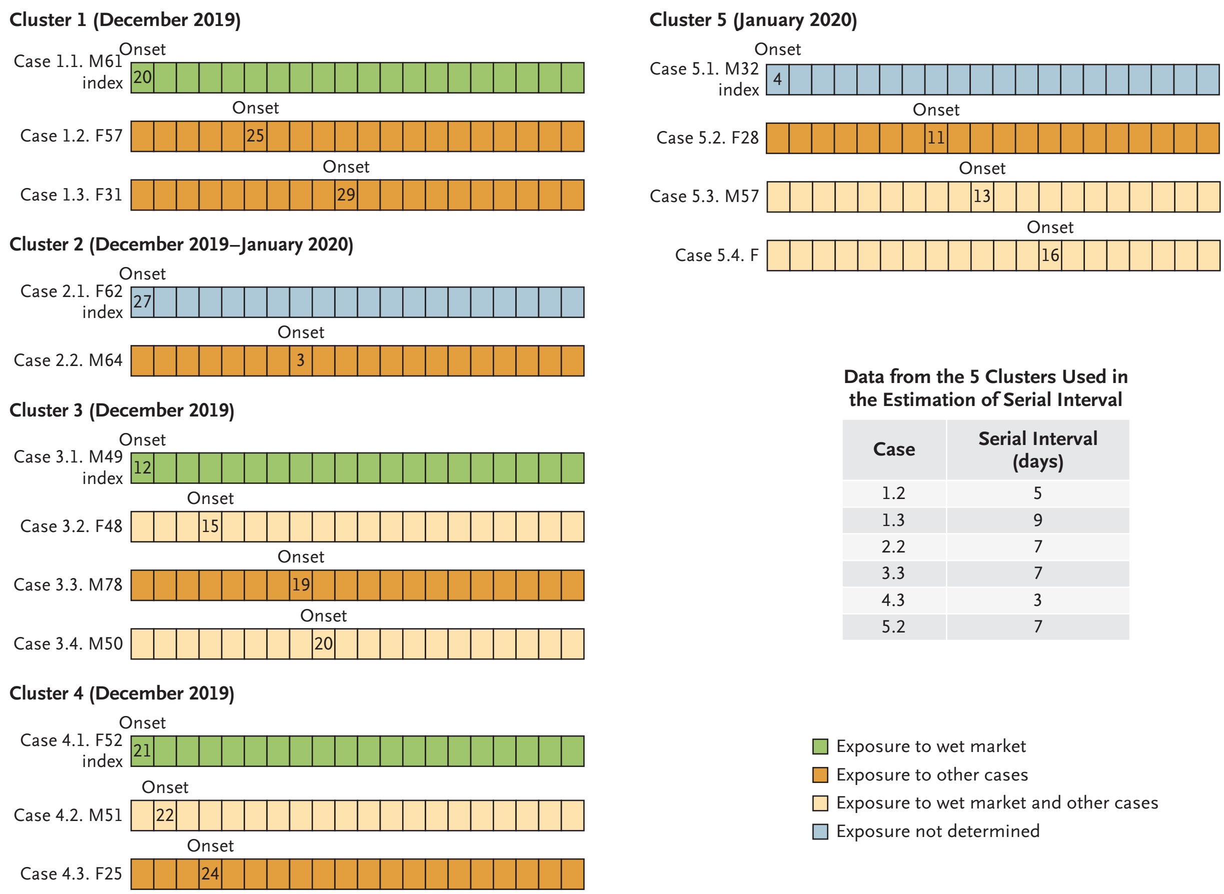


Figure 2. **Key Time-to-Event Distributions.**
The estimated incubation period distribution (i.e., the time from infection to illness onset) is shown in Panel A. The estimated serial interval distribution (i.e., the time from illness onset in successive cases in a transmission chain) is shown in Panel B. The estimated distributions of times from illness onset to first medical visit are shown in Panel C. The estimated distributions of times from illness onset to hospital admission are shown in Panel D.

R_0 of SARS was estimated to be around 3,[12] and SARS outbreaks were successfully controlled by isolation of patients and careful infection control.[13] In the case of NCIP, challenges to control include the apparent presence of many mild infections[14] and limited resources for isolation of cases and quarantine of their close contacts. Our estimate of R_0 was limited to the period up to January 4 because increases in awareness of the outbreak and greater availability and use of tests in more recent weeks will have increased the proportions of infections ascertained. It is possible that subsequent control measures in Wuhan, and more recently elsewhere in the country as well as overseas, have reduced transmissibility, but the detection of an increasing number of cases in other domestic locations and around the world suggest that the epidemic has continued to increase in size. Although the population quarantine of Wuhan and neighboring cities since January 23 should reduce the exportation of cases to the rest of the country and overseas, it is now a priority to determine whether local transmission at a similar intensity is occurring in other locations.

It is notable that few of the early cases occurred in children, and almost half the 425 cases were in adults 60 years of age or older, although our case definition specified severe enough illness to require medical attention, which may vary according to the presence of coexisting conditions. Furthermore, children might be less likely to become infected or, if infected, may show milder symptoms, and either of these situations would account for underrepresentation in the confirmed case count. Serosurveys after the



Data from the 5 Clusters Used in the Estimation of Serial Interval

Case	Serial Interval (days)
1.2	5
1.3	9
2.2	7
3.3	7
4.3	3
5.2	7

Figure 3. Detailed Information on Exposures and Dates of Illness Onset in Five Clusters Including 16 Cases.
Numbers in boxes are calendar dates in December 2019 and January 2020. Data from the 5 secondary cases (patients who had clear exposure to only one index case and had no other potential source of infection) were used to estimate the serial interval distribution. The first four clusters were identified in Wuhan, and the fifth cluster was identified in Huanggang.

first wave of the epidemic would clarify this question. Although infections in health care workers have been detected, the proportion has not been as high as during the SARS and MERS outbreaks.[15] One of the features of SARS and MERS outbreaks is heterogeneity in transmissibility, and in particular the occurrence of super-spreading events, particularly in hospitals.[16] Super-spreading events have not yet been identified for NCIP, but they could become a feature as the epidemic progresses.

Although delays between the onset of illness and seeking medical attention were generally short, with 27% of patients seeking attention within 2 days after onset, delays to hospitalization were much longer, with 89% of patients not being hospitalized until at least day 5 of illness (Fig. 2). This indicates the difficulty in identifying and isolating cases at an earlier stage of disease. It may be necessary to commit considerable resources to testing in outpatient clinics and emergency departments for proactive case finding, both as part of the containment strategy in locations without local spread yet as well as to permit earlier clinical management of cases. Such an approach would also provide important information on the subclinical infections for a better assessment of severity.

Our preliminary estimate of the incubation period distribution provides important evidence to support a 14-day medical observation period or quarantine for exposed persons. Our estimate was based on information from 10 cases and is somewhat imprecise; it would be important for further studies to provide more information on this distribution. When more data become available on epidemiologic characteristics of NCIP, a detailed comparison with the corresponding characteristics of SARS and MERS, as well as the four coronaviruses endemic in humans, would be informative.

Our study suffers from the usual limitations of initial investigations of infections with an emerging novel pathogen, particularly during the earliest phase, when little is known about any aspect of the outbreak and there is a lack of diagnostic reagents. To increase the sensitivity for early detection and diagnosis, epidemiology history was considered in the case identification and has been continually modified once more information has become available. Confirmed cases could more easily be identified after the PCR diagnostic reagents were made available to Wuhan on January 11, which helped us shorten the time for case confirmation. Furthermore, the initial focus of case detection was on patients with pneumonia, but we now understand that some patients can present with gastrointestinal symptoms, and an asymptomatic infection in a child has also been reported.[17] Early infections with atypical presentations may have been missed, and it is likely that infections of mild clinical severity have been under-ascertained among the confirmed cases.[18] We did not have detailed information on disease severity for inclusion in this analysis.

In conclusion, we found that cases of NCIP have been doubling in size approximately every 7.4 days in Wuhan at this stage. Human-to-human transmission among close contacts has occurred since the middle of December and spread out gradually within a month after that. Urgent next steps include identifying the most effective control measures to reduce transmission in the community. The working case definitions may need to be refined as more is learned about the epidemiologic characteristics and outbreak dynamics. The characteristics of cases should continue to be monitored to identify any changes in epidemiology — for example, increases in infections among persons in younger age groups or health care workers. Future studies could include forecasts of the epidemic dynamics and special studies of person-to-person transmission in households or other locations, and serosurveys to determine the incidence of the subclinical infections would be valuable.[14] These initial inferences have been made on a "line list" that includes detailed individual information on each confirmed case, but there may soon be too many cases to sustain this approach to surveillance, and other approaches may be required.[19]

The views expressed in this article are those of the authors and do not represent the official policy of the China CDC. All the authors have declared no relationships or activities that could appear to have influenced this work.

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APPENDIX

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