Abstract

The objectives of this study are to identify sources of the transmission, the starting date of outbreak, epidemic trend of the 2019-nCoV in China, risk of global spread, case definition for surveillance, detection, prevention, control, diagnosis, and promising therapeutic interventions. Coronavirus were found in the mid-1960s that can infect both humans and animals (birds and mammals), whereas seven coronaviruses are known to infect humans, such as Betacoronavirus HCoV-OC43 and HCoV-HKU1 and Alphacoronavirus HCoV-229E. These coronaviruses primarily target on epithelial cells in the respiratory and gastrointestinal tracts through various routes of transmission, such as respiratory droplets, airborne, fecal-oral or fomites. On December 31, 2019, the Wuhan Municipal Health Commission in Wuhan City, Hubei province, China reported a cluster of 27 pneumonia cases of unknown etiology, including 7 severe cases, with a common reported connection with Wuhan’s Huanan Seafood Wholesale Market (a wholesale fish and live animal market selling different animal species). These cases presented with several infectious respiratory disease, such as fever, dyspnea, and bilateral pulmonary infiltrates on chest roentgenograms. Nevertheless, on January 19, 2020, first 2019-nCoV-infected case of 35-year-old man presented to an urgent care clinic in Snohomish County, Washington was detected and reported in the United States. These drugs should be evaluated in humans infected with 2019-nCoV. As of February 10, 2020, 2019-nCoV has been reported in 25 countries across 4 continents and more than 40,000 cases have been laboratory confirmed. In conclusion, without implementation of proper infection prevention and control measures at the point of care for individuals under investigation, there will be a likelihood of disease outbreaks, particularly via traveler transmission, transmission on aircrafts, and healthcare-related transmission in the destination countries. Further investigations for 2019-nCoV, particularly antiviral efficacy of several promising agents in clinical trials are urgently needed due to its potentially global health threat.

Keywords: Novel 2019-Coronavirus; Case Definition; Epidemic; Outbreak; Surveillance; Wuhan; China; Respiratory; Pneumonia; Prevention; Control; Diagnosis; Treatment; Promising Agents For 2019-nCoV

Abbreviations


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Objectives of the Study

The objectives of this study are to identify sources of the transmission, the starting date of outbreak, epidemic trend of the 2019-nCoV in China, risk of global spread, case definition for surveillance, detection, prevention, control, diagnosis, and promising therapeutic interventions.

Introduction

Coronavirus were found in the mid-1960s that can infect both humans and animals (birds and mammals), whereas seven coronaviruses are known to infect humans, such as Beta coronavirus HCoV-OC43 and HCoV-HKU1 and Alphacoronavirus HCoV-229E. These coronaviruses primarily target on epithelial cells in the respiratory and gastrointestinal tracts through various routes of transmission, such as respiratory droplets, airborne, fecal-oral or fomites. These coronaviruses cause common colds as well as severe lower respiratory tract infections in the youngest and oldest age groups [1].

Wuhan, a city of more than 11 million residents is connected to other cities in China via high-speed railway and commercial airline flights. During January 2017, there were 670,417 passenger bookings departing Wuhan, the top destinations being Shanghai of 53,214 bookings, Beijing of 51,066 bookings, and Kunming of 40,120 bookings [2]. Wuhan is connected internationally via both direct and indirect flights [3]. Novel coronavirus-2019 (2019-nCoV) was first identified from a patient with pneumonia, related to the cluster of acute respiratory illness cases from Wuhan, China with close relation to SARS-CoV and genetically clusters within the genus Beta coronavirus, subgenus Sarbecovirus [4]. With bases on the epidemiological characteristics of respiratory infections caused by SARS-CoV and MERS-CoV, its incubation period of 2 to 7 days and up to 14 days is possible. Approximately 20% of the laboratory-confirmed cases are seriously or critically ill and at least 4 confirmed cases have died [5].

On December 31, 2019, the Wuhan Municipal Health Commission in Wuhan City, Hubei province, China reported a cluster of 27 pneumonia cases of unknown etiology, including 7 severe cases, with a common reported connection with Wuhan's Huanan Seafood Wholesale Market (a wholesale fish and live animal market selling different animal species) [6]. These cases presented with several infectious respiratory disease, such as fever, dyspnea, and bilateral pulmonary infiltrates on chest roentgenograms. Chinese authorities placed all cases under isolation, initiated contact tracing activities and hygiene and environmental sanitation activities at this market, which was closed to the public on January 1, 2020. At that time, no significant human-to-human transmission and no cases among healthcare workers were reported by the Chinese authorities. Between December 31, 2019 and January 20, 2020, 295 2019-nCoV-laboratory-confirmed cases, including 4 deaths, have been reported [7]. Of the 295 laboratory-confirmed cases, 291 cases were reported by China (270 cases in Wuhan City, 5 cases in Beijing, 14 cases in Guangdong, and 2 cases in Shanghai) [7]. Fifteen healthcare workers in Wuhan were the reported cases during that period [8]. During that period, Wuhan City reported that 169 cases were hospitalized, of which 35 cases were seriously and 9 cases were critically ill [9]. In Guangdong, China, 2 of the 14 reported cases had not travelled to Wuhan, China, but had a history of contact with laboratory-confirmed cases were the first confirmed human-to-human transmission cases [10], whereas the other four laboratory-confirmed cases were outside-China-travel-related [11-13]. Of the four reported deaths (January 9-19, 2020), all were in China with the ages ranked between 61 to 89 years [9,11,14,15]. For the majority of the reported cases, the history of exposure to the Wuhan’s Huanan Seafood Wholesale Market or other live markets is unknown [13]. Nevertheless, on January 19, 2020, first 2019-nCoV-infected case of 35-year-old man presented to an urgent care clinic in Snohomish County, Washington was detected and reported in the United States [16]. As of February 10, 2020, 2019-nCoV has been reported in 25 countries across 4 continents and more than 40,000 cases have been laboratory confirmed [17].

Case definition for surveillance

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Suspected case requiring diagnostic testing

Patients with acute respiratory infection who have sudden onset of at least one of the following symptoms: cough, sore throat, shortness of breath requiring hospitalization or not. In 14 days prior to onset of symptoms, met at least one of the following epidemiological criteria: 1) Were in close contact with a confirmed or probable case of 2019-nCoV infection; or 2) Had a history of travel to areas with presumed ongoing community transmission of 2019-nCoV; or 3) Worked in or attended a health care facility where patients with 2019-nCoV infections were being treated [18].

Close contact

Close contact is defined as: 1) Healthcare associated exposure, including providing direct care for patients with 2019-nCoV infection, working with healthcare workers infected with novel coronavirus, visiting patients or staying in the same close environment as a 2019-nCoV patient; 2) Working together in close proximity or sharing the same classroom environment with a 2019-nCoV patient; 3) Travelling together with a 2019-nCoV patient in any kind of conveyance; and 4) Living in the same household as a 2019-nCoV patient. The epidemiological association may have occurred within a 14-day period before or after the onset of illness in the case under consideration [18].

Probable case

The probable case is a suspected case for whom testing for 2019-nCoV is inconclusive by the result of the test reported by the laboratory section or for whom testing was positive on a pan-coronavirus assay [18].

Confirmed case

The confirmed case is an individual with laboratory confirmation of 2019-nCoV infection, irrespective of clinical manifestations [18].

Criteria to initiate testing for 2019-nCoV

Prompt case confirmation is essential for rapidly ensuring and effectively contact tracing, implementation of infection prevention and control measures according to national recommendations, and collection of relevant epidemiological and clinical data. Any individual fulfilling the criteria for a suspected case should be tested for 2019-nCoV infection. The laboratory test should be initiated immediately [18].

Epidemic trend by mathematical modelling

Mathematical modelling for the epidemic trend of the 2019-nCoV outbreak in China conducted by Shen, et al. demonstrated that the national epidemic of 2019-nCoV may lead to at least a total of 8,042 (95% Confidential Interval (CI): 4,199 - 11,884) infections and at least 898 (95% CI: 368 - 1,429) deaths, equivalent to a fatality rate of 11.02% (95% CI: 9.26-12.78%) [19]. This fatality rate is lower than the rates of the Middle-East Respiratory Syndrome (MERS, 34.4%) [20] and the Severe Acute Respiratory Syndrome (SARS, 14-15%) [21], indicating that 2019-nCoV may be a less virulent strain among the coronavirus family [19].

When the epidemic of 2019-nCoV in China started on December 12, 2029, the basic reproductive number (R0) of 2019-nCoV (an indication of the initial transmissibility of the virus) was estimated to be 4.71 (95% CI: 4.50 - 4.92), whereas its effective reproductive number (Re) has decreased to 2.08 (95% CI: 1.99 - 2.18) as of January 22, 2020 [19]. With the assumption of no resurges of 2019-nCoV epidemic and the continually declining trend, Re will decrease below one within three months (77 (95% CI: 75 - 80) days) of the epidemic initiation, indicating that the 2019-nCoV epidemic will gradually die off after this time [19]. In comparison with MERS and SARS, R0 of 2019-nCoV was similar to MERS in Jeddah (95% CI: 3.5-6.7) and Riyadh (95% CI: 2.0 - 2.8), Kingdom of Saudi Arabia, in 2014 [22] and SARS (R0 = 4.91) in Beijing, China, in 2003 [23]. Nevertheless, Zhao, et al. concluded that the mean estimate of R0 for the 2019-nCoV ranges from 2.24 (95% CI: 1.96 - 2.55) to 3.58 (95% CI: 2.89 - 4.39), and significantly larger than 1 if the reporting effort has been increased by a
factor of between 8- and 2-fold after the diagnostic protocol released on January 17, 2020 and several medical supplies reached Wuhan, and indicates the potential of 2019-nCoV to cause outbreaks [24].

**Laboratory testing methodology**

Rapid collection of the following specimens should be considered: when possible, specimens from both lower and upper respiratory tracts should be collected. For lower respiratory tract: expectorated sputum, endobronchial aspirate, and bronchoalveolar lavage. For upper respiratory tract: nasopharyngeal aspirate or nasal wash, oropharyngeal swab, and nasopharyngeal swab. The additional specimens for later testing are: when serological testing is available (serum: acute and convalescent specimens—possibly 2 - 4 weeks after acute phase). The other additional specimens for later testing are blood, urine, and feces [18].

Currently, the specific test recommended by the World Health Organization (WHO) for the diagnosis and confirmation of 2019-nCoV is real-time Reverse Transcriptase-Polymerase Chain Reaction (RT-PCR) supported by the study on detection of 2019-nCoV infection that conducted by Corman., et al [25]. A single positive test should be confirmed by a second RT-PCR assay targeting a different 2019-nCoV gene. A single negative 2019-nCoV test, particularly if specimens obtained from upper respiratory tract or a positive test result for another respiratory pathogen, indicates that the result does not exclude 2019-nCoV infection. If there is a strong suspicion for 2019-nCoV infection, another specimen should be tested with primary and secondary RT-PCR assays. When possible, sequence information should be generated from positive specimens [18].

**Potential repurposing therapeutic candidates for 2019-nCoV**

Patients with 2019-nCoV infection are being recruited in randomized clinical trials to evaluate the efficacy of favipiravir plus phase III clinical trial were began in early February 2020 to evaluate intravenous remdesivir (200 mg on day 1 and 100 mg once daily for 9 days) in 2019-nCoV-infected patients (NCT04252664 and NCT04257656), with estimated completion dates in April 2020. Favipiravir (T-705), an approved guanine analogue with effective inhibition of the RNA-dependent RNA polymerase of RNA viruses was reported recently against 2019-nCoV (EC50 = 61.88 µM in Vero E6 cells). Other approved nucleoside analogues (ribavirin) and experimental nucleoside analogue (galidesivir) may have potential against 2019-nCoV. Nucleoside analogues in the form of adenine or guanine derivatives target the RNA-dependent RNA polymerase and block viral RNA synthesis in a broad spectrum of RNA viruses, including human coronavirus [17].

HIV protease inhibitors (lopinavir and ritonavir) have been initiated to test in 2019-nCoV-infected patients in clinical trials (ChiCTR2000029539, etc.). Lopinavir and ritonavir appeared to be associated with improved clinical outcomes of SARS and MERS patients in a non-randomized open-label trial by hypothesized inhibition of the 3-chymotrypsin-like protease of SARS and MERS. Nevertheless, it is questionable whether HIV protease inhibitors could effectively inhibit the papain-like and 3-chymotrypsin-like proteases of 2019-nCoV. Griffithsin, a red-alga-derived lectin (spike glycoprotein) is also a promising target against 2019-nCoV. Subcutaneous interferon therapies should be closely monitored and dose reduction or discontinuation of therapy may be needed due to its multiple adverse effects. Nitazoxanide could also inhibit 2019-nCoV (EC50 = 2.12 µM in Vero E6 cells). Chloroquine, an approved immune modulator demonstrates inhibitory effects against 2019-nCoV (EC50 = 1.13 µM in Vero E6 cells). Small-molecule agents may also modulate the virus-host interactions of 2019-nCoV [17].

**Discussion**

By January 2, 2020, Huang., et al. studied on clinical features of 41 admitted hospital patients with laboratory confirmation of 2019-nCoV infection revealed that the common symptoms at onset of illness were fever (40 of 41, 98%), cough (31 of 41, 76%), and fatigue or myalgia (18 of 41, 44%). The less common symptoms were sputum production (11 of 39, 28%), headache (3 of 38, 8%), hemoptysis (2 of 39, 5%), and diarrhea (1 of 38, 3%). Dyspnea occurred in 22 of 40 patients (55%) with median time from illness onset to dyspnea 8.0 days (Interquartile Range: 5.0-13.0). Twenty-six of 41 patients (63%) demonstrated lymphopenia. All 41 patients had pneumonia with
pulmonary infiltrates on the plain chest roentgenography (Figure 1) and chest computerized tomography (Figure 2). The complications included acute respiratory distress syndrome (12, 29%), RNAemia (6, 15%), acute cardiac injury (5, 12%), and secondary infection (4, 10%). In comparison with non-ICU patients, ICU patients had higher plasma levels of interleukin (IL)-2, IL-7, IL-10, Granulocyte-Colony Stimulating Factor (GCSF), Interferon Gamma-Induced Protein10 (IP-10), Monocyte Chemoattractant Protein-1 (MCP-1), Monocyte Inflammatory Protein-1A (MIP-1A), and tumor necrosis factor (TNF)-alpha [26]. Among 41 hospitalized patients, most of the infected patients were men (30 of 41, 73%); less than 50% of the patients had underlying diseases (13 of 41, 32%), including diabetes mellitus (8 of 41, 20%), hypertension (6 of 41, 15%), and cardiovascular disease (6 of 41, 15%). The median age was 49.0 years (IQR: 41.0-58.0). Twenty-seven of 41 patients had been exposed to Huanan seafood market [26]. Both SARS-CoV and MERS-CoV were believed to originate in bats, these pathogens were transmitted directly to human from market civets and dromedary camels, respectively [27]. In 2013, a study [28] demonstrated the whole genome sequence of a SARS-like coronavirus in bats with ability to use human Angiotensin-Converting Enzyme 2 (ACE2) as a receptor for replication potentials in human cells [29]. Reliable rapid pathogen tests and feasible differential diagnosis based on clinical description are critical for clinicians in their first contact with suspected 2019-nCoV-infected patients. A key uncertainty of this outbreak is when it started. Surveillance in China and elsewhere only began once the outbreak was identified in Wuhan, China. Had the outbreak began before January 2020 and in early January 2020, both domestically and internationally. If a substantial proportion of infection has been due to multiple exposures to various animals. These currently available data may represent a period of high transmission that will not be sustained over long periods of time. There is much uncertainty in both scale of the outbreak and key epidemiological information of transmission due to still being in the early days of this outbreak. By observation in outbreaks of either MERS-CoV or SARS, the rapidity of the growth of cases since the outbreak recognition is much greater, indicating that control or containment of this pathogenic organism may be much more difficult. In consideration of antiviral therapy, first 2019-nCoV-infected case report ed in the United States [16], intravenous remdesivir [a novel nucleoside analogue prodrug in development] was administrated on the evening of day 7 of hospitalization due to the patient’s ongoing fevers, the persistent positive 2019-nCoV RNA at multiple sites, and notification of rales in both lungs at a period consistent with the development of roentgenographic pneumonia. On hospital day 8 (illness day 12), there is improvement of the patient’s clinical condition. As of January 30, 2020, the patient is afebrile and has resolution of all symptoms, except his cough, that is decreasing in severity [16]. Another recent study on 2019-nCoV inhibition In vitro by remdesivir and chloroquine demonstrated that these drugs were highly effective in the control of 2019-nCoV infection In vitro [32]. These drugs should be evaluated in humans infected with 2019-nCoV. HIV protease inhibitors (lopinavir, ritonavir) are specific optimized to fit the C2 symmetry in the catalytic site of the HIV protease dimer, but this C2-symmetrical pocket is absent in coronavirus proteases in addition to HIV protease belonging to the aspartic protease family. Additionally, the coronavirus proteases (papain-like and 3-chymotrypsin-like proteases) are from the cysteine protease family. If HIV protease inhibitors alter host pathways to indirectly interfere with coronavirus infections, their potency remain a problem [17].

Figure 1: Female, 40 years old, fever and cough for one day, travelling from Wuhan City, China, demonstrating pulmonary infiltrates with air bronchograms in the right lower lung zone on plain chest radiography (arrow) Source: case contributed by Medico Assistente Dr. Chong Kung Sang, Sam; radiopaedia.org>cases>2019-novel-coronavirus-infected-pneumonia (accessed on February 11, 2020).
Conclusion

With bases on the genetic similarities between 2019-nCoV and SARS-CoV, the limited epidemiological data available from China and the case detection through entry screening outside of China, we hypothesize that new cases will be detected among travelers from Wuhan, China. Without implementation of proper infection prevention and control measures at the point of care for individuals under investigation, there will be a likelihood of disease outbreaks, particularly via traveler transmission, transmission on aircrafts, and health-care-related transmission in the destination countries. Further investigations for 2019-nCoV are urgently needed due to its potentially global health threat, particularly antiviral efficacy of several promising agents in clinical trials. Nevertheless, in the global experiences, systematic implementation of infection prevention and control measures were effective in controlling both SARS-CoV and MERS-CoV.

Authors Contributions

Dr. Attapon Cheepsattayakorn conducted the study framework and wrote the manuscript. Associate Professor Dr. Ruangrong Cheepsattayakorn contributed to scientific content and assistance in manuscript writing. Both authors read and approved the final version of the manuscript.

Competing Interests

The authors declare that they have no actual or potential competing financial interests.

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