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Review

A literature review of 2019 Novel Coronavirus during the early outbreak period: Epidemiology, causes, clinical manifestation and diagnosis, prevention and control

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Abstract: The 2019-nCoV has been identified as the cause of an outbreak of respiratory illness in Wuhan, Hubei Province, China beginning in December 2019. This epidemic had spread to 19 countries with 11,791 confirmed cases, including 213 deaths, as of January 31, 2020. The World Health Organization declared it as a Public Health Emergency of International Concern. This study analyzed and discussed 70 research articles published until January 31, 2020 for a better understanding of the epidemiology, causes, clinical diagnosis, prevention and control of this virus. Studies thus far have shown origination in connection to a seafood market in Wuhan, but specific animal association has not been confirmed. The reported symptoms include fever, cough, fatigue, pneumonia, headache, diarrhea, hemoptysis, and dyspnea. Preventive measures such as masks, hand hygiene practices, avoidance of public contact, case detection, contact tracing, and quarantines are being recommended for reducing the transmission. To date, no specific antiviral treatment is proven effective, hence, infected people primarily rely on symptomatic treatment and supportive care. Although these studies had relevance to control a public emergency, more research need to be conducted to provide valid and reliable ways to manage this kind of public health emergency in both short- and long- term.

Keywords: 2019-nCoV, epidemiology, causes, prevention and control, review

1. Introduction

The Coronavirus belongs to the family of virus that causes viral pneumonia including fever, breathing difficulty, and lung infection [1]. These viruses are common in animals worldwide, but very few cases of them are known to affect humans. The World Health Organization (WHO) used the term 2019 novel coronavirus (2019-nCoV) to refer to the coronavirus that was diagnosed from the lower respiratory tract of patients with pneumonia in Wuhan, China on 29 December, 2019 [2-4]. It was reported that the human infection of the virus originated from the local Huanan South China Seafood Market in Wuhan, Hubei Province, China [5]. Consequently, The Chinese Center for Disease Control and Prevention (China CDC) dispatched a rapid response team to accompany Hubei provincial and Wuhan city health authorities to conduct epidemiological and etiological investigations. The WHO reported that the outbreak of the coronavirus epidemic was associated

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with the marketplace, but no specific animal association has been identified [6]. Scientists immediately started to research the source of coronavirus. The first genome of 2019 – nCoV was published by the research team led by Prof. Yong-Zhen Zhang, on January 10, 2020 [7]. Within one month, this virus spread quickly throughout China and globally during the Chinese New Year when there is high level of human mobility among Chinese. Although it is still early to predict the susceptible population, early patterns have shown a similar trend with Severe Acute Respiratory Syndrome (SARS) and Middle East respiratory syndrome (MERS) coronavirus, showing associations with age, biological sex and other health conditions [8]. 2019-nCoV has now been declared as Public Health Emergency of International Concern by WHO [9].

Given the spread of the new coronavirus and its impacts on human health, the research community has responded rapidly to the new virus and many preliminary research articles have already been published about this epidemic (Appendix Table). We conducted a review of all the published scientific articles regarding the new coronavirus in January 2020. This review aims to provide a summary and critical analysis of early findings on the epidemiology, causes, clinical diagnosis, prevention and control of 2019-nCoV. This review can provide meaningful information for future research related to the topic and may support government decision-making on strategies to handle this public health emergency at the community, national and international level.

2. Materials and Methods

2.1 Literature search

Literature for this review was identified by searching the following online databases: bioRxiv, medRxiv, ChemRxiv, Google scholar, Pubmed, as well as CNKI and Wan Fang (the two primary databases for biomedical research in mainland China). These online databases contain archives of most English and Chinese biomedical journals. In addition, some white papers published online by the National Health Commission of China, National Center of Disease Prevention and Control, and WHO were also searched and included in the analysis. We searched scientific publications from 1 January to 31 January 2020. The search terms were 'nCoV', '2019 novel coronavirus', '2019-nCoV', 'novel coronavirus', 'Pneumonia', '新型冠状病毒' (Chinese), '新型肺炎' (Chinese), and '新冠病毒' (Chinese). We included all the relevant scientific publications written in English or Chinese in the review. Commentary, reports and news articles were excluded from the analysis.

Two researchers (Y.W. and S.P.A), searched the literatures independently. The two sets of literature were compared. Disagreements on inclusion or exclusion of literature were resolved through discussion or, if necessary, including a third researcher (H.Z.) to make the decision. Duplicate articles were eliminated. Eventually, 70 unique academic publications were included in this analysis (Appendix Table). Figure 1 presents a flow diagram showing the process of searching and selecting the research articles.

2.2 Data analysis

Articles were classified into one of four research domains: epidemiology, causes, clinical manifestation and diagnosis, prevention and control; the research domain that has the best fit was chosen by two researchers (Y.W. and S.P.A). The research domains, published dates, journal language, and authors' affiliations were analyzed respectively. A publication was considered as deriving from 'inside China' when all affiliations of the authors were from an Institute with the address in China; a publication was considered as deriving from 'outside China' when all affiliations were from an Institute with the address outside China; a publication was considered as deriving from 'international collaboration' when at least one affiliation was from an Institute with the address in China, and one outside China. All findings and statements that are mentioned regarding the outbreak in this review are based on published information as listed in the references.

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3. Results and discussion

3.1 Characteristics of published studies

Among the 70 research articles included in the analysis, more than 30 were on preprint servers, and 36 are published in peer-reviewed journals, including The Lancet and the New England Journal of Medicine. Most of the publications (n=60, 85.71 %) are in English and few (n=10, 14.29 %) are in Chinese (Table 1).

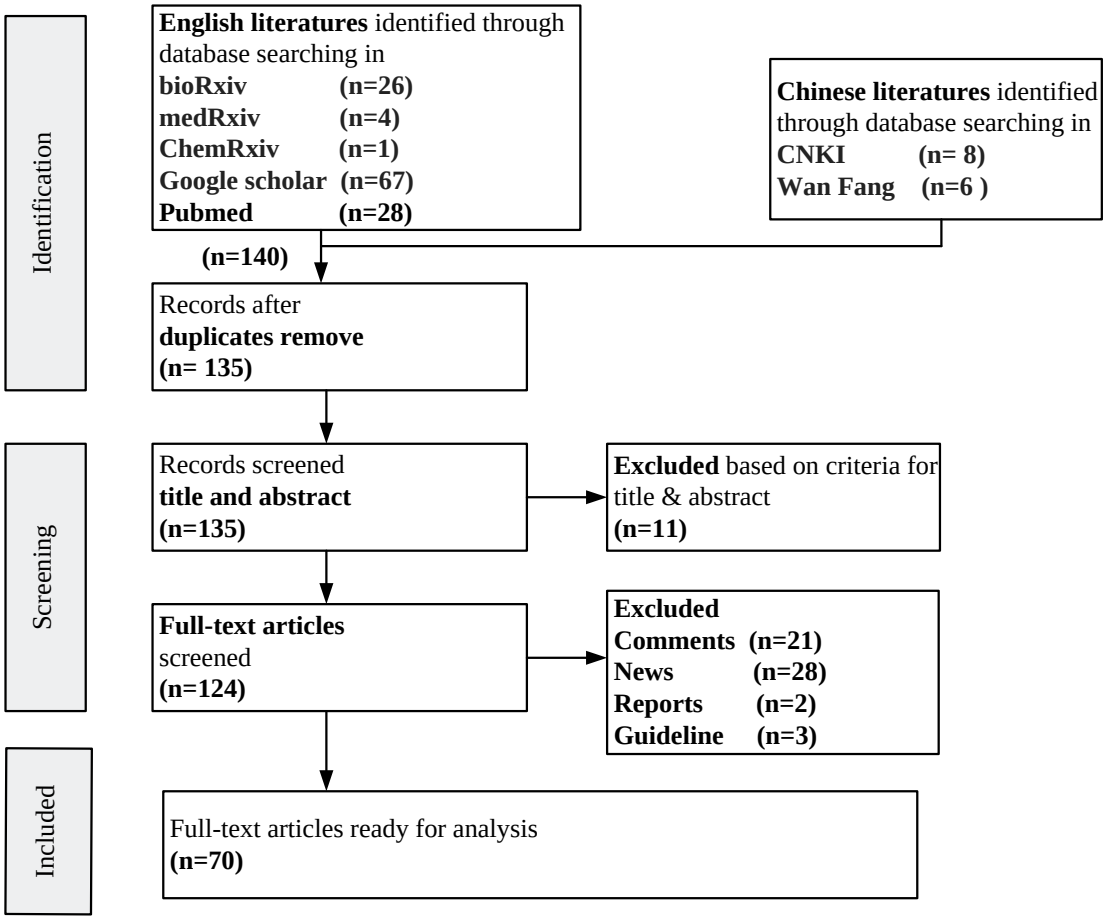

Figure 1: Flow diagram for selection process of articles

Table 1: Breakdown of 2019-nCoV research articles by language (published in January 2020)

	English literature		Chinese literature		Total	
Research Domains	n	%	n	%	n	%
Epidemiology	20	33.33	0	0	20	28.57
Causes	25	41.67	1	10	26	37.14
Clinical manifestation and diagnosis	7	11.67	2	20	9	12.86
Prevention and control	8	13.33	7	70	15	21.43
Total	**60**	**85.71**	**10**	**14.29**	**70**	**100**

Academic publications are distributed across the following research domains: epidemiology, causes, clinical manifestation and diagnosis, as well as prevention and control. The largest portion of the papers (n=26, 37.14%) are related to causes, followed by papers on epidemiology (n=20, 28.57%),

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while 21.43% examined prevention and control and 12.86% reported clinical manifestations and diagnosis (Figure 2). Research articles initially focused on causes of the virus, while prevention and control studies have gradually increased over time (Figure 3). Around 80% of English language publications focus on epidemiology and causes, while 70% of Chinese papers have focused on prevention and control. The majority of the articles (n=46, 65.71 %) are published by Chinese scholars whereas 30% (n=21) articles are from scholars outside of China, and few (n=3, 14.29 %) are based on collaborative research by scholars from different countries (Table 2).

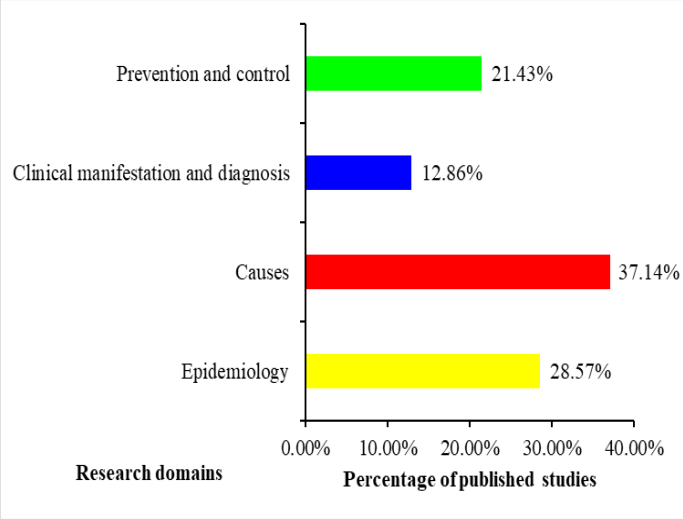
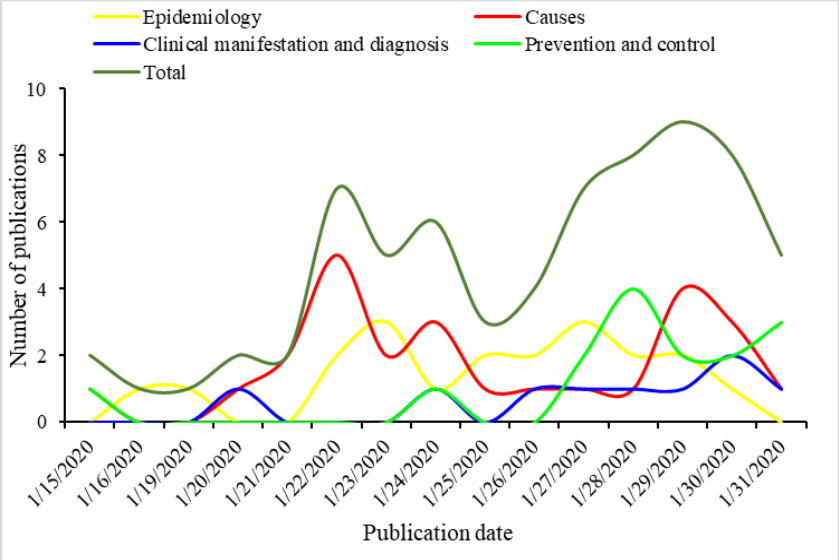


Figure 2: Percentage of published research articles



. Figure 3: Publication of research articles according to date

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Table 2: Breakdown of 2019-nCoV research articles by type of collaboration

	Inside China		Outside China		International Collaboration		Total	
Research domains	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**
Epidemiology	8	17.39	9	42.86	3	100	20	28.57
Causes	17	36.96	9	42.86	0	0	26	37.14
Clinical manifestation and diagnosis	8	17.39	1	4.76	0	0	9	12.86
Prevention and control	13	28.26	2	9.52	0	0	15	21.43
Total	**46**	**65.71**	**21**	**30**	**3**	**4.29**	**70**	**100**

3.2 Research domains

3.2.1 Epidemiology

On 29 December 2019, the first four cases of an acute respiratory syndrome of unknown etiology among people linked to a seafood market ("wet market") were reported in Wuhan city, Hubei province, China [4]. Research is underway to understand more about transmissibility, severity, and other features associated with 2019-nCoV [2]. It appeared most of the early cases had contact history with the original seafood market [4, 10-12]. Soon, the secondary source of infection was found to be human-to-human transmission among close contacts. There was an increase of infected people with no history of exposure to wildlife or visiting Wuhan, and multiple cases of infection were detected among medical professionals [4, 12-15]. The 2019-nCoV infection occurs through exposure to the virus, and both the immunosuppressed and normal population appear susceptible. Some studies have reported an age distribution of adult patients between 25 and 89 years old. Most adult patients are between 35 and 55 years old. There are fewer identified cases among children and infants [12, 16]. A study on early transmission dynamics of the virus reports the median age of patients to be 59 years, ranging from 15 to 89 years, with the majority (59%) being male [4]. In this publication it was suggested that the population at most risk may be people with poor immune function such as older people and people with renal and hepatic dysfunction [4].

Several public health measures were mentioned that may prevent or slow down the transmission of the 2019-nCoV; these include case isolation, identification and follow-up of contacts, environmental disinfection, and use of personal protective equipment's [17]. The 2019-nCoV has been found to have higher levels of transmissibility and pandemic risk than the SARS-CoV as the effective reproductive number (R) of 2019-nCoV (2.9) is estimated to be higher than the reported effective R of SARS (1.77) at the early stage [13]. The average incubation duration of 2019-nCoV were estimated to be 4.8±2.6, ranging from 2-11 days [13] and 5.2 days (95 % Confidence interval , 4.1 to 7) [4]. The latest guidelines from Chinese health authorities mentioned an average incubation duration of 7 days, ranging from 2-14 days [18].

In China, 11,791 cases were confirmed and 17,988 were suspected cases in 34 provinces as of 24:00, January 31, 2020 (Figure 4) [19]. The studies mentioned a relatively quick spread of the 2019-nCoV, and also reported the spread to several other countries after its outbreak in China; there were 213 deaths reported globally on January 31, 2020 [20]. Confirmed cases were reported in the following 19 countries outside of China: Australia (9), Canada (3), Cambodia (1), France (6), Finland(1), Germany (5), India (1), Italy (2), Japan (14), Nepal (1), Malaysia (8), Philippines (1), Republic of Korea (11), Singapore (13), Sri Lanka (1), Thailand (14), United States of America (6), United Arab Emirates(4) and Vietnam (5) (Figure 5) [20].

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3.2.2 Causes

3.2.2.1 Virology and Pathogenesis

Coronaviruses are enveloped single-stranded RNA viruses that are zoonotic in nature and cause symptoms ranging from those similar to the common cold to more severe respiratory, enteric, hepatic and neurological symptoms [5, 21]. Other than 2019-nCoV, there are six known coronaviruses in human: HCoV-229E, HCoV-OC43, SARS-CoV, HCoV-NL63, HCoV-HKU,1 and MERS-CoV [2, 18, 22, 23]. Coronavirus has caused two large scale pandemics in the last two decades: SARS [24] and MERS [10, 25].

To detect the infection source of 2019-nCoV, the China CDC researchers collected 585 environmental samples from the Huanan Seafood Market in Wuhan, Hubei Province, China on January 1 and January 12, 2020. They detected 33 samples containing 2019-nCoV and indicated that it originated from wild animals sold in the market [26]. Then, researchers used the lung fluid, blood, and throat swab samples of 15 patients to conduct laboratory tests. These laboratory tests found the virus-specific nucleic acid sequences in the sample, which has a different coronavirus-specific nucleic acid sequences from known human coronavirus species. Laboratory results also indicated that 2019-nCoV is similar to some of the beta (β) coronaviruses genera identified in bats [10, 16, 27], which is situated in a group of SARS/ SARS-like CoV [10].

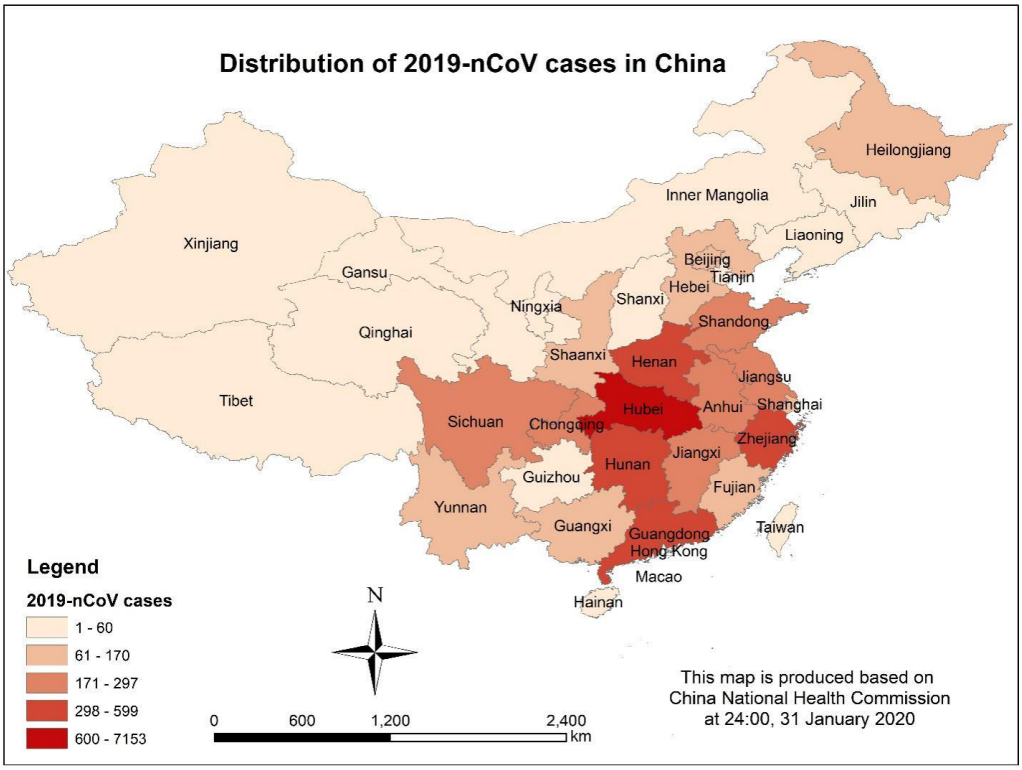

Figure 4: Distribution of 2019-nCoV cases in China [19]

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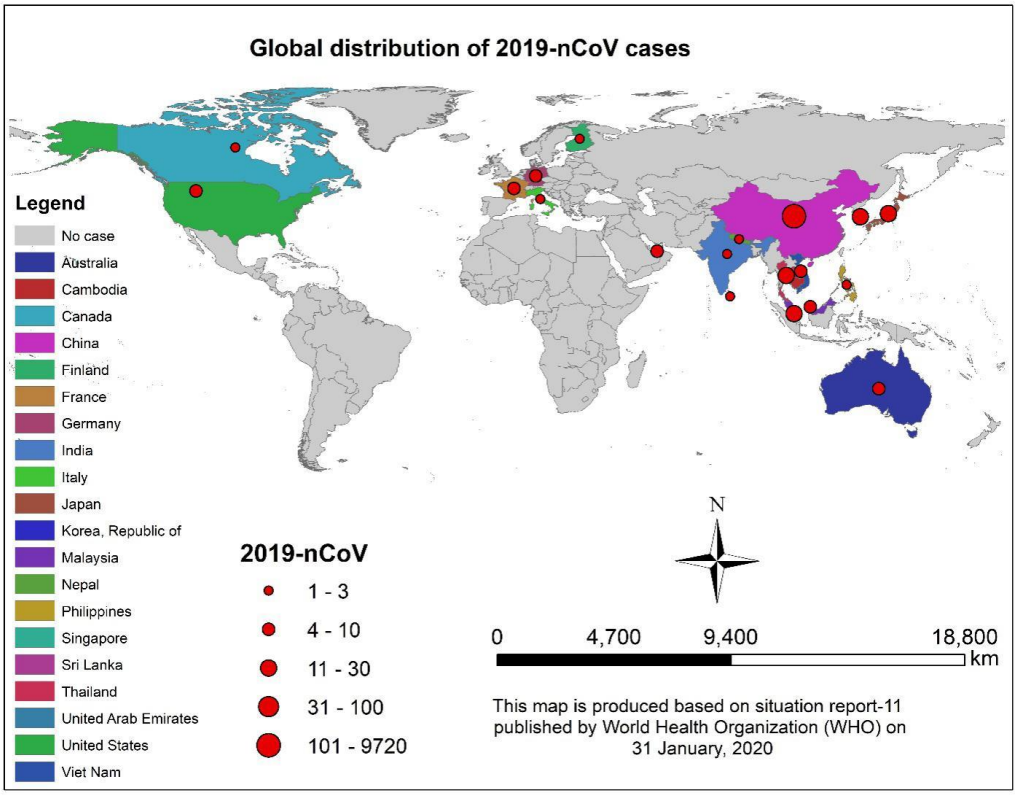

Figure 5: Global distribution of 2019-nCoV cases [20]

To conduct next-generation sequencing from bronchoalveolar lavage fluid and cultured isolates, researchers enrolled nine inpatients with viral pneumonia and negative in common respiratory pathogens in Wuhan. The results of this next-generation sequencing indicated that 2019-nCoV was more distant from SARS-CoV (with about 79% sequence identity) and MERS-CoV (with about 50% sequence identity) than from two bat-derived SARS-like coronaviruses--bat-SL-CoVZC45 (with 87.99% sequence identity) and bat-SL-CoVZXC21(with 87.23% sequence identity) [28]. Studies also reported that 2019-nCoV S-protein supported strong interaction with human ACE2 molecules despite its sequence diversity with SARS-CoV [10, 29].

3.2.2.2 Transmission pattern

Many domestic and wild animals, including camels, cattle, cats, and bats, may serve as hosts for coronaviruses [18]. It is considered that, generally, animal coronaviruses do not spread among human beings [3]. However, there are exceptions, such as SARS and MERS, which were mainly spread though close contact with infected people via respiratory droplets from cough or sneezing. With regard to 2019-nCoV, early patients were reported to have some link to the Huanan Seafood Market in Wuhan, China, suggesting that these early infections were due to animal-to-person transmission. Soon, more cases were reported among medical staff and others with no history of exposure to that market or visiting Wuhan, which was taken as an indication for human-to-human transmission [4, 13-15].

The latest guidelines from Chinese health authorities [18, 30], described three main transmission routes for the 2019-nCoV: 1) direct transmission, 2) aerosol transmission, 3) contact transmission. Direct transmission are reported to occur when respiratory droplets (as produced when an infected person coughs or sneezes) are ingested or inhaled by individuals nearby in close proximity; Aerosol transmission may occur when respiratory droplets mix into the air, forming aerosols and causing infection when inhaled into the lungs; and Contact transmission may occur when a subject touches a surface or object contaminated with the virus. According to the literature, individuals could be infected when they subsequently touch their mouth, nose, or, possibly, eyes

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[18, 30]. In addition to these three routes, one study also indicated the digestive system as a potential transmission route for 2019-nCoV infection. Since patients had abdominal discomfort and diarrhea symptoms, researchers analyzed 4 datasets with single-cell transcriptomes of digestive system and found that ACE2 was highly expressed in absorptive enterocytes from ileum and colon [31].

3.2.3 Clinical manifestation and diagnosis

The complete clinical manifestation is not clear yet, as the reported symptoms range from mild to severe, sometimes even resulting in death [2]. The most commonly reported symptoms are fever, cough, myalgia or fatigue, pneumonia and complicated dyspnea, whereas less common reported symptoms include headache, diarrhea, hemoptysis, runny nose, and phlegm-producing cough [2, 14]. Patients with mild symptoms were reported to be usually recovered after 1 week while severe cases were reported to experience progressive respiratory failure due to alveolar damage from the virus, which may lead to death [11]. Cases resulting in death were primarily middle-aged and elderly patients with pre-existing diseases (tumor surgery, cirrhosis, hypertension, coronary heart disease, diabetes, and Parkinson's disease) [11]. Case definition guidelines mention the following symptoms: fever, decrease in lymphocytes and white blood cells, new pulmonary infiltrates on chest radiography, and no improvement in symptoms upon three days of antibiotics treatment [4].

For patients with suspected infection, the following procedures have been suggested for diagnosis: performing real-time fluorescence RT-PCR to detect the positive nucleic acid of 2019-nCoV in sputum, throat swabs, and secretions of the lower respiratory tract samples [11, 12, 30]. To date, no specific antiviral treatment has been confirmed to be effective. Regarding, infected patients with 2019-nCoV, it has been recommended to apply appropriate symptomatic treatment and supportive care [2, 14].

3.3.4 Prevention and Control

Prevention and control strategies and methods are reported at three levels: national level, case-related population level, and general population level. At the national level, the National Health Commission of the People's Republic of China issued the "No.1 announcement" on January 20, 2020, which officially included the 2019-nCoV into the management of class B legal infectious diseases, and allowed for class A infectious diseases preventive and control measures to be implemented [32]. Under this policy, medical institutes can adopt isolation treatment and observation protocols to prevent and control the spread of the 2019-nCoV. On January 22nd, 2020, the National Health Commission published national guidelines for the prevention and control of 2019-nCoV for medical institutes to prevent the nosocomial infection [33]. On January 28, 2020, the National Health Commission issued protocols for rapid prevention and control measures in order to effectively contain the spread of epidemic through a "big isolation and big disinfection" during the Chinese Spring Festival [34]. National-level strategies have also been issued with targeted measures for rural areas (issued on January 28, 2020) and the elderly population (issued on January 31, 2020) [35, 36].

Studies have also explored the prevention of nosocomial infection and psychological health issues associated with the 2019-nCoV. A series of measures have been suggested to reduce nosocomial infection, including knowledge training for prevention and control, isolation, disinfection, classified protection at different degrees in infection areas, and protection of confirmed cases [16, 37, 38]. Concerning psychological health, some suggested psychological intervention for confirmed cases, suspected cases, and medical staffs [16, 39].

For the general population, at this moment there is no vaccine preventing 2019-nCoV. The best prevention is to avoid being exposed to the virus [40]. Airborne precautions and other protective measures have been discussed and proposed for prevention. Infection preventive and control (IPC) measures that may reduce the risk of exposure include: Preventive measures that may reduce the risk of exposure include the following: use of face masks, covering coughs and sneezes with tissues (or flexed elbow) that are then safely disposed of; regular hand washing with soap or disinfection

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with hand sanitizer containing at least 60% alcohol (if soap and water is not available); avoidance of contact with infected people and keeping the distance as much as possible (at least 1 meter); and the refrain from touching the eyes, nose, and mouth with unwashed hands [2]. The detail advice on the use of face masks at the community, during care at home and in the health care settings in 2019-nCoV is discussed by the WHO [41]. In this document, health care workers are recommended to use the particulate respirator such as certified N95 or FFP2 when performing aerosols generating procedures, and to use medical masks while providing any care to suspected or confirmed cases. According to this document, individuals with respiratory symptoms are advised to use medical masks both at the health care settings and home care properly following the infection prevention guidelines. According to this advice, at the community, individual without respiratory symptoms do not require a medical mask but if coughing and sneezing should cover nose and mouth with tissues or flexed elbow and perform regular hand hygiene; proper use and disposal of masks are important to avoid any increase in risk of transmission [41]. In addition to articles published in research journals, the China CDC published a guideline to raise awareness of the prevention and control of 2019-nCoV among the general population. This guideline contains plenty information on the 2019-nCoV itself and its prevention. The key messages of the guideline include: the causes of 2019-nCoV, how to choose and wear face masks, proper hand washing habits, preventive measures at different locations (e.g., at home, on public transportation, and in public space), disinfection methods, and medical observation at home [42]. In addition to scientific knowledge on ways to handle the 2019-nCoV outbreak, the guideline also suggests ways to eliminate panic among the general population [42].

4. Conclusions

There has been a rapid surge in research in response to the outbreak of 2019-nCoV. During this early period, studies have been published exploring the epidemiology, causes, clinical manifestation and diagnosis, prevention and control of the novel coronavirus. Thus far, most studies have focused on the epidemiology and potential causes. Studies exploring prevention and control measures have begun to gradually increase. Studies providing evidence on prevention and control measures are urgently needed to minimize the impact of the outbreak. Government agencies have quickly incorporated recent scientific findings into public policies at community, regional, and national levels to slow down and/or prevent the further spread of the 2019-nCoV.

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Conflicts of Interest: The authors declare no conflict of interest.

Appendix A

Appendix 1: Published research articles on 2019-nCoV in January, 2020 (submitted in separate file).

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