

The Novel Coronavirus: A Bird's Eye View

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Abstract

The novel coronavirus (2019-nCoV) outbreak, which initially began in China, has spread to many countries around the globe, with the number of confirmed cases increasing every day. With a death toll exceeding that of the SARS-CoV outbreak back in 2002 and 2003 in China, 2019-nCoV has led to a public health emergency of international concern, putting all health organizations on high alert. Herein, we present on an overview of the currently available information on the pathogenesis, epidemiology, clinical presentation, diagnosis, and treatment of this virus.

Keywords: Coronavirus; Novel coronavirus; 2019-nCoV; Middle East respiratory syndrome coronavirus; SARS coronavirus; Outbreak; China; Wuhan; Emerging viruses

Introduction

Coronaviruses typically result in respiratory and enteric infections affecting both animals and humans, and were considered relatively benign to humans before the severe acute respiratory syndrome (SARS-CoV) outbreak in 2002 and 2003 in China.¹⁻⁴ A decade later, Middle East respiratory syndrome coronavirus (MERS-CoV), another pathogenic coronavirus with a clinical picture reminiscent of SARS, was isolated in patients presenting with pneumonia in the Middle Eastern countries.⁵ Just recently, in December 2019, a novel coronavirus (2019-nCoV) has emerged in Wuhan, China and has turned into a global health concern.⁶

Virology and Pathogenesis

Coronaviruses are enveloped positive-stranded RNA viruses that belong to the family *Coronaviridae* and the order *Nidovirales*.⁷ People around the globe are frequently infected with four human coro-

naviruses (229E, NL63, OC43, and HKU1 with the first two classified as antigenic group 1 and the latter two belonging to group 2) typically leading to an upper respiratory tract infection manifested by common cold symptoms. However, coronaviruses, which are zoonotic in origin, can evolve into a strain that can infect human beings leading to fatal illness.⁸ Examples are SARS-CoV, MERS-CoV, and the recently identified 2019-nCoV.

The expansion of genetic diversity among coronaviruses and their consequent ability to cause disease in human beings is mainly achieved through infecting peridomestic animals, which serve as intermediate hosts, nurturing recombination and mutation events.⁹ The spike glycoprotein (S glycoprotein), which attaches the virion to the host cell membrane, is postulated to play a dominant role in host range restriction.¹⁰ While SARS-CoV infects type 2 pneumocytes and ciliated bronchial epithelial cells utilizing angiotensin converting enzyme 2 as a receptor, MERS-CoV exploits dipeptidyl peptidase 4

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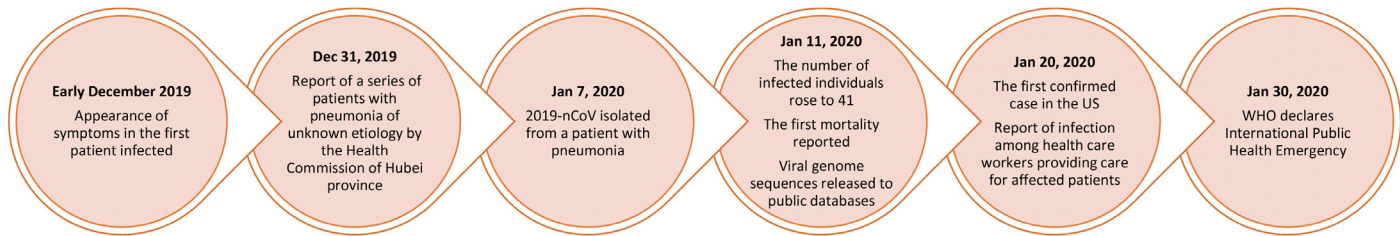


Figure 1: Timeline of the key events in the early stages of the outbreak

(DPP4), a transmembrane glycoprotein, to infect type 2 pneumocytes and unciliated bronchial epithelial cells.¹¹⁻¹⁴

In general, coronaviruses first replicate in epithelial cells of the respiratory and enteric cells, which leads to cytopathic changes.¹⁵ Thorough studies have not yet been conducted to elucidate the molecular basis of the pathogenicity of 2019-nCoV. However, preliminary data obtained through whole-genome sequencing of the viral RNA extracted from host cell-depleted nasopharyngeal and sputum samples and subsequent bioinformatics analyses have shown that the novel virus is phylogenetically related to SARS-related coronaviruses first isolated in Chinese horseshoe bats during the period of 2015 to 2017.^{16,17} It has also been hypothesized that the novel virus might use angiotensin converting enzyme 2 as a receptor similar to SARS-CoV.¹⁸ Unlike SARS-CoV or MERS-CoV, primary human airway epithelial cells provide better growth conditions for 2019-nCoV than standard tissue culture cells.⁶

Epidemiology

A series of patients with pneumonia of unknown etiology were initially reported by the Health Commission of Hubei province, China, on December 31, 2019 (Fig 1).¹⁹ Although 27 patients were initially announced to be afflicted with this mysterious disease, the number rose to 41 with seven critically ill patients; one death was noted in the subsequent report on Janu-

ary 11, 2020.²⁰ The Chinese authorities reporting to WHO stated that some of the patients were operating dealers or vendors in the Huanan seafood market, which was subsequently reported to be selling live and freshly slaughtered hunted animals.^{16,21} Several reports of clusters of cases among families and infection of 16 health care workers pointed to human-to-human transmission of the virus.^{16,22,23}

Despite recognition of the outbreak within a few weeks by the Chinese using their efficient surveillance network and laboratory infrastructure, efforts to prevent the spread of this virus were not sufficient; as of February 3, 2020, at least 17496 cases with a death toll of 362 in more than 25 countries have been reported (Fig 2).²⁴ With a crowded population eclipsing that of New York City by more than 2.5 million and its role as one of China's major transportation hubs, the city of Wuhan was the ideal breeding ground for an outbreak.²⁵ Peak travel season due to the Chinese New Year was probably an important factor that led to the global spread of the infection.

In a study of 425 cases infected up to January 4, the basic reproductive number, or R_o , of the virus was estimated to be approximately 2.2.²⁶ This means that each patient can, on average, spread the infection to more than two healthy persons. This number was around 3 for the SARS-CoV outbreak, which was eventually contained as a result of efficient infection control measures.^{9,27} Presence of cases with mild clinical presentation and lack of

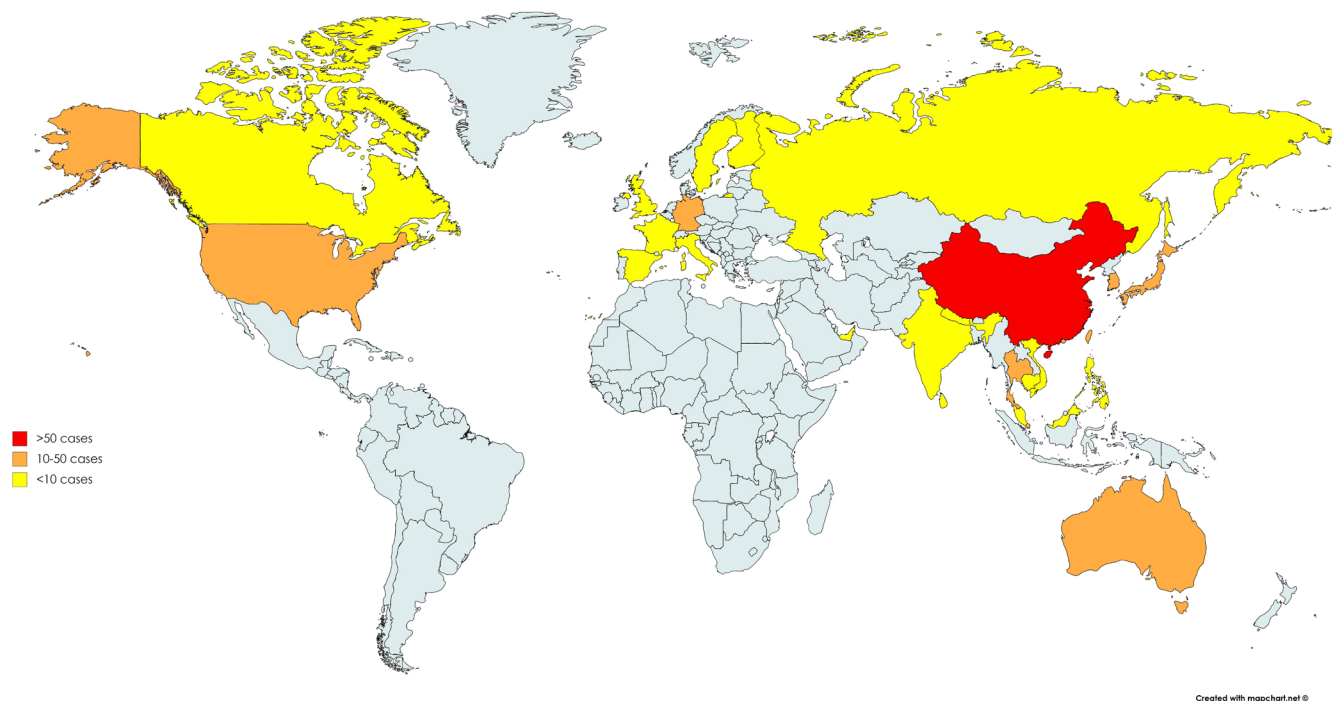


Figure 2: Global distribution of 2019-nCoV as of February 3, 2020

infrastructure to provide isolation for infected individuals and their close contacts, particularly in resource-limited countries, are nonetheless all hurdles to control this infection. Furthermore, based on experience, proper precautionary measures to prevent nosocomial transmission of the virus is mandatory; the majority of patients with SARS-CoV and MERS-CoV had become infected in health care settings.²⁸ Considering the plethora of comorbid conditions present in hospital populations, dire complications could arise in the setting of an outbreak.

Clinical Manifestations and Diagnosis

Overall, infection caused by the 2019-nCoV shares many clinical similarities with infection caused by SARS-CoV. A typical human coronavirus has an incubation period of 2–4 days; it is estimated to

be 3–6 days for the 2019-nCoV, and 4–6 days for SARS-CoV.^{15,16,29,30} Infection with 2019-nCoV, similar to SARS-CoV, presents with non-specific symptoms such as malaise, fever, and dry cough at the prodromal phase.^{16,29,30} In a study of 425 patients with confirmed 2019-nCoV infection, the mean duration from illness onset to the first medical visit was 5.8 (95% CI 4.3 to 7.5) days for cases with disease onset before January 1, 2020, and 4.6 (95% CI 4.1 to 5.1) days for patients with illness onset between January 1 and 11.²⁶ A report by Huang, *et al*, on 41 confirmed cases of 2019-nCoV infection who were admitted to Wuhan Hospital indicated that fever (98%), cough (76%), dyspnea (55%), and myalgia or fatigue (44%) were the most common presenting signs and symptoms.³⁰ In another report from China, these findings were corroborated.²⁹ In contrast to patients with typical human coronavirus infections, few of those affected with the

novel coronavirus had upper respiratory tract signs and symptoms (*eg*, sore throat, rhinorrhea). Unlike SARS-CoV, intestinal presentations (*eg*, diarrhea) seem to be infrequent in patients with 2019-nCoV.^{29,31} Given the similarities between SARS-CoV and 2019-nCoV, it is tempting to speculate about viremia and affected tissues beyond the respiratory tract. However, we are not aware of any data on this yet.

Chest X-ray and computed tomography (CT) findings showed bilateral lung involvement in 114 (81%) of 140 confirmed patients studied in two reports,^{29,30} again similar to infection with SARS-CoV. Among these 140 cases, 61 (44%) had lymphopenia; 58 (41%) had an elevation of either aspartate aminotransferase (AST) or alanine aminotransferase (ALT) above the upper limit of the reference range^{29,30} (also seen in SARS-CoV). Among infection-related biomarkers, procalcitonin levels have been normal among most of the reported individuals; elevated levels were observed in those with secondary infections.^{29,30} However, elevated serum ferritin and C-reactive protein levels were, respectively, reported in 63% and 86% of the patients reported by Chen, *et al.*²⁹ Similar to the findings in SARS-CoV infection, an increase in plasma pro-inflammatory cytokines levels has also been reported, correlating with the severity of the illness.^{30,32} However, increased levels of interleukin 10, which is an anti-inflammatory cytokine, suggest a pattern different from that of SARS-CoV infection.^{30,33} Further investigations to characterize the cytokine profile of patients could shed light on 2019-nCoV pathogenesis.

In the wake of the peak of influenza and other respiratory viral infections in the northern hemisphere and nonspecific clinical findings resembling other cases of viral pneumonia, early detection of those infected with 2019-nCoV is an onerous task for health care professionals around the globe.

Eliciting the exposure history of suspicious cases could have been an effective strategy in the earlier stages of the outbreak in China. However, the global spread of the virus and human-to-human transmission seen in recent weeks have made the situation more complicated.³⁴ In general, infected patients had a median age ranging from 49 to 61 years; male individuals are more frequently infected.^{26,29,30} Lack of serious disease in children is also a feature of SARS-CoV infection, and a feature of some (but not all) coronavirus infections in other species.¹⁵ Immune-related genes on the X chromosome and sex hormones, which influence both innate and adaptive immune responses, might explain the higher susceptibility to the infection in males.^{35,36} Higher likelihood of exposure to the virus due to occupational risk could be another contributory factor.

The full genomic sequence of the 2019-nCoV was released shortly after the start of the outbreak to public databases.³⁷ This, in turn, paved the way for the development of PCR assays to detect the virus. Rapid collection and nucleic acid amplification testing of appropriate respiratory samples (*ie*, nasopharyngeal and oropharyngeal swab in outpatient cases and sputum and/or endotracheal aspirate or bronchoalveolar lavage in patients with more critical conditions) for suspicious cases are currently recommended by WHO.³⁸

Treatment

There are no vaccines or specific antivirals for 2019-nCoV.³⁹ Nonetheless, there are ongoing efforts for vaccine development.⁴⁰ Remdesivir, an antiviral drug developed for the treatment of Ebola virus disease, was used for the treatment of the first US case of 2019-nCoV.⁴¹ An ongoing randomized controlled trial evaluating the efficacy and safety of lopinavir-ritonavir and interferon- α 2b in patients infected

with the novel coronavirus was launched on January 10, 2020.⁴² However, isolation and supportive care including oxygen therapy, fluid management, and administration of antimicrobials for treatment of secondary bacterial infections to alleviate the symptoms and prevent end-organ dysfunction is currently recommended by WHO for suspected and confirmed cases requiring hospital admission.⁴³

Conclusion

The novel coronavirus, which comes from a viral family that was thought to be rather benign before the turn of the century, has led to a public health emergency of international concern according to WHO.⁴⁴ Outbreaks like this highlight the importance of effective public health strategies to counteract the never-ending threats imposed by emerging pathogens.

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